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New aspects on the selective synthesis of 7-arylpyrido[2,3-*d*]pyrimidines

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Abstract—Pyrido[2,3-*d*]pyrimidines have been synthesized via a selective cyclocondensation reaction between 6-aminopyrimidines **1** and the Mannich bases, propiophenone hydrochlorides **2**. Intermediates for this reaction, such as the Michael addition adduct and the further hydrated pyrido[2,3-*d*]pyrimidine were isolated to prove the postulated mechanism. NMR analysis of bidimensional experiments allowed to determine unambiguously the process to obtain 7-arylpyrido[2,3-*d*]pyrimidines. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The one-step assemblage of monocyclic as well as polycyclic heterocycles represents a practical approach in modern organic synthesis. This class of reactions are of particular interest in combinatorial chemistry[1] because it allows the production of vast arrays of molecules in an efficient mode. Recently, we have reported the selective preparation of a number of condensed heterocycles as potential biologically active compounds.[2] Amongst these, pyrido[2,3-*d*]pyrimidines are of great interest due to the shown antitumor,[3] antifolate,[4] antibacterial,[5] growth regulator,[6] etc. activities. The therapeutic importance of this nucleus enthused us to developed selective procedures of synthesis in which substituents could be arranged in a pharmacophoric pattern to display high order pharmacological activities.

Compounds with pyrido[2,3-*d*]pyrimidine ring system have earlier been prepared either by base-catalyzed condensation reaction with benzalacetophenone or benzalpinacolone with aminouracil[7] or by heating methyl vinyl ketone with 6-amino-1,3-dimethyluracil in acetic acid.[7] Reaction of 6-aminouracil with active methylene compounds[8] or electron rich enamines[9] or benzylidene Meldrum's acid derivatives[10] separately afforded pyrido[2,3-*d*]pyrimidines derivatives. Acid-catalyzed intramolecular cyclization of nicotinonitriles[11] or cyclocondensation of aminopyrimidines[12] with urea, thiourea in formamide separately also afforded the title compound. They have also been prepared by base-catalyzed (KOH) ring transformation reactions of 6-amino-1,3-dimethyluracil with 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones.[13]

From early studies[14] an empirical rule has emerged which specify that in annelation reactions involving substituted 6-aminopyrimidines, which have multiple competing sites for possible ring-annelation, and biselectrophiles such as β-keto aldehydes, β-keto esters, β-dialdehydes as well as α-halo ketones, the 5-position of the pyrimidine is the most nucleophilic and attacks the most electrophilic carbon of the biselectrophile, followed by ring closure between the 6-amino group and the second electrophilic center (recently alkynones have also been used as biselectrophiles[15]). This experimental observation is supported by computational studies via AM1 and PM3 calculations, which make known a direct correlation between charge densities at the C5-carbon of the 6-aminopyrimidine and their enamine-like nucleophilicity toward enones.[16] However, unexpected reactions have also been observed in some cases, depending on the substitution in the pyrimidine, the biselectrophile and the solvent used.[17]

Our recent studies provided a convenient method for the preparation of pyrido[2,3-*d*]pyrimidines by reactions of 6-aminopyrimidines with α,β-unsaturated carbonyl and carboxylic compounds.[18] As part of our continuing interest in the reaction of aminopyrimidines with α,β-unsaturated compounds and their precursors, Mannich bases, we have synthesized 7-arylpyrido[2,3-*d*]pyrimidines **3** in moderate to good yields via cyclocondensation reaction between

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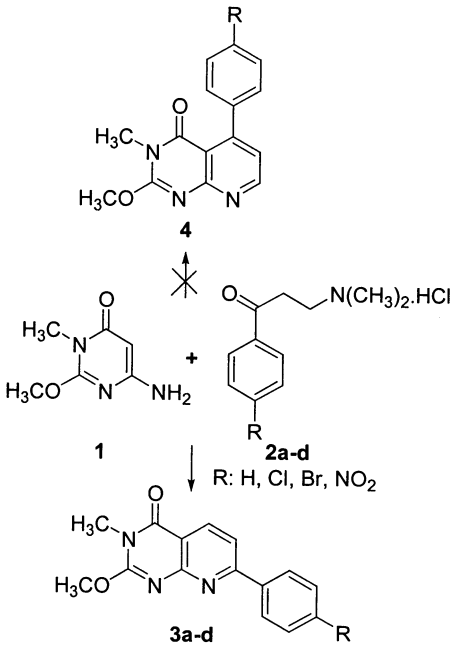


Scheme 1.

6-aminopyrimidin-4-ones **1** and 3-dimethylaminopropiophenone hydrochlorides **2**.

In this paper we demonstrate that the reaction of 6-amino-2-methoxy-3-methylpyrimidin-4(3*H*)-one **1** with α,β-unsaturated ketones, which are generated in situ by the corresponding precursor Mannich bases **2**, as biselectrophiles also agrees with the above mentioned rule, and lead regioselectively to 7-substituted pyrido[2,3-*d*]pyrimidines and not to the 5-substituted isomer.

2. Results and discussion

Aminopyrimidinone **1** reacts with equimolecular amounts of 3-dimethylaminopropiophenone hydrochloride **2** in absolute ethanol under reflux to afford 7-arylpyrido[2,3-*d*]pyrimidines **3a**–**d** as unique product (see Scheme 1).

3-Dimethylaminopropiophenones are relatively unstable and easily lose the amino group forming aryl vinyl ketones.[19]

Michael type nucleophilic addition of carbon atom C-5 at the pyrimidine ring to the formed aryl vinyl ketone and subsequent cyclization with water elimination yields **3a**–**d**. On the other hand, initial addition from amino group at **1** in a similar fashion could afford **4**. We have found that the condensation between compounds **1** and **2** was regioselective and no other compound was formed (TLC control) and agrees with that found for others aminopyrimidines and biselectrophiles.[14,15]

Table 1. ^{1}H NMR data of **3a**–**e**

Entry	3a	3b	3c	3d	3e
2-OCH_3, s	4.10	4.10	4.10	4.10	4.15
3-NCH_3, s	3.36	3.39	3.36	3.40	3.43
5-H, d[a]	8.44	8.38	8.45	8.43	8.51
6-H, d[a]	7.97	7.90	7.98	7.94	8.01
Ar, H_o, m	8.22	8.18	8.23	8.14	8.42
Ar, H_m, m	7.56	7.09	7.60	7.72	8.32

OCH_3 group for **3e** at 3.85 ppm.
[a] J=8.3 Hz.

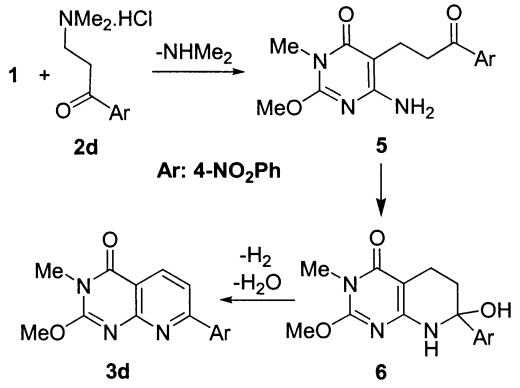
Table 2. ^{13}C NMR chemical shifts (δ in ppm) of compounds **3a**–**e**

Entry	3a	3b	3c	3d	3e
OCH_3	56.0	55.9	56.0	56.0	56.0
NCH_3	28.0	27.9	28.0	28.0	28.1
C-2	159.9	155.8	156.0	156.0	156.4
C-4	161.8	161.8	162.0	161.8	161.9
C-4a	111.6	110.8	111.9	111.9	112.8
C-5	137.1	136.8	137.3	137.2	137.7
C-6	116.8	116.0	116.7	116.6	117.7
C-7	161.3	161.1	160.0	160.0	159.3
C-8a	156.8	156.8	157.0	156.8	157.1
C_i	137.5	130.0	136.3	136.7	143.8
C_o	127.3	128.9	128.9	129.3	123.8
C_m	128.8	114.2	129.1	131.8	128.7
C_p	130.2	161.0	135.1	124.0	148.7

OCH_3 group for **3e** 55.3 ppm.

Data from ^{1}H and ^{13}C NMR spectra are displayed in Tables 1 and 2, where the assignment for carbon atoms was based in DEPT experiments along with bidimensional HMBC and HSQC (^{1}H–^{13}C) experiments; HMBC and NOESY experiments gave the definitive assignment to determine the regioselectivity in compounds **3a** and **3c**, hence the heteronuclear correlation observed in the HMBC experiment between signal assigned to H-5 and C-4, along to the NOESY correlation found between *ortho* proton at the phenyl residue and H-6 were the clue to propose structures **3**.

To corroborate the above proposed steps sequence in the formation of compounds **3**, we carried out the reaction between **1** and 3-dimethylamino-*p*-nitropropiophenone hydrochloride **2d** under similar conditions, either shorter reaction time or lower temperature (see Section 4). In those situations, the Michael adduct **5**, the hydrated cyclic product **6** or well the desired product **3d** were isolated depending on the reaction time. So as logic in time order compound **5** was obtained first, then **6** and the last one was **3d**. Hence the formation of **3d** is assumed to proceed as indicated above, that is by an initial Michael type addition



Scheme 2.

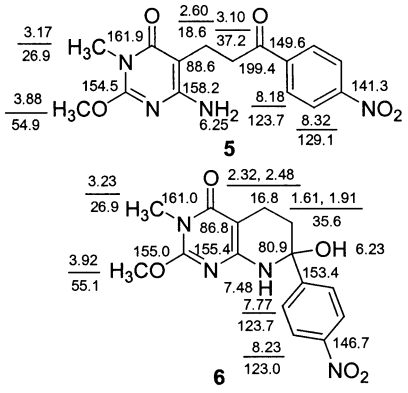


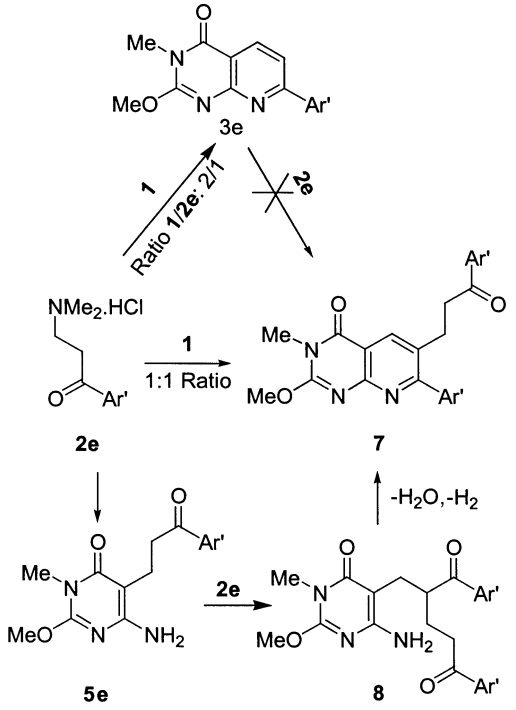
Figure 1.

of the most nucleophilic carbon atom in aminopyrimidine to the activated double bond of aryl vinyl ketone[18b,e,f,20] yielding Michael adduct **5** which by an intramolecular cyclization between amino and carbonyl group gives compound **6**. Finally, one molecule of water is eliminated from **6** giving 6,7-dihydropyrido[2,3-*d*]pyrimidinones, which further oxidation yields the aromatic compound **3d** (Scheme 2).

The structures of intermediates **5** and **6** were also completely characterized by spectroscopic and analytical methods. ^{1}H and ^{13}C NMR data are displayed in Fig. 1.

According to the mentioned results, the rest of compounds **3a–c** should be formed by a like way to **3d**.

The reaction of **1** with **2e** led to **3e** (Ar′=p-CH_3O′Ph) in 60% yield when the molar relation was 2:1 (see Scheme 3). Surprisingly when the ratio was 1:1, a different and yellow crystalline product was separated.



Scheme 3.

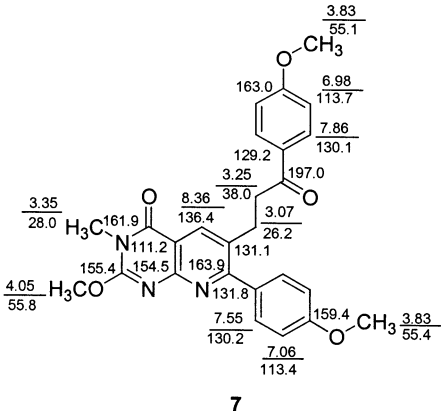


Figure 2.

Elemental analysis and mass spectral data suggest that the adduct resulted from the condensation of one molecule of aminopyrimidine **1** with two of compound **2e** accompanied by loss of water molecule. Such product was fully characterized by analytical and spectroscopic methods as compound **7** (^{1}H and ^{13}C NMR spectroscopic data shown in Fig. 2). The assumption that initially pyrido[2,3-*d*]pyrimidine ring system **3e** is formed, and then reacts with a second molecule of α,β-unsaturated ketone through C-6 at pyrido[2,3-*d*]pyrimidine to yield compound **7** is discarded because **7** is not formed when **3e** is reacted directly with the Mannich base **2e** (Scheme 3). We consider that the reaction should proceed through a second alkylation of the initial Michael adduct (**5e**) on the active methylene, then the new intermediate **8** would proceed in the same manner as above, through cyclocondensation to compound **7** (Scheme 3). This type of alkylation was observed in the case of methoxy derivatives of chalcones,[21] and it is also well-known that alkylation of CH groups activated by carbonyl groups have mainly been carried out using ketonic Mannich bases.[22]

3. Conclusions

We have demonstrated that the cyclocondensation of 6-aminopyrimidine **1** with 3-dimethylaminopropiophenone hydrochlorides **2** affords selectively the 7-arylpyrido[2,3-*d*]pyrimidines **3** under mild conditions, in moderate to good yields. That supports and agrees with the previously formulated empirical rule about cyclocondensation between 6-aminopyrimidines and biselectrophiles. Intermediates type **5** and **6** in the pathway to pyrido[2,3-*d*]pyrimidines **3** have been isolated and characterized for first time, what provides definitive evidence about the mechanism.

4. Experimental

4.1. General methods

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were run on a Bruker DPX 300 spectrometer operating at 300 and 75 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The

mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) and operating at 70 eV. The elemental analysis has been obtained using a LECO CHNS-900 equipment. Reaction progress and purity of the products were monitored by thin layer chromatography (TLC) on Merck Silica Gel $60GF_{254}$ (0.2 mm) aluminium precoated sheets with fluorescent indicator, the spots were visualized by ultraviolet irradiation, and using chloroform as eluent.

4.2. General procedure for the preparation of the 7-aryl-2-methoxy-3-methylpyrido[2,3-*d*]pyrimidin-4-ones 3

A solution of 6-aminopyrimidine **1** (2.0; 4.0 mmol for reaction between **1** and **2e**) and an equimolar amount of the 3-dimethylaminopropiophenone hydrochloride **2** (2.0 mmol) in ethanol (10 ml) was heated at reflux for 1–2 h. Then the reaction mixture was cooled overnight. The resulting precipitated was filtered, washed with ethanol and recrystallized from ethanol to afford the desired products **3**.

4.2.1. 2-Methoxy-3-methyl-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one 3a. This compound was obtained according to general procedure as white crystals. Mp 178°C, yield 60%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=267 (M^+, 100), 252 (12), 238 (31), 223 (20), 167 (11), 140 (16). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.55; H, 4.83; N, 15.63.

4.2.2. 7-(*p*-Chlorophenyl)-2-methoxy-3-methylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-one 3b. This compound was obtained according to general procedure as white crystals. Mp 218°C, yield 62%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=303/301 (M^+, 36/100), 286 (14), 272 (38), 257 (23). Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.57; H, 4.14; N, 13.79.

4.2.3. 7-(*p*-Bromophenyl)-2-methoxy-3-methyl-7-phenyl-pyrido [2,3-*d*]pyrimidin-4(3*H*)-one 3c. This compound was obtained according to general procedure as white crystals. Mp 218°C, yield 60%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=347/345 (100/98, M^+), 332 (12), 316 (37), 303 (24), 288 (12), 247 (10), 166 (21), 140 (13), 72 (15), 56 (12), 42 (10). Anal. Calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.04; H, 3.49; N, 12.14. Found: C, 52.15; H, 3.35; N, 12.26.

4.2.4. 2-Methoxy-3-methyl-7-(*p*-nitrophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one 3d. This compound was obtained according to general procedure as pale yellow crystals. Mp 275°C, yield 70%. This compound also was obtained by heating at reflux in ethanol of compound **6** for 1 h, yield 70%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=312 (100, M^+), 297 (11), 283 (32), 268 (23), 254 (12), 194 (10), 166 (10), 72 (10). Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.61; H, 3.74; N, 17.79.

4.2.5. 7-(*p*-Methoxyphenyl)-2-methoxy-3-methylpyrido-[2,3-*d*]pyrimidin-4-one 3e. This compound was obtained according to general procedure, using two moles of amine and one mole of propiophenone **2e**, as white crystals. Mp 173°C, yield 60%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=298 (32), 297 (M^+, 100), 282 (13), 268 (31), 267 (11), 253 (20), 197 (14), 72 (10), 64 (10), 56 (10). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.56; H, 5.16; N, 14.08.

4.2.6. Synthesis of 6-amino-2-methoxy-3-methyl-5-[3-(4-nitrophenyl)-3-oxopropyl]pyrimidin-4(3*H*)-one 5. A solution of 6-aminopyrimidine **1** (2.0 mmol) and an equimolar amount of the 3-dimethylamino-*p*-nitropropiophenone hydrochloride **2d** (2.0 mmol) in ethanol (25 ml) was stirred overnight at room temperature, then, part of solvent was removed under reduced pressure and the reaction mixture was cooled overnight. The resulting orange precipitate was filtered, washed with ethanol and recrystallized from ethanol. Mp 220°C, yield 65%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=332 (M^+, 25), 312 (52), 283 (18), 268 (13), 182 (100), 167 (81), 155 (26), 72 (16), 57 (24). Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.27; H, 4.81; N, 16.96.

4.2.7. Synthesis of 7-hydroxy-2-methoxy-3-methyl-7-(4-nitrophenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one 6. *Method A*: A solution of compound **5** (2.0 mmol) in ethanol (10 ml) was heated at reflux for 10 min, then the resulting white precipitate was filtered, washed with ethanol and recrystallized from ethanol. Yield 68%.

Method B: A solution of 6-aminopyrimidine **1** (2.0 mmol) and an equimolar amount of the 3-dimethylamino-*p*-nitropropiophenone hydrochloride **2d** (2.0 mmol) in ethanol (15 ml) was heated at reflux during 10 min, then the resulting white precipitate was filtered, washed with ethanol and recrystallized from ethanol. Mp 209°C, yield 72%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=332 (M^+, 36), 315 (30), 314 (33), 313 (27), 282 (12), 182 (100), 167 (85), 155 (29), 111 (26), 72 (22), 57 (22). Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.31; H, 4.74; N, 16.73.

4.2.8. Synthesis of 2-methoxy-6-(*p*-methoxyphenetyl)-7-(*p*-methoxyphenyl)-3-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one 7. This compound was obtained according to general procedure (**3a**–**e**) as white crystals. Mp 177°C, yield 45%. The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%)=459 (M^+, 43), 324 (100), 310 (95), 135 (64), 77 (20). Anal. Calcd for $C_{26}H_{25}N_3O_5$: C, 67.96; H, 5.48; N, 9.14. Found: C, 67.88; H, 5.53; N, 9.22.

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