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Ionic Liquid–Mediated Knoevenagel Condensation of Meldrum's Acid and Aldehydes

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Abstract: A simple, efficient, and green protocol for Knoevenagel condensation of Meldrum's acid and aldehydes in ionic liquid at room temperature without any catalyst is described. The reaction has been performed in different ionic liquids. The enhancement in the rate is observed in Brönsted acidic ionic liquid 1-methylimidazolium trifluoroacetate [Hmim]Tfa, which furnishes quantitative yields with 4–30 min in most of the cases. Furthermore, ionic liquid is easily reused without any appreciable loss in activity.

Keywords: Brönsted acidic ionic liquid, Knoevenagel condensation, Meldrum's acid, recyclability, ylidenes

Knoevenagel condensation of Meldrum's acid and aldehydes gives rise to corresponding ylidene derivatives. The ylidene derivatives obtained are versatile substrates for variety of reactions.[1] They are used in cycloaddition reactions,[2] 1,4-conjugate addition reactions and preparation of monoalkyl Meldrum's acid derivatives,[3] preparation of deuterated carboxylic acid derivatives,[4] and so forth. These derivatives are also used in the preparation of ketenes by flash vacuum pyrolysis, which are then used for preparation of different compounds such as cyclobutadiene derivatives, α,β-unsaturated esters, α,β-unsaturated amides, and synthesis of phenols.[5]

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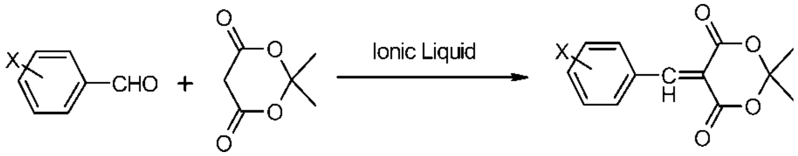
Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane) has attracted considerable attention because of its anomalously high acidity (pKa = 7.3 in DMSO at 25°C)[6] and rigid cyclic structure. The Knoevenagel condensation of Meldrum's acid with aldehyde was carried out using a number of catalysts such as K_3PO_4 in ethanol,[7] heterogeneous basic catalysts such as $Zr(O_3POK)$,[8] anhydrous $ZnCl_2$ under solvent-free conditions,[9] and piperidine/glacial acetic acid in benzene with water removal.[2] We have previously reported such reactions catalyzed by clays under solvent-free conditions.[10] The reaction has also been reported without any catalyst in an aqueous medium under reflux conditions.[11] Hedge and colleagues have reported such reactions without any catalyst at room temperature in highly polar solvents such as dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF), which are known to be highly toxic and teratogenic and are suspected carcinogens.[12]

In recent years, ionic liquids have attracted considerable interest as a green reaction media because of their fascinating properties such as negligible vapor pressure, ability to solvate a wide range of both organic and inorganic substrates, highly polar yet noncoordinating nature, and immiscibility with a number of organic solvents, as well as (in some cases) water.[13] Further, they are also regarded as designer solvents because their properties, such as hydrophilicity/hydrophobicity, polarity, acidity/basicity, viscosity, and recyclability, can be tuned by proper selection of cation and anion. Some of the ionic liquids are found to play the dual roles of solvent and catalyst. We have previously investigated a number of reactions in ionic liquids such as Fries rearrangement, Knoevenagel condensation of malonic acid with aldehydes, Pechmann condensation, synthesis of aryl keto acids, sulphonylation, sulfamoylation, and Michael reaction.[14] We have also investigated acylation of nucleosides as well as some biotransformations in these neoteric solvents.[15]

In an effort to exploit the potential of ionic liquid further and to explore the effect of these neoteric polar media, we considered it worthwhile to investigate the Knoevenagel condensation of Meldrum's acid with aldehydes in ionic liquids (Scheme 1).

During our investigation, we have carried out the reaction in different ionic liquids viz. 1-butyl-3-methylimidazolium hexafluorophosphate $[bmim]PF_6$, 1-hexyl-3-methylimidazolium tetrafluoroborate $[hmim]BF_4$, 1-butyl-3-methylimidazolium tetrafluoroborate $[bmim]BF_4$, and 1-methylimidazolium



Scheme 1. Knoevenagel condensation of Meldrum's acid and aldehyde.

trifluoroacetate [Hmim]Tfa. 4-Methoxy benzaldehyde was chosen as a model substrate. The percentage conversion of aldehyde into product was monitored using gas chromatography. Interestingly, it was found that after a specified time, the product precipitates out of the reaction mixture. The results are presented in Table 1. (Conversions in all cases were monitored with respect to decay of aldehyde by GC. A gas chromatograph Nucon 5765 equipped with FID and RH-17 capillary column was employed for analysis. The column was programmed initially at 50°C with a gradient of 10°C/min to 280°C. The detector and injector temperature was set at 300°C.)

As evident from the results shown in Table 1, the ionic liquid [Hmim]Tfa was found to be a better alternative compared to ionic liquids, namely [bmim]PF_6, [hmim]BF_4, and [bmim]BF_4. The stupendous increase in the percentage conversion as well as in the rate of reaction of [Hmim]Tfa ionic liquid may be attributed to its Brönsted acidic nature. The Brönsted acidic nature of this ionic liquid has been already utilized in Mannich reaction by Zhao et al.[16] Further, the isolation of product is also easier for [Hmim]Tfa. It can be effected by adding water to the reaction mixture, which dissolves the ionic liquid along with unreacted components, and the product can be isolated merely by filtration. The product obtained after sufficient washings with water was found to be pure. No bis-adduct was formed.

Because excellent results were obtained for [Hmim]Tfa ionic liquid, we employed this particular ionic liquid for subsequent studies. To explore the versatility of the reaction, we selected a number of different substituted benzaldehydes and hetero-aromatic aldehydes. Good yields were obtained with aldehydes that have activating groups, as well as with hetero aromatic aldehydes, as shown in Table 2.

The recyclability of [Hmim]Tfa ionic liquid was tested in the reaction of 4-methoxybenzaldehyde with Meldrum's acid under same experimental conditions, and as shown in Table 3, no considerable change in activity of ionic liquid was observed even after three consecutive runs.

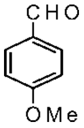
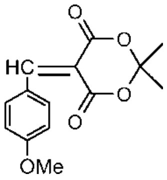
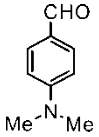
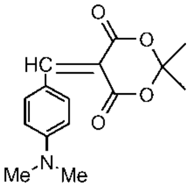
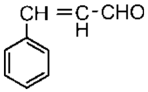
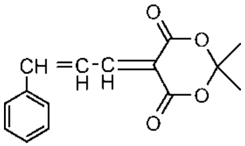
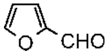
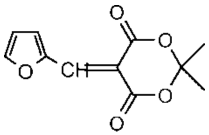
In conclusion, [Hmim]Tfa-mediated Knoevenagel condensation of Meldrum's acid with various aromatic and hetero-aromatic aldehydes presents an efficient, expeditious, and green route for the synthesis of

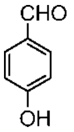
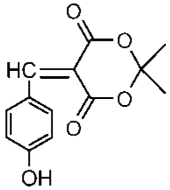
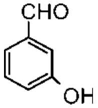
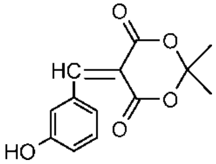
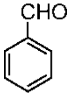
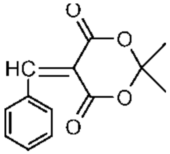
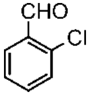
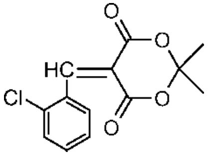
Table 1. Knoevenagel condensation of Meldrum's acid and 4-mehoxy benzaldehyde in different ionic liquids

Entry	Ionic liquid	Time	Conversion[a] (%)
1	[bmim]PF_6	24 h	54
2	[hmim]BF_4	24 h	77
3	[bmim]BF_4	24 h	76
4	[Hmim]Tfa	0.5 h	94

[a] Conversions based on gas chromatography analysis.

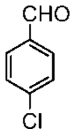
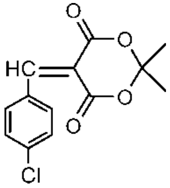
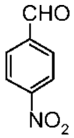
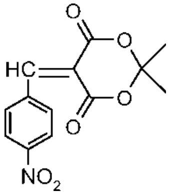
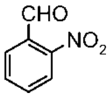
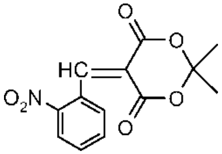
Table 2. Knoevenagel condensation of Meldrum's acid and aldehydes in [Hmim]Tfa

Entry	Aldehyde	Product	Reaction time (min)	Conversion[a] (%)	Isolated yield (%)	Mp (Lit. mp)[1,9,10] (°C)
1			30	94	90	123 (124)
2			4	95	91	173 (174)
3			20	92	88	109 (109)
4			30	95	85	96 (97)

5			20	93	87	196 (197)
6			30	80	79	175 (175)
7			5	67	60	84 (85)
8			10	73	70	133 (133)

(*continued*)

Table 2. Continued

Entry	Aldehyde	Product	Reaction time (min)	Conversion[a] (%)	Isolated yield (%)	Mp (Lit. mp)[1,9,10] (°C)
9			10	71	69	162 (162)
10			10	69	67	217 (217)
11			20	50	49	119 (119)

[a] Conversions based on gas chromatography analysis.

Table 3. Recycling of [Hmim]Tfa

No. of cycles	Conversion[a] (%)	Isolated yield (%)
1	94	90
2	93	88
3	93	87

[a]Conversions based on gas chromatography analysis.

various ylidene derivatives in good to excellent yields. Further, the ionic liquid can be easily recycled without any appreciable loss in the yields.

EXPERIMENTAL

Meldrum's acid and ionic liquids are prepared as per the procedures reported in the literature.[1,13,16] The aldehydes were purchased from SRL and Sd Fine Chemicals and were used as received. The product was characterized by ^{1}H NMR and GC-MS. ^{1}HNMR was recorded on a JEOL (300 MHz) instrument using $CDCl_3$ as solvent. GC-MS was recorded on a Schimadzu QP 2010 spectrophotometer equipped with a dp5 column.

Typical Procedure

In a typical experiment, 1 mmol of aldehyde is added to 200 mg of [Hmim]Tfa in a 50-ml round-bottom flask equipped with efficient magnetic stirrer. Stirring is continued until a homogeneous mixture is formed at room temperature. To this, 1 mmol of Meldrum's acid is added. The reaction is monitored using thin-layer chromatography (TLC), and stirring is continued until the specified time. The product precipitates out, and the reaction mixture solidifies. To this mixture, water is added so that ionic liquid dissolves in it, and the product is isolated simply by filtration. It is washed with water to remove excess ionic liquid along with unreacted components to get the crude product, which is found to be pure in most of the cases. However, in case of chloro- and nitro-derivatives, the yields are comparatively low and the crude product contains some amount of starting material, which is removed by crystallization. The products are characterized using GC-MS and ^{1}H NMR. In the case of solid aldehydes, the [Hmim]Tfa is melted by a little warming ($\sim$65°C), and rest of the procedure is followed at room temperature as given previously. The ionic liquid is recovered by removing excess water from the filtrate under a vacuum in a rotary evaporator. The unreacted components are removed by extracting with toluene to purify the ionic liquid.

Spectral Data of the Two Representative Compounds

Isopropylidene *p*-methoxybenzalmalonate (entry 1): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.79$ (6H, s), 3.91 (3H, s), 6.98 (2H, d, $J = 9$ Hz), 8.23 (2H, d, $J = 9$ Hz), 8.38 (1H, s). MS m/z (%): 262 (M^+, 22.64), 204 (58.5), 160 (100), 145 (60.0), 117 (48.9).

Isopropylidene *p-N,N*-dimethylbenzalmalonate (entry 2): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.77$ (6H, s), 3.16 (6H, s), 6.69 (2H, d, $J = 9$ Hz), 8.25 (2H, d, $J = 9$ Hz), 8.31 (1H, s). MS m/z (%): 275 (M^+, 7.3), 173 (69.5), 172 (100), 144 (96.33).

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