Notes

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Reaction of Silver Trifluoroacetate with Some Alkyl Halides[1]

JAMES G. TRAYNHAM AND JOHN S. DEHN

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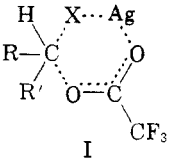
Replacement reactions involving alkyl halides and silver salts have been of interest for some time. Because of the sparing solubility of most silver salts, the reactions are heterogeneous, or involve a polar solvent, such as water, alcohol, or acetic acid, which can take part in the reaction, or would give products which would be difficult to characterize, such as perchlorates. Silver trifluoroacetate, however, is soluble in nonpolar organic solvents such as ether and benzene, and alkyl trifluoroacetates are quite stable. Preparations of triethylsilyl trifluoroacetate[2] and of triphenylmethyl trifluoroacetate[3] from the appropriate halide and silver trifluoroacetate have been described. We have investigated the reaction of silver trifluoroacetate with some alkyl halides in inert solvents with a view toward elucidating the mechanism of the replacement reaction.

A reaction path that seemed an attractive possibility involved a *quasi*-6-membered ring intermediate (I). The relatively undissociated silver trifluoro-



I

acetate solute seemed likely to be a reagent capable of substitution (ester formation) in ether solution by appropriate electron shifts in a *quasi*-ring intermediate. Such as intermediate is analogous to the *quasi*-4-membered one used in some early descriptions of the S_Ni reaction.[4,5] The formation of a *quasi*-6-membered ring is expected to be favored energetically over the formation of a 4-membered one.

Reaction of optically active reactants by way of a *quasi*-ring intermediate should lead to products with retention of configuration. An ionic mechanism, with significant dissociation of ion pair intermediates,[5] should give extensively racemized products with some inversion.

Optically active 2-bromo-octane and silver trifluoroacetate in ethyl ether rapidly gave *s*-octyl trifluoroacetate, silver bromide, and considerable amounts of olefin.[6] The reaction was carried out by the very slow addition of highly dilute 2-bromo-octane to excess silver trifluoroacetate in ether. The use of excess silver trifluoroacetate together with its rapid reaction with alkyl halide minimized the racemization of 2-bromo-octane by precipitated silver bromide. A summary of our stereochemical data follows:

s-$C_8H_{17}Br$	⟶	*s*-$C_8H_{17}O{-}CO{-}CF_3$	⟶	*s*-$C_8H_{17}OH$
−35.24°				−2.23°
(35.24°)				(6.59°)

The numbers directly under the formulas are observed rotations (α_D^{20}). The numbers in parentheses are equivalent rotations; *i.e.*, rotations for samples of bromide and alcohol of equal optical purity.[7] Since the small amount of ester obtained could not be completely freed of alcohol contaminant (indicated by infrared spectrum), the ester was saponified to give alcohol of the indicated rotation.

The over-all result was transformation of 2-bromo-octane to 2-octanol with 66% racemization and 34% inversion. Since saponification of *s*-octyl trifluoroacetate proceeds with complete retention of configuration,[8] the over-all stereochemical result in the transformation of bromide to alcohol must be ascribed to the replacement reaction with silver trifluoroacetate. These results are those to be expected for a reaction by an ionic path with imperfect shielding by the departing anion. The low yield of ester and the extensive formation of olefin

(1) Presented at the Southeastern Regional Meeting of the ACS, Durham, N. C., November 15, 1957.

(2) H. H. Anderson and G. M. Stanislow, *J. Org. Chem.*, **18**, 1716 (1953). No solvent, 93% yield of ester.

(3) D. W. A. Sharp and N. Sheppard, *J. Chem. Soc.*, 681 (1957). Ether solvent, yield unspecified.

(4) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937); E. D. Hughes, C. K. Ingold, and I. C. Whitfield, *Nature*, **147**, 206 (1941).

(5) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 730–2 (1956), summarizes the evidence for the view, apparently more favored now, that such reactions proceed by way of ion-pair intermediates.

(6) In neither of the trifluoroacetate preparations reported earlier[2,3] could dehydrohalogenation be a competing reaction.

Dr. John H. Pomeroy, in a personal communication, mentioned "some preliminary and unpublished work on the preparation of esters by this reaction with results similar to [ours]."

(7) The rotations of related alcohol and bromide are calculated from the data of H. Brauns, *Rec. trav. chim.*, **65**, 805 (1946), recently quoted and evaluated by N. Kornblum, L. Fishbein, and R. A. Smiley, *J. Am. Chem. Soc.*, **77**, 6261 (1956).

(8) J. G. Traynham, *J. Am. Chem. Soc.*, **74**, 4277 (1952).

are consistent with this picture of the reaction and important contributions from a *quasi*-ring intermediate are improbable. Further evidence for the ionic path was obtained from the attempted reaction of silver trifluoroacetate with 1-chloronorbornane. Bridgehead halides react but sluggishly, if at all, by ionic dissociation.[9] When solutions of 1-chloronorborane and silver trifluoroacetate in ether, benzene, or dioxane were refluxed for 58 hours, no evidence for reaction between the two solutes was obtained. This is in striking contrast to the very fast reaction between 2-bromooctane and silver trifluoroacetate.

EXPERIMENTAL

Preparation of materials. Silver trifluoroacetate was prepared by adding an ether solution of trifluoroacetic acid[10] to a suspension of silver oxide in ether. The solution was filtered from the slight excess of silver oxide, the ether was removed by distillation, and the residue was recrystallized from benzene.

(+)2-Bromooctane was prepared by treating (−)2-octanol (α_D^{25} −7.32°) with an equivalent amount of PBr_3; b.p. 75° (15 mm.), n_D^{20} 1.4507, α_D^{20} +35.24°.

1-Chloronorbornane was prepared[11] by the $AlCl_3$- catalyzed hydrogen-chlorine exchange between pentane and 2,2-dichloronorbornane.[11] The yield of twice-distilled material was 39%; b.p. 82-84° (87 mm.), n_D^{20} 1.4710, d_4^{20} 1.016.

Silver trifluoroacetate with 2-bromooctane. A solution of 33.5 g. (0.152 mole) of silver trifluoroacetate in 750 ml. of anhydrous ethyl ether was placed in a 1-l. flask equipped with a high dilution cycle.[12] While the solution was refluxed gently, a solution of 20.5 (0.106 mole) of (+)2-bromooctane in 150 ml. of ether was added through the dilution cycle during 48 hr. Openings to the atmosphere were protected with drying tubes. Precipitation of AgBr began soon after the addition of 2-bromo-octane was begun.[13] The mixture was refluxed for 4 hr. longer and about half of the ether was removed by distillation. The remaining solution was washed with water, K_2CO_3 solution, water, $Na_2S_2O_3$ solution, and water. It was dried with $MgSO_4$ and distilled. After considerable amount of forerun which decolorized $KMnO_4$ and Br_2 solutions (probably octenes) had been removed, (−)*s*-octyl trifluoroacetate[8] was obtained in 11% yield; b.p. 71–71.3° (17 mm.), n_D^{20} 1.3780, d_4^{20} 1.002. In another experiment, a 17% yield of ester was obtained. The infrared spectra of the two samples of ester were essentially identical and indicated slight contamination by alcohol. The samples of ester were combined, redistilled, and saponified by refluxing for 2.5 hr. with excess 10% NaOH solution.

The mixture was steam-distilled and (−)2-octanol was isolated in the usual way; $n_D^{20.5}$ 1.4240, d_4^{20} 0.823, α_D^{20} −2.23°.

Silver trifluoroacetate with 1-chloronorbornane. Three solutions of 1-chloronorbornane (1.0 g., 0.008 mole) and silver trifluoroacetate (1.9 g., 0.009 mole) in 30 ml. of solvent (benzene, ethyl ether, and dioxane, separately) were refluxed in the dark for 58 hr. No trace of AgCl precipitate was observed. A small amount of a brown precipitate formed in the dioxane solution. This material dissolved in aqueous ammonia but did not reappear when that solution was made acidic with HNO_3. The brown solid was probably silver oxide.

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COATES CHEMICAL LABORATORIES
LOUISIANA STATE UNIVERSITY
BATON ROUGE, LA.

(9) P. D. Bartlett and L. N. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, Jr., *J. Am. Chem. Soc.*, **75**, 1008 (1953).

(10) Research sample supplied without charge by Minnesota Mining and Manufacturing Co., St. Paul, Minn.

(11) W. P. Whelan, Jr., Ph.D. dissertation, Columbia University, 1952; *Dissertation Abstr.*, 1556 (1954).

(12) The apparatus was essentially the same as that described by C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5328 (1952).

(13) In a preliminary experiment 2-bromo-octane was poured into a solution of silver trifluoroacetate in ether. Precipitation of AgBr began immediately, the ether began to boil, and the reaction appeared to be over in less than 5 min.

Synthesis of Isotopically Labeled Medicinals. I. 2-Thiouracil-S^{35}

J. B. ZIEGLER, A. C. SHABICA, AND M. SONENBERG

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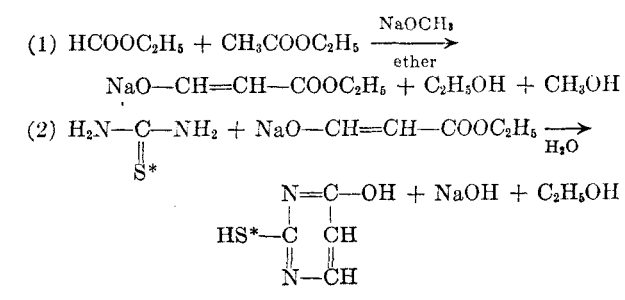
2-Thiouracil is well known as a substance with potent biological, especially antithyroid, activity,[1] and there has been considerable interest in the incorporation of various isotopic tracer atoms into this molecule. The first such preparation appears to have been that of Plentl and Schoenheimer[2] who labeled the molecule with the stable N^{15} isotope. At a later date Bennett[3] prepared this substance with the C^{14} label in the 2-position, and shortly thereafter Jeener and Rosseels[4] reported the use of this compound containing the S^{35} label in an investigation concerned with tobacco mosaic virus. However, the latter workers gave no preparative details, and since we required a sample of this particular variant for biological studies, it was necessary to work out a synthesis on a micro scale. This was accomplished, starting with S^{35}-labeled 2-thiourea, according to the following scheme.



(1) A. Burger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, 1951, Volume I, p. 485 ff.

(2) A. A. Plentl and R. Schoenheimer, *J. Biol. Chem.*, **153**, 203 (1944).

(3) L. L. Bennett, Jr., *J. Am. Chem. Soc.*, **74**, 2432 (1952).

(4) R. Jeener and J. Rosseels, *Biochem. et Biophys. Acta*, **11**, 438 (1953).