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One-pot three component condensation reaction in water: an efficient and improved procedure for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

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Abstract—The environment-friendly three component condensation reactions of *N*,*N*′-dimethylbarbituric acid, 4-nitrobenzaldehyde and alkyl or aryl isocyanides to afford the corresponding furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones, in water, in high yields after several minutes are reported.

1. Introduction

It is well known that pyrimidine systems as purine analogues exhibit a wide range of biological activities.[1–4] Among them, the furo[2,3-*d*]pyrimidine derivatives act as sedatives, antihistamines, diuretics, muscle relaxants and antiulcer agents.

The synthesis of furopyrimidines has received little attention and only few procedures have been reported in the literature,[2,5–9] most of which rely on multi-step reactions with yields being low[2,5,6] (Scheme 1).

In connection with our previous work on the reaction of isocyanides with electron-deficient heterodienes,[10–14] we wish to report a facile and rapid protocol for the three component condensation reactions of *N*,*N*′-dimethylbarbituric acid **1**, 4-nitrobenzaldehyde **2** and alkyl or aryl isocyanides **3** in water at 75°C (Scheme 1).

The one-pot three component condensation reactions of *N*,*N*′-dimethylbarbituric acid **1**, 4-nitrobenzaldehyde **2** and alkyl or aryl isocyanides **3** proceeded spontaneously at 75°C in water and were complete after several minutes. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structure of compounds **4a–e** was deduced from elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

The formation of these heterocycles can be rationalized by initial formation of a conjugated electron-deficient heterodiene by standard Knoevenagel condensation of the aldehyde **2** and the *N*,*N*′-dimethylbarbituric acid **1**,[15,16] followed by a [1+4] cycloaddition reaction[10–14,17–20] or a Michael-type[16,21] addition reaction with isocyanide **3** to afford an iminolactone **5**, which then isomerizes to yield the furo[2,3-*d*]pyrimidines (**4a–e**) (Scheme 2).

In conclusion, we have shown that the three component condensation reactions of *N*,*N*′-dimethylbarbituric acid **1**, 4-nitrobenzaldehyde **2** and an alkyl or aryl isocyanide **3** efficiently occurs in water without needing a catalyst at 75°C in a few minutes, providing a convenient and efficient synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. The one-pot nature and the use of the water as an eco-compatible reaction solvent makes it an interesting alternative to multi-step approaches.[2]

2. Experimental

2.1. Typical procedure for the preparation of 5-*p*-nitrophenyl-6-*tert*-butylamino-1,3-dimethylfuro[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (4a)

To a magnetically stirred mixture of *N*,*N*′-dimethylbarbituric acid (0.172 g, 1.1 mmol) and 4-nitrobenzalde-

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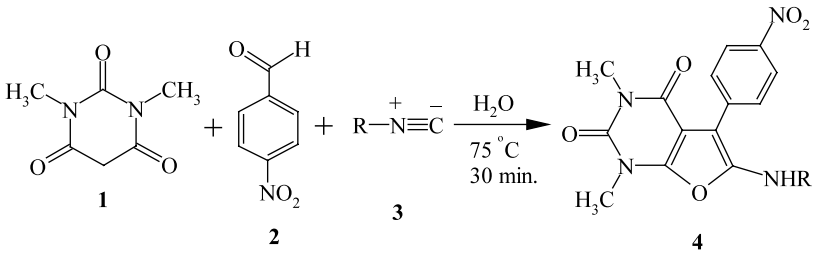

4	R	Yield (%)
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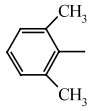
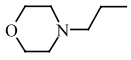
b		89
c		81
d		73
e		74

Scheme 1.

hyde (0.151 g, 1 mmol) in water (20 mL) was added *tert*-butyl isocyanide (0.084 g, 1 mmol) via a syringe and heated for 30 min at 75°C. After cooling to room temperature, the resulting red precipitate was filtered and washed with water (50 mL).

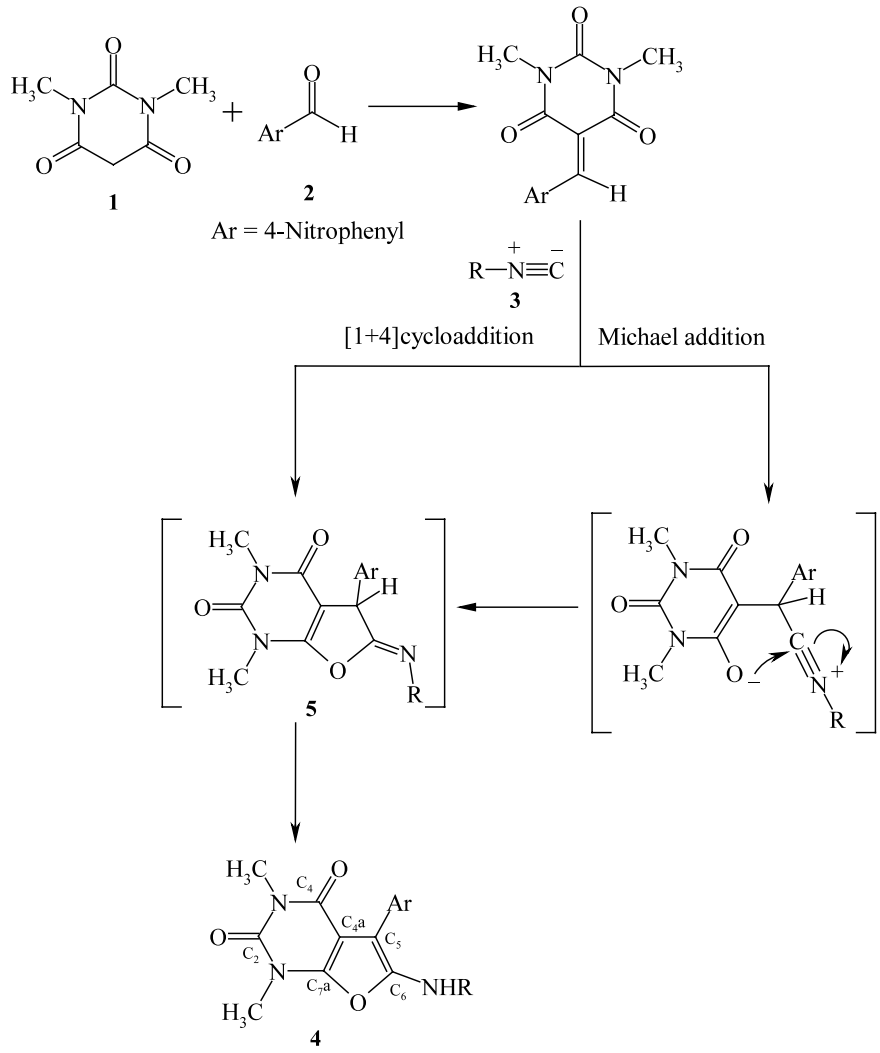
The solid residue was dried and crystallized from CH_2Cl_2–EtOH (1:2) to yield **4a** as red crystals (0.286 g, 77%). Mp 179–181°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3360 (N–H), 1708 and 1653 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.19 (9 H, s, $C(CH_3)_3$), 3.38 and 3.57 (6 H, 2 s, 2 NCH_3), 3.51 (1 H, s, NH), 7.84 and 8.21 (4 H, 2 d, $^3J_{HH}=8.7$ Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 28.35 and 29.49 (2 NCH_3), 30.24 (CMe_3), 54.83 (CMe_3), 95.01 (C_4a), 109.37 (C_5), 123.24 (C_{meta}-NO_2), 130.20 (C_{ortho}-NO_2), 137.81 (C_{para}-NO_2), 146.43 (C-NO_2), 148.94 (C_6), 150.30 (C_7a), 151.90 (C_2), 158.10 (C_4). MS (*m*/*z*,%) 372 (M^+, 72), 316 (98), 295 (83), 231 (24), 187 (90), 141 (29), 57 (100). Anal. calcd for $C_{18}H_{20}N_4O_5$ (372.41): C, 58.05; H, 5.41; N, 15.04%. Found: C, 57.90; H, 5.46; N, 14.92%.

2.2. 5-*p*-Nitrophenyl-6-cyclohexylamino-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b)

Red crystals (0.355 g, 89%). Mp 180–181°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3255 (N–H), 1708 and 1661 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.18–1.96 (10 H, m, 5 CH_2), 3.26 (1 H, m, N–CH), 3.38 and 3.56 (6 H, 2 s, 2 NCH_3), 3.85 (1 H, d, $^3J_{HH}=6.9$ Hz, NH), 7.78 and 8.20 (4 H, 2 d, $^3J_{HH}=8.7$ Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.71, 25.44 and 33.98 (5 CH_2), 28.39 and 29.52 (2 NCH_3), 55.06 (N–CH), 95.47 (C_4a), 101.36 (C_5), 123.47 (C_{meta}-NO_2), 129.47 (C_{ortho}-NO_2), 138.04 (C_{para}-NO_2), 145.87 (C-NO_2), 149.93 (C_6), 150.14 (C_7a), 150.96 (C_2), 158.07 (C_4). MS (*m*/*z*,%) 398 (M^+, 100), 316 (38), 288 (47), 259 (42), 187 (50), 141 (26), 110 (25), 83 (65), 67 (68), 55 (98). Anal. calcd for $C_{20}H_{22}N_4O_5$ (398.45): C, 60.28; H, 5.56; N, 14.06%. Found: C, 60.36; H, 5.49; N, 14.19%.

2.3. 5-*p*-Nitrophenyl-6-benzylamino-1,3-dimethylfuro-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4c)

Orange crystals (0.329 g, 81%). Mp 201–202°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3280 (N–H), 1706 and 1664 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 3.37 and 3.52 (6 H, 2 s, 2 NCH_3), 4.36 (1 H, t, $^3J_{HH}=4.9$ Hz, NH), 4.37 (2 H, d, $^3J_{HH}=4.9$ Hz, CH_2), 7.27–7.32 (5 H, m, C_6H_5), 7.67 and 8.15 (4 H, 2 d, $^3J_{HH}=8.4$ Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 28.41 and 29.46 (2 NCH_3), 50.22 (CH_2), 95.60 (C_4a), 100.62 (C_5), 123.52, 127.73, 128.06, 128.91, 129.45, 137.67, 137.91 and 146.00 (arom.), 149.92 (C_6), 150.10 (C_7a), 150.86 (C_2), 158.07 (C_4). MS (*m*/*z*,%) 406 (M^+, 54), 315 (95), 258 (53), 187 (15), 141 (13), 91 (100). Anal. calcd for $C_{21}H_{18}N_4O_5$ (406.43): C, 62.06; H, 4.46; N, 13.78%. Found: C, 62.19; H, 4.51; N, 13.93%.



Scheme 2.

2.4. 5-*p*-Nitrophenyl-6-(2,6-dimethylphenylamino)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d)

Orange crystals (0.307 g, 73%). Mp 200–201°C. IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H), 1701 and 1658 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 2.16 (6 H, s, 2 CH_3), 3.37 and 3.44 (6 H, 2 s, 2 NCH_3), 5.76 (1 H, s, NH), 6.93–6.98 (3 H, m, $C_6H_3Me_2$), 7.75 and 8.08 (4 H, 2 d, $^3J_{HH}=8.6$ Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 18.36 (2 CH_3), 28.44 and 29.53 (2 NCH_3), 95.47 (C_4a), 103.30 (C_5), 123.01, 124.85, 129.13, 129.63, 130.76, 136.83, 136.96 and 146.05 (arom.), 146.16 (C_6), 150.11 (C_7a), 151.19 (C_2), 158.08 (C_4). MS (m/z,%) 420 (M^+, 100), 348 (24), 320 (15), 288 (23), 131 (55), 77 (47). Anal. calcd for $C_{22}H_{20}N_4O_5$ (420.45): C, 62.84; H, 4.79; N, 13.32%. Found: C, 62.70; H, 4.88; N, 13.47%.

2.5. 5-*p*-Nitrophenyl-6-(2-morpholinoethylamino)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e)

Deep violet crystals (0.318 g, 74%). Mp 186–187°C. IR (KBr) (ν_{max}, cm^{-1}): 3275 (N–H), 1704 and 1671 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 2.46 (4 H, m, CH_2NCH_2), 2.58 (2 H, t, $^3J_{HH}=5.7$ Hz, NCH_2), 3.30 (2 H, d of t, $^3J_{HH}=5.7$ Hz, $^3J_{HH}=5.5$ Hz, $NHCH_2$), 3.39 and 3.57 (6 H, 2 s, 2 NCH_3), 3.66 (4 H, m, CH_2OCH_2), 4.95 (1 H, t, $^3J_{HH}=4.8$ Hz, NH), 7.80 and 8.23 (4 H, 2 d, $^3J_{HH}=8.7$ Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 28.45 and 29.49 (2 NCH_3), 41.70 ($NHCH_2$), 53.31 (CH_2NCH_2), 57.12 (NCH_2), 66.98 (CH_2OCH_2), 95.66 (C_4a), 98.33 (C_5), 123.57 (C_{meta}-NO_2), 129.15 (C_{ortho}-NO_2), 138.14 (C_{para}-NO_2), 145.74 (C-NO_2), 150.10 (C_6), 150.66 (C_7a), 150.97 (C_2), 158.09 (C_4). MS (m/z,%) 429 (M^+, 16), 288 (10), 114 (33), 100 (98), 87 (100), 70 (26), 42 (88). Anal. calcd for $C_{20}H_{22}N_5O_6$ (429.47): C, 55.93; H, 5.39; N, 16.30%. Found: C, 55.81; H, 5.48; N, 16.38%.

Acknowledgements

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