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Rate accelerations of 1,3-dipolar cycloaddition reactions in ionic liquids

Joan Fraga Dubreuil and Jean Pierre Bazureau*

Synthèse & Electrosynthèse Organiques 3, UMR 6510, Université de Rennes 1, Bât. 10A, Campus de Beaulieu,
Avenue du Général Leclerc, F-35042 Rennes, France

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Abstract

The 1,3-dipolar cycloaddition reactions between imidate **1** derived from diethyl aminomalonate and 2-ethoxybenzaldehyde **2** as dipolarophile has been investigated in various air and moisture stable ionic liquids. Significant rate enhancements and improved yields at 70°C have been observed with [emim][BF_4] and [emim][NfO] ionic liquids. The reactivity of dipolarophiles covalently grafted on the ionic liquids were also evaluated. © 2000 Elsevier Science Ltd. All rights reserved.

Room temperature ionic liquids[1] are a new class of solvents that are entirely constituted of ions. These solvents possess a number of interesting properties, especially their lack of vapour pressure, a wide accessible temperature range with lack of flammability and ease of reuse. Room temperature ionic liquids are attracting increasing interest as environmentally benign reaction media and have been found to be excellent solvents for a number of purposes such as Friedel–Crafts reactions,[2] arene hydrogenation,[3] dimerizations[4] of alkenes, allylation of aldehydes,[5] Heck reactions[6] and Diels–Alder reactions.[7] Recent studies on Diels–Alder reactions in non-aqueous solvents show strong selectivities which were also associated with considerable acceleration of the process.[8]

One of the continuing aims of our laboratory is to develop new synthetic routes to five-membered heterocycles by [3+2] reactions using solvent-free conditions,[9] eventually assisted by focused microwave irradiation.[10] Our interest was to explore the ionic liquid methodology in 1,3-dipolar cycloaddition reactions. Here, we have examined reactions of imidate[11] **1** derived from diethyl aminomalonate with 2-ethoxybenzaldehyde **2** as dipolarophile at 70°C (Scheme 1). For this study, the air stable ionic liquids employed were 1-ethyl-3-methylimidazolium tetrafluoroborate[12a,b] ([emim][BF_4]), 1-ethyl-3-methylimidazolium hexafluorophosphate[12c] ([emim][PF_6]), 1-ethyl-3-methylimidazolium nonafluoro 1-butanesulfonate[12d] ([emim][NfO]) and the novel 3-(5-carboxy-

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* Corresponding author. Fax+33 0299286374; e-mail: jean-pierre.bazureau@univ-rennes1.fr

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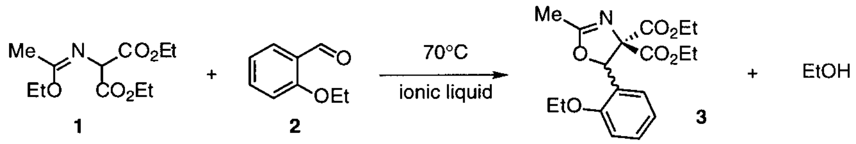
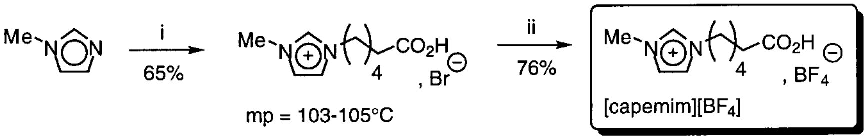
pentyl)-1-methylimidazolium tetrafluoroborate[13] ([capemim][BF_4]) which was easily prepared in two steps using standard procedures (Scheme 2).



Scheme 1.



Scheme 2. Synthesis of [capemim][BF_4]. (i) $Br(CH_2)_5CO_2H$ 1 equiv.; 70°C, 4 h. (ii) NH_4BF_4 2.5 equiv.; dry MeCN, 60°C, 18 h

In a typical reaction, imidate **1** (1 equiv.) and dipolarophile **2** (1 equiv.) were added to the ionic liquid directly (0.1–1 equiv.). Two phases were formed at room temperature. At 70°C, the mixture became homogeneous and was stirred vigorously during the appropriate reaction time (monitored by ^1H NMR). Then, the reaction mixture was allowed to cool, the organic layer was separated and the cycloadduct **3** could be extracted from the ionic liquid with diethyl ether or ethyl acetate to leave the pure ionic liquid which may be reused.

Table 1 shows the results of a number of 1,3-dipolar cycloadditions in ionic liquids under various reactions conditions. Reaction rates had to be calculated on the disappearence of imidate

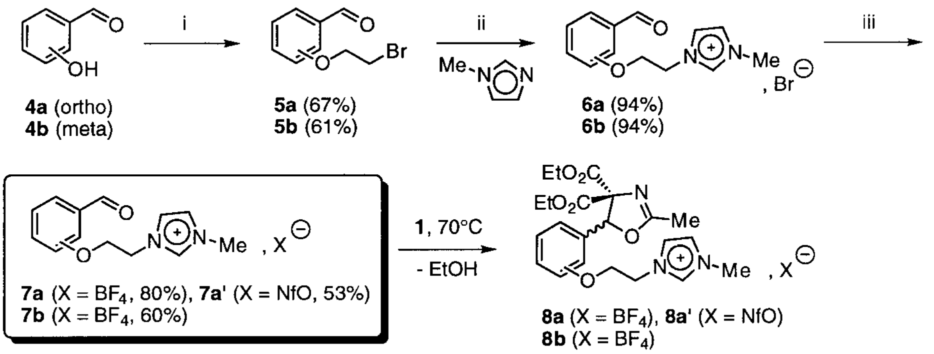
Table 1

Results of the 1,3-dipolar cycloaddition reactions of imidate **1** with **2** in ionic liquids at 70°C in an oil bath or under focused microwave irradiations (μω)

Entry	Reactions conditions		Time	Conv. of **1**[a]	Yield[b] of **3**	Conv. of **1**	acceleration
	ionic liquid (eq.)	additive	(hrs)	(%)	(%)	after 2 hrs	after 2 hrs
1	-	-	15[c]	99	84	40	1
2	[emim][BF_4] (0.1)	-	10[c]	99	76	64	1.6
3	[emim][BF_4] (1)	-	6[c]	99	78	90	2.3
4	[emim][BF_4] (1)	μω[d]	3	99	70	97	2.4
5	[emim][PF_6] (1)	-	10[c]	99	92	80	2
6	[emim][NfO] (1)	-	7.5[c]	99	86	60	1.5
7	-	AcOH[e]	8.5[c]	93	74	-	-
8	[emim][BF_4] (1)	AcOH[e]	2.5[c]	99	52	98	2.45
9	[emim][BF_4] (1)	AcOH[e] + μω	1	99	37	99[f]	2.5[f]
10	[emim][PF_6] (1)	AcOH[e] + μω	1.5	99	64	99[f]	2.5[f]
11	[capemim][BF_4] (0.1)	-	2.5[c]	99	51	98	2.45

[a] Conversion of **1** into **3** estimated by ^1H NMR (200 MHz, in $CDCl_3$, TMS as internal reference). [b] Isolated yield of **3** after extraction from the crude reaction mixture. [c] Reactions were run in a thermostated oil bath, variation ± 1°C. [d] μω = reactions were run in the focused microwave reactor Synthewave® 402 (Merck Eurolab, Fr). [e] AcOH : 5% of glacial acetic acid. [f] reaction time < 2 hrs.

1 and were determined by ^{1}H NMR. All reactions exhibited pronounced rate accelerations and good yields were obtained for isolated products **3** with [emim][PF_6] (entry 5) and [emim][NfO] (entry 6). However, it should be noted that the reaction rate in an ionic liquid is dependent upon the ionic liquid chosen and in this case, [emim][NfO] gives a lower rate enhancement (entry 6) than the [emim][BF_4] and [emim][PF_6] ionic liquids (entries 4 and 5). The addition of 5% of glacial acetic acid as Brönsted catalyst[14] in the ionic liquid (entry 9) increases the reaction rate. Association of focused microwave irradiations[15] with glacial acetic acid in [emim][BF_4] (entry 10) is suitable for increasing the reaction rate and the yield of isolated cycloadduct **3**. With [capemim][BF_4] (entry 11), we have observed the same rate accelerations but the yield of **3** after extraction from the crude reaction mixture is moderate[16] (**3**: 51% yield). According to the pronounced rate enhancement observed previously, it was decided to investigate the reactivity of benzaldehyde bound to the ionic liquid. The synthesis of the corresponding ionic liquid dipolarophiles **7(a,b)** ($X = BF_4$) and **7a′** (X = NfO) is shown in Scheme 3. The aldehydes **5(a,b)** were prepared by a coupling reaction of the sodium salt of 2-hydroxybenzaldehyde[17] **4a** or 3-hydroxybenzaldehyde **4b** with 2 equiv. of 1,2-dibromoethane. Next, reaction of methyl imidazole with **5a** or **5b** at reflux results in the quantitative formation of the corresponding N(1)-alkyl-3-methylimidazolium bromides **6(a,b)**. The imidazolium bromides **6(a,b)** were readily isolated as pale yellow solids by repeated washings of the residue with ether (94% yield). Subsequent anion methathesis with NH_4BF_4 (2.5 equiv.) or $C_4F_9SO_3K$ (1.5 equiv.) in deionized water followed by extraction with CH_2Cl_2 and vacuum evaporation leads to the desired ionic liquid dipolarophiles **7a**, **7a′** and **7b**. Their purity has been established by acquisition of clean ^{1}H and ^{13}C NMR as well as by FAB-MS. The *meta* ionic liquid **7b** remains liquid for weeks, the *ortho* compounds **7a** and **7a′** slowly glassify at room temperature and are reliquified by mild heating (**7a** at 56°C and **7a′** at 48°C). The three organic ionic liquids appear to be stable at room temperature for several weeks.



Scheme 3. (i) $(CH_2Br)_2$ 2 equiv., NaOH 1.2 equiv., Δ, 48 h. (ii) for **6a**: TCE, Δ, 72 h; for **6b**: 80°C, 15 h. (iii) for **7a** and **7b**: NH_4BF_4 2.5 equiv., H_2O, 60°C, 18 h; for **7a′**: $n C_4F_9SO_3K$ 1.5 equiv., H_2O, 70°C, 18 h

In order to define the ability of ionic liquid dipolarophiles **7a**, **7a′** and **7b** for cycloaddition reactions, we have examined the reactivity of imidate **1** in the same reactions conditions (at 70°C in oil bath) with a ratio of **1**/**7**:1/1. The results summarized in Table 2 show that reaction of **7a** with imidate **1** at 70°C is not accomplished after a reaction time of 1.5 h (entry 1); the crude reaction mixture (which contains **8a**, unreacted products **7a** and **1** together with by product due to partial hydrolysis of imidate[16] **1**) becomes a soft yellow solid which changes to a gelatinous state at 100–120°C before becoming fully liquid at 130°C to force the reaction to completion.

With the same experimental conditions, reactions of **1** with **7a**′ (entry 2) and **7b** (entry 3) are finished over a period of 6–7 h; the respective crude reaction mixture appears as a yellowish wax. It is noteworthy that the reaction of imidate **1** with ionic liquid dipolarophile **7a**′ *ortho* (Table 2, entry 2: 6.5 h) is more rapid than reaction of **1** with 2-ethoxybenzaldehyde **2** (Table 1, entry 6: 7.5 h) in [emim][NfO] ionic liquid. This acceleration observed with **7a**′ *ortho* is probably due to the intramolecular interaction between the CHO group of dipolarophile and the polar 3-methylimidazolium moiety.

Table 2
Results of 1,3-dipolar cycloadditions obtained at 70°C in an oil bath with 2-hydroxy- and 3-hydroxybenzaldehydes covalently grafted on the ionic liquids (**7a**, **7a**′ and **7b**)

Entry	dipolarophile	Reaction time (hrs)	Disap. of **1**[a] (%)	Conv. of **7** into **8**[b] (%)
1	**7a** *ortho* (X = BF_4)	1.5	77	64
2	**7a'** *ortho* (X = NfO)	6.5	99	75
3	**7b** *meta* (X = BF_4)	7	99	80

[a] Disappearence of **1** estimated by ^1H NMR (200 MHz, in $CDCl_3$, TMS as internal reference). [b] Conversion of **7** into **8** also estimated by ^1H NMR with the same analytic conditions.

In summary, the room temperature ionic liquids [emim][BF_4], [emim][PF_6] and [emim][NfO] give significant rate accelerations and good isolated cycloadduct yields when compared to solvent-free cycloaddition reaction conditions. However, the factors that affect this improvement are at present not fully understood. They are potentially useful solvents particularly for moisture sensitive reagents, because cycloadducts can be isolated simply by extraction from the crude reaction mixture and the ionic liquid may be reused. Further studies of possible applications of dipolarophiles appended to the ionic liquid are also being actively pursued. The results of these and related studies will be reported in due course.

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13. Selected spectral data of 3-(5-carboxypentyl)-1-methylimidazolium tetrafluoroborate ([capemim][BF_4]): ^{1}H NMR (acetone d^6, 300 MHz, TMS) δ 1.40 (m, 2H); 1.64 (quint., 2H, J = 7.7 Hz); 1.97 (quint., 2H, J = 7.5 Hz); 2.32 (t, 2H, J = 7.4 Hz); 4.02 (s, 3H); 4.35 (t, 2H, J = 7.3 Hz); 7.68 (t, 1H, J = 1.7 Hz, H-4); 7.75 (t, 1H, J = 1.6 Hz, H-5); 8.96 (s, 1H, H-2); ^{13}C NMR (acetone d^6, 75 MHz, TMS) δ 24.91 (tm, J = 127 Hz); 26.23 (tm, J = 125 Hz); 30.52 (tm, J = 128 Hz); 33.94 (tm, J = 127 Hz); 36.63 (q, J = 144 Hz); 50.23 (tm, J = 144 Hz); 123.43 (dm, J = 202 Hz, C-5); 124.80 (dm, J = 203 Hz, C-4); 137.67 (dm, J = 216 Hz, C-2); 174.95 (sm, CO). After filtration of the crude reaction mixture and evaporation of MeCN by rotary evaporation, [capemim][BF_4] is dried in vacuo to avoid moisture. It is recommendable to handle under an inert atmosphere at 4°C.
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