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Solvent-free multicomponent assembling of aldehydes, *N,N′*-dialkyl barbiturates and malononitrile: fast and efficient approach to pyrano[2,3-*d*]pyrimidines

Abstract: Potassium fluoride-catalyzed solvent-free multicomponent reaction of aldehydes, *N*,*N′*-dialkyl barbiturates and malononitrile results in the fast (15 min) and efficient (yields 89–95%) formation of substituted pyrano[2,3-*d*]pyrimidines. The improved synthetic methodology for this class of bioactive compounds is important from the viewpoint of diversity-oriented large-scale processes and represents an environmentally benign solvent-free synthetic concept for multicomponent reactions strategy.

Keywords: aldehydes; multicomponent reaction; *N*,*N′*-dialkyl barbiturates; pyrano[2,3-*d*]pyrimidines; solvent-free.

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Introduction

Pyrano[2,3-*d*]pyrimidines have received considerable attention owing to their wide range of diverse pharmacological activity. They are nicotinic acid receptor (NAR) agonists [1] and show antitumor [2], hepatoprotective [3], antibronchitic [4], and anti-AIDS activity [5], among others.

The procedures for the preparation of pyrano[2,3-*d*]pyrimidines usually include the reaction of benzylidenemalononitriles with barbiturates in the presence of base catalysts [6, 7]. Multicomponent procedures have also been suggested for synthesis of pyrano[2,3-*d*]pyrimidines from aldehydes, malononitrile and *N*,*N′*-dialkyl barbiturates, using polyethylene glycol-stabilized Ni(0) nanoparticles in ethylene glycol [8], with triethylamine under sonication [9], in ethanol under electrolysis conditions [10] and under microwave radiation [11]. All these procedures for the synthesis of pyrano[2,3-*d*]pyrimidines have merits, but the fast, facile, and environmentally benign multicomponent solvent-free methodology is yet not known and should be developed.

Considering our preliminary results on the solvent-free transformation of C–H acids and salicylaldehydes [12–14] as well as the certain biomedical application of pyrano[2,3-*d*]pyrimidines mentioned above, it was of interest to design a convenient solvent-free methodology for the efficient synthesis of substituted pyrano[2,3-*d*]pyrimidines based on multicomponent reaction of aldehydes, *N*,*N′*-dialkyl barbiturates and malononitrile.

Results and discussion

We report the results on a fast multicomponent transformation of aldehydes **1a–h**, *N*,*N′*-dialkyl barbiturates **2a**,**b** and malononitrile into substituted pyrano[2,3-*d*]pyrimidines **3a–k** under solvent-free conditions (Scheme 1).

Solvent-free reaction of aldehyde **1a**, *N*,*N′*-dimethylbarbituric acid **2a** and malononitrile without catalyst at 60°C after 15 min resulted in the formation of pyrano[2,3-*d*]pyrimidine **3a** in the low yield of 15%. In the presence of 5 mol% of NaOAc as catalyst, under otherwise identical conditions, pyrano[2,3-*d*]pyrimidine **3a** was obtained in 39% yield. Using 10 mol% and 30 mol% of NaOAc led to **3a** in 51% and 65% yields, respectively. In the presence of 5% of KF (potassium fluoride) as catalyst the yield of **3a** was 71%. Finally, at 60°C after 15 min the excellent yield of 95% of **3a** was obtained with 10 mol% of KF.

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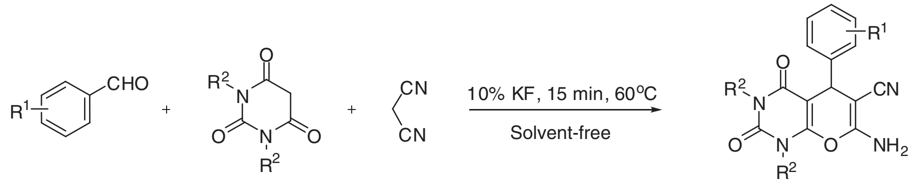


1a-h **2a,b** **3a-k**

1a: R^1 = H
1b: R^1 = 4-Me
1c: R^1 = 4-MeO
1d: R^1 = 4-F
1e: R^1 = 2-Cl
1f: R^1 = 4-Cl
1g: R^1 = 3-Br
1h: R^1 = 4-NO_2

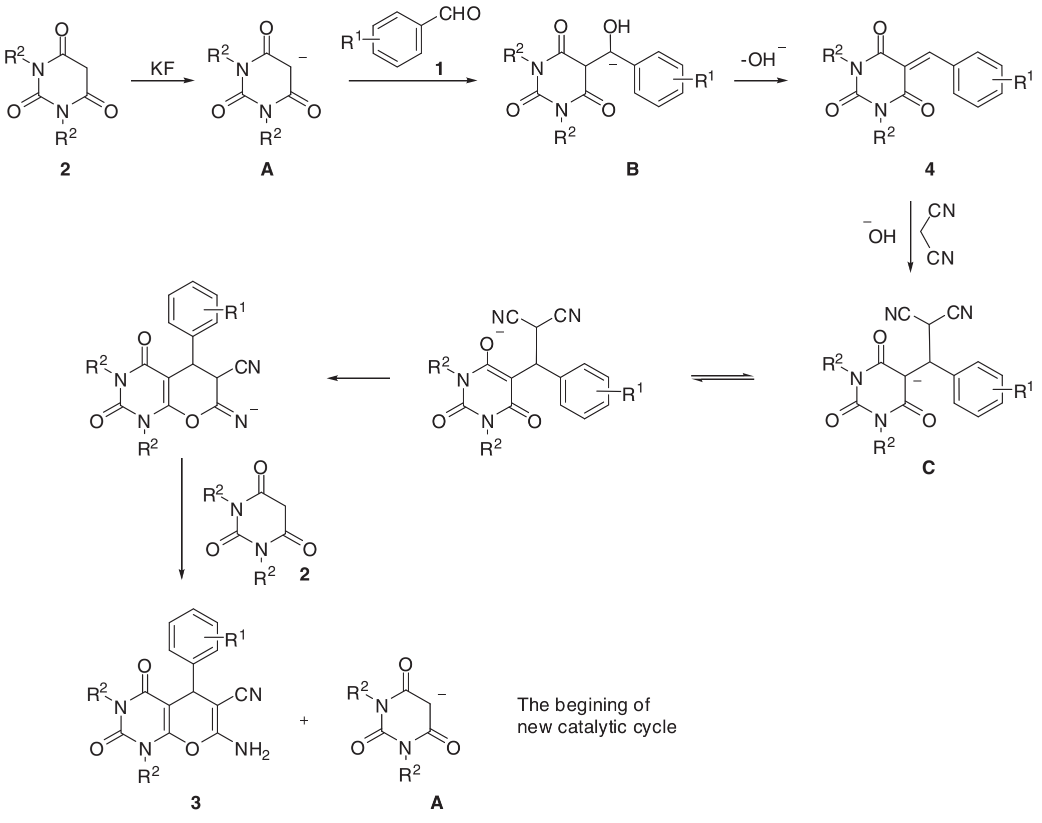
2a: R^2 = Me
2b: R^2 = Et

3a: R^1 = H; R^2 = Me
3b: R^1= 4-Me; R^2 = Me
3c: R^1 = 4-MeO; R^2 = Me
3d: R^1 = 4-F; R^2 = Me
3e: R^1 = 2-Cl; R^2 = Me
3f: R^1 = 4-Cl; R^2 = Me
3g: R^1 = 3-Br; R^2 = Me
3h: R^1 = 4-NO_2; R^2 = Me
3i: R^1 = 2-H; R^2 = Et
3j: R^1 = 4-F; R^2 = Et
3k: R^1 = 2-Cl; R^2 = Et

Scheme 1

By using the optimized conditions of 10 mol% of KF as catalyst at 60°C with 15 min reaction time, other substituted pyrano[2,3-*d*]pyrimidines **3a–k** were obtained in yields of 89–95%. These high yields ensured analytical purity of the products after a simple workup without crystallization. Thus, this solvent-free procedure for synthesis of substituted pyrano[2,3-*d*]pyrimidines **3a–k** developed by us is one step closer to the 'ideal synthesis' [15].

With the above results taken into consideration, the following mechanism for the potassium fluoride catalyzed multicomponent transformation of aldehydes **1**, *N*,*N′*-dialkyl barbituric acids **2** and malononitrile into substituted pyrano[2,3-*d*]pyrimidines **3** can be suggested (Scheme 2). The initiation step of the catalytic cycle begins with the deprotonation of a molecule of *N*,*N′*-dialkyl barbituric acid **2** by the action of potassium fluoride, which



Scheme 2

generates the anion **A** of *N*,*N′*-dialkyl barbituric acid. Then Knoevenagel condensation of aldehyde **1** with barbituric acid anion **A** takes place with the elimination of hydroxide anion and formation of corresponding 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **4**. The subsequent hydroxide-promoted Michael addition of malononitrile to electron deficient Knoevenagel adduct **4** followed by intramolecular cyclization leads to corresponding pyrano[2,3-*d*]pyrimidine **3** with regeneration of barbituric acid anion **A** at the last step. Generation of the intermediate products **B** and **C** in this cascade of reactions can be noted.

Conclusion

Potassium fluoride (KF) is an efficient catalyst for selective solvent-free multicomponent transformation of aldehydes, *N*,*N′*-dialkyl barbituric acids and malononitrile into substituted pyrano[2,3-*d*]pyrimidine-6-carbonitriles in excellent (89–95%) yields. This new process opens an efficient and convenient solvent-free multicomponent way to synthesize substituted pyrano[2,3-*d*]pyrimidines – the promising compounds for a variety of biomedical applications.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra were recorded with a Bruker Avance II-300 at ambient temperature in DMSO-d_6 solutions.

General procedure for 3a–k

A mixture of benzaldehyde **1a–h** (5 mmol), *N*,*N′*-dialkyl barbituric acid **2a,b** (5 mmol), malononitrile (5 mmol) and potassium fluoride (KF; 0.029 g, 0.5 mmol) was stirred at 60°C for 15 min, and then cooled to 20°C. Water (10 mL) was added, the mixture was stirred for 15 min and filtered to isolate the solid product, which was washed with water (2 × 5 mL), ice-cold ethanol (5 mL), and dried under reduced pressure.

7-Amino-1,3-dimethyl-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimi-dine-6-carbonitrile (3a) This compound was obtained from **1a** and **2a**; yield 1.47 g (95%); mp 219–222°C (lit [11] mp 210°C); ^{1}H NMR: δ 3.08 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 4.32 (s, 1H, CH), 7.15–7.39 (m, 7H, Ar, NH_2).

7-Amino-1,3-dimethyl-5-(4-methylphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3b) This compound was obtained from **1b** and **2a**; yield 1.48 g (91%); mp 202–203°C (lit [10] mp 203°C); ^{1}H NMR: δ 2.25 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.28 (s, 1H, CH), 7.05–7.15 (m, 4H, Ar), 7.28 (s, 2H, NH_2).

7-Amino-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano-[2,3-*d*]pyrimidine-6-carbonitrile (3c) This compound was obtained from **1c** and **2a**; yield 1.53 g (90%); mp 225–226°C (lit [10] mp 225–227°C); ^{1}H NMR: δ 3.15 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.36 (s, 1H, CH), 6.32 (s, 2H, NH_2), 6.74 (d, J = 8.4 Hz, 2H, Ar), 7.12 (d, J = 8.4 Hz, 2H, Ar).

7-Amino-5-(4-fluorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3d) This compound was obtained from **1d** and **2a**; yield 1.51 g (92%); mp 229–232°C (lit [10] mp 230–232°C); ^{1}H NMR: δ 3.13 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.38 (s, 1H, CH), 6.69 (s, 2H, NH_2), 6.90 (t, J = 8.7 Hz, 2H, Ar), 7.19 (dd, J = 8.1 Hz and 5.1 Hz, 2H, Ar).

7-Amino-5-(2-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3e) This compound was obtained from **1e** and **2a**; yield 1.57 g (91%); mp 236–238°C (lit [10] mp 237–238°C); ^{1}H NMR: δ 3.07 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 4.87 (s, 1H, CH), 7.16–7.42 (m, 6H, Ar, NH_2).

7-Amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3f) This compound was obtained from **1f** and **2a**; yield 1.60 g (93%); mp 239–241°C (lit [16] mp 241–242°C); ^{1}H NMR: δ 3.08 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.35 (s, 1H, CH), 7.18–7.47 (m, 6H, Ar, NH_2).

7-Amino-5-(3-bromophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3g) This compound was obtained from **1g** and **2a**; yield 1.79 g (92%); mp 215–217°C (lit [10] mp 217°C); ^{1}H NMR: δ 3.16 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 4.38 (s, 1H, CH), 6.47 (s, 2H, NH_2), 7.11 (t, J = 7.3 Hz, 1H, Ar), 7.19 (d, J = 7.3 Hz, 1H, Ar), 7.27 (d, J = 8.0 Hz, 1H, Ar), 7.44 (s, 1H, Ar).

7-Amino-1,3-dimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3h) This compound was obtained from **1h** an **2a**; yield 1.69 g (95%); mp 211–214°C (lit [10] mp 212–214°C); ^{1}H NMR: δ 3.06 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.51 (s, 1H, CH), 7.49 (s, 2H, NH_2), 7.55 (d, J = 8.1 Hz, 2H, Ar), 8.15 (d, J = 8.1 Hz, 2H, Ar).

7-Amino-1,3-diethyl-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3i) This compound was obtained from **1a** and **2b**; yield 1.51 g (89%); mp 147–150°C; ^{1}H NMR: δ 1.01 (t, J = 7.3 Hz, 3H, CH_3), 1.22 (t, J = 7.3 Hz, 3H, CH_3), 3.67–3.82 (m, 2H, CH_2), 3.90–4.05 (m, 2H, CH_2), 4.33 (s, 1H, CH), 7.15–7.40 (m, 7H, Ar, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.6, 13.8, 35.8, 36.4, 37.8, 58.6, 89.2, 119.0, 126.7, 127.2 (2C), 128.3 (2C), 144.0, 149.1, 150.9, 157.7, 160.0 ppm; IR (KBr): ν 3382, 3187, 2208, 1687, 1632, 1486, 1382, 1238 cm^{-1}; MS (EI): *m/z* (%) 338 (7) [M]$^+$, 271 (32), 184 (100), 131 (73), 103 (86), 70 (81), 56 (74), 44 (95). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.71; H, 5.47; N, 16.42.

7-Amino-1,3-diethyl-5-(4-fluorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3j) This compound was obtained from **1f** an **2b**; yield 1.60 g (90%); mp 159–162°C (lit [10] mp 160–162°C); ^{1}H NMR: δ 1.01 (t, J = 7.3 Hz, 3H, CH_3), 1.22 (t, *J* = 7.3 Hz, 3H, CH_3), 3.65–3.83 (m, 2H, CH_2), 3.88–4.05 (m, 2H, CH_2), 4.35 (s, 1H, CH), 7.10 (t, *J* = 8.8 Hz, 2H, Ar), 7.21–7.31 (m, 2H, Ar) 7.34 (s, 2H, NH_2).

7-Amino-5-(2-chlorophenyl)-1,3-diethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (3k) This compound was obtained from **1e** and **2b**; yield 1.71 g (92%); mp 185–187°C (lit [10] mp 186–187°C); ^1H NMR: δ 1.00 (t, *J* = 6.8 Hz, 3H, CH_3), 1.23 (t, *J* = 6.8 Hz, 3H, CH_3), 3.71 (q, *J* = 6.8 Hz, 2H, CH_2), 3.98 (q, *J* = 6.8 Hz, 2H, CH_2), 4.84 (s, 1H, CH), 7.15–7.44 (m, 6H, Ar, NH_2).

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