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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3753–3756

Ionic liquids as novel and recyclable reaction media for N-alkylation of amino-9,10-anthraquinones by trialkyl phosphites

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Received 2 January 2007; revised 4 March 2007; accepted 14 March 2007
Available online 19 March 2007

Abstract—Ionic liquids such as 1,3-dialkylimidazolium bromides make excellent catalysts and solvents for N-alkylation of amino-9,10-anthraquinones in the presence of trialkyl phosphites. For triethyl phosphite, [bpim][Br] gave better results. The ionic liquids are successfully regenerated and reused.

Ionic liquids (ILs) have attracted considerable attention in recent years due to their unique properties, such as lack of measurable vapor pressure, non-flammability and recyclability.[1] Their high polarity and ability to dissolve both inorganic and organic materials can result in enhanced rates of chemical processes and can provide higher/different selectivities compared to conventional solvents. Thus, as a result of their 'green' credentials and potential to enhance rate and selectivity,[2,3] ILs have been used as solvents in chemical transformations. However, the ability of ILs to serve as catalysts[4] and reagents[5] has not been explored to any great extent.[6,7]

9,10-Anthraquinone is the parent compound for a large palette of anthraquinone dyes and so is the most important starting material in their production. Furthermore, anthraquinone is gaining importance as a catalyst in wood pulping, and it is known to exhibit quite potent anticancer activities.[8] Amino- and hydroxy-substituted 9,10-anthraquinones are important in the dye industry, biology and pharmaceutical chemistry.[8,9]

The alkylation of neutral amines by alkyl halides is complicated from a synthetic point of view because of the possibility of multiple alkylation which can proceed to give the quaternary ammonium salt in the presence of excess alkyl halide. Even with a limited amount of the alkylating agent, the equilibria between protonated products and the neutral starting amines are sufficiently fast such that a mixture of products may be obtained. For this reason, when monoalkylation of an amine is desired, the reaction is usually best carried out by reductive amination. The conventional method for the preparation of alkylaminoanthraquinones involves the reaction of 1-chloroanthraquinone with DMF under reflux (140–150 °C) for up to 32 h. This reaction produces a mixture of products.[10]

In this Letter, ILs are employed as useful and novel reaction media for alkylation of amino-9,10-anthraquinones in the presence of trialkyl phosphites, avoiding the use of base and highly polar organic solvents. The effects of some important variables, such as reaction temperature and the type of IL used on the activity and selectivity of the reaction, are investigated. Thus, the reaction of 1-amino-9,10-anthraquinone (**1-AAQ**) in the presence of triethyl phosphite (TEP) or trimethyl phosphite (TMP) in different imidazolium-based ILs at various temperatures led to 1-alkylamino-9,10-anthraquinones in high yields[11] (Scheme 1 and Table 1).

An initial reaction of **1-AAQ** and trialkyl phosphites was carried out under different conditions. The results indicated that ionic liquids [YY′im][Br] (Y,Y′ = Me, Et, *n*-Pr, *n*-Bu, or Bn) exhibited excellent catalytic activities. In contrast, no reaction was observed in the ILs containing a PF_6^- anion. When the reactions were carried out in water or CH_2Cl_2, no product was observed, except for the reaction of **1-AAQ** and TMP (see Table 1). The poor solubility of **1-AAQ** in the hydrophobic IL [bmim][PF_6] and in water or CH_2Cl_2 may be responsible for this behaviour. It is interesting to note that ILs

Keywords: Amino-9,10-anthraquinone; Ionic liquid; N-alkylation; Trialkyl phosphite.
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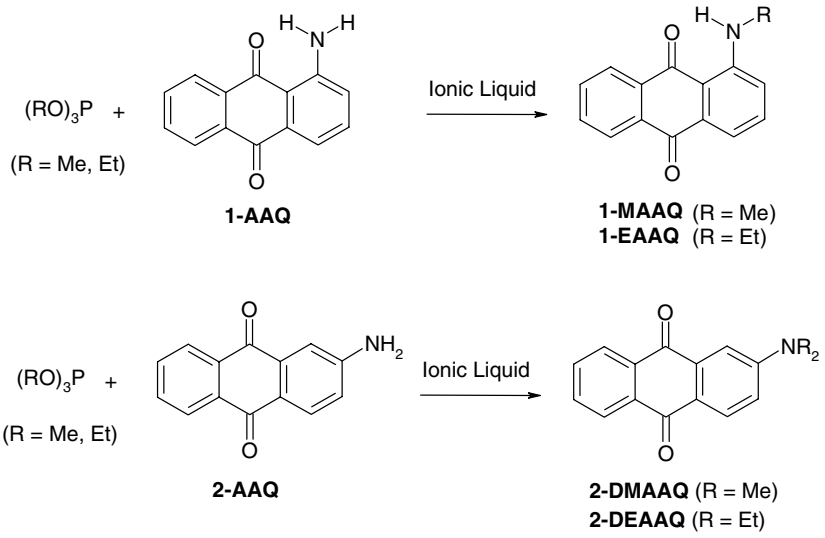
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.03.077



Scheme 1. The reaction of **1-AAQ** or **2-AAQ** with trialkyl phosphites in ILs as solvent and catalyst.

Table 1. Influence of the reaction media on the yield and time of reaction of **1-AAQ** (1 mmol) or **2-AAQ** (1 mmol) and trialkyl phosphites (1 mmol) in different ILs (1.0 g) at 120 °C

Entry	Solvent[a]	1-AAQ				2-AAQ			
		TEP		TMP		TEP		TMP	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1	[eeim][Br]	8	60	6	68	7	62	6	68
2	[bbim][Br]	8	85	6	84	7	95	6	98
3	[emim][Br]	8	65	6	75	7	65	6	65
4	[bmim][Br]	8	60	6	65	7	60	6	60
5	[bpim][Br]	8	85	6	95	7	85	6	87
6	[Bnmim][Br]	12	55	11	65	7	65	6	65
7	[Bnbim][Br]	12	52	11	63	7	60	6	60
8	[pmim][Br]	8	82	6	87	7	85	6	85
9	Water	24	No product	12	No product	24	No product	6	60
10	CH_2Cl_2	24	No product	12	No product	24	No product	6	85

[a] [eeim][Br] (e, e = Et, Et); [bbim][Br] (b, b = *n*-Bu, *n*-Bu); [emim][Br] (e, m = Et, Me); [bmim][Br] (b, m = *n*-Bu, Me); [bpim][Br] (b, p = *n*-Bu, *n*-Pr); [Bnmim][Br] (Bn, m = Benzyl, Me); [Bnbim][Br] (Bn, b = Benzyl, *n*-Bu); [pmim][Br] (p, m = *n*-Pr, Me).

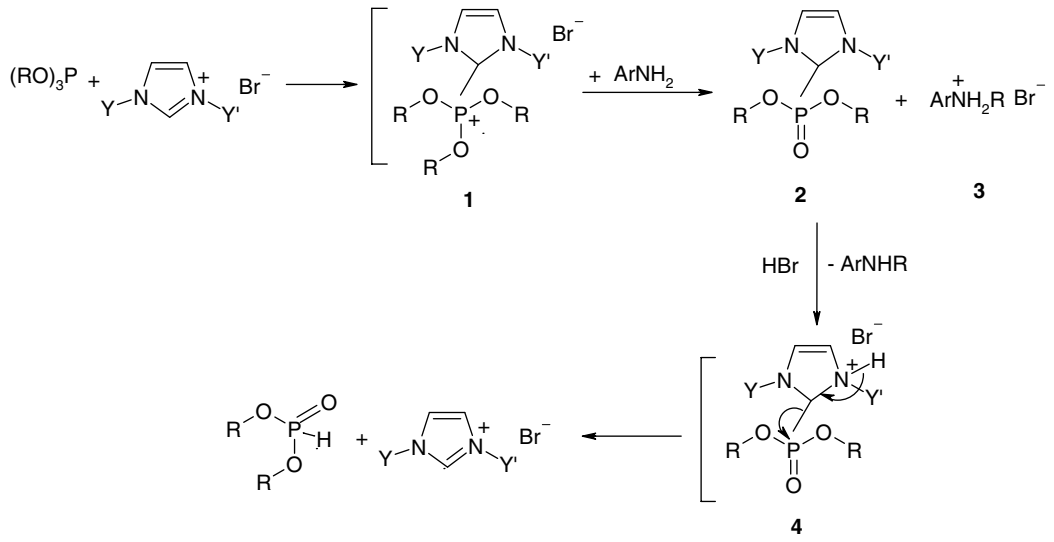
having longer cationic carbon chains were found to be more effective for N-alkylation of **1-AAQ**. Thus, [bpim][Br] appeared to be the most suitable IL to perform this reaction (see Table 1). No reaction was observed between **1-AAQ** and $(PhO)_3P$ or Ph_3P in the ILs studied in this work.

Mechanistically, the reaction may involve the attack of the phosphorus nucleophile on the electrophilic carbon atom of the imidazolium cation to form an intermediate phosphonium salt.[12] As amines are found to be more nucleophilic in ILs than in common organic solvents,[13] the **AAQ** attacks the electrophilic carbon atom of intermediate **1** to form ammonium salt **3** which is converted to **1-AAQ** by loss of HBr. Protonation of intermediate **2** by HBr leads to **4**, which dialkyl hydrogen phosphite eliminates and regenerates the IL (Scheme 2).

These results show that the ILs play a role as a catalyst as well as a reaction medium during these processes. The reaction of **1-AAQ** and TMP in [bpim][Br] was followed by ^{31}P NMR spectroscopy. After 2 h, the ^{31}P signal of TMP disappeared and a signal at δ(P) 4.95 ppm was observed for the H–P(O)$(OMe)_2$ species. Observation of a sharp doublet at δ(H) 6.08 ppm ($^1J_{PH} = 670$ Hz) for the H–P(O)$(OMe)_2$ in the ^1H NMR of the reaction mixture confirmed the proposed mechanism (Scheme 2).

The reaction of **2-AAQ** with trialkyl phosphites was also studied in different imidazolium-based ionic liquids at various temperatures. Although **2-MAAQ** is expected to be less nucleophilic compared to **2-DMAAQ** in conventional solvents,[13] the reactivity of the former towards N-alkylation in the ILs used is at least two orders of magnitude higher than the latter.

Dialkylation of **2-AAQ** takes place in the presence of 1 equiv of TMP. In order to obtain information about the mechanism of this transformation, the reaction mixture of **2-AAQ** and TMP was monitored by ^1H and ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum of the reaction mixture of **2-AAQ** and TMP in [bpim][Br] after



Scheme 2. A plausible mechanism for the alkylation of **1-AAQ** by trialkyl phosphites in ILs.

2 h showed a major signal at 5.0 ppm due to the presence of H–P(O)$(OMe)_2$. This signal gradually disappeared and two new ^{31}P signals appeared at 2.0 and 8.0 ppm, which were attributed to H–P(O)(OMe)(OH) and H–P(O)$(OH)_2$ as side products of dealkylation of TMP. The presence of OH groups was confirmed by ^1H NMR spectroscopy, which showed a very broad signal at 4.0–7.0 ppm. The ^1H NMR spectrum of the reaction mixture also showed the appearance of two doublets ($^1J_{PH} = 600$ Hz) at 7.4 and 7.7 ppm due to the P–H protons in H–P(O)(OMe)(OH) and H–P(O)$(OH)_2$. These observations are consistent with a second (and perhaps third) dealkylation of TMP in the presence of **2-AAQ** in ILs.

The effect of temperature change on the formation of **1-MAAQ** was studied in the temperature range of 25–140 °C. At reaction temperatures above 120 °C, no change in the yield of the reaction was observed. Therefore, 120 °C is inferred to be a suitable reaction temperature. Similar results were obtained for the reaction of **2-AAQ** and TMP in [bbim][Br] at various temperatures.

In conclusion, ILs are proved to be useful and novel reaction media for the N-alkylation of **1-AAQ** and **2-AAQ** by trialkyl phosphites, avoiding the use of base and highly polar organic solvents. The effects of reaction temperature and the type of IL used on the activity and selectivity were investigated. The IL [bpim][Br] was found to be the most effective. The use of room-temperature imidazolium ILs significantly enhanced the rate of N-alkylation of **AAQ**s.

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11. All ILs were prepared and purified in accordance with the procedure described previously.[14] *General procedure for N-alkylation of* **1-AAQ** *or* **2-AAQ**. The phosphite (1 mmol) was added to a solution of the **AAQ** (1 mmol) in [bpim][Br] (1.0 g) and the solution was heated at 120 °C for 6–8 h (see Table 1). The reaction mixture was cooled to ambient temperature before work-up. The products were extracted with CH_2Cl_2 (3×4 mL) followed by solvent evaporation. The IL was recovered by the addition of water (5 mL), then collected and dried under vacuum. The products were obtained in high yields and purified after short filtration chromatography through silica gel. These reactions were performed without any protective atmosphere of inert gas. *1-(Methylamino)-9,10-anthraquinone* (**1-MAAQ**): Red powder, yield: 0.23 g (95%). Mp 169–170 °C (reported[10] 170 °C). IR (KBr) (υ_{max}/cm^{-1}): 1663, 1623 (2C=O), 3285 (N–H). ^1H NMR (500 MHz, $CDCl_3$): 3.10 (3H, d, $^3J = 5.0$, Me), 7.09 (1H, dd, $^3J = 7.0$, $^4J = 1.3$, CH), 7.59–7.65 (2H, m, 2CH), 7.73–7.84 (2H, m, 2CH), 8.28 (1H, dd, $^3J = 6.5$, $^4J = 1.2$, CH), 8.31 (1H, dd, $^3J = 6.5$, $^4J = 1.2$, CH), 9.69 (1H, s, br, NH). ^{13}C NMR

(125.7 MHz, $CDCl_3$): 29.6 (Me), 113.1 (C), 115.3 (CH), 118.1 (CH), 126.7 (CH), 126.9 (CH), 133.4 (C), 133.5 (CH), 134.5 (CH), 134.9 (C), 135.8 (C), 153.0 (N–C), 183.4, 184.8 (2C=O). *1-(Ethylamino)-9,10-anthraquinone* (**1-EAAQ**): Red powder, yield: 0.21 g (85%). Mp 113–114 °C. IR (KBr) (v_{max}/cm^{-1}): 1647, 1619 (2C=O), 3268 (N–H). ^1H NMR (500 MHz, $CDCl_3$): 1.39 (3H, t, $^3J = 7.3$, Me), 3.40 (2H, q, $^3J = 7.3$, CH_2), 7.05–7.06 (1H, m, CH), 7.52–7.59 (2H, m, 2CH), 7.68–7.71 (1H, m, CH), 7.74–7.77 (1H, m, CH), 8.24 (1H, dd, $^3J = 6.5$, $^4J = 1.0$, CH), 8.27 (1H, dd, $^3J = 6.5$, $^4J = 1.1$, CH), 9.70 (1H, s, br, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.5 (Me), 37.6 (CH_2), 112.8 (C), 115.8 (CH), 118.8 (CH), 127.1 (CH), 127.3 (CH), 133.8 (C), 133.9 (CH), 134.9 (CH), 135.1 (C), 135.4 (C), 135.8 (C), 152.6 (N–C), 183.8, 185.3 (2C=O). *2,2-(Dimethylamino)-9,10-anthraquinone* (**2-DMAAQ**): IL = [bbim][Br], orange powder, yield: 0.25 g (98%). Mp 190–191 °C (reported[10] 186 °C), IR (KBr) (v_{max}/cm^{-1}): 1660, 1586 (2C=O). ^1H NMR (500 MHz, $CDCl_3$): 3.22 (6H, s, 2Me), 7.14 (1H, dd, $^3J = 8.7$, $^4J = 1.8$, CH), 7.42–7.43 (1H, m, CH), 7.68–7.94 (2H, m, 2CH), 8.10–8.12 (1H, m, CH), 8.22–8.25 (2H, m, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 39.7 (2Me), 108.1 (CH), 116.4 (CH), 122.0 (C), 126.8 (CH), 126.9 (CH), 129.6 (CH), 133.5 (CH), 134.1 (C), 134.4 (CH), 134.7 (C), 135.1 (C), 154.4 (N–C), 180.9, 183.9 (2C=O). *2,2-(Diethylamino)-9,10-anthraquinone* (**2-DEAAQ**): IL = [bbim][Br], orange powder, yield: 0.26 g (95%). Mp 195–199 °C. IR (KBr) (v_{max}/cm^{-1}): 1645, 1618 (2C=O). ^1H NMR (500 MHz, $CDCl_3$): 0.83 (6H, t, $^3J = 7.2$, 2Me), 3.50 (4H, q, $^3J = 7.2$, $2CH_2$), 6.94 (1H, dd, $^3J = 8.9$, $^4J = 1.9$, CH), 7.46–7.47 (1H, m, CH), 7.71–7.76 (1H, m, 2CH), 8.17–8.19 (1H, m, CH), 8.26 (1H, dd, $^3J = 7.3$, $^4J = 1.1$, CH), 8.30 (1H, dd, $^3J = 7.7$, $^4J = 1.5$, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.0 (2Me), 38.4 ($2CH_2$), 108.0 (CH), 115.4 (CH), 125.6 (CH), 126.0 (C), 126.9 (CH), 128.1 (CH), 128.2 (CH), 133.7 (C), 133.9 (CH), 134.5 (C), 135.3 (C), 151.7 (N–C), 181.3, 184.4 (2C=O).

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