Tetrahedron Letters No. 45, pp 4515 - 4518, 1973. Pergamon Press. Printed in Great Britain.

OXIDATIONS BY THIONYL CHLORIDE. V. MECHANISM OF β-CHLORINATION OF CARBOXYLIC ACIDS[1]

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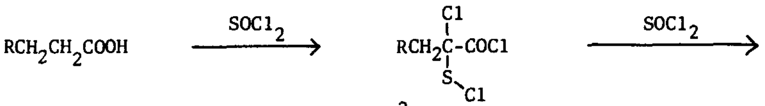
(Received in USA 19 July 1973; received in UK for publication 2 October 1973)

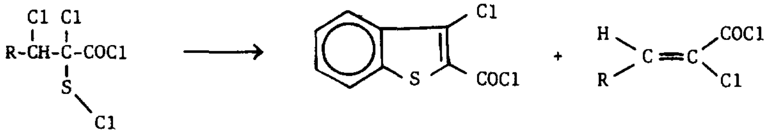
The broad utility of thionyl chloride as a reagent for the preparation of sulfur-containing heterocyclic compounds has recently received increasing attention.[2-5] Although much effort has been expended toward increasing the scope of these reactions, comparatively little effort thas been given to an investigation of the mechanism(s) by which these products arise. We recently proposed[5b] that sulfenyl chlorides, 3 (R = Ar), were intermediates in the conversion of β-phenylpropanoic acids, 1, to benzo[b]thiophenes, 4. It appeared logical enough, especially in view of a number of reported instances,[6] that the formation of 3 from 2 proceeded by means of a benzylic chlorination step (i.e., the presence of the aromatic ring was required). We now wish to report evidence that 3 is indeed an intermediate between 2 and 4, and that it is formed not by benzylic chlorination but by a process in which the carbon atom beta to the carbonyl group is chlorinated by thionyl chloride.



$RCH_2CH_2COOH \xrightarrow{SOCl_2} RCH_2C(Cl)(SCl)\text{-}COCl \xrightarrow{SOCl_2}$

2

1a, R = Ph
b, R = 2,6-$C_6H_3Cl_2$
c, R = CH_3



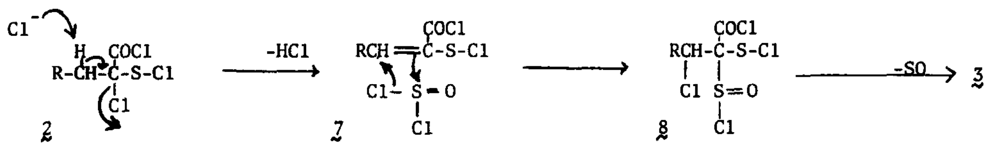
3 4 5

Sulfenyl chloride, 2a,[7] was treated with an excess of thionyl chloride at reflux and in the presence of a catalytic amount of pyridine over a 177-hr period. During this time there was observed, as determined at approximately 24-hr intervals by nmr spectroscopy, the slow conversion of 2a to 4 and 5a [the methylene hydrogens (τ 6.36) of 2a gradually disappeared as the vinyl hydrogen (τ 1.80) of 5a and the complex aromatic signals of 4 and 5a gradually increased in intensity]. At no time was there any evidence for the presence of 3a,[5b] whose methine hydrogen appears at τ 4.18 in thionyl chloride solution. Evidently the conversion of 3a to 4 and 5a proceeds at a much faster rate than the formation of 3a from 2a. We therefore determined to observe 3 by choosing systems that cannot undergo cyclization.

As 3-(2,6-dichlorophenyl)propanoic acid, 1b (mp 96-98°, prepared by diimide reduction of 2,6-dichlorocinnamic acid in 56% yield) was heated under reflux with excess thionyl chloride in the presence of 0.12 equivalent of pyridine for seven days, progress of the reaction was again followed by nmr spectroscopy. After 21 hr, just a trace of the acid chloride of 1b (methylene protons at ~ τ 6.9) remained, and 2b (methylene protons as an AB quartet at τ 5.80 and 6.07) appeared to be the major constituent and 3b (methine proton at τ 2.24) a minor component. At the end of 45 hr, the reaction components consisted of a mixture (roughly 1:1:1) of 2b, 3b and 5b (vinyl proton at τ 1.78); and after 119 hr, little 2b or 3b remained and 5b was the major component. These observations led to two significant conclusions: (1) 3 was indeed formed by chlorination of 2 under reaction conditions; and (2) 5 was formed from 3 by an apparent elimination of sulfur dichloride. If the latter were the case, it would appear to be the first reported instance of such an elimination, which is contrary to the generally observed tendency of facile sulfur dichloride addition to carbon-carbon multiple bonds.[8] Sulfur dichloride elimination apparently is so favorable in this case that we have thus far been unsuccessful in preparing 3 by the addition of sulfur dichloride to acrylic acid, 5.[9]

Butanoic acid, 1c, was similarly treated with thionyl chloride and pyridine for seven days. This time the nmr spectra revealed the presence of only 2c (methyl protons at τ 8.79) at the end of 22 hr, the initial appearance of 3c[10] [diastereomeric methyl protons (a pair of doublets) at τ 8.15 and 8.20] after 66 hr, and an approximately 1:1 mixture of 2c and 3c after 123 hr. These data conclusively eliminated the requirement of a benzylic chlorination step and provided strong support for chlorination by thionyl chloride at the carbon atom beta to the carbonyl group. Furthermore, treatment of 3c[10] with pyridine hydrochloride in refluxing thionyl chloride revealed the gradual disappearance of 3c and the appearance of 5c (ratio of 4:1 after 14 hr). This lent additional support to a sulfur dichloride elimination step. Finally, the possibility of a β-chlorination being a free-radical process was eliminated by heating 2a at benzene reflux for 48 hr in the presence of sulfuryl chloride and dibenzoyl peroxide: 2a was recovered unchanged.

The mechanism of β-chlorination of carboxylic acids by thionyl chloride is best explained in terms of an elimination of hydrogen chloride from 2(to form 7) that has both E$_2$ and E$_1$ character. Some E$_2$ character is consistent with the finding[5] that successful benzo[b]thiophene formation is related to the acidity of the benzylic hydrogen atom.[11] Rapid addition of thionyl chloride across the polarized carbon-carbon double bond of 7,[7,13] subsequently would provide sulfinyl chloride, 8, which should readily expel sulfur monoxide[14] to afford 3.



Because the α-chloro-α-chlorosulfenyl acid chloride function can be converted to a variety of other potentially useful groups [e.g. RCHXCH$_2$COOH, RCHXCOCOOH, and RCHXC(OR')$_2$COOH][15], this β-chlorination process has possible application to the preparation of unusual and otherwise difficult to obtain polyfunctional molecules. In particular, the technique should offer the possibility of functionalization at both α- and β-carbon atoms. We are presently investigating sulfur dichloride eliminations and the significance and utility of β-chlorination, and are pursuing extensions of this latter technique to other carbonyl compounds.[16]

FOOTNOTES AND REFERENCES

1. Taken in part from the Ph.D. dissertation of T. H., The Ohio State University, 1971.

2. M. Davis, H. Szkuta, and A. J. Krubsack, *Mech. React. Sulfur Cmpds.*, **5**, 1 (1970), and references cited therein.

3. S. Nakagawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naito, *Tetrahedron Lett.*, 3719 (1970).

4. W. B. Wright, Jr., and H. J. Brabander, *J. Heterocycl. Chem.*, **8**, 711 (1971); W. B. Wright, Jr., *op. cit.*, **9**, 879 (1972).

5. (a) A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 4823 (1972); (b) *ibid.*, 125 (1973).

6. E. Wenkert, F. Haglid, and S. L. Mueller, J. Org. Chem., **34**, 247 (1969); W. R. Boon, *J. Chem. Soc.*, 601 (1945); R. Graf and F. Zettl, *J. Prakt. Chem.*, **147**, 188 (1936).

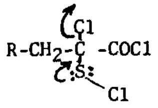
7. A. J. Krubsack and T. Higa, Tetrahedron Lett., 5149 (1968).

8. For example, see F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2627 (1968), and references cited therein.

9. U. Hasserodt, *Chem. Ber.*, **100**, 1482 (1967).

10. Authentic **3c** was prepared by treating crotonic acid with 7 equiv of thionyl chloride and 0.08 equiv of pyridine at reflux for 3 hr. Distillation afforded **3c** in 55% yield. An analytical sample (bp 56-56.5°/0.45 mm) gave a satisfactory elemental analysis.

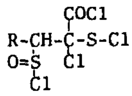
11. That there also is some E_1 character, i.e., i, is suggested by the report that α-halothioethers readily split off HX at 70-110°, and that α-chlorothioethers are hydrolyzed much faster than primary or secondary alkyl chlorides because of involvement of an E_1 mechanism.[12] The electron-withdrawing character of the chlorine on sulfur and the destabilizing effect of the chlorocarbonyl group very likely shift the nature of the mechanism from pure E_1 to one intermediate between E_1 and E_2.



i

12. L. Brandsma and J. F. Arens in *The Chemistry of the Ether Linkage*, S. Patai, Ed., Interscience Publishers, London, 1967, Chapter 13.

13. The alternative mode of addition of thionyl chloride (to afford ii) is unlikely, since ii would be expected to give a Pummerer-type product which we do not observe.



$R\text{-}CH(S(=O)Cl)\text{-}C(COCl)(Cl)\text{-}S\text{-}Cl$

ii

14. Note the sequence of **5** to **6** and **7**, apparently via **8**, in reference 7. See also H. M. Relles, *J. Org. Chem.*, **37**, 3630 (1972).

15. M. S. Simon, J. B. Rogers, W. Saenger, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **89**, 5838 (1967).

16. We thank the National Science Foundation for a grant (GP 31761X) in partial support of this work.