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Ionic Liquid as Catalyst and Reaction Medium. The Dramatic Influence of a Task-Specific Ionic Liquid, [bmIm]OH, in Michael Addition of Active Methylene Compounds to Conjugated Ketones, Carboxylic Esters, and Nitriles

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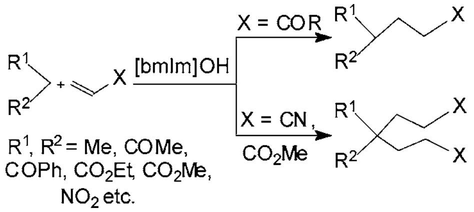
ABSTRACT



A task-specific ionic liquid, [bmIm]OH, has been introduced as a catalyst and as a reaction medium in Michael addition. Very interestingly, although the addition to α,β-unsaturated ketones proceeds in the usual way, giving the monoaddition products, this ionic liquid always drives the reaction of open-chain 1,3-dicarbonyl compounds with α,β-unsaturated esters and nitriles toward bis-addition to produce exclusively bis-adducts in one stroke.

Ionic liquids have attracted increasing interest in the context of green synthesis in recent times. Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility,[1] today they have marched far beyond this border, showing their significant role in controlling the reaction as catalysts.[1c,2] The first successful use of an ionic liquid, dialkylimidazolium chloroaluminate, as a catalyst in Friedel−Crafts acylations was reported in 1986.[2a] However, moisture sensitivity and decomposition of this chloroaluminate salt under normal atmospheric conditions are two major drawbacks to its practical use. Thus, a number of similar ionic liquids have been developed subsequently by replacement of chloroaluminate with anionic species such as tetrafluoroborate and hexafluorophosphate.[1c] As a part of our program to explore the full potential of ionic liquids in chemical transformations, we have already demonstrated the very efficient role of ionic liquids as catalysts[3] and reagents[4] in various reactions. In this letter, we report the dramatic

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(1) (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73. (e) Yao, Q. *Org. Lett.* **2002**, *4*, 2197. (f) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. *Org. Lett.* **2003**, *5*, 55. (g) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004**, *69*, 1419. (h) Gu, D.-G.; Ji, S.-J.; Jiang, Z.-Q.; Zhou, M.-F.; Loh, T.-P. *Synlett* **2005**, 959.

(2) (a) Boon, J. A.; Levinsky, J. A.; Pflug, J. I.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480. (b) Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Lett.* **2002**, *43*, 1127. (c) Namboodiri, V. V.; Varma, R. S. *Chem. Commun.* **2002**, 342. (d) Sun, W.; Xia, C.-G.; Wang, H.-W.; *Tetrahedron Lett.* **2003**, *44*, 2409. (e) Qiao, K.; Yakoyama, C. *Chem. Lett.* **2004**, *33*, 472. (f) Akaiyama, T.; Suzuki, A.; Fuchibe, K. *Synlett.* **2005**, 1024.

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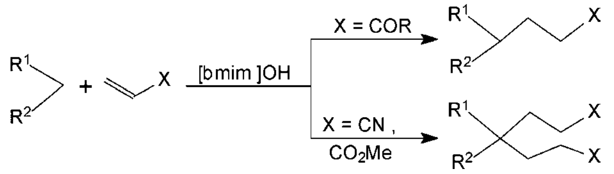
influence of a new tailor-made, task-specific, and stable ionic liquid, [bmIm]OH, in Michael addition.

The Michael addition is one of the most useful carbon−carbon bond-forming reactions and has wide synthetic applications in organic synthesis.[5] This reaction is traditionally catalyzed by strong bases that often lead to undesirable side reactions.[6] A variety of Lewis acids are found to catalyze this reaction, and these procedures are also not free from disadvantages.[7] Thus, a number of milder reagents such as Al_2O_3,[8a] K_2CO_3,[8b] rhodium complex,[8c] ruthenium complex,[8d] clay-supported nickel bromide,[8e] quaternary ammonium salt,[8f] and *N*-phenyltris(dimethylamino)iminophosphorane immobilized on polystyrene resin[8g] have been developed over the past few years. Recently, room-temperature ionic liquids, particularly [bmIm]BF_4, have been used as alternative green solvents to carry out the Michael addition using Ni(acac)$_2$[9a] and Cu(II) triflate[9b] as catalysts. However, we have discovered that a task-specific ionic liquid [bmIm]OH[10] efficiently promotes the Michael addition of 1,3-dicarbonyl compounds, cyano esters, and nitro alkanes to a variety of conjugated ketones, carboxylic esters, and nitriles without requiring any other catalyst and solvent. The dramatic influence of this catalyst in additions to certain conjugated alkenes is observed (Scheme 1).

Scheme 1



A variety of structurally diverse active methylene compounds underwent Michael additions with several α,*β*-unsaturated ketones, carboxylic esters, and nitriles by this procedure[11] to provide the corresponding adducts in high yields. The results are summarized in Table 1. Very interestingly, all open-chain 1,3-dicarbonyl compounds such as acetylacetone, ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate reacted with methyl vinyl ketone (entries 1, 4, 7, 15, 19, 22, 24) and chalcone (entries 9−12, 18) to give the usual monoaddition products, whereas the same reactions with methyl acrylate (entries 2, 6, 13, 16) or acrylonitrile (entries 3, 14, 17) provided exclusively bis-addition products. The use of 0.5 equiv or less of methyl acrylate or acrylonitrile in these reactions also did not produce any monoaddition product; only the bis-adducts were isolated in proportionate yields. On the other hand, use of excess methyl vinyl ketone did not furnish any bis-addition product under identical reaction conditions. Surprisingly, the reaction of nitroethane with methyl vinyl ketone, methyl acrylate, or acrylonitrile proceeded in the normal way, providing the monoadduct (entries 24−26). Although all the conventional reagents[6−9] produce the monoadduct in Michael additions with these conjugated alkenes, the formation of bis-adducts in one stroke with methyl acrylate and acrylonitrile is not unprecedented and was reported in one procedure using *trans*-hydrido(*n′*-*o*-enolato)ruthenium(II) complex.[8d] But, the serious drawbacks of using this ruthenium catalyst are a long reaction time (48−96 h) at 50−70 °C and relatively low yields (60−89%). However, in general, the great significance of this rather unusual bis-addition is the formation of two C−C bonds in one step; moreover, these adducts (entries 2, 3, 6, 13, 14, 16, 17) have great synthetic potential, as they contain several important functional groups. This ionic liquid, [bmIm]OH, is very successful in catalyzing

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(3) (a) Ranu, B. C.; Das, A.; Samanta, S. *J. Chem. Soc., Perkin Trans. 1* **2002,** 1520. (b) Ranu, B. C.; Dey, S. S. *Tetrahedron Lett*. **2003**, *44*, 2865. (c) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2003**, *59*, 2417. (d) Ranu, B. C.; Dey, S. S. *Tetrahedron* **2004**, *60*, 4183. (e) Ranu, B. C.; Das, A. *Aust. J. Chem*. **2004**, *57*, 605. (f) Ranu, B. C.; Jana, R.; Dey, S. S. *Chem. Lett*. **2004**, *33*, 274. (g) Ranu, B. C.; Jana, R. *Eur. J. Org. Chem*. **2005**, 775.

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(5) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4.

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(10) **Preparation of 1-Butyl-3-methylimidazolium Hydroxide [bmIm]OH.** This was prepared by modification of a reported related procedure.[13] Solid potassium hydroxide (2.3 g, 40 mmol) was added to a solution of [bmIm]Br (8.8 g, 40 mmol) in dry methylene chloride (20 mL), and the mixture was stirred vigorously at room temperature for 10 h. The precipitated KBr was filtered off, and the filtrate was evaporated to leave the crude [bmIm]OH as a viscous liquid that was washed with ether (2 × 20 mL) and dried at 90 °C for 10 h to prepare the pure ionic liquid for use. This was characterized by spectroscopic data: IR (neat) 3435, 3060, 1569, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, $J = 7.2$ Hz, 3H), 1.15−1.32 (m, 2H), 1.76−1.86 (m, 2H), 3.18−3.25 (bs, 1H), 4.00 (s, 3H), 4.23 (t, $J = 7.2$ Hz, 2H), 7.46 (d, $J = 1.5$ Hz, 1H), 7.59 (d, $J = 1.5$ Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (75 MHz) δ 13.1, 19.0, 31.8, 36.4, 49.3, 122.0, 123.5, 136.5; HRMS calcd for $C_8H_{16}N_2O$ ($M^+ - OH$) 139.2182, found 139.2355.

(11) **Representative Experimental Procedure for Michael Addition of Methyl Vinyl Ketone with Ethyl 2-Oxo-cyclopentane Carboxylate (Entry 19).** Methyl vinyl ketone (420 mg, 6 mmol) was added dropwise to a well stirred mixture of ethyl 2-oxo-cyclopentane carboxylate (755 mg, 5 mmol) in [bmIm]OH (468 mg, 3 mmol), and the reaction mixture was stirred for 0.5 h until completion of the reaction (TLC). The product was then distilled off directly from the reaction mixture to provide pure Michael adduct (1.08 g, 96%) as a colorless oil. If the reaction was carried out in a relatively smaller scale (1−2 mmol), the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4), and evaporated, leaving the crude product, which was purified by column chromatography over silica gel to provide the pure product. The compound was identified by comparison of its IR and ^{1}H and ^{13}C NMR spectroscopic data with those reported.[9b] The ionic liquid left in the reaction vessel was rinsed with ether (2 mL) and dried under vacuum at 90 °C for 2 h to eliminate any water trapped from moisture and reused for subsequent reactions. To compensate for the loss of some ionic liquid during washing, an amount (200 mg) of fresh ionic liquid was added after five runs. This procedure was followed for all the reactions listed in Table 1. However, in bis-additions, 2 equiv of methyl acrylate and acrylonitrile was used.

Table 1. Michael Addition Catalyzed by [bmIm]OH

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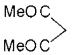
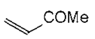
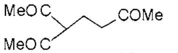
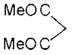
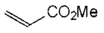
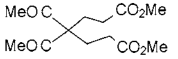
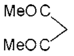
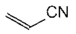
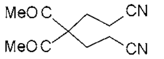
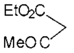
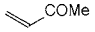
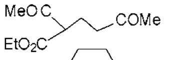
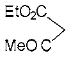
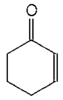
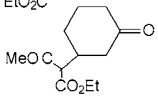
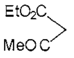
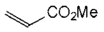
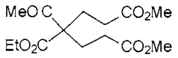
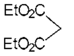
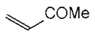
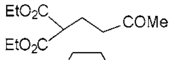
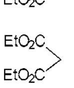
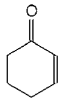
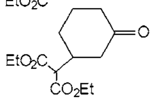
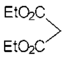
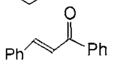
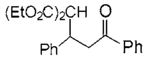
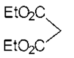
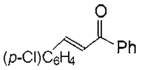
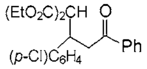
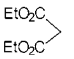
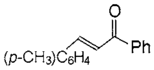
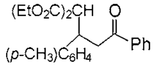
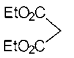
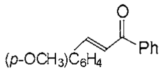
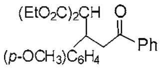
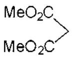
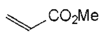
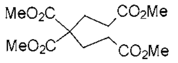
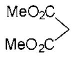
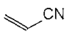
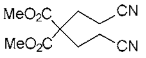
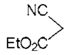
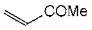
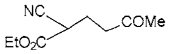
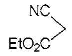
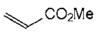
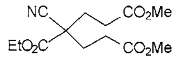
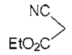
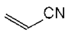
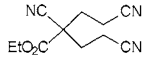
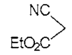
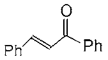
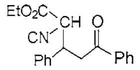
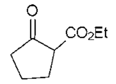
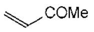
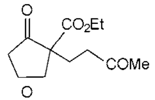
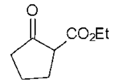
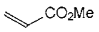
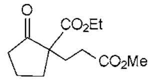
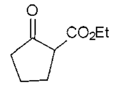
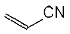
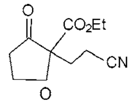
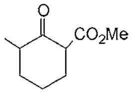
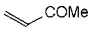
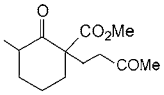
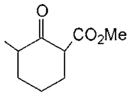
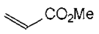
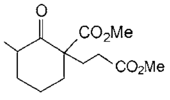
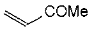
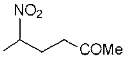
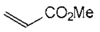
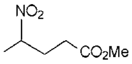
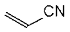
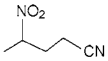
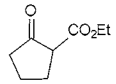
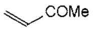
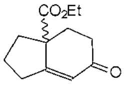
1				0.5	95	8a
2				2.0	95	14
3				2.0	85	15
4				0.75	90	8a
5				3.5	90	9b
6				2.5	95	
7				1.5	95	8a
8				4.0	90	16
9				2.5	95	8b
10				3.0	90	8b
11				3.0	90	8b
12				3.0	85	8b
13				2.5	85	8b
14				3.0	82	8d
15				0.5	96	8a
16				2.5	92	
17				2.5	92	
18				2.5	92	8b
19				0.5	96	9b
20				2.0	90	
21				2.0	92	17
22				1.0	90	
23				2.0	92	
24	$CH_3CH_2NO_2$			0.5	90	8a
25	$CH_3CH_2NO_2$			3.0	90	8a
26	$CH_3CH_2NO_2$			3.0	90	18
27				2.5[b]	80	19

[a] Yields refer to those of pure isolated products characterized by IR and ^1H and ^{13}C NMR spectroscopic data. [b] Reaction was carried out at 110 °C.

this process making it feasible within a reasonable time period (1.5−2.5 h) at room temperature with very high yields of products (85−95%). We must admit that the reason for this unusual behavior of this ionic liquid toward reaction with methyl acrylate and acrylonitrile is not known at this stage. However, the dramatic influence of ionic liquids on the outcome of chemical reaction has also been observed in the reaction of toluene with nitric acid as reported recently.[12]

The cyclic β-keto esters underwent smooth additions by this procedure (entries 19−23). However, reaction of ethyl cyclopentanone carboxylate (entry 27) with methyl vinyl ketone at 110 °C furnished the annulated bicyclic conjugated ketone by a tandem reaction of Michael addition followed by aldol condensation. Certainly, this is of much synthetic importance.

In general, all the reactions are very clean and reasonably fast. The reaction conditions are mild (room temperature), accepting several functional groups present in the molecules. In relatively larger scale (3 mmol and greater) reactions, the products are distilled directly from the reaction vessel, thus avoiding organic solvents totally. The ionic liquid has been reused[11] in up to six runs without loss of activity.

In conclusion, the present procedure using a basic (pH 9.3 at 30 °C) and easily available ionic liquid [bmIm]OH provides an efficient and convenient procedure for Michael addition of active methylene compounds with conjugated alkenes without requirement of any other catalyst and organic solvent. This method offers marked improvements with regard to operational simplicity, reaction time, reaction conditions, general applicability, high isolated yields of products, and greenness of procedure, avoiding hazardous organic solvents and toxic catalysts, and thus it provides a

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better and practical alternative to the existing procedures.[6−8] However, most significantly, this procedure demonstrates the dramatic influence of the ionic liquid [bmIm]OH in directing Michael addition of open-chain 1,3-dicarbonyl compounds with methyl acrylate and acrylonitrile to bis-addition products, which are difficult to achieve by conventional methods in one step. Certainly, this observation provides great promise toward additional useful applications.

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Supporting Information Available: Experimental procedures and characterization (IR and ^{1}H and ^{13}C NMR spectroscopic data and elemental analysis) for the new compounds reported in Table 1 (listed in entries 6, 16, 17, 20, 22, 23). This material is available free of charge via the Internet at http://pubs.acs.org.

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