Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Method for the Conversion of Halides to Alcohols

Jose Alexander [a], Mara L. Renyer [a] & Hemalatha Veerapanane [a]
[a] INTERx Research Division of Merck and Co., Inc., Lawrence, Kansas, 66047
Version of record first published: 23 Sep 2006.

To cite this article: Jose Alexander , Mara L. Renyer & Hemalatha Veerapanane (1995): A Convenient Method for the Conversion of Halides to Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:23, 3875-3881

To link to this article: http://dx.doi.org/10.1080/00397919508011463

SYNTHETIC COMMUNICATIONS, 25(23), 3875-3881 (1995)

A CONVENIENT METHOD FOR THE CONVERSION OF HALIDES TO ALCOHOLS

Jose Alexander*, Mara L. Renyer and Hemalatha Veerapanane

INTERx Research Division of Merck and Co., Inc.,
Lawrence, Kansas 66047

Abstract: The displacement of halides in unactivated primary bromides and iodides, allylic and benzylic primary and secondary bromides, and primary and secondary α-bromoketones by formate, using triethylammonium formate as the formylating agent, followed by acid or base catalyzed hydrolysis has been found to be an efficient method for the conversion of halides to alcohols.

Halo compounds are often prepared from alcohols and a multitude of reactions[1] are available for this conversion. However, methods for halide to alcohol transformation, despite the potential usefulness, are fewer[2]. Halide displacement by acyloxy group, followed by hydrolysis, is one of the most commonly used methods for this purpose. Sodium or potassium formate seem to be the preferred reagents and have been used in solvents such as methanol[3], dioxane[4], dimethyl sulfoxide[5] and hexamethylphosphoramide,[6,7] at various temperatures. This reaction works best with activated halides such as

* To whom correspondence should be addressed.

allyl and benzyl. Other methods, which are suitable mostly for primary or benzylic bromides and iodides, are the silver-assisted reaction of bis(tributyltin)-oxide[8] and the use of polymer-bound carbonate[9] in refluxing benzene or tetrahydrofuran. For unactivated primary halides, heating with solid sodium formate at 115-125 °C in the presence of tetrabutylammonium bromide as a phase transfer agent has been reported[10] to be successful. Mercuric acetate in diglyme, catalyzed by triacetoxyborane, has been used[6] for the substitution of halides by acetate.

Seeking mild conditions for the replacement of unactivated halide groups in molecules with labile functions, we briefly investigated the scope of halide displacement reaction by the triethylammonium salt of formic acid. This reagent was reported[11] to convert an allylic bromide to the corresponding allyl formate. The reaction seemed attractive for preparative scale synthesis because of the ready availability of the reagents and the easy work up.

$$RX + HCOO^- Et_3NH \longrightarrow ROCHO + Et_3NH^+ X^-$$

$$ROCHO + H_2O \longrightarrow ROH + HCOOH$$

Scheme

We observed that the conversion of unactivated primary bromo and iodo compounds to formate esters can be carried out in very good yields, in most cases at room temperature, using triethylammonium formate. The results are

Table 1. Formyloxylation of Alkyl Halides Using Triethylammonium Formate

Alkyl Halide	Reaction Conditions[a] time/solvent/temperature °C	Yield (%)[b]
$Br-(CH_2)_5-COOH$	18 h / none	80
$Br-(CH_2)_5-COOCH_2CCl_3$	16 / none / 50	83
$Br-(CH_2)_5-COOCH_2CCl_3$	8h / MeCN / reflux	92
$I-(CH_2)_5-COOCH_2CCl_3$	18 h / none	76
$I-(CH_2)_7-COOCH_2CCl_3$	18 h / none	79
t-Butyl iodide	24 h / none	0
Cyclohexyl bromide	18 h / none / 50	0
Cyclohexyl iodide	18 h / none / 50	0
(1-Bromoethyl)benzene	12 h / none	95
(1-Bromoethyl)benzene	24 h / MeCN / reflux	20
$p-MeOPh-CO-CH_2Br$	2 h / MeCN	97
$Ph-CO-CHBr-CH_3$	2 h / MeCN	98
$p-MeOPh-CO-CHBr-CH_3$	1.5 h / MeCN	96
4-Bromomethyl-5-methyl-1,3-dioxol- 4-ene-2-one	1 h / MeCN	80
4-Bromomethyl-5-phenyl-1,3-dioxol-4-ene-2-one	1.5 h / MeCN	92

[a] The reactions were done at room temperature unless otherwise indicated.
[b] Isolated yield of formate ester, non-optimized; products characterized by elemental analysis and/or ^1H and ^{13}C NMR (200 MHz).

given in Table 1. Our investigation was limited to bromo and iodo compounds because numerous methods are available for the direct bromination of organic compounds. Most bromo and chloro compounds can be readily converted to the corresponding iodo derivatives by the Finkelstein reaction[12] using sodium iodide. Unactivated primary bromides and iodides were reacted in the absence of any solvent using three to five-fold molar excess of triethylamine and formic acid. A reaction mixture containing 10% molar excess of formic acid compared to triethylamine was used for base sensitive halides. Although 6-bromohexanoic acid reacted readily at room temperature, trichloroethyl 6-bromohexanoate needed to be heated at 50 °C with triethylammonium formate for the reaction to occur. The bromide displacement on this ester could also be carried out in refluxing acetonitrile. α-Phenethyl bromide gave quantitative yield of the corresponding formate at room temperature in the absence of a solvent. In acetonitrile solution, there was only about 20% substitution after 24 hours of refluxing. The attempts to displace the halide in α-phenethyl chloride with sodium acetate in hexamethylphosphoramide, or with silver acetate in the presence of triacetoxy borane as a catalyst, have been reported[6] to give very poor yields. Cyclohexyl bromide did not react with triethylammonium formate at 50 °C. Cyclohexyl iodide produced cyclohexene. The reaction of t-butyl iodide at room temperature resulted in the formation of elimination products. The primary and secondary α-bromoketones we studied were converted rapidly and quantitatively to the corresponding α-formyl esters at room temperature with a molar equivalent of triethylammonium formate in acetonitrile.

The formyl esters were hydrolyzed to the corresponding alcohols by acid or base catalysis in methanolic solution at room temperature. During the acid catalyzed removal of the formate group in trichloroethyl 6-formyloxyhexanoate and trichloroethyl 8-formyloxyoctanoate, the trichloroethyl ester suffered no detectable hydrolysis. Potassium carbonate in methanol worked best for the hydrolysis of α-phenethyl formate.

Our experimental results demonstrate that triethylammonium formate is a convenient reagent for the formyloxylation of a variety of unactivated primary, allylic and benzylic bromides and iodides as well as for elimination-prone α-bromoketones. Mild base or acid catalyzed hydrolysis of these formyl esters is a convenient high yield method for the preparation of the corresponding alcohols.

EXPERIMENTAL

Typical Procedure: Preparation of trichloroethyl 6-formyloxyhexanoate. To a mixture of trichloroethyl 6-bromohexanoate (31.2 g, 95.7 mmol) and formic acid (20.1 g, 0.22 mol) cooled in an ice bath, triethylamine (20.2 g, 0.2 mol) was added dropwise with stirring in the course of 15 min. The cooling bath was removed and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was diluted with brine (100 mL) and extracted with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid, aqueous sodium bicarbonate, water and brine. The extract was dried over sodium sulfate and evaporated. The residue (26.8 g) was chromatographed

over silica gel (200 g). The pure formate ester was eluted with ethyl acetate-hexane (15:85), 23.2 g (83%). ^{1}H NMR ($CDCl_3$) δ 1.46 (2H, m), 1.71 (4H m), 2.49 (2H, t), 4.17 (2H, t), 4.75 (2H, s), and 8.06 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.25, 25.29, 28.12, 33.68, 63.58, 73.84, 94.96, 161.04, 171.72; IR (film) 2950, 1755, 1726, 1161 cm^{-1}; Anal: calc. for $C_9H_{13}O_4Cl_3$: C, 37.07, H, 4.49; found, C, 36.92, H, 4.44.

Trichloroethyl 6-hydroxyhexanoate. The above formate ester (4 g) was dissolved in methanol (50 mL) and one drop of concentrated hydrochloric acid was added. The reaction mixture was stirred at room temperature for 2 h. Most of the methanol was evaporated off in vacuum and the residue was taken up in ethyl acetate and washed with aqueous sodium bicarbonate, water and brine. The residue obtained on evaporation of solvent (3.69 g, 99%) was practically pure by TLC and NMR spectroscopy. An analytical sample was prepared by short path distillation, bp 137 °C /0.65 mm. ^{1}H NMR ($CDCl_3$) δ 1.3-1.8 (6H, m), 2.48 (2H, t), 3.65 (2H, t) and 4.74 (2H, s); ^{13}C NMR ($CDCl_3$) 24.42, 25.15, 32.17, 33.79, 62.45, 94.99, 171.95; IR (film) 3345, 2939, 2866, 1755, 1140 cm^{-1}; Anal: calc. for $C_8H_{13}O_3Cl_3$: C, 36.45, H, 4.97; found: C, 36.35, H, 4.95.

REFERENCES

1. Larock, R.C., "Comprehensive Organic Transformations", VCH, New York, **1986**, pp 353-360.

2. Ref 1, pp 481-482.

3. Yamamoto, S., Itani, H., Takahashi, H., Tsuji, T., and Nagata, W. *Tetrahedron Lett.* **1984**, *25*, 4545.

4. Henbest, H. B. *J. Chem. Soc.* **1951**, 1074-1078.

5. Radominska-Pyrek, A., Huynh, T., Lester, R., and Pyrek, J. S. *J. Lipid Res.* **1986**, *27*, 102.

6. Larock, R.C. *J. Org. Chem.* **1974**, *25*, 3721.

7. Harris, M. and Bull, M. *J. Synth. Comm.* **1985**, *15*, 1225.

8. Chan, T.H. and Gingras, M. *Tetrahedron Lett.* **1989**, *30*, 279.

9. Cardillo, G., Orena, M., Porzi, G. and Sandri, S. *Synthesis* **1981**, 793.

10. Zahalka, H. A. and Sasson, Y. *Synthesis* **1986**, 763.

11. Alpegiani, M., Zarini, F. and Perrone, E. *Synth. Comm.* **1992**, *22*, 1277.

12. March, J. "Advanced Organic Chemistry", John Wiley, New York, **1992**, p 430.

(Received in the USA 07 May 1995)