oxidation of the glucan,[61] mannan,[51] and galactan[52] give theoretical values of periodate consumption and formic acid liberation. The final specific rotations of the three oxidized polysaccharides are identical, as they should be, since the configurational differences at C-2 and C-4 are destroyed on oxidation. Neither the glucan nor the mannan precipitates with concanavalin A, and therefore both must be linear.[66,67] The glucan has been subjected to enzymic analysis and is reported to be 100% α and 97–98% α-1,6 linked.[68] A high molecular weight sample of the mannan has been degraded by an exo-α-mannanase to the extent of 42–44%. This result indicates that the product is about 99% α-D-mannopyranan.[69]

In spite of the great similarity in structures differing as they do only in the configuration of a single carbon atom per sugar unit, these polysaccharides are greatly different in solubility. The glucan is water soluble,[61] the mannan dispersible in water and soluble in dimethyl sulfoxide,[51] while the galactan is insoluble in almost all solvents effective for hydroxyl-bearing polymers.[52] Only two unusual complexing solvents were found to be effective in dissolving this polymer. Because of its extreme insolubility, the galactan resists enzymic attack.[70]

The α-1,6-linked glucan and mannan structures are found in a number of biologically significant polysaccharides produced by microorganisms, lichen, fungi and higher plants.[71] They include the multibranched bacterial dextran used clinically for osmotic pressure control, blood volume and viscosity control in surgery, and extracorporeal circulation. A similar dextran is present in dental plaque. Related glucans and mannans induce various allergic reactions and activate the interferon system (a natural defense against virus attack) and are reported to be active against neoplastic growths including sarcomas. The synthetic glucan and mannan have been tested in a few biological systems.[71]

(65) J. W. P. Lin and C. Schuerch, *J. Polym. Sci., Part A-1,* **10,** 2045 (1972).
(66) I. J. Goldstein, R. D. Poretz, L. L. So, and Y. Yang, *Arch. Biochem. Biophys.,* **127,** 787 (1968).
(67) R. Robinson and I. J. Goldstein, *Carbohyd. Res.,* **13,** 425 (1970).
(68) E. T. Reese and F. W. Parrish, *Biopolymers,* **4,** 1043 (1966).
(69) J. S. Tkacz, J. O. Lampen, and C. Schuerch, *Carbohyd. Res.,* **21,** 465 (1972).
(70) J. E. Courtois, personal communication.

Summary

It is unfortunate that ring-opening reactions are not generally applicable to the formation of polysaccharides with other linkages. Ethers of two 1,4-anhydroglycopyranoses apparently have too great ring strain and polymerize to give products with a mixture of anomeric linkages and both pyranose and furanose rings.[72] 1,6-Anhydro-2,3,5-tri-*O*-benzyl-α-D-galactofuranose appears to have little conformational or steric strain and polymerizes sluggishly to very low molecular weight products,[73] so high molecular weight 1,6-linked glycofuranoses are probably not available from this reaction. The only accessible 1,2-anhydro sugar, "Brigl's anhydride," contains ester functions that complicate its polymerization enormously.[74] It will, therefore, be necessary to look to other reactions for the synthesis of many other polysaccharides.

At its present state of development, the chemical synthesis of polysaccharides allows us to make simple correlations between molecular structure and physical properties and provides us with a few well-defined substrates for biological testing and biochemical investigation. Perhaps their greatest utility is in encouraging us to believe that the synthesis of many more of these important natural polymers is not beyond the reach of organic chemistry.

Studies on the chemical synthesis of polysaccharides have been supported by the Division of General Medical Sciences of the National Institutes of Health through Grant GM 06168.

(71) C. Schuerch, *Advan. Polym. Sci.,* **10,** 174 (1972).
(72) J. Kops and C. Schuerch, *J. Polym. Sci., Part C,* **11,** 119 (1965).
(73) J. W. P. Lin and C. Schuerch, *Macromolecules,* **5,** 656 (1972).
(74) J. Zachoval and C. Schuerch, *J. Polym. Sci., Part C,* **28,** 187 (1969).

New Amino-Protecting Groups in Organic Synthesis

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Received November 20, 1972

The synthesis of molecules of ever-increasing sensitivity or complexity demands the availability of a variety of protective groups to ensure the survival of common reactive functional groups such as the hydroxyl and amino functions. Early workers made considerable use of simple acyl functions with removal at an appropriate stage ("deblocking") by hydrolytic techniques. In many situations of current interest such deblocking conditions are far too drastic; therefore much recent effort has been devoted to the development of new protective groups capable of removal under exceptionally mild and/or highly specific conditions.[1] Deblocking techniques cover a wide spectrum of conditions, depending on the remainder

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In addition to devising new amino-protecting groups, his research interests encompass the generation and study of unusual transitory species, potentially aromatic and antiaromatic systems, especially small-ring heterocycles, and the development of new synthetic methods and reagents.

of the molecule under consideration and the specific use to which the protective group is to be put.

Our work in the area of amino-protecting groups has concentrated on nonhydrolytic deblocking under mildly acidic, mildly basic, and solvolytic conditions. Other investigators have employed photochemical,[2] electrolytic,[3] reductive,[4] and other[5] techniques. A considerable portion of the work in this field has been related to the synthesis of complex polypeptides where the demand for a variety of protective groups is particularly high. Because of the special nature of this field, the less specialized synthetic organic chemist is often unaware of the introduction of new and useful protective functions and their possible applicability in other situations. It is the purpose of this Account to delineate some of our contributions to this area, to point out the utility of certain of these methods in organic synthesis, especially of sensitive nitrogen compounds, and, to some degree, to point the way to possible future developments. Regrettably, due to space limitations, the equally important work of other investigators cannot receive more than passing notice.

Acid-Labile Protective Groups

Aside from common acyl functions the classic amino-protecting group, first introduced into peptide chemistry by Bergmann and Zervas,[6] is the benzyloxycarbonyl ("carbobenzoxy") group. Work on the related carbo-*tert*-butoxy (BOC, often "t-box" in conversation) group was initiated during an attempt to use the former in a proposed synthesis of monosubstituted diimidium salts by hydrogen bromide cleavage of a substituted benzyl azoformate[7] (**1**). However, the cleavage agent, hydrogen bromide, first effected reduction of the azo linkage (eq 1), a

$$\underset{\mathbf{1}}{RN{=}NCOOCH_2C_6H_5} \xrightarrow{HBr} RNHNHCOOCH_2C_6H_5 \quad (1)$$

fact which triggered an attempt to develop a group capable of cleavage by a much milder, nonreducing acid, if possible at low temperatures and preferably one which would yield only gaseous by-products.[8]

To this end the carbo-*tert*-butoxy group was examined and it was found that it could, indeed, be cleaved by milder acids which in some cases were nonreducing (CF_3CO_2H, HF)[9]. Even though this group did not serve to solve the original problem for which it was devised,[10] the ease of cleavage and the demonstration that after reaction only the desired amine salt was present in the solution (eq 2) have

$$RNHCOOCMe_3 \xrightarrow{H^+} RNH_3^+ + CO_2 + Me_2C{=}CH_2 \quad (2)$$

led to a more complete general study of this protective group. The BOC function may now be considered one of the "workhorses" of the field, especially in peptide synthesis, along with the carbobenzoxy group.[11]

While deblocking conditions are nearly ideal,[12] considerable difficulty was encountered in devising suitable techniques for introduction of the BOC group onto an amino function. The relative instability of *tert*-butyl chloroformate[13] (**2**) precludes its use except at low temperatures or under special conditions.[14] Over the years many carbo-*tert*-butoxylating agents have been developed. Foremost among these is *tert*-butyl azidoformate[15] (**3**), but *tert*-butyl fluoroformate[16] and a variety of mixed *tert*-butyl carbonates have been recommended.[17]

(1) For extensive (although no longer current) reviews on amino-protecting groups see: (a) Y. Wolman in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 11; (b) R. A. Boissonnas, *Advan. Org. Chem.*, **3**, 159 (1963); (c) J. F. W. McOmie, *ibid.*, **3**, 191 (1963).

(2) (a) J. A. Barltrop and P. Schofield, *J. Chem. Soc. C*, 4758 (1965); (b) J. W. Chamberlin, *J. Org. Chem.*, **31**, 1658 (1966); (c) A. Abad, D. Mellier, J. P. Pete, and C. Portella, *Tetrahedron Lett.*, 4555, 4559 (1971); (d) A. Patchornik, B. Amit, and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 6333 (1970).

(3) (a) L. Horner and H. Neumann, *Ber.*, **98**, 3462 (1965); (b) E. Kasafirek, *Tetrahedron Lett.*, 2021 (1972); (c) M. F. Semmelhack and G. E. Heinsohn, *J. Amer. Chem. Soc.*, **94**, 5139 (1972).

(4) (a) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967); (b) D. Stevenson, and G. T. Young, *J. Chem. Soc. C*, 2389 (1969); (c) F. Weygand and E. Frauendorfer, *Ber.*, **103**, 2437 (1970); (d) J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 345 (1970); (e) G. L. Southard, B. R. Zaborowsky, and J. M. Pettee, *J. Amer. Chem. Soc.*, **93**, 3302 (1971).

(5) (a) M. Masaki, J. Kitahara, H. Kurita, and M. Ohta, *J. Amer. Chem. Soc.*, **90**, 4508 (1968); (b) A. Fontana and E. Scoffone, *Gazz. Chim. Ital.*, **98**, 1261 (1968); (c) C. Toniolo and A. Fontana, *ibid.*, **99**, 1017 (1969); (d) F. D'Angeli, F. Filira, and E. Scoffone, *Tetrahedron Lett.*, 605 (1965); (e) W. L. Haas, E. V. Krumkalns, and K. Gerzon, *J. Amer. Chem. Soc.*, **88**, 1988 (1966); (f) M. Rasmussen and N. J. Leonard, *ibid.*, **89**, 5439 (1967).

(6) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(7) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 96 (1957).

(8) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957); (b) L. A. Carpino, Abstracts, 129th National Meeting of the American Chemical Society, Dallas, Texas, April 1956, p 59N.

(9) At about the same time, F. C. McKay and N. F. Albertson [*J. Amer. Chem. Soc.*, **79**, 4686 (1957)] and G. W. Anderson and A. C. McGregor [*ibid.*, **79**, 6180 (1957)] initiated a study of the applicability of the BOC group in peptide synthesis.

(10) Subsequently Kosower developed useful routes to a variety of monosubstituted diimides. See E. M. Kosower, *Accounts Chem. Res.*, **4**, 193 (1971).

(11) See J. H. Jones in "Specialist Periodical Reports, Amino-acids, Peptides and Proteins," Vol. 2, G. T. Young, Ed., The Chemical Society (London), London, 1970, p 145.

(12) In addition to the commonly used trifluoroacetic acid and hydrogen chloride–solvent combinations a number of other deblocking reagents have been recommended for special purposes. These include (a) formic acid: B. Halpern and D. E. Nitecki, *Tetrahedron Lett.*, 3031 (1967); (b) mercaptoethanesulfonic acid: A. Loffet and C. Dremier, *Experientia*, **27**, 1003 (1971); (c) *p*-toluenesulfonic acid: R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffmann, *J. Org. Chem.*, **36**, 1259 (1971); G. L. Southard, G. S. Brooke, and J. M. Pettee, *Tetrahedron*, **27**, 1359 (1971); (d) boron trifluoride etherate: R. G. Hiskey, L. M. Beacham, III, V. G. Matl, J. N. Smith, E. B. Williams, Jr., A. M. Thomas, and E. T. Wolters, *J. Org. Chem.*, **36**, 488 (1971); (e) ion-exchange resins: G. T. Gray and A. M. Khoujah, *Tetrahedron Lett.*, 2647 (1969). For a study of the selectivity of BOC cleavage in the presence of related protective groups see E. Schnabel, H. Klostermeyer, and H. Berndt, *Justus Liebigs Ann. Chem.*, **749**, 90 (1971).

(13) A. R. Choppin and J. W. Rogers, *J. Amer. Chem. Soc.*, **70**, 2967 (1948).

(14) (a) R. B. Woodward, K. Heusler, H. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966); (b) R. B. Woodward, *Angew. Chem.*, **78**, 557 (1966); (c) S. Sakakibara, I. Honda, K. Takeda, M. Miyoshi, T. Ohnishi, and K. Okumura, *Bull. Chem. Soc. Jap.*, **42**, 809 (1969).

(15) L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza, and P. H. Terry, *Org. Syn.*, **44**, 15 (1964).

(16) E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke, and I. Ugi, *Justus Liebigs Ann. Chem.*, **716**, 175 (1968).

(17) For an extensive listing see L. A. Carpino, K. N. Parameswaran, R. K. Kirkley, J. W. Spiewak, and E. Schmitz, *J. Org. Chem.*, **35**, 3291 (1970), footnote 3. Other more recently described reagents or techniques for BOC introduction include: (a) *tert*-butyl dicarbonate: D. S. Tarbell, Y. Yamamoto and B. M. Pope, *Proc. Nat. Acad. Sci. U. S.*, **69**, 730 (1972); C. S. Dean, D. S. Tarbell, and A. W. Friederang, *J. Org. Chem.*, **35**, 3393 (1970); (b) various water-soluble quaternary salts: E. Guibe-Jampel and M. Wakselman, *Chem. Commun.*, 267 (1971); E. Guibe-Jampel, G. Bram and M. Vilkas, *Tetrahedron Lett.*, 4037 (1969); (c) use of carbamoyl chlorides: K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972); (d) *in situ* methods involving Curtius rearrangement: K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3060 (1971); *J. Org. Chem.*, **34**, 395 (1969); N. Koga and J.-P. Anselme, *ibid.*, **33**, 3963 (1968); J.-P. Anselme and N. Koga, *Org. Prep. Proc.*, **2**, 125 (1970); H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, **87**, 1141 (1965); (e) catalyzed processes involving phenyl *tert*-butyl carbonate: G.

$ClCOOCMe_3$ $N_3COOCMe_3$

2 **3**

The simplest route to *tert*-butyl azidoformate is outlined in eq 3. Other facile routes to the key inter-

$$MeSCOCl \xrightarrow[C_5H_5N]{Me_3COH} MeSCOOCMe_3 \xrightarrow{NH_2NH_2}$$

$$NH_2NHCOOCMe_3 \xrightarrow{HNO_2} N_3COOCMe_3 \quad (3)$$

4

mediate, *tert*-butyl carbazate (**4**), involve reaction of the ethyl,[18] phenyl,[19] or *p*-nitrophenyl[20] carbonates **5** with hydrazine. Recently tritium-labeled *tert*-butyl azidoformate has been described.[21]

$ROCOOCMe_3$

5a, R = Ar
b, R = Et

tert-Butyl azidoformate has proved to be a convenient source of other key synthetic intermediates bearing the BOC group such as the hydrazodiformate[22] **6**, the azodiformate[23,24] **7**, and the *N*-hydroxycarbamate[25] **8**. The synthetic utility of some of these key intermediates in the synthesis of special nitrogen compounds will be discussed below. Besides the specific uses mentioned here, the BOC group has often been used in cases involving the interconversions of ordinary amino groups.[26]

$Me_3COCON{=}NCOOCMe_3$

7

NBS, C_5H_5N

$Me_3COCONHNHCOOCMe_3$

6

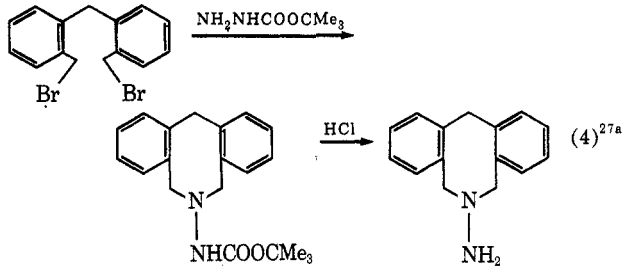
$N_3COOCMe_3$ (C_5H_5N, $NH_2NHCOOCMe_3$)

NH_2OH, NaOH

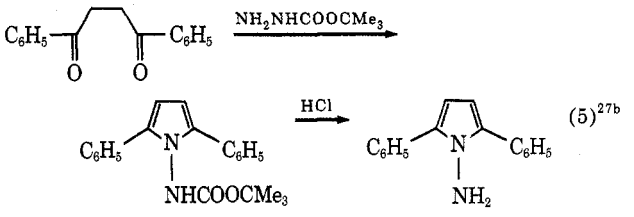
$HONHCOOCMe_3$

8

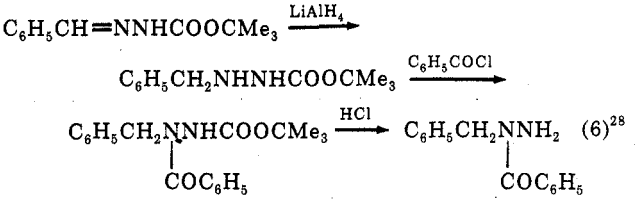
Preparation of 1,1-Disubstituted Hydrazines. Alkylation of *tert*-butyl carbazate occurs readily by means of alkyl halides. Subsequent cleavage yields the desired hydrazine with avoidance of 1,2 disubstitution. The technique has been especially useful in the synthesis of cyclic benzylic hydrazines. Examples are outlined in eq 4–6.



(4)[27a]

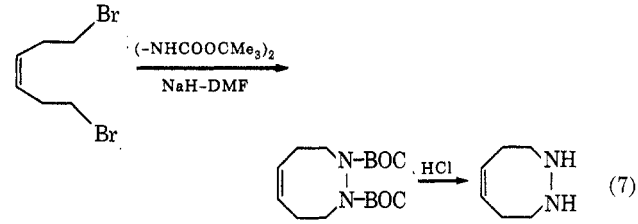


(5)[27b]

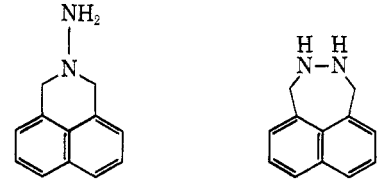


(6)[28]

Preparation of 1,2-Disubstituted Hydrazines. Avoidance of 1,1 disubstitution of hydrazine is readily achieved by use of *tert*-butyl hydrazodiformate, a technique which is particularly well adapted to the synthesis of medium-ring cyclic systems.[29] An example is shown in eq 7.[30,31] In the case of 1,8-(bromomethyl)naphthalene, *tert*-butyl carbazate leads to the



(7)



9 **10**

Bram, *Tetrahedron Lett.*, 469 (1973); U. Ragnarsson, S. M. Karlsson, and B. E. Sandberg, *Acta Chem. Scand.*, **26**, 2550 (1972). See also A. Ali, F. Fahrenholz, and B. Weinstein, *Angew. Chem.*, **84**, 259 (1972).

(18) M. Muraki and T. Mizoguchi, *Chem. Pharm. Bull.*, **18**, 217 (1970).

(19) L. A. Carpino, B. A. Carpino, C. A. Giza, R. W. Murray, A. A. Santilli, and P. H. Terry, *Org. Syn.*, **44**, 22 (1964).

(20) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belg.*, **68**, 409 (1959); T. Inoue, M. Kanayama, and H. Otsuka, *Nippon Kagaku Zasshi*, **85**, 599 (1964).

(21) J. F. Kennedy, C. J. Gray, S. A. Barker, and S. Ramonvongse, *J. Labelled Compounds*, **8**, 99 (1972).

(22) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 4427 (1957).

(23) L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, **26**, 4336 (1961).

(24) Recently the cis isomer of the azodiformate, which should be more reactive than the trans form in cycloaddition reactions, has been obtained. See E. K. von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitch, *J. Org. Chem.*, **35**, 1155 (1970).

(25) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959).

(26) For examples see ref 17, footnote 2, as well as the following: (a) phenolic benzylamines: C. Birr, C. Just, and T. Wieland, *Justus Liebigs Ann. Chem.*, **736**, 88 (1970); (b) octahydrophenanthrylamines: C. Rufer, R. Albrecht, and E. Schröder, *ibid.*, **728**, 193 (1969); (c) aminopyrroles: B. Frydman, S. Reil, A. Valasinas, R. B. Frydman, and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 2738 (1971); (d) cephalosporins and penicillins: D. M. Brunwin and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 589 (1972); D. M. Brunwin, G. Lowe, and J. Parker, *ibid.*, 865 (1971); *J. Chem. Soc. C*, 3756 (1971); R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, **55**, 423 (1972); (e) nucleosides: F. W. Lichtenhaler. G. Trummlitz, and P. Emig, *Tetrahedron Lett.*, 2061 (1970); B. P. Gottikh, A. A. Krayevsky, N. B. Tarussova, P. P. Purygin, and T. L. Tsilevich, *Tetrahedron*, **26**, 4419 (1970).

(27) (a) L. A. Carpino, J. Ferrari, S. Göwecke, and S. Herliczek, *J. Org. Chem.*, **34**, 2009 (1969). For related acylations, see J. G. Krause, S. Kwon, and B. George, *ibid.*, **37**, 2040 (1972). (b) L. A. Carpino, *ibid.*, **30**, 736 (1965).

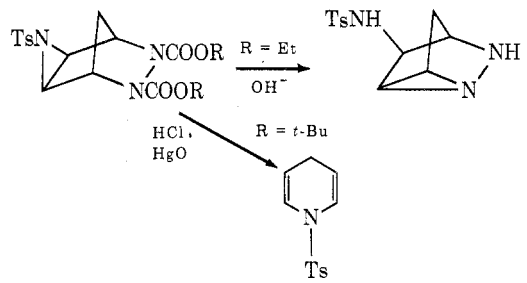
(28) L. A. Carpino, A. A. Santilli, and R. W. Murray, *J. Amer. Chem. Soc.*, **82**, 2728 (1960).

(29) L. A. Carpino, *J. Amer. Chem. Soc.*, **85**, 2144 (1963).

(30) L. A. Carpino and J. P. Masaracchia, *J. Org. Chem.*, **37**, 1851 (1972).

(31) For a similar case in which the BOC derivative was obtained but deblocking could not be effected, see H. Lingman and K.-H. Linke, *Ber.*, **104**, 3723 (1971).

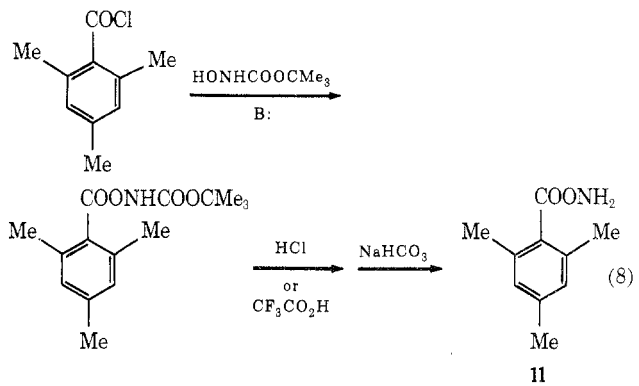
Scheme I



formation of **9**, whereas the hydrazodiformate gives **10**.[29] It should be noted that in all of these examples deblocking of the appropriate BOC derivative occurs under conditions little different from those required to convert an amine to its hydrochloride. For example, passing gaseous hydrogen chloride through a solution of the BOC derivative at room temperature usually leads to immediate precipitation of the amine or hydrazine hydrochloride.[27,29,30,32] On the other hand, in the case of compounds having two or more BOC groups it is sometimes possible to cleave one selectively.[33]

Particularly noteworthy are the synthetic routes reported by Jensen of thio- and selenosemicarbazides and related compounds of substitution patterns not easily obtained in other ways.[34a-c] In a recently described route to 1,4-dihydropyridines critical advantage was taken of the nature of cleavage of the BOC group relative to that of the carbethoxy group (Scheme I).[34d]

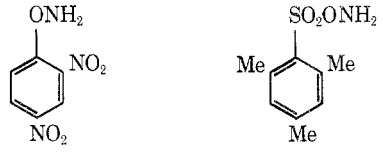
Preparation of O-Substituted Hydroxylamines. Prior to the development of the BOC group simple O-substituted hydroxylamines, especially the *O*-acyl derivatives, were not available by any general technique. Application of the BOC function now allows the synthesis of a variety of such compounds, some of which have proved to be valuable aminating agents. An example is *O*-mesitoylhydroxylamine (**11**; "mesitoxyamine") prepared as in eq 8.[35-37] The aryl-



(8)

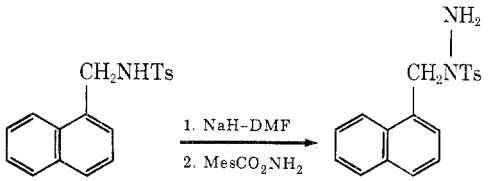
11

oxy[39,40] and arylsulfonoxy[35] analogs **12** and **13**, re-



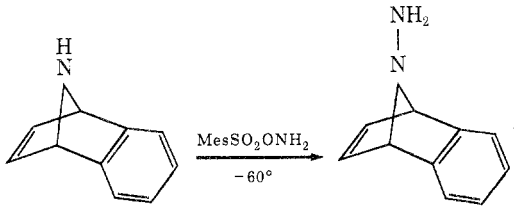
12 **13**

spectively, are available by similar procedures. Compounds which have been aminated[39,41] by means of **11–13** include secondary amines, imides, pyrroles, amides, etc. (*e.g.*, eq 9, in which $MesCO_2NH_2$ stands



(9)

for mesitoxyamine). The *O*-sulfonyl derivatives such as **13** are unusually reactive, even at low temperatures (−60°). An example is presented in eq 10.[42]

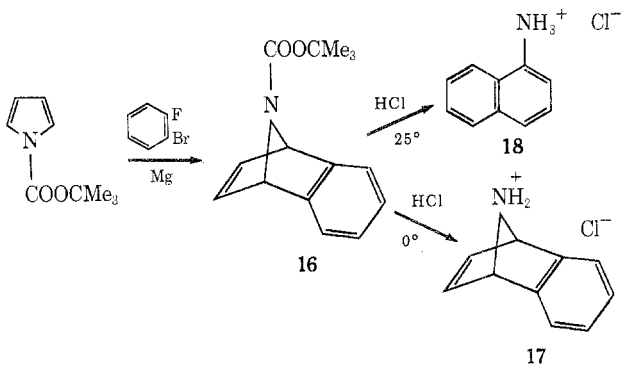


(10)

14 **15**

Mesitoxyamine does not react with **14** under the same conditions. Hydrazine **15**, on the other hand, is unstable even at 0°. The precursor **14** is obtained *via* the Diels–Alder addition of benzyne to the carbo-*tert*-butoxy derivative of pyrrole (Scheme II).[43]

Scheme II



16 **17**

(32) The rapidity of cleavage suggested that similar optically active protective groups could be of considerable utility as resolving agents for racemic primary and secondary amines. For examples, see L. A. Carpino, *Chem. Commun.*, 858 (1966).

(33) (a) R. Geiger, *Justus Liebigs Ann. Chem.*, **750**, 165 (1971); (b) H. Arold and S. Reissmann, *Z. Chem.*, **7**, 182 (1967).

(34) (a) K. A. Jensen, G. Felbert, C. Th. Pedersen, and U. Svanholm, *Acta Chem. Scand.*, **20**, 278 (1966); (b) K. A. Jensen, U. Anthoni, B. Kägi, C. Larsen, and C. Th. Pedersen, *ibid.*, **22**, 1 (1968); (c) K. A. Jensen, U. Anthoni, and A. Holm, *ibid.*, **23**, 1916 (1969); (d) A. I. Meyers, D. M. Stout, and T. Takaya, *J. Chem. Soc., Chem. Commun.*, 1260 (1972).

(35) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960); (b) W. N. Marmer and G. Maerker, *J. Org. Chem.*, **37**, 3520 (1972).

(36) L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964).

(37) The carbobenzoxy group was first examined in this connection but could not be used since the deblocking reagent (HBr) caused reduction of the N–O linkage. Similarly hydrogen chloride cannot be used in the case of **13**, which is a more potent oxidant than **11**. However, both hydrogen fluoride[35] and trifluoroacetic acid[38] are successful.

(38) J. G. Krause, *Synthesis*, 140 (1972).

(39) T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron*, **28**, 3833 (1972).

(40) T. Sheradsky, *J. Heterocycl. Chem.*, **4**, 413 (1967).

(41) L. A. Carpino, *J. Org. Chem.*, **30**, 321 (1965).

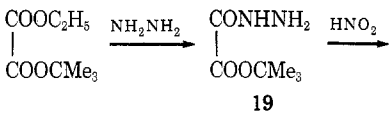
(42) Unpublished results with J. G. Krause. The enhanced reactivity of mesitosulfonoxyamine (**13**) has also been noted recently by Tamura and coworkers who have shown that weakly basic sulfides, sulfoxides, and phosphines are easily aminated with this reagent [Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Lett.*, 4133 (1972); Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *ibid.*, 4137 (1972)].

(43) L. A. Carpino and D. E. Barr, *J. Org. Chem.*, **31**, 764 (1966).

Cleavage of **16** again illustrates the mild conditions which can be chosen for the deblocking process. Cleavage occurs readily at 0° without incident to give **17**, whereas at room temperature only α-naphthylamine hydrochloride is obtained *via* rupture of the strained C–N bond of the azabicyclic amine.

Modifications of these techniques have been used in the synthesis of a wide range of N-substituted *O*-acylhydroxylamines and *N,O*-bis(carbamoyl)hydroxylamines of definite substitution pattern.[44,45]

Bis Protection by the Carbo-*tert*-butoxy Group. It is sometimes useful to be able to protect a primary amino group with two carbo-*tert*-butoxy groups in order to avoid complications arising from the presence of the remaining amide-type hydrogen of the mono derivative. Previously the phthalimido function has served this purpose in specific instances.[46] As a possible contribution to solution of this problem, a route was developed to *tert*-butyl iminodicarboxylate (**20**; eq 11) by Curtius rearrangement[36] of the acyl azide derived from *tert*-butyl oxalylhydrazide (**19**).



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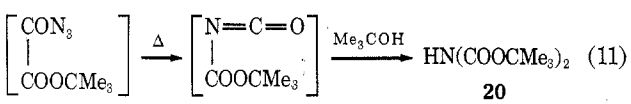
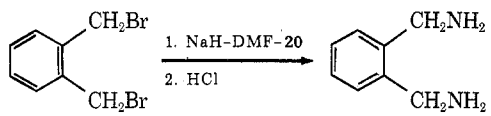


20 (11)

One example of the synthetic use of **20** is the Gabriel-like preparation of **21** (eq 12).[36,47] This tech-



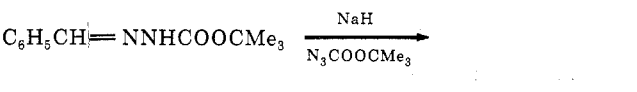
21 (12)

nique has only rarely been employed, probably because of the present lack of an efficient high-yield synthetic route to the key intermediate **20.** Amination of **20** by means of mesitoxyamine yields hydrazine **22,** a reagent which can be used in the synthesis

$$H_2NN(COOCMe_3)_2$$

22

of cyclic 1,1-disubstituted hydrazines in cases where the mode of coupling must be assured. An alternative preparation of bis-protected derivatives involves acylation of the monosubstituted compound as in the case of **23** (eq 13).[36] A similar technique, in con-



23 (13)

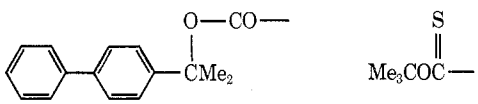
junction with deblocking, can be used in special cases to exchange the BOC group by another acyl or sulfonyl group.[27b] A compound which might be suitable as a bis-protected hydroxylamine is **24** which may be formally considered as the oxime of di-*tert*-butyl carbonate. Although several attempts[48] to prepare this compound were unsuccessful, a derivative (**25**) has recently been reported.[49] As expected,

24 **25**

treatment of **25** with trifluoroacetic acid gives *O*-*p*-toluenesulfonylhydroxylamine.

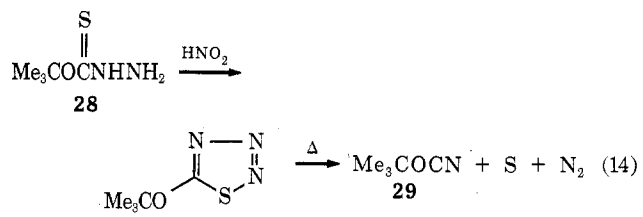
Super-Sensitive Acid-Labile Protective Groups

Protective groups deblocked under acidic conditions even milder than those required for the BOC group are clearly of considerable potential interest. Among those which have been in use for some time may be cited the trityl[1] and *o*-nitrophenylsulfenyl[1,50] groups, each of which, however, suffers certain disadvantages. A new BOC-related group, **26,** has been described by Sieber and Iselin[51] and has recently acquired a place in the field of peptide synthesis.



26 **27**

A protective group of this type which leads to volatile by-products is the thionocarbo-*tert*-butoxy group[23] (**27**). Substitution of sulfur for the carbonyl oxygen provides a mechanism for an enormously faster acidic cleavage. However, for at least two reasons this group has not been used in any practical manner. First, the presence of an unoxidized sulfur function can be disadvantageous; second, there is as yet no generally useful thionocarbo-*tert*-butoxylating agent. Treatment of *tert*-butyl thionocarbazate (**28**) with nitrous acid yields not the azidoformate but instead the rare and unstable *tert*-butyl cyanate[52] (**29**; eq 14). Indeed, this is currently the only synthetic



28 **29** (14)

route to **29.** It is worthy of note that the thiono derivatives of primary and secondary carbalkoxy groups (*e.g.*, EtOCS–, Me_2CHOCS–) are cleaved by acids about as easily as the BOC group.[23]

Investigation of a second group which does not exhibit the disadvantages of such a sulfur-containing function has been initiated. Since the lowest molecular weight, inert hydrocarbon fragment capable of

(44) H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **34,** 1430 (1969).
(45) (a) G. Zinner and M. Hitze, *Arch. Pharm.*, **302,** 788, 916 (1969); **303,** 139 (1970); (b) G. Zinner, G. Nebel, and M. Hitze, *ibid.*, **303,** 317 (1970).
(46) The recently introduced 4,5-diphenyl-4-oxazolin-2-one derivatives are also in this category. See J. C. Sheehan and F. S. Guziec, Jr., *J. Amer. Chem. Soc.*, **94,** 6561 (1972).
(47) A. M. Felix and R. I. Fryer, *J. Heterocycl. Chem.*, **5,** 291 (1968).
(48) Unpublished results.
(49) J. Perchais and J.-P. Fluery, *Tetrahedron*, **28,** 2267 (1972).
(50) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85,** 3660 (1963); L. Zervas and C. Hamalidis, *ibid.*, **87,** 99 (1965).
(51) (a) P. Sieber and B. Iselin, *Helv. Chim. Acta*, **51,** 614, 622, 1525 (1968); (b) E. Schnabel, G. Schmidt, and E. Klauke, *Justus Liebigs Ann. Chem.*, **743,** 69 (1971).
(52) K. A. Jensen, A. Holm, and J. Wolff-Jensen, *Acta Chem. Scand.*, **23,** 1567 (1969).

significantly affecting the stability of the cation generally believed to be involved in the acidic cleavage of a carbalkoxy group is the cyclopropyl substituent,[53] the dicyclopropylmethyloxycarbonyl group has been examined. Remarkably, this group, as in the

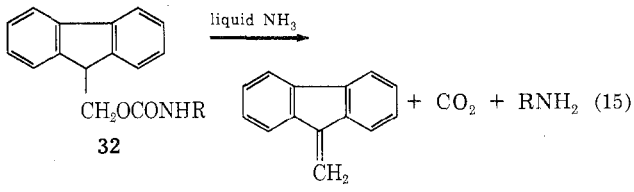
$(c\text{-}C_3H_5)_2CHOCONHC_6H_5$ (30) $(c\text{-}C_3H_5)_2CHNHC_6H_5$ (31)

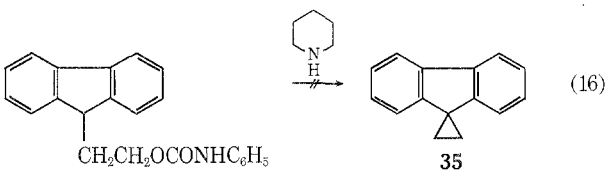
urethane **30**, is cleaved even by the weakly acidic alcohol, hexafluoro-2-propanol, $pK_a = 9.3$.[54] However, in addition to aniline, there is formed *N*-(dicyclopropylmethyl)aniline (**31**), presumably *via* capture of the intermediate cation by the aniline released.[55] A similar N-alkylation during removal of the *p*-diphenylyldimethylcarbinyloxycarbonyl group (**26**) has been noted previously.[56] The use of special solvents as cation scavengers may permit practical utilization of the dicyclopropylcarbinyloxycarbonyl group.

Base-Sensitive Protective Groups

Where strong aqueous or alcoholic alkali may be used in the deblocking of a protected amino function, any simple acyl group may be used. For labile systems, however, it would be valuable to have a set of alkali-sensitive protective groups which could be deblocked by a graded set of *nonhydrolytic* basic reagents, as is now the case for the acid-sensitive spectrum of protective functions. Although work in this area is only in its early stages, at least one such group has been developed which promises to be of general applicability. By-products, unfortunately, are not volatile and vary to some extent with the cleavage technique chosen.

Treatment of the 9-fluorenylmethyloxycarbonyl (FMOC) derivative of an amine (*e.g.*, **32**) with liquid ammonia for several hours gives the parent amine in good yield (eq 15).[57,58] Solution of **32** in ethanolamine, piperidine, or morpholine for a few minutes at room temperature also effects cleavage. In liquid ammonia or ethanolamine the by-product obtained is dibenzofulvene, whereas with piperidine or morpholine, the adduct of dibenzofulvene and the secondary amine is obtained. Either dibenzofulvene or its amine adducts may be easily separated from the desired amine, and since dibenzofulvene undergoes polymerization readily, a further simplification in the work-up procedure can be made by allowing this polymerization to proceed to completion. The resulting polymer is insoluble in a variety of solvents which may then be used to extract the amine.[58] Little difficulty is encountered in introducing the FMOC group since the corresponding chloroformate is both stable and reactive. Current effort is involved in structural modifications of **32** which would further increase the lability toward liquid ammonia or related bases. The 9-fluorenylethyl analogs such as **34**[59] proved to be stable toward piperidine, showing that the corresponding cyclopropanation (eq 16) does not occur under mild conditions.





A β-elimination process similar to that employed in the 9-fluorenylmethyl case has been used in a sulfone system (*e.g.*, **36**) by Kader and Stirling,[60a] although the removal conditions reported were less mild than desirable. More recently it has been found that this group responds to the same deblocking conditions used for the FMOC group.[58] Since hydracrylonitrile ($HOCH_2CH_2CN$) is inexpensive and available on a large scale, the most practical system of this type may prove to be the β-cyanoethyloxycarbonyl group. This function is readily cleaved by ethanolamine at room temperature.[48] By-products are water-soluble, thus facilitating their separation from a liberated water-insoluble amine. Furthermore selective cleavage is possible since the β-cyanoethyloxycarbonyl group is not cleaved at room temperature by morpholine under conditions which cause extremely rapid deblocking of the FMOC group. Wünsch[60b] has investigated a tertiary analog of this group. The analogous nitroethyl systems **37** appear to be *too* sensitive toward bases to be of general, practical utility.[57,58,60a] In considering systems somewhere between the fluorene and nitroethyl cases we sought to obtain carbamates such as **38** for further investigation. Although from the point of view of their acidity the methanesulfonyl derivatives appeared to be a better choice, the more readily available benzenesulfonyl analogs were first examined. The pK_a values of appropriate models include methyl phenyl sulfone (~27), fluorene (~23), bis(methanesulfonyl)methane (12.5), bis(phenylsulfonyl)methane (11.2), nitromethane (10.2), and nitroethane (8.5).[61] The additional alkyl group required in converting a sulfone such as methyl phenyl sulfone or bis(phenylsulfonyl)methane to the corresponding substituted ethanol

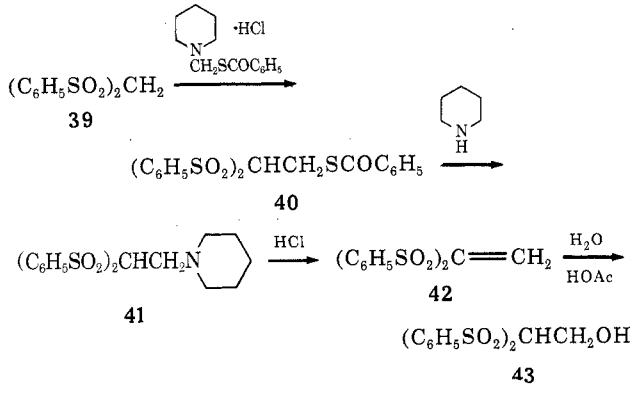
$TsCH_2CH_2OCONHR$ (36) $O_2NCH_2CH_2OCONHR$ (37)

$(RSO_2)_2CHCH_2OCONHC_6H_5$

38a, R = CH_3
b, R = C_6H_5

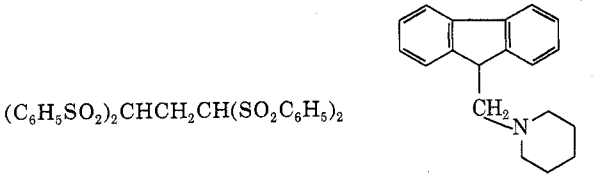
(53) Compare N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 4533 (1965).
(54) W. J. Middleton and R. V. Lindsey, Jr., *ibid.*, **86**, 4948 (1964).
(55) Unpublished work with T. Kowalewski and C. H. Han.
(56) T. Sheradsky, G. Salemnick, and M. Frankel, *Israel J. Chem.*, **9**, 263 (1971).
(57) L. A. Carpino and G. Y. Han, *J. Amer. Chem. Soc.*, **92**, 5748 (1970).
(58) L. A. Carpino and G. Y. Han, *J. Org. Chem.*, **37**, 3404 (1972).
(59) Prepared from the corresponding alcohol. See E. J. Greenhow, E. N. White, and D. McNeil, *J. Chem. Soc.*, 2848 (1951).
(60) (a) A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 258 (1964). For related work see Th. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966). (b) E. Wünsch and R. Spangenberg, *Ber.*, **104**, 2427 (1971).
(61) (a) F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967); (b) E. J. Corey, H. König, and T. H. Lowry, *Tetrahedron Lett.*, 515 (1962); (c) J. Crosby and C. J. M. Stirling, *J. Amer. Chem. Soc.*, **90**, 6869 (1968).

Scheme III



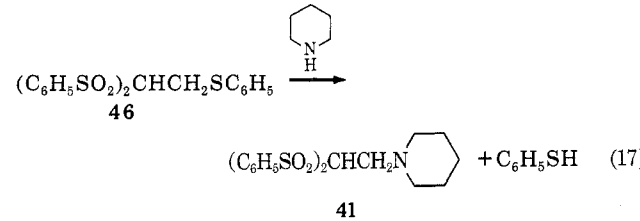
would be expected to increase the pK_a values by about 1.5–2 pK_a units.[61a]

Although it was possible to synthesize alcohol **43**[48] (Scheme III) *via* Smissman's thiomethylation reactior,[62] all attempts to convert the alcohol to simple esters or a urethane such as **38b** by reaction with acid chlorides, anhydrides, or isocyanates gave only the dehydration product **42.** The inductive effects of the two sulfone groups apparently make **43** less reactive than simple alcohols, and under the conditions required for reaction, elimination occurs. If catalysis is attempted by the inclusion of a base such as triethylamine, the only compound isolated is **44,** which appears to be derived by the reverse aldol reaction of **43** followed by addition of the displaced bis(phenylsulfonyl)methyl anion to the concomitantly formed olefin **42.** On the other hand, conversion of thio ester **40** to amine **41** by piperidine (similar[58] cleavage of **32** by piperidine gives **45**) shows that the desired de-



44 **45**

blocking process is feasible. In fact, even simple thioethers such as **46** may be deblocked by piperidine (eq 17), and since **46** can be obtained by the addition of benzenethiol to olefin **42** this represents a possible new protective group for thiols, a topic, however, which is beyond the scope of this Account.

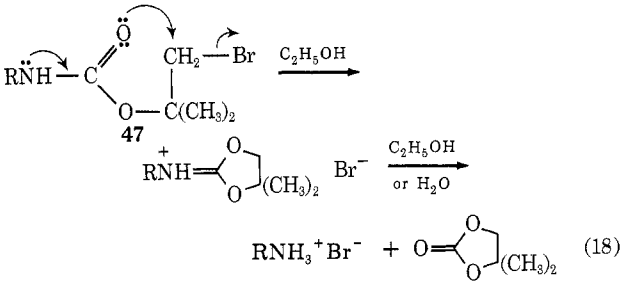


(17)

41

Solvent-Sensitive Protective Groups

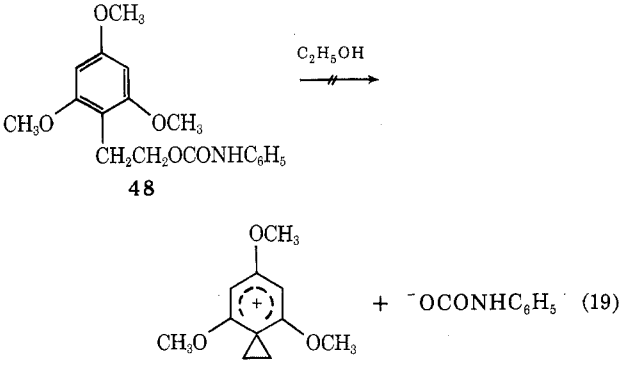
From a long-term point of view, perhaps the most desirable type of protective function is one which would be stable in a variety of solvents but subject to rapid deblocking upon solution in an appropriate specific neutral solvent. Conceivably, such systems might be developed on the basis of simple solvolytic reactions, neighboring group effects, concerted fragmentations, etc. One such group was discovered accidentally, and this unique example has stimulated a search for other more appropriate and more generally useful functions of this type. While investigating several indirect methods for the introduction of the BOC group, a number of α-bromo-BOC derivatives such as **47** were synthesized. Curiously these were stable in solvents such as benzene or methylene dichloride but on solution in ethanol, even at room temperature, although more rapidly on heating, underwent conversion to the amine hydrobromide (eq 18).[17] This result can be rationalized on the basis of



(18)

the neighboring group process pictured. Since the simple β-iodo- or β-bromoethyloxycarbonyl group is stable[63] under the same conditions, the internal displacement reaction must be greatly accelerated by the *gem*-dimethyl substituent. This case is unique in that the protective group carries within itself the agent of its eventual removal. The practical utilization of this self-cleavage process has recently been established.[64]

Ordinary solvolytic reactions are also feasible candidates for the development of new protective groups of this type, and our present knowledge of the detailed mechanisms of such reactions can serve as a guide to these studies except that for the present purposes a leaving group, the carbamoyloxy group, which is poorer than those normally used in solvolytic studies, will be involved. A possible candidate is depicted in eq 19.[65] However, the 2,4,6-trimethoxy-



(19)

48

phenylethyl derivative **48** is stable in hot ethanol or even acetic acid over a period of 24 hr, showing that the anchimeric assistance which might theoretically

(62) E. E. Smissman, J. R. J. Sorenson, W. A. Albrecht, and M. W. Creese, *J. Org. Chem.*, **35,** 1357 (1970).

(63) (a) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia,* **13,** 183 (1957); (b) J. Grimshaw, *J. Chem. Soc.*, 7136 (1965).

(64) T. Ohnishi, H. Sugano, and M. Miyoshi, *Bull. Chem. Soc. Jap.*, **45,** 2603 (1972).

(65) Compare S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78,** 4801 (1956).

be provided by the methoxy substituents is not sufficient to overcome the lethargic nature of the leaving group.

I am greatly indebted to my excellent coworkers whose names are cited in the references for their important contributions to this work. In addition our BOC studies were markedly facilitated by the unique ability of our undergraduate "summer preps" students, Ilona Heine Thomasson, Joseph Mayo, and Fred Tibbetts, in being able to supply us with massive quantities of tert-butyl carbazate, tert-butyl azidoformate, and tert-butyl N-hydroxycarbamate. I also wish to credit a few fascinating comments by Professor R. C. Fuson during his "advanced organic chemistry" course at the University of Illinois in 1950 regarding the difficulty of preparing tert-butyl esters by the usual techniques as the spark which first led us to the idea of using the BOC group as a substitute for the carbobenzoxy function. Financial support for our work has been generously provided by the Research Corporation, the National Science Foundation, the U. S. Army Research Office, the Petroleum Research Fund, administered by the American Chemical Society, the Air Force Office of Scientific Research, and the National Institutes of Health.

From Kinetics to the Synthesis of Chiral Tetraorganotin Compounds

Marcel Gielen

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Received November 13, 1972

Organometallic chemistry has been for many years a puzzling area with its own peculiar rules. For example, the reactivity of Grignard reagents, which are quite sensitive to water and to air, very strongly depends on the presence of traces of impurities. Quantitative information is therefore hard to get in this field. Only a few elements, M, give R_nM compounds (R = alkyl, aryl) which are stable toward air and water; tin, mercury, and lead belong to this category.

The cleavage and the formation of carbon–metal bonds are the most important reaction types in organometallic chemistry.[1] We therefore started our studies in physical organometallic chemistry by investigating kinetic aspects of the cleavage reactions of carbon–tin bonds. Precise information on their mechanisms would hopefully prove to be sufficiently general to apply to analogous reactions involving less stable organometallic species.

If one defines an organometallic derivative as a molecule which contains at least one carbon–metal bond, and if a metal is defined as an element which is less electronegative than carbon, then the expected polarity of the carbon–metal bond $C^{\delta-}$–$M^{\delta+}$ suggests that organometallic compounds might be good substrates for studying both electrophilic substitution at carbon[3] and nucleophilic substitution at the metal atom.[4]

Cleavage of the sp^3 Carbon to Tin Bond

Symmetric Tetraalkyltins, R_4Sn. Symmetric tetraorganotin compounds, R_4Sn, react with various electrophiles (symbolized E–N) with the following stoichiometry

$$R_4Sn + E\text{–}N = R\text{–}E + N\text{–}SnR_3$$

The kinetics of cleavage reactions induced by certain electrophiles have been thoroughly investigated.[5] The most significant data[6] are summarized in Table I.[7-13]

The first striking feature of these data is that the reactivity sequence is reversed as the nucleophilicity of the solvent decreases from methanol to carbon tetrachloride[14] and as the nucleophilicity of E–N in-

Professor Gielen's research is in the area of physical organometallic chemistry, particularly in reaction mechanisms, including kinetics and stereochemistry, and topological graphic and matrix representations of reactions. In 1963 he received his Ph.D from the French Free University in Brussels for work on electrophilic aliphatic substitution carried out under the direction of Professor J. Nasielski. Since 1969 he has been Full Professor at the Flemish Free University of Brussels.

(1) M. Gielen and J. Nasielski in "Organotin Compounds," A. K. Sawyer, Ed., Vol. 3, Marcel Dekker Inc., New York, N. Y., 1972, pp 625–825; M. Gielen, *Ind. Chim. Belg.*, **38**, 20, 138 (1973).
(2) R. Gupta and B. Majee, *J. Organometal. Chem.*, **40**, 107 (1972).
(3) M. Gielen, C. Dehouck, and B. De Poorter, *Chem. Weekbl.*, **68** (41), 17 (1972).
(4) M. Gielen, C. Dehouck, H. Mokhtar-Jamai, and J. Topart, *Rev. Si, Ge, Sn, Pb Compounds*, **1**, 9 (1972); M. Gielen, C. Dehouck, and B. De Poorter, *Chem. Weekbl.*, **68** (42), 15 (1972).
(5) M. Gielen and J. Nasielski, *Bull. Soc. Chim. Belg.*, **71**, 32 (1962); *Recl. Trav. Chim. Pays-Bas*, **82**, 228 (1963).
(6) M. Gielen, S. Boué, M. De Clercq, and B. De Poorter, *Rev. Si, Ge, Sn, Pb Compounds*, in press.
(7) M. H. Abraham and G. F. Johnston, *J. Chem. Soc. A*, 193 (1970).
(8) M. Gielen and J. Nasielski, *J. Organometal. Chem.*, **7**, 273 (1967).
(9) M. Gielen and J. Nasielski, *Bull. Soc. Chim. Belg.*, **71**, 601 (1962).
(10) C. Deblandre, M. Gielen, and J. Nasielski, *Bull. Soc. Chim. Belg.*, **73**, 214 (1964).
(11) M. Gielen and J. Nasielski, *J. Organometal. Chem.*, **1**, 173 (1963). The halodemetalations of tetraalkyltins in chlorobenzene are in fact better described by $v = k_2^{exp}[R_4Sn][X_2] + k_3^{exp}[R_4Sn][X_2]^2$; the third-order term contribution is, however, not very important up to tetrapropyltin, but becomes very important for tetraisopropyltin; see, for instance, ref 12.
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