Communications

Borane Complexes in Trifluoroacetic Acid. Reduction of Indoles to Indolines and Generation of Bis(trifluoroacetoxy)borane

Summary: Borane–tetrahydrofuran (THF) in trifluoroacetic acid produces acid-stable $BH[OC(O)CF_3]_2$·THF, and constitutes a convenient, rapid, high-yield method for the selective reduction of indoles to indolines in the presence of other functional groups.

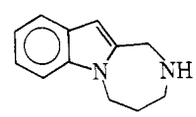
Sir: In the area of selective reductions, we have been exploring the properties of borane complexes in trifluoroacetic acid (TFA). Such mixtures may give rise to mono- and/or bis(trifluoroacetoxy)boranes, potentially useful reducing agents.[1] We have found that bis(trifluoroacetoxy)borane (**1**) is readily formed and that it is *stable to excess TFA*, thus providing one of the few "hydride" reducing agents usable in a strongly acidic medium. Borane–tetrahydrofuran (THF) in TFA has been developed into a convenient, mild, rapid procedure for the conversion of indoles to indolines. This indole reduction study has also served as a vehicle for defining the selectivity of the reagent to various functional groups.

Our choice of borane–THF in TFA was based on the reported inertness of trichloroacetic acid to reduction by borane complexes at 25 °C.[2] Addition of borane–THF to a large excess of anhydrous TFA evolved gas (hydrogen) immediately. Subsequent addition of water to the resultant mixture caused further gas evolution, indicating that the TFA had not consumed all of the available hydride. Hydrogen evolution was measured in two different experiments: (1) treatment of excess TFA with commercial 1 M borane–THF (with 5% $NaBH_4$ present) at 0 °C gave 2.1 molar equiv of hydrogen; (2) commercial 10 M borane–methyl sulfide gave 2.0 molar equiv of hydrogen.[3] Thus, an intermediate adduct such as **1**, or a mixture of species representing its stoichiometric equivalent, was generated.

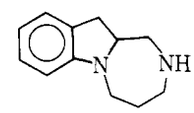
$$BH_3\cdot THF + 2CF_3COOH \rightarrow [CF_3C(O)O]_2BH\cdot THF + 2H_2$$
1

Evaporation (in vacuo, 30 °C) of excess THF, in an experiment involving the treatment of 2 molar equiv of TFA with 1 M borane–THF at 0–5 °C, left a colorless liquid. ^1H NMR (neat) showed only complexed THF (no B–H resonance was discernible). However, the IR spectrum (neat) exhibited a single, strong B–H absorption at 2540 cm^{-1} (indicating a monomeric, nonbridged species),[4] a carbonyl absorption at 1780 cm^{-1}, and typical C–H and C–F stretching bands. A ^{11}B NMR study of a fresh solution of borane–THF in excess TFA showed disappearance of the B–H coupling of borane–THF (quartet at δ −1.2), giving rise to a broad singlet at $\delta \sim +2.5$ (both in parts per million downfield from boron trifluoride etherate). These spectral data are consistent with formation of tetracoordinate species **1**.[5] An NOE-suppressed, ^1H-decoupled ^{13}C NMR spectrum of the isolated neat liquid showed no uncomplexed THF (THF resonances occur at δ 25.8, 67.9) and strongly supported the assignment: δ [Me_4Si; external D_2O lock; 14-μs (90°) pulse; 20-s repetition] 25.4 (s), 76.4 (broadened s), 135.2 (q, $^1J_{CF}$ = 284 Hz), 157.8 (q, $^2J_{CF}$ = 40.9 Hz); relative integrated areas 2.0, 1.9, 2.2, 1.8, respectively.

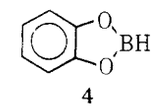
To apply this new reducing agent, we looked initially at the (hydride) reduction of indoles to indolines, which generally requires a strongly acidic medium since reduction presumably proceeds via a 3*H*-indolenium ion. Substrate **2**[6] was chosen for study because a number of published methods were found to be unsatisfactory for transforming it to indoline **3**[7] (see Table I). Although isolated **1** and TFA, and unisolated **1** generated in excess TFA, were successful, we favored a procedure in which the indole was reduced while **1** was being produced. This made use of any viable reducing agents preceding formation of **1** [i.e., BH_3–THF or $CF_3C(O)OBH_2$]. Addition of borane–THF to a solution of **2** in TFA at 0 °C completely reduced **2** to **3** in ~2 min! The yield of **3** was 98% (GLC) (86% isolated). Significantly, production of trifluoroacetyl and 2,2,2-trifluoroethyl byproducts, formed with $NaBH_4$ in TFA[8] (see Table I), was avoided. The minimum reagent ratio required for complete reduction was determined to be 1.5 mol of BH_3–THF per mole of indole.



2



3



4

Table I. Reduction of 2 to 3

reducing agent	isolated yield of 3, %[a]	remarks
isolated 1 in TFA	86	2.5 mol of 1 per mole of indole
BH_3·THF/TFA	86 (98[b])	
BH_3·pyridine/TFA	90	
BH_3·Me_2S/THF/TFA[c]	72	15% unreacted **2**
4/TFA	78	
BH_3·NMe_3/TFA	(~20)	incomplete reduction
$NaBH_3CN$/TFA[11]	81	
$NaBH_3CN$/HOAc[8,12]	(<5)	
$NaBH_4$/TFA[8]	(~35)	*d*
BH_3·THF/CH_3OH/NaO-CH_3[e]	(~20)	~75% unreacted **2**
BH_3·THF/aqueous HCl[11,f]	(~30)	~70% unreacted **2**
BH_3·NMe_3/aqueous HCl[13]	(~15)	~85% unreacted **2**
Tin/concentrated HCl/Δ	(~5)	48-h reaction time
H_2/5% Pd on $BaSO_4$/acid[7]	(<5)	

[a] GLC yield in parentheses. [b] GLC yield using internal reference and detector response factor. [c] Without added THF this reduction is not satisfactory. [d] CH_2CF_3 indoline (~10%), CH_2CF_3 indole (~15%), and $C(O)CF_3$ indole (~15%) byproducts were formed (identified by GLC/mass spectrometry). [e] S. A. Monti and R. R. Schmidt, III, *Tetrahedron*, **27**, 3331 (1971). [f] H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Justus Liebigs Ann. Chem.*, **680**, 69 (1964).

From the comparative data (Table I), borane–THF, borane–pyridine,[9] and catecholborane (**4**),[10] all in TFA, are effective reagents for the reduction of **2**. $NaBH_3CN$ in TFA[11] is also effective.[12] Borane–methyl sulfide with added THF is good and borane–trimethylamine[13] is poor. Catecholborane (**4**) is interesting in its structural relationship to **1**; consequently, the similarity of **1** and **4** in the reduction of **2** was not unpredictable. Use of Cl_3CCOOH or $F_2CHCOOH$ with borane–THF was unsatisfactory for converting **2** to **3**.

0022-3263/78/1943-2733$01.00/0

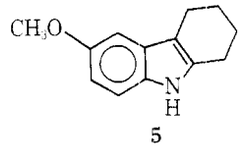
Table II. Reduction of Various Indoles to Indolines[a]

entry	substrate	yield of indoline, %[b]	remarks
1	tetrahydrocarbazole	80 (90)[c]	only cis product[d,e]
2	**5**[f]	90[g]	only cis product
3	tryptamine	86[h]	
4	2-methylindole	88	
5	5-nitroindole	(70)	some "dimeric" product
6	indole	(27)	"dimeric" product formed
7	indole	(84)	inverse addition
8	2,3-dimethylindole	82	trans/cis = ~2[e]
9	1-cyanomethylindole[i]	73[j]	inverse addition
10	1-(2-aminoethyl)indole[k]	~65[j]	inverse addition
11	**6**[l]	80[m]	only cis product
12	**7**[11]	70	only cis product[11]
13	**8**[n]	80[o]	isomer ratio = ~2.5
14	2-phenylindole	0	indole unchanged
15	2-carbethoxyindole	0	indole unchanged
16	*N*-benzoyltryptamine	80[9]	inverse addition

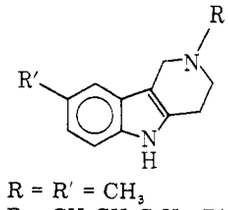
[a] Normal addition procedure unless otherwise noted. All indoles and indolines are known compounds. Indoline products were characterized by ^{1}H NMR and, when appropriate, by IR, UV, and melting point data. (See paragraph on supplementary material at end of paper). [b] Isolated yield; GLC yield, obtained using internal reference and detector response factor, given in parentheses. [c–o] See supplementary material.

The borane–THF procedure, applied to a variety of indoles (see Table II), generally afforded instantaneous reduction at 25 °C. The method is well suited to the reduction of indoles bearing basic nitrogen functionality, substitution which impedes reduction or causes formation of undesirable byproducts with many other methods. Selectivity of the reagent is evident from the unreactiveness of ester (entry 15), nitrile (entry 9), nitro (entry 5), ether (entry 2),[14] and amide (entry 16). The method herein is not effective for the reduction of indoles with phenyl (entry 14) and carbethoxy (entry 15) substituents at the 2 position. Although certain indoles "dimerize" (entries 5 and 6) or suffer other side reactions under the standard reduction conditions, this problem can be improved by employing an inverse addition scheme (entries 7, 9, 10, and 16).

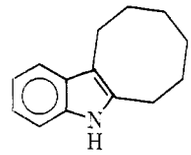
Stereochemical results for reduction of tetrahydrocarbazole, **5**, 2,3-dimethylindole, **6**, **7**, and **8** are shown in Table II (entries 1, 2, 8, and 11–13). A 2,3-fused six-membered ring gave only *cis*-indoline, regardless of whether the fused ring was carbocyclic or heterocyclic. On the other hand, 2,3-dimethyl substitution and 2,3-eight-membered ring fusion gave a mixture of *cis*- and *trans*-indolines.



5



6, R = R′ = CH_3
7, R = $CH_2CH_2C_6H_5$; R′ = H



8

General experimental procedures are as follows (see paragraph on supplementary material at end of paper). **(1) Normal Addition.** The indole (1 mmol) in 3 mL of TFA at 0 °C under nitrogen is treated slowly with 2 mL of BH_3–THF (1 M in THF). After addition, the reaction mixture is diluted with 0.1 mL of H_2O. The TFA and THF are evaporated and the residual mixture is basified with 10% NaOH. Extraction with CH_2Cl_2 and evaporation of the (extract) solvent provides the indoline product.

(2) Inverse Addition. The indole (1 mmol) in 2 mL of BH_3–THF is cooled to 0 °C and treated slowly with 2 mL of TFA. Workup similar to the above furnishes the indoline product.

In summary, borane–THF in TFA offers a rapid, mild, high-yield method for the reduction of indoles to indolines. The method is particularly useful for aminoalkyl-substituted indoles, substrates on which other methods are often deficient. Bis(trifluoroacetoxy)borane,[15] easily synthesized from borane–THF and TFA, is potentially interesting as a selective reducing agent, especially since it is stable in a strongly acidic medium. Catecholborane should also be useful as a reducing agent in TFA.[16] We are currently investigating the reactivity of **1** with other functional groups.

Acknowledgment. The authors thank Mr. Albert J. Molinari for some experimental data, and Mr. Martin S. Mutter and Ms. Roberta R. Acchione for spectral data. We also are grateful to Dr. William Wise (University of Pennsylvania) for use of ^{11}B NMR facilities.

Supplementary Material Available: References (c through o) to compounds in Table II and specific experimental procedures (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Acyloxyborane species have been discussed, see: (a) H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970); (b) C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, **39**, 3052 (1974); (c) A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, *J. Chem. Soc. D*, 347 (1970); (d) C. F. Lane, *Chem. Rev.*, **76**, 773 (1976); (e) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).
(2) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
(3) Evolution of the ~2 molar equiv of hydrogen was instantaneous. On standing at 0 °C, the resultant solutions evolved 0.1 molar equiv of additional hydrogen in 30 min, then evolution virtually ceased. Subsequent addition of water released hydrogen, in an amount corresponding to theory (total of 3 molar equiv).
(4) L. J. Bellamy, "Advances in Infrared Groups Frequencies", Chapman and Hall, London, 1968, p 118, and references cited.
(5) Our IR and ^{11}B NMR results are in accord with data recently reported on bis(acyloxy)boranes: H. C. Brown and T. P. Stocky, *J. Am. Chem. Soc.*, **99**, 8218 (1977).
(6) B. E. Reynolds and J. R. Carson, U.S. Patent 3 867 374 (1975); 3 689 503 (1972). Compound **2**, which was assigned the name azepindole by the USAN Council on Drugs, is an antidepressant of clinical interest.

(7) R. Jonas, H. Müller-Calgan, and H.-J. Schliep, U.S. Patent 3 980 797 (1976).
(8) G. W. Gribble, P. Lord, J. Skotnicki, S. Dietz, J. Eaton, and J. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).
(9) A report on the reduction of indoles using borane–pyridine and aqueous or ethanolic mineral acids appeared during the course of our research, see: Y. Kikugawa, *J. Chem. Res.*, 212 (1977).
(10) For a survey of the reducing properties of **4** see: G. W. Kabalka, J. D. Baker, Jr., and G. W. Neal, *J. Org. Chem.*, **42**, 512 (1977).
(11) J. G. Berger, F. Davidson, and G. Langford, *J. Med. Chem.*, **20**, 600 (1977).
(12) For a report on $NaBH_3CN$ in acetic acid see: G. W. Gribble and J. H. Hoffman, *Synthesis*, 859 (1977).
(13) J. G. Berger, *Synthesis*, 508 (1974).
(14) Ethers, such as THF and anisole, can be cleaved by borane reagents; e.g., see M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976), and references cited therein.
(15) The isolated THF complex, **1**, was not stable to prolonged storage at room temperature under dry nitrogen. After a few days, no active hydride remained and the liquid became very viscous. Therefore, we suggest the use of freshly prepared material. In the preparation of **1**, too slow addition of BH_3–THF and unnecessary standing of the reaction mixture were avoided, since polymerization of THF was observed. Removal of excess THF to give **1** alleviated the polymerization problem.
(16) Catecholborane and **1** reduced **2** at about the same rate.

Bruce E. Maryanoff,* David F. McComsey
Chemical Research Department, McNeil Laboratories
Fort Washington, Pennsylvania 19034
Received February 14, 1978

Dimethylaluminum Methylselenolate: A Remarkable Reagent for the Preparation of Active Acyl-Transfer Agents

Summary: The preparation of a new aluminum reagent, dimethylaluminum methylselenolate (**1**), has been achieved. This reagent has been shown to react with a variety of *O*-alkyl esters to provide methylselenol esters, active acyl-transfer agents, in excellent yield.

Sir: We would like to report the preparation and use of a remarkably efficient and versatile reagent for the conversion of *O*-alkyl esters to their corresponding methylselenol esters. This reagent, dimethylaluminum methylselenolate (**1**), is conveniently prepared by heating a toluene solution of trimethylaluminum (Texas Alkyls) with powdered selenium (ROC/RIC) for 2 h at reflux.[1]

$$Me_3Al + Se \xrightarrow[\text{2 h}]{\text{toluene, reflux}} Me_2AlSeMe \quad \mathbf{1}$$

The yellow-colored solution so generated is then ready for use. Aliquots of the reagent are withdrawn by syringe and transferred to the reaction vessel containing the ester, or other organic substrate, dissolved in argon-degassed methylene chloride. All reactions are carried out under an argon atmosphere in a good fume hood.

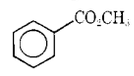
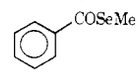
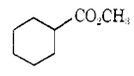
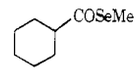
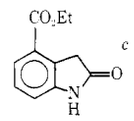
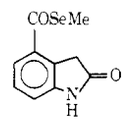
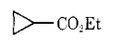
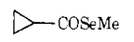
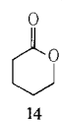
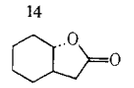
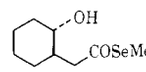
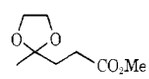
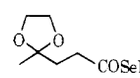
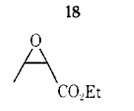
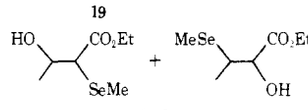
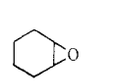
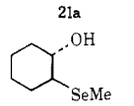
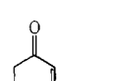
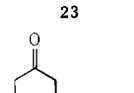
The transformation of a variety of exemplary methyl and ethyl esters to their corresponding selenol esters was found to be complete within 1 h (30 min at 0 °C, followed by an additional 30 min with warming to room temperature)!

The reaction mixtures were quenched with moist sodium sulfate and the products extracted with ether. Concentration of the organic extracts under reduced pressure and bulb-to-bulb distillation of the yellow oils gave the desired products in high yield and high purity as ascertained by NMR, IR, and mass spectral analysis (Table I).

The use of related aluminum reagents and their reactions with esters have previously been explored by Y. Ishii[2] (Et_2AlSEt) and E. J. Corey ($Me_2AlS(CH_2)_3SAlMe_2$, Me_2AlSPh, Me_2AlSCH_2Ph).[3] In addition, S. Weinreb and R. Hatch have recently reported the preparation of *tert*-butyl thioesters by reaction of dimethylaluminum 2-methyl-2-propanethiolate with *O*-alkyl esters.[4] Two equivalents of this aluminum reagent and a reaction time of 4–24 h were required for complete conversion of ester to *tert*-butyl thioester. In contrast, only 1.1 equiv of the selenium reagent **1** are required in most cases for the preparation of the selenol esters.

As is evidenced from Table I, methyl and ethyl esters react with equal facility. The ethyl ester of cyclopropanecarboxylate undergoes reaction without concomitant opening of the strained carbocycle. Only for 4-carboethoxyoxindole (**8**), which possesses a very acidic proton at C-3, is it essential to employ 2 equiv of **1** for complete conversion to the selenol ester

Table I. Reactions of Dimethylaluminum Methylselenolate (1)

starting material[a]	product[b]	isolated yield, %
$CH_3(CH_2)_5CO_2CH_3$ (**2**)	$CH_3(CH_2)_5COSeMe$ (**3**)	95
 (**4**)	 (**5**)	99
 (**6**)	 (**7**)	93
 (**8**)	 (**9**)	80
 (**10**)	 (**11**)	96
$EtO_2C(CH_2)_5CO_2Et$ (**12**)	$MeSeCO(CH_2)_5COSeMe$ (**13**)	95
 (**14**)	$HO(CH_2)_4COSeMe$ (**15**)	78
 (**16**)	 (**17**)	80
 (**18**)	 (**19**)	93
 (**20**)	 (**21a**, ~3:1; **21b**)	92
 (**22**)	 (**23**)	96
 (**24**)	 (**25**)	87

[a] All starting materials were distilled prior to reaction. [b] All products with the exception of **9** were purified by bulb-to-bulb distillation under reduced pressure. Compound **9**, which was obtained in near quantitative yield as the crude product, was recrystallized from methanol. [c] Prepared by the method of A. P. Kozikowski and M. Kuniak, *J. Org. Chem.*, **43**, 2083 (1978).

0022-3263/78/1943-2735$01.00/0