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Organic Reactions in Ionic Liquids: Alkylation of Meldrum's Acid

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ABSTRACT

The room temperature ionic liquid *N*-butylpyridinium tetrafluoroborate, $[bpy]BF_4$ is used as a "green" recyclable alternative to classical molecular solvents for the alkylation of Meldrum's acid.

Ionic liquids have been the subject of considerable interest as environmentally benign reaction media for organic synthetic chemistry in the last few years. These solvents possess a number of interesting

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properties, notably their lack of vapor pressure, ease of reuse, lack of flammability, and large accessible temperature range.^[1] To date some of the more important reactions have been carried out and investigated in ionic liquids, for example, Diels–Alder reactions,^[2] Wittig reactions,^[3] Heck reactions,^[4] Michael additions,^[5] Suzuki cross-coupling reactions,^[6] epoxidations,^[7] and Cr(salen) catalyzed asymmetric ring opening reactions of epoxides,^[8] Ni(0) catalyzed coupling reactions of aryl halides,^[9] lipase-catalyzed ammoniolysis,^[10] 1,3-dipolar cycloaddition reactions,^[13] Cu(I) mediated radical polymerizations,^[14] hydrogenation, isomerization, and hydroformylation reactions of alkenes,^[15] the Knoevengel and Robinson annulation reactions^[16] etc.

These encouraging results prompted us to investigate the range of organic reactions possible in ionic liquids for developing clean synthesis. The alkylations of active methylene compounds are very important methods for the formation of carbon–carbon bond in organic synthesis. We were interested in the reaction of isopropylidene malonate (1; 2,2-dimethyl-4, 6-dioxo-1,3-dioxane, Meldrum's acid), it has high acidity ($PK_a = 4.97$) and rigid cyclic structure, and can undergo alkylation easily to form alkylated products which are important intermediates in organic synthesis.^[17] The reactions of **1** with various alkyl halides (Sch. 1) was examined in [bpy]BF₄^[18] at 60–70°C using triethylamine as base; the products were conveniently extracted with ether, and almost exclusive dialkylation to form **3** was seen in all cases. The results are outlined in Table1.

These reactions were carried out, typically as 1 mmol of 1 in [bpy]BF₄ (2 mL) using 2.5 mmol of alkyl halide 2 and 2.5 mmol of NEt₃. Reactions were complete in 4–12 h as shown in Table1. The dialkylated products 3 were characterized by ¹H NMR, IR, m.p., and elemental analysis which were consistent with literature data.^[17] The ionic liquid can be recovered by treatment with CH₂Cl₂ (5 mL), filtration of precipitate and removal of solvent. The recovered solvent has been recycled numerous times with no



Scheme 1.

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Entry	Product	R	X	Time (h)	$T(^{\circ}C)$	Yield ^c (%)
1	3a	Н	Ι	5	60	82
2	3b	CH ₃	Ι	7	60	80
3	3c	CH ₃ CH ₂ CH ₂	Br	10	70	75
4	3d	C_6H_5	C1	4	60	90
5	3d	C_6H_5	C1	4	60	88^{a}
6	3d	C_6H_5	C1	4	60	89 ^b
7	3e	$p-NO_2-C_6H_5$	Br	5	65	86
8	3e	p-NO ₂ -C ₆ H ₅	Br	5	65	86 ^a
9	3f	$CH_2 = CH$	C1	12	60	31
10	3g	α-Aphthalenyl	C1	12	70	78
11	3h	C ₆ H ₅ CO	Br	6	65	85

 Table 1.
 Dialkylation of isopropylidene malonate.

^aThe using second times recovered ionic liquid [bpy]BF₄.

^bThe using third times recovered ionic liquid [bpy]BF₄.

^cIsolated yields based on isopropylidene malonate 1.

appreciable decrease in yield (Table 1 Entries 5, 6, 8), with only small mechanical losses.

In conclusion, room temperature ionic liquid [bpy]BF₄, is an attractive clean synthetic alternative to classical molecular solvents for alkylation of Meldrum's acid. The present reaction represents the first example of the alkylation of active methylene compounds in ionic liquids, and further studies on the alkylation of other active methylene compounds in ionic liquids are in progress in our laboratory. Room temperature ionic liquids are neoteric solvents, and studies are under way to demonstrate their obvious potential as an alternative to classical molecular solvents for organic synthesis.

EXPERIMENTAL

Melting points were determined on a X₄-Data microscopic melting point apparatus and were uncorrected. ¹H NMR and spectra were obtained at 400 MHz (AVANCE DMX400, Bruker) or 90 MHz (EM90) in CDCl₃ using TMS as an internal standard. Infrared spectra were recorded on a VECTOR 22 (Bruker) spectrometer at r.t. MS were obtained by electron impact at 70 eV (HP5989B). Elemental analyses were performed on a EA-1110 instrument. **MA**

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General Procedure

In a typical reaction, isopropylidene malonate 1 1 mmol (144 mg) was dissolved in ionic liquid [bpy]BF₄(2.0 mL), then triethylamine (2.5 mmol) and alkyl halide 2 (2.5 mmol) were added respectively. The resulting mixture was stirred for 4–12 h at $60-70^{\circ}$ C, until TLC indicates complete disappearence of starting material 1. The reaction mixture is then extracted with ethyl ether (3 × 10 mL) exhaustively. After removal of the solvent, the product was purified by crystallization or chromatography on silica gel (petroleum-ethyl acetate 4:1). The used ionic liquid can be recycled by disolving in CH₂Cl₂ (5 mL), then filtrating the precipitate and removing of solvent.

Physical and Spectroscopic Data

3a. Colorless crystal; m.p. 59–60°C (Lit. 60°C^[17]). IR (KBr) $\nu_{max} =$ 1774, 1732, 1380, 1370 cm⁻¹. ¹H NMR (CDC1₃, 80 MHz): $\delta = 1.65$ (s, 6H), 1.54 (s, 6H).

3b. Colorless crystal; m.p. $39-41^{\circ}$ C (Lit. $40-41^{\circ}$ C^[17]). IR (KBr) $\nu_{max} = 1761, 1729, 1388, 1372 \text{ cm}^{-1}$. ¹H NMR (CDC1₃, 80 MHz): $\delta = 0.91$ (t, 6H), 1.68 (s, 6H), 2.01 (q, 4H).

3c. Colorless crystal; m.p. 85–86°C (86–87°C^[17]). IR (KBr) $\nu_{max} =$ 1765, 1726, 1385, 1376 cm⁻¹. ¹H NMR (CDC1₃, 80 MHz): $\delta = 1.92$ (t, 4H), 1.67 (s, 6H), 1.25 (m, 8H), 0.81 (t, 6H).

3d. Colorless crystal; m.p. 232–233°C (Lit. 232–233°C^[17]). IR (KBr) $\nu_{\text{max}} = 1760, 1727, 1381, 1370, 760, 700 \text{ cm}^{-1}.$ ¹H NMR (CDC1₃, 400 MHz): $\delta = 7.20-7.30$ (m, 10H), 3.46 (s, 4H), 0.63 (s, 6H).

3e. Colorless crystal; m.p. 257–258°C (Dec.) (Lit. 258–259°C^[17]). IR (KBr) $\nu_{\text{max}} = 1763$, 1732, 1518, 1378, 1341, 854 cm⁻¹. ¹H NMR (CDC1₃, 400 MHz): $\delta = 8.18$ (d, J = 8.8 Hz, 4H), 7.40 (d, J = 8.8 Hz, 4H), 3.58 (s, 4H), 0.74 (s, 6H).

3f. Yellow oil. IR (film): $\nu_{max} = 3018$, 2928, 1757, 1738, 1444, 1351, 1216, 759 cm⁻¹. ¹H NMR (CDC1₃, 400 MHz): $\delta = 5.69$ (m, 2H), 5.20 (dd, J = 10.1, 6.0 Hz, 4H), 2.74 (d, J = 7.6 Hz, 4H), 1.69 (s, 6H). Anal. calcd. for C₁₂H₁₆O₄: C, 64.27; H, 7.19; O, 28.54. Found C, 64.35; H, 7.21; O, 28.55.

3g. White solid; m.p. 128–130°C; IR (KBr): $\nu_{max} = 3019$, 1759, 1734, 1215, 757, 669 cm⁻¹. ¹H NMR (CDC1₃, 400 MHz): $\delta = 8.32$ (d, J = 8.6 Hz, 2H), 7.72–7.79 (m, 4H), 7.36–7.59 (m, 8H), 4.15 (s, 4H), 0.44 (s, 6H). MS (EI): 424 (5.20, M⁺), 207 (5.94), 165 (8.17), 153

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(9.96), 152 (13.9), 142 (18.0), 141 (100), 115 (19.2), 43 (9.8). Anal. calcd. for $C_{28}H_{24}O_4$ C, 79.22; H, 5.70; O, 15.08. Found C, 79.24; H, 5.71; O, 15.10.

3h. White solid; m.p. 206–207°C (Dec.) (207–208°C^[17]). IR (KBr): $\nu_{\text{max}} = 1750, 1715, 1682, 1391, 1375, 748, 685 \text{ cm}^{-1}$. ¹H NMR (CDC1₃, 400 MHz): $\delta = 7.91$ (d, J = 7.5 Hz, 4H), 7.59 (t, J = 7.3 Hz, 2H), 7.46 (t, J = 7.8 Hz, 4H), 3.94 (s, 4H), 2.18 (s, 6H).

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