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Unusually Facile Dealkylation of Alkyl 2-(Methylthiomethyl)phenyl Sulfoxides with Triflic Anhydride *via* Dithia Dications: Stereochemical and Kinetic Studies

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Abstract: *Alkyl 2-(methylthiomethyl)phenyl sulfoxides undergo facile monodealkylation on treatment with triflic anhydride in CH_3CN to afford the corresponding thiasulfonium salts and alkyl iminium salts quantitatively. The dealkylation proceeds by an S_N1 process which gives thiasulfonium salt and alkyl cation via an initial formation of the corresponding dithia dication species.*

Organo-chalcogen dication species are of considerable current interest in heteroatom chemistry.[1] Although, monooxides of cyclic bissulfides afford readily the corresponding stable dithia dications *via* through–space interaction between the sulfur atoms,[2] the acyclic analogues have not been studied well due to their instability.[3] Recently, we found that the unusually facile dealkylation of monooxides of 2,2'-bis(alkylthio)biphenyls takes place on treatment with triflic anhydride *via* dithia dications.[4] This result implies that the formation of dications provides new source of carbocations, and hence further extension of the present study is required. Firstly, we employed alkyl 2-(methylthiomethyl)phenyl sulfoxides **1** as a simple reaction system. In this paper, we report facile monodealkylation from the sulfoxides **1** proceeding *via* an initial formation of highly reactive dithia dications **2** which subsequently undergo the dealkylation to give thiasulfonium salts and *N*-alkylacetamides on hydrolysis.

Initially, **1a**(R = Et) was treated with 1 equivalent of Tf_2O in CD_3CN at –40 °C and its ^1H NMR spectrum was measured in situ. One set of an AB quartet peak at δ 5.51 and 5.82 ppm (J = 16.8 Hz) as the benzyl (–SCH_2–) peak, a quartet peak at 4.13 ppm of the methylene group (S–$\underline{CH_2}CH_3$), a singlet peak at δ 3.52 ppm of the methyl group (S–CH_3) and a triplet peak at 1.51 ppm of the methyl group (S–$CH_2\underline{CH_3}$) were obtained in the ^1H NMR spectrum suggesting the generation of dithia dication **2a** at –40 °C, which was also supported by the ^{13}C NMR spectrum.[5] However, the peaks were changed gradually to one set of an AB quartet peak appeared at δ 5.00 and 5.29 ppm (J = 16.4 Hz, Ar–$\underline{CH_2}$–S^+–CH_3), a quartet peak at 4.71 ppm (–$\underline{CH_2}CH_3$), one methyl singlet peak at 3.00 ppm (S^+–$\underline{CH_3}$)and a triplet peak at 1.46 ppm (–$CH_2\underline{CH_3}$) in the ^1H NMR spectrum at 0 °C which indicate the formation of methyl thiasulfonium salt **3a** and ethyl triflate.[6] Actually, the formation of one equivalent of ethyl triflate was confirmed by ^1H NMR spectrum showing the identical peaks with that of authentic compound and the triflate formed in the reaction readily alkylated acetonitrile to form *N*–ethylacetamide after hydrolysis.[7] These results demonstrate that **3a** is apparently generated *via* the deethylation from dithia dication **2a** as shown in Scheme 1. Next, we tried to isolate the

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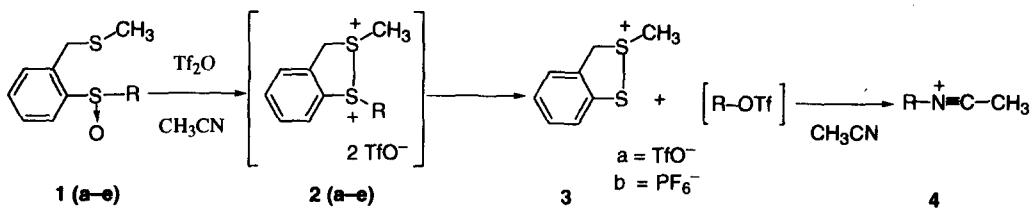
thiasulfonium salt **3** by treatment of the bissulfide of **1a** with 2 equiv. of $NOPF_6$ in anhydrous CH_3CN at –40 °C to 20 °C. After isolation and recrystallization from CH_3CN–Et_2O, methylthiasulfonium salt **3b** (70%) was characterized by ^1H, ^{13}C, ^{19}F and ^{31}P NMR and FAB MS spectra.[8]

Scheme 1



1 (a–e) **2 (a–e)** **3** **4**

The similar reactions using the sulfoxides **1(b-d)** were examined. The formation of dithia dications **2 (b-d)** was not observed spectroscopically at all even at –40 °C, and the direct formation of the thiasulfonium salt **3** was observed quantitatively by ^1H and ^{13}C NMR. For example, in the case of **1c**, *N*-benzyl acetamide which would be produced by the reaction of benzyl group with acetonitrile used as a solvent was obtained quantitatively (98%) besides **3**. These results demonstrate that the dications **2(b–d)** would be very unstable due to the highly leaving ability of the R group like Ritter reaction.[9] The data are summarized in Table 1.

Table 1.

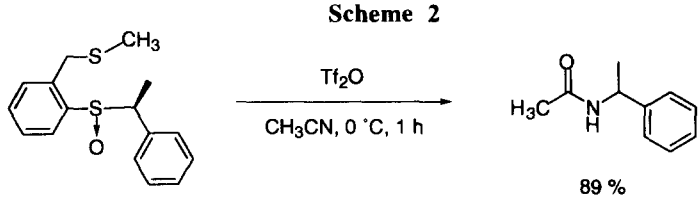
Sulfoxide	R[c]	Product	Yield
1a	ethyl	EtOTf	91%[a]
1b	isopropyl	*N*–isopropylacetamide	89%[a]
1c	benzyl	*N*–benzylacetamide	98%[b]
1d	(*S*)–α–phenethyl	*N*–α–phenethyllacetamide	89%[b]
1e	2,2–diphenylethyl	*trans*–stilbene	74%[b]

[a] Determined by ^1H–NMR. [b] Determined by GC. [c] R = CH_3 gave different products.

In order to determine the mechanism for the dealkylation from dithia dications namely, whether the reaction proceeds *via* an S_N1 type and or an S_N2 or a ligand coupling process, chiral phenethyl sulfoxide **1d**[10] was prepared in 99%d.e. and subjected to the reaction under the same conditions. The resulting *N*-phenethyl acetamide was isolated in 89% yield on hydrolysis and its optical activity was determined to be 1.7% e.e. The acetamide obtained was found to be nearly racemized suggesting that the mechanism for the reaction is an S_N1 process (Scheme 2). The racemization of the intermediate nitrilium species **4** was well known in the Ritter reaction by the facile nitrile exchange at room temperature but in this reaction less than 10% nitrile exchange was observed at –40 °C for 30 min.[11] In order to confirm whether the racemization occurs before nitrile exchange of **4d**, we carried out this reaction at –40 °C for 1 min and on hydrolysis it was found to give almost racemic

product (1.2 %e.e.). This result supports clearly that the racemization occurs at the dealkylation process from the dithia dication.

Scheme 2



1 d

89 %

1.7 % e.e.

In addition, the dealkylation using dithia dication of 2,2-diphenylethyl sulfoxide **1e** subjected under the same reaction conditions afforded *trans*–stilbene in 75% yield together with thiasulfonium salt **3**. This result indicates that the one phenyl group in the 2,2-diphenylethyl group migrates to the 1-position in the carbonium cation formed, supporting also the S_N1-type process.

Furthermore, kinetic study of the dealkylation from dithia dication **2a** was carried out using variable temperature ^1H NMR method. The rate of dealkylation was measured by monitoring the decrease of AB quartet peaks at δ 5.51 and 5.82 ppm (Ar-C<u>H</u>$_2$-SMe). After the reaction was followed by the third half-lives, the plot of ln([a]/[a-x]) vs. time, where [a] was initial concentration and [a–x] was the concentration of **2a** as a function of time, clearly gave a straight line with a good correlation coefficient ($r^2 \simeq 0.997$–0.999), indicating that the reaction obeys the first order equation on the concentration of dithia dication **2a**. Even if the concentration of the substrate was changed from 41 mM to 169 mM at 0 °C, the reaction followed the first order kinetic equation to give k_1 : 9.241 ± 0.170 x 10^{-4} (41 mM), 9.454 ± 0.470 x 10^{-4} (69 mM), 9.877 ± 0.113 x 10^{-4} (169 mM) . The dealkylations were monitored at the following temperature range (–10, –5, 0, 5 °C). All the plots of ln([a]/[a-x]) vs. time gave good straight lines. The rate constants k_1 obtained are listed in Table 2. Activation parameters for this dealkylation were determined from the temperature dependence of the rate constants k_1. The Arrhenius plot was linear (r^2 = 1.00) and gave the values for activation energy Ea. The Eyring plot was also linear and allowed for determination of the activation parameters, $\Delta H^{\neq}$, $\Delta S^{\neq}$ as shown in Table 2.

Table 2. Activation Parameters for the Dealkylation of Dithia Dication.

k_1 (s^{-1})	Ea (kcal•mol^{-1})	$\Delta H^{\neq}_{298}$ (kcal•mol^{-1})	$\Delta S^{\neq}_{298}$ (eu)
1.892 ± 0.013 x 10^{-3} (5 °C)	20.5 ± 0.2	20.0 ± 0.3	0.72 ± 0.63
9.808 ± 0.035 x 10^{-4} (0 °C)			
4.824 ± 0.171 x 10^{-4} (–5 °C)			
2.302 ± 0.027 x 10^{-4} (–10 °C)			

In general, dealkylation of sulfonium salts requires high temperature.[12] These kinetic results indicate the high reactivity of the dithia dications **2** which are activated by the neighboring group participation between the two sulfur atoms and support the S_N1 character in the dealkylation from the dithia dications **2**.

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5. **2a**: ^{1}H NMR (400 MHz, CD_3CN, –40 °C) δ 1.51 (t, J = 7.2 Hz, 3H), 3.52 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 5.51, 5.82 (ABq, J = 16.8 Hz, 2H), 7.82 (t, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.94 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN, –40 °C) δ 11.1, 28.5, 49.5, 53.0, 122.8, 130.6, 130.9, 132.7, 136.4, 140.3.
6. **3a**: ^{1}H NMR (400 MHz, CD_3CN) δ 3.00 (s, 3H), 5.00, 5.29 (ABq, J = 16.4 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 29.5, 54.7, 125.5, 128.8, 129.4, 131.2, 132.1, 133.9; ^{19}F NMR (376 MHz, CD_3CN) –75.7; FABMS (pos.) m/z 169 ([M–$CF_3SO_3^-$]$^+$), 487 ([2M–$CF_3SO_3^-$]$^+$) (matrix: 2-nitrophenyl *n*-octyl ether).
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8. **3b**: pale yellow crystals. mp 110–112 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 3.00 (s, 3H), 4.96, 5.28 (ABq, J = 16.4 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 29.6, 54.9, 125.7, 128.9, 129.6, 131.4, 132.2, 133.9; ^{19}F NMR (254 MHz, CD_3CN) δ –69.2 (d, J_{P-F} = 706 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ –144.7 (sept, J_{P-F} = 706 Hz); FABMS (pos.) m/z 169 ([M–PF_6^-]$^+$), 483 ([2M–PF_6^-]$^+$) (matrix: *m*–nitrobenzyl alcohol).
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10. **1d**: white crystals. mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, J = 7.1 Hz, 3H), 1.96 (s, 3H), 2.99, 3.40 (ABq, J = 13.9 Hz, 2H), 4.05 (q, J = 7.1 Hz, 1H), 7.06–7.12 (m, 2H), 7.22–7.30 (m, 3H), 4.26 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 15.1, 33.2, 66.3, 125.0, 128.0, 128.3, 128.5(2), 128.6(2), 129.6, 131.1, 136.1, 137.0, 141.7; EI-MS (m/z) 290 (M^+); Anal. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25. Found: C, 65.91; H, 6.33.
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