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5-Cyanoacetylpyrimidines as intermediates for 7-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-5-ones

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ABSTRACT

The reactions of N^4- and 5-cyanoacetyl derivates of 4-aminopyrimidines with aromatic aldehydes have yielded the *N*-(pyrimidin-4-yl)-3-arylacrylamides and the dihydropyrido[2,3-*d*]pyrimidines, respectively. The first reaction was a Claisen–Schmidt reaction catalysed by base, and the second one proceeded via thermal cyclocondensation.

Pyrimidine-fused heterocycles are important targets in chemical biology or medicinal chemistry, and among them, pyrido[2,3-*d*]pyrimidine derivatives have attracted much attention because they are deazapteridines which have shown interesting bio-activities.[1–3] The preparation of this kind of fused pyrimidines has been extensively investigated and well documented.[1,4] They usually require forcing conditions,[5] long reaction times,[6] and complex synthetic pathways.[7] Thus, the search for new and simple synthetic routes of these molecules still attracts considerable attention in order to develop high-throughput methods.[2c,8]

As a matter of fact, we have already reported the regioselective synthesis of several 5-aryl-6-cyanopyrido[2,3-*d*]pyrimidines by the multicomponent reaction of 6-aminopyrimidines, aryl aldehydes, and ethyl cyanacetate[8e] or 3-oxo-3-phenylpropanenitrile analogues.[8f] On the other hand, the cyanoacetyl group has been used as methylene active residue to prepare diverse and versatile precursors and heterocyclic products.[9]

Accordingly, we consider that cyanoacetyl-subtituted 6-aminopyrimidines constitute good precursors for the preparation of versatile functionalized pyrido[2,3-*d*]pyrimidines. In fact, we have recently reported the regioselective preparation of 3-pyrimidin-5-yl-3-oxopropanenitriles and *N*-(pyrimidin-4-*yl*)-2-cyanoacetamides[10] through the reaction of 6-aminopyrimidines with cyanoacetic acid and acetic anhydride (Scheme 1).[11] Our synthetic strategy is based on the nucleophilic character of methylene carbon in cyanoacetylated compounds.[1] These compounds may be used as intermediates to prepare (via aryl aldehyde through a Claisen-Schmidt cyclocondensation) the regioisomers 7-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-5-ones or 5-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-7-ones.[12]

First, we have used the compound 3-(6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)-3-oxo-propanenitrile **1** in the reaction with aromatic aldehydes **2** by heating in DMF for 15 h to render the desired cyclocondensation products **3**–**11** in acceptable to good yields. The formation of pyrido[2,3-*d*]pyrimidines **3**–**11** is assumed initially to proceed by the formation of the corresponding heterocyclic cyanochalcone **I** as intermediate,[13] that would suffer an intramolecular Michael addition via the amino group, followed by an oxidative process which is favored under reaction conditions (Scheme 2).[14] The reactions proceeded quite well with different substituted aldehydes with electron-donating/electron-withdrawing groups giving moderate to good yields. These results are given in Table 1.

Next, the 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acetamide **12** was put to react with aromatic aldehydes **2** in similar conditions in order to prepare the regioisomeric pyrido[2,3-*d*]pyrimidines. In turn, the 2-cyano-*N*-(2,6-dimethoxipyrimidin-4-yl)-3-arylacrylamides **13–24** were isolated in moderate to good yields by a simple condensation reaction (Scheme 3). Formation of pyridopyrimidines was not observed.[15] After reaction optimization, the compounds

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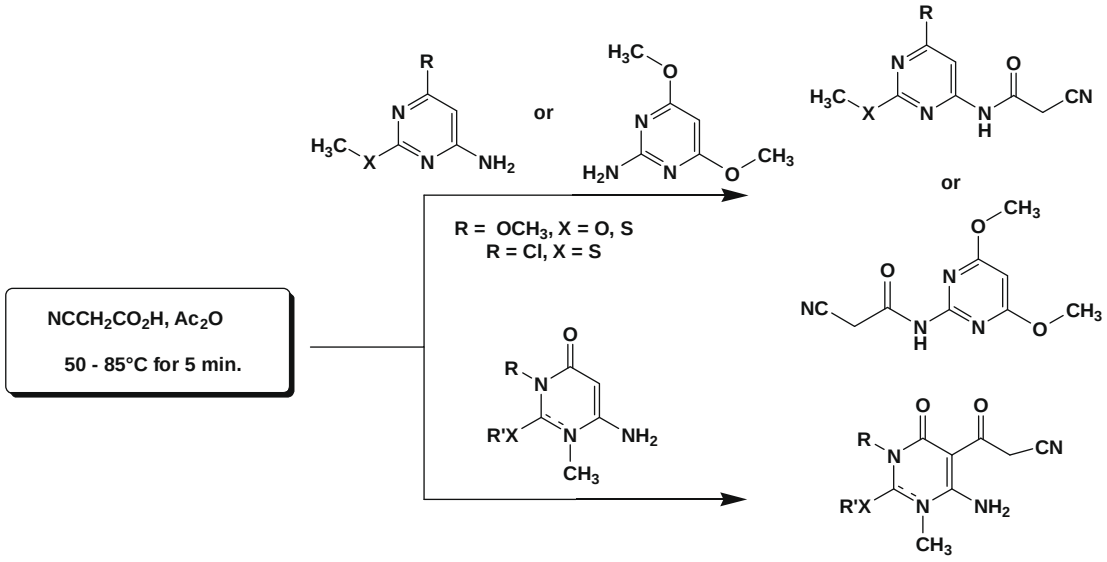
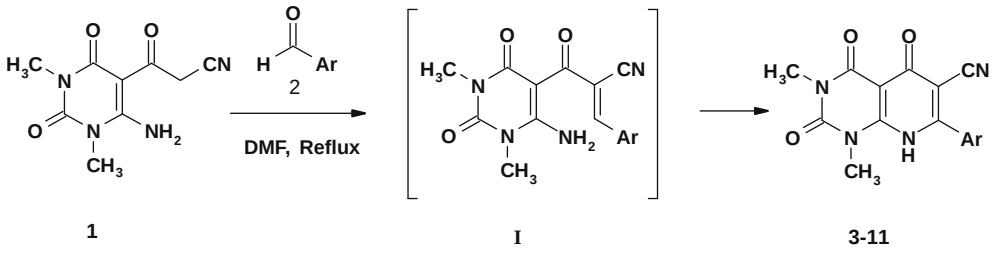


Scheme 1.



Scheme 2.

Table 1
Results for the preparation of pyrido[2,3-*d*]pyrimidines by conventional method

Product	Ar	Mp °C	Yield (%)
3	C_6H_5	220–222	60
4	4-ClC_6H_4	229–231	50
5	4-BrC_6H_4	248–250	90
6	4-FC_6H_4	230–232	58
7	4-$H_3CC_6H_4$	255–257	50
8	4-$H_3COC_6H_4$	227–229	42
9	3-Pyridyl	319–321	70
10	3,4,5-*tri*-$H_3COC_6H_2$	260–262	73
11	4-$F_3CC_6H_4$	267–269	95

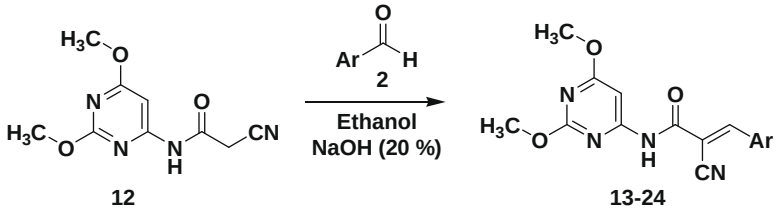
could be prepared in 56–95% in ethanol with base catalyst at room temperature for 2–3 h. Applying this new set of conditions the cyclocondensation between **1** and **2** did not proceed even under heating.

It is important to point out that this method allowed us to obtain the regioisomeric pyrido[2,3-*d*]pyrimidin-5-one while the previous three-component reactions among 6-amino-4-pyrimidinones, benzaldehydes, and cyanoacetyl derivatives led to the formation of the pyrido[2,3-*d*]pyrimidin-7-one.[8e]

It follows from Tables 1 and 2 that although the yields of all products ranging from good to excellent, nevertheless no relationship was found between them and the nature of the substituents of the aldehydes.

The structures of all new compounds were determined from analytical and spectral data, NMR 1D and 2D mainly, MS, and elemental analysis.

In conclusion, we have described the preparation of novel 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-3-arylacrylamides (in moderate to good yields) as products from the reaction of 2-cyano-*N*-(2,6-dimethoxipyrimidin-4-yl)-acetamide and aromatic aldehydes and the preparation of new 7-aryl-6-cyano-1,



Scheme 3.

Table 2
Synthesis of 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-3-arylacrylamides derivatives by condensation reaction between 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acetamide **12** and aldehydes using NaOH as catalyst

Product	Ar	Mp °C	Yield (%)
13	C_6H_5	148–150	60
14	4-ClC_6H_4	229–231	60
15	4-BrC_6H_4	238–240	56
16	2-FC_6H_4	165–167	61
17	4-FC_6H_4	218–220	73
18	4-$H_3CC_6H_4$	221–223	82
19	4-$H_3COC_6H_4$	211–213	56
20	3,4-OCH_2O-C_6H_3	227–229	72
21	4-$O_2NC_6H_4$	252–254	80
22	2-HOC_6H_4	211–213	95
23	4-$(H_3C)_2NC_6H_4$	253–255	76
24	3-Pyridyl	174–176	93

3-dimethyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-*d*]-pyrimidin-2,4,5-triones. This is an efficient, simple, and regioselective alternative via cyclocondensation reactions from the isomeric precursor 3-(6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)-3-oxopropanenitrile.

The chemical and biological properties of the new compounds obtained in these experiments are under investigation.

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14. *7-Aryl-6-cyano-1,3-dimethyl-l-2,4,5-trioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidines* **3**–**11**. A solution of 3-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-3-oxopropanenitrile **1** (1.0 mmol) and aromatic aldehydes **2** (1.0 mmol) in DMF (1.0 mL) was heated during 15 h. The resulting precipitate was filtered, washed with ethanol, and recrystallized from a mixture of EtOH–DMF (7:3). Data for 6-cyano-1,3-dimethyl-7-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidin-2,4,5-trione **3**: Yellow solid mp 220–222 °C. Yield 60%. IR (KBr, cm^{-1}): 3250 (NH), 2218 (C≡N), 1708, 1646 (C=O), 1600 (C=N). ^{1}H NMR (DMSO-d_6, 400 MHz, rt) δ (ppm): 3.24 (s, 3H, 3-NCH_3), 3.52 (s, 3H, 1-NCH_3), 7.53 (t, 1H, H_p), 7.60 (d, 2H, H_m, J = 8.42 Hz), 7.91 (d, 2H, H_o, J = 8.42 Hz,), 8.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz, rt) δ (ppm): 27.4 (3-NCH_3), 29.5 (1-NCH_3), 94.5 (C≡N), 95.8 (C9), 117.0 (C6), 128.3 (C_m), 130.4 (C_o), 135.2 (C_i), 136.3 (C_p), 150.7 (C2), 153.3 (C10), 162.0 (C7), 162.5 (C4), 172.8 (C5). The mass spectrum shows the following peaks: MS (30 eV) m/z (%): 308 (M^+). Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.34; H, 3.92; N, 18.17. Found C, 62.26; H, 3.86; N, 18.09.
15. *3-Aryl-2-cyano-N-(2,6-dimethoxypyrimidin-4-yl)-acrylamides* **13**–**24**. A solution of 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)acetamide **12** (1.0 mmol) and aromatic aldehyde **2** (1.0 mmol) in ethanol with a catalytic amount of NaOH (20%, 5 drops) was stirred during 2–3 h at room temperature. The resulting precipitate was filtered, washed with ethanol, and recrystallized from a mixture of DMF–ethanol. Data for 2-cyano-*N*-(2,6-dimethoxy-pyrimidin-4-yl)-3-phenylacrylamide **13**: Yellow solid, mp 148–150 °C. Yield 60 %. IR (KBr, cm^{-1}): 3335 (NH), 2219 (C≡N), 1697 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz, rt) δ (ppm): 3.91 (s, 6H, OCH_3), 7.10 (s, 1H, H-5), 7.60 (m, 3H, H_m and H_p), 7.98 (d, 2H, H_o, J = 8.00 Hz), 8.39 (s, 1H, H_β), 11.08 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz, rt) δ (ppm): 53.9 (OCH_3), 54.1 (OCH_3), 88.5 (C5), 107.0 (C≡N), 129.2 (C_m), 130.2 (C_o), 131.8 (C_i), 132.6 (C_p), 151.8 (C_β), 164.4 (C6), 172.4 (C2). The mass spectrum shows the following peaks: MS (30 eV) m/z (%): 310 (M^+, 100), 309 (23), 281 (32), 233 (25), 205 (55), 156 (30), 128 (65), 101 (36), 77 (58). Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.05. Found C, 61.82; H, 4.60; N, 18.11.