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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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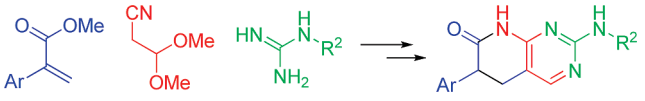

An unusual Michael addition between 2-aryl-substituted acrylates and 3,3-dimethoxypropanenitrile which leads, depending on the reaction temperature (60 or −78 °C, respectively), to a 4-methoxymethylene-substituted 4-cyanobutyric ester or to a 4-dimethoxymethyl 4-cyanobutyric ester is described. These 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]

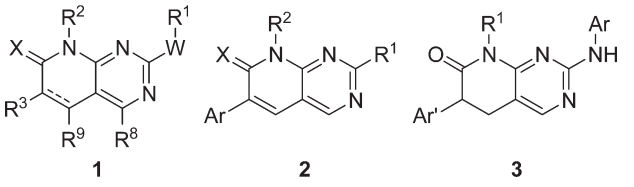

FIGURE 1. Some biologically active pyridopyrimidine scaffolds.

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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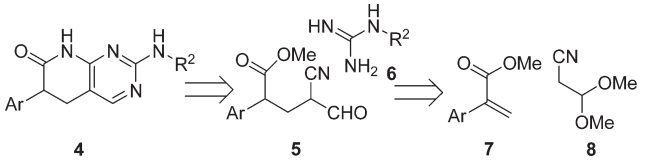


FIGURE 2. Retrosynthetic analysis for the preparation of 6-aryl-substituted 5,6-dihydropyrido[2,3-*d*]pyrimidines (**4**).

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]

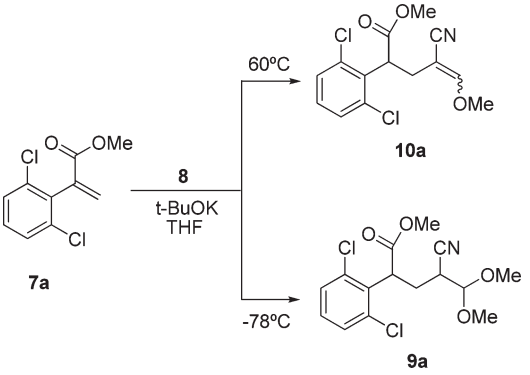
In fact, there are only a few examples in the literature of a Michael addition of a so poor active methylene such as the addtion of acetonitrile to chalcones.[10] In the case of 3,3-dimethoxypropanenitrile (**8**) there are only examples of a few condensations with aldehydes catalyzed by NaOMe/MeOH.[11]

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]

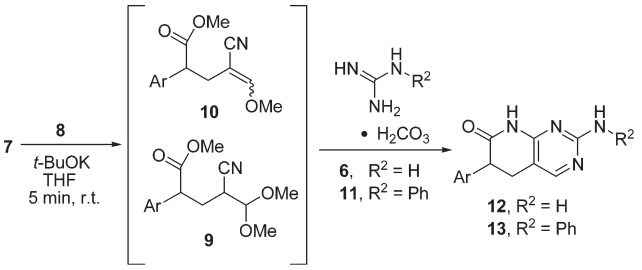
The reaction afforded, in most of the cases, a mixture of the (*E*)- and (*Z*)-3-methoxyacrylonitrile as a result of a MeOH elimination from 3,3-dimethoxypropanenitrile (**8**). Only the use of a 0.1 M solution of *t*-BuOK in THF gave positive results, the starting α,β-unsaturated ester **7a** being 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

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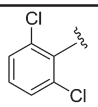
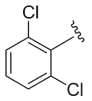
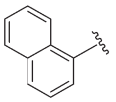
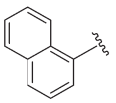
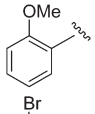
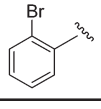
TABLE 1. Examples of 5,6-Dihydropyrido[2,3-*d*]pyrimidines 12 and 13 Synthesized

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

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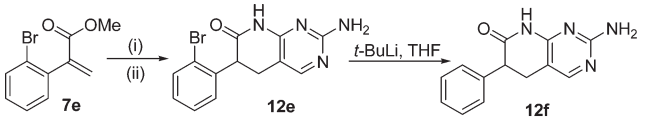
SCHEME 3. Synthesis of 12e and Debromination to 12f



(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) ν_{max} 3379, 3199, 2894, 1691, 1627, 1570, 1480, 1435, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 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) δ 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) ν_{max} 3289, 3204, 3145, 1685, 1602, 1579, 1498, 1446, 1241, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 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) δ 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) ν_{max} 3333, 3153, 3067, 2896, 1682, 1632, 1573, 1496, 1228, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 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) δ 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.

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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.

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