5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione, 29668-95-9; diethyl 4,4-dicyanopimelate, 29668-96-0.

Acknowledgments.—A Summer Research Fellowship from the Research Council of the University of Colorado in partial support of this work is appreciated. Thanks are extended to Mr. James D. Specht for his aid in checking much of the work and for the preparation of **3**.

The Direct Preparation of *tert*-Butyl Azidoformate

K. SAKAI AND J.-P. ANSELME*[1]

Department of Chemistry, University of Massachusetts, Boston, Massachusetts 02116

Received January 19, 1971

The carbo-*tert*-butoxy (BOC) function has achieved a role of major importance as a blocking group, particularly in peptide chemistry.[2] The "carbo-*tert*-butoxylating" agent of choice is *tert*-butyl azidoformate (**3**).[3] The value of the carbo-*tert*-butoxy group and the rather high cost of the reagent created a demand for a better and more convenient synthesis of **3**.

The instability of *tert*-butyl chloroformate (**1**) prevented its use as a direct precursor of **3** by displacement *via* the usual "azide method" and the azido group had to be built by the hydrazide–nitrosation route (eq 1).

$$\underset{\mathbf{2}}{H_2NNHCO_2(CH_3)_3} \xrightarrow{HONO} \underset{\mathbf{3}}{N_3CO_2C(CH_3)_3} \not\leftarrow \quad \overset{N_3^-\ (aq)}{\underset{ClCO_2C(CH_3)_3}{+}} \quad (1)$$
$$\mathbf{1}$$

Thus, most attempts at improving Carpino's method centered on the precursor of **3**, *tert*-butyl carbazate (**2**).[4] The several routes to **2** which have been published differ from Carpino's original procedure and each other only in the nature of the group being displaced by hydrazine (X in **4**).[5]

$$\underset{\mathbf{4}}{XCO_2C(CH_3)_3} + H_2NNH_2 \longrightarrow \underset{\mathbf{2}}{H_2NNHCO_2C(CH_3)_3} \quad (2)$$

Our general interest in azides[6] and in selective protective groups[7] provided a strong impetus to the search for an improved synthesis of *tert*-butyl azidoformate. In 1966, Papa[8] reported the synthesis of guanidinium azides which are ionic and *soluble* in organic solvents. Since *tert*-butyl chloroformate (**1**) is easily prepared in high yield from the reaction of *tert*-butyl alcohol and phosgene at −78°,[9] it was felt that the reaction of tetramethylguanidinium azide (TMGA) (**5**) with **1** might provide a more convenient and direct synthesis of *tert*-butyl azidoformate.

$$\underset{\mathbf{1}}{ClCO_2C(CH_3)_3} + \underset{\mathbf{5}}{N_3^-H_2\overset{+}{N}=C(NMe_2)_2} \longrightarrow$$
$$\underset{\mathbf{3}}{N_3CO_2C(CH_3)_3} + Cl^-H_2\overset{+}{N}=C(NMe_2)_2$$

The results of the experiment exceeded our expectations. The reaction of *tert*-butyl chloroformate with TMGA gave a near-quantitative yield of *tert*-butyl azidoformate, isolated as an amber liquid, *without distillation*. Its purity as judged from comparison of its infrared spectrum with that of a commercial sample appeared to be better than 98%. Phenyl and *tert*-amyl azidoformates[10] were obtained in 97 and 84% yields, respectively.

Tetramethylguanidinium azide is prepared very simply in high yields (86%)[8,11] by the addition of an ethereal solution of hydrazoic acid to tetramethylguanidine.[12] Although it is hygroscopic and thus immediate use is recommended, TMGA can be kept in a desiccator in the cold for long periods of time. *tert*-Butyl chloroformate was prepared by the addition of phosgene to *tert*-butyl alcohol at −78° in the presence of pyridine. The reaction of **1** with TMGA was carried out at 0° in ether with pyridine as the base. The ease and high yields of this procedure coupled with the ready availability of the required starting materials recommend it as a convenient and direct source of *tert*-butyl azidoformate and related azides.

Experimental Section

***tert*-Butyl Azidoformate.**—*tert*-Butyl chloroformate was prepared in solution as follows. Dry phosgene was introduced into a solution of 18 g (0.24 mol) of *tert*-butyl alcohol in 500 ml of anhydrous ether until about 52 g (0.5 mol) had been absorbed and the mixture was cooled in a Dry Ice–acetone bath. Then a solution of 20 g (0.25 mol) of pyridine in 200 ml of anhydrous ether was added dropwise with vigorous stirring. The reaction mixture was stored overnight in a Dry Ice box. The precipitated pyridine hydrochloride was filtered and the volume of the filtrate was reduced to ~70 ml at reduced pressure with cooling in an ice–water bath.[13] This cold solution of *tert*-butyl chloroformate was added over 30 min to a vigorously stirred solution of 31.6 g (0.2 mol) of tetramethylguanidinium azide in 200 ml of chloroform;[8,14] the temperature was kept at 0° throughout the addition. The bath was removed and the reaction mixture stirred for an additional hour and then poured into 500 ml of ice water containing ~2 ml of acetic acid. Extraction with two 60-ml portions of ether followed by careful evaporation of the dried (magnesium

(1) Alfred P. Sloan Fellow.

(2) M. Bodansky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966, p 29 ff.

(3) L. A. Carpino, *et al.*, *Org. Syn.*, **44**, 20 (1964).

(4) See, however, M. A. Insalaco and D. S. Tarbell, *ibid.*, **50**, 9 (1970); and H. Yajima and H. Kawatani, *Chem. Pharm. Bull.*, **16**, 183 (1968); **18**, 850 (1970).

(5) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957); (b) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957); (c) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belg.*, **68**, 409 (1959); (d) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961); (e) M. Muraki and T. Misoguchi, *Chem. Pharm. Bull.*, **18**, 217 (1970).

(6) For the latest paper in this general area, see K. Sakai, N. Koga, and J.-P. Anselme, *Tetrahedron Lett.*, 4553 (1970).

(7) N. Koga and J.-P. Anselme, *Org. Prep. Proced.*, **2**, 125 (1970).

(8) A. J. Papa, *J. Org. Chem.*, **31**, 1426 (1966).

(9) (a) S. Sakakibara, *et al.*, *Bull. Chem. Soc. Jap.*, **38**, 1522 (1965); **40**, 2415 (1967); (b) R. B. Woodward, *et al.*, *J. Amer. Chem. Soc.*, **88**, 852 (1966).

(10) TMGA was *not* isolated and weighed in this case and thus the actual yield of this reaction is probably nearly quantitative also.

(11) Dr. Papa has informed us that he has prepared TMGA on a molar scale about a dozen times without incident although he *strongly* urges the usual *extreme* caution that must be observed with *any* azide. Of course, the toxic and explosive properties of hydrazoic acid are well known and should be respected.

(12) Tetramethylguanidine is available from American Cyanamid Co. whom we thank for a sample.

(13) It is advisable as a cautionary measure to purge the reaction mixture of any excess phosgene by bubbling nitrogen through the *cold*, stirred reaction mixture. Carbonyl azide which would be formed during the reaction with TMGA is an extremely potent explosive.

(14) Concentrated hydrochloric acid was used instead of concentrated sulfuric acid to generate hydrazoic acid. The product obtained was used without purification.

sulfate) organic phase gave *tert*-butyl azidoformate as a pale amber liquid in quantitative yield.[15]

tert-Amyl azidoformate[9a] was prepared in 84% yield[10] from *tert*-amyl chloroformate. Similarly phenyl azidoformate was prepared in better than 97% yield using chloroform as the sole solvent; in this case, tetramethylguanidinium chloride (87% yield) crystallized out of solution.

Registry No.—**3**, 1070-19-5.

Acknowledgment.—The generous support of this work by the National Institutes of Health under Grant GM 13689-04 is hereby acknowledged with deep appreciation.

(15) Neutralization of the aqueous layer followed by extraction with ether allows recovery of tetramethylguanidine.

Dimethyl Sulfide–Borane. A Convenient Hydroborating Agent

LINDA M. BRAUN, RAYMOND A. BRAUN, H. RAY CRISSMAN, MYLES OPPERMAN, AND ROY M. ADAMS*

Geneva College, Beaver Falls, Pennsylvania 15010

Received August 8, 1970

The utility of hydroboration as a tool in reducing and synthetic reactions has received extensive study since the extent of the reaction was first indicated by Brown and Subba Rao.[1,2] However, the application of this tool has been limited by certain properties of the reagent diborane and its solutions. These properties follow: (1) diborane itself is not stable at room temperature and hence it must normally be generated *in situ* in the glycol ethers, (2) it may be purchased as a quite dilute (1.5 wt %) solution in tetrahydrofuran,[3] but this solvent and the glycol ethers are slowly cleaved by borane at room temperature, (3) both these solvents are relatively expensive and hazardous to store and purify. They are also miscible with both polar and nonpolar solvents and hence difficult to separate from desired products.

It seemed to us that dimethyl sulfide–borane (I), which was first reported by Burg and Wagner[4] and studied by Stone, *et al.*,[5,6] might have certain advantages as a storable hydroboration agent. Chief among these is that I is a stable liquid at room temperature. Samples stored in a nitrogen atmosphere have retained their hydridic activity after several months at room temperature. The density was found to be 0.80 g/ml at room temperature (23°). Since the formula weight is 76 g/mol, 1.0 mmol is conveniently 0.10 ml. Tetrahydrofuran–borane solution has a millimolar volume tenfold greater and gaseous diborane in the dilutions which can be shipped at ambient temperatures has a millimolar volume 10^5 greater. I is also miscible with inexpensive, unreactive volatile solvents such as petroleum ether, benzene, diethyl ether, and methylene chloride.

(1) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).
(2) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.
(3) Alfa Inorganics, Beverly, Mass.
(4) A. B. Burg and R. I. Wagner, *J. Amer. Chem. Soc.*, **76**, 3307 (1954).
(5) W. A. G. Graham and F. G. A. Stone, *J. Inorg. Nucl. Chem.*, **3**, 1964 (1956).
(6) T. D. Coyle, H. D. Kaesz, and F. G. A. Stone, *J. Amer. Chem. Soc.*, **81**, 2989 (1959).

CHART I

aldehydes	⟶	alcohol
ketones	⟶	alcohol
acid chloride	⟶	no reaction
lactone	⟶	glycol
epoxide	⟶	alcohol
ester	⟶	alcohol (slow)
carboxylic acid	⟶	alcohol (fast)
nitrile	⟶	amine
nitro	⟶	no reaction
olefin	⟶	organoborane (fast)

Brown and Subba Rao[1,2] listed reduction products (Chart I) from hydroboration (after hydrolysis) for some of the common functional groups. They initially studied the reactivity of borane in ethers toward these groups on a millimolar scale. The results were evaluated by measuring the residual hydridic hydrogen after reaction between stoichiometric quantities of the borane and the reducible moiety. Hence we studied the reactivity of I as a hydroborating agent on a millimolar scale by a procedure parallel to that of Brown and Subba Rao. I (2.0 mmol, measured in a glove bag as 0.20 ml with a hypodermic syringe) was injected into 5 ml of benzene in a 25-ml two-necked flask, one neck of which was fitted with a serum cap and the other with a gas delivery tube leading through a mercury bubbler to a gas measuring tube over water. The reducible organic compound (6 mmol) was then added. The benzene was generally necessary as a heat diluent to avoid uncontrolled reactions. After the mixture was stirred for 30 to 45 min, 5 ml of methanol was added to consume any unreacted borane. The gas evolved was measured over water and assumed to be hydrogen. Results with

$$(CH_3)_2SBH_3 + 3CH_3OH \longrightarrow B(OCH_3)_3 + 3H_2 + (CH_3)_2S$$

typical organic functional groups are presented in Table I. The data represents averages of at least three determinations. In the last column comparable results by Brown and Subba Rao[1] with diborane in ethers are tabulated.

Coyle, Kaesz, and Stone[6] reported that tetrahydrothiophene, another readily available sulfide, is a weaker base toward borane than dimethyl sulfide. This should make tetrahydrothiophene–borane (II) a better hydroborating agent. We found that tetrahydrothiophene absorbed diborane quite slowly at room temperature and required very vigorous stirring to completely absorb 1 equiv of borane. II also proved to dissolve slowly in benzene, requiring about 15 min to form a homogeneous solution with moderate magnetic stirring. The density was measured to be 0.94 g/ml. Its reaction with several substrates was tested. These are summarized in Table II and again compared with the results of Brown and coworkers.

Discussion

In general the reactivity of dimethyl sulfide–borane parallels that of the ether–boranes. Table I indicates significantly less reaction with acids, nitriles, epoxides, and lactones. With epoxides the ether–boranes have been reported to react very slowly except in the presence of traces of borohydride.[7] Traces of boron trifluoride catalyze the reduction of lactones.[8] These substances are generally present in diborane generated *in situ* by the following reaction in the dimethyl ether of dieth-

(7) H. C. Brown and N. M. Yoon, *ibid.*, **90**, 2686 (1968).
(8) K. M. Biswas and A. H. Jackson, *J. Chem. Soc. C*, 1667 (1970).