Reaction of *N*-Acyl- and *N*-Sulfonylcarboxamides with Triethyl Orthoformate

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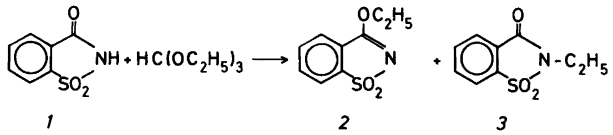
In connection with our investigation on the reaction of triethyl orthoformate with carboxamides[1] we became interested in the reaction between triethyl orthoformate and *N*-sulfonylcarboxamides, especially saccharine.

The reaction of secondary amides with triethyl orthoformate has not been reported in the literature. We have found that *N*-acetylacetamide, *N*-acetylbenzamide and *N*-benzoylbenzamide react very slowly compared with *N*-unsubstituted and *N*-monosubstituted carboxamides, and we were unable to isolate anything but starting material and esters. On the contrary phthalimide reacts easily with triethyl orthoformate under formation of *N*-diethoxymethylphthalimide *i.e.* a reaction product analogous to the product from *N*-monosubstituted sulfonamides.[2] An analogous product from the reaction between 2,3-dihydro-1,2-benzisothiazol-3-one-1,1-dioxide (saccharine) *1* and triethyl orthoformate could be expected, but instead a mixture of 3-ethoxy-1,2-benzisothiazol-1,1-dioxide *2* and 2-ethyl-2,3-dihydro-1,2-benzisothiazol-3-one-1,1-dioxide *3* was formed (Scheme 1). It is well known that *2* upon heating rearranges to *3*.[3] The reaction could therefore proceed through the 2-diethoxymethyl-2,3-dihydro-1,3-benzisothiazol-3-one-1,1-dioxide *4*, fragmentation to *2* and subsequent rearrangement to *3* (Scheme 2). Ethyl formate was detected together with ethanol in the reaction mixture.

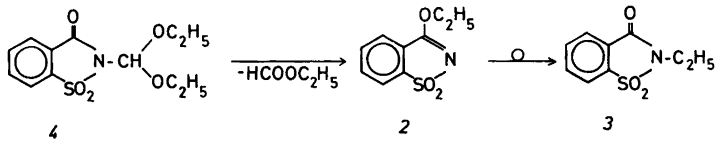
Another possible path for the reaction in which ethyl 2-sulfamidobenzoate is formed primarily and then cyclized to *2* could be ruled out because only ethyl *N*-(2-ethoxycarbonylbenzenesulfonyl)formimidate was formed when ethyl 2-sulfamidobenzoate was reacted with triethyl orthoformate (Scheme 3). If ethyl 2-sulfamidobenzoate was heated in an inert solvent like xylene no *2* was formed but only saccharine. Neither could *2* be prepared by ethylation of saccharine with ethyl benzoate, ethyl acetate or diethyl sulfate.

A mechanism in which both *2* and *3* are formed by direct ethylation, eventually by a carbenium ion formed in the presence of *p*-toluenesulfonic acid as catalyst is probably of minor importance since *2* and *3* were formed in the same overall yield without added catalyst. The product distribution was 1:5 instead of 1:2 with catalyst, presumably because of the prolonged reaction time.

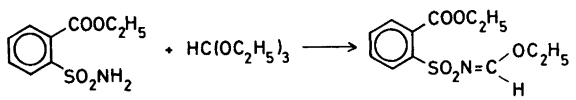
In order to find out whether *3* was formed from *2* or direct by fragmentation of *4*, we conducted the synthesis at lower temperature where the Chapman rearrangement of *2* to *3* proceeds slowly.[3] At 110 °C we found the rearrangement to proceed 10 % in



Scheme 1.



Scheme 2.



Scheme 3.

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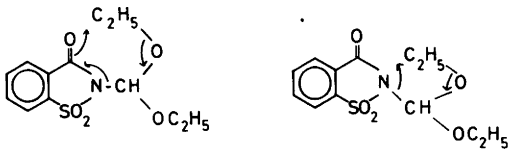

Scheme 4.

18 h and at that temperature both products *2* and *3* were formed in the usual ratio from the reaction of *1* with triethyl orthoformate.

It therefore seems plausible that the first formed *4* is mainly fragmented directly to *2* and *3*. This can proceed in two ways, namely, by a mechanism involving a six-membered ring and a four-membered ring (Scheme 4). We also investigated the reaction of two open chain *N*-sulfonylcarboxamides with triethyl orthoformate namely *N-p*-toluenesulfonylacetamide and *N-p*-toluenesulfonylbenzamide and found different reaction products in each case. For *N-p*-toluenesulfonylbenzamide only ethyl *N-p*-toluenesulfonylbenzimidate *7b* was formed presumably through the six-membered intermediate. For *N-p*-toluenesulfonylacetamide both *N*-ethyl-*N-p*-toluenesulfonylacetamide *6a* and ethyl *N-p*-toluenesulfonylacetimidate *7a* were formed in the ratio 2:1 (Scheme 5). Electronic factors must be the cause of this product distribution, the phenyl group decreasing the electron density on the nitrogen atom making *N*-diethoxymethyl-*N-p*-toluenesulfonylbenzamide to fragment through the six-membered intermediate.

Experimental. The experimental equipment was reported earlier.[1] Melting points are uncorrected.

2-Ethyl-2,3-dihydro-1,2-benzisothiazol-3-one-1,1-dioxide 3 *and 3-ethoxy-1,2-benzisothiazol-1,1-dioxide* 2. 2,3-Dihydro-1,2-benzisothiazol-3-one-1,1-dioxide (0.1 mol) was refluxed with triethyl orthoformate (0.3 mol) and *p*-toluenesulfonic acid (0.02 mol) so the formed ethanol and ethyl formate could distil from the reaction mixture. After collection of 11 ml the reaction was cooled and a mixture of *2* and *3* was filtered off in a yield of 79 %. Recrystallization from ethanol gave 68 % of *3* and recrystallization of the residue from toluene gave 32 % of *2*.

N-*Diethoxymethylphthalimide.* Phthalimide, triethyl orthoformate and *p*-toluenesulfonic acid were refluxed as described above. Yield 55 %, m.p. 73 °C. Anal. $C_{13}H_{15}NO_4$: C, H, N, ^{1}H NMR ($CDCl_3$): δ 1.32 (6 H, t), 3.25 (4 H, m), 6.15 (1 H, s), 7.77–7.92 (4 H, m). IR ($CHCl_3$, cm^{-1}): 1780 (s), 1730 (s), 1380 (m), 1360 (m).

Ethyl N-p-*toluenesulfonylbenzimidate* 7b. *N-p*-Toluenesulfonylbenzamide and triethyl orthoformate were refluxed as described above. Excess triethyl orthoformate evaporated and the residue distilled *in vacuo*. Yield 94 %, b.p. 210–215 °C/0.5 mmHg, m.p. 52 °C (toluene, light petroleum). Anal. $C_{16}H_{17}NO_3S$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 1.25 (3 H, t), 2.30 (3 H, s), 4.23 (2 H, q), 7.05–8.00 (9 H, m). IR ($CHCl_3$, cm^{-1}): 1615 (s), 1600 (s), 1580 (s), 1315 (s), 1295 (s), 1160 (s).

N-*Ethyl*-N-p-*toluenesulfonylacetamide* 6a and *ethyl* N-p-*toluenesulfonylacetimidate* 7a were prepared from *N-p*-toluenesulfonylacetamide and triethyl orthoformate as described above. The overall yield was 76 % distributed with 66 % of *N*-ethyl-*N-p*-toluenesulfonylacetamide and 33 % of ethyl *N-p*-toluenesulfonylacetimidate determined from the NMR spectrum of the distillate. B.p. of the mixture 138–140 °C/0.05 mmHg. Anal. $C_{11}H_{15}NO_3S$: C, H, N. IR ($CHCl_3$, cm^{-1}): 3000 (m), 1700 (s), 1605 (s), 1360 (s), 1320 (s), 1160 (s). ^{1}H NMR ($CDCl_3$): δ 1.26 (1 H, t), 1.28 (2 H, t), 2.32 (2 H, s), 2.43 (3 H, s), 2.48 (1 H, s), 3.85 (1.33 H, q), 4.12 (0.66 H, q), 7.06–7.95 (4 H, m). The assignments of the chemical shifts were made from the NMR spectra of the authentic compounds.

N-*Ethyl*-N-p-*toluenesulfonylacetamide* was prepared from *N*-ethyl-*p*-toluenesulfonamide and acetic anhydride. B.p. 123–127 °C/0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.32 (3 H, t), 2.32 (3 H, s), 2.45 (3 H, s), 3.92 (2 H, q), 7.15–7.97 (4 H, m). IR ($CHCl_3$, cm^{-1}): 1700 (s), 1360 (s), 1160 (s).

Ethyl N-p-*toluenesulfonylacetimidate* was prepared from *p*-toluenesulfonamide and triethyl orthoacetate. B.p. 146 °C/0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.36 (3 H, t), 2.41 (3 H, s), 2.46 (3 H, s), 4.15 (2 H, q), 7.20–8.00 (4 H, m). IR ($CHCl_3$, cm^{-1}): 1615 (s), 1320 (s), 1160 (s).

1. a. Treppendahl, S. and Jakobsen, P. *Acta Chem. Scand. B 32* (1978) 777: b. *Ibid. B 35* (1981) 465.
2. Yale, H. L. and Sheehan, J. T. *J. Org. Chem. 26* (1961) 4315.
3. Hettler, H. *Tetrahedron Lett.* (1968) 1793.

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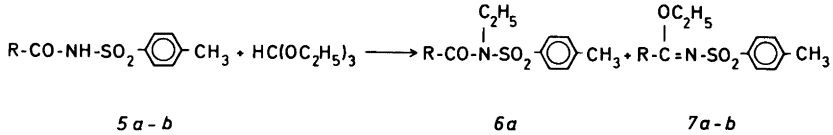

5a-b *6a* *7a-b*

Scheme 5. a: R = CH_3, b: R = C_6H_5