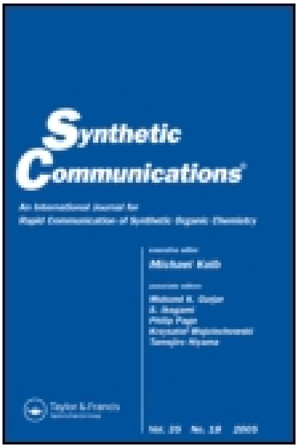
This article was downloaded by: [University of Wyoming Libraries]
On: 01 October 2013, At: 07:52
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Organic Reactions in Ionic Liquids: Ionic Liquid Ethylammonium Nitrate-Promoted Knoevenagel Condensation of Meldrum's Acid With Aromatic Aldehydes

Yi Hu [a] [b] , Ping Wei [a] , He Huang [a] , Zhang-Gao Le [c] & Zhen-Chu Chen [b]

[a] College of Life Science and Pharmaceutical Engineering, Nanjing University of Technology, Nanjing, China

[b] Department of Chemistry, Zhejiang University (Xi Xi Campus), Hangzhou, China

[c] Department of Applied Chemistry, East China Institute of Technology, Fuzhou, China

Published online: 21 Aug 2006.

To cite this article: Yi Hu , Ping Wei , He Huang , Zhang-Gao Le & Zhen-Chu Chen (2005) Organic Reactions in Ionic Liquids: Ionic Liquid Ethylammonium Nitrate-Promoted Knoevenagel Condensation of Meldrum's Acid With Aromatic Aldehydes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:23, 2955-2960

To link to this article: http://dx.doi.org/10.1080/00397910500278362

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

Synthetic Communications®, 35: 2955–2960, 2005
Copyright © Taylor & Francis, Inc.
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500278362

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

Organic Reactions in Ionic Liquids: Ionic Liquid Ethylammonium Nitrate–Promoted Knoevenagel Condensation of Meldrum's Acid With Aromatic Aldehydes

Yi Hu
College of Life Science and Pharmaceutical Engineering,
Nanjing University of Technology, Nanjing, China and Department
of Chemistry, Zhejiang University (Xi Xi Campus), Hangzhou, China

Ping Wei and He Huang
College of Life Science and Pharmaceutical Engineering,
Nanjing University of Technology, Nanjing, China

Zhang-Gao Le
Department of Applied Chemistry, East China Institute of Technology,
Fuzhou, China

Zhen-Chu Chen
Department of Chemistry, Zhejiang University (Xi Xi Campus),
Hangzhou, China

Abstract: The Knoevenagel condensation of Meldrum's acid with aromatic aldehydes proceeded efficiently in a reusable ionic liquid, ethylammonium nitrate, at room temperature in the absence of any catalyst with high yields.

Keywords: Aromatic aldehydes, ionic liquids, Knoevenagel condensation, Meldrum's acid

Received in Japan March 27, 2005

Address correspondence to Yi Hu, Department of Chemistry, Zhejiang University (Xi Xi Campus), Hangzhou, 310028, China. E-mail: amit-129@hotmail.com

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

The reactivity of the Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione) as a methylene active compound was explored about 40 years after its preparation, when the structure was correctly attributed by Davidson et al.,[1] who assigned the acidic proton to the central carbon. Its high acidity is still a subject of study.[2] It is known that Meldrum's acid undergoes standard Knoevenagel condensation with aromatic aldehydes to furnish the corresponding arylidene derivatives, which are important intermediates in organic synthetic chemistry and used as versatile substrates for different kinds of reactions.[3,4] The Knoevenagel condensation of Meldrum's acid with aromatic aldehydes is generally catalyzed by bases, such as pyridine,[1,5] or by piperdine/glacial acetic acid in benzene with water removal,[6] often using an excess of aldehyde to minimize the undesired formation of a bis adduct resulting from Michael addition with a second molecular of the methylene component.[3c,6a,7] Uncatalyzed reactions were reported in the literature[8] using DMF or DMSO as solvents, which are toxic, teratogenic, suspected carcinogens, and difficult to reuse. After long reaction times at room temperature, these gave mixtures of one (mono) condensation product and a Michael addition product for some aromatic aldehydes. Recently, Shi et al.[9] and Bigi et al.[4] reported this uncatalyzed condensation reaction performed in DMF and water respectively. The reactions need energy supply and sometimes only moderate yields were obtained. Besides, Lewis acid catalysts,[10] microwave irradiation,[11] ultrasound irradiation,[6] and melt reaction[12] were applied to facilitate this condensation reaction. Considering the importance of the product, arylmethylene isopropylidene malonate, we think it is still significant to develop more facile and efficient methods with environmentally sound technologies to prepare these compounds.

In recent years ionic liquids are emerging as potential "greener" alternatives to volatile organic solvents[13] and they have been used as environmentally benign media for many important organic reactions.[14] To date, some reports have shown the Knoevenagel condensation could be performed more efficiently using various catalysts in ionic liquids than the traditional methods.[15] Previously, we have also reported an effective Knoevenagel condensation catalyzed by ethylenediammonium diacetate in ionic liquids [Bmim]BF_4 or [Bmim]PF_6.[16] In continuation of our interest in using ionic liquids as a recyclable, ecofriendly reaction medium in the Knoevenagel condensation, we found that Knoevenagel reaction of Meldrum's acid with aromatic aldehydes occurred in ionic liquid ethylammonium nitrate (EAN) without any added catalyst. Shingare et al. reported a reaction of pyrazolone with aromatic aldehydes in ethylammonium nitrate.[17]

First, we investigated the efficacy of EAN compared to the most commonly used ionic liquids, [Bmim]PF_6 and [Bmim]BF_4 ([Bmim] = 1-butyl-3-methylimidazolium); some organic solvents; and water by the model condensation between *p*-N,N-dimethylaminobenzaldehyde and Meldrum's acid. The experimental results summarized in Table 1 showed that the ionic liquid, EAN, was truly comparable with the other traditional

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

Table 1. Condensation of *p*-N,N-dimethylaminobenzaldehyde with Meldrum's acid in different solvents

Entry[a]	Solvent	Yields (%)[b]
1	EAN	95
2	$[Bmim]PF_6$	41
3	$[Bmim]BF_4$	35
4	Water	33
5	Ethanol	18
6	Benzene	65.2[c]
7	DMF	81[d]

[a] All reactions were run with *p*-N,N-dimethylaminobenzaldehyde (2 mmol) and Meldrum's acid (2 mmol) in 2 ml of solvent at room temperature for half an hour.

[b] Isolated yield.

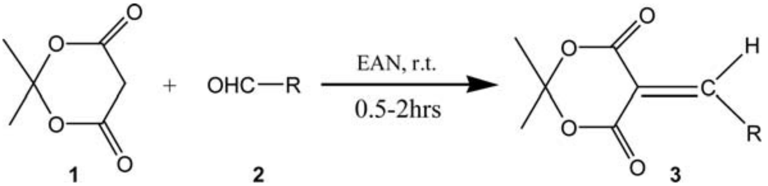
[c] Literature[5b] reported yield obtained in refluxing benzene catalyzed by piperdine/glacial acetic acid.

[d] Literature[8] reported yield obtained after 1 h at 80°C in DMF.

solvents, $[Bmim]PF_6$ and $[Bmim]BF_4$, with the advantage of rate acceleration and increase of yield. Obviously, EAN played a dual role as solvent and promoter in this reaction.

Next, the scope of the Knoevenagel condensation of Meldrum's acid with various aromatic aldehydes in the ionic liquid EAN was investigated (Scheme 1). The results are summarized in Table 2. The products were characterized by melting points, ^1H NMR, and IR, which were consistent with the literature data.

As can be seen from Table 2, this procedure was found to be general and applicable to the aromatic aldehydes bearing various substituents such as choloro, nitro, methoxyl, hydroxyl, N,N′-dimethylamino, and so forth. It is noteworthy that aromatic aldehydes bearing electron-donating groups reacted more easily compared with those containing electron-withdrawing groups, which is different from the previous literature.[6,8,9] The reaction of



Scheme 1.

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

Table 2. Condensation of Meldrum's acid with aromatic aldehydes in EAN

Entry[a]	R	Time (h)	Product	Yield[b] (%)	Mp[c] (°C)	Lit. mp (°C)
1	C_6H_5	1	**3a**	90	83–84	82–83[6]
2	p-$Me_2NC_6H_4$	0.5	**3b**	97	163–164	162–164[8]
3	p-$MeOC_6H_4$	1	**3c**	96	124–125	126[5b]
4	p-OHC_6H_4	1	**3d**	95	194–195	192–194[8]
5	3,4-$(OCH_2)C_6H_3$	1	**3e**	92	166–167	167–169[8]
6	p-ClC_6H_4	2	**3f**	92	161–162	162[10]
7	p-$NO_2C_6H_4$	2	**3g**	94	214–215	217[5b]
8	o-$NO_2C_6H_4$	2	**3h**	93	117–118	119[5b]
9	2-Furyl	2	**3i**	80	90–91	92[5b]
10	$C_6H_5CH{=}CH$	1	**3j**	91	108–109	108[5b]
11	p-$Me_2NC_6H_4$	0.5	**3b**	95[d]	163–164	
12	p-$Me_2NC_6H_4$	0.5	**3b**	97[e]	163–164	

[a] All reactions were run with Meldrum's acid (2 mmol) and aromatic aldehyde (2 mmol) in 2 ml of EAN at room temperature.

[b] Isolated yields.

[c] Melting points are uncorrected.

[d,e] Second and third recycling of EAN, respectively.

2-furancarboxaldehyde (Entry 9) and the aromatic α,β-unsaturated aldehyde, cinnamic aldehyde (Entry 10), with Meldrum's acid also could be completed with high yields. Unfortunately, as simple as this reaction is, we could not obtain satisfactory results when it was applied to aliphatic aldehydes and ketones under the same reaction conditions. In addition, the ionic liquid could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Entries 11 and 12).

In conclusion, we have demonstrated that the Knoevenagel condensation of Meldrum's acid with aromatic aldehydes can be effectively performed at room temperature in the ionic liquid EAN. The present method has many obvious advantages compared to previous methods, including no need for any catalyst, being environmentally more benign, the easy of product isolation, the simplicity of methodology, the higher yield, the generality, and the potential for recycling of ionic liquid. We have shown the ionic liquids play a dual role as solvent and promoter in this reaction and gives a simpler system—a good example of green chemistry.

EXPERIMENTAL

Melting points were determined on digital melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Vector22 (Brucker), and ^1H NMR spectra were recorded on a Bruker 400-MHz spectrometer using $CDCl_3$

as the solvent with TMS as an internal standard. The ionic liquids [Bmim]PF_6 and [Bmim]BF_4 were synthesized according to the literature,[18] and ethylammonium nitrate (EAN) was synthesized according to the literature.[19]

General Procedure for the Knoevenagel of Meldrum's Acid with Aromatic Aldehydes

Meldrum's acid **1** (2 mmol) and aromatic aldehyde **2** (2 mmol) were dissolved in ionic liquid EAN (2 ml). The reaction mixture was stirred at room temperature for 0.5 to 2 h, and the reaction was monitored by TLC. Upon completion of the reaction, all the insoluble material in the reaction mixture was filtered and washed with water to give the desired products **3** in high yields with essential purity. After isolation of the product, the remainder of the ionic liquids ENA was dried for 4 h under vacuum at 50°C. The next run was performed under identical reaction conditions.

ACKNOWLEDGMENTS

This work is supported by the Natural Sciences Foundation of China (No: 20336010), and the State Key Basic Research and Development Project of China (No: 2003CB7160004).

REFERENCES

1. Davidson, D.; Bernhard, S. *J. Am. Chem. Soc.* **1948**, *70*, 3426.
2. Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974.
3. For reviews see (a) Chen, B.-C. *Heterocycles* **1991**, *32*, 529; (b) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345; (c) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p. 341.
4. Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203.
5. Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897.
6. (a) Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347; (b) Scuster, P. O.; Polansky, E.; Wessely, F. *Monatsch. Chem.* **1964**, *95*, 53.
7. Liu, H. M.; Liu, H. L.; Yuan, Y. J.; Tang, R. X.; Ji, S. J. *Chin. J. Org. Chem.* **2003**, *23*, 1159.
8. Hedge, J. A.; Kruse, C. W.; Snyder, H. R. *J. Org. Chem.* **1961**, *26*, 3166.
9. Shi, D. Q.; Wang, Y. C.; Lu, Z. S.; Dai, G. Y. *Synth. Commun.* **2000**, *30*, 713.
10. Rao, P. S.; Venkataratnam, R. V. *India J. Chem. B* **1993**, *32*, 484.
11. (a) Abdallah-El, A. S.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258; (b) Huang, Z. Z.; Wu, L. L.; Huang, X. *Hecheng Huaxue* **1998**, *6*, 184.
12. Kaupp, G.; Naimi-Jamal, M. R.; Schmeyers, J. *Tetrahedron* **2003**, *59*, 3753.

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013

13. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Edit.* **2000**, *39*, 3772; (c) Sheldon, R. *Chem. Commum.* **2001**, 2399; (d) Jairton, D.; Robeerto, F.; Paulo, A. Z. S. *Chem. Rev.* **2002**, *102*, 3667; (e) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal Today* **2002**, *74*, 157.
14. Wasserscheid, P.; Welton, T., Eds. Ionic Liquids in Synthesis. VCH Wiley: Weinheim, Germany, 2002.
15. (a) Morrison, D. W.; Forbes, D. C.; Davis, J. H. *Tetrahedron Lett.* **2001**, *42*, 6053; (b) Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Lett.* **2002**, *43*, 1127; (c) Formentin, P.; Garcia, H.; Leyva, A. *J. Mol. Catal. A: Chem.* **2004**, *214*, 137; (d) Khan, F. A.; Dash, J.; Satapathy, R.; Upadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 3055.
16. Su, C.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* **2003**, 555.
17. Hangarge, R. V.; Jarikote, V.; Shingare, M. S. *Green Chem.* **2002**, *4*, 266.
18. Owens, G. S.; Abu-Omer, M. M. *J. Mol. Catal. A: Chem.* **2002**, *187*, 215.
19. Turmine, M.; Duviver, S.; Mayaffre, A.; Letellier, P. *J. Phys. Chem. B* **2003**, *107*, 1256.

Downloaded by [University of Wyoming Libraries] at 07:52 01 October 2013