Generation and Reactions of Ammonium Ylides in Basic Two-Phase Systems: Convenient Synthesis of Cyclopropanes, Oxiranes and Alkenes Substituted with Electron-Withdrawing Groups

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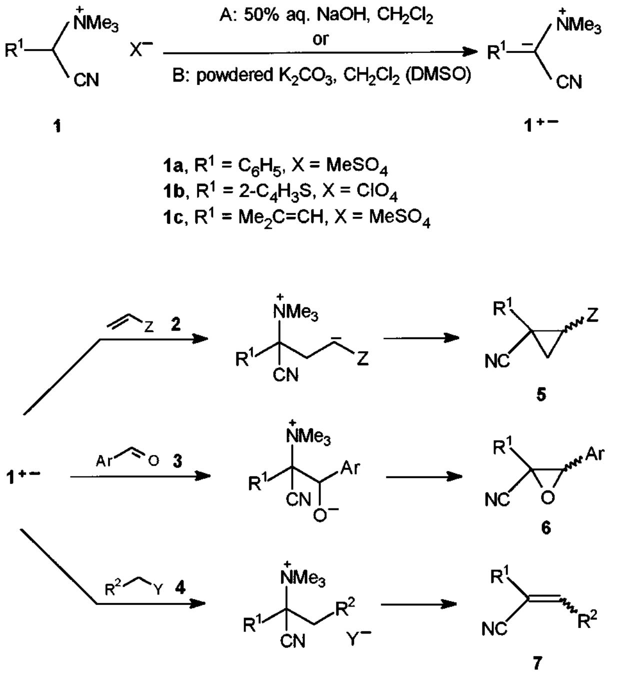
Abstract: Quaternary ammonium salts **1** react with electrophilic alkenes **2**, aromatic aldehydes **3** and alkylating agents **4**, in the presence of 50% aq sodium hydroxide or powdered potassium carbonate, in dichloromethane, to form cyclopropanes **5**, oxiranes **6** and alkenes **7**, respectively, usually in high yields. A key-step of these transformations is the deprotonation of salts **1** which generates ammonium ylides $\mathbf{1}^{+-}$, undergoing further reactions.

Key words: quaternary ammonium salts, ammonium ylides, cyclopropanes, oxiranes, alkenes

Ammonium,[1] unlike phosphorus[2] ylides have attracted chemist's attention mainly because they undergo interesting sigmatropic rearrangements.[3] Searching of the literature reveals that reactions of ammonium ylides with electrophiles like Michael acceptors, carbonyl compounds or alkylating agents etc., have not been sufficiently explored. Thus, an ylide generated from cyanomethyl(trimethyl)-ammonium iodide by means of sodium hydride in THF was allowed to react with chalcones, ethyl acrylate and cinnamate, to give the corresponding cyclopropanes in 21–86% yield.[4] Pyridinium ylides formed from the corresponding salts,[5] also resin-bound ones,[6] with triethylamine in ethanol[5] or DMF,[6] entered the reaction with methylidene malonate derivatives to afford functionalized cyclopropanes in good yields. However, these reactions are restricted to alkenes substituted with two electron-withdrawing groups (EWG). Furthermore, pyridinium ylides can also react as 1,3-dipoles with electrophilic alkenes.[1,5,7] Reactions of alkyl halides and carbonyl compounds engage nucleophilic center of ammonium ylides affording functionalized ammonium salts.[1]

Now, we have found that reactions of ammonium ylides with electrophilic alkenes, aldehydes or alkyl halides open up a synthetically attractive approach to functionalized cyclopropanes, oxiranes and alkenes, respectively. Thus, ylides $\mathbf{1}^{+-}$ generated from phenyl- **1a**, 2-thienyl- **1b** or 2-methyl-1-propenyl- **1c** substituted salts,[8] by means of 50% aq. sodium hydroxide (conditions A) or powdered potassium carbonate (conditions B), in dichloromethane, react with electrophilic alkenes **2** to form cyclopropanes **5**[9,10] (Scheme 1, Table 1).

Cyclopropanes **5** were obtained in good to excellent yields as mixtures of *Z* and *E* isomers. In the case of perchlorate **1b** which is poorly soluble in dichloromethane, beneficial



1a, $R^1 = C_6H_5$, $X = MeSO_4$
1b, $R^1 = 2\text{-}C_4H_3S$, $X = ClO_4$
1c, $R^1 = Me_2C{=}CH$, $X = MeSO_4$

2a, Z = CN
2b, $Z = CO_2Me$
2c, $Z = CO_2\text{-}t\text{-}Bu$
2d, Z = CHO
2e, Z = COMe
2f, Z = COPh
2g, $Z = SO_2Ph$

3a, $Ar = C_6H_5$
3b, $Ar = 4\text{-}MeC_6H_4$
3c, $Ar = 4\text{-}ClC_6H_4$

4a, $R^2 = CH_2{=}CH$, Y = Br
4b, $R^2 = Me_2C{=}CH$, Y = Br
4c, $R^2 = PhCH{=}CH$, Y = Cl
4d, $R^2 = Ph$, Y = Br

Scheme 1

Table 1 Synthesis of cyclopropanes **5**.

Entry	Substrates	Conditions	2/1 (mol/mol)	Time (h)	Product[a]	Yield[b] (%)
1	**1a + 2a**	A	3	6	**5aa**	96[c]
2	**1a + 2b**	B	5	7.5	**5ab**	80[d]
3	**1a + 2c**	A	3	7.5	**5ac**	91[c]
4	**1a + 2d**	B	7	7.5	**5ad**	46
5	**1a + 2e**	B	5	3.5	**5ae**	90
6	**1a + 2f**	B	1	6	**5af**	60
7	**1a + 2g**	A	0.5	3	**5ag**	60
8	**1b + 2c**	A	3	6	**5bc**	84
9	**1b + 2f**	B[e]	1	2	**5bf**	79
10	**1c + 2c**	A	1.5	4.5	**5cc**	82
11	**1c + 2e**	B	5	2.5	**5ce**	92

[a] Mixtures of *E* and *Z* isomers. [b] Isolated yield. All compounds were identified by ^{1}H NMR, HRMS or elemental analyses. [c] Ref. 10. [d] Ref. 12. [e] With DMSO.

effect of DMSO under conditions B, was noticed. Conditions B are recommended for reactions with methyl acrylate (**2b**) and α,β-unsaturated carbonyl compounds **2d-f**, which under conditions A undergo undesired processes. Preliminary experiments indicated that the use of α- or β-alkyl substituted electrophilic alkenes, significantly decrease the yields of the products.[13]

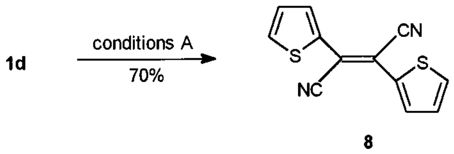
Stirring of salts **1a,c** with aromatic aldehydes under conditions A led to formation of substituted oxiranes **6**, in moderate yields (Scheme 1, Table 2). In all reactions, formation of significant amounts of decomposition products (dark material which remained on silica gel column) was observed. Furthermore, the mixtures from salt **1c** contained products of the Canizzaro reaction (in the case of **3a** benzyl alcohol and benzoic acid). ^{1}H NMR spectra of crude reaction mixtures from salt **1a** exhibit that only one, *Z* stereoisomer of **6** was produced. On the other hand, oxiranes **6ca** and **6cc** were formed as mixtures of *Z* and *E* isomers, the corresponding structures were ascribed as the result of NOE experiments.[14] To the best of our knowledge, such an approach to the synthesis of oxiranes is unprecedented.[9a,10,15]

Table 2 Synthesis of oxiranes **6**.

Entry	Substrates^a	3/1 (mol/mol)	Time (h)	Product	Yield^d (%)
1	**1a + 3a**	1	20	**6aa**^{b}	50^e
2	**1a + 3b**	0.5	8	**6ab**^{b}	46^e
3	**1a + 3c**	1	9	**6ac**^{b}	47^f
4	**1c + 3a**	2	7	**6ca**^{c}	52
5	**1c + 3c**	1	10	**6cc**^{c}	32

[a] All reactions were carried out under conditions A. [b] Pure (by ^{1}H NMR) *Z* isomers. [c] *Z/E* ca 2.5 (by ^{1}H NMR). [d] Isolated yield. All compounds were identified by ^{1}H NMR, HRMS or elemental analyses. [e] Ref. 16. [f] Ref. 10.

Hetaryl substituted salt **1b** did not form the corresponding oxirane when it was allowed to react with benzaldehyde (**3a**), but fumaronitrile derivative **8** was produced, instead. The same product was isolated when salt **1b** was stirred without aldehyde, under conditions A[17] (Scheme 2).



Scheme 2

Finally, alkylation of salts **1a** and **1c** afforded alkenes, conjugated dienes or trienes, substituted with a cyano group **7** (Scheme 1, Table 3).

Except for **7ad** (*Z* isomer), all products were formed as mixtures of *Z* and *E* isomers. This reaction is restricted to active alkylating agents, like benzyl or allyl halides, and requires conditions A. Olefination of alkyl halides by means of ammonium ylides complements earlier methodologies which rely on use dimethylsulfonium methylide[21] or triphenylarsonium alkylides.[22] Reaction of salt **1b** with benzyl bromide (**4d**) again led to formation of dinitrile **8**, instead of the expected cyanoalkene.

Table 3 Synthesis of alkenes **7**.

Entry	Substrates^a	4/1 (mol/mol)	Time (h)	Product	Yield^b (%)
1	**1a + 4a**	15	1.5	**7aa**	93
2	**1a + 4b**	5	3	**7ab**	94
3	**1a + 4d**	1	2.5	**7ad**	80^{c,d}
4	**1c + 4b**	1	4	**7cb**	93
5	**1c + 4c**	1.25	7	**7cc**	72
6	**1c + 4d**	1	4	**7cd**	89^e

[a] All reactions were carried out under conditions A. [b] Isolated yields All compounds were identified by ^{1}H NMR, HRMS or elementa analyses. [c] *Z* isomer, in other cases mixtures of *Z* and *E* isomers [d] Ref. 19. [e] Ref. 20.

The reactions reported above consist in deprotonation of salts **1**, addition of ylides **1**$^{+-}$ to alkenes **2** or aldehydes **3**, and cyclization of the betaines thus formed to cyclopropanes **5** and oxiranes **6**, respectively. On the other hand, alkylation of ylides **1**$^{+-}$ with **4** produces alkylated salts which form alkenes **7** via base-mediated elimination of amine (Scheme 1). The reactions are very simple, consist in stirring of the salt **1** with electrophiles **2-4**, usually used in excess, in a two-phase basic system, at ca 25 °C, and are exemplified by the synthesis of **5ac**, **5bf**, **6ac** and **7cd**.[23] This approach to products **5-7** is fully competitive with known methods, and is recommended for laboratory praxis.

Acknowledgement

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(8) The crystalline salts **1a,c** were prepared by reaction of the corresponding aminonitrile with methylsulfate, carried out at ca –10 °C. Oily methylsulfate of thienylaminonitrile was

converted into crystalline perchlorate **1b** with 60% aq $HClO_4$.
1a:80%; mp 115–116 °C (AcOEt/AcMe ~ 1:3); ^1H NMR, δ (ppm, 200 MHz, $CDCl_3$):3.35 (9H, s, N^+Me_3), 3.65 (3H, s, $MeSO_4^-$), 6.60 (1H, s, CH), 7.45–7.60 (3H, m, ArH), 7.65–7.75 (2H, m, ArH). Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78. Found: C, 50.01; H, 6.39; N, 9.69.
1b:91%; mp 169–171 °C (MeOH); ^1H NMR, δ (ppm, 200 MHz, DMS*O*-d_6):3.23 (9H, s, N^+Me_3), 6.82 (3H, s, CH), 7.31 (1H, dd, *J* = 5.2 Hz, *J* = 3.7 Hz, ArH), 7.60 (1H, dd, *J* = 3.7 Hz, *J* = 1.2 Hz, ArH), 8.05 (1H, dd, *J* = 5.2 Hz, *J* = 1.2 Hz, ArH). Calcd for $C_9H_{13}N_2O_4ClS$: C, 38.51; H, 4.67; N, 9.98. Found: C, 38.52; H, 4.76; N, 9.90.
1c:84%; mp 99–101 °C (AcMe); ^1H NMR (ppm, 200 MHz, DMSO-d_6):1.84 (3H, d, *J* = 1.4 Hz, Me), 1.88 (3H, d, *J* = 1.2 Hz, Me), 3.15 (9H, s, N^+Me_3), 3.38 (3H, s, $MeSO_4^-$), 5.50–5.65 (1H, m, C=CH), 5.70–5.80 (1H, m, CH). Calcd for $C_{10}H_{20}N_2O_4S$: C, 45.44; H, 7.63; N, 10.60. Found: C, 45.49; H, 7.63; N, 10.57.

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(13) For example, reaction of salt **1a** with an excess of methacrylonitrile under conditions A, gives 1,2-dicyano-1-methyl-2-phenylcyclopropane, in 27% yield.

(14) Irradiation of signals of oxirane protons at δ = 4.10 ppm or δ = 4.51 ppm in *Z* and *E* isomers mixture of **6ca** resulted in increase of only one signal of olefinic protons at δ = 5.40 – 5.45 ppm (m), namely from *Z*-isomer.

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(17) The formation of dinitrile **8** via carbanionic route (alkylation of ylide **1b**$^{+-}$ with **1b**, followed by elimination of trimethylamine), as previously suggested for similar transformation of α-chloro(phenyl)acetonitrile in PTC system,[18] seems feasible. Alternatively, cleavage of ylide **1b**$^{+-}$ may generate cyano-2-thienyl carbene which after dimerization produces **8**. However, our attempts to intercept this carbene with n-butylvinyl ether, failed.

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(23) **5ac**: to a vigorously stirred solution of **1a** (1.43 g, 5 mmol) in CH_2Cl_2 (20 mL), ester **2c** (1.92 g, 15 mmol) then 50% aq. NaOH (7 mL) were added, and the mixture was stirred at RT for 7.5 h. The mixture was diluted with water, the phases were separated, the water phase was extracted with CH_2Cl_2, the combined organic extracts were washed with water, dried ($MgSO_4$), the product was purified by column chromatography on a short pad of silica gel (Merck Silica gel 60, finer than 230 mesh, eluent hexane-AcOEt, gradient) to give 1.10 g (91%) of oily **5ac** (Table 1, Entry 3).
5bf: the solution of **1b** (1.40 g, 5 mmol) in CH_2Cl_2 (60 mL) and DMSO (15 mL) was vigorously stirred while ketone **2f** (0.66 g, 5 mmol) then powdered K_2CO_3 (6.9 g) were added. Stirring at RT was continued for 2 h, the reaction was worked up as described for **5ac**, and the product was purified by Kugelrohr distillation [bp 130–140 °C (oven)/0.15 Torr] to give 1.00 g (79%) of **5bf** (Table 1, Entry 9).
6ac: to vigorously stirred **1a** (1.43 g, 5 mmol), aldehyde **3c** (0.70 g, 5 mmol) and CH_2Cl_2 (30 mL), 50% aq NaOH (12 mL) was added, and stirring was continued at RT for 0.5 h and refluxed for 8.5 h. The mixture was worked up as described for **5ac**, and the product was crystallized (MeOH) to give 0.60 g (47%) of **6ac**, mp 111–113 °C (Table 2, Entry 3).
7cd: the solution of **1c** (1.32 g, 5 mmol) in CH_2Cl_2 (20 mL) was vigorously stirred, bromide **4d** (0.86 g, 5 mmol) then 50% aq NaOH (7 mL) were added (exothermal effect), reaction was continued for 4h, and worked up as described for **5ac**. The product was purified by Kugelrohr distillation [bp 125–130 °C (oven)/0.03 Torr] to give 0.81 g (89%) of oily **7cd** (Table 3, Entry 6).

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