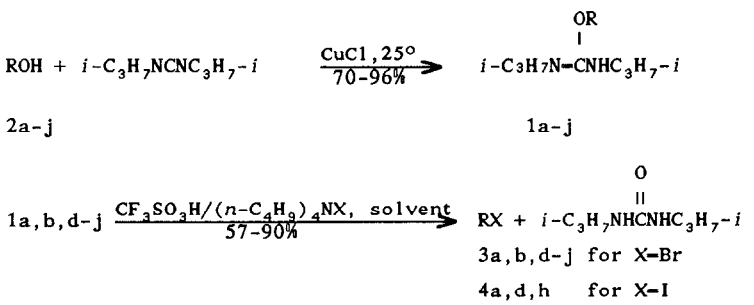
Tetrahedron Letters,Vol.28,No.38,pp 4445-4448,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CONVERSION OF ALCOHOLS INTO ALKYL BROMIDES AND IODIDES *VIA O*-ALKYLISOUREAS

Stephen P Collingwood, Alan P Davies, and Bernard T Golding*
Department of Organic Chemistry, Bedson Building, The University,
Newcastle upon Tyne, NE1 7RU, United Kingdom (SPC and BTG)
Unilever Research, Colworth Laboratory, Colworth House, Sharnbrook,
Bedford MK44 1LQ, United Kingdom (APD)

Summary : Treatment of O-alkylisoureas with trifluoromethanesulphonic acid and a tetrabutylammonium salt (bromide or iodide) affords alkyl halides in high yields.

We have found that *O*-alkylisoureas (**1**) [*cf* Table 1] readily formed by the reaction of alcohols (**2**) with di-isopropylcarbodiimide catalysed by a copper halide,[1,2] can be efficiently converted into alkyl bromides and iodides [*cf* Table 2] by treatment with one mol equivalent of trifluoromethanesulphonic acid in the presence of an excess of tetrabutylammonium bromide or iodide. The conversion into halide can be performed either with the pure isolated *O*-alkylisourea, or with crude isourea (examples 3b, 3d and 3h), without detriment to yield.



2	R	2	R
a	n-C_8H_{17}	f	$CH_3C{\equiv}CCH_2$
b	$C_6H_{13}CH(CH_3)$	g	$CH_3C{\equiv}CC_2H_4$
c	c-C_6H_{11}	h	$CH_3CH{=}^{E}CHCH_2CH{=}^{E}CHCH_2$
d	$C_6H_5CH_2$	i	$CH_3CH{=}^{E}CHCH_2C{\equiv}CCH_2$
e	$CH_3CH{=}^{E}CHCH_2$	j	$CH_2{=}CHCH_2C(CH_3)_2CH_2$

There are precedents for such transformations,[2-5] but the opportunities presented by *O*-alkylisoureas made as described were not apparent until now. Thus, *O*-alkylisoureas prepared by the addition of either an alcohol or alkoxide to a diimide or *N*-cyanoimine were shown to give alkyl chlorides on reaction with dilute aqueous hydrochloric acid (e.g. *O*-ethyl-*N*-phenylisourea gave chloroethane).[3] A few examples of the reaction of *N*,*N*'-dicyclohexyl-*N*-methylcarbodiimidium iodide with alcohols to give alkyl iodides have been published.[4] In a review of the reactions of *O*-alkylisoureas, the formation of iodomethane from the reaction of *O*-methylisourea with hydrogen iodide was mentioned.[2b]

Table 1. New *O*-Alkylisoureas **1**

Substrate	Product	Reaction Conditions Time	Yield [%]	b.p. [°C] (mmHg)
2b	1b	60h	70	50-55° (0.2)
2e	1e	24h	80	75-76° (3)
2f	1f	15h	85	40-50° (0.02)
2g	1g	18h	96	60-65° (4)
2h	1h	40h	88	86-88° (0.5)
2i	1i	120h	79	90-95° (0.2)
2j	1j	40h	91	69-72° (0.05)

We required a satisfactory procedure for converting unsaturated alcohols into the corresponding bromides. The traditional method employing phosphorus tribromide[6] often affords products of insufficient purity. *O*-Alkylisoureas are activated towards nucleophilic attack by protonation at nitrogen. This principle is used in the reaction between *O*-alkylisoureas and carboxylic acids to give esters.[2,7] The work of McKee[3] suggested that this method of activation could be applied to the synthesis of alkyl halides in general. Our use of trifluoromethanesulphonic acid allows accurate control over the quantity of acid and avoids nucleophilic competition between added halide and the counterion of the acid.

Kinetic studies of the reaction of the hydrotrifluoromethanesulphonate of *O*-alkylisourea (**1d**) and tetrabutylammonium bromide showed a first order rate dependence on *O*-alkylisourea salt concentration. Reactivity was enhanced with polar aprotic solvents: hexamethylphosphoramide > dimethylsulphoxide ~ acetonitrile > chloroform ~ dichloromethane >> methanol. The reactivity of isoureas decreased in the order: allylic ~ propargylic ~ benzylic > primary > secondary. (*S*)-2-*O*-Octyl-isourea gave (*R*)-2-bromo-octane of 38% optical purity when the reaction was stopped at ~ 30% completion. Optical purity decreased with length of reaction, consistent with racemisation of 2-bromo-octane in the presence of bromide ion. These facts are consistent with the mechanism of the reaction being S_N2 attack by halide on the alkyl group of the protonated *O*-alkylisourea, with *N*,*N*'-di-isopropylurea as the leaving group. *O*-Alkylisourea (**1e**) gave 5% of the S_N2' product [*cf* Table 2] equivalent to the best ratio obtainable using phosphorus tribromide.[6] However, *O*-alkylisourea (**1h**) gave only alkyl bromide (**3h**), no S_N2' product being observed. *O*-Alkylisourea (**1c**) underwent β-elimination to give eventually 1,2-dibromocyclohexane.

For preparative reactions we find dichloromethane or chloroform to be very suitable solvents because of their ease of handling and acceptable reaction rate. However, for less reactive isoureas, acetonitrile or hexamethylphosphoramide may be necessary. As the examples in Table 2 show the method is suitable for molecules containing either a double or triple bond, or two such bonds in 'skipped' arrangement, and also for cyclopropylcarbinols.[8] The method described should be suitable for the preparation of alkyl bromides or iodides from alcohols containing sensitive functional groups. It is particularly useful that *O*-alkylisoureas

Table 2. Halides Prepared 3 + 4

Substrate	Product [a]	Reaction Conditions Solvent/Temperature/Time	Yield [%]	b.p.[°C](mmHg) found	reported
1a	3a	$CHCl_3$/65°C/7.5h	83	88- 91°(14)	202.2° [9]
2b	3b	$CHCl_3$/61°/24h	90	30- 35°(0.5)	78°(16) [10]
1c	b	$(CD_3)_2SO$/100°C/18h	31		
2d	3d	CH_2Cl_2/25°C/26h	88	80- 85°(14)	198° [11]
1e	3e[d]	CH_2Cl_2/25°C/24h	66	102-104°(760)	26.8°(34) [12]
1f	3f	CH_2Cl_2/40°C/15h	58	76- 78°(150)	82°(136) [13]
1g	3g	$CHCl_3$/61°C/43h	57	22°(0.1)	44-46°(1) [14]
2h	3h	$CHCl_3$/25°C/2h	81	62- 65°(14)	88-91°(12) [15]
1i	3i	$CDCl_3$/25°C/26h	82	62-66°(6)	-
1j	3j	$((CH_3)_2N)_3PO$/120°C/60h	74	50-54°(25)	c
1a	4a	$CDCl_3$/65°C/2.5h	71	45-50°(0.35)	108°(18) [16]
1d	4d	$CDCl_3$/25°C/70min	79	50- 55°(0.2)	98-102°(14) [17]
1h	4h	$CDCl_3$/25°C/10min	80	50- 55°(0.2)	-

[a] Products characterized by M.S., I.r. and ^{1}H-N.M.R. spectroscopy.

[b] 1,2-Dibromocyclohexane was the only product obtained.

[c] No boiling point quoted in original reference Hill, E. A., Link, D. C., Donndelinger P., J.Org.Chem. 1981, 46, 1177.

[d] ^{1}H-N.M.R analysis showed the product to be a mixture containing 95% (E)-1-bromo-but-2-ene and 5% 3-bromo-but-1-ene.

are relatively inert compared to other derivatives of alcohols (e.g. methanesulphonates) and are only triggered to undergo further reaction by titration with a non-nucleophilic acid.

Method A. (*E*)-1-Bromohept-2-yn-5-ene (3i); Typical Procedure

To (*E*)-*N*,*N*'-diisopropyl-*O*-hept-2-yn-5-enylisourea (**1i**, 105 mg, 0.445 mmol) in deuteriochloroform (0.5 ml) is added trifluoromethanesulphonic acid (37 μl, 0.42 mmol). After thorough mixing, a solution of tetrabutylammonium bromide (172 mg, 0.53 mmol) in deuteriochloroform (0.5 ml) is added. After 26 h at room temperature, purification by silica chromatography (light petroleum - dichloromethane, 1:1) and distillation (bulb to bulb) gives (*E*)-1-bromohept-2-yn-5-ene (**3i**, 63 mg, 82%), b.p. 62-66°C at 6 mmHg.

Method B. 2-Bromo-octane (3b); **Typical Procedure:**

Octan-2-ol (**2b**, 213 mg, 1.78 mmol) and *N*,*N*'-di-isopropylcarbodiimide (213 mg, 1.83 mmol) are stirred in the presence of copper(I) chloride (5 mg) for 6 days at room temperature. The mixture is diluted with chloroform (5 ml) and tetrabutylammonium bromide (860 mg, 2.67 mmol) is added with stirring. Trifluoromethanesulphonic acid (0.154 ml, 1.74 mmol) is then slowly added. After heating under reflux for 24 h, purification by silica chromatography (dichloromethane) gives 2-bromo-octane (**3b**, 310 mg, 90%), b.p. 30-35°C at 0.5 mmHg (bulb to bulb distillation).

Acknowledgement :

We thank SERC for a CASE studentship to SPC, and Dr N Winterton (ICI) for initiating this study by bringing the work of McKee (ref 3) to our attention.

References

(1) Schmidt, E. *Liebigs Ann Chem.* **1955,** *597,* 235.
(2) a) Mathias, L. J. *Synthesis* **1979,** 561; b) Mathias, L. J. *Org. Prep. Proc. Int.* **1980,** *12,* 309.
(3) McKee, R. H. *Am. Chem. J.* **1901,** *26,* 209.
(4) Scheffold, R., Saladin, E. *Angew. Chem. Int. Ed.* **1972,** *11,* 229.
(5) Cramer, F., Pawelzik, K., Lichtenthaler, F. W. *Chem. Ber.* **1958,** *91,* 1555.
(6) Winstein, S., Young, W. G. *J. Am. Chem. Soc.* **1936,** *58,* 104; Smith, L. H. *Org. Synth.* **1955** *Coll. Vol. 3,* 793.
(7) Vowinkel, E. *Chem. Ber.* **1967,** *100,* 16.
(8) S. P. Collingwood, A. P. Davies, B. T. Golding, and P. J. Sellars, unpublished results.
(9) Mumford, S. A., Phillips, J. W. C. *J. Chem. Soc.* **1950,** 75.
(10) Beringer, F. M., Schultz, H. S. *J. Am. Chem. Soc.* **1955,** *77,* 5533.
(11) Schmid, H., Karrer, P. *Helv. Chim. Acta.* **1946,** *29,* 573.
(12) England, B. D. *J. Chem. Soc.* **1955,** 1615.
(13) Ashworth, P. J., Whitham, G. H., Whiting, M. C. *J. Chem. Soc.* **1957,** 4633.
(14) Ansell, M. F., Emmett, J. C., Coombs, R. V. *J. Chem. Soc. (C).* **1968,** 217.
(15) Chin, S. K., Golding, B. T., Pierpoint, C. *J. Chem. Res. (S)* **1985,** 71; *(M)* **1985,** 946.
(16) Berlak, M. C., Gerrard, W. *J. Chem. Soc.* **1949,** 2309.
(17) Bacher, W., Wagner, J. *Z. Phys. Chem. [B].* **1939,** *43,* 191.

(Received in UK 24 July 1987)