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Reactions of the carbanion of chloromethyl methyl sulfone with aldehydes and ketones

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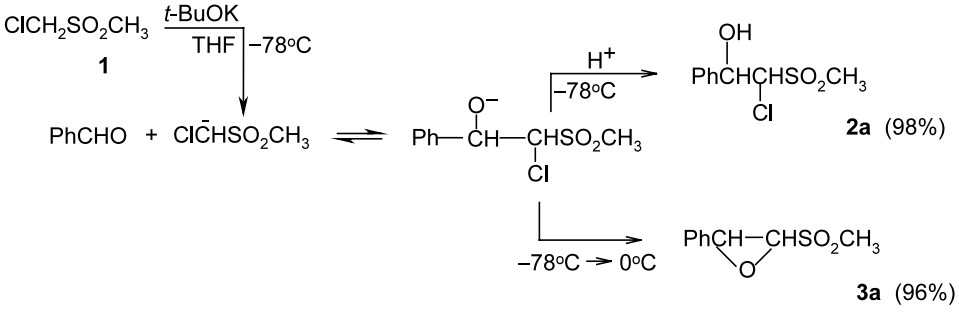
Abstract—Addition of the carbanion of chloromethyl methyl sulfone to aldehydes and ketones proceeds faster than its degradation via the Ramberg–Baecklund reaction. Chlorohydrins and oxiranes produced from aldehydes treated with an excess of base undergo the Ramberg–Baecklund reaction giving allylic alcohols, whereas the reaction of ketones gives the oxiranes.

Carbanions of chloromethyl sulfones are versatile reactants of great value in organic synthesis widely used for synthesis of oxiranes,[1–3] vicarious nucleophilic substitution of hydrogen,[4,5] etc. However only aryl or *t*-butyl chloromethyl sulfones can be used as the carbanion precursors since alkyl chloromethyl sulfones treated with strong bases undergo rapid Ramberg–Baecklund (R–B) reaction.[6,7] A literature search revealed that there is one example of an intermolecular reaction of the carbanion of chloromethyl methyl sulfone **1**, the simplest representative of such sulfones. It's reaction with cyclohexanone gave the corresponding chlorohydrin and oxirane.[3]

On the other hand reactions of such carbanions could offer interesting possibilities in organic synthesis, for example addition of the carbanion of **1** to an aldehyde followed by the Ramberg–Baecklund reaction should give an allylic alcohol.

Initial experiments in which benzaldehyde and chloromethyl methyl sulfone **1** were reacted in the presence of concentrated aqueous NaOH and tetrabutylammonium chloride, under PTC conditions,[8] gave negative results, although these conditions were used efficiently for the Darzens condensation of chloromethyl aryl sulfones.[2,8] On the other hand when these reactants were treated with *t*-BuOK in THF at low temperature (−78°C) the expected chlorohydrin was produced in high yield. When the reaction mixture was quenched with aqueous NH_4Cl at −78°C the chlorohydrin **2a** was isolated as a mixture of two diastereoisomers (*syn*:*anti*≈70:30 on the basis of NMR spectra namely the magnitudes of the coupling constants $^3J_{HH}$



Scheme 1.

Keywords: allylic alcohols; carbanions; chloromethyl methyl sulfone; Ramberg–Baecklund reaction.
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for the HCCl and HCOH protons), but when the mixture was warmed to 0°C before quenching, intramolecular substitution took place to give the expected methylsulfonyl oxirane **3a** (*trans*:*cis* >98:2) on the basis of NMR spectra-coupling constant values $^3J_{HH}$ for the HCHPh and $HCSO_2CH_3$ protons) (Scheme 1).

Thus avoiding an excess of base and working at low temperature it was possible to execute a typical carboanionic reaction of the carbanion of chloromethyl methyl sulfone: addition to the carbonyl group producing chlorohydrin **2** and subsequently the formation of oxirane **3** which proceeded much faster than the R–B reaction. It should be stressed that the carbanion of **1** is relatively stable at −78°C. When **1** was treated at −78°C with *t*-BuOK, and benzaldehyde added after 5 s and the mixture quenched, **2a** was obtained in 96% yield. Further conversion of the chlorohydrin or the oxirane via the R–B reaction proceeds when they are treated with an excess of strong base: *t*-BuOK. Thus direct treatment of a mixture of benzaldehyde and **1** with *t*-BuOK (3 equiv.) at −78°C and subsequently warming the mixture to 0°C gave 1-phenylallyl alcohol **4a**. The same alcohol was obtained upon treatment of the isolated chlorohydrin **2a** or oxirane **3a** with 2 equiv. of *t*-BuOK. Other aromatic aldehydes: *o*-chloro- and *p*-methoxybenzaldehyde and also aliphatic aldehydes, e.g. isobutyraldehyde react with **1** in a similar way to give the corresponding allylic alcohols **4b–d** (Scheme 2). In the latter cases the reaction was carried out in the presence of a threefold excess of *t*-BuOK at −78→0°C as a one-pot procedure, the corresponding allylic alcohols being obtained as the only products.

The allylic alcohols can be produced in the reactions of aldehydes with **1** via the R–B reaction in two ways (Scheme 2).

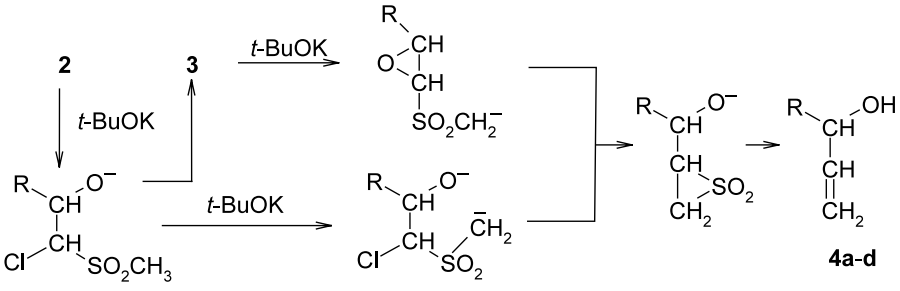
The intermediate chlorohydrin **2a** on treatment with an excess of base can undergo direct intramolecular substitution of the halogen with the methylsulfonyl carbanion to form a substituted episulfone and subsequently the allylic alcohol **4a**. Alternatively cyclization of the chlorohydrin anion may give the oxirane **3a**, which undergoes intramolecular epoxide ring opening with the methylsulfonyl carbanion. The latter process is supported experimentally because the oxirane **3a**, when separately prepared, does undergo the intramolecular reaction producing the allylic alcohol when treated with an excess of base. The R–B reaction proceeding via epoxide ring opening to give allylic alcohols has been reported earlier.[9]

In order to clarify whether conversion of the chlorohydrin **2a** to the alcohol **4a** proceeds via the intermediate oxirane **3a**, chlorohydrin **2a** (a mixture of *syn* and *anti*) was treated with 3 equiv. of *t*-BuOK at −50°C. Quenching the mixture after 5 min gave **4a** (40%), unreacted **2a** (45%) and oxirane **3a** (15%). In a separate experiment it was shown that under such conditions the oxirane **3a** is converted into **4a** to a much lower degree (20%), the majority of the oxirane (80%) being recovered. Thus in the presence of an excess of base, **2a** is converted directly into **4a** much faster than the conversion of **2a**→**3a** and then **3a**→**4a**.

A facile one-pot synthesis of allylic alcohols in the base promoted reaction of **1** with aldehydes indicates that addition of the carbanion of **1** to aldehydes proceeds faster than the competing R–B reaction and that this carbanion can be considered as a synthetic equivalent of a vinyl carbanion.[10,11]

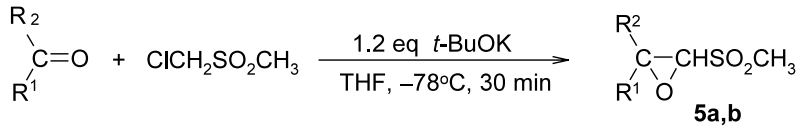
The carbanion of **1** can also be trapped efficiently by aliphatic ketones, the corresponding oxiranes being the final products. These reactions were conducted as described for the synthesis of chlorohydrin **2a**.[11] Standard workup gave analytically pure compounds **5a**,**b**[12] (Scheme 3).

Contrary to the observations reported earlier,[3] where lithium bases were used, in this case the reaction cannot be stopped at the chlorohydrin stage because further cyclization of its potassium salts to oxiranes is a very fast process. These oxiranes do not enter the R–B reaction under these conditions as do the oxiranes produced from aldehydes. We have not observed formation of allylic alcohols when these oxiranes were treated with an excess of *t*-BuOK even at room temperature.



R = Ph, **4a**, 63%; *o*-ClPh, **4b**, 68%; *p*-MeOPh, **4c**, 35%; *i*-Pr, **4d**, 66%

Scheme 2.



5a: R^1, $R^2 = (CH_2)_5$; 98%, **5b**: $R^1 = R^2$ = Et; 97%

Scheme 3.

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10. Potassium *t*-butoxide (0.27 g, 2.4 mmol. 1.2 equiv.) was added to a cooled (−78°C) solution of **1** (0.26 g, 2 mmol) and benzaldehyde (0.21 g, 2 mmol) in dry THF (2 ml). The mixture was stirred for 30 min at −78°C and quenched with an excess of aqueous NH_4Cl. Standard work-up (EtOAc (3×5 ml), Na_2SO_4) gave pure chlorohydrin **2a** (0.46 g, 98%) as a mixture of two diastereoisomers (*syn*:*anti* = 68:32). Double recrystallization from CH_2Cl_2/pentane gave a single diastereoisomer *syn*-**2a**: mp 142–143°C (racemic mixture). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3–7.5 (m, 5H, Ph), 5.8 (d, J = 1.3 Hz, 1H, CH(OH)); 4.7 (d, J = 1.3 Hz, 1H, $CH(SO_2CH_3)$); 3.2 (s, 3H, CH_3); 1.7 (br.s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.0; 128.8; 128.7; 126.0; 78.1; 70.3; 38.7. MS (EI 70 eV): m/z (%) 236 (0.9); 234 (2.5); 156 (1.9); 154 (5.9); 107 (100); 91 (17.2); 79 (37.9); 78 (10.4); 77 (16.7). Calcd for $C_9H_{11}SO_3Cl$: C, 46.15; H, 4.74; S, 13.66; Cl, 14.94. Found: C, 46.29; H, 4.88; S, 13.47; Cl, 15.01%. *anti*-**2a**: ^{1}H NMR: δ 7.3–7.5 (m, 5H, Ph); 5.2 (d, J = 8.4 Hz, 1H, CH(OH)); 4.8 (d, J = 8.4 Hz, 1H, $CH(SO_2CH_3)$); 3.1 (s, 3H, CH_3), 1.7 (br. s, 1H, OH). ^{13}C NMR: δ 137.8; 129.1; 128.4; 127.4; 75.2; 73.8; 39.7. When the mixture was warmed to 0°C before quenching, pure oxirane **3a** (*trans*:*cis*>98:2) was obtained (0.38 g, 96%). Recrystallization from hexane/CH_2Cl_2 gave pure *trans*-**3a**: mp 86–87°C. ^{1}H NMR: δ 7.4 (m, 3H, Ph), 7.3 (m, 2H, Ph), 4.6 (d, J = 1.6 Hz, 1H, PhCH), 4.3 (d, J = 1.6 Hz, 1H, $CHSO_2CH$); 3.1 (s, 3H, CH_3). ^{13}C NMR: δ 132.3; 129.6; 128.7; 126.0; 69.7; 56.8; 38.9. MS (EI 70 eV); m/z (5) 198 (1.9); 119 (34); 91 (100); 65 (19.5). Calcd for $C_9H_{10}SO_3$: C, 54.54; H, 5.09; S, 16.14. Found: C, 54.39; H, 5.16; S, 16.00%. When *t*-BuOK was used in threefold excess (0.7 g) and the mixture warmed to 0°C before quenching, the standard workup (Et_2O (3×5 ml), Na_2SO_4) gave 1-phenylallyl alcohol **4a** (0.17 g, 63%): ^{1}H NMR: δ 7.3–7.5 (m, 5H, Ph), 6.1 (m, 1H, $CH{=}CH_2$), 5.4 ($\approx$dt, J_1 = 17.1 Hz, $J_2 \approx$ 1.6 Hz, 1H, CH(OH)), 5.2 (m, 2H, $CH{=}CH_2$), 2.2 (br. s, 1H, OH). ^{13}C NMR: δ 142.5; 140.1; 128.4; 127.6; 126.2; 114.9; 75.2. Data for the other allylic alcohols obtained in the reaction of **1** with *o*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and isobutyraldehyde (Scheme 2). **4b**: 68% ^{1}H NMR: δ 7.5–7.6 (m, 1H, Ar), 7.2–7.4 (m, 3H, Ar), 6.0 (m, 1H, $CH{=}CH_2$), 5.6 (d, J = 4 Hz, 1H, CHOH), 5.3 (m, 2H, $CH_2{=}CH$), 3.1 (br. s., 1H, OH). ^{13}C NMR: δ 140.4; 138.9; 130.0; 129.3; 128.2; 127.7; 116.2; 71.9. **4c**: ^{1}H NMR δ 6.9–7.4 (m, 4H, Ar), 6.1 (m, 1H, $CH{=}CH_2$), 5.3 (m, 3H, $CH{-}CH{=}CH_2$), 3.8 (s, 3H, OCH_3), 2.2 (br.s, 1H, OH). **4d**: ^{1}H NMR: δ 5.9 (m, 1H, $CH{=}CH_2$), 5.2 (m, 2H, $CH_2{=}CH$), 3.9 (m, 1H, CHOH), 2.6 (br.s, 1H, OH), 1.8 (m, 1H, $CH(CH_3)_2$), 1.1 (m, 6H, CH_3); ^{13}C NMR: δ 139.4; 115.4; 78.6; 33.6; 17.8; 15.2.
11. Although episulfones are considered short lived intermediates in the R–B reaction, they can be deprotonated at low temperature. The carbanions produced react with aldehydes to form the aldols, with loss of SO_2 giving allylic alcohols, thus, episulfones behave as vinyl anion equivalents.
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12. **5a**: ^{1}H NMR: δ 3.8 (s, 1H, $CHSO_2CH_3$), 2.9 (s+m, 3H, SO_2CH_3), 2.0 (m, 2H, Cy), 1.5 (m, 8H, Cy). ^{13}C NMR: δ 73.0; 68.2; 40.8; 34.9; 28.0; 24.8; 24.7; 24.6. MS (EI 70 eV): m/z (%) 111 (20.0); 99 (31.3); 93 (100); 81 (90.0); 67 (67.7); 39 (44.4); 41 (43.7); 43 (31.8); 55 (71.3). Calcd for $C_8H_{14}SO_3$: C, 50.51; H, 7.42; S, 16.82. Found: C, 50.37; H, 7.25; S, 16.76%. **5b**: ^{1}H NMR: δ 3.8 (s, 1H, $CHSO_2CH_3$), 3.0 (s, 3H, SO_2CH_3), 2.1 (m$\approx$qd, J_1 = 7.5 Hz, $J_2 \approx$ 2.1 Hz, 2H, CH_2CH_3), 1.7 ($\approx$q, J'_1 = 7.4 Hz, 2H, $(CH_2CH_3)'$), 1.1 (t, J_1 = 7.5 Hz, 3H, CH_2CH_3), 0.9 (t, J'_1 = 7.4 Hz, 3H, $(CH_2CH_3)'$). ^{13}C NMR: δ 72.3; 70.8; 41.0; 27.1; 22.3; 9.7; 8.2. MS (EI 70 eV); m/z (%) 99 (12.0); 87 (13.4); 81 (17.6); 69 (30.8); 57 (36.1); 55 (32.3); 43 (100); 41 (61.3); 39 (15.3). Calcd for $C_7H_{14}SO_3$: C, 47.17; H, 7.92; S, 17.6. Found: C, 47.10; H, 7.75; S, 17.70%. Molecular ions are absent in the MS of **5a** and **5b**.