Conversion of Alcohols into Haloalkanes in Tertiary Phosphine/Methyl Halide/4-Methyl-1,2,4-triazolidine-3,5-dione (MTAD) System

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(Received November 28, 1983)

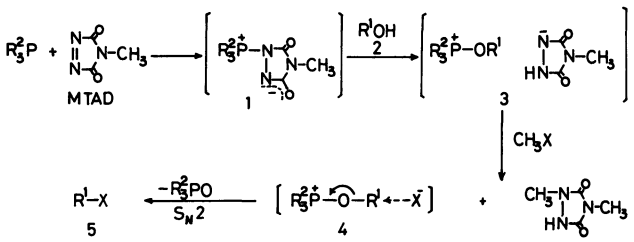
Synopsis. Alcohols were succesfully converted to the corresponding alkyl halides using the betaine provided by tertiary phosphine/4-methyl-1,2,4-triazolidine-3,5-dione (MTAD) system. Stereospecific reaction involving inversion of configuration on the carbon atom (S_N2 reaction) was clarified.

In a series of studies on 4-methyl-1,2,4-triazolidine-3,5-dione (MTAD), reaction of diene and ene components were examined. These are known to act as a dienophile or enophile[1] towards MTAD.[2] The previous studies on MTAD were mainly limited to the addition reaction.

This report describes the transformation of alcohols **2** such as benzyl alcohol (**2a**), cyclohexanol (**2b**), (−)-menthol (**2c**), (−)-borneol (**2d**), and (−)-2-octanol (**2e**) to the haloalkanes **5** using tertiary phosphine and MTAD system. Stereospecific conversion of alcohols into haloalkanes with inversion of configuration by using the conventional method with well known reagents such as dihalophosphine[3,4] afforded the inverted products. However, conversion of alcohols into haloalkanes using a betaine formed from reaction of triphenylphosphine with MTAD has not previously been reported. Reaction of triphenylphosphine with diethyl azodicarboxylate is known to form a betaine-like intermediate **1**.[5]

Results and Discussion

In the present reaction, the yields of **5** were extremely high and they did not depend on the choice of the tertiary phosphine used *i.e.*, triphenylphosphine or tributylphosphine (Table 1). The reaction can be explained by assuming the successive formation of a betaine **1** and an alkoxyphosphonium salt **3**. Methyl halide methylate intermediates **3** liberate a halide anion which, in turn, attacks the carbon atom of the alkoxide group in the Arbzov type intermediate, *i.e.*, alkoxyphosphonium salt **4**.[6,7] By using this procedure, alcohols **2c** and **2e** were successfully converted into the corresponding halides with inversion of configuration (S_N2 type reaction)[6] at the carbon atom (Table 2).



Attempted reaction of compound **2b** with methyltriphenylphosphonium bromide to promote the dissociation of the halogen in the presence of an equimolar amount of MTAD was unsuccessful. These results show that the tertiary phosphine/methyl halide/MTAD system does not proceed *via* a formation of methyltriphenylphosphonium halide, that the system is effective for halogenation of alcohols in the yield and stereospecificity, and that the intermediate of first formed key betaine **1** as well as the last Arbzov type one

TABLE 1. CONVERSION OF ALCOHOLS **2** INTO HALOALKANES **5** (TERTIARY PHOSPHINE/METHYL HALIDE/MTAD SYSTEM)

Alcohol **2a—e** R^1OH	R^2_3P	CH_3X	Product **5a—e**[a] R^1X	Purity/% G.L.C.	Yield /%	IR (cm^{-1})	Bp (°C)/mmHg, (mp °C) Found	reported
Benzyl alcohol	Ph	I	Benzyl halide[b]	100	92	1200, 645	101—102/15	102/15[11]
(**2a**)	Ph	Br	(**5a**)	100	91	1158, 680	81—82/18	80—81/16[3]
	n-Bu	I		100	89	1200, 645		
	n-Bu	Br		100	87	1158, 680		
Cyclohexanol	Ph	I	Cyclohexyl halide[b]	95	74	1170, 650	68—69/10	72/15[11]
(**2b**)	Ph	Br	(**5b**)	95	71	1160, 680	58—60/15	163—165[12]
	n-Bu	Br		95	75	1170, 650		
(−)-Menthol	Ph	I	Neomenthyl halide[b]	100	88	1170, 650	120—121/15	122—123/17[8]
(**2c**)	Ph	Br	(**5c**)	100	88	1165, 645	103—104/15	91/7[13]
	n-Bu	Br		100	88	1165, 645		
(−)-Borneol	Ph	Br	(+)-Bornyl bromide[c]	—	75	1180, 685	(129—131)	(133)
(**2d**)	*n*-Bu	Br	(**5d**)	—	76	1180, 685		
(−)-2-Octanol	Ph	I	(+)-2-Iodooctane	81	65	1180, 680	101—102/18	42/0.5[4]
(**2e**)			(**5e**)					

a) Satisfactory ^1H NMR spectra have been obtained for all haloalkanes **5**. b) Haloalkanes **5a**, **5b**, and were identified by G.L.C. being compared with authentic samples. c) Haloalkane **5d** was isolated by chromatography on silica gel.

Table 2. Haloalkanes **5c—e** from optically active alcohols **2c—e** (Tertiary phosphine/methyl halide/MTAD system)

Haloalkane[a] (**5c—e**)	Temp °C	$[\alpha]_D$ Found	$[\alpha]_D$ Reported
Neomenthyl iodide (**5c**)	17.0	+39.6° (c=1.01, EtOH)	+41.2° [8]
Neomenthyl bromide (**5c**)	13.5	−7.26° (c=1.01, EtOH)	−10.45° [8]
(+)-Bornyl bromide (**5d**)	15.0	−2.39° (c=1.01, EtOH)	+21.2° [9]
(+)-2-Iodooctane (**5e**)	17.0	+23.8° (c=1.02, EtOH)	+19.53° [4]

a) Optical rotations of the alcohols **2c**, **2d**, and **2e** were −49°, −37.7°, and −9.9°, respectively.

Table 3. Conversion of alcohols **2** into haloalkanes **5** (Ph_3P/CH_3I/DEADC[a] system)

R^1OH	Product	Purity/% (G.L.C)	Yield[b]/%	$[\alpha]_D$
2a	Benzyl iodide	98	90	—
2b	Cyclohexyl iodide	78	61	—
2c	Neomenthyl iodide	100	92	+39.4 (c=1.02, EtOH)
2e	(+)-2-Iodooctane	96	92	+23.5 (c=1.02, EtOH)

a) DEADC=Diethyl azodicarboxylate (EtO-C(=O)-N=N-C(=O)-OEt). b) Isolated yield by distillation.

play an important role in the stereospecific halogenation. Comparison of the yield and stereospecificity of the present method with that using the triphenylphosphine/diethyl azodicarboxylate/methyl iodide system[5] in conversion of alcohols **2** into iodoalkanes **5** (Table 3) shows that this method is an exellent alternative for preparation of haloalkanes. No large difference in the purity of haloalkanes was recognized in the tow methods.

This new procedure has some advantages in preparing haloalkanes, *i.e.*, mild reaction conditions, high product yield, and facile work up to remove tertiary phosphine oxide and 2,4-dimethyl-1,2,4-triazolidine-3,5-dione.

Identification of the products **5** was established by comparison with authentic samples by IR and ^1H NMR spectra, optical rotation, and/or retention time of G. L. C.

Experimental

Measurements. Melting points were measured on a Yanagimoto Seisakusho micro melting point apparatus. ^1H NMR spectra were recorded on a Hitachi R-24 (60 MHz) spectrometer with TMS as an internal standard, IR spectra on a JASCO A-3 infrared spectrophotometer, G. L. C. on a Yanagimoto Gas Chromatograph GCG-550T, and optical rotations were determined with JASCO DIP-4 digital and Atago Polax photometers.

Preparation of Neomenthyl Iodide (5c); Typical Procedure: A solution of MTAD (2.4 g, 21 mmol) in tetrahydrofuran (20 ml) was added to a tetrahydrofuran (30 ml) solution of (−)-menthol (**2c**) (3.0 g, 19 mmol) and triphenylphosphine (5.5 g, 21 mmol) at a temperature of 0 °C. After 10—15 min, methyl iodide (2.7 g, 19 mmol) in tetrahydrofuran (5 ml) was added to the solution (excess methyl halide caused the yield of haloalkanes to be decreased). The mixture was stirred for 6 h at room temperature, then, the solvent was evaporated under reduced pressure. The product was taken up into ether, the insoluble material filtered off and washed with ether to removed triphenylphosphine oxide and 2,4-dimethyl-1,2,4-triazolidine-3,5-dione.

The filtrate was evaporated under reduced pressure, and the residue separated by thin-layer chromatography (silica gel, 1:1 ether/benzene) or distilled under reduced pressure (bp 120—121 °C/15 mmHg, 1 mmHg=133.322 Pa) to give pure neomenthyl iodide (**5c**) in 88% yield, ^1H NMR ($CDCl_3$), δ=0.86 (d, J=7.1 Hz, 3H, CH_3), 0.96 (d, J=7.1 Hz, 6H, $CH(C\underline{H}_3)_2$), 0.63—2.43 (m, 9H, $C\underline{H}(CH_3)_2$ and ring protons other than CHI), and 4.63 (m, 1H, CHI); $IR\nu_{max}^{neat}$, 1170 cm^{-1} (C-I); $[\alpha]_D^{17.0}$ +39.6° (c=1.01, C_2H_5OH) (lit,[8] neomenthyl iodide $[\alpha]_D$ +41.2°); G. L. C. retention time 2 min (column: Versamide 20%, 900 on Neopack 1A, 60/80 mesh; carrier gas; H_2 (1 Kg/cm^2); column temperature: 141 °C; column length: 2 m).

The authers wish to express their thanks to Professor M. Suzuki's laboratory of Shizuoka University for providing facility for measurement of the optical rotation.

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