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Imidazolium salts as phase transfer catalysts for the dialkylation and cycloalkylation of active methylene compounds

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Abstract—The dialkylation and cycloalkylation reactions of active methylene compounds in the presence of readily available imidazolium salts (ionic liquids) as phase transfer catalysts were performed to afford the respective dialkylated or cycloalkylated products. This method is very efficient for the synthesis of 1,1-disubstituted derivatives and cyclopropane and cyclopentane ring systems in a facile manner.

Cyclopropane and cyclopentane derivatives are very important intermediates in the pharmaceutical industry[1] and for natural product synthesis.[2] Phase transfer catalysts (PTCs) are powerful reagents in chemical transformations,[3] the characteristics of which include mild reaction conditions, safety, operational simplicity and selectivity. Thus, finding a new phase transfer catalyst to promote various organic transformations is of considerable interest. Phase transfer catalysts are often used in nucleophilic displacement reactions to facilitate reactions between organic reactants and ionic inorganic salts.[3] Although many phase transfer catalysts are known quaternary salts formed from ammonia[3,4] are only used for alkylation reactions. The presence of bulky substituents on quaternary salts results in good phase transfer catalysts for nucleophilic displacement reactions.[3] Thus, we planned to use imidazolium salts (generally known as ionic liquids) having bulky cations as phase transfer catalysts for alkylations. Recently, ionic liquids have played increasing roles in organic chemistry and have been used in various organic transformations[5] as solvent, reagent or Brønsted acid. To the best of our knowledge, only *N*-methylimidazolium bromide has been indirectly implicated[6] as a phase transfer catalyst. We herein report a range of ionic liquids as phase transfer catalysts for dialkylation and cycloalkylation reactions to synthesize 1,1-disubstituted products and cycloalkane ring systems.

To study the dialkylation processes, we synthesized the ionic liquids [bmim]BF_4, [bbim]BF_4, [bmim]Br, [bmim]PF_6, [mmim]BF_4 and [mmim]I as described in the literature (Fig. 1).[7] Initially, we carried out the dialkylation reaction of ethyl acetoacetate, allyl bromide and potassium carbonate in the presence of [bmim]BF_4 as a phase transfer catalyst using dimethylformamide as solvent. The reaction mixture was stirred at room temperature for 2 h to give a white suspension, which subsequently turned orange. Work-up furnished[8,9] the product **2a** in 96% yield (Scheme 1). Interested by this result, further dialkylation reactions were carried out using [bmim]BF_4 to furnish the products **2b–d**. The dialkylation reaction was then performed with an equimolar mixture of different alkyl halides under the above experimental conditions to afford the products **2e**,**f** having different alkyl groups in very good yield (Scheme 1).

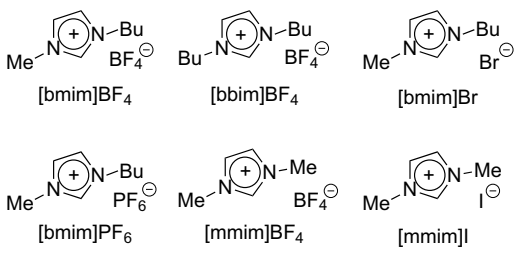

Figure 1. Ionic liquids synthesized for phase transfer catalysis.

Keywords: Phase transfer catalysts; Ionic liquid; Alkylation; Imidazolium cations.
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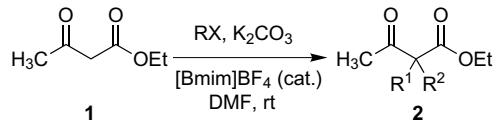


RX= methyl iodide, allyl bromide, propargyl bromide or benzyl bromide

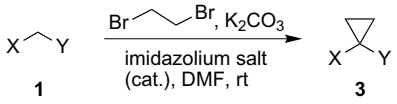
2a; R^1, R^2=allyl, 96%
2b; R^1, R^2=CH_3, 94%
2c; R^1, R^2=propargyl, 95%
2d; R^1, R^2=benzyl, 96%
2e; R^1=CH_3, R^2=propargyl, 87%
2f; R^1=CH_3, R^2=allyl, 88%

Scheme 1. Dialkylation of ethyl acetoacetate with various alkyl halides.

In order to extend the utility of this method, we investigated the cycloalkylation of active methylene compounds using imidazolium salts. Initially, we performed the cyclopropanation using ethyl acetoacetate, 1,2-dibromoethane and K_2CO_3 in the presence of a catalytic amount of [bmim]BF_4 at room temperature to furnish[8,9] **3a** in 86% yield via an intramolecular dialkylation reaction (Scheme 2). To generalize this process, reactions of 1,2-dibromoethane with various active methylene compounds (acetylacetone, diethyl malonate, dimethyl malonate and ethyl cyanoacetate) in the presence of a catalytic amount of several imidazolium salts ([bmim]BF_4, [bmim]PF_6, [bmim]Br, [bbim]BF_4) in DMF were studied (Table 1). Analysis of the results revealed that all four imidazolium salts were effective phase transfer catalysts for the cycloalkylation reactions. However, the reaction of phenylacetic acid ethyl ester under similar experimental conditions did not furnish the cyclopropane derivative **3f** (Table 1) because of the weak acidity of the substrate due to the phenyl group. This reaction was repeated with strong bases such as 7 N NaOH or KOH in aqueous media to furnish 1-phenylcyclopropanecarboxylic acid in 76% yield.

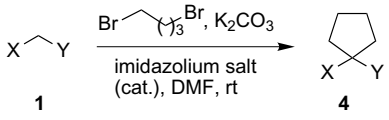
The use of excess active methylene compound in the above process would lead only to cyclopropane ring formation without any side reactions. This shows that the cyclopropanation formation was facile rather than mono-alkylation or intermolecular bis-nucleophilic displacement to give compound of type **6**. Representatively, the reaction of ethyl acetoacetate was performed in [bmim]BF_4 as solvent without addition of any organic solvent like DMF to afford the product **3a** in 30% yield after 7 h duration. However, the same reaction was carried out in DMF as a control experiment[10] without adding any imidazolium salt as a catalyst affording the product **3a** in only 63% yield. Similarly, the reaction with other active methylene compounds (ethyl cyanoacetate, diethyl malonate, acetylacetone) in the absence of the imidazolium salt furnished the corresponding products in the range of only 60–70% yields. This result demonstrates that imidazole based PTCs give the products with improved yields.

Next, we investigated the role of imidazolium salts as PTCs in cyclopentane ring formation using 1,4-dibromobutane via cycloalkylation. We carried out the reaction of ethyl acetoacetate, 1,4-dibromobutane, K_2CO_3 and a catalytic amount of [bmim]Br to deliver[8,9] the cyclopentane derivative **4a** in 94% yield (Scheme 3). Cyclopentane ring formation was generalized with several active methylene compounds and a catalytic amount of imidazolium salts (Table 2). Reactions in



3a; X= COMe, Y= COOEt
3b; X= COOMe, Y= COOMe
3c; X= COOEt, Y= COOEt
3d; X= CN, Y= COOEt
3e; X= COMe, Y= COMe
3f; X= Ph, Y= COOEt

Scheme 2. Cyclopropane ring formation in the presence of a catalytic amount of various imidazolium salts.



4a; X= COMe, Y= COOEt
4b; X= COOMe, Y= COOMe
4c; X= COOEt, Y= COOEt
4d; X= CN, Y= COOEt
4e; X= COMe, Y= COMe
4f; X= Ph, Y= COOEt

Scheme 3. Cyclopentane ring formation in the presence of a catalytic amount of imidazolium salts.

Table 1. Cyclopropanation of active methylene compounds using different ionic liquids

Entry	X	Y	[bmim]BF_4		[bmim]PF_6		[bbim]BF_4		[bmim]Br	
			Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)
3a	COMe	COOEt	86	6	85	6	83	7	88	6
3b	COOMe	COOMe	92	6	87	7	92	7	94[b]	6
3c	COOEt	COOEt	92	6	89	7	92	6	94[b]	8
3d	CN	COOEt	89	4	85	4	86	4	89	4
3e	COMe	COMe	75	9	74	9	73	8	74	9
3f	Ph	COOEt	0	12	0	12	0	12	0	12

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **3**.
[b] Potassium carbonate (20.0 mmol) and imidazolium salt (2.0 mmol) was additionally added and the reaction heated to 70 °C for 3 h for complete conversion.

Table 2. Cyclopentanation of active methylene compound using different ionic liquids

Entry	X	Y	[bmim]BF_4		[bmim]PF_6		[bbim]BF_4		[bmim]Br	
			Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)
4a	COMe	COOEt	96	6	92	6	94	7	94	6
4b	COOMe	COOMe	95	7	90	7	96	6	94	7
4c	COOEt	COOEt	93	8	88	6	90	6	93	7
4d	CN	COOEt	96	5	94	4	93	5	90	5
4e	COMe	COMe	85	8	86	7	86	7	84	8
4f	Ph	COOEt	0	12	0	12	0	12	0	12

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **4**.

the presence of different imidazolium salts furnished the cyclopentane derivatives **4** in 90–96% yields. However, the reaction of acetylacetone afforded only in 84% yield of product **4e** (Table 2). The formation of cyclopentane ring systems was also observed when the reactions were repeated with excess active methylene compounds. This result showed that cyclopentane ring formation is a facile reaction under these experimental conditions.

We also studied the cycloalkylation reactions in the presence of imidazolium salts using different solvents. Thus, the reaction was repeated with solvents such as benzene, acetone and toluene to furnish the cyclopropane derivatives in 80–88% yields and cyclopentane derivatives in 90–96% yields employing potassium or sodium carbonate as base under reflux conditions (Table 3). Further, we investigated the dialkylation and cycloalkylation reactions using the known PTC catalysts (TBAB and TBAI) instead of imidazoium salts under similar experimental conditions and the results are shown in Table 4. This result indicates that the imidazolium salts act as PTC catalysts like TBAB and TBAI.

Finally, we studied the role of imidazolium salts in the formation of the cyclobutane[3c] ring system. The initial study with ethyl acetoacetate, 1,3-dibromopropane and K_2CO_3 in the presence of a catalytic amount of [bmim]BF_4 showed that the unexpected mono-alkylated product **5a** was formed in 96% yield rather than the cyclobutane. Cyclobutane ring formation also failed with other active methylene compounds, even at elevated temperatures and with excess K_2CO_3 (Scheme 4) in the presence of imidazolium salts and furnished only the mono-alkylated compounds **5b–e** in good yields. Further, the use of excess active methylene compound in the above reaction afforded the corresponding bis-alkylated products **6** (56–65%) via intermolecular dinucleophilic displacement and mono-alkylated products **5** (10–20%) under these experimental conditions (Scheme 5).

Table 4. Representative reactions of active methylene compounds in the presence of tetrabutyl ammonium halides salts

Entry	PTC	Time (h)	Product	Yield[a] (%)
1	TBAI	2	**2a**	96
2	TBAB	2	**2a**	94
3	TBAI	6	**3a**	88
4	TBAB	7	**3a**	85
5	TBAB	6	**4a**	93
6	TBAI	5	**4a**	96

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds.

5a; X= COMe, Y= COOEt, 94%
5b; X= COOMe, Y= COOMe, 90%
5c; X= COOEt, Y=COOEt, 96%
5d; X= CN, Y= COOEt, 87%
5e; X= COMe, Y= COMe, 80%

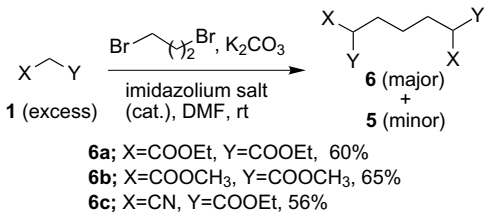
Scheme 4. Mono-alkylation of active methylene compounds with 1,3-dibromopropane in the presence of imidazolium salts.

In conclusion, we have demonstrated that environmentally benign imidazolium salts can be used as phase transfer catalysts for the dialkylation and cycloalkylation reactions of active methylene compounds under mild conditions. Notably, cyclopropane and

Table 3. Reaction of ethyl acetoacetate in different solvent media in the presence of ionic liquids

Solvent	Conditions	Catalyst	Cyclopropanation **3a** (yield, %)[a]	Cyclopentanation **4a** (yield, %)[a]
Benzene	Reflux, 7 h	[bmim]BF_4	83	94
Benzene	Reflux, 7 h	[bmim]PF_6	80	93
Benzene	Reflux, 7 h	[bmim]Br	85	94
Benzene	Reflux, 7 h	[mmim]I	86	96
Acetone	Reflux, 6 h	[bmim]BF_4	88	94
Acetone	Reflux, 6 h	[mmim]I	88	96
Acetone	Reflux, 6 h	[mmim]BF_4	86	92
Toluene	Reflux, 6 h	[bmim]BF_4	86	90

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **3a** and **4a**.



Scheme 5. Intermolecular dialkylation of active methylene compounds in the presence of imidazolium salts.

cyclopentane derivatives were obtained in very good yields at room temperature.

Acknowledgements

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References and notes

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8. General procedure for the dialkylation and cycloalkylation reactions using imidazolium salts as PTCs: To a vigorously stirred solution of active methylene compound (20.0 mmol) and powdered anhydrous potassium carbonate (50.0 mmol) in DMF (50.0 mL) was added the appropriate dihaloalkane (22.0 mmol). To this reaction mixture a catalytic amount of imidazolium salt (2.0 mmol) was added and the mixture stirred at room temperature for the appropriate time. The reaction mixture was filtered and the solid washed with diethyl ether. The filtrate was diluted with water (200 mL) and extracted with diethyl ether (4×75 mL). The organic layers were combined and washed with brine solution. Finally, evaporation of the organic layer afforded the crude product, which was chromatographed through a short alumina column (10% EtOAc/hexane) to yield the respective pure products.
9. All compounds exhibited spectral data consistent with their structures. Selected spectral data: Compound **2a**: colourless liquid; IR (neat) 3080, 2982, 2935, 1739, 1714, 1641, 1442, 1358, 1279, 1211, 1181, 1141, 922 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 5.67–5.50 (m, 2H, C*H*), 5.14–5.06 (m, 4H, CH_2), 4.25–4.15 (q, $J = 7.0$ Hz, 2H, OCH_2), 2.67–2.59 (m, 4H, CH_2), 2.13 (s, 3H, CH_3), 1.30–1.23 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) 203.8 (*C*=O), 171.6 (*C*=O), 132.1 (*C*H), 118.9 (*C*H_2), 62.9 (*quat*-*C*), 61.2 (O*C*H_2), 35.9 (*C*H_2), 26.7 (*C*H_3), 13.9 (*C*H_3); MS (FD^+) *m*/*z* 210 (M^+). Compound **3a**:[10] Colourless liquid; IR (neat) 2984, 2937, 1725, 1702, 1628, 1417, 1398, 1362, 1312, 1187, 1121 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.26–4.16 (q, $J = 7.0$ Hz, 2H, OCH_2), 2.47 (s, 3H, CH_3), 1.46 (s, 4H, CH_2), 1.33–1.27 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) 204.4 (*C*=O), 170.7 (*C*=O), 61.0 (O*C*H_2), 59.2 (*quat*-*C*), 29.5 (*C*H_3), 18.8 (*C*H_2), 13.9 (CH_3); MS (FD^+) *m*/*z* 156 (M^+). Compound **4c**: Colourless liquid; IR (neat) 2980, 2910, 2871, 1731, 1449, 1367, 1297, 1262, 1174, 1028 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.23–4.14 (q, $J = 7.0$ Hz, 4H, OCH_2), 2.22–2.15 (m, 4H, CH_2), 1.72–1.65 (m, 4H, CH_2), 1.28–1.21 (t, $J = 7.0$ Hz, 6H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) 172.5 (*C*=O), 61.0 (O*C*H_2), 60.2 (*quat*-*C*), 34.3 (*C*H_2), 25.3 (*C*H_2), 13.8 (*C*H_3); MS (FD^+) *m*/*z* 214 (M^+). Compound **4d**: Colourless liquid; IR (neat) 2980, 2878, 2242, 1742, 1450, 1368, 1297, 1193, 1025 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.32 (q, $J = 7.0$ Hz, 2H, OCH_2), 2.30–2.24 (m, 4H, CH_2), 1.91–1.84 (m, 4H, CH_2), 1.37–1.30 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) 169.5 (*C*=O), 120.9 (*quat*-*C*), 62.5 (O*C*H_2), 47.4 (*quat*-*C*), 37.5 (*C*H_2), 25.0 (*C*H_2), 13.8 (*C*H_3); MS (FD^+) *m*/*z* 167 (M^+). Compound **6b**: White solid; mp 48–50 °C; IR (KBr) 2960, 2927, 2863, 1744, 1468, 1440, 1349, 1270, 1250, 1221, 1161 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.74 (s, 12H, OCH_3), 3.40–3.32 (t, $J = 8.0$ Hz, 2H, C*H*), 2.0–1.91 (q, $J = 8.0$ Hz, 4H, CH_2), 1.38–1.22 (m, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) 169.5 (*C*=O), 52.4 (O*C*H_3), 51.2 (*C*H), 28.2 (*C*H_2), 25.0 (*C*H_2); MS (FD^+) *m*/*z* 304 (M^+); Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62%. Found: C, 51.18; H, 6.54%.
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