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Short Communication

Ionic Liquid Promoted One-Pot Synthesis of Furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

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Summary. The three-component condensation of aldehyde, *N*,*N*′-dimethylbarbituric acid and alkyl or aryl isocyanide afforded the corresponding furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in 1-butyl-3-methylimidazolium bromide as an ionic liquid in high yields at room temperature within several minutes.

Keywords. Multicomponent reaction; Isocyanide; Ionic liquid; Furo[2,3-*d*]pyrimidine; [*bmim*]Br.

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 and 2-aminofuran derivatives has received little attention, and only few procedures have been reported in literature [5–6]. During recent years, ionic liquids have attracted interest as environmentally benign reagents due to their favorable properties and a variety of catalytic reactions have been successful using ionic liquids [7]. The solvophobic properties of ionic liquids are able to generate an internal pressure and promote the association of the reactants in a solvent cavity during the activation process and accelerate a reaction. This property of ionic liquids is very efficient for multicomponent reactions (MCRs) in which the entropy of reaction is decreased in the transition state.

In continuation of our studies on the development of new routes for the synthesis of organic compounds using ionic liquids [8] and our interest in isocyanide-based MCRs [9], we developed the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones *via* the three-component condensation of *N*,*N*′-dimethylbarbituric acid (**1**), aldehyde

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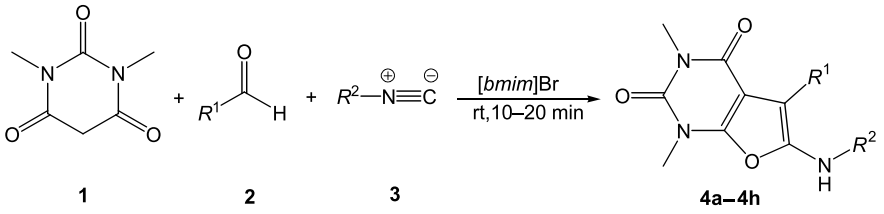

Scheme 1

2, and an alkyl or aryl isocyanide **3** in 1-butyl-3-methylimidazolium bromide ([*bmim*]Br) as the solvent and promotor at room temperature (Scheme 1).

Results and Discussion

As indicated in Table 1, the reaction of aldehydes with **1** and alkyl or aryl isocyanides afforded furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in [*bmim*]Br as a promoter in high yield within several minutes.

To explore the scope and limitations of this reaction, we studied the reactions of **1** and alkyl or aryl isocyanides with benzaldehydes bearing either electron-releasing or electron-withdrawing substituents. We found that the presence of electron-withdrawing functional groups is necessary for the formation of the desired product. On the contrary, with aromatic aldehydes carrying electron-releasing groups (such as 4-CH_3, or 4-OCH_3) products were obtained in poor yields.

To illustrate the need for [*bmim*]Br, the reaction of *p*-nitrobenzaldehyde, **1**, and cyclohexyl isocyanide was studied in the absence of [*bmim*]Br. The yield of product was only 60% at room temperature after 24 h. Thus, obviously [*bmim*]Br is an important component of the reaction.

One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. We were able to separate [*bmim*]Br from the reaction medium easily by washing with water and evaporating the solvent under vacuum, and reuse the ionic liquid for subsequent reactions.

In conclusion, we describe ionic liquids (ILs) as novel and recyclable solvents for the synthesis of highly functionalized 2-aminofuran derivatives *via* three component condensation of **1**, aldehyde, and alkyl or aryl isocyanide. This new pro-

Table 1. Synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in [*bmim*]Br

Entry	R^1	R^2	Product	Time/min	Yield/%
1	4-$O_2NC_6H_4$	Cyclohexyl	**4a**	10	90
2	4-$O_2NC_6H_4$	*tert*-Butyl	**4b**	10	85
3	4-$O_2NC_6H_4$	2,6-$(Me)_2C_6H_3$	**4c**	15	86
4	3-$O_2NC_6H_4$	Cyclohexyl	**4d**	15	75
5	3-$O_2NC_6H_4$	*tert*-Butyl	**4e**	15	78
6	3-$O_2NC_6H_4$	2,6-$(Me)_2C_6H_3$	**4f**	15	81
7	2-$O_2NC_6H_4$	Cyclohexyl	**4g**	20	40
8	C_6H_5	Cyclohexyl	**4h**	20	55

cedure offers several significant advantages, such as operational simplicity, mild reaction conditions, enhanced rates, improved yields, ease of isolation of products, recyclability, and the ecofriendly nature of the solvent, which makes it to an useful and attractive strategy for the synthesis of 2-aminofuran derivatives.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$ and *DMSO*-d_6 using *TMS* as internal standard. *N,N′*-Dimethylbarbituric acid, aldehydes, and isocyanides were purchased from Fluka and Merck and were used without purification.

General Procedure

To a solution of 0.15 g **1** (1 mmol), 1 mol aldehyde, and 1 mmol alkyl or aryl cyclohexyl isocyanide were added 0.3 g [*bmim*]Br. The resulting mixture was stirred for 10 min at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with H_2O ($2 \times 10\,cm^3$) and the solid residue was recrystallized from CH_2Cl_2/*n*-hexane (2/1) to give the products.

All the products (except **4d**, **4e**, **4f**, and **4g**) are known compounds, which were characterized by IR and ^{1}H NMR spectral data and their mps compared with literature data reports [9b, 9f].

6-(Cyclohexylamino)-1,3-dimethyl-5-(3-nitrophenyl)furo[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4d**, $C_{20}H_{22}N_4O_5$)

Red crystals (0.30 g, 75%); mp 160–162°C. IR (KBr): $\bar{\nu} = 3280$ (NH), 2930, 2856, 1705, 1660, 1528, 1341 cm^{-1}; MS: m/z (%) = 398 (M^+, 25), 316 (45), 299 (50), 288 (49), 258 (45), 242 (35), 187 (90), 141 (40), 67 (53), 55 (80), 41 (100); ^{1}H NMR ($CDCl_3$): $\delta = 1.23$–1.95 (m, $5CH_2$–cyclohexyl), 3.19 (m, CH–N–cyclohexyl), 3.40 (s, NCH_3), 3.50 (s, NH), 3.58 (s, NCH_3), 7.57–8.55 (m, H–Ar) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.65$, 25.44 (C–cyclohexyl), 28.33, 29.48 ($2NCH_3$), 33.89 (C–cyclohexyl), 55.54 (CH–N–cyclohexyl), 95.43, 103.71, 121.52, 123.66, 128.99, 132.40, 135.58, 148.07, 149.29, 150.21, 151.08, 158.13 ppm.

6-(tert-Butylamino)-1,3-dimethyl-5-(3-nitrophenyl)furo[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4e**, $C_{18}H_{20}N_4O_5$)

Orange crystals (0.29 g, 78%); mp 195–197°C. IR (KBr): $\bar{\nu} = 3281$ (NH), 2974, 1703, 1663, 1475, 1359 cm^{-1}; MS: m/z (%) = 372 (M^+, 20), 316 (90), 299 (60), 288 (30), 259 (55), 242 (50), 187 (95), 141 (100), 57 (95), 41 (95); ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (s, $C(CH_3)_3$), 3.29 (s, NH), 3.41, 3.59 (2s, $2NCH_3$), 7.56–8.65 (m, H–Ar) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.36$, 29.48 ($2NCH_3$), 30.23 ($C(CH_3)_3$), 54.77 ($C(CH_3)_3$), 95.02, 110.74, 122.00, 124.22, 128.89, 132.35, 136.04, 147.96, 148.37, 150.37, 151.95, 158.17 ppm.

6-(2,6-Dimethylphenylamino)-1,3-dimethyl-5-(3-nitrophenyl)furo[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4f**, $C_{22}H_{20}N_4O_5$)

Yellow crystals (0.34 g, 81%); mp 214–216°C (dec). IR (KBr): $\bar{\nu} = 32.84$ (NH), 2916, 1702, 1660, 1497, 1343 cm^{-1}; MS: m/z (%) = 420 (M^+, 100), 403 (63), 348 (15), 288 (30), 272 (15), 242 (15), 1387 (30), 77 (20), 53 (10); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.03$ (s, $2CH_3$), 3.21, 3.33 (2s, $2NCH_3$), 6.72 (s, NH), 6.80–8.15 (m, H–Ar) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.68$ ($2CH_3$) 28.42, 29.80 ($2NCH_3$), 94.70, 101.72, 121.27, 123.61, 123.88, 128.97, 130.96, 132.06, 135.90, 137.81, 146.48, 147.23, 150.16, 151.50, 158.08 ppm.

6-(Cyclohexylamino)-1,3-dimethyl-5-(2-nitrophenyl)furo[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4g**, $C_{20}H_{22}N_4O_5$)

Yellow crystals (0.16 g, 40%); mp 193–194°C (dec). IR (KBr): $\bar{\nu} = 3390$(NH), 2932, 2853, 1727, 1648, 1540, 1361 cm^{-1}; MS: m/z (%) = 398 (M^+, 5), 374 (7), 348 (10), 272 (100), 258 (35), 187 (30), 159 (95), 130 (95), 56 (20); ^{1}H NMR ($CDCl_3$): $\delta = 1.31$–2.05 (m, 5CH_2–cyclohexyl), 3.40 (s, 2NCH_3), 3.82 (m, CH–N–cyclohexyl), 6.65 (s, NH), 7.38–9.32 (m, H–Ar) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.50$, 25.31 (C-cyclohexyl), 28.28 (2NCH_3), 32.77 (C–cyclohexyl), 49.86 (CH–N–cyclohexyl), 93.63, 112.19, 118.46, 125.05, 130.54, 137.26, 144.76, 149.05, 151.52, 172.26 ppm.

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