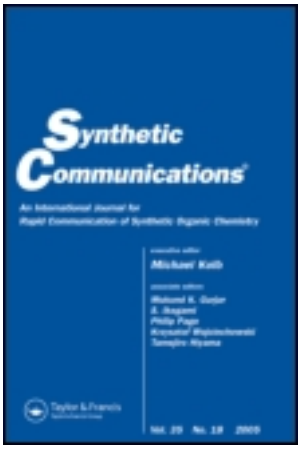

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

Green Synthesis of Pyrano[2,3-d]-pyrimidine Derivatives in Ionic Liquids

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Version of record first published: 20 Aug 2006.

To cite this article: Jing Yu & Hanqing Wang (2005): Green Synthesis of Pyrano[2,3-d]-pyrimidine Derivatives in Ionic Liquids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:24, 3133-3140

To link to this article: http://dx.doi.org/10.1080/00397910500282661

Synthetic Communications®, 35: 3133–3140, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500282661

Green Synthesis of Pyrano[2,3-*d*]-pyrimidine Derivatives in Ionic Liquids

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Abstract: Pyrano[2,3-*d*]pyrimidine derivatives were synthesized in high yields by a condensation reaction between arylmethylidenemalononitrile and barbituric acid using room-temperature ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([BMIm]BF_4) or 1-butylpyridinium tetrafluoroborate ([BPy]BF_4) as solvents under neutral conditions.

Keywords: Barbituric acid, green synthesis, ionic liquid, pyrano[2,3-*d*]pyrimidine

INTRODUCTION

Pyrano[2,3-*d*]pyrimidine derivatives are annelated uracils that have received considerable attention during the past years because of their wide range of biological activity. Compounds with these ring systems have diverse pharmacological activity such as antitumor, cardiotonic, hepatoprotactive, antihypertensive, antibronchitic, and antifungal activity.[1–4] Therefore, for the preparation of these complex molecules, large efforts have been directed

Received in Japan March 22, 2005
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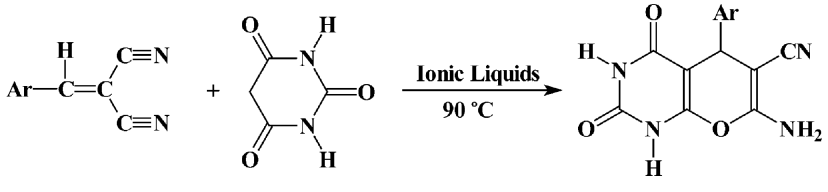
toward the synthetic manipulation of uracils. As a result, a number of reports have appeared in literature,[5] which usually require forcing conditions, long reaction times, and complex synthetic pathways. Thus, new routes for the synthesis of these molecules have attracted considerable attention in the search for a rapid entry to these heterocycles.

Room-temperature ionic liquids, especially those based on the 1-alkyl-3-methylimidazolium, have promise as attractive alternatives to conventional solvents. Besides their special characteristics,[6] they can even not only promote some organic reactions,[7] but also provide the chemoselectivity to some reaction processes[8] and simple and convenient isolation of product in catalytic reactions.[9] Especially in the condensation reactions with some nitrogen-containing compounds, the reaction rate could be greatly accelerated in ionic liquids as evidenced by many recent published works.[10–12] Our new approach reported herein involves the use of room-temperature ionic liquids as solvents for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives by condensation reaction between arylmethylidenemalononitrile and barbituric acid reaction under solvent-free conditions.

EXPERIMENTAL

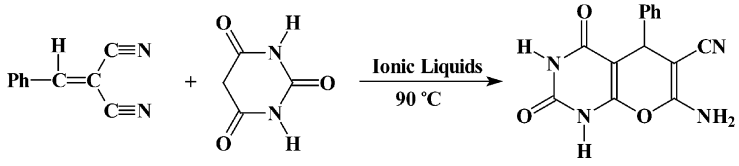
A Representative Procedure

Phenylmethylidenemalononitrile (5 mmol) and barbituric acid (5 mmol) were dissolved into 1.5 g of ionic liquid in a 50-mL round-bottom flask equipped with a magnetic stirrer, and the mixture was heated at 90°C for 3 h with vigorous stirring. After the reaction, the resulting solid product with pale yellow color was crushed, washed with water, filtered, and dried in vacuum to afford the primary product. A pure product was obtained by further recrystallization of the primary product with a mixture solvent containing water and DMF (yield: 84%) (Scheme 1). The characterization of the products is well known, therefore, only the basic identifications including FT-IR (IFS 120HR, Bruker), ^{1}H NMR (FT-80A, using TMS as internal standard), and melting-points measurements were conducted.



Scheme 1.

Table 1. Condensation reaction between phenylmethylidenemalononitrile and barbituric acid in different solvents



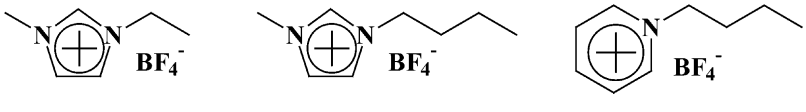
Entry	Solvents	Time (h)	Temp. (°C)	Yield (%)
1	$[BMIm]BF_4$	3	90	84
2	$[EMIm]BF_4$	3	90	72
3	$[BPy]BF_4$	3	90	65
4	Toluene	10	90	0
5[a]	$ClCH_2CH_2Cl$	10	90	0
6	$[BMIm]BF_4$	1	90	57
7	$[BMIm]BF_4$	3	60	46

[a]The reaction was performed at reflux temperature.

RESULTS AND DISCUSSION

We have performed condensation reaction between arylmethylidenemalononitrile and barbituric acid in ionic liquids as well as in organic solvents to compare the efficiency of ionic liquids, and the results are presented in Table 1. The choice of ionic liquids was motivated by their wide use, and they are therefore the most widely available (see Scheme 2).

Initial experimentation was undertaken in $[BMIm]BF_4$ using phenylmethylidenemalononitrile and barbituric acid as substrates under an air atmosphere, the mixture was heated at 90°C for 3 h (Table 1, entry 1). After reaction, the reaction vessel was cooled to room temperature, and the solid compound obtained was recrystallized from a water/DMF mixture solvent to give ***a*** (1.19 g, 84%) mp 210–212°C. The structure was confirmed as ***a*** from the spectroscopic data and elemental analysis. The IR spectra exhibited sharp bands at 3268 cm^{-1} (NH_2) and 2179 cm^{-1} (CN). The NMR spectra showed



$[EMIm]BF_4$ **$[BMIm]BF_4$** **$[BPy]BF_4$**

Scheme 2. Ionic liquids used in the present work.

the absence of the methylene proton of the barbituric acid and the presence of a proton at 7.14 (s, 2H, NH_2). The other signals appeared at δ 7.55–7.78 (m, 5H, ArH), 11.19 (s, 1H, NH), and 12.21 (s, 1H, NH). Some other ionic liquids, such as 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm]BF_4) and 1-butylpyridinium tetrafluoroborate ([BPy]BF_4), also worked well, but the yields of ***a*** were slightly inferior as compared with that of [BMIm]BF_4 (Table 1, entries 2 and 3). No reaction could be observed at 90°C in organic solvents, such as toluene and 1, 2-dichloroethane (entries 4 and 5). These results clearly show the determining role of ionic liquid in these reactions as compared to organic solvents. The subsequent condition-optimization experiments revealed that both the 3 h time and 90°C temperature were necessary to complete the reaction. When 1 h or 60°C was used, the pyrano[2,3-*d*]pyrimidine yield only reached 57% and 46%, respectively (entries 6 and 7).

In subsequent studies, we used [BMIm]BF_4 to promote the condensation reaction of various aromatic aldehydes with barbituric acid, and the results are summarized in Table 2. Analogous with procedure of ***a***, compounds ***b***–***f*** could be synthesized by utilizing corresponding aromatic aldehydes and barbituric acid, and the structures were confirmed from the spectroscopic data and elemental analysis (Table 2).

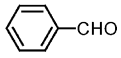
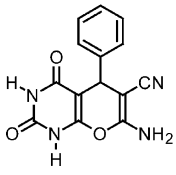
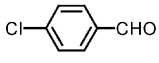
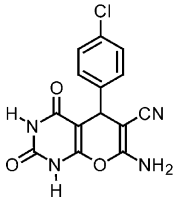
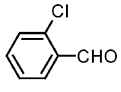
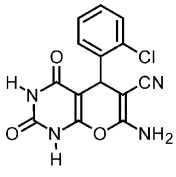
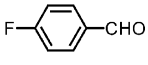
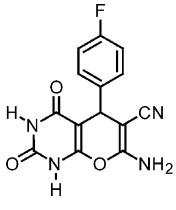
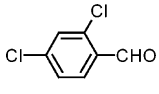
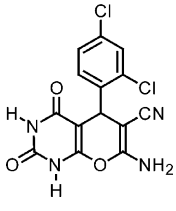
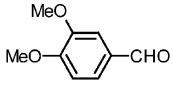
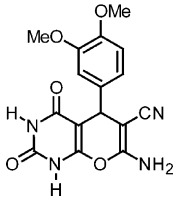
According the structure of product, the mechanism of the condensation reaction most likely involves a Michael addition of arylmethylidenemalononitrile to barbituric acid; the resulting product **(1)** readily undergoes an interconvertible isomerization to form an enol **(2)**; an intramolecular cycloaddition between hydoxy (–OH) and CN then occurred to afford an imine **(3)**, which could be isomerized to give the desired product **(4)** (Figure 1).

One of the main aims of using ionic liquids as solvents was to study the possibility of its recyclability and reusability. Because [BMIm]BF_4 is an air- and moisture-stable ionic liquid, it could be recovered from the resulting aqueous solution by means of removal of volatile components under vacuum conditions (at 80°C in 12-mm Hg for 2 h). It was reused for the condensation reaction between phenylmethylidenemalononitrile and barbituric acid. The reaction was carried out three times in consecutive runs with only a slight decrease in isolated yields (Table 2, entry 7).

Analytical Data for Our Products

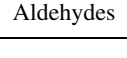
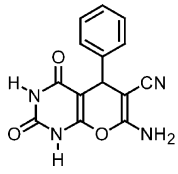
a: Yield: 84%, mp 224–225°C (lit.[13] 225°C); ^{1}H NMR (DMSO-d_6) δ: 4.25 (s, 1H, CH), 7.14 (s, 2H, NH_2), 7.55–7.78 (m, 5H, ArH), 11.19 (1H, NH), 12.21 (s, 1H, NH); IR (KBr) ν: 3380, 3300, 3268, 3085, 2179, 1710, 1671, 1633 cm^{-1}. Anal. calcd. for $C_{14}H_{10}N_4O_3$ (M: 282.258): C, 59.57; H, 3.57; N, 19.85; found C, 59.76; H, 3.44; N, 20.01.

Table 2. Synthesis of pyrano[2,3-*d*]pyrimidine derivatives in $[BMIm]BF_4$

Entry	Aldehydes	Products	Number	Time (h)	Yield (%)	Mp. (°C)
1			***a***	3	84	224–225
2			***b***	3	92	242–244
3			***c***	3	94	215–216
4			***d***	3	90	225–226
5			***e***	5	88	201–203
6			***f***	5	95	210–212

(*continued*)

Table 2. Continued

Entry	Aldehydes	Products	Number	Time (h)	Yield (%)	Mp. (°C)
7[a]			***a***	3	82	210–212

[a]Reused a third time.

b: Yield: 92%, mp 242–244°C; ^{1}H NMR (DMSO-d_6) δ: 4.55 (s, 1H, CH), 7.17 (s, 2H, NH_2), 7.30–7.78 (m, 4H, ArH), 11.09 (1H, NH), 12.18 (s, 1H, NH); IR (KBr) ν: 3381, 3301, 3188, 2979, 2205, 1722, 1679, 1641, 1600 cm^{-1}. Anal. calcd. for $C_{14}H_9ClN_4O_5$ (M: 316.703): C, 53.09; H, 2.86; N, 17.69; found C, 53.20; H, 2.73; N, 17.93.

c: Yield: 94%, mp 215–216°C; ^{1}H NMR (DMSO-d_6) δ: 4.74 (s, 1H, CH), 7.08 (s, 2H, NH_2), 7.28–7.49 (m, 4H, ArH), 11.17 (1H, NH), 12.26 (s, 1H, NH); IR (KBr) ν: 3469, 3423, 3375, 3312, 2831, 2202, 1715, 1667 cm^{-1}. Anal. calcd. for $C_{14}H_9ClN_4O_5$ (M: 316.703): C, 53.09; H, 2.86; N, 17.69; found C, 53.31; H, 2.78; N, 17.49.

d: Yield: 90%, mp 225–226°C; ^{1}H NMR (DMSO-d_6) δ: 4.26 (s, 1H, CH), 7.11 (s, 2H, NH_2), 7.47–7.59 (m, 4H, ArH), 11.09 (1H, NH), 12.14 (s, 1H, NH); IR (KBr) ν: 3389, 3307, 3260, 3181, 2200, 1722, 1677, 1644 cm^{-1}. Anal.

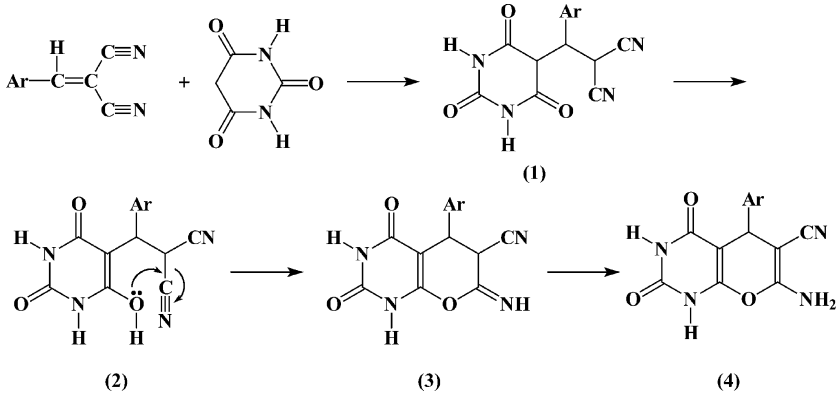


Figure 1. Possible mechanism for the present synthesis of pyrano[2,3-*d*]pyrimidine.

calcd. for $C_{14}H_9FN_4O_3$ (300.249): C, 56.00; H, 3.02; N, 18.66; found C, 56.17; H, 2.83; N, 18.89.

e: Yield: 88%, mp 201–203°C; ^{1}H NMR (DMSO-d_6) δ: 4.73 (s, 1H, CH), 7.20 (s, 2H, NH_2), 7.54–7.75 (m, 3H, ArH), 11.16 (1H, NH), 12.20 (s, 1H, NH); IR (KBr) ν: 3387, 3301, 3253, 3181, 3074, 2190, 1718, 1671, 1640 cm^{-1}. Anal. calcd. for $C_{14}H_8Cl_2N_4O_3$ (M: 351.148): C, 47.89; H, 2.30; N, 15.96; found C, 48.16; H, 2.19; N, 16.11.

f: Yield: 95%, mp 210–212°C; ^{1}H NMR (DMSO-d_6) δ: 3.86 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 4.20 (s, 1H, CH), 7.10 (s, 2H, NH_2), 7.60–7.89 (m, 3H, ArH), 11.43 (1H, NH), 12.22 (s, 1H, NH); IR (KBr) ν: 3384, 3228, 3150, 3079, 2228, 1743, 1699, 1660 cm^{-1}. Anal. calcd. for $C_{16}H_{14}N_4O_5$ (M: 342.310): C, 56.14; H, 4.12; N, 16.37; found C, 56.39; H, 3.98; N, 16.19.

CONCLUSION

In summary, ionic liquids proved to be excellent media and catalysts for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives from arylmethylidenemalononitrile and barbituric acid. Many pyrano[2,3-*d*]pyrimidines could be obtained in good to excellent yields. The ionic liquid [BMIm]BF_4 can be recovered conveniently and reused three times, although with a slight loss of activity. Moreover, this methodology offers significant improvements with regard to yield of products, simplicity in operation, and green aspects (avoiding toxic catalysts and solvents). These advantages of this novel catalytic system are expected to contribute to the development of more benign synthesis of pyrano[2,3-*d*]pyrimidine derivative.

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