procedure, using reversed phase Waters Prep PAK-500/C_{18} cartridge column and 7% aqueous MeOH as eluting solvent, gave pure 1 as judged from analytical reversed phase HPLC [Spectra Physics Model 3500B liquid chromatograph equipped with a UV detector set at 254 nm: Whatman Partisil PXS 10/25 ODS 2 C_{18} (25 cm × 4.6 mm i.d.) column; 7% aqueous MeOH].

Uvaricin (1). The IR [(CCl_4) 3590, 2940, 2860, 1768, 1745, 1650, 1465, 1370, 1317, 1240, 1195, 1115, 1065, 1023, 945, 875, 850, 715 cm^{-1}], UV [λ_{max} (EtOH) 207 nm (ϵ 12730)], ^1H and ^{13}C NMR (Table I), and mass (Schemes I and II) spectra were in accord with structure 1.

Anal. Calcd for $C_{39}H_{68}O_7$: C, 72.2; H, 10.4. Found: C, 71.8; H, 10.9.

Uvaricinone (2), prepared from CrO_3-pyridine oxidation followed by purification by preparative TLC [SiO_2-60 PF-254; methylene chloride/EtOAc (90:10)], an oil. Its IR [(CCl_4) 1765, 1742, 1718, 1235, 710 cm^{-1}], ^1H NMR (Table I), and mass (Scheme I) spectra were in accord with structure 2.

Uvaricin (1) demonstrated an activity of 157% test/control (T/C) at 1.4 mg/kg in the PS test system. Activity in the PS system is defined as an increase in the survival of treated animals over that of controls resulting in a T/C ≥ 125%.[1] Uvaricin has been selected by the NCI for tumor panel testing.

Acknowledgment. This investigation was supported by Grants No. 5-R01-CA22336-02 and 1-R01-CA29626-01, awarded by the National Cancer Institute, Department of Health, Education and Welfare, Bethesda, MD.

Registry No. 1, 82064-83-3; 2, 82064-84-4.

Selective Reductions. 29. A Simple Technique To Achieve an Enhanced Rate of Reduction of Representative Organic Compounds by Borane-Dimethyl Sulfide

Herbert C. Brown,* Yong Moon Choi,[1] and S. Narasimhan[1]

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

Received February 12, 1982

A dramatic increase in the rate of reduction of esters by borane–dimethyl sulfide (BMS) is observed when dimethyl sulfide is removed from the reaction mixture. On the basis of this observation, a new, improved procedure has been developed for the reduction by BMS of respresentative organic functional groups, such as esters, nitriles, and amides. The procedure involves addition of BMS to the substrate in refluxing tetrahydrofuran, allowing the liberated dimethyl sulfide to distill off during the reaction. Stoichiometric studies established the minimum amount of BMS required for the complete reduction of these functional groups. Thus, esters require 2 equiv of hydride (HB<) for the reduction of >C=O to >CH_2. Employing this stoichiometry, the reduction of aliphatic esters is quite rapid, complete in 0.5 h, while the reduction of aromatic esters is slower, requiring 4–16 h. The corresponding alcohols are produced in excellent yields. On the other hand, nitriles require 3 equiv of hydride (one borane unit/nitrile) and are reduced rapidly in 0.25 h to the corresponding borazine complex, readily hydrolyzed to the corresponding amines. On the other hand, amides require different equivalents of hydride, depending on the particular type of amide undergoing reduction. Thus, tertiary amides require 5 equiv of hydride and form the amine–borane adducts in 0.25 h. Secondary amides liberate hydrogen prior to forming the amine–borane complex, utilizing 6 equiv of hydride in 0.25–1.0 h. However, primary amides require only 4 equiv of hydride, 2 for hydrogen liberation and 2 for reduction, producing in 1.0–2.0 h the amine dibora derivatives, which are sufficiently weakly basic as not to complex with BMS. The ease of reduction of amides follows the order tertiary ≥ secondary > primary. A simple procedure has been described for the reduction of tertiary and secondary amides using decreased amounts of BMS in the presence of boron trifluoride etherate. Unlike lithium aluminum hydride, super hydride, etc., the tendency for C–N bond cleavage to produce the alcohol is completely absent in these reductions of BMS. The reagent permits the presence of many common substituents, such as nitro, chloro, methoxy, etc. The reaction is not significantly susceptible to electronic and steric effects. Simple procedures have been developed for isolating the products. This study establishes a convenient synthetic route for the selective reduction of various organic functional groups with BMS where this transformation is desired in synthetic operations.

Since the discovery of sodium borohydride,[2] it has been utilized as an excellent reagent for the reduction of aldehydes and ketones.[3] However, it is generally too slow for the convenient reduction of carboxylic esters.[3] The reduction of such esters by diborane,[4] borane–tetrahydrofuran,[5] or by borane–dimethyl sulfide[6,7] is also relatively slow. Accordingly, lithium aluminum hydride,[8,9] lithium borohydride,[10,11] or calcium borohydride[12] have been the preferred reagents for such reductions.[13] On the

(1) Postdoctoral research associate on grant ARO DAAG-29-79-C-0027 provided by the U.S. Army Research Office (Durham).
(2) Schlesinger, H. I.; Brown, H. C.; Hoekstra, R. H.; Rapp, L. R. *J. Am. Chem. Soc.* **1953**, *75*, 199.
(3) Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122.
(4) Brown, H. C.; Schlesinger, H. I.; Burg, A. B. *J. Am. Chem. Soc.* **1939**, *61*, 673.
(5) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637.
(6) Braun, L. M.; Braun, R. A.; Crissman, H. R.; Opperman, M.; Adams, R. M. *J. Org. Chem.* **1971**, *36*, 2388.
(7) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 20.
(8) Finholt, A. E.; Bond, A. C., Jr.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 1199.
(9) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.
(10) Schlesinger, H. I.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, *62*, 3429.
(11) Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 3245.
(12) Kollonitsch, J.; Fuchs, O.; Gábor, V. *Nature (London)* **1955**, *175*, 346.
(13) For a recent review of such hydride reducing agent, see Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

0022-3263/82/1947-3153$01.25/0

other hand, reduction of carboxylic acid amides to the corresponding amines has been examined with a variety of complex metal hydrides and metal hydrides, such as lithium aluminum hydride, lithium trimethoxyaluminohydride, and aluminum hydride.[14] However, borane–tetrahydrofuran (H_3B·THF)[15] and borane–dimethyl sulfide (H_3B·SMe_2, BMS)[7] have proven to be the reagents of choice over any complex metal hydride[14] for most reductions of carboxylic acid amides to amines. Also, borane reagents, such as diborane,[16] borane–tetrahydrofuran (BH_3·THF),[17] and borane–dimethyl sulfide (BMS),[7] are known to be very effective for the conversion of nitriles to amines. Unfortunately, reactions are often quite slow,[18] especially with BMS, although BMS has a number of advantages in handling over diborane and BH_3·THF.[7]

We recently reported an extensive investigation of an improved procedure for borane–dimethyl sulfide reductions of carboxylic esters,[19] primary amides,[20] and nitriles[21] in tetrahydrofuran (eq 1–3). In the course of that investigation, it was observed that carboxylic esters, primary amides, and nitriles were reduced by borane–dimethyl sulfide to the corresponding primary alcohols[19] and primary amines[20,21] rapidly and quantitatively when dimethyl sulfide was distilled out of the reaction mixture as the reduction was proceeding.[19-21] Encouraged by the results of our preliminary exploratory observations, we undertook a detailed study of the selective reductions of carboxylic esters, carboxylic acid amides, and nitriles containing various other functional groups in order to establish the influence of the electronic and steric characteristics of the substrate structure. The results of these investigations are reported in the present paper.

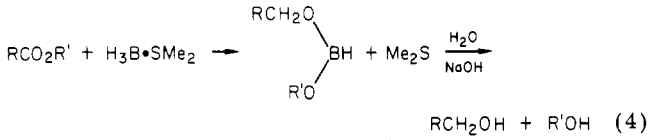
$$RCO_2R' + H_3B{\cdot}SMe_2 \rightarrow \rightarrow RCH_2OH + \ldots \quad (1)$$

$$RCONH_2 + H_3B{\cdot}SMe_2 \rightarrow \rightarrow RCH_2NH_2 + \ldots \quad (2)$$

$$RC{\equiv}N + H_3B{\cdot}SMe_2 \rightarrow \rightarrow RCH_2NH_2 + \ldots \quad (3)$$

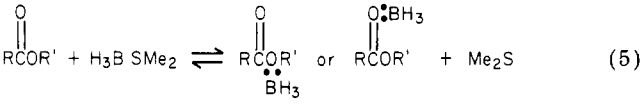
Results and Discussion

Enhanced Rates by Distillation of Dimethyl Sulfide. It was established that BMS is stable in refluxing tetrahydrofuran (THF) for long periods of time. Under these conditions, the reagent reduces esters to an intermediate, presumably the dialkoxyborane,[5] at a reasonable rate (eq 4). Simple hydrolysis with water or, preferably, aqueous alkali gives the corresponding alcohol (eq 4). In applying this procedure to ethyl benzoate, a relatively resistant ester,[5] we noted that the reaction was 67% complete in 0.25 h, but then required more than 8 h to go to essential completion (98%). The date are summarized in Table I.



(4)

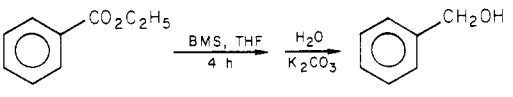
In reviewing the literature data, it appeared that the reduction of esters was fastest with complexed diborane,[4] slower with borane–THF,[5] and slowest with BMS.[6,7] Evidently, the more tightly coordinated the borane, the slower the reduction. This suggested that the reduction probably proceeds through a transfer of borane from its complexes to the ester group[4] (eq 5). On this basis, the decrease in the rate of reduction of ethyl benzoate by BMS as the reaction proceeds could be attributed to a combination of two factors. First, the accumulation of dimethyl sulfide in the reaction mixture would repress the transfer of borane to the ester group to give the desired intermediate (eq 5). Second, the accumulation of dimethyl sulfide, bp 38 °C, would reduce the temperature of the refluxing reaction mixture (THF, bp 67 °C). It appeared that a simple distillation from the reaction mixture of dimethyl sulfide, as it was liberated, would overcome the difficulty. Indeed, that proved to be the case. With distillation, the reaction was essentially complete (100%) in 1.0 h. The data are summarized in Table I.



(5)

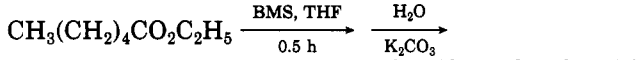
Reduction of Carboxylic Esters. In the course of investigating the advantages of distilling dimethyl sulfide out of the reaction mixture, we examined the possibility of decreasing the amount of BMS from the 50% excess used in these initial experiments on the rate of reaction to essentially the stoichiometric amount (1.0 ester/0.67 BMS; eq 6). Consequently, we examined reductions of esters using this stoichiometric quantity of BMS plus 10% excess to take care of small amounts of active hydrogen impurities (water, alcohol, acid) in the ester and in the apparatus. In order to minimize the solvent required, we also increased the concentration of each of the reactants, 3.0 M (30 mmol) in ester and 2.2 M (22 mmol) in BMS. Indeed, the reduction of ethyl benzoate appeared to be complete in 4 h, since examination of the reaction mixture of GLC (SW-20M, 6 ft × $^1/_8$ in.) revealed the absence of residual ester. Accordingly, we adopted this procedure and applied it to a number of representative esters containing a wide variety of functional groups. As mentioned, the reduction of ethyl benzoate required approximately 4.0 h, providing a 90% yield of isolated benzyl alcohol (eq 7).

$$3RCO_2R' + 2H_3B{\cdot}SMe_2 \rightarrow 2(RCH_2O)_x(R'O)_{3-x}B + 2Me_2S \quad (6)$$

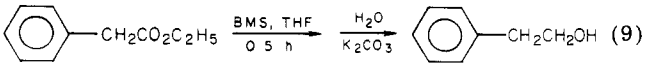


90% (7)

The reduction of aliphatic esters proceeded much more rapidly. Thus, ethyl hexanoate and ethyl phenylacetate were converted into 1-hexanol and 2-phenylethanol in 0.5 h, respectively (eq 8 and 9) and ethyl cyclohexanecarboxylate was reduced to cyclohexane methanol in the same time (eq 10). Indeed, even the highly hindered

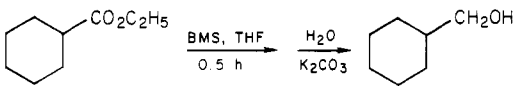


89% (8)



92% (9)

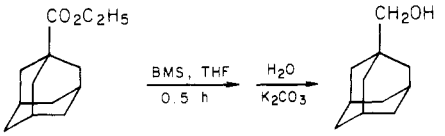
(14) (a) Gaylord, N. G. "Reductions with Complex Metal Hydrides"; Interscience: New York, 1956; pp 544–592. (b) Zabicky, J. "The Chemistry of Amides"; Interscience: New York, 1970; pp 795–801. (c) Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458. (d) Lane, C. F. *Aldrichimica Acta* **1977**, *10*, 49.
(15) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.
(16) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681.
(17) Fowler, J. S.; MacGregor, R. R.; Ansari, A. N.; Atkins, H. L.; Wolf, A. P. *J. Med. Chem.* **1974**, *17*, 246.
(18) Brown, H. C.; Korytnyk, W. *J. Am. Chem. Soc.* **1960**, *82*, 3866.
(19) Brown, H. C.; Choi, Y. M. *Synthesis* **1981**, 439.
(20) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441.
(21) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Synthesis* **1981**, 605.



(10)

89%

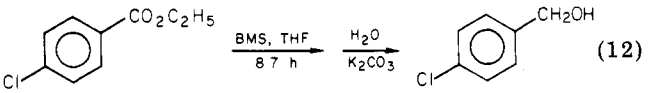
derivative, ethyl adamantane-1-carboxylate, was reduced to 1-adamantanemethanol in essentially quantitative yield (eq 11).



(11)

97%

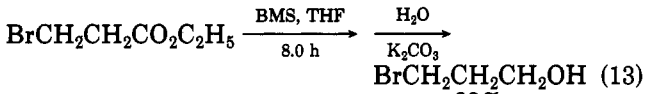
We also examined the possibility of achieving the selective reductions of carboxylic esters containing common functional groups, such as chloro, bromo, nitro, methoxy, as well as other derivatives. Thus, the reduction of ethyl *p*-chlorobenzoate was complete in 8.0 h without loss of the chlorine substituent and we isolated a 96% yield of *p*-chlorobenzyl alcohol (eq 12). Similarly, other substituents,



(12)

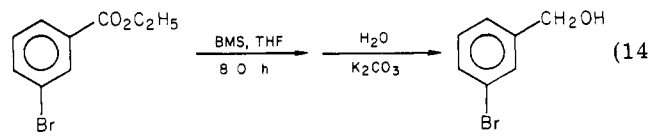
96%

such as bromo, nitro, methoxy, were readily tolerated during the reduction of the ester group (eq 13–17).



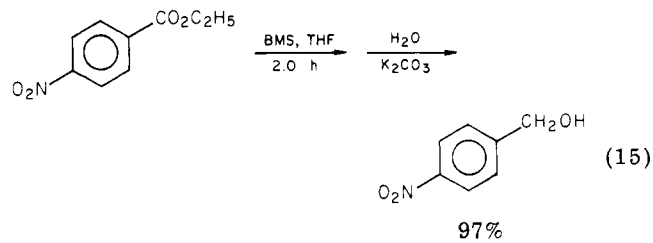
(13)

88%



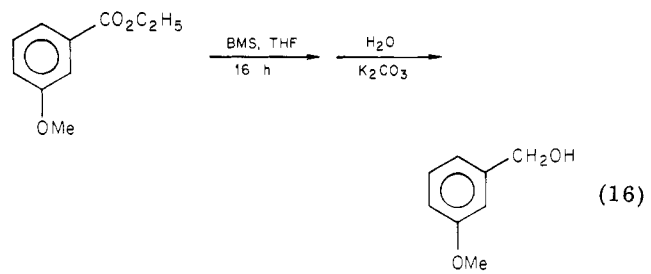
(14)

94%



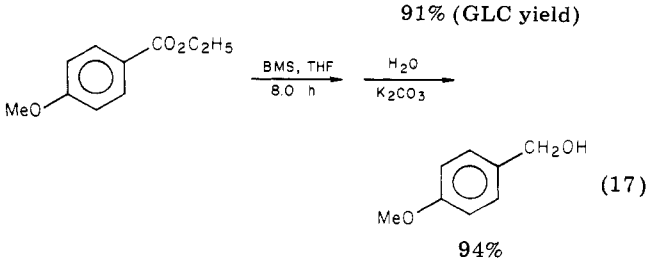
(15)

97%



(16)

91% (GLC yield)



(17)

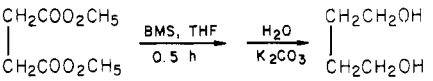
94%

Table I. Reduction of Ethyl Benzoate with Borane-Methyl Sulfide in Tetrahydrofuran at Reflux[a]

rctn time, h	accum of Me_2S hydride used, mmol/mmol of compd	% rctn	with distillation of Me_2S hydride used, mmol/mmol of compd	% rctn
0.25	1.35	67	1.49	75
0.50	1.48	74	1.66	83
1.00	1.65	83	2.00	100
2.00	1.88	94		
4.00	1.95	97		
8.00	1.96	98		

[a] The initial concentrations were 2.0 M in ethyl benzoate and 2.0 M in borane-methyl sulfide.

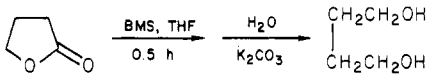
Moreover, the aliphatic diester, diethyl succinate, was reduced rapidly to 1,4-butanediol in a yield of 85% (eq 18).



(18)

85%

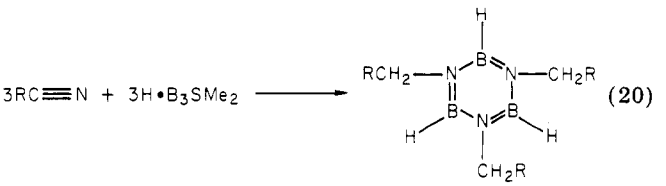
Finally, γ-butyrolactone was also reduced to the corresponding 1,4-butanediol in a yield of 87% (eq 19). However, the aromatic analogue, phthalide, produced a mixture of phthalyl alcohol (73%) and phthalan (22%). The data are summarized in Table II. In a competitive reaction between ethyl benzoate, ethyl caproate, and BMS, 1-hexanol is obtained in 85% yield (by GLC), providing the possibility of reduction of aliphatic esters in the presence of aromatic esters.



(19)

87%

Reduction of Nitriles. We examined the same procedure for the reduction of nitriles. Indeed, under these conditions, BMS rapidly reduced nitriles to an intermediate, presumably the borazine derivatives[22] (eq 20).



(20)

Although nitriles should require only two hydrides for complete reduction to amines, experimentally we found that three hydrides were required, apparently because of the requirement for one hydride/nitrile in the formation of the borazine. This stoichiometry was established by the following experiment in which we attempted to use only two hydrides/nitrile. Benzonitrile (30 mmol, 3.0 M) in 4.7 mL of THF was heated to reflux and 2.3 mL (22 mmol, 2.2 M, 10% excess) of BMS was added. The dimethyl sulfide liberated in the course of the reaction was allowed to distill off (a total of 2.4 mL was recovered within 15 min, a quantitative recovery). The heating was continued for 5 h to insure completion of the reduction. Examination of the reaction mixture by GLC (6 ft × $^1/_8$ in. Carbowax-20M) revealed the presence of unreacted benzonitrile in

(22) Emelus, H. J.; Wade, K. *J. Chem. Soc.* **1960**, 2614.

Table II. Reduction of Esters and Lactones by BMS in THF at Reflux Temperature Allowing DMS To Distill Off[a]

ester	rctn time, h	product	% yield[b]
ethyl benzoate	4.0	benzyl alcohol	90
ethyl hexanoate	0.5	1-hexanol	89
ethyl phenylacetate	0.5	2-phenylethanol	92
ethyl cyclohexanecarboxylate	0.5	(hydroxymethyl)cyclohexane	89
ethyl adamantane-1-carboxylate	0.5	(hydroxymethyl)adamantane	97
ethyl 3-bromopropionate	0.5	3-bromopropanol	88
ethyl *m*-bromobenzoate	8.0	*m*-bromobenzyl alcohol	94
ethyl *p*-chlorobenzoate	8.0	*p*-chlorobenzyl alcohol	96
ethyl *p*-nitrobenzoate	2.0	*p*-nitrobenzyl alcohol	97
ethyl *m*-methoxybenzoate	16.0	*m*-methoxybenzyl alcohol	91[c]
ethyl *p*-methoxybenzoate	8.0	*p*-methoxybenzyl alcohol	94
diethyl succinate[d]	0.5	1,4-butanediol	85
γ-butyrolactone	0.5	1,4-butanediol	87
phthalide	3.0	phthalyl alcohol	73
		phthalan	22
ethyl benzoate[e]	2.0	benzyl alcohol	92[c]

[a] 3.0 M (30 mmol) in ester and 2.2 M (22 mmol) in BMS (Procedure A). All of the products were fully characterized by ^{1}H NMR, spectra, and physical constants (bp/mp, n^{20}D). [b] Isolated yields. [c] GLC yield. [d] 1.5 M (15 mmol) in ester, since two $COOC_2H_5$ groups are present, and 2.2 M (22 mmol) in BMS. [e] Reduction from $NaBH_4$ and $BF_3 \cdot OEt_2$ in THF.

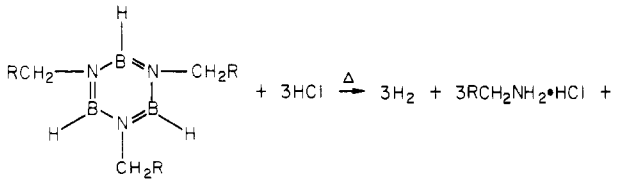
Table III. BMS Reduction of Nitriles[a]

nitrile	amine or amine hydrochloride[a]	rctn time, h	procedure	% yield[b]
capronitrile	*n*-hexylamine	0.25	B	72
cyclopropyl cyanide	cyclopropanemethylamine hydrochloride	0.25	C	76
benzonitrile	benzylamine	0.25	B	76
pivalonitrile	neopentylamine hydrochloride	0.25	C	88 (98)[c]
diphenylacetonitrile	2,2-diphenylethylamine	0.25	B	93[b]
p-chlorobenzonitrile	*p*-chlorobenzylamine	0.25	B	78
m-nitrobenzonitrile	*m*-nitrobenzylamine hydrochloride	0.25	C	85
o-tolunitrile	*o*-xylylamine	0.25	B	79 (96)[d]
p-methoxybenzonitrile	*p*-methoxybenzylamine	0.25	B	61
adiponitrile[e]	1,6-diaminohexane	0.25	B	61

[a] 3.0 M (30 mmol) in nitrile and 3.3 M (33 mmol) in BMS. [b] All of the products were fully characterized by ^{1}H NMR spectra and physical constants (bp/mp, n^{20}D). Unless otherwise stated, yields represent pure isolated products. [c] Crude yield. [d] GLC yield. [e] 30 mmol of nitrile, 66 mmol of BMS.

a yield of 23%. The same quantity was present when the reaction mixture was analyzed after a total of 8 h of heating. However, the use of 33 mmol (3.3 M) of BMS caused the reaction to be complete in 0.25 h, producing an essentially quantitative yield of benzylamine. Hence, the stoichiometry of three hydride (one BH_3)/nitrile group was employed in the subsequent reduction of a selected range of organic nitriles.

Hydrolysis of the borazine with hydrochloric acid, followed by neutralization with sodium hydroxide, produced the amine in essentially quantitative yield (eq 21).



$$3B(OH)_3 \xrightarrow{6\ NaOH} 3RCH_2NH_2 + 3NaCl + 3H_2O + 3NaB(OH)_4 \quad (21)$$

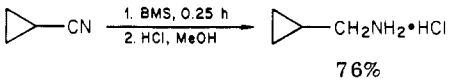
An alternative procedure for isolating the product was to treat the reaction mixture with methanolic hydrogen chloride (1.0 M) and reflux for 4 h, allowing methylborate to distill off as the azeotrope (1:1) with methanol.[23] The pure amine hydrochloride was readily isolated as the product. This can be purified by recrystallization from absolute ethanol.

(23) Extent of methanolysis could be determined by estimating methyl borate in the distillate, titrating with sodium hydroxide in the presene of mannitol to the phenolphthalein endpoint.

The yields of the initial products appear to be essentially quantitative, either by GLC analysis for the free amine, or by weighing the hydrochloride. Following isolation of the product by distillation or recrysatllization, the yields were in the range of 70–80%. A number of nitriles were reduced following this general procedure. Thus, capronitrile was reduced to *n*-hexylamine (eq 22). Similarly,

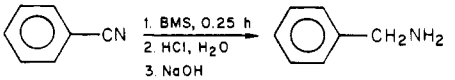
$$CH_3(CH_2)_4CN \xrightarrow[2.\ HCl,\ H_2O \\ 3.\ NaOH]{1.\ BMS,0.25\ h} \underset{72\%}{CH_3(CH_2)_5NH_2} \quad (22)$$

cyclopropyl cyanide was reduced to cyclopropanemethylamine hydrochloride (eq 23). Aromatic nitriles were easily reduced (eq 24 and 25). Substituents, such as nitro



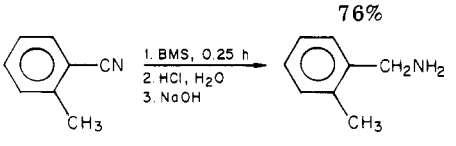
(23)

76%



(24)

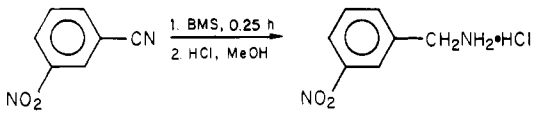
76%



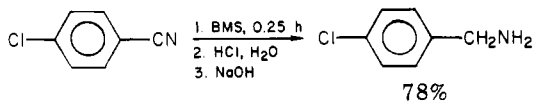
(25)

(96% GLC) 79%

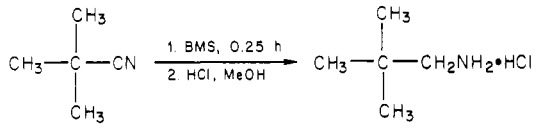
and chloro, were readily tolerated (eq 26 and 27). Even the reduction of the relatively hindered pivalonitrile was quite facile (eq 28). Finally, the procedure proved sat-



85% (26)

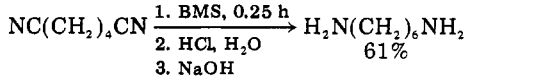


78% (27)



88% (98% crude) (28)

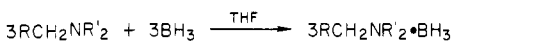
isfactory for the reduction of adiponitrile to the diamine (eq 29). The data are summarized in Table III.



(29)

Reduction of Tertiary Amides. Tertiary amides are rapidly reduced following this procedure. The stoichiometry of the reaction between amides and borane in tetrahydrofuran has been reported[15] to be in accordance with the following reactions (eq 30 and 31). The amine–borane

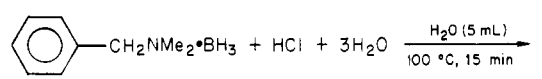
(30)



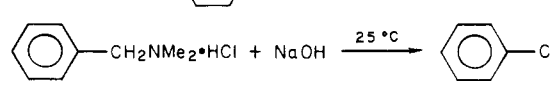
(31)

adduct is inert toward further hydride transfer reactions. Hence, for the complete reduction, 5 equiv of hydride (H–B<) was recommended. We confirmed that this stoichiometry holds for BMS through the following experiment. *N,N*-Dimethylbenzamide (5 mmol) in THF (1.3 mL) was heated to reflux and BMS (0.39 mL, 3.7 mmol, 11.1 hydrides) was added in drops, allowing dimethyl sulfide to distill off. After 4 h, the product was dissolved in THF (5 mL) and an aliquot (0.5 mL) was analyzed by ^{11}B NMR. A quartet was observed around δ −7.5. The decoupled spectrum shows a signal at δ −7.5, corresponding to the amine–borane complex. No peak due to residual BMS (δ −19.9) was observed. A second portion of the THF solution (0.5 mL) was hydrolyzed with 6 N hydrochloric acid (0.5 mL), neutralized with sodium hydroxide, and saturated with anhydrous potassium carbonate. The THF layer was analyzed by GLC (6 ft × $^1/_8$ in. Carbowax-20M). There was present 45% unreacted amide. However, when 5 equiv of hydride/amide (27.5 mmol of hydride) was used, the reduction was complete in 0.25 h, and an essentially quantitative yield of amine was obtained.

Amines were isolated from the amine–borane complex as follows (eq 32 and 33).

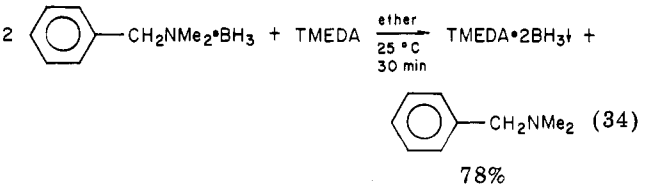


(32)



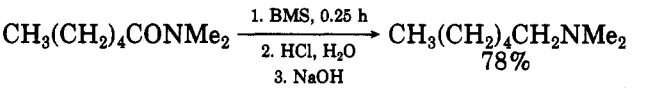
(33)

An alternative procedure for isolating the product involved utilizing the insolubility of the borane complex with *N,N,N',N'*-tetramethylethylenediamine (TMEDA)[24] (eq 34). The TMEDA·2BH_3 complex was separated by centrifugation. Fractional distillation of the centrifugate yielded the pure amine.

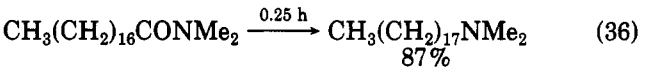


(34)

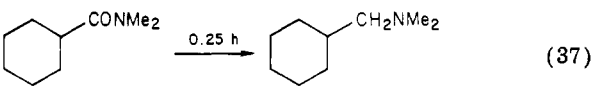
In this way a wide variety of amides were reduced to the corresponding amines (eq 35–39). Reduction of amides



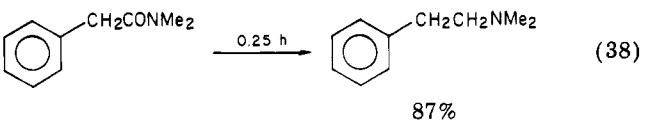
(35)



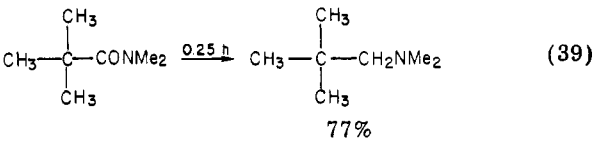
(36)



(37)

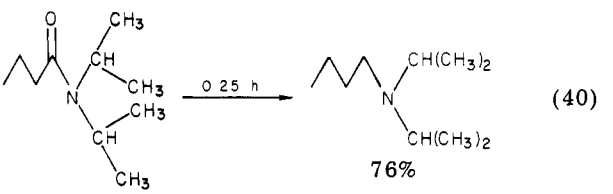


(38)

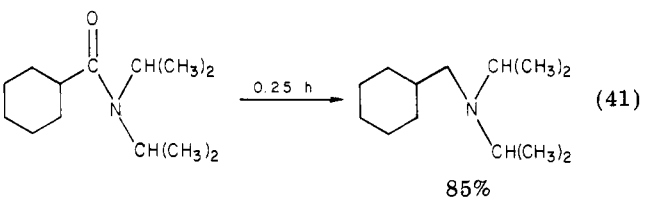


(39)

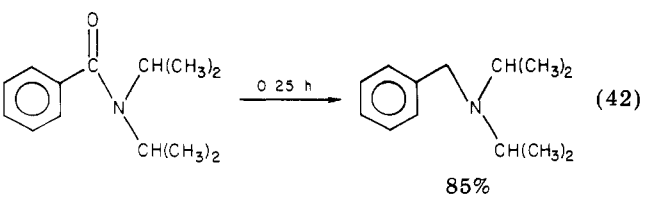
with bulky groups present on the nitrogen atom did not affect either the rate or the nature of the product of the reaction (eq 40–42), *N*-Alkyl heterocyclic compounds were



(40)



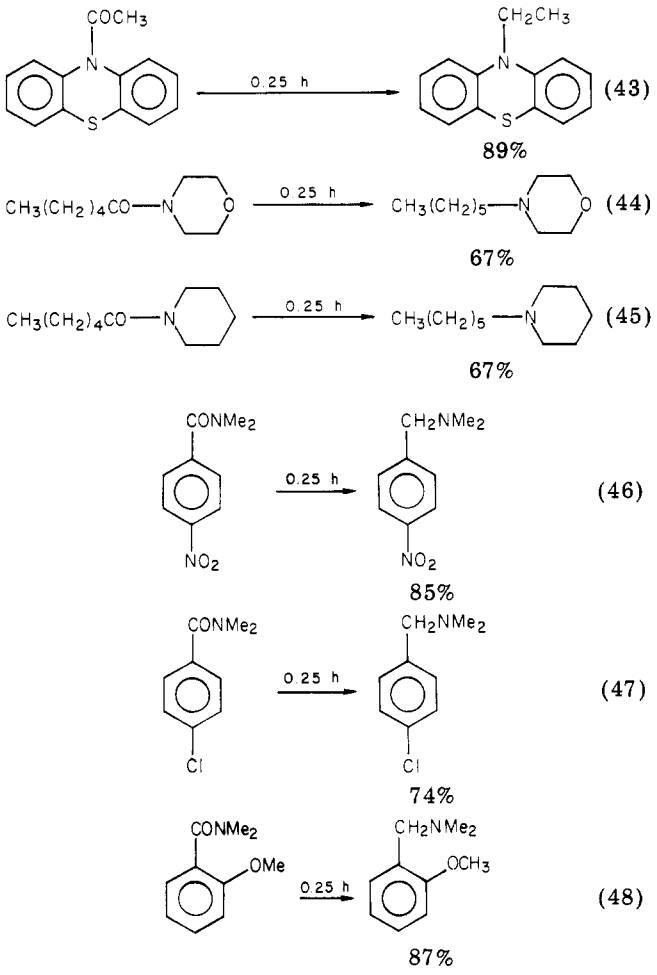
(41)



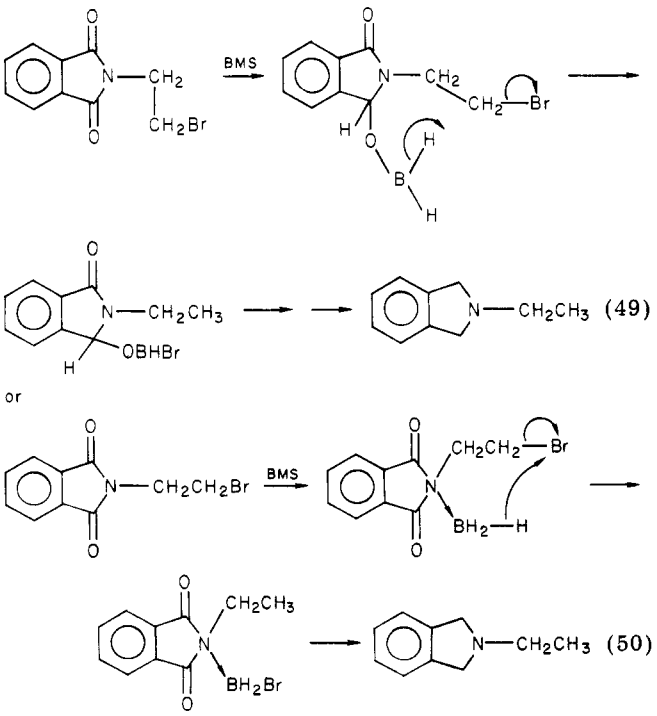
(42)

obtained from the corresponding *N*-acyl compounds (eq 43–45). A number of substituents, such as nitro, chloro, etc., were readily tolerated (eq 46–48). However, the

(24) Brown, H. C.; Singaram, B. *Inorg. Chem.* **1980**, 19, 455.

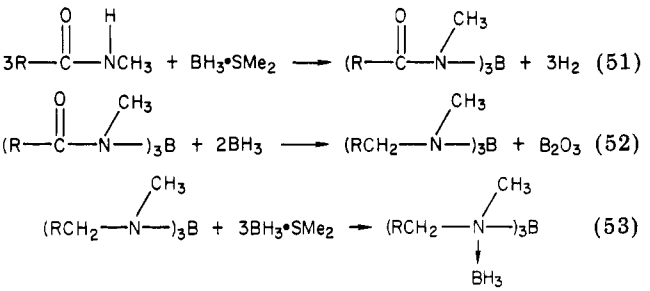


reduction of an imide, *N*-(2-bromoethyl)phthalimide, produced *N*-ethylisoindoline in 37% yield. The reduction of C–Br bond could be due to the proximity of the reactive B–H center[25] (eq 49 and 50). The results are summarized in Table IV.

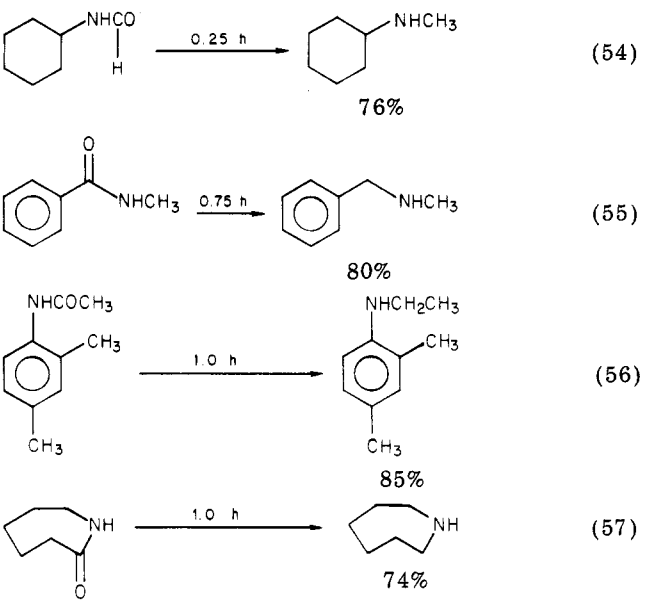


(25) Houminer, Y. *J. Org. Chem.* **1975**, *40*, 1361.

Reduction of Secondary Amides. The stoichiometry of the reaction between a secondary amide and BMS was established as follows. *N*-Methylbutyramide (5 mmol) in THF (1.1 mL) was heated to reflux and BMS (0.58 mL, 5.5 mmol) was added in drops. The hydrogen envolved was collected and measured (130 mL, 5 mmol, a quantitative liberation of hydrogen for the N–H bond). After 4 h, the product was analyzed by ^{11}B NMR. A broad peak was observed at δ 4.2–0.6 and no BMS signal was obtained. Analysis of the product after hydrolysis by GLC showed unreduced amide. It required 10 mmol of BMS (6 equiv of hydride) for complete reduction of the amide, according to the following equations (eq 51–53). The formation of



amine–borane complex is possible, in spite of the deactivation by boron atom bonded to nitrogen, due to the presence of the electron-releasing methyl group on nitrogen. Taking advantage of the distillation of dimethyl sulfide during the course of reaction, the following secondary amides were rapidly and quantitatively reduced to the corresponding amines (eq 54–57). The results are summarized in Table V.



Reduction of Primary Amides. The earlier methods[7,15] for the reduction of primary amides using borane reagents recommended 7 equiv of hydride ($2H^-$ for reduction, $2H^-$ for hydrogen evolution, and $3H^-$ for complex formation). However, we discovered that primary amides do not require an additional mole of BMS.[20] The following experiment established the stoichiometry of the reaction and the requirement for considerably less borane reagent than previously recommended. Five millimole of *n*-hexanamide in 1.0 mL of THF was heated to reflux and 0.74 mL (7.3 mmol) of BMS added. The hydrogen evolved was collected and measured: 230 mL, 9 mmol, 90% theoretical. The dimethyl sulfide liberated in the course of the reaction was distilled off. After 4 h, the product was analyzed. An aliquot (0.1 mL) was diluted fivefold and examined by ^{11}B

Table IV. BMS Reduction of Tertiary Amides in THF

amide	rctn time, h	product	procedure	% yield[a]
N,N-dimethylhexanamide	0.25	*N,N*-dimethylhexylamine	D	78
N,N-dimethyloctadecanamide	0.25	*N,N*-dimethyloctadecylamine	D	87
N,N-dimethylcyclohexanecarboxamide	0.25	[(dimethylamino)methyl]cyclohexane	E	80
N,N-dimethylbenzylamide	0.25	*N,N*-dimethylbenzylamine	E	83
N,N-dimethylphenylacetamide	0.25	*N,N*-dimethyl-2-phenylethylamine	D	87
N,N-dimethylpivalamide	0.25	*N,N*-dimethylneopentylamine	D	77
N,N-diisopropylbutyramide	0.25	*N,N*-diisopropylbutylamine	D	76
N,N-diisopropylcyclohexanecarboxamide[b]	0.25	[(diisopropylamino)methyl]cyclohexane	D	85
N,N-diisopropylbenzamide[c]	0.25	*N,N*-diisopropylbenzylamine	D	85
N,N-dimethyl-*p*-chlorobenzamide	0.25	*N,N*-dimethyl-*p*-chlorobenzylamine	D	74
N,N-dimethyl-*p*-nitrobenzamide	0.25	*N,N*-dimethyl-*p*-nitrobenzylamine	D	85
N,N-dimethyl-*o*-methoxybenzamide		*N,N*-dimethyl-*o*-methoxybenzylamine	D	87
N,N-dimethyl-*p*-methoxybenzamide	0.25	*N,N*-dimethyl-*p*-methoxybenzylamine	D	83
N-hexylpiperidine	0.25	*N*-hexylpiperidine	E	67
N-acetylphenothiazine	0.25	*N*-ethylphenothiazine	E	89
N-hexylmorpholine	0.25	*N*-hexylmorpholine	E	67
N-(2-bromoethyl)phthalimide[d]	0.25	*N*-ethylisoindoline	D	37

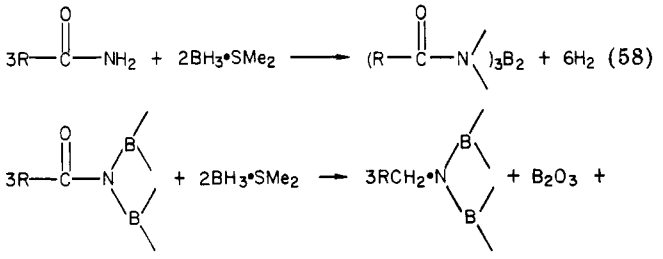
[a] All of the products were fully characterized by ^{1}H NMR spectra and physical constants (bp/mp, n^{20}D). Yields represent pure isolated products. [b] Mass spectral data (*m/e* 197.215) is consistent with the molecular weight (197) and hence the molecular formula ($C_{13}H_{27}N$) of the product. [c] The product was characterized by its picrate derivative: mp 133–135 °C [lit.[15] mp 135 °C]. [d] [Imide] = 30 mmol; [BMS] = 77 mmol.

Table V. BMS Reduction of Secondary Amides

amide	rctn time, h	product	procedure	% yield[a]
N-methylbutyramide	0.25	*N*-methylbutylamine hydrochloride	F	86
N-cyclohexylformamide	0.25	cyclohexylmethylamine	D	76
N-methylbenzamide	0.75	*N*-methylbenzylamine	D	80
2,4-dimethylacetanilide	1.0	2,4-dimethyl-*N*-ethylaniline	D	85
caprolactam	1.0	homopiperidine	D	74

[a] All of the products were fully characterized by ^{1}H NMR spectra and physical constants (bp/mp, n^{20}D). Yields represent pure isolated products.

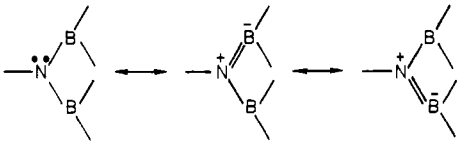
NMR. The decoupled spectrum indicated two peaks at δ −19.9 (BMS) and −23.3. The remaining reaction mixture was treated with 0.83 mL of 6 N hydrochloric acid (5 mmol) at 25 °C. Hydrolysis was facile under these conditions (in contrast to the behavior of the amine–borane complex). Excess (50%) sodium hydroxide was added to neutralize the solution and separate the THF layer. This layer was dried and analyzed by GLC. The starting amide was absent; an essentially quantitative yield of *n*-hexylamine was present. This observation could be explained as follows:



(58)

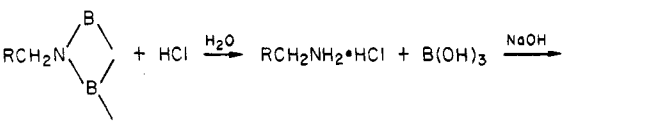
(59)

The resulting product presumably contains two boron atoms attached to the nitrogen through σ bonds. Apparently, this dibora derivative does not coordinate strongly with borane in the way the tertiary amine does, probably due to the following electron shift (eq 60), which renders nitrogen less basic.



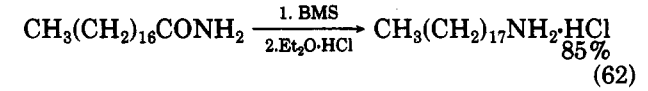
(60)

Amine was isolated by the hydrolysis method, using hydrochloric acid as before (eq 61).



(61)

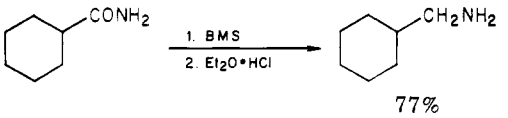
Another method for isolating the product was to treat the reaction mixture with methanol, followed by a solution of hydrogen chloride in ethyl ether (1.15 M). The amine hydrochloride usually precipitated cleanly and could be recovered by filtration. In this way, a number of primary amides were reduced to the corresponding amines (eq 62–67). The data are summarized in Table VI.



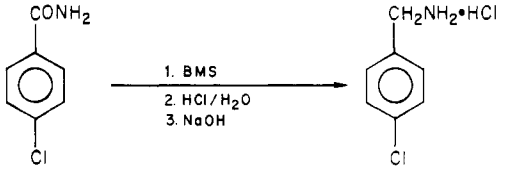
(62)

Reduction of Secondary and Tertiary Amides in the Presence of Boron Trifluoride Etherate.[26] By following the general procedure, we demonstrated the rapid reduction of a number of secondary and tertiary amides. However, the reaction requires a large excess of the reagent (eq 30, 31), which is wasted during the isolation of the product (eq 32, 34). Hence, it was desirable to develop a method in which BMS is utilized only for reduction purposes, the complexation being effected with a stronger Lewis acid. A suitable choice for the Lewis acid was based on the following considerations: (1) the reagent should not react with BMS, (2) it should form a strong complex with

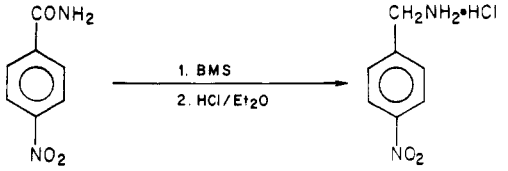
(26) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996.



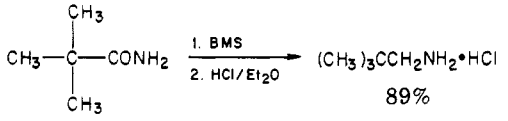
77% (63)



76% (64)



74% (65)



89% (66)

85% (67)

amines, (3) isolation of amine should be facile, (4) cost. The acid strength of the boron trihalides follows the order:[27]

$$BI_3 > BBr_3 > BCl_3 > BF_3 \quad (68)$$

However, the choice is limited to BF_3 since the other boron trihalides (e.g., boron trichloride) react with BMS.[28] Also, the observation that diborane does not display BF_3 from amine–boron trifluoride adducts indicates that BF_3 forms a strong complex with amines.[29] The complexed amine could be liberated simply by the addition of TMEDA, which forms a highly insoluble bis adduct with BF_3.[24] Fractional distillation of the centrifugate should produce pure amine. Also, BF_3·OEt_2 is much more economical than BMS, providing an economical substitute for excess BMS utilized for complex formation in these reductions.

In order to confirm the formation of the amine–boron trifluoride adduct in the presence of BMS, we analyzed a mixture of *N,N*-dimethylbenzylamine (0.5 mmol), BF_3·OEt_2 (0.5 mmol), and BMS (0.5 mmol) in 1 mL of THF by ^{11}B NMR and compared the spectrum with those for standard samples ($\delta_{amine\text{-}BF_3} = -0.13$; $\delta_{amine\text{-}BH_3} = -7.8$). The decoupled spectrum showed chemical shifts at δ −0.12 (singlet in a coupled spectrum) and −19.8 (BMS), indicating the formation of amine–boron trifluoride complex only. Following the general procedure, *N,N*-dimethylbenzamide (30 mmol) was reduced with BMS (22 mmol) in the presence of BF_3·OEt_2 (30 mmol). The reaction mixture was analyzed by GLC as before after 0.25 h. *N,N*-Dimethylbenzylamine was present in quantitative yield.

The following reactions demonstrate the isolation of amines with TMEDA:

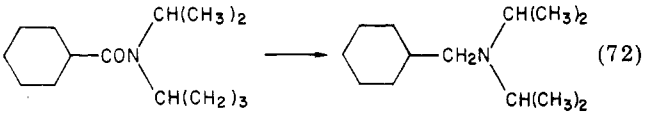
$$3RCONMe_2 + 2BMS + 3BF_3{\cdot}OEt_2 \rightarrow 3RCH_2NMe_2{\cdot}BF_3 \quad (69)$$

$$2RCH_2NMe_2{\cdot}BF_3 + TMEDA \xrightarrow[30\ min]{ether} 2RCH_2NMe_2 + TMEDA{\cdot}2BF_3\downarrow \quad (70)$$

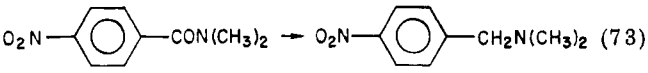
Typical examples of the reduction of amides in the presence of BF_3·OEt_2 are given in (eq 71–77). The results are summarized in Table VII.

$$CH_3(CH_2)_4CON(CH_3)_2 \xrightarrow[3.\ NaOH]{1.\ BF_3{\cdot}OEt_2/BMS;\ 2.\ HCl,\ H_2O} CH_3(CH_2)_5N(CH_3)_2 \quad (71)$$

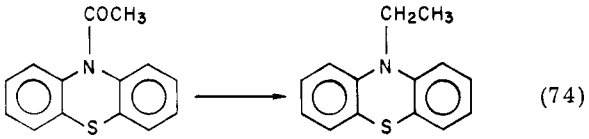
80%



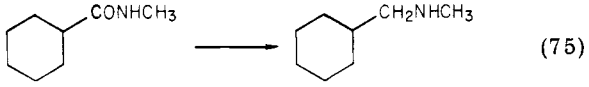
83% (72)



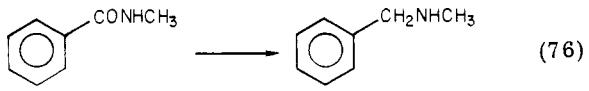
86% (73)



89% (74)



77% (75)



80% (76)

72% (77)

Limitations. Two limitations should be pointed out in using BMS. The presence of carbon–carbon unsaturation will lead to hydroboration. Consequently, such unsaturated derivatives cannot be reduced. The presence of readily reducible groups, such as aldehyde, ketones, carboxylic acids, and esters, will involve competitive reduction. The presence of amine groups would require the introduction of additional reagent to compensate for the formation of amine–borane complexes. However, BF_3·OEt_2 can be used as a protective group for such amino groups, thereby avoiding the need for excess BMS.

Conclusion

The study has brought out several unique reduction characteristics of BMS.

(1) The reagent exhibits enhanced reactivity, comparable to that of uncomplexed diborane, when dimethyl sulfide is removed from the reaction mixture.

(2) Aliphatic esters are rapidly reduced. This provides a unique possibility for reducing side chain esters in the presence of ester groups attached to the aromatic ring. Complex metal hydrides do not show such selectivity.

(3) The reduction of tertiary amides proceeds rapidly and quantitatively to amines, unlike $LiAlH_4$ and $LiEt_3BH$

(27) McDivitt, J. K.; Humphrey, G. L. *Spectrochim. Acta, Part A*, **1974**, *30*, 1021.
(28) Brown, H. C.; Ravindran, N. *Inorg. Chem.* **1977**, *16*, 2938.
(29) Graham, W. A. G.; Stone, F. G. A. *J. Inorg. Nucl. Chem.* **1956**, *3*, 164.

Table VI. BMS Reduction of Primary Amides

amide	rctn time, h	product	procedure	% yield[a]
hexanamide	1.0	*n*-hexylamine hydrochloride	G	75
n-octadecanamide	1.0	octadecylamine hydrochloride	G	85
cyclohexanecarboxamide	1.0	(aminomethyl)cyclohexane	D	77
benzamide	1.0	benzylamine	D	78
pivalamide	1.0	neopentylamine hydrochloride	G	89
2-methylbenzamide	2.0	2-methylbenzylamine hydrochloride	G	81
2-methoxybenzamide	2.0	2-methoxybenzylamine	D	73
4-chlorobenzamide	1.0	4-chlorobenzylamine hydrochloride	G	76
4-nitrobenzamide	1.0	4-nitrobenzylamine hydrochloride	G	74
2,2-dimethylmalonamide[b]	2.0	neopentanediamine dihydrochloride	G	85

[a] All of the products were fully characterized by ^{1}H NMR spectra and physical constants (bp/mp, n^{20}D). Yields represent pure isolated products. [b] [Amide] = 30 mmol; [BMS] = 88 mmol.

Table VII. BMS Reduction of Tertiary[a] and Secondary[b] Amides in the Presence of $BF_3 \cdot OEt_2$

amide	rctn time, h	product	procedure	% yield[c]
N,N-dimethylhexanamide	0.25	*N,N*-dimethylhexylamine	D	80
N,N-dimethylcyclohexanecarboxamide	0.25	[(dimethylamino)methyl]cyclohexane	E	78
N,N-dimethylbenzamide	0.25	*N,N*-dimethylbenzylamine	E	82
N,N-dimethyl-*p*-nitrobenzamide	0.25	*N,N*-dimethyl-*p*-nitrobenzylamine	E	86
N,N-diisopropylcyclohexanecarboxamide	0.50	[(diisopropylamino)methyl]cyclohexane	E	83
N,N-diisopropylbenzamide[d]	1.0	*N,N*-diisopropylbenzylamine	E	87
N-acetylphenothiazine	0.25	*N*-ethylphenothiazine	E	89
N-cyclohexylformamide[b]	0.25	cyclohexylmethylamine	D	77
N-methylbenzamide[b]	0.75	*N*-methylbenzylamine	D	80
caprolactam[b]	1.0	homopiperidine	D	72

[a] [Amide] = 30 mmol; [BMS] = 22 mmol; [$BF_3 \cdot OEt_2$] = 30 mmol. [b] [Amide] = 30 mmol; [BMS] = 33 mmol; [$BF_3 \cdot OEt_2$] = 30 mmol. [c] All of the products were fully characterized by ^{1}H NMR spectra and physical constants (bp/mp, n^{20}D). Yields represent pure isolated products. [d] $BF_3 \cdot OEt_2$ was added following the addition of BMS, since the normal addition results in the formation of a precipitate and retards the reaction rate (4 h).

in which C–N bond cleavage, with formation of alcohols, occurs competitively.

(4) The reaction is relatively insensitive to polar substituent effects.

(5) Even sterically hindered esters, nitriles, and amides are easily reduced.

(6) The reagent is highly selective and can tolerate many substituents, such as halogen, alkoxy, nitro, and sulfone.

The procedure dscribed in this study demonstrates the rapid reduction of representative esters, nitriles, and amides (primary, secondary, and tertiary), using stoichiometric quantities of BMS and simple isolation methods. These characteristics, together with the advantages over available reagents, appears to make BMS the reagent of choice for these reductions.

Experimental Section

Materials. Borane–dimethyl sulfide (~10 M, Aldrich) was used after standardization. Most of the organic compounds utilized in this study were commercial products of very high purity. However, they were further purified by distillation or recrystallization when necessary. Some compounds were synthesized by use of standard procedures.[30] In all of the cases, the physical constants agreed well with literature values. Tetrahydrofuran was distilled over lithium aluminum hydride under nitrogen and stored over 5-Å molecular sieves.[31]

All glassware was dried thoroughly in a drying oven and cooled under a dry stream of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere, and hypodermic syringes or double-ended needle technique was used to transfer the compounds or solvent.[31]

Reduction of Carboxylic Esters. The following procedures are representative.

BMS Reduction of Ethyl Benzoate with Accumulation of Dimethyl Sulfide. Borane–dimethyl sulfide was standardized before use as follows. An aliquot of BMS was hydrolyzed with a 1:1:1 mixture of glycerine/water/THF.[31] From the volume of hydrogen liberated, the concentration of borane in the BMS was calculated (8.73 M). In a typical experiment, a 50-mL flask equipped with a side arm, magnetic stirring bar, and a reflux condenser connected to the nitrogen source through a mercury bubbler was cooled under nitrogen. The flask was charged with 5.73 mL (50 mmol, 8.73 M) of BMS and 12.03 mL of tetrahydrofuran. The solution was stirred and 7.24 mL (50 mmol) of ethyl benzoate was added slowly at 25 °C. The flask was immersed in an oil bath and maintained at a gentle reflux. Samples were removed periodically for analysis of residual BMS by hydrolysis, as above. A blank experiment was performed under identical conditions, without the ester. Aliquots were withdrawn periodically for analysis of residual hydride. From the data (Table I), the number of millimoles of hydride used for reduction in the various time intervals could be calculated. At the conclusion of the reaction, the material was hydrolyzed and subjected to GLC analysis (CW-20M, 6 ft × $^1/_8$ in.). This analysis revealed the absence of ester and the presence of benzyl alcohol in a yield of essentially 100%.

BMS Reduction of Ethyl Benzoate with Distillation of Dimethyl Sulfide. The procedure was identical with that described, with one exception. A 12-in. Vigreaux column, maintained at ~40 °C by a heating jacket, was attached to the reaction flask. Dimethyl sulfide was distilled off as fast as it was formed. A total of 2.1 mL (95%) was collected by the end of the reaction. The hydrolysis of aliquots revealed the progress of the reaction. The data are summarized in Table I. Here also, GLC analysis (CW-20M, 6 ft × $^1/_8$ in.) of the completed reaction revealed the absence of ester and the presence of an essentially 100% yield of benzyl alcohol (following hydrolysis).

General Procedure. BMS Reduction of Ethyl Benzoate with Distillation of Dimethyl Sulfide. Procedure A. An oven-dried, 50-mL flask containing a septum-capped inlet and a magnetic stirring bar was equipped with a 12 in. Vigreaux

(30) (a) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 705. (b) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(31) For a description of the experimental procedures, see Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.

column. A measuring cylinder was fitted to the end of the receiver. The outlet was connected through a mercury bubbler to a source of nitrogen to maintain an inert atmosphere. The whole system was assembled under nitrogen. The flask was charged with 2.52 mL (22 mmol) of BMS, ~3 mL of THF, and 4.34 mL (30 mmol) of ethyl benzoate to be reduced. The total volume was 10 mL (2.2 M in BMS and 3.0 M in ester). The reaction mixture was heated to reflux and the dimethyl sulfide collected as it was distilled through the Vigreaux column. A total of 20.8 mmol (95%) was obtained. When no more dimethyl sulfide distills, the reaction is over. The reaction mixture is brought to room temperature and 15 mL of water added to the stirred reaction mixture. Then 2 g of anhydrous potassium carbonate is added to hydrolyze the borate ester and to extract the boric acid. Additional potassium carbonate is added to saturate the aqueous phase. Ether (10 mL) was added and the ether–THF extract fractionally distilled to provide the corresponding benzyl alcohol in a yield of 90% (2.92 g): bp 96–98 °C (15 mm) [lit.[32] bp 93 °C (10 mm)]; ^{1}H NMR ($CDCl_3$) δ 4.7 (s, 2 H, CH_2), 5.6 (s, 1 H, OH), 7.4 (s, 5 H, aromtic protons); n^{20}_D 1.5391 [lit.[32] n^{20}_D 1.5396].

The data for reduction of various carboxylic esters are summarized in Table II.

BMS Reduction of Nitriles. Reduction of *o*-Tolunitrile. Procedure B. The experimental setup was identical with that described above. The flask was charged with 3.64 g (3.55 mL, 30 mmol) of *o*-tolunitrile and 2.90 mL of tetrahydrofuran and brought to reflux. Then 3.55 mL (33 mmol) of borane–methyl sulfide was added dropwise over a period of 10 min. The dimethyl sulfide distilled off and collected in the receiver (2.4 mL, 100%). After 0.25 h, the reaction mixture was cooled to room temperature and 18 mL of 6 N hydrochloric acid (108 mmol) was added dropwise. (Hydrogen evolved essentially immediately following each addition of acid.) The reaction mixture was then heated under reflux for 0.5 h. The clear solution was cooled to 0 °C and 4.05 g (162 mmol) of sodium hydroxide was added. (In the case of water soluble amines, the aqueous phase should be saturated with potassium carbonate.) The liberated amine was extracted with ether (3 × 10 mL) and dried over anhydrous potassium carbonate. Analysis of the ether extract by GLC (6 ft × $^1/_8$ in., Carbowax-20M) using undecane as the internal standard indicated the presence of a 96% yield of *o*-xylylamine. In a duplicate experiment, without the internal standard, fractional distillation of the ether extract provided 2.87 g (79%) of *o*-xylylamine: bp 116–117 °C (15–17 torr) [lit.[33] bp 201 °C (718 torr)]; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 2 H, NH_2), 2.28 (s, 3 H, CH_3), 3.8 (s, 2 H, CH_2), 6.92–7.28 (m, 4 H, aromatic protons); n^{20}_D 1.5430 [lit.[33] n^{20}_D 1.5435].

Reduction of Pivalonitrile. Procedure C. Following the above procedure, 2.46 g (3.32 mL, 30 mmol) of pivalonitrile was reduced with borane-methyl sulfide (3.55 mL, 33 mmol). After 0.25 h, the flask was cooled to room temperature and 31 mL of 1.0 M methanolic hydrogen chloride (31 mmol) was carefully added over 10 min. Vigorous evolution of hydrogen occurs. The solution was heated to reflux, allowing the methyl borate to distill off as a 1:1 azeotrope with methanol. After 4 h, when all of the solvent had distilled off, 10 mL of methanol was added and removed under suction to ensure complete removal of residual boric acid. The resulting solid weighed 3.675 g, a 98% yield of amine hydrochloride: mp 289–291 °C [lit.[34] mp 275 mp °C, 299 °C[20]]. The solid was dissolved in 10 mL of absolute ethanol, cooled to 0 °C, and 50 mL ether was added. The precipitate was filtered, dried, and weighed. There was obtained 3.32 g, a yield of 88% of pure neopentylamine hydrochloride: mp 294–295 °C; ^{1}H NMR (D_2O) δ 1.0 (s, 9 H, 3 CH_3), 2.8 (s, 2 H, CH_2).

The data for reductions of nitriles are summarized in Table III.

BMS Reduction of Tertiary Amides. Reduction of *N,N*-Dimethylbenzamide. Procedure D. The experimental setup was as described above. To the flask was added 4.48 g (30 mmol) of *N,N*-dimethylbenzamide and 4.2 mL of THF. The solution was heated to reflux and 5.8 mL (55 mmol) of BMS was added in drops over a period of 15 min. Dimethyl sulfide distilled off and collected in the receiver (3.6 mL). The reaction was monitored by GLC as described above. After 15 min, the solvent was removed under suction. The amine–borane complex was heated to 100 °C and 5 mL of 6 N HCl (30 mmol) added. After 30 min, the clear solution obtained was cooled and 7.5 mL of NaOH (6 N, 45 mmol) added. The aqueous layer was saturated with anhydrous K_2CO_3. The liberated amine was extracted with ether (3 × 10 mL) and dried (anhydrous K_2CO_3). Fractional distillation provided 3.35 g of 83% pure *N,N*-dimethylbenzylamine: bp 78–80 °C (25–30 mm) [lit.[35] bp 73–74 °C (15 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 6 H, 2 CH_3), 3.4 (s, 2 H, CH_2), 7.23 (s, 5 H, aromatic protons); n^{20}_D 1.4995 [lit.[35] n^{20}_D 1.5011].

Reduction of *N,N*-Dimethylcyclohexanecarboxamide. Carboxamide. Procedure E. Following the above procedure, 4.66 g (30 mmol) of the amide was reduced with 5.8 mL (55 mmol) of BMS. After 15 min, the solvent was removed under suction. To the residue was added ether (10 mL) and 2.25 mL (15 mmol) of TMEDA and stirred for 30 min at 25 °C. The precipitate was centrifuged and the centrifugate collected. The solid was washed with ether (3 × 10 mL), and the washings were collected after centrifugation. Fractional distillation of the ether extract provided 3.39 g (80% yield) of the amine: bp 78–79 °C (30 mm) [lit.[36] 76 °C (29 mm)]; ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 (m, 11 H, 5 CH_2, 1 CH), 2.26 (s, 8 H, 2 CH_3 and CH_2); n^{20}_D 1.4475 [lit.[36] n^{20}_D 1.4462].

The data for reduction of tertiary amides are summarized in Table IV.

BMS Reduction of Secondary Amides. Reduction of *N*-Methylbutyramide. Procedure F. The procedure was identical with that described with one exception. In the experimental setup, provision was made for measuring the liberated hydrogen by connecting the outlet to a gas measuring buret through a dry ice–acetone trap. To 3.03 g (30 mmol) of *N*-methylbutyramide was added 3.1 mL of THF and the mixture heated to reflux. BMS (6.9 mL, 66 mmol) was added slowly and hydrogen collected and measured. Quantitative evolution of hydrogen (810 mL, 30 mmol) was observed in 15 min. Addition of BMS was completed in 20 min. After 0.25 h, the solvent was removed and 38.5 mL of methanolic hydrogen chloride (0.78 M, 30 mmol) was added. The solution was refluxed for 30 min and methanol was distilled. To the residue, 10 mL of methanol was added and removed under suction to insure complete removal of residual boric acid. The residue weighed 3.09 g, a yield of 86% amine hydrochloride: mp 172–174 °C [lit.[37] mp 173–174 °C]; ^{1}H NMR (D_2O) δ 1.0 (t, 3 H, CH_3), 1.4–1.8 (m, 4 H, 2 CH_2), 2.8 (s, 3 H, NCH_3), 3–3.3 (t, 2 H, NCH_2), 4.8 (s, D_2O–NH_2 exchange).

Secondary amines were isolated by following procedure D. The results are summarized in Table V.

BMS Reduction of Primary Amides. Reduction of Pivalamide. Procedure G. The experimental setup was made as described in procedure F. The flask was charged with pivalamide (3.03 g, 30 mmol) and 5.54 mL of THF and heated to reflux. BMS (4.46 mL, 44 mmol) was added dropwise over a period of 20 min. The hydrogen evolved was collected and measured (49 mmol, 82% of the theoretical value). Meanwhile, the dimethyl sulfide was distilled off and collected in the receiver (3.5 mL). Completion of the reaction was tested as before. After 1 h, the flask was cooled to room temperature and methanol (5.3 mL, 132 mmol) was added dropwise. The hydrogen evolved was collected. the volume corresponded to 12.6 mmol, indicating the reaction to be almost complete. A solution of dry HCl in ether was prepared and added (26 mL, 1.15 M, 30 mmol) dropwise. A white precipitate formed immediately. The reaction mixture was stirred for 30 min at 25 °C and 15 min at 0 °C and then filtered. The residue was washed with ether (3 × 10 mL) and dried. The crude product weighed 3.49 g 95% yield. It was recrystallized from ethanol–ether mixture, providing 3.30 g of the amine hydrochloride, a yield of 89%: mp 299 °C [lit.[34] mp 275 °C]; ^{1}H NMR (D_2O) δ 1.0 (s, 9 H, 3 CH_3), 2.8 (s, 2 H, CH_2). A small portion was neutralized with NaOH. The liberated amine was isolated and found to be identical with the standard sample of neopentylamine: bp 80–82 °C [lit.[34] bp 81–82 °C].

The results are summarized in Table VI.

(32) Weast, R. C. "Handbook of Chemistry and Physics", 4th ed.; The Chemical Rubber Co.: Cleveland, OH, 1968.
(33) Kröber, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1026.
(34) Freund, M.; Lenze, F. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2156.
(35) *Beilstein* **12**, 1019.
(36) Cope, A. C.; Ciganek, E. *Org. Synth.* **1959**, *39*, 19–22.
(37) *Beilstein* **4**, 157.

BMS Reduction of Tertiary and Secondary Amides in the Presence of BF_3·OEt_2. Reduction of *N*,*N*-Dimethylbenzamide. Procedure H. The experimental setup was as described in procedure D. The flask was charged with 4.48 g (30 mmol) of *N*,*N*-dimethylbenzamide and 3.91 mL of THF. Then BF_3·OEt_2 (3.69 mL, 30 mmol) was added and the mixture heated to reflux. To the clear solution was added 2.32 mL (22 mmol) of BMS in drops over a period of 10 min. Dimethyl sulfide and ether distilled off and were collected and measured (3.6 mL). The reaction was monitored as described earlier. After 0.25 h, the product was isolated either with HCl/NaOH (procedure D) or TMEDA (procedure E).

The results are summarized in Table VII.

Reduction of *N*-Methylbenzamide. The above procedure was folllowed, except that 33 mmol of BMS was added instead of 22 mmol. The amine was isolated by following procedure D.

Registry No. Benzyl alcohol, 100-51-6; 1-hexanol, 111-27-3; 2-phenylethanol, 60-12-8; (hydroxymethyl)cyclohexane, 100-49-2; (hydroxymethyl)adamantane, 770-71-8; 3-bromopropanol, 627-18-9; *m*-bromobenzyl alcohol, 15852-73-0; *p*-chlorobenzyl alcohol, 873-76-7; *p*-nitrobenzyl alcohol, 619-73-8; *m*-methoxybenzyl alcohol, 6971-51-3; *p*-methoxybenzyl alcohol, 105-13-5; 1,4-butanediol, 29733-86-6; phthalyl alcohol, 612-14-6; phthalan, 496-14-0; *n*-hexylamine, 111-26-2; cyclopropanemethylamine hydrochloride, 7252-53-1; benzylamine, 100-46-9; neopentylamine hydrochloride, 15925-18-5; 2,2-diphenylethylamine, 3963-62-0; *p*-chlorobenzylamine, 104-86-9; *m*-nitrobenzylamine hydrochloride, 26177-43-5; *o*-xylylamine, 89-93-0; *p*-methoxybenzylamine, 2393-23-9; 1,6-diaminohexane, 124-09-4; *N*,*N*-dimethylhexylamine, 4385-04-0; *N*,*N*-dimethyloctadecylamine, 124-28-7; [(dimethylamino)methyl]cyclohexane, 16607-80-0; *N*,*N*-dimethylbenzylamine, 103-83-3; *N*,*N*-dimethyl-2-phenylethylamine, 1126-71-2; *N*,*N*-dimethylneopentylamine, 10076-31-0; *N*,*N*-diisopropylbutylamine, 41781-44-6; [(diisopropylamino)methyl]cyclohexane, 80934-61-8; *N*,*N*-diisopropylbenzylamine, 34636-09-4; *N*,*N*-dimethyl-*p*-chlorobenzylamine, 15184-98-2; *N*,*N*-dimethyl-*p*-nitrobenzylamine, 15184-96-0; *N*,*N*-dimethyl-*o*-methoxybenzylamine, 58774-83-7; *N*,*N*-dimethyl-*p*-methoxybenzylamine, 15175-54-9; *n*-hexylpiperidine, 7335-01-5; *N*-ethylphenothiazine, 1637-16-7; *N*-hexylmorpholine, 31866-75-8; *N*-ethylisoindoline, 36139-84-1; *N*-methylbutylamine hydrochloride, 6973-82-6; cyclohexylmethylamine, 100-60-7; *N*-methylbenzylamine, 103-67-3; 2,4-dimethyl-*N*-ethylaniline, 1742-94-5; homopiperidine, 111-49-9; *n*-hexylamine hydrochloride, 142-81-4; octadecylamine hydrochloride, 1838-08-0; (aminomethyl)cyclohexane, 3218-02-8; 2-methylbenzylamine hydrochloride, 14865-38-4; 2-methoxybenzylamine, 6850-57-3; 4-chlorobenzylamine hydrochloride, 42365-43-5; 4-nitrobenzylamine hydrochloride, 18600-42-5; neopentanediamine dihydrochloride, 29082-53-9; ethyl benzoate, 93-89-0; ethyl hexanoate, 123-66-0; ethyl phenylacetate, 101-97-3; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl adamantane-1-carboxylate, 2094-73-7; ethyl 3-bromopropionate, 539-74-2; ethyl *m*-bromobenzoate, 24398-88-7; ethyl *p*-chlorobenzoate, 7335-27-5; ethyl *p*-nitrobenzoate, 99-77-4; ethyl *m*-methoxybenzoate, 10259-22-0; ethyl *p*-methoxybenzoate, 94-30-4; diethyl succinate, 123-25-1; γ-butyrolactone, 96-48-0; phthalide, 87-41-2; capronitrile, 628-73-9; cyclopropyl cyanide, 5500-21-0; benzonitrile, 100-47-0; pivalonitrile, 630-18-2; diphenylacetonitrile, 86-29-3; *p*-chlorobenzonitrile, 623-03-0; *m*-nitrobenzonitrile, 619-24-9; *o*-tolunitrile, 529-19-1; *p*-methoxybenzonitrile, 874-90-8; adiponitrile, 111-69-3; *N*,*N*-dimethylhexanamide, 5830-30-8; *N*,*N*-dimethyloctadecanamide, 3886-90-6; *N*,*N*-dimethylcyclohexanecarboxamide, 17566-51-7; *N*,*N*-dimethylbenzylamide, 611-74-5; *N*,*N*-dimethylphenylacetamide, 18925-69-4; *N*,*N*-dimethylpivalamide, 24331-71-3; *N*,*N*-diisopropylbutyramide, 38161-09-0; *N*,*N*-diisopropylcyclohexanecarboxamide, 61259-25-4; *N*,*N*-diisopropylbenzamide, 20383-28-2; *N*,*N*-dimethyl-*p*-chlorobenzamide, 14062-80-7; *N*,*N*-dimethyl-*o*-methoxybenzamide, 7291-34-1; *N*,*N*-dimethyl-*p*-methoxybenzamide, 7291-00-1; *N*-acetylphenothiazine, 1628-29-1; *N*-(2-bromoethyl)phthalimide, 574-98-1; *N*-methylbutyramide, 17794-44-4; *N*-cyclohexylformamide, 766-93-8; *N*-methylbenzamide, 613-93-4; 2,4-dimethylacetanilide, 2050-43-3; caprolactam, 105-60-2; hexanamide, 628-02-4; *n*-octadecanamide, 124-26-5; cyclohexanecarboxamide, 1122-56-1; benzamide, 55-21-0; pivalamide, 754-10-9; 2-methylbenzamide, 527-85-5; 2-methoxybenzamide, 2439-77-2; 4-chlorobenzamide, 619-56-7; 4-nitrobenzamide, 619-80-7; 2,2-dimethylmalonamide, 41882-44-4; *N*,*N*-dimethylbenzamide, 611-74-5; *N*,*N*-dimethyl-*p*-nitrobenzamide, 7291-01-2.

Notes

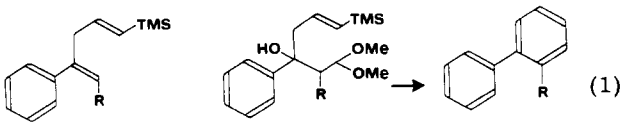
Benzoannelation of Ketones

Marcus A. Tius* and Sadaquat Ali

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

Received December 7, 1981

Aromatic annelation, the elaboration of aromatic rings from nonaromatic precursors, is not always a general or a preparatively useful process. This gap in current synthetic methodology has resulted in a renewal of interest in aromatic chemistry.[1] Our early contribution to this area was a general method for the synthesis of unsymmetrical biphenyls from alkyl aryl ketones.[2] Our method relied upon an intramolecular cationic cyclization, followed by loss of methanol and water as depicted in eq 1. This was the first example of a cationic ketone benzoannelation, and certain problems were evident. Although the preparation of the starting materials was straightforward, it was tedious

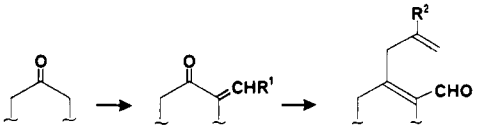


(1)

1

to perform on a large scale. Also, the method did not appear well suited for the more general preparation of benzoannelated aliphatic ketones. Furthermore, the isolation of byproduct 1 showed that a delicate balance existed between cyclization and other competing processes. Additional work was clearly necessary in order to develop a more useful benzoannelation.

The first problem was the conversion, in one or two operations, of an α-methylene ketone to a β-allylic unsaturated aldehyde or its equivalent (eq 2). The presence



(2)

2

of the α,β-double bond is crucial to the success of the

(1) (a) Paquette, L. A.; Melega, W. P.; Kramer, J. D. *Tetrahedron Lett.* **1976**, 4033. (b) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002. (c) Boger, D. L., Panek, J. S. *Ibid.* **1981**, *46*, 2179. (d) Sukumaram, K. B.; Harvey, R. G. *Ibid.* **1981**, *46*, 2740 and references cited therein.

(2) Tius, M. A. *Tetrahedron Lett.* **1981**, 3335.

0022-3263/82/1947-3163$01.25/0