Table I. Reactions of Formaldehyde in Aqueous HX

present before reaction[a]			reaction conditions		present after reaction, %		
formaldehyde	HCO_2H	solvent	temp. °C	time, h	CH_3CO_2H[b]	CH_3I[b]	HCO_2H[c]
(1.0)	1.0	65% HI	~105	24	76	6	18
(1.0)	1.2	65% HI	~105	24	90	5	33
(1.0)[d]	1.0	65% HI	~130	4.5	83	7	trace
(1.0)	1.2	65% HI	~130	4.5	93	5	9
(1.0)	1.0	43% HI	~130	4.5	12	12	83
1.0		65% HI	~130	4.5	12	12	
1.0		65% HI	~160	1	12	11	
1.0		43% HI	~130	4.5		15	31[b]
(1.0)	1.0	37% HCl	~130	4.5	60[e]		

[a] Amounts given are relative. [b] Based on formaldehyde. [c] Based on HCO_2H, unless noted otherwise. [d] Use of CH_3CO_2H instead of formaldehyde resulted in quantitative recovery of the CH_3CO_2H; use of CH_3OH instead of formaldehyde resulted in no production of CH_3CO_2H. [e] The product is $ClCH_2CO_2H$. CAUTION: CH_3OCH_2Cl and $ClCH_2OCH_2Cl$ are carcinogens.

CO and yields carboxylic acids from substrates that can produce carbonium ions. Reports of the use of *stoichiometric* quantities of formic acid to convert alcohols to ^{13}C-labeled carboxylic acids[4a] and paraformaldehyde to glycolic acid and its polymers[4b] stimulated us to think of the possibility that HCO_2H could be a useful and practical substitute for CO in reactions that we had reported and more generally.

We have now found that reaction of formaldehyde with a stoichiometric amount of formic acid in aqueous HI gives acetic acid in high yield (eq 3) and that formaldehyde alone also yields some acetic acid (eq 4). Some representative

$$\text{formaldehyde} + HCO_2H \xrightarrow{HI,\ H_2O} CH_3CO_2H \quad (3)$$

$$\text{formaldehyde} \xrightarrow{HI,\ H_2O} CH_3CO_2H \quad (4)$$

results are in Table I.[5] We anticipate the utility of near-equivalent amounts of HCO_2H, introduced as such or formed in situ, as a substitute for CO in a wide variety of reactions.

In addition, we have found the also new, but less novel, reaction in eq 5 (Table I), a reaction that may model the first portion of the pathway operative in aqueous HI.

$$\text{formaldehyde} + HCO_2H \xrightarrow{HCl,\ H_2O} ClCH_2CO_2H \quad (5)$$

Experimental Section

All materials were of commercial origin. The 65% HI was obtained from Fluka; 43% HI is 65% HI that has been diluted with an equal volume of water.

^1H and ^{13}C NMR spectra were recorded on Varian A-60A and XL-200 spectrometers, respectively.

The initial reaction mixtures (1 mmol of formaldehyde as trioxane,[6a] 0.40 mL of solvent, other reagents as indicated in Table I) were sealed under vacuum in 4-mm i.d., 5- or 6-mm o.d. Pyrex tubes.[6b] They were heated in an oven under the conditions specified in Table I.

Final reaction mixtures were similar to those encountered earlier.[1] They were monitored and analyzed by use of NMR spectroscopy. Any opening of a tube was done after it had been cooled in liquid nitrogen; it was then fitted with a serum cap while at that temperature and any transfers were made through the cap by use of a gas-tight syringe after the mixture had warmed to room temperature. Since the product CH_3I was incompletely miscible with the aqueous HI, the reaction mixture was treated with benzene to facilitate analysis for CH_3I.

Acknowledgment. We are grateful to Prof. Robert G. Salomon for making laboratory facilities available to us and to Dr. Adrian Valeriu for obtaining ^{13}C NMR spectra.

Registry No. HCO_2H, 64-18-6; CH_3CO_2H, 64-19-7; $ClCH_2CO_2H$, 79-11-8; formaldehyde, 50-00-0.

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(5) See ref 1 for a discussion of reaction pathways that may be relevant. In addition, see footnote *d* to Table I and note that formaldehyde is known to undergo an acid-catalyzed self-Cannizzaro reaction to yield CH_3OH + HCO_2H.

(6) (a) α-Polyoxymethylene also exhibits this chemistry. (b) The reaction proceeds well also when run in an open system.

A Detailed, Convenient Preparation of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate

Dale L. Boger,*[1a,c] Robert S. Coleman,[1b,c] and James S. Panek

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045-2500

F. X. Huber and J. Sauer*

Institute for Organic Chemistry, University of Regensburg, Regensburg, Germany

Received November 6, 1984

In the course of recent studies[2] we required substantial quantities of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1), an electron-deficient heterocyclic aza diene especially suited for inverse electron demand ($LUMO_{diene}$ controlled) Diels–Alder reactions with electron-rich dienophiles and heterodienophiles,[3] and have developed an optimal, im-

(1) (a) Searle scholar recipient, 1981–1985. Recipient of a National Institutes of Health career development award, 1983–1988 (Grant CA 01134/00898), Alfred P. Sloan Research Fellow, 1985–1989. (b) National Institutes of Health predoctoral trainee, 1984–1985 (Grant GM 07775). (c) Department of Chemistry, Purdue University, West Lafayette, IN 47907.

(2) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621; *Tetrahedron Lett.* **1983**, *24*, 4511; *J. Am. Chem. Soc.* **1985**, *107*, 5745. Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405. Sellner, I.; Schuster, H.; Sichert, H.; Sauer, J.; Nöth, H. *Chem. Ber.* **1983**, *116*, 3751. Balcar, J.; Chrisam, G.; Huber, F. X.; Sauer, J. *Tetrahedron Lett.* **1983**, *24*, 1481. Schuster, H.; Sichert, H.; Sauer, J. *Tetrahedron Lett.* **1983**, *24*, 1485. Schuster, H.; Sauer, J. *Tetrahedron Lett.* **1983**, *24*, 4087.

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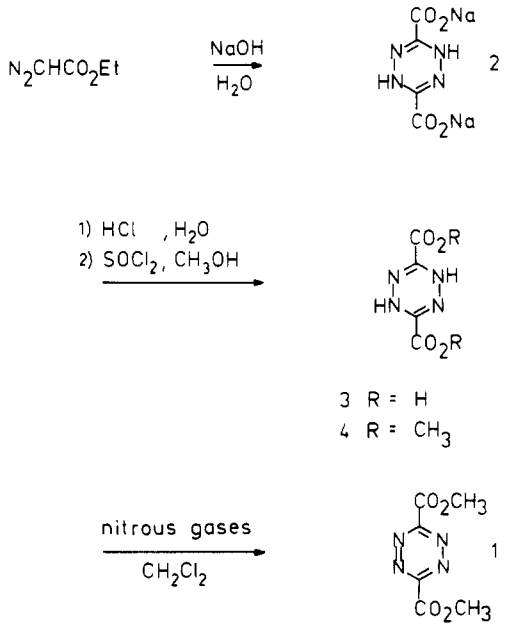
Scheme I



proved procedure for its preparation. We have had occasional difficulty conveniently reproducing the preparation of 1 from the information that is available in prior published work, and to date no report details a complete procedure for the preparation of 1.

Herein, we detail a convenient, large scale, four-step preparation of 1 that is capable of providing 20–40 g of material (34% overall yield) and is based on the original base-promoted dimerization of ethyl diazoacetate reported by Curtis,[4a] an improved protonation procedure detailed originally by Wiberg,[4b] an improved and convenient esterification developed by Sauer,[4c] and a new, modified oxidation procedure utilizing nitrous gases (Scheme I).

Attempts to shorten this procedure by direct conversion of 2 to 4 have not been successful,[5] attempts to convert 3 to 4 utilizing other methods of esterification have been less successful,[6] efforts to esterify 1,2,4,5-tetrazine-3,6-dicarboxylate[7] have not been successful, and alternative oxidation methods for the conversion of 4 to 1[8] were less successful. The failure of these attempts and the modest yields in two of the steps we describe can be attributed to the reactivity of the system. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1) is not completely stable to chromatography on silica gel, undergoes slow decomposition upon warming, and like dihydro-1,2,4,5-tetrazines 3/4 is prone to acid-promoted rearrangement.

Experimental[9] Section

Disodium Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (2).[10a] Ethyl diazoacetate (200 g, 1.75 mol) was added dropwise to a mechanically stirred solution of sodium hydroxide (320 g, 8.00 mol) in 500 mL of water at such a rate so as to maintain the temperature of the reaction between 60 and 80 °C (approximately 1.5 h). After cooling to room temperature, the reaction slurry was poured onto 2 L of 95% ethanol, the slurry mixed well, and the liquid decanted. This washing procedure was repeated five times using 1.5 L of 95% ethanol each time. The precipitate was filtered, the collected solid washed with 1 L of absolute ethanol and 1 L of Et_2O, and air-dried (12 h) to afford 175–184 g (92–97%) of 2 as a yellow-brown solid.

Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic Acid (3).[10b] A slurry of 2 (74.0 g, 0.342 mol) in 80 mL of water containing 80 g of crushed ice was cooled with an ice/NaCl bath, and concentrated hydrochloric acid (150 mL) was added dropwise over 40–50 min. The product was immediately collected by suction filtration (if necessary, the reaction was diluted with a maximum of 20 mL of ice water prior to filtration). The solid product was suspended in 200 mL of ice water, stirred at 0 °C for 30 min, and then filtered using a Buchner funnel. The product was washed with 20 mL of ice water and then was dried for a short time on clay plates and finally dried in vacuo to constant weight to afforded 44.1–45.9 g (75–78%) of 3 as a yellow powder: mp 144–148 °C; IR (KBr) ν_{max} 3700–3100, 3320, 3000–1850, 1710, 1630 cm^{-1}.

Drying the free acid should be rapid and with a large surface area since traces of acid in the wet product promote hydrolysis to hydrazine salts. Slight warming (≤60 °C) during drying accelerates the drying procedure.

Liberating the acid from the disodium salt with sulfuric acid[4b] decreases the yield of this step considerably.

Dimethyl Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (4).[10b] A three-necked flask containing 240 mL of dry methanol, which was equipped with a mechanical stirrer and dropping funnel, was cooled to −30 °C and freshly distilled thionyl chloride (40 mL) was added dropwise. Dry 3 (37 g, 0.215 mmol) was suspended in 270 mL of dry methanol and was added in four portions (over 30 min) to the stirred reaction mixture. The temperature was maintained at −30 °C during the additions. The reaction mixture was then allowed to warm to room temperature and subsequently was warmed at 35–40 °C (internal temperature) for 2 h. The mixture was cooled to 0 °C internal temperature with an ice bath and the precipitate collected by filtration. The precipitate was washed with 20 mL of dry methanol and 20 mL of dry ether, and dried in vacuo. Cooling the remaining mother liquor to −30 °C afforded a second smaller, impure crop of product.

The combined product was extracted with dry methylene chloride in a Soxhlet apparatus in order to remove inorganic solids. The liquid extracts were evaporated in vacuo to afford 24.0–26.5 g (56–61%) of pure 4 as an orange-yellow powder: mp 171–172 °C; ^1H NMR ($CDCl_3$, ppm) 7.42 (br s, 2 H, NH), 3.92 (s, 6 H, CO_2CH_3); IR (KBr) ν_{max} 3160, 3050, 1740, 1720 cm^{-1}.

The residue from the Soxhlet extraction, a colorless water-soluble powder, is a hydrazine salt.

Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate (1).[10a] A slurry of 4 (20 g, 0.10 mol) in 800 mL of CH_2Cl_2 was cooled with an ice/water bath. Nitrous gases were generated in a separate vessel by the disproportionation of nitrous acid (HONO): 200 mL of 6 N $NaNO_2$ (1.2 mol) was added dropwise (15 min) with stirring to 125 mL of concentrated HCl (1.5 mol). The brown gases evolved were bubbled directly into the stirred reaction mixture for 15 min

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(5) For instance, treatment of 2 with thionyl chloride in methanol at 0 °C (0.5 h) and 25 °C (6 h) failed to provide 4.

(6) For instance, treatment of 3 with diazomethane in ether provided only poor yields of 4 in addition to *N*-methylated material; see also: Lin, C. H.; Lieber, E.; Horwitz, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 427. Simple Fischer esterification (methanol/hydrochloric acid) failed to produce 4.

(7) For instance, treatment of 1,2,4,5-tetrazine-3,6-dicarboxylic acid with diazomethane in ether or with methanol/dicyclohexylcarbodiimide/1-hydroxybenzotriazole in dimethylformamide failed to provide 1. Treatment of disodium 1,2,4,5-tetrazine-3,6-dicarboxylate with methyl iodide in dimethylformamide or hexamethylphosphoramide or with thionyl chloride in methanol failed to provide 1.

(8) Our methods explored in an effort to convert 4 to 1 were unsuccessful (MnO_2 in methylene chloride) or less successful than the procedure detailed herein (KNO_2, acetic acid/benzene).

(9) Proton nuclear magnetic resonance spectra (^1H NMR) was recorded on a Varian FT-80A spectrometer. Infrared spectra (IR) were recorded on an IBM FTIR-32 spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and chloroform ($CHCl_3$) were dried and distilled before use. Methanol was distilled from magnesium turnings immediately before use. Ethyl diazoaceate can be used as received from Aldrich Chemical Co., but the varying amounts of CH_2Cl_2 present may reduce the yield of the base-promoted dimerization step. All other reagents were used as received from commercial sources.

(10) (a) Inquiries concerning this work should be addressed to Dale L. Boger. (b) Inquiries concerning this work should be addressed to J. Sauer.

through a 5-mm (i.d.) glass tube using a nitrogen stream. (*Caution!* All operations involving nitrous gases must be conducted in a well-ventilated hood due to the toxicity of these gases.) The color of the reaction mixture changed from orange to bright red during the addition. Stirring was continued for 1.5 h as the reaction was allowed to warm to room temperature. The solvent and excess nitrous gases were removed in vacuo to afford 19.7 g (100%) of 1 as a bright red, crystalline solid: mp 173–175 °C, ^{1}H NMR ($CDCl_3$, ppm) 4.22 (s, 6 H, CO_2CH_3); IR (KBr) ν_{max} 2970, 1752, 1445, 1385, 1219, 1175, 1082, 960, 912 cm^{-1}; UV (dioxane) λ_{max} (log ϵ) 520 nm (2.754).

Acknowledgment. This work was assisted financially by the Searle scholars program, the National Institutes of Health, and the Deutsche Forschungsgemeinschaft.

Registry No. 1, 2166-14-5; 2, 96898-32-7; 3, 3787-09-5; 4, 3787-10-8; ethyl diazoacetate, 623-73-4.

Dimethylboron Bromide Interconversion of Protecting Groups: Preparation of MTM Ethers, *O,S*-Acetals, and Cyanomethyl Ethers

Howard E. Morton* and Yvan Guindon

Merck Frosst Canada Inc., Pointe Claire-Dorval, Quebec, Canada H9R 4P8

Received April 18, 1985

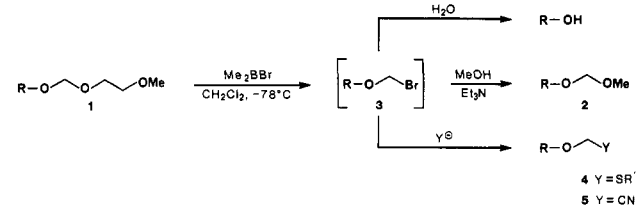
Previously, we have reported on the synthetic utility of dimethylboron bromide for a variety of different chemical transformations such as the mild reduction of sulfoxides to sulfides,[1] the cleavage of ethers (alkyl, aryl, cyclic) to alcohols,[2] and the conversion of acetals and ketals (including MEM, MOM, and THP ethers) to the corresponding aldehydes, ketones, and alcohols.[3] As part of a mechanistic study related to the cleavage of MEM ethers,[3] methanol–MEM ether (1; R = menthyl) was transformed by sequential treatment with dimethylboron bromide and methanol–triethylamine into the corresponding MOM ether 2 (Scheme I). The efficient formation of 2 strongly suggested the presence of the α-bromo ether 3 as the initial product of the cleavage reaction.

This facile route to the α-bromo ether intermediates 3,[4] combined with the general availability of primary, secondary, and tertiary MEM and MOM ethers[5] has prompted us to investigate the reaction of 3 with a variety of other nucleophiles with the intention of developing an approach for the formation of functionalities that are otherwise difficult to obtain. We are reporting herein on the successful utilization of this approach for the general preparation of *O,S*-acetals including MTM [(methylthio)methyl] ethers 4 (R′ = Me) and cyanomethyl ethers 5.

Results and Discussion

MTM ethers are useful functionalities for the protection of alcohols owing to their unique stability characteristics.[6]

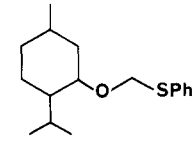
Scheme I



Moreover, they can be selectively removed under very mild conditions (e.g. $HgCl_2$, CH_3CN–H_2O[5], Me_2BBr[3]). However, their utilization in organic synthesis has been somewhat restricted due to problems encountered in their preparation. For example, halomethyl methyl sulfide–sodium hydride has been used for their preparation; however, this method is restricted to primary alcohols[6] and phenols.[7] Acetic anhydride–Me_2SO[8] is useful only for the protection of tertiary alcohols since primary and secondary alcohols are oxidized under these conditions.[9] The use of acetic acid–acetic anhydride–Me_2SO avoids some of these problems; however, prolonged reaction times are required.[10] More recently, modest yields of MTM ethers have been achieved with chloromethyl methyl sulfide–silver nitrate–triethylamine.[11]

Some of the results that we have obtained for the preparation of MTM ethers are summarized in Table I.[12,13] Under our experimental conditions, primary, secondary, and even tertiary MOM (methoxymethyl) and MEM [(2-methoxyethoxy)methyl] ethers are converted into the corresponding MTM ethers in high yield. Thus, treatment of a CH_2Cl_2 solution of menthol–MOM ether 8 with 2.0 equiv of dimethylboron bromide at −78 °C for 1 h and quenching with diisopropylethylamine and methanethiol gave, after flash chromatography, pure menthol–MTM ether 9 (91% yield) (entry 2). The only detectable side product was a small amount of the parent alcohol. It is noteworthy that benzylic (entry 5) and even tertiary allylic (entry 6) MEM and MOM ethers can be smoothly converted into the desired MTM ethers in good yield. The previously described routes to the latter compounds are generally less efficient.[11]

Other S-substituted thiomethyl ethers are also readily prepared utilizing this methodology. Thus, treatment of menthol-MEM ether 10 with dimethylboron bromide (2.0 equiv, CH_2Cl_2, −78 °C) and quenching with diisopropylethylamine (3.0 equiv) and thiophenol (2.5 equiv) produced the corresponding (phenylthio)methyl ether 21 (84%).



21

O,S-Acetals also find application as useful carbonyl protecting groups.[5] Cyclic *O,S*-acetals are readily obtain-

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(12) Recently the interconversion of MEM ethers to isopropyl thiomethyl ethers using *i*-PrS_2BBr was reported. The utility of MOM ethers was not exemplified. Corey, E. J.; Hua, D. H.; Seitz, S. P. *Tetrahedron Lett.* **1984**, 3.
(13) All new compounds reported herein exhibited spectral properties (IR, ^{1}H NMR, MS) in full accord with their assigned structures and gave satisfactory combustion analyses.

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