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A regiospecific three-component one-step cyclocondensation to 6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones using microwaves under solvent-free conditions

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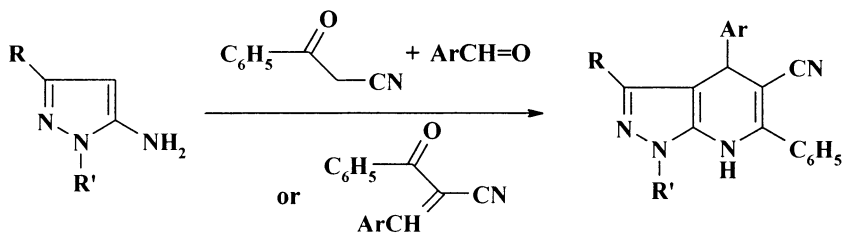
Abstract—In a solvent-free system, regiospecific three-component one-step cyclocondensation to dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **4** starting from readily available aminopyrimidin-4-ones **1**, benzoylacetonitrile **2** and benzaldehydes **3** by microwave radiation was carried out. This rapid method produces pure products in high yields (70–75%).

Cyclocondensation reactions are among the most valuable synthetic methods for the preparation of heterocycles. Recently, we described a new, simple and efficient synthesis of pyrazolopyridines,[1,2] in the reaction of aminopyrazoles with benzylidenbenzoylacetonitrile, or with its precursors, benzoylacetonitrile and aldehydes, which are interesting biological targets (Eq. (1)).



(1)

In the course of our research field aimed at the preparation of bioactive nitrogen containing heterocycles, we addressed the synthesis of dihydropyrido[2,3-*d*]pyrimidines. The pyrido[2,3-*d*]pyrimidines, deaza-analogs of pteridines, and their oxoderivatives have been of interest for their potential biological activities.[3]

The microwave irradiation can be used to carry out a wide range of reactions in short times and with high yield and regioselectivity, without the need for solvents. Recent developments in microwave solventless organic syntheses are summarized.[4] On the other hand, multicomponent condensations (MCCs) constitute a specially attractive synthetic strategy for rapid and efficient library generation due to the fact that products are formed in a single step and the diversity can be achieved simply by varying the reacting components.[5]

In this paper, we describe a facile three-component, one-pot condensation reaction of 5-aryl-6-cyano-7-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **4** using microwave irradiation, a process that is adaptable for the assembly of a library of compounds, which has recently gained much attention in pharmaceutical research.[6]

Equimolar amounts of starting compounds **1**, **2** and **3** were placed into Pyrex-glass open vessels and irradiated in a domestic microwave oven for 15–20 min (at 600 W). When the irradiation was stopped, the solid was treated with ethanol and filtered to give the products **4a–g** in 70–75% yields (Eq. (2)).

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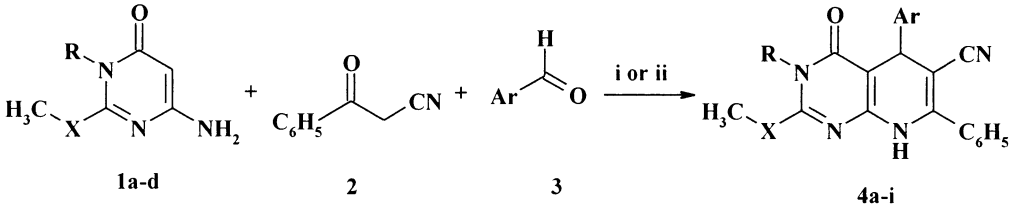


(2)

i) Microwave irradiation during 15-20 min. under solvent-free conditions.
ii) Refluxing in absolute ethanol during 40-48 hours.

X = O, S; R = H, CH_3; Ar = C_6H_5-, 4-$CH_3OC_6H_4$, 4-ClC_6H_4-

A long heating (40–48 h) of equimolar amounts of compounds **1**, **2** and **3** in absolute ethanol to reflux allowed the isolation of 5-aryl-6-cyano-7-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **4** in poor yields (21–25%).

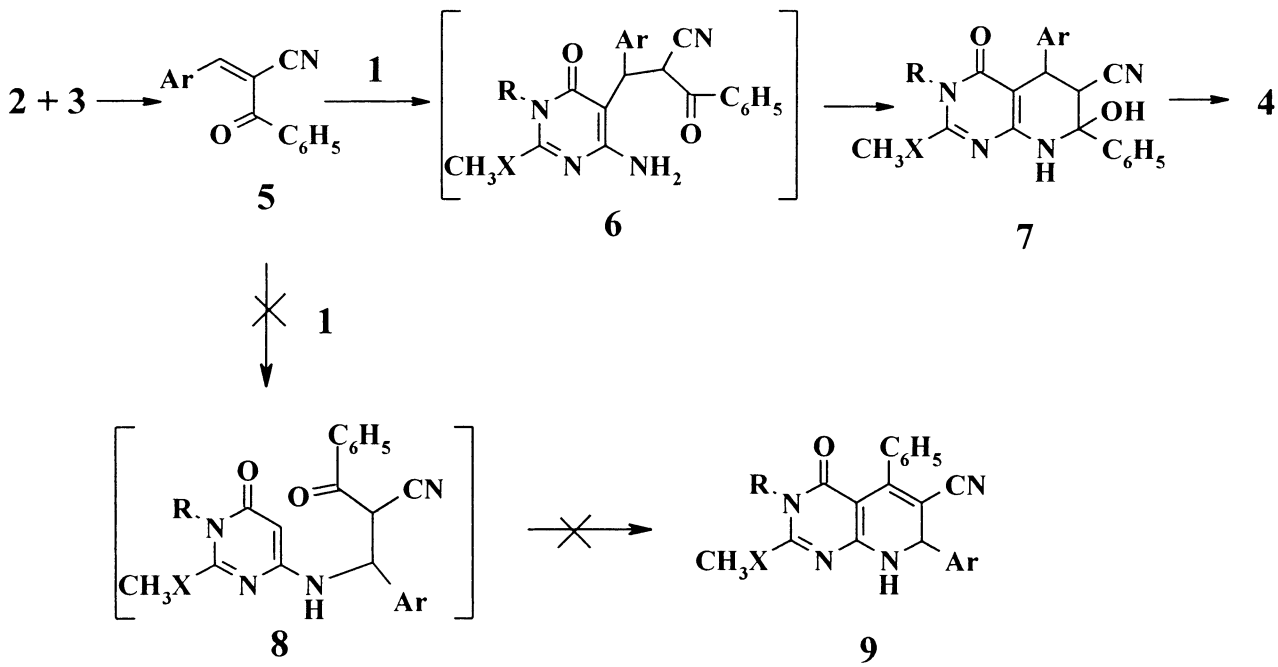
It is important to point out the fact that when the aminopyrimidines **1**, benzoylacetonitrile **2** and benzaldehydes **3** were irradiated for just 8–12 min, in all cases the reaction leads to the formation of the stable hydrated intermediates **7**, which were isolated and characterized.

Thus, we assume that the formation of **4** proceeds by a Michael type addition from the free ring carbon atom in aminopyrimidine **1** to the activated double bond of the benzylidenbenzoylacetonitrile intermediate **5** (formed in situ by a Knoevenagel condensation between benzoylacetonitrile **2** and benzaldehyde **3**), with subsequent cyclization of the previously formated Michael adduct **6** to give **7** (Eq. (3)). When compound **7** is continuously irradiated (an additional 6–10 min) it looses a water molecule yielding 5-aryl-6-cyano-7-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (**4**). The formation of the Michael adduct **6** as intermediate in the second step (C-alkylation) is key to explaining the right orientation of the reaction. In the contrary case, if a *N*-alkylation (Michael adduct **8**) were proceeded, 7-aryl-6-cyano-5-phenyl-7,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **9** would have been obtained instead of compound **4** (Eq. (3)).

The probable formation of the benzylidenbenzoylacetonitrile (α-cyanochalcone) **5** as intermediate of the reaction in study, was confirmed by the fact that the direct interaction of amines **1** with previously synthesized benzylidenbenzoylacetonitrile **5** using microwave radiation under the same conditions permitted in all cases the same 5-aryl-6-cyano-7-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)ones **4** (Eq. (3)) to be obtained.

Based on ^1H, ^{13}C NMR, DEPT, HMQC, HMBC and NOESY techniques, it was possible to assign all protons and carbon atoms of 5-aryl-6-cyano-7-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidines **4** and their hydrated precursors **7**.[7]

In conclusion, the present three-component one-step procedure described in this paper is a very regioselective, facile and practical method for the preparation of novel 6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-



(3)

ones from 6-amino-4-pyrimidinones, benzoylacetonitrile and benzaldehydes. This work is a further example of the utility of microwaves in organic synthesis. When conventional thermal procedures require a considerable reaction time, microwave irradiation can substitute classical methods allowing easy and rapid access to new heterocycles, reducing the reaction times from hours to minutes with improved yields.

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7. All products gave satisfactory elemental analyses and spectral data (IR, MS, and NMR) consistent with their structures. Data for representative compounds follow. Compound **4a** (R = H; X = O; Ar = C_6H_5): mp 283°C, yield 75%. MS: (70 eV) m/z (%) = 356 (9, M^+), 280 (19), 279 (100, $M^+-C_6H_5$), 247 (8), 192 (8), 77 (11), 51 (10). δ_H (300 MHz, DMSO) 3.99 (s, 3H, CH_3O), 4.67 (s, 1H, 5-H), 10.16 (s, 1H, 8-NH), 12.09 (s, 1H, 3-NH), 7.22–7.38 (m, 5H, 5-C_6H_5), 7.46–7.55 (m, 5H, 5-C_6H_5); δ_C (75 MHz, DMSO) 39.3 (C-5), 54.6 (CH_3O), 84.1 (C-6), 92.9 (C-4a), 120.1 (CN), 149.7 (C-7), 152.3 (C-8a), 156.8 (C-2), 162.0 (C=O). Anal. calcd for $C_{21}H_{16}N_4O_2$: C, 70.78; H, 4.53; N, 15.72. Found: C, 70.71; H, 5.44; N, 15.83. Compound **7a** (R = H; X = O; Ar = C_6H_5): mp 244°C, yield 75%. MS: (70 eV) m/z (%) = 374 (1, M^+), 356 (3, M^+-H_2O), 280 (8), 279 (37), 233 (28), 232 (12), 141 (13), 106 (9), 105 (100), 78 (8), 77 (80), 51 (41), 50 (14), 39 (7). δ_H (300 MHz, DMSO) 3.84 (s, 3H, CH_3O), 3.14 (d, 1H, 6-H), 4.02 (d, 1H, 5-H), 6.79 (s, 1H, 7-OH), 7.73 (s, 1H, 8-NH), 11.45 (s, 1H, 3-NH); δ_C (75 MHz, DMSO) 40.6 (C-5), 54.1 (CH_3O), 49.4 (C-6), 80.7 (C-7), 89.7 (C-4a), 118.6 (CN), 157.5 (C-8a), 156.6 (C-2), 161.0 (C=O). Anal. calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.46; H, 4.78; N, 14.89.