# Anexos.

MINISTERIO
DE INDUSTRIA, TURISMO
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Oficina Española
de Patentes y Marcas

Universitat Ramon Llull

18 MAIG 2009

ENTRADA Núm: 23097RT SORTIDA Núm:

UNIV.RAMON LLULL,FUNDACIO
PRIVADA-INST.QUIMIC DE SARRIA
CETS,FUNDACIO PRIVADA
CLARAVALL, 1-3
08022 BARCELONA

Madrid, 12 de mayo de 2009

**Asunto: ENVIO DOCUMENTOS**

Remito a Vd. los siguientes documentos correspondientes a **su solicitud de patente nº P200901191**

X- Copia de la Solicitud
- Justificante de pago

OFICINA ESPAÑOLA DE PATENTES Y MARCAS (S.G.)
Salida
Nº 200900086994
12/05/2009 12:36:20

Atentamente le saluda

Fdo.: Ana López-Quiroga Valencia
Jefe Negociado de Depósito de Invenciones

**Comunicación al Interesado**: Los plazos de resolución se señalan en el justificante de presentación comenzarán a computarse desde la fecha de recepción que figura en la copia que se adjunta.

**NOTA IMPORTANTE:**
**Indicación de prioridad**: El código del país con el número de su solicitud de prioridad, que ha de utilizarse para la presentación de solicitudes en otros países en virtud del Convenio de París, es: **ES 200901191**

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MINISTERIO DE INDUSTRIA, TURISMO Y COMERCIO

Oficina Española de Patentes y Marcas

# INSTANCIA DE SOLICITUD

NUMERO DE SOLICITUD P200901191

Data 29 ABR. 2003 Hora

Registre d'Entrada 20612

FECHA Y HORA DE PRESENTACIÓN EN LA O.E.P.M. 13'21

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(1) MODALIDAD:
☒ PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD

(2) TIPO DE SOLICITUD:
☐ ADICIÓN A LA PATENTE
☐ SOLICITUD DIVISIONAL
☐ CAMBIO DE MODALIDAD
☐ TRANSFORMACIÓN SOLICITUD PATENTE EUROPEA
☐ PCT: ENTRADA FASE NACIONAL

(3) EXP. PRINCIPAL O DE ORIGEN:
MODALIDAD
N° SOLICITUD
FECHA SOLICITUD

(4) LUGAR DE PRESENTACIÓN: BARCELONA — CÓDIGO 08

| (5) SOLICITANTE (S): APELLIDOS O DENOMINACIÓN SOCIAL | NOMBRE | NACIONALIDAD | CÓDIGO PAÍS | DNI/CIF | CNAE | PYME |
|---|---|---|---|---|---|---|
| UNIVERSITAT RAMON LLULL, FUNDACIÓ | | ESPAÑOLA | ES | G590697740 | | |
| PRIVADA- INSTITUT QUÍMIC DE SARRIÀ | | ESPAÑOLA | ES | G58022849 | | |
| CETS, FUNDACIÓ PRIVADA | | | | | | |

(6) DATOS DEL PRIMER SOLICITANTE:
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PROVINCIA BARCELONA
PAÍS RESIDENCIA ESPAÑA
NACIONALIDAD ESPAÑOLA

TELÉFONO 936022200
FAX
CORREO ELECTRÓNICO
CÓDIGO POSTAL 08022
CÓDIGO PAÍS ES
CÓDIGO PAÍS ES

| (7) INVENTOR (ES): APELLIDOS | NOMBRE | NACIONALIDAD | CÓDIGO PAÍS |
|---|---|---|---|
| BERZOSA RODRÍGUEZ | XAVIER | ESPAÑOLA | ES |
| BORRELL BILBAO | JOSE IGNACIO | ESPAÑOLA | ES |

(8)
☐ EL SOLICITANTE ES EL INVENTOR
☒ EL SOLICITANTE NO ES EL INVENTOR O ÚNICO INVENTOR

(9) MODO DE OBTENCIÓN DEL DERECHO:
☒ INVENC. LABORAL ☐ CONTRATO ☐ SUCESIÓN

(10) TÍTULO DE LA INVENCIÓN:
**SÍNTESIS Y USOS DE 4-CIANOPENTANOATOS Y 4-CIANOPENTENOATOS SUSTITUIDOS**

(11) EFECTUADO DEPÓSITO DE MATERIA BIOLÓGICA: ☐ SI ☒ NO

(12) EXPOSICIONES OFICIALES: LUGAR FECHA

| (13) DECLARACIONES DE PRIORIDAD: PAÍS DE ORIGEN | CÓDIGO PAÍS | NÚMERO | FECHA |
|---|---|---|---|
| | | | |

(14) EL SOLICITANTE SE ACOGE AL APLAZAMIENTO DE PAGO DE TASAS PREVISTO EN EL ART. 162. LEY 11/86 DE PATENTES ☐

(15) AGENTE /REPRESENTANTANTE: NOMBRE Y DIRECCIÓN POSTAL COMPLETA. (SI AGENTE P.I., NOMBRE Y CÓDIGO) ( RELLÉNESE, ÚNICAMENTE POR PROFESIONALES)

(16) RELACIÓN DE DOCUMENTOS QUE SE ACOMPAÑAN:
☒ DESCRIPCIÓN Nº DE PÁGINAS: 15
☒ Nº DE REIVINDICACIONES: 20
☐ DIBUJOS. Nº DE PÁGINAS:
☐ LISTA DE SECUENCIAS Nº DE PÁGINAS:
☐ RESUMEN
☐ DOCUMENTO DE PRIORIDAD
☐ TRADUCCIÓN DEL DOCUMENTO DE PRIORIDAD
☐ DOCUMENTO DE REPRESENTACIÓN
☒ JUSTIFICANTE DEL PAGO DE TASA DE SOLICITUD
☐ HOJA DE INFORMACIÓN COMPLEMENTARIA
☐ PRUEBAS DE LOS DIBUJOS
☐ CUESTIONARIO DE PROSPECCIÓN
☐ OTROS:

FIRMA DEL SOLICITANTE O REPRESENTANTE
Esther Giménez-Salinas, Enric Julià
(VER COMUNICACIÓN)

FIRMA DEL FUNCIONARIO

NOTIFICACIÓN SOBRE LA TASA DE CONCESIÓN:
Se le notifica que esta solicitud se considerará retirada si no procede al pago de la tasa de concesión; para el pago de esta tasa dispone de tres meses a contar desde la publicación del anuncio de la concesión en el BOPI, más los diez días que establece el art. 81 del R.D. 2245/1986.

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MOD. 3101 – 1 – EJEMPLAR PARA EL EXPEDIENTE

NO CUMPLIMENTAR LOS RECUADROS ENMARCADOS EN ROJO

MINISTERIO
DE INDUSTRIA, TURISMO
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Oficina Española
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(12) # SOLICITUD DE PATENTE DE INVENCIÓN

| (21) NÚMERO DE SOLICITUD | |
|---|---|
| (22) FECHA DE PRESENTACIÓN | |
| (62) PATENTE DE LA QUE ES DIVISORIA | |

DATOS DE PRIORIDAD

| (31) NÚMERO | (32) FECHA | (33) PAÍS |
|---|---|---|
| | | |

(71) SOLICITANTE (S)

**UNIVERSITAT RAMON LLULL, FUNDACIÓ PRIVADA, INTITUT QUÍMIC DE SARRIÀ, CETS FUNDACIÓ PRIVADA**

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(51) Int. Cl.

GRÁFICO (SÓLO PARA INTERPRETAR RESUMEN)

(54) TÍTULO DE LA INVENCIÓN

**Síntesis y usos de 4-clanopentanoatos y 4-clanopentenoatos y sustituidos.**

(57) RESUMEN

**La presente invención se refiere a 4-clanopentanoatos sustituidos de fórmula general 1 y 4-clanopentenoatos sustituidos de fórmula general 2 y a un procedimiento para su obtención.**

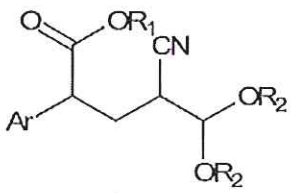
Mod. 3106i

PRIMERA PÁGINA DE LA MEMORIA

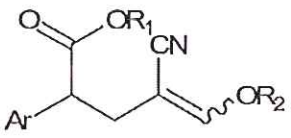
# SÍNTESIS Y USOS DE 4-CIANOPENTANOATOS Y 4-CIANOPENTENOATOS SUSTITUIDOS

## Campo de la técnica

La presente invención se refiere a 4-cianopentanoatos sustituidos de fórmula general **1** y 4-cianopentenoatos sustituidos de fórmula general **2** y a un procedimiento para su obtención. La invención se refiere asimismo al empleo de los 4-cianopentanoatos sustituidos de fórmula general **1** y 4-cianopentenoatos sustituidos de fórmula general **2** como intermedios de síntesis en la obtención de compuestos 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos.




**1**




**2**

## Estado de la técnica

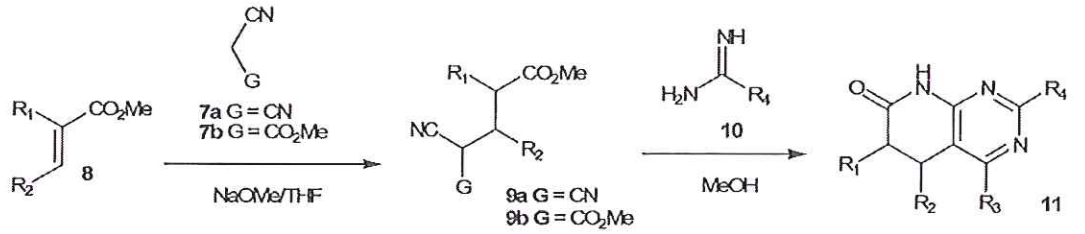
Las Proteína Quinasas (PKs) se hallan implicadas en procesos tan diversos como la angiogénesis, restenosis, arteriosclerosis y, en particular, en los procesos de crecimiento tumoral. En consecuencia, el desarrollo de inhibidores selectivos de PKs se ha convertido en un área muy activa de investigación. Los compuestos 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos **3** y sus sales farmacéuticamente aceptables han demostrado ser inhibidores selectivos de diversas proteína quinasas. Concretamente KDR (kinase insert domaincontainig receptor) y FGFR (fibroblast growth factor receptor) quinasas (US709833B2). Este hecho hace que estos compuestos dihidropiridinónicos **3** tengan actividad antiproliferativa y por lo tanto sean útiles en el tratamiento o control del cáncer, concretamente en el caso de tumores sólidos.


**3**

Estos compuestos de fórmula general **3** donde $R_4$ puede ser H, alquilo, arilo, heteroarilo, heterociclo, cicloalquilo, alquenilo o alquinilo sustituidos o no y $R_3$ y Ar

pueden ser arilo o heteroarilo sustituidos o no se obtienen en la actualidad a partir del uracilo en un mínimo de seis etapas sintéticas (US709833B2).

En este entorno Borrell y colaboradores (Nuria Mont, Jordi Teixidó, C. Oliver Kappe, José I. Borrell, *Molecular Diversity* **2003** *7*, 153-159) desarrollaron previamente una ruta sintética para la obtención de sistemas piridopirimidínicos referibles **11** por tratamiento de un éster α,β-insaturado **8** con un acetonitrilo con un sustituyente aceptor G (**7a** y **7b**) y posteriormente con una guanidina o amidina sustituida **10**.




12 $R^3 = NH_2$, $R^4 = NH_2$, alquilo, arilo
13 $R^3 = OH$, $R^4 = NH_2$, alquilo, arilo

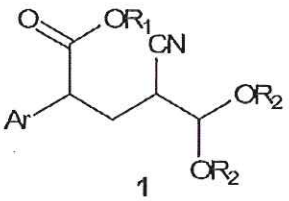
Estos sistemas piridopirimidínicos **11** presentan un grupo amina o alcohol en posición 4 del anillo de pirimidina. Para obtener piridopirimidinas **3** con un H en posición 4 en lugar del alcohol o la amina es necesario utilizar un acetonitrilo en el que G fuese un grupo aldehído. Por lo tanto el compuesto a utilizar sería el cianoacetaldehído, compuesto no accesible sintéticamente. Una alternativa al uso de cianoacetaldehído es el 3,3-dimetoxipropanonitrilo **5** donde $R_2$ es Me, que presenta el grupo aldehído protegido en forma de acetal. El grupo acetal no es un aceptor al contrario que el aldehído por lo que la acidez de los H del metileno presente en el 3,3-dimetoxipropanonitrilo disminuye drásticamente respecto los acetonitrilos usados por Borrell y colaboradores. Éste hecho hace necesaria la búsqueda de una base más fuerte que el NaOMe usado por Borrell y colaboradores. El 3,3-dimetoxipropanonitrilo da una reacción de eliminación por tratamiento con bases fuertes o bajo catálisis ácida generando 3-metoxiacrilonitrilo (US 2002028962 (A1)). Sorprendentemente el uso de bases concretas como NaOH/DMF o *t*-ButOK/THF permiten la ionización del 3,3-dimetoxipropanonitrilo sin que tenga lugar la citada eliminación. Esto permite su uso para la obtención de 4-cianopentanoatos sustituidos de fórmula general **1** y 4-cianopentenoatos sustituidos de fórmula general **2** sobre los que se refiere la presente invención.

A la vista de lo expuesto anteriormente existe en el estado de la técnica la necesidad de proporcionar una ruta sintética más sencilla para la obtención de sistemas 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos **3**. Esta ruta sintética pasa por la

obtención de 4-cianopentanoatos sustituidos de fórmula general **1** o 4-cianopentenoatos sustituidos de fórmula general **2**, pudiendo obtenerse compuestos de fórmula general **3** en dos etapas sintéticas.

**Objeto de la invención**

En un aspecto la invención se refiere por tanto a 4-cianopentanoatos sustituidos de fórmula general **1** donde



**1**

$R_1$ puede ser un radical alquilo $C_{1-6}$ y donde

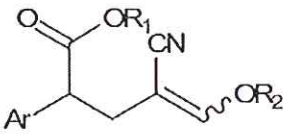
$R_2$ puede ser un radical alquilo $C_{1-6}$ y donde

Ar puede ser arilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un naftilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un heteroarilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro.

En otro aspecto la invención se refiere por tanto a 4-cianopentenoatos sustituidos de fórmula general **2** donde



**2**

$R_1$ puede ser un radical alquilo $C_{1-6}$ y donde

$R_2$ puede ser un radical alquilo $C_{1-6}$ y donde

Ar puede ser arilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un naftilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un heteroarilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro.

En una realización preferida el compuesto de fórmula **1** se selecciona del grupo formado por:

[1] 2-(2,6-diclorofenil)-4-ciano-5,5-dimetoxipentanoato de metilo

[2] 4-ciano-5,5-dimetoxi-2-o-tolilpentanoato de etilo

[3] 4-ciano-5,5-dimetoxi-2-(2-metoxifenil)pentanoato de metilo

[4] 4-ciano-5,5-dimetoxi-2-(naftalen-1-il)pentanoato de metilo

[5] 4-ciano-5,5-dimetoxi-3-fenilpentanoato de metilo

En una realización preferida el compuesto de fórmula **2** se selecciona del grupo formado por:

[6] 2-(2,6-diclorofenil)-4-ciano-5-metoxipent-4-enoato de metilo

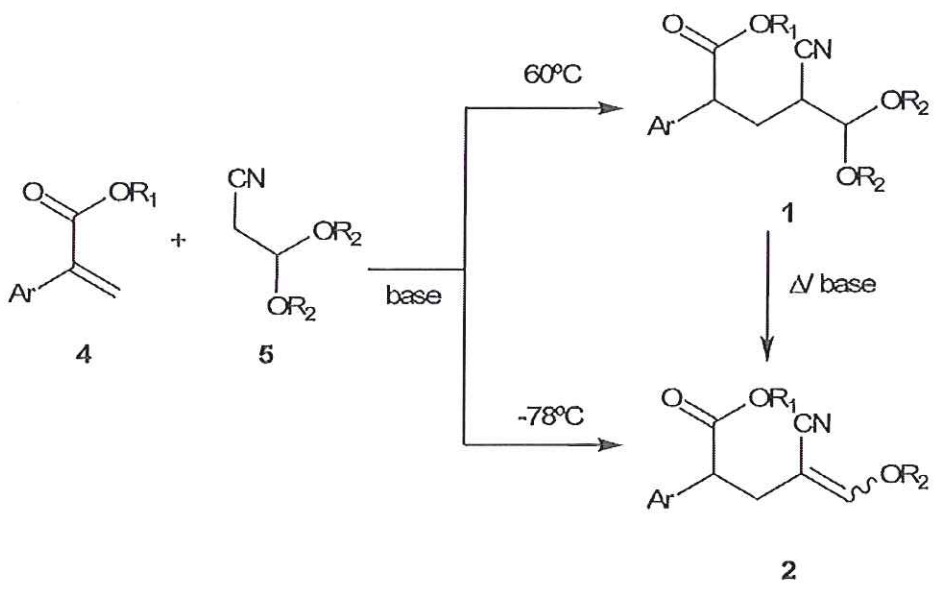
[7] 4-ciano-5-metoxi-2-o-tolilpent-4-enoato de etilo

[8] 4-ciano-5-metoxi-2-(2-metoxifenil)pent-4-enoato de metilo

[9] 4-ciano-5-metoxi-2-(naftalen-1-il)pent-4-enoato de metilo

[10] 4-ciano-5-metoxi-3-fenilpent-4-enoato de metilo

En otro aspecto la invención se refiere a un procedimiento de obtención de los 4-cianopentanoatos sustituidos **1** y 4-cianopentenoatos sustituidos **2** de fórmula general de la invención. Dicho procedimiento, en adelante procedimiento de la invención comprende tratar un éster α,β-insaturado de fórmula general **4** con un propionitrilo de fórmula general **5** en presencia de una base en un disolvente inerte. Cuando la reacción se lleva a cabo a bajas temperaturas (-78°C) se obtiene mayoritariamente el 4-cianopentanoato sustituido de fórmula general **1** mientras que si la reacción se hace a temperaturas mayores (60°C) el compuesto mayoritario es el 4-cianopentenoato sustituido de fórmula general **2**. La obtención de 4-cianopentenoatos sustituidos de fórmula general **2** también es posible por calefacción de los 4-cianopentanoatos sustituidos de fórmula general **1** en presencia de una base. La reacción de adición conjugada se representa en el Esquema 1, donde $R_1$, $R_2$ y Ar tienen el significado anteriormente definido.




**Esquema 1**

En una realización particular del procedimiento de invención la base utilizada es un alcóxido alcalino como por ejemplo tert-butóxido potásico o un hidróxido alcalino como por ejemplo hidróxido sódico. El disolvente inerte es un disolvente que no interfiere en la reacción y puede seleccionarse de un amplio grupo de disolventes orgánicos convencionales. En una realización particular se utiliza un disolvente de tipo éter, preferiblemente tetrahidrofurano u otros tipos de disolventes como dimetilformamida.

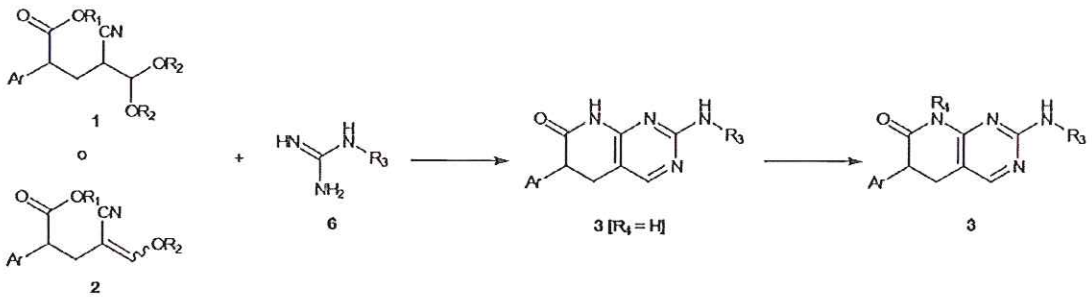
Los 4-cianopentanoatos sustituidos de fórmula general **1** y los 4-cianopentenoatos sustituidos de fórmula general **2** obtenidos pueden purificarse y/o aislarse del medio de reacción según procedimientos que los expertos en la técnica conocen, por ejemplo procedimientos cromatográficos o destilación.

Si los compuestos de fórmula general **1** o **2** se obtienen en forma de una mezcla de estereoisómeros, particularmente diastereoisómeros, dichas mezclas pueden separarse mediante procedimientos convencionales que los expertos en la técnica conocen, por ejemplo procedimientos cromatográficos.

En otro aspecto de la invención se relaciona el empleo de los compuestos de fórmula general **1** y **2** como precursores en la síntesis de compuestos 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos **3**. En este sentido la presente invención se relaciona por tanto con un procedimiento para la preparación de sistemas dihidropirimidinónicos sustituidos **3** que comprende el paso a través de un compuesto de fórmula general **1** o **2** y que de acuerdo con una realización particular del mismo comprende las siguientes etapas de reacción (Esquema 2):

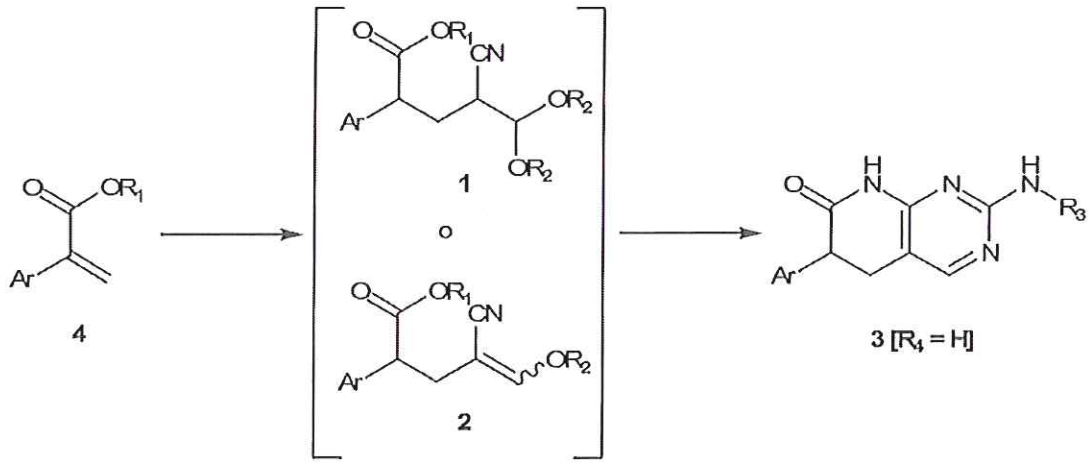
a) ciclación del 4-cianopentanoato sustituido **1** o 4-cianopentenoato sustituido **2** por reacción con una guanidina o sal de guanidina sustituida de formula general **6**, donde $R_3$ puede ser H, alquilo $C_{1-6}$, arilo, sustituido o no, y hetroarilo, sustituido o no, obteniéndose un compuesto de fórmula general **3** con $R_4$ = H.

b) si se desea se puede derivatizar el nitrógeno lactámico en posición 8. Éste puede ser arilado por tratamiento con haluros de arilo en presencia de CuI, un ligando 1,2-diamina y un carbonato alcalino como base o alquilado por reacción con un haluro de alquilo en presencia de una base como hidruro sódico. Así se obtienen compuestos 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos **3**.




**Esquema 2**

En una realización particular, el procedimiento de obtención de compuestos 5,8-dihidro-6H-pirido[2,3-d]pirimidin-7-ona sustituidos **3** donde $R_4$ es H se lleva a cabo sin aislar intermedio de fórmula general **1** o **2** tal y como se representa en el Esquema 3. De acuerdo con esta realización particular se hace reaccionar un éster α,β-insaturado de fórmula general **4** con un propionitrilo de fórmula general **5** en presencia de tert-butóxido potásico. Se neutraliza con ácido acético, se elimina el disolvente a presión reducida y se añade la sal de guanidina **6** en presencia de piridina o $Na_2CO_3$. Si la sal de guanidina es un carbonato no es necesario añadir ninguna base. Se deja reaccionar a 150 °C - 180 °C bajo agitación obteniéndose el compuesto de fórmula general **3** con un rendimiento mayor.




**Esquema 3**

En una realización preferente $R_3$ es un grupo alquilo $C_{1-6}$, arilo, preferentemente fenilo o H.

A continuación, para una mejor comprensión de la presente invención, sin que deba ser interpretado como limitaciones a la misma, se exponen los siguientes ejemplos.

Ejemplos:

Obtención del 2-(2,6-diclorofenil)-4-ciano-5-metoxipent-4-enoato de metilo (2. $R_1$ = Me, $R_2$ = Me, Ar = 2,6-diclorofenil)

A una disolución de 1,15 g (5 mmol) de 4 ($R_1$ = Me Ar = 2,6-diclorofenil) en 0,85 mL (7,5 mmol) de 5 ($R_2$ = Me) se añadieron 50 mL de disolución 0,1M de t-ButOK en THF. Se agitó a 60°C durante 5 min. Se neutralizó con AcOH glacial. Se eliminó el disolvente a P reducida. El residuo se purificó por cromatografía flash y posteriormente por destilación. Se obtuvieron 0,96 g (3 mmol, 61%) de aceite amarillo correspondiente a la mezcla de diastereoisómeros del producto deseado. Se describe espectroscopicamente de isómero mayoritario (E).IR (KBr) $\nu_{max}$: 2949, 2209, 17,39, 1645, 1437, 1266, 1222, 783. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32 (d, $J$ = 8.0 Hz, 2H), 7.17 (t, $J$ = 8.0 Hz), 6.69 (s), 4.68 (dd, $J^3$ = 10.0 Hz, $J^3$ = 5.5 Hz), 3.71 (s, 3H), 3.66 (s, 3H), 3.12 (dd, $J^3$ = 5.5 Hz, $J^2$ = 14.4), 2.92 (dd, $J^3$ = 10.0 Hz, $J^2$ = 14.4). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 161.1, 134.4, 129.0, 128.6, 119.3, 89.3, 61.6, 52.5, 45.4, 25.5. HRMS ($EI^+$) *m/z* calculado para $C_{14}H_{13}Cl_2NO_3$ 313.0272. Obtenido 313.0271.

Obtención del 6-(2,6-diclorofenil)-5,6-dihidro-2-(fenilamino)pirido[2,3-d]pirimidin-7(8H)-ona (**3**, $R_3$ = Ph, $R_4$ = H, Ar = 2,6-diclorofenil)

A una disolución de 0.46 g (2 mmol) de **4** ($R_1$ = Me Ar = 2,6-diclorofenil) en 0,35 mL (3 mmol) de **5** ($R_2$ = Me) se añadieron 20 mL de disolución 0,1M de t-ButOK en THF. Se agitó a $T_{amb}$ durante 5 min. Se neutralizó con AcOH glacial. Se realizó un filtrado cromatográfico usando como fase estacionaria gel de sílice y como fase móvil 200 mL de mezcla AcOEt/Hexano 1:1. Se eliminó el disolvente a P reducida. Se añadieron al residuo 1,07g (6 mmol) de carbonato de fenilguanidina **6** ($R_3$ = Ph) y se calentó la mezcla a 150ºC bajo agitación durante una noche. Se suspendió el residuo sólido en MeOH, se filtró y se lavó con agua y posteriormente con MeOH. Se obtuvieron 0,28 g (0,7 mmol, 36%) de sólido blanco. IR (KBr) $\nu_{max}$: 3289, 3204, 3145, 1685, 16,02, 1579, 1498, 1446, 1241, 756. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 10.96 (s), 9.41 (s), 8.19 (s), 7.82 (d, $J$ = 7.8 Hz, 2H), 7.56 (d, $J$ = 8.2 Hz), 7.52 (d, $J$ = 7.9 Hz), 7.39 (t, $J$ = 8.1 Hz), 7.24 (t, $J$ = 7.9 Hz, 2H), 6.91 (t, $J$ = 7.3 Hz), 4.76 (dd, $J^3$ = 13.8 Hz, $J^2$ = 8.0 Hz), 3.23 (m), 2.99 (dd, $J^3$ = 15.8 Hz, $J^2$ = 8.0 Hz). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ = 169.8, 158.8, 157.4, 155.6, 140.7, 135.3, 134.9, 134.8, 129.9, 129.8, 128.4 (2C), 121.0, 118.6 (2C), 104.3, 43.3, 25.0. HRMS ($FAB^+$) *m/z* calculado para $C_{19}H_{14}Cl_2N_4O$ 385.0623. Obtenido 385.0622.

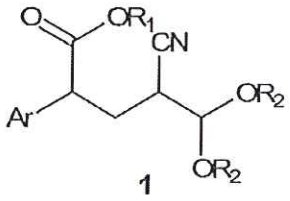
Obtención del 2-amino-5,6-dihidro-6-(naftalen-1-il)pirido[2,3-d]pirimidin-7(8H)-ona (**3**, $R_3$ = H, $R_4$ = H, Ar = naftil)

A una disolución de 0.45 g (2 mmol) de **4** ($R_1$ = Me, Ar = naftil) en 0,35 mL (3 mmol) de **5** ($R_2$ = Me) se añadieron 20 mL de disolución 0,1M de t-ButOK en THF. Se agitó a $T_{amb}$ durante 5 min. Se neutralizó con AcOH glacial. Se realizó un filtrado cromatográfico usando como fase estacionaria gel de sílice y como fase móvil 200 mL de mezcla AcOEt/Hexano 1:1. Se eliminó el disolvente a P reducida. Se añadieron al residuo 0,54g (6 mmol) de carbonato de guanidina **6** ($R_3$ = H) y 4 mL de piridina y se calentó la mezcla en microondas 1h a 180ºC. Se añadió agua a la disolución, se filtró el precipitado obtenido y se lavó éste con agua y posteriormente con MeOH. Se obtuvieron 0,26 g (0,9 mmol, 44%) de sólido blanco. IR (KBr) $\nu_{max}$: 3368, 3331, 3161, 2895, 1682, 1630, 1573, 1497, 1231, 776. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 10.80 (s), 8.10 (m), 7.95 (m), 7.90 (s), 7.85 (d, $J$ = 8.1 Hz), 7.54 (m, 2H), 7.45 (t, $J$ = 7.7 Hz), 7.35 (d, $J$ = 7.1 Hz), 6.40 (s, 2H), 4.70 (t, $J$ = 8.5 Hz), 3.08 (d, $J$ = 8.5 Hz). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 162.5, 158.0, 155.6,

135.3, 133.6, 131.2, 128.7, 127.5, 126.1, 125.6, 125.4, 125.2, 124.0, 103.5, 42.9, 27.9. HRMS ($FAB^+$) *m/z* calculado para $C_{17}H_{14}N_4O$ 291.1246. Obtenido 291.1247.

## REIVINDICACIONES

1. Compuesto de fórmula general **1**,




**1**

donde,

$R_1$ puede ser un radical alquilo $C_{1-6}$ y donde

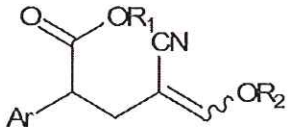
$R_2$ puede ser un radical alquilo $C_{1-6}$ y donde

Ar puede ser arilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un naftilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un heteroarilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro.

2. Compuesto de fórmula general **2**,




**2**

donde,

$R_1$ puede ser un radical alquilo $C_{1-6}$ y donde

$R_2$ puede ser un radical alquilo $C_{1-6}$ y donde

Ar puede ser arilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un naftilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro;

un heteroarilo, opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$, haluro.

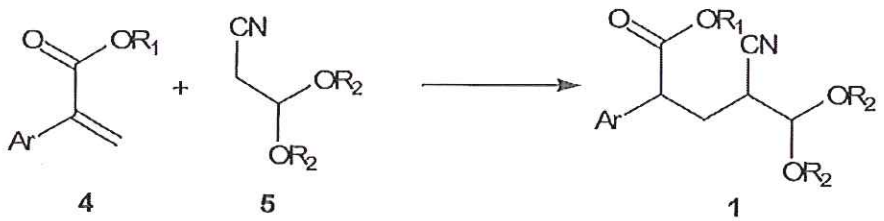
3. Compuesto según la reivindicación 1, en el que Ar es arilo preferiblemente naftilo o fenilo, opcionalmente sustituido por uno o mas sustituyentes seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$ y haluro.

4. Compuesto según la reivindicación 2, en el que Ar es arilo preferiblemente naftilo o fenilo, opcionalmente sustituido por uno o mas sustituyentes seleccionados de alquilo $C_{1-6}$, alcoxilo $C_{1-6}$ y haluro.

5. Un compuesto según la reivindicación 1 seleccionado del grupo formado por:
   [1] 2-(2,6-diclorofenil)-4-ciano-5,5-dimetoxipentanoato de metilo
   [2] 4-ciano-5,5-dimetoxi-2-o-tolilpentanoato de etilo
   [3] 4-ciano-5,5-dimetoxi-2-(2-metoxifenil)pentanoato de metilo
   [4] 4-ciano-5,5-dimetoxi-2-(naftalen-1-il)pentanoato de metilo
   [5] 4-ciano-5,5-dimetoxi-3-fenilpentanoato de metilo

6. Un compuesto según la reivindicación 2 seleccionado del grupo formado por:
   [6] 2-(2,6-diclorofenil)-4-ciano-5-metoxipent-4-enoato de metilo
   [7] 4-ciano-5-metoxi-2-o-tolilpent-4-enoato de etilo
   [8] 4-ciano-5-metoxi-2-(2-metoxifenil)pent-4-enoato de metilo
   [9] 4-ciano-5-metoxi-2-(naftalen-1-il)pent-4-enoato de metilo
   [10] 4-ciano-5-metoxi-3-fenilpent-4-enoato de metilo

7. Un procedimiento para la preparación de un compuesto de fórmula **1** que comprende hacer reaccionar un compuesto de fórmula general **4** con un compuesto de fórmula general **5** en presencia de una base.

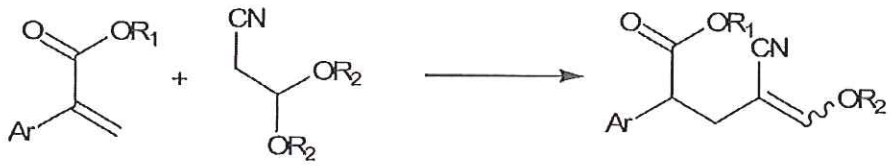



**4** **5** **1**

8. Un procedimiento para la preparación de un compuesto de fórmula **1** según la reivindicación 7, donde la base se selecciona entre un alcóxido alcalino y un hidróxido alcalino.

9. Un procedimiento para la preparación de un compuesto de fórmula **1** según la reivindicación 7 o 8, donde el alcóxido alcalino es tert-butóxido potásico y el hidróxido alcalino es NaOH.

10. Un procedimiento para la preparación de un compuesto de fórmula **2** que comprende hacer reaccionar un compuesto de fórmula general **4** con un compuesto de fórmula general **5** en presencia de una base.

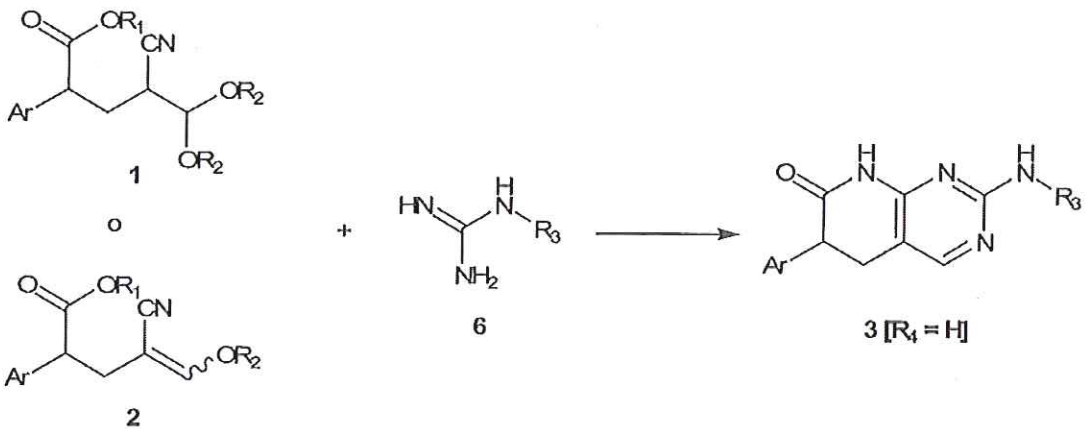



**4** **5** **2**

11. Un procedimiento para la preparación de un compuesto de fórmula **2** según la reivindicación 10, donde la base se selecciona entre un alcóxido alcalino y un hidróxido alcalino.

12. Un procedimiento para la preparación de un compuesto de fórmula **2** según la reivindicación 10 o 11, donde el alcóxido alcalino es tert-butóxido potásico y el hidróxido alcalino es NaOH.

13. Un procedimiento para la preparación de un compuesto de fórmula general **3** donde $R_4$ es H, que comprende hacer reaccionar un compuesto de fórmula general **1** o **2** con un compuesto de fórmula general **6** o una sal de éste en presencia de una base.




14. Un procedimiento para la preparación de un compuesto de fórmula **3** donde $R_4$ es H según la reivindicación 13, donde la base se selecciona entre un alcóxido alcalino, un carbonato o una amina.

15. Un procedimiento para la preparación de un compuesto de fórmula **3** donde $R_4$ es H según la reivindicación 13 o 14, donde el alcóxido alcalino es NaOMe, el carbonato es $Na_2CO_3$ y la amina es piridina.

16. Un procedimiento one-pot para la preparación de un compuesto de fórmula **3** donde $R_4$ es H que comprende hacer reaccionar un compuesto de fórmula general **4** con un compuesto de fórmula general **5** en presencia de una base.

17. Un procedimiento one-pot para la preparación de un compuesto de fórmula **3** donde $R_4$ es H según la reivindicación 16 que comprende hacer reaccionar un compuesto de fórmula general **4** con un compuesto de fórmula general **5** en presencia de una base y a continuación con un compuesto de fórmula general **6** en presencia de una segunda base.

18. Un procedimiento one-pot para la preparación de un compuesto de fórmula **3** donde $R_4$ es H según las reivindicaciones 16 y 17 donde la primera base se selecciona entre un un alcóxido alcalino y un hidróxido alcalino y la segunda base se selecciona entre un alcóxido alcalino, un carbonato o una amina.

19. Un procedimiento one-pot para la preparación de un compuesto de fórmula **3** donde $R_4$ es H según cualquiera de las reivindicaciones de 16 a 18 donde el alcóxido alcalino es NaOMe o tert-butóxido potásico, el hidróxido alcalino es NaOH, el carbonato es $Na_2CO_3$ y la amina es piridina.

20. Empleo de un compuesto de fórmula general **3** donde $R_4$ es H como intermedio de síntesis en la preparación de un compuesto de fórmula general **3** donde $R_4$ puede ser alquilo, arilo, heteroarilo, heterociclo, cicloalquilo, alquenilo o alquinilo sustituidos o no.


**3**

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# An Unusual Michael Addition of 3,3-Dimethoxypropanenitrile to 2-Aryl Acrylates: A Convenient Route to 4-Unsubstituted 5,6-Dihydropyrido[2,3-*d*]pyrimidines

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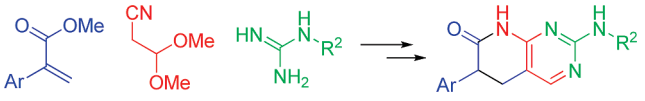

An unusual Michael addition between 2-aryl-substituted acrylates and 3,3-dimethoxypropanenitrile which leads, depending on the reaction temperature (60 or −78 °C, respectively), to a 4-methoxymethylene-substituted 4-cyanobutyric ester or to a 4-dimethoxymethyl 4-cyanobutyric ester is described. These compounds can be subsequently converted to 4-unsubstituted pyrido[2,3-*d*]-pyrimidines upon treatment with a guanidine system under microwave irradiation.

Pyrido[2,3-*d*]pyrimidines represent a heterocyclic ring system of considerable interest due to several biological activities associated with this scaffold. Particularly, this kind of heterocycles are able to inhibit the protein kinase catalytic activity by blocking the ATP binding site and, subsequently, preventing the phosphorylation of the corresponding natural substrates.[1]

Thus, compounds of general structure **1** (Figure 1) inhibit cyclin-dependent kinase so they can be used for the treatment of neurodegenerative diseases.[2] On the other hand, 6-aryl-substituted pyrido[2,3-*d*]pyrimidines (**2**) are useful in treating cellular proliferation mediated diseases due to their capability to inhibit protein kinases.[3]

Particularly, 6-aryl-substituted 5,6-dihydropyrido[2,3-*d*]-pyrimidin-7(8*H*)-ones (**3**) are selective inhibitors of the kinase insert domain-containig receptor (KDR) and fibroblast growth factor receptor (FGFR).[4] More recently, several pyrido[2,3-*d*]pyrimidines have been identified as antibacterials in a drug design program targeting eukaryotic tyrosine protein kinases.[5]

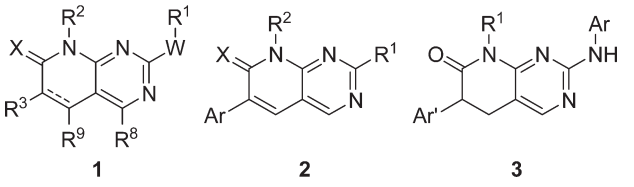

**FIGURE 1.** Some biologically active pyridopyrimidine scaffolds.

The synthesis of such compounds is usually achieved by multistep procedures in which the pyridone ring is constructed onto a preformed pyrimidine ring. Thus, for instance, compounds **3** are prepared with use of uracil as starting material in at least six steps.[4]

Our group has broad experience in the synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones, with up to five diversity centers, from α,β-unsaturated esters. The two straightforward strategies developed construct the pyrimidine ring onto a preformed pyridone[6] or, alternatively, form both rings from an intermediate Michael adduct.[7] More recently, we have described an efficient multicomponent reaction providing 4-amino- or 4-oxopyrido[2,3-*d*]-pyrimidines in a one-pot microwave-assisted cyclocondensation of α,β-unsaturated esters, guanidine systems, and malononitrile or methyl cyanoacetate in NaOMe/MeOH, respectively.[8]

However, in no case were we able to obtain 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines **4** (Figure 2), being thus referable to active compounds **2** and **3**, by an expeditive synthetic approach similar to our preceding strategies. Here-

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(6) (a) Victory, P.; Diago, J. *Afinidad* **1978**, *35*, 154–158. (b) Victory, P.; Diago, J. *Afinidad* **1978**, *35*, 161–165. (c) Victory, P; Jover, J. M.; Sempere, J. *Afinidad* **1981**, *38*, 491–495. (d) Victory, P.; Borrell, J. I. 6-Alkoxy-5-cyano-3,4-dihydro-2-pyridones as starting materials for the synthesis of heterocycles. In Menon, J., Ed. *Trends in Heterocyclic Chemistry*; Council of Scientific Research Integration: Trivandrum, India, 1993; Vol. 3, pp 235−247 and references cited therein. (e) Victory, P.; Jover, J. M.; Nomen, R. *Afinidad* **1981**, *38*, 497–500. (f) Victory, P.; Nomen, R.; Colomina, O.; Garriga, M.; Crespo *Heterocycles*. **1985**, *23*, 1135–1141.

(7) (a) Borrell, J. I.; Teixidó, J.; Matallana, J. L.; Martínez-Teipel, B.; Colominas, C.; Costa, M.; Balcells, M.; Schuler, E.; Castillo, M. J. *J. Med. Chem.* **2001**, *44*, 2366–2369. (b) Borrell, J. I.; Teixidó, J.; Martínez-Teipel, B.; Serra, B.; Matallana, J. L.; Costa, M.; Batllori, X. *Collect. Czech. Chem. Commun.* **1996**, *61*, 901–909.

(8) (a) Mont, N.; Teixidó, J.; Borrell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385–5387. (b) Mont, N.; Teixidó, J.; Kappe, C. O.; Borrell, J. I. *Mol. Diversity* **2003**, *7*, 153–159.

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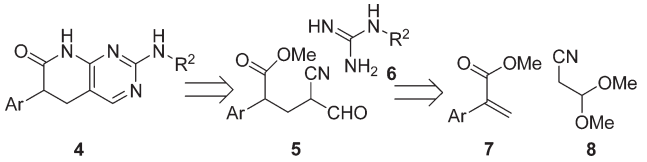


**FIGURE 2.** Retrosynthetic analysis for the preparation of 6-aryl-substituted 5,6-dihydropyrido[2,3-*d*]pyrimidines (**4**).

in we disclose a new method for the synthesis of 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines via a novel type of intermediates.

A retrosynthetic analysis of compounds **4** (Figure 2) pointed to a 4-formyl-substituted 4-cyanobutyric ester (**5**) as the key intermediate to be cyclized with a guanidine system **6**. A further disconnection of the formyl substituted compound **5** suggested a Michael addition between a 2-aryl-susbstituted acrylate (**7**) and 3,3-dimethoxypropanenitrile (**8**), a commercially available formyl protected synthetic equivalent of the unstable 3-formyl-acetonitrile.

Although this design was quite attractive, a major drawback was the extremely low acidity of the α-cyano methylene to be ionized in **8** (calculated $pK_a = 25.94$).[9]

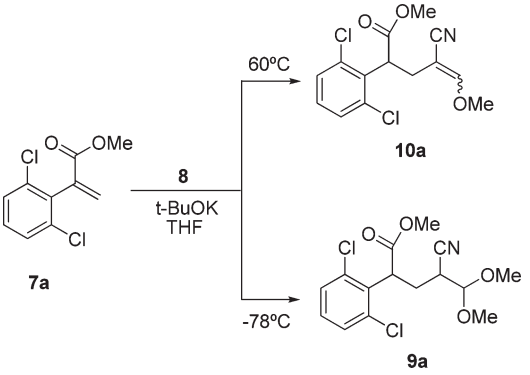
In fact, there are only a few examples in the literature of a Michael addition of a so poor active methylene such as the addtion of acetonitrile to chalcones.[10] In the case of 3,3-dimethoxypropanenitrile (**8**) there are only examples of a few condensations with aldehydes catalyzed by NaOMe/MeOH.[11]

With this information in mind we tested the Michael addition of 3,3-dimethoxypropanenitrile (**8**) to methyl 2-(2,6-dichlorophenyl)acrylate (**7a**) as a model compound in the presence of a wide range of strong bases (NaOMe/MeOH, NaHMDS/THF, LiHMDS/THF, NaOMe/DMF, *t*-BuOK/THF). **7a**, obtained upon condensation of 2-(2,6-dichlorophenyl)acetate with paraformaldehyde in CaO/$K_2CO_3$/DMF (94% yield),[12] was selected because the 2,6-dichlorophenyl substituent is present in several biologically active pyrido[2,3-*d*]pyrimidines.[3,4]

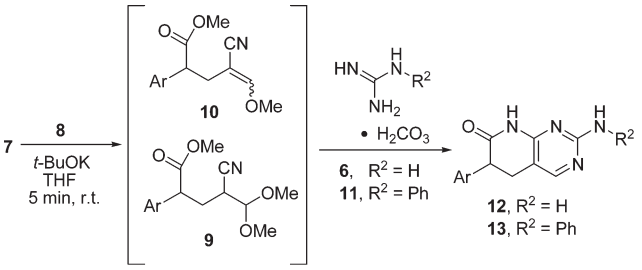
The reaction afforded, in most of the cases, a mixture of the (*E*)- and (*Z*)-3-methoxyacrylonitrile as a result of a MeOH elimination from 3,3-dimethoxypropanenitrile (**8**). Only the use of a 0.1 M solution of *t*-BuOK in THF gave positive results, the starting α,β-unsaturated ester **7a** being immediately converted to a mixture of compounds (as revealed by NMR) in which the expected acetal **9a** (as a mixture of diastereomers) was the minor component. The presence in the $^1$H NMR spectrum of two singlets at 6.45 and 6.69 ppm pointed to the *E*/*Z* mixture of the enol ether **10a**, formed by an E1cB elimination of MeOH from **9a**, as the major component of the mixture (Scheme 1).

The reaction was then studied at different temperatures showing that the MeOH elimination is minimized at lower ones. Thus, when the reaction was carried out at −78 °C the

**SCHEME 1. Synthesis of 9a and 10a from 2-Phenylacrylate 7a**



**SCHEME 2. Synthesis of 4-Unsubstituted 5,6-Dihydropyrido-[2,3 *d*]pyrimidines 12 and 13 from 2-Aryl-Substituted Acrylates 7**



mixture of diastereomers of the acetal **9a** was obtained as the major product. On the contrary, when the reaction was conducted at 60 °C the MeOH elimination proceeds smoothly giving the *E*/*Z* mixture of the enol ether **10a** as the major product (Scheme 1).

In all cases the resulting mixture between the acetal **9a** and the enol ethers **10a** represents roughly an 80% yield. The main difficulty for the isolation of these compounds was the presence of the unreacted excess of 3,3-dimethoxypropanenitrile (**8**), which could not be separated by column cromatography so it was necessary to remove it by concentrating in vacuo (80 °C, 30 mbar).

Thus, the reaction crude obtained at 60 °C was column cromatographed (silica gel 60 A C.C 35−70 μm with a 1:3 mixture of AcOEt/Hex as eluent) to afford a 61% yield of the *E*/*Z* mixture of the enol ether **10a** (66% *E* isomer, 34% *Z* isomer). This mixture was further column chromatographed to obtain analytical samples of both isomers. The *E*/*Z* isomer assignment was supported by NOESY-1D spectroscopy. Similarly, the reaction crude obtained at −78 °C was column cromatographed (silica gel 60 A C.C 35−70 μm with a 1:3 mixture of AcOEt/Hex as eluent) to afford the diastereomeric mixture of the acetal **9a** in a 68% yield.

Once the preparation of the Michael adduct **9a** and the MeOH elimination product **10a** were achieved, we started the study of their conversion to the corresponding 5,6-dihydropyrido[2,3-*d*]pyrimidines **12a** and **13a** by cyclization with guanidine **6** ($R^2$ = H) and phenylguanidine **11** ($R^2$ = Ph), respectively (Scheme 2).

Initial experiments were carried out with the *E*/*Z* mixture of the enol ether **10a** and guanidine carbonate **6** by heating the mixture under microwaves in the presence of NaOMe/MeOH, a base previosuly used in our group for referable cyclizacions with guanidine.[8] The desired product **12a** was

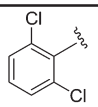
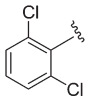
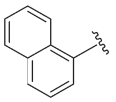
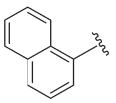
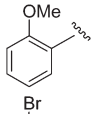
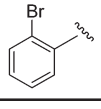
(9) Hilal, S. H.; Karickhoff, S. W.; Carreira, L. A. *Quant. Struct.−Act. Relat.* **1995**, *14*, 348.

(10) (a) Shibata, K.; Urano, K.; Matsui, M. *Chem. Lett.* **1987**, 519–20. (b) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **1996**, 965–966.

(11) Elliott, A. J.; Morris, P. E. Jr.; Petty, S. L.; Williams, C. H. *J. Org. Chem.* **1997**, *62* (23), 8071–8075.

(12) Holan, G.; Walser, R. A. Preparation of alkyl 2-aryl acrylates, EP0003670(A1), August 22, **1979** (CAN 92:94079).

**TABLE 1. Examples of 5,6-Dihydropyrido[2,3-*d*]pyrimidines 12 and 13 Synthesized**

| entry | product | Ar | $R^2$ | yield[a] |
|---|---|---|---|---|
| 1 | **12a** |  | H | 53% |
| 2 | **13a** |  | Ph | 36% |
| 3 | **12b** |  | H | 44% |
| 4 | **13b** |  | Ph | 35% |
| 5 | **12c** |  | H | 44% |
| 6 | **13c** |  | Ph | 17% |
| 7 | **12d** |  | H | 30% |
| 8 | **12e** |  | H | 40% |

[a]Overall yield from the corresponding 2-aryl acrylates **7a**−**e**.

obtained but in a very poor yield (20%), so we tested different reaction conditions using pyridine as base and solvent. Pyridine was selected due to its non-nucleophilic character and high boiling point, which allows heating under microwave irradiation at high temperatures without reaching high pressures. When a mixture of 1 equiv of **10a** and 3 equiv of **6** was heated under microwave irradiation for 1 h at 180 °C in pyridine, the desired pyridopyrimidine **12a** was formed in a 70% yield. **12a** was collected by filtration after the addition of water to the reaction crude.

However, when we tried the aforementioned procedure but using phenylguanidine carbonate **11** instead of guanidine carbonate **6**, the expected 5,6-dihydropyrido[2,3-*d*]pyrimidine **13a** was not obtained. In fact, there are many examples in the literature of the formation of heterocyclic rings with guanidine **6** but only a few with arylguanidines.[13] Finally, using a modification of the reaction conditions described by Shigekazu and co-workers,[13b] consisting of heating a 1:3 molar mixture of **10a** and phenylguanidine carbonate **11** without any solvent at 150 °C overnight with stirring, the desired 5,6-dihydropyrido[2,3-*d*]pyrimidine **13a** was obtained in a 44% yield.

To our delight, the cyclizations to form **12a** and **13a** proceeded with similar yields when a mixture of the enol ether **10a** and the acetal **9a** was used instead of the pure **10a**. As a result, in order to obtain pyridopyrimidines **12** and **13** it is not necessary to obtain a pure sample of the corresponding enol ether **10**, instead a mixture of the enol ether **10** and the acetal **9** in any ratio can be used.

At this point we decided to investigate the possibility of combining these two separate processes into a one-pot reaction useful to obtain a wide range of pyridopyrimidines **12** and **13**. To asses the substrate scope of such a procedure, a variety of 2-aryl-substituted acrylic esters were tested (Table 1). The Michael addition of the corresponding 2-aryl-substituted acrylate **7** and 3,3-dimethoxypropanenitrile (**8**) gave, in all cases, an almost pure mixture of the corresponding enol ether **10** and acetal **9** after neutralization with AcOH, filtration through a short pad of silica, and elimination of THF and nitrile **8** under reduced pressure. Then, guanidine carbonate **6** or phenylguanidine carbonate **11** was added to the reaction crude and the mixture was heated under the conditions stated before for each type of guanidine. Substituted pyridopyrimidines **12** and **13** were obtained in acceptable overall yields through this two-step procedure without intermediate isolation, which is clearly shorter than the 6−7 steps long procedures previously used for such types of compounds.[4]

To establish the scope of the procedure, we tested it with alkyl-susbtituted acrylates (such as methyl methacrylate or methyl crotonate) and 3-aryl-susbtituted acrylates (such as methyl cinnamate). Although the reaction proceeded in all cases the yields were very low (less than 15%). In the case of the less reactive methyl cinnamate, an increase of the reaction temperature led to large quantities of potassium cinnamate as a byproduct caused possibly by the nucleophilic attack of the *tert*-butoxide anion onto the ester methyl group.

Consequently, this methodology seems to be restricted to 2-aryl-substituted acrylates **7**, which lead to 6-aryl-substituted 5,6-dihydropyrido[2,3-*d*]pyrimidines **12** and **13**, precisely the position and type of substituents that have been claimed as necessary to confer biological activity to structures **2** and **3**.[3−5]

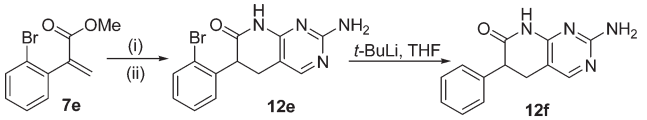
However, even in the case of 2-aryl-substituted acrylates **7**, when the reaction was assayed with methyl atropate (2-phenyl acrylate, **7f**) the reaction led to large quantities of a polymeric material instead of the corresponding pyridopyrimidine **12f**. This observation agrees with the known instability of 2-aryl acrylates without ortho substituents, particularly in the presence of strong bases,[14] confirmed by the practical impossibility of buying methyl atropate and other 2-aryl acrylates from commercial sources.

To overcome such a limitation, we considered the use of a 2-(ortho-substituted)phenyl acrylate in which the ortho substituent could be removed after the formation of the corresponding pyrido[2,3-*d*]pyrimidine. We selected methyl 2-(*o*-bromophenyl)acrylate **7e**, easily obtainable from methyl 2-(*o*-bromophenyl)acetate in 84% yield, to prepare the corresponding 5,6-dihydropyrido[2,3-*d*]pyrimidine **12e** (Scheme 3) in 40% yield (in this case the condensation with 3,3-dimethoxypropanenitrile **8** was carried out for 1 min at 0 °C instead of

(13) (a) Gueremy, C.; Audiau, F.; Uzan, A.; Le Fur, G.; Leger, J. M.; Carpy, A. *J. Med. Chem.* **1982**, *25* (12), 1459–65. (b) Shigekazu, I.; Katsumi, M.; Shoji, K.; Toshihiro, N.; Yoshiyuki, K.; Nobumitsu, S.; Shinichiro, M. Pyrimidine derivatives and agricultural or horticultural fungicidal composition contaning the same. EP0270111 (A1), June 08, **1988** (CAN 109:124400).

(14) (a) Yuki, H.; Hatada, K.; Ohshima, J.; Komatsu, T. *Polym. J.* **1971**, *2*, 812–814. (b) Jiang, J.; Jia, X.; Pang, Y.; Huang, J. *J. Macromol. Sci., Pure Appl. Chem.* **1998**, *A35*, 781–792. (c) Liu, C.; Xu, X.; Huang, J. *J. Appl. Polym. Sci.* **2004**, *94*, 355–360.

**SCHEME 3. Synthesis of 12e and Debromination to 12f**




(i) **8**, *t*-BuOK, THF; (ii) **6**, Microwave

−78 °C due to the lower reactivity of **7e** and the instability of the enol ether **10e**).

A literature search revealed that *t*-BuLi in THF could be the best solution to remove the bromine atom.[15] Therefore **12e** was suspended in THF and 10 equiv of *t*-BuLi was added. After 1 h at room temperature MeOH was added and the crude was neutralized with AcOH to afford the desired 6-phenyl-substituted pyridopyrimidine **12f** in 83% yield (33% from 2-(*o*-bromophenyl)acrylate **7e**).

This approach seems to constitute a general solution for phenyl substituents not containing an ortho substituent because there are more than 30 commercially available 2-bromophenylacetic acids and esters (the starting products for 2-aryl acrylates **7**) carrying other substituents in the phenyl ring compatible with the aforementioned debromination.

Finally, as is shown in Table 1, the yields obtained for 2-phenylamino-substituted pyridopyrimidines **13** ($R^2$ = Ph) are lower than those obtained for the 2-amino-substituted ones **12** ($R^2$ = H), a result that agrees with the lower reactivity of phenylguanidine **11** with respect to guanidine **6**.

In conclusion we have developed a new and very simple methodology for the preparation of 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidine systems **12** and **13** based on a novel Michael addition.[16] This unusual addition can be a way to obtain other heterocyclic rings in the future.

## Experimental Section

**General Procedure for the Preparation of 5,6-Dihydropyrido-[2,3-*d*]pyrimidines 12a−e.** A solution of *t*-BuOK (0.34 g, 2 mmol) in THF (20 mL) was added to a mixture of the corresponding 2-aryl acrylate **7a−e** (2 mmol) and 3,3-dimethoxypropanenitrile **8** (0.35 mL, 3 mmol). After 5 min of stirring at room temperature, the solution was neutralized with AcOH and filtered through a short pad of silica with 200 mL of hexanes/AcOEt 1:1 as eluent. The solvent was removed under reduced pressure and guanidine carbonate **6** (0.54 g, 6 mmol) and pyridine (4 mL) were added to the residue and the mixture was heated under microwave irradiation at 180 °C for 1 h. Water was added to the solution and the precipitate was collected by filtration and washed with water and cold MeOH to afford the corresponding **12a−e**.

**2-Amino-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12a):** 53%, white solid, mp > 250 °C; IR (KBr) $\nu_{max}$ 3379, 3199, 2894, 1691, 1627, 1570, 1480, 1435, 783 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.66 (s, 1H), 7.96 (s, 1H), 7.55 (m, 2H), 7.37 (t, $J$ = 8.1 Hz, 1H), 6.40 (s, 2H), 4.65 (dd, $J$ = 13.8, 7.9 Hz, 1H), 3.14 (m, 1H), 2.88 (dd, $J$ = 15.6, 7.9 Hz, 1H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 169.8, 162.5, 157.5, 155.9, 135.2, 134.9, 134.7, 129.8, 128.4, 102.0, 43.5, 24.9; HRMS (FAB$^+$) $m/z$ calcd for $C_{13}H_{10}Cl_2N_4O$ 309.0310, found 309.0304.

**General Procedure for the Preparation of Pyrido[2,3-*d*]-pyrimidines 13a−c.** A solution of *t*-BuOK (0.34 g, 2 mmol) in THF (20 mL) was added to a mixture of the corresponding 2-aryl acrylate **7a−c** (2 mmol) and 3,3-dimethoxypropanenitrile **8** (0.35 mL, 3 mmol). After 5 min of stirring at room temperature the solution was neutralized with AcOH and filtered through a short pad of silica with 200 mL of hexanes/AcOEt 1:1 as eluent. The solvent was removed under reduced pressure, phenylguanidine carbonate **11** (1.07 g, 6 mmol) was added to the residue, and the mixture was stirred at 150 °C overnight. The reaction crude was suspended in MeOH. The precipitate formed was collected by filtration and washed with water and MeOH to afford the corresponding **13a−c**.

**6-(2,6-Dichlorophenyl)-2-(phenylamino)-5,6-dihydropyrido-[2,3-*d*]pyrimidin-7(8*H*)-one (13a):** 36%, white solid, mp > 250 °C; IR (KBr) $\nu_{max}$ 3289, 3204, 3145, 1685, 1602, 1579, 1498, 1446, 1241, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.96 (s, 1H), 9.41 (s, 1H), 8.19 (s, 1H), 7.82 (d, $J$ = 7.8 Hz, 2H), 7.56 (d, $J$ = 8.2 Hz, 1H), 7.52 (d, $J$ = 7.9 Hz, 1H), 7.39 (t, $J$ = 8.1 Hz, 1H), 7.24 (t, $J$ = 7.9 Hz, 2H), 6.91 (t, $J$ = 7.3 Hz, 1H), 4.76 (dd, $J$ = 13.8, 8.0 Hz, 1H), 3.23 (m, 1H), 2.99 (dd, $J$ = 15.8, 8.0 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 169.8, 158.8, 157.4, 155.6, 140.7, 135.3, 134.9, 134.8, 129.9, 129.8, 128.4 (2C), 121.0, 118.6 (2C), 104.3, 43.3, 25.0; HRMS (FAB$^+$) $m/z$ calcd for $C_{19}H_{14}Cl_2N_4O$ 385.0623, found 385.0622.

**Procedure for the Preparation of 2-Amino-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12f).** A 0.192 g (0.6 mmol) sample of 2-amino-6-(2-bromophenyl)-5,6-dihydropyrido[2,3-d]-pyrimidin-7(8*H*)-one (**12e**) was suspended in 20 mL of THF and 3.53 mL of a 1.7 M solution of *t*-BuLi in pentane (6 mmol) was added dropwise. The mixture was stirred for 1 h at room temperature. Ten milliliters of MeOH was added and the mixture was neutralized with AcOH. The solvent was removed under reduced pressure and the residue was suspended in water. The precipitate was collected by filtration and washed with water and cyclohexane to give 0.19 g (83%) of **12f** as a white-brown solid: mp > 250 °C; IR (KBr) $\nu_{max}$ 3333, 3153, 3067, 2896, 1682, 1632, 1573, 1496, 1228, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.62 (s, 1H), 7.93 (s, 1H), 7.34−7.28 (m, 2H), 7.27−7.21 (m, 3H), 6.34 (s, 2H), 3.86 (t, $J$ = 7.9, 1H), 2.99−2.93 (m, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 172.15, 162.48, 157.88, 155.48, 138.90, 128.29, 128.13, 126.86, 103.41, 46.19, 27.86; HRMS (FAB$^+$) $m/z$ calcd for $C_{13}H_{13}N_4O$ (MH$^+$) 241.1089, found 241.1091.

**Acknowledgment.** X. Berzosa is grateful for a fellowship from Generalitat de Catalunya (2006-2009, grant 2006FI 00058).

**Supporting Information Available:** General experimental methods, characterization data for **7a−e**, **9a**, **10a**, **10e**, **12a−f**, and **13a−c**, and copies of $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 7921–7928. (b) Klein, C.; Graf, E.; Hosseini, M. W.; De Cian, A.; Kyritsakas-Gruber, N. *Eur. J. Org. Chem.* **2002**, 802–809.

(16) Berzosa, X.; Borrell, J. I. Síntesis y usos de 4-cianopentanoatos y 4-cianopentenoatos sustituidos. ES200901191, April 29, **2009**.

Communication

# A diversity oriented synthesis of 3-(2-amino-1,6-dihydro-6-oxo-pyrimidin-5-yl)propanoic esters

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**Keywords:** Michael addition, α,β-unsaturated ester, methyl 3,3-dimethoxypropionate, pyrimidin-5-ylpropanoic acids

**Summary**

The synthesis of dimethyl 2-(methoxymethylene)pentanedioates by an unusual Michael addition of 3,3-dimethoxypropionate to α,β-unsaturated esters is described. These new intermediates can subsequently be converted in methyl 3-(2-amino-1,6-dihydro-6-oxo-pyrimidin-5-yl)propanoates upon treatment with guanidine carbonate. The resulting pyrimidine derivatives are open-chain analogs of pyrido[2,3-*d*]pyrimidines with interesting biological activities.

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## Introduction

3-(Pyrimidin-5-yl)propanoic acids and derivatives have shown in the past interesting biological activities. Thus, structures **1** were claimed as antidiabetic agents [1] due to their excellent GPR40 (Orphan G Protein-coupled Receptor) agonistic activity, carboxylic acids **2** were described as tetrahydrofolic acid analogues [2], and systems **3** shown antiulcer, broncholytic, hypotensive, diuretic and vasodilator properties [3] (Figure 1). Other similar structures such as pyridines **4** are inhibitors of TAFIa (activated Thrombin-Activatable Fibrinolysis Inhibitor) [4].

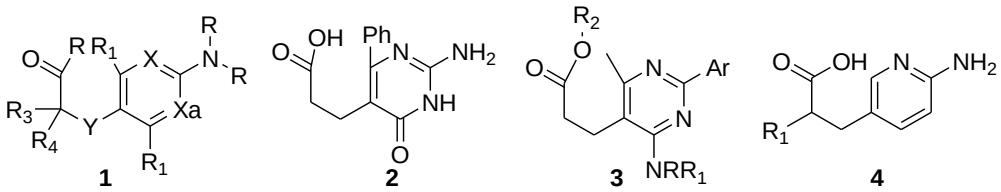
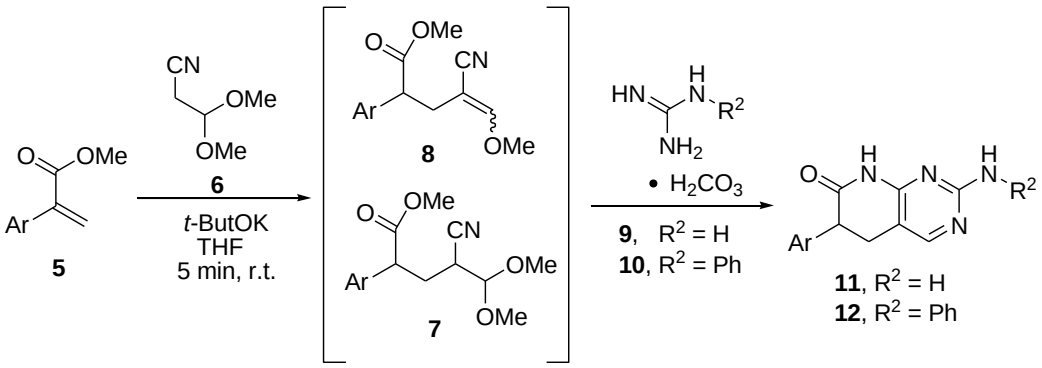



**Figure 1.** Biologically active 3-(pyrimidin-5-yl)propanoic acids and referable compounds.

As a part of our research in the field of potential tyrosine kinase inhibitors, we have recently disclosed a straightforward methodology for the synthesis of 4-unsubstituted pyrido[2,3-*d*]pyrimidines **11** and **12** [5] which is based on an unusual Michael addition between 3,3-dimethoxypropanenitrile (**6**), commercially available formyl protected synthetic equivalent of the unstable 3-formylacetonitrile, and a 2-aryl substituted acrylate (**5**) in the presence of *t*-BuOK/THF. The resulting mixture of the corresponding acetal **7** and the (*E*) and (*Z*)-enol ethers **8**, formed by an E1cB elimination of MeOH from **7**, can be subsequently converted to the desired 4-unsubstituted pyrido[2,3-*d*]pyrimidines **11** and **12** upon treatment with a guanidine system, **9** or **10** respectively, under microwave irradiation (Scheme 1).

The good results obtained with 3,3-dimethoxypropanenitrile (**6**) as an active methylene compound in the Michael addition to acrylates **5** prompted us to assay the Michael addition between acrylates and methyl 3,3-dimetoxypropanoate (**13**) as a way, upon an ulterior cyclization with a guanidine system, to obtain 3-(2-amino-1,6-dihydro-6-oxo-pyrimidin-5-yl)propanoic esters. The present paper deals with the results obtained in such study.




**Scheme 1.** Synthesis of 4-unsubstituted pyrido[2,3-d]pyrimidines **11** and **12** from 2-aryl substituted acrylates **5**.

## Materials and methods

*General*

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian 400-MR ($^{1}H$ at 400 MHz and $^{13}C$ at 100.6 MHz) spectrometer. All NMR data were obtained in $CDCl_3$ and DMSO-$d_6$. Chemical shifts are reported in parts per million (ppm, δ) and are referenced to the residual proton signal of the solvent. Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s: singlet, d: doublet, t: triplet, q: quartet, m: complex multiplet (chemically non-equivalent H's), brs: broad signal. All melting points were determined with a Büchi 530 capillary apparatus and are uncorrected. Infrared spectra were recorded in a Nicolet Magna 560 FTIR spectrophotometer. All MS were registered at the Unidade de Espectrometria de Masas (Universidade de Santiago de Compostela) using a Micromass Autospec spectrometer. Flash chromatography was performed using silica gel 60 A C.C 35-70 μm (SDS ref. 2000027). Elemental microanalyses were obtained in a Carlo-Erba CHNS-O/EA 1108 elemental analyzer. All microwave irradiation experiments were carried out in a dedicated Biotage-Initiator microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 400 W with utilization of the standard absorbance level of 400 W maximum power. Reactions were carried out in 10-mL glass tubes, sealed with aluminium/Teflon crimp tops, which can be exposed up to 250°C and 20 bar internal pressure. Temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60–120 s) to ambient temperature by air jet cooling. Automatic flash chromatography was done in an Isco Combiflash medium pressure liquid chromatograph with Redisep silica gel columns (35-70 μm).

Solvents and reagents were reagent-grade and were used without further purification (Aldrich). Methyl 3,3-dimethoxypropionate (**13**), guanidine carbonate (**9**), methyl arylacetates, methyl methacrylate (**14e**), and methyl cinnamate (**14f**) were commercially available (Acros, Aldrich, Alfa-Aesar, Sigma).

*Synthesis*

*General procedure for the synthesis of methyl 2-arylacrylates* (**14a-d**) [6].

The corresponding methyl arylacetate (65 mmol) is dissolved in DMF (50 mL) and paraformaldehyde (4.11 g, 130 mmol), potassium carbonate (8.98 g, 65 mmol) and calcium oxide (3.65 g, 65 mmol) are added at once. The reaction temperature is kept at 40 ºC during 16 h. The reaction mixture is quenched with water and extracted with dichloromethane. The solvent was dried ($MgSO_4$) and removed under reduced pressure to afford the corresponding methyl 2-arylacrylate **14a-d**.

*Methyl 2-(2,6-dichlorophenyl)acrylate* (**14a**).

As above using methyl 2-(2,6-dichlorophenyl)acetate. 94% yield, white solid, m.p.: 47-48 ºC. IR (KBr) $\nu_{max}$: 3083, 2999, 2953, 1726, 1558, 1430, 1210 $cm^{-1}$. $^{1}H$-NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.8 Hz, 2H), 7.21 (m, 1H), 6.79 (d, *J* = 0.9 Hz, 1H), 5.83 (d, *J* = 0.9 Hz, 1H), 3.77 (s, 3H). $^{13}C$-NMR (100 MHz, $CDCl_3$): δ = 165.4, 136.4, 135.1, 134.9, 131.9, 129.5, 127.8, 52.4. MS (70 eV) *m/z* calcd for $C_{10}H_8Cl_2O_2$ 230, found 230; Anal. (%) calcd for $C_{10}H_8Cl_2O_2$: C, 51.98; H, 3.49. Found: C, 52.02; H, 3.45.

*Methyl 2-(naphthalen-4-yl)acrylate* (**14b**) [7].

As above using methyl 2-(naphthalen-4-yl)acetate. 84% yield, white solid, m.p.: 45-47 ºC. IR (KBr) $\nu_{max}$: 3060, 3001, 2952, 1721, 1231, 782 $cm^{-1}$. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ = 7.91 – 7.82 (m, 2H), 7.77 – 7.69 (m, 1H), 7.50 – 7.45 (m, 3H), 7.36 (dd, *J* = 1.2, 7.0 Hz, 1H), 6.72 (d, *J* = 1.7 Hz, 1H), 5.89 (d, *J* = 1.7 Hz, 1H), 3.72 (s, 3H). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ = 167.5, 140.6, 135.2, 133.4, 131.7, 129.9, 128.6, 128.3, 126.9, 126.2, 125.8, 125.2, 52.3.

*Methyl 2-o-tolylacrylate* (**14c**) [8].

As above using methyl 2-*o*-tolylacetate. 70% yield, colourless oil. IR (film) $\nu_{max}$: 3061, 3021, 2951, 1723, 1435, 1313, 1211, 1084, 730 $cm^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.12 (m, 4H), 6.51 (d, *J* = 1.7 Hz, 1H), 5.70 (d, *J* = 1.7 Hz, 1H), 3.76 (s, 3H), 2.20 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 167.16, 141.69, 137.17, 136.09, 129.85, 129.45, 128.63, 128.16, 125.66, 52.21, 19.78.

*Methyl 2-(2-methoxyphenyl)acrylate* (**14d**) [9].

As above using methyl 2-(2-methoxyphenyl)acetate. 40% yield, yellow oil. IR (film) $\nu_{max}$: 2999, 2950, 2838, 1726, 1491, 1435, 1274, 1244, 1205, 755 $cm^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.30 (m, 1H), 7.22 (dd, *J* = 1.7, 7.4 Hz, 1H), 6.96 (td, *J* = 1.0, 7.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 1.5 Hz, 1H), 5.74 (d, *J* = 1.4 Hz, 1H), 3.79 (s, 3H), 3.76 (d, *J* = 1.3 Hz, 3H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 167.92, 156.88, 139.82, 130.01, 129.79, 127.02, 126.41, 120.68, 110.78, 55.63, 52.05.

*General procedure for the synthesis of dimethyl 2-(methoxymethylene)pentanedioates* (**15a-f**).

A solution of *t*-ButOK (0.34g, 2 mmol) in THF (20 mL) was added to a mixture of the corresponding substituted methyl acrylate (**14a-f**) (2 mmol) and methyl 3,3-dimetoxypropanoate (**13**) (0.44 mL, 3 mmol). After 5 minutes of stirring at 60 ºC the solution was neutralized with AcOH. The solvent was removed under reduced pressure and the residue was purified by automatic $SiO_2$ flash chromatography (hexanes-AcOEt; gradient 100:0 to 50:50 in 20 min).

*Dimethyl 2-(2,6-dichlorophenyl)-4-(methoxymethylene)pentanedioate* (**15a**).

As above using methyl 2-(2,6-dichlorophenyl)acrylate (**14a**). 90% yield, colourless oil. IR (film) $\nu_{max}$: 2949, 2847, 1739, 1645, 1435, 1251, 1103 $cm^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 7.08 (dd, *J* = 7.6, 8.5 Hz, 1H), 4.68 (dd, *J* = 4.5, 11.2 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.49 (s, 3H), 3.23 – 3.16 (m, 1H), 3.12 – 3.06 (m, 1H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.52, 168.43, 160.37, 135.35, 128.23, 106.91, 61.03, 52.27, 51.15, 45.60, 23.52. Anal. (%) calcd for $C_{15}H_{16}Cl_2O_5$: C, 51.89; H, 4.65. Found: C, 51.96; H, 4.60.

*Dimethyl 2-(methoxymethylene)-4-(naphthalen-1-yl)pentanedioate* (**15b**).

As above using methyl 2-(naphthalen-4-yl)acrylate (**14b**). 80% yield, white solid, m.p.: 77-79ºC. IR (KBr) $\nu_{max}$: 3452, 2997, 2949, 2848, 1738, 1697, 1649, 1304, 1250, 1222, 1150, 1105 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.3 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.40 (m, 4H), 7.16 (s, 1H), 4.77 (t, *J* = 7.8, 1H), 3.65 (s, 3H), 3.62 (s, 6H), 3.13 (dd, *J* = 8.1, 13.8 Hz, 1H), 2.96 (dd, *J* = 7.6, 13.8 Hz, 1H).$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 174.40, 168.48, 160.20, 135.19, 133.80, 131.89, 128.71, 127.62, 126.11, 125.43, 125.34, 125.27, 123.43, 107.67, 61.23, 51.93, 51.17, 45.30, 27.61. Anal. (%) calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.55; H, 6.25.

*Dimethyl 2-(methoxymethylene)-4-o-tolylpentanedioate* (**15c**).

As above using methyl 2-*o*-tolylacrylate (**14c**). 70% yield, colourless oil. IR (film) $\nu_{max}$: 3020, 2950, 2847, 1735, 1707, 1646, 1435, 1249, 1098 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 7.0 Hz, 1H), 7.21 (s, 1H), 7.17 – 7.09 (m, 3H), 4.21 (t, *J* = 7.9 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.62 (s, 3H), 2.95 (dd, *J* = 7.7, 13.8 Hz, 1H), 2.78 (dd, *J* = 8.0, 13.8 Hz, 1H), 2.33 (s, 3H).$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 174.34, 168.52, 160.11, 137.26, 136.41, 130.13, 127.56, 126.82, 125.86, 107.61, 61.26, 51.81, 51.17, 45.32, 27.31, 19.64. Anal. (%) calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.58; H, 6.62.

*Dimethyl 2-(methoxymethylene)-4-(2-methoxyphenyl)pentanedioate* (**15d**).

As above using methyl 2-(2-methoxyphenyl)acrylate (**14d**). 34% yield, white solid, m.p.: 78-80ºC. IR (film) $\nu_{max}$: 3004, 2954, 2839, 1733, 1697, 1646, 1433, 1296, 1246, 1217, 1153, 1094, 753 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.21 – 7.16 (m, 2H), 7.14 (s, 1H), 6.87 (td, *J* = 1.1, 7.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 4.17 (dd, *J* = 6.8, 9.1 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.56 (s, 3H), 2.87 (dd, *J* = 5.8, 7.9 Hz, 2H).$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 174.47, 168.55, 159.69, 157.24, 129.31, 127.98, 127.58, 120.22, 110.38, 107.88, 61.05, 55.46, 51.75, 51.07, 43.53, 26.24. Anal. (%) calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.43; H, 6.72.

*Dimethyl 2-(methoxymethylene)-4-methylpentanedioate* (**15e**).

As above using methyl methacrylate (**14e**) and stirring 1 hour at 60 ºC under microwave irradiation in a sealed vial. 86% yield, colourless oil. IR (film) $\nu_{max}$: 2951, 2848, 1736, 1709, 1646, 1458, 1437, 1377, 1302, 1249, 1124, 993, 769 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.36 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.71 – 2.55 (m, 2H), 2.41 (dd, *J* = 7.8 Hz, 13.4, 1H), 1.11 (d, *J* = 6.9 Hz, 3H).$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 176.73, 168.55, 160.01, 108.05, 61.38, 51.44, 51.23, 38.44, 27.85, 16.32. HRMS ($FAB^+$) *m/z* calcd for $C_{10}H_{16}O_5$: 216.0998. Found: 216.1000. Anal. (%) calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.01; H, 7.94.

*Dimethyl 2-(methoxymethylene)-3-phenylpentanedioate* (**15f**).

As above using methyl cinnamate (**14f**) and stirring 1 hour at 60 ºC under microwave irradiation in a sealed vial. 30% yield, colourless oil. IR (film) $\nu_{max}$: 3026, 2950, 2849, 1738, 1705, 1638, 1436, 1246, 1149, 1107 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.35 (s, 1H), 7.35 – 7.31 (m, 2H), 7.28 – 7.22 (m, 2H),

7.19 – 7.14 (m, 1H), 4.60 – 4.54 (m, 1H), 3.85 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.18 (dd, *J* = 8.7, 15.8 Hz, 1H), 3.07 (dd, *J* = 7.4, 15.8 Hz, 1H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.95, 167.81, 159.73, 142.74, 128.13, 127.59, 126.22, 112.27, 61.72, 51.47, 51.16, 37.24, 37.14. Anal. (%) calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.88; H, 6.61.

*General procedure for the synthesis of methyl 3-(2-amino-1,6-dihydro-6-oxopyrimidin-5-yl)propanoates* (**16**).

Guanidine carbonate (**11**) (0.14 g, 1.5 mmol) was added to a solution of sodium methoxyde (0.81g, 1.5 mmol) in MeOH (10 mL) and heated at 80 ºC for 15 minutes under microwave irradiation. The resulting precipitate was filtered and the solution was added to the corresponding dimethyl 2-(methoxymethylene)pentanedioate (**15**) and the mixture was heated with stirring in a sealed vial at 120 ºC for 16 hours. The solution was neutralized with AcOH, the solvent was removed under reduced pressure and the residue was purified by automatic SiO2 flash chromatography (dichlorometane-MeOH; gradient 100:0 to 80:20 in 20 min).

*Methyl 3-(2-amino-1,6-dihydro-6-oxopyrimidin-5-yl)-2-(2,6-dichlorophenyl) propanoate* (**16a**).

As above using dimethyl 2-(2,6-dichlorophenyl)-4-(methoxymethylene)pentanedioate (**15a**). 91% yield, white solid, m.p.: >250ºC. IR (KBr) $\nu_{max}$: 3305, 3092, 2948, 1739, 1666, 1501, 1433, 1224 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) δ = 10.89 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 8.1 Hz, 1H), 6.77 (s, 1H), 6.30 (s, 2H), 4.64 (dd, *J* = 3.8, 10.7 Hz, 1H), 3.62 (s, 3H), 3.32 – 3.27 (m, 1H), 2.64 (dd, *J* = 10.8, 13.6 Hz, 1H).$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ = 172.14, 155.76, 135.24, 129.99, 129.26, 110.83, 52.68, 45.88, 31.19, 27.40. Anal. (%) calcd for $C_{14}H_{13}Cl_2N_3O_3$: C, 49.14; H, 3.83; N, 12.28. Found: C, 49.15; H, 3.82; N, 12.41.

*Methyl 3-(2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-methylpropanoate* (**16e**).

As above using dimethyl 2-(methoxymethylene)-4-methylpentanedioate (**15e**). 85% yield, white solid, m.p.: 216-218ºC. IR (KBr) $\nu_{max}$: 3343, 3067, 2975, 1737, 1655, 1491, 605 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) δ = 10.87 (s, 1H), 7.33 (s, 1H), 6.36 (s, 2H), 3.55 (s, 3H), 2.71 (dd, *J* = 7.1, 14.2 Hz, 1H), 2.45 (d, *J* = 7.3 Hz, 1H), 2.24 (dd, *J* = 7.2, 13.5 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H).$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 175.87, 155.26, 111.50, 51.22, 37.87, 31.07, 16.48. HRMS (FAB$^+$) *m/z* calcd for $C_9H_{14}N_3O_3$ ($MH^+$): 212.1035. Found: 212.1030. Anal. (%) calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.40; H, 6.19; N, 19.67.

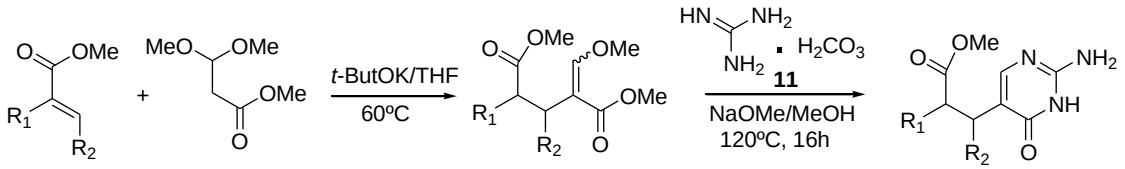
*Methyl 3-(2-amino-1,6-dihydro-6-oxopyrimidin-5-yl)-3-phenylpropanoate* (**16f**).

As above using dimethyl 2-(methoxymethylene)-3-phenylpentanedioate (**15f**). 60% yield, white solid, m.p.: 89-91ºC. IR (KBr) $\nu_{max}$: 3338, 3117, 2925, 1737, 1662, 1492, 1262, 1157, 700 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.26 (m, 2H), 7.26 – 7.16 (m, 4H), 6.57 (s, 2H), 4.45 (t, *J* = 8.0 Hz, 1H), 3.58 (s, 3H), 3.09 (dd, *J* = 8.1, 15.6 Hz, 1H), 2.88 (dd, *J* = 7.8, 15.6 Hz, 1H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ

172.89, 155.65, 141.86, 128.81, 127.81, 127.03, 52.04, 39.36, 38.73. HRMS ($FAB^+$) *m/z* calcd for $C_{14}H_{16}N_3O_3$ ($MH^+$): 274.1192. Found: 274.1190.

**Results and discussion**

Taking into account our previous experience with the Michael additions of 3,3-dimethoxypropanenitrile (**6**) to α,β-unsaturated esters [5], we tested the reaction between methyl 3,3-dimetoxypropanoate (**13**) and a series of 2-aryl susbstituted acrylates **14a-d** ($R_1$ = aryl, $R_2$ = H), easily accessible from commercially available methyl 2-aryl substituted acetates by condensation with paraformaldehyde in the presence of $CaO/K_2CO_3$/DMF in yields ranging from 94% to 40% [6], using a suspension of *t*-ButOK in THF previously heated at 60 ºC as base (Scheme 2). This suspension was added to a 1:1.5 molar mixture of the corresponding 2-arylacrylate **14** and methyl 3,3-dimetoxypropanoate (**13**), and the resulting mixture was heated at 60ºC with stirring for 5 min when all the α,β-unsaturated ester was consumed. After the *work-up* the corresponding dimethyl 2-(methoxymethylene)pentanedioate adducts (**15a-d**) were obtained in 34-90% yields (Table 1).




**14** **13** **15** **16**

**Scheme 2.** Michael addition of methyl 3,3-dimethoxypropionate (**13**) to acrylates (**14**) and subsequent cyclization with guanidine carbonate (**11**) to methyl 3-(2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)propanoates (**16**).

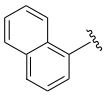
In order to establish the scope of the procedure, we tested it with alkyl susbtituted acrylates, such as methyl methacrylate (**14e**, $R_1$ = Me, $R_2$ = H) or methyl crotonate (**14g**, $R_1$ = H, $R_2$ = Me), and 3-aryl susbtituted acrylates, such as methyl cinnamate (**14f**, $R_1$ = H, $R_2$ = Ph). In the case of methyl methacrylate (**14e**) and methyl cinnamate (**14f**) the reaction afforded the corresponding enol ethers **15e** and **15f** in 86% and 30%, respectively, but changing the reaction conditions to a microwave irradiation at 60ºC for 1 hour in a sealed vial. In the case of the less reactive methyl cinnamate, such increase of the reaction temperature led to large quantities of potassium cinnamate as a by-product caused by the nucleophilic attack of the *tert*-butoxide anion onto the ester methyl group.

An unexpected result was found in the case of methyl crotonate (**14g**, $R_1$ = H, $R_2$ = Me) when the reaction afforded (*E*)-dimethyl 2-ethylidene-3-methylpentanedioate instead of the expected enol ether **15g**. Such dimerization of methyl crotonate is similar to that reported in the literature for methyl acrylate when treated with phosphatranes as non-ionic bases [10].

Once the dimethyl 2-(methoxymethylene)pentanedioate systems (**15a-f**) were obtained, the cyclization of **15a** ($R_1$ = 2,6-dichlorophenyl, $R_2$ = H), **15e** ($R_1$ = Me, $R_2$ = H), and **15f** ($R_1$ = H, $R_2$ = Ph), as model compounds, with guanidine carbonate (**11**) was tested (Scheme 2). Thus, guanidine carbonate was

dissolved in a solution of NaOMe/MeOH and heated at 80 ºC during 15 min. The resulting mixture was filtered to remove $Na_2CO_3$ and the corresponding dimethyl 2-(methoxymethylene)pentanedioate (**15**) was added to the filtrate. The resulting solution was heated with stirring in a sealed vial at 120 ºC for 16 hours. After the *work-up* the corresponding methyl 3-(2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)propanoates **16a** ($R_1$ = 2,6-dichlorophenyl, $R_2$ = H), **16e** ($R_1$ = Me, $R_2$ = H), and **16f** ($R_1$ = H, $R_2$ = Ph) were obtained in 91%, 85%, and 60% yield, respectively.

**Table 1**. Yields of the Michael addition of methyl 3,3-dimethoxypropionate (**13**) to alkyl and aryl substituted acrylates (**14**).

| Entry | Product | $R_1$ | $R_2$ | yield[a] |
|---|---|---|---|---|
| 1 | **15a** |  | H | 90% |
| 2 | **15b** |  | H | 80% |
| 3 | **15c** |  | H | 70% |
| 4 | **15d** |  | H | 34% |
| 5 | **15e** | Me | H | 86% |
| 6 | **15f** | H | Ph | 30% |

Compounds **16** can be considered as open-chain analogs of the 2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones described by our group [11-12] and others [13-14] in connection with their kinase inhibitory properties [15-16] and other interesting biological activities [17].

## Conclusion

In conclusion we have developed a new synthetic approach to methyl 3-(2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)propanoates (**16**) based on the cyclization of guanidine carbonate (**11**) of a new kind of intermediates, the substituted dimethyl 2-(methoxymethylene)pentanedioates (**15**) easily accessible by an unusual Michael addition of 3,3-dimethoxypropionate (**13**) to acrylates (**14**). Intermediates **15** are interesting multifunctional substrates for the preparation of other heterocyclic systems while compounds **16** can be considered as open-chain analogs of pyrido[2,3-*d*]pyrimidines with interesting biological activities.

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