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METHYLTHIOMETHYL ESTERS FROM ACID CHLORIDES
REEXAMINATION OF A REPORTED β-KETOSULFOXIDE SYNTHESIS

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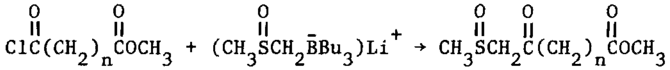
Reexamination of the reported (1) synthesis of β-ketosulfoxides from acid chlorides and reagent 2 revealed that the products formed were actually methylthiomethyl esters (4).

Negishi and coworkers have reported (1) a mild method for the preparation of ketones by reaction of acyl halides with lithium tetralkylborates. A variation of this reagent (2) involving replacement of an alkyl with a methylsulfinylmethyl group, allowed preferential transfer of this latter substituent from boron to yield β-ketosulfoxides such as 3a.



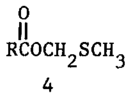
$$\mathrm{Cl\overset{O}{\overset{\|}{C}}(CH_2)_n\overset{O}{\overset{\|}{C}}OCH_3 + (CH_3\overset{O}{\overset{\|}{S}}CH_2\bar{B}Bu_3)Li^+ \rightarrow CH_3\overset{O}{\overset{\|}{S}}CH_2\overset{O}{\overset{\|}{C}}(CH_2)_n\overset{O}{\overset{\|}{C}}OCH_3}$$

1a, n=2 2 3a

1b, n=3 3b

We carried out this reaction on 1b in order to obtain 3b as an intermediate in a planned synthetic sequence. Although the ^1H NMR (2) was consistent with the desired product, absence of a sulfoxide stretching band in the infrared spectrum and subsequent failures to alkylate the active methylene led to examination of the substance by ^{13}C NMR (3). The carbon count and peak multiplicities were as expected, but both carbonyl resonances were located at frequencies indicative of esters with no absorbance for a ketone.

We postulated that isomeric 4a fit all the spectral characteristics and consequently subjected a sample of the isolated material to lithium aluminum hydride reduction. The product from this reaction was identical (GC-MS) to a commercial sample of 1,5 pentanediol



$$\mathrm{R\overset{O}{\overset{\|}{C}}OCH_2SCH_3}$$

4

R (Purified Yields)

4a - $(CH_2)_3CO_2CH_3$ (72%)
4b - $(CH_2)_2CO_2CH_3$
4c - CH_2OCH_2Ø (44%)
4d - Ø
4e - Ø-pNO_2 (29%)

rather than the diol sulfide which would result from β-ketosulfoxide 3b.

We have not been able to reconcile the different products 4a-4e obtained by us and those reported by Negishi (1). Although we have altered the reaction and work-up conditions and the order of addition of reagents, we have always obtained only the methylthiomethyl esters 4a-e with no detectable β-ketosulfoxides (4). Since spectral data were not published(1), the only point of reference between our work and that of Negishi is a melting point reported (44-45°C) for the product obtained from p-nitrobenzoyl chloride. In our hands, the purified product 4e (5) melted 55.5-56°C (6).

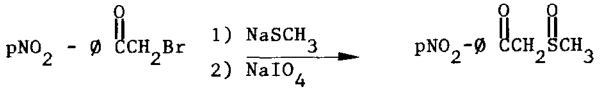
The mechanism of this formal Pummerer rearrangement of dimethylsulfoxide is not known to us at this time. The possiblity that the β-ketosulfoxide is actually formed and subsequently rearranges has not been discounted but seems unlikely(7).

The methylthiomethyl group is a useful carboxylate protecting group which can be cleaved by neutral non-hydrolytic methods (8). Although we have not pursued optimization of reaction conditions, we feel that the reaction observed in this report could serve as another mild method for preparation of these unique esters. Yields of 4a-4e, purified by distillation or column chromatography ranged from 29-72% (see above).

In a typical procedure, a solution of dry dimethylsulfoxide (7.1 ml, 0.1 mol) in distilled THF (300 ml) was cooled to -78° before the addition of n-butyllithium in hexane (0.1 mol) over 10 min. The milky solution was stirred at -78° for 30 min and at 0° for 3 h. To this mixture was added a solution of tri-n-butylborane (0.1 mol) in THF over 5 min. The clear solution was stirred at 0° for 80 min and methyl glutamoyl chloride (16.45 g, 0.1 mol) was added. The mixture was allowed to warm to ambient temperature and stir overnight. It was partitioned between dilute HCl (aq) and ethyl ether. The organic layer was dried and concentrated and the crude oil residue distilled to yield 14.8 g (72%) of 4a.

REFERENCES

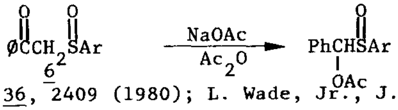
1. E. Negishi, K. W. Chin, T. Yosida, J. Org. Chem, 40, 1676 (1975).
2. This material had a mass spectral molecular ion (CI and EI) of 203. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.8-2.7 (6H, methylenes), 2.25 (3H, s, SCH_3), 3.7 (3H, s, CO_2CH_3), 5.2 (2H, s, CO_2CH_2S).
3. ^{13}C NMR ($CDCl_3$, Me_4Si) δ 15.4(q), 20.0(t), 32.9(t), 33.3(t), 51.6(q), 68.2(t), 172.6(s), 173.3(s).
4. In all cases the characteristic methylene ($-CO_2CH_2S-$) was observed (^{1}H NMR) at δ 5.2-5.35 rather than δ 4.5 as reported for β-ketosulfoxides.
5. This product was purified by column chromatography followed by recrystallization (hexane) and analyzed correctly (± 0.1) for C,H,N,S.
6. A sample of β-ketosulfoxide 5, the product reported by Negishi, was synthesized as pictured below. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.8 (3H, s, CH_3), 4.5 (2H, s, $COCH_2SO$), 8.25 (bS, aromatics) and mass spectral analysis m/e 227; 64, 65($-SOCH_3$) verified the structure. A crude sample of this unstable material after column chromatography had mp 88-100°C.



$$pNO_2-\emptyset\overset{O}{\overset{\|}{C}}CH_2Br \xrightarrow[2)\ NaIO_4]{1)\ NaSCH_3} pNO_2-\emptyset\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{S}}CH_3$$

5

7. A previous study by S. Iriuchijima, K. Maniwa, G. Tsuchihashi, J. Amer. Chem. Soc., 97, 596 (1975) has shown that Pummerer reaction of 6 gives 7.



$$\underset{6}{\emptyset\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{S}}Ar} \xrightarrow[Ac_2O]{NaOAc} Ph\underset{OAc}{\underset{|}{C}}H\overset{O}{\overset{\|}{S}}Ar$$

7

8. E. Haslam, Tetrahedron, 36, 2409 (1980); L. Wade, Jr., J. Gerdes, R. Wirth, Tetrahedron Lett., 731 (1978); T.-L. Ho, C. Wang, J.C.S. Chem. Commun., 224 (1973); T.-L. Ho, Syn. Commun., 9, 267 (1979); L. Wade, Jr. Tetrahedron Lett., 689, (1979).

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