Monatshefte für Chemie 128, 1283–1289 (1997)

Monatshefte für Chemie
Chemical Monthly

Diborane as a Reducing Agent IX [1]: Reduction of a *Tris*(trifluoroacetyl)enaminospiroindoline

K. M. Biswas*, H. Mallik, and **S. Halder**

Department of Chemistry, University College of Science, University of Calcutta, Calcutta 700009, India

Summary. Reduction of the title compound (**2**) with diborane furnishes 1-trifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)-3-vinylindoline (**4**), 1-hydroxy-trifluoroethyl-3-(2′-(trifluoroethylamino)-ethyl)indole (**5**), and 1-methyl-2-trifluoroethyl-1,2,3,4-tetrahydro-β-carboline (**6**). However, treatment of **2** with lithium aluminum hydride, H_2/Pd on charcoal, and sodium borohydride affords hydroxyspiroindolenine **8**, hydroxy-*bis*(trifluoroacetyl)enaminospiroindoline **9**, and *N*-ethyltryptamine **7**, respectively. The results are discussed and the mechanisms of the reactions leading to **4–8** are presented.

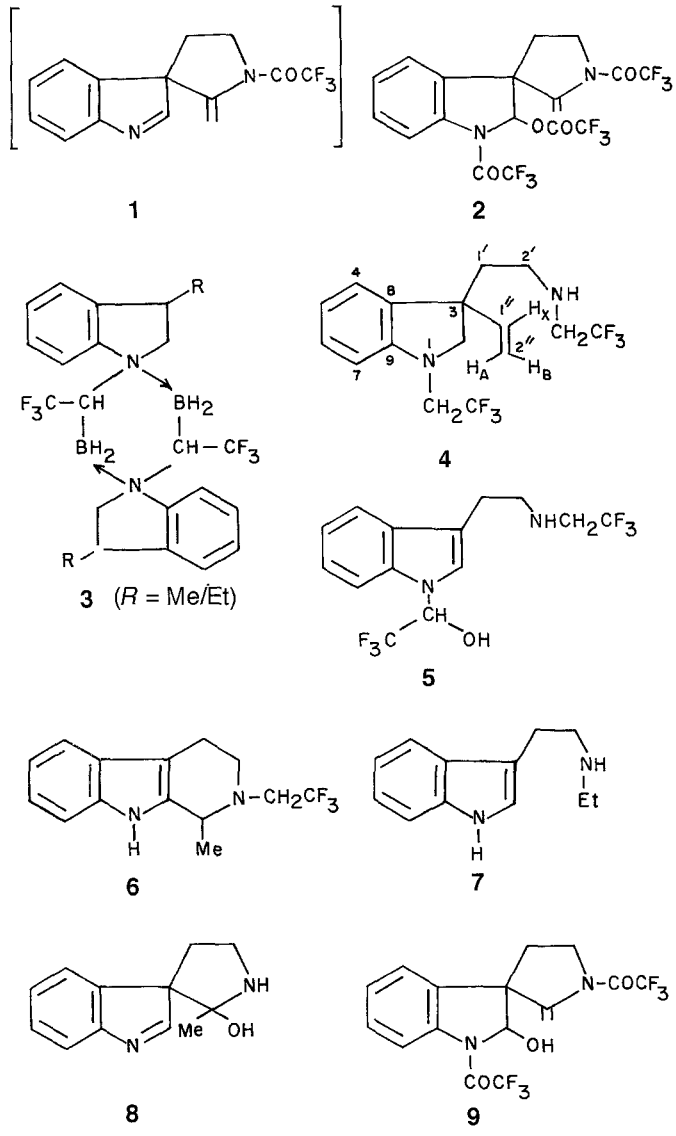
Keywords. *Tris*(trifluoroacetyl)enaminospiroindoline; Diborane; 1-Trifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)-3-vinylindoline; Hydroxyspiroindolenine.

Diboran als Reduktionsmittel, 9. Mitt. [1]**: Reduktion eines *Tris*(trifluoroacetyl)enaminospiroindolins**

Zusammenfassung. Reduktion der Titelverbindung (**2**) mit Diboran ergibt 1-Trifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)-3-vinylindolin (**4**), 1-Hydroxy-trifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)indol (**5**) und 1-Methyl-2-trifluoroethyl-1,2,3,4-tetrahydro-β-carbolin (**6**). Behandlung von **2** mit Lithiumaluminiumhydrid, H_2/Pd auf Aktivkohle und Natriumborhydrid führt jedoch zu Hydroxyspiroindolenin **8**, Hydroxy-*bis*(trifluoroacetyl)enaminospiroindolin **9** und N-Ethyltryptamin (**7**). Die Ergebnisse werden diskutiert und die Mechanismen der zu den Produkten **4–8** führenden Reaktionen werden vorgestellt.

Introduction

Recently, we have shown that N_b-acetyltryptamine undergoes intramolecular cyclization at position 3 with trifluoroacetic anhydride to afford the spiroindolenine intermediate **1** which can be trapped by trifluoroacetic anhydride through nucleophilic attack at position 2 in an intermolecular fashion to afford the novel *tris*(trifluoroacetyl)enaminospiroindoline **2** [2, 3]. We have utilized this mechanistic concept in the synthesis of spiropentacyclic indolines, structurally related to indole alkaloids [4–6]. We have also reported recently that the diborane reduction of 1-, 2-, or 3-trifluoroacetylindoles furnishes novel and interesting products including the borane containing dimeric indolines **3** [1]. These results prompted us



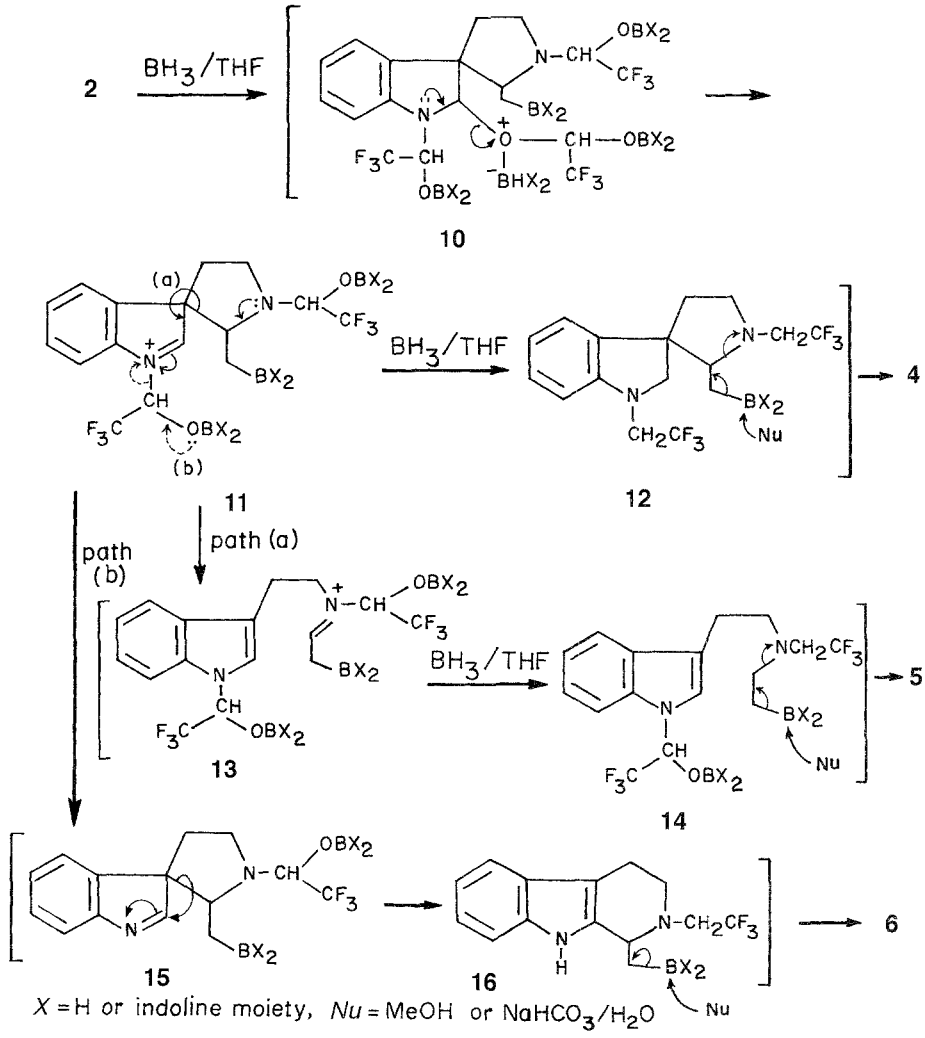
to study the reduction of **2** which contains four reducible chromophores, including an enamine function, with various reducing agents, especially because lithium aluminum hydride was reported to react violently with trifluoroacetamides [7, 8] and because trifluoroacetyl groups of trifluoroacetyl peptides are known to undergo reductive cleavage with sodium borohydride even under very mild conditions [9]. Moreover, much interest has recently been shown in the reduction of enamines with borane reagents [10–12].

Results and Discussion

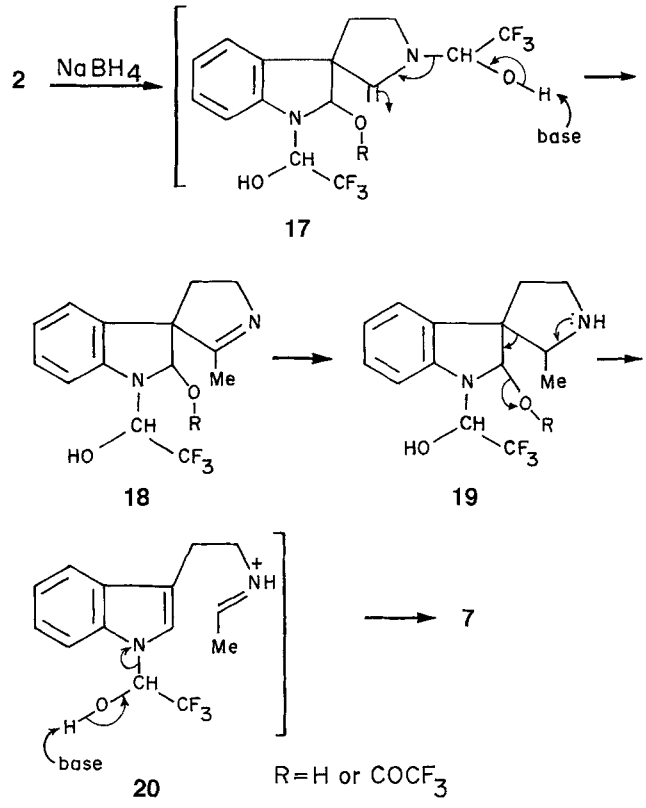
Indoline **2** was prepared following literature procedures [2, 3]. It was reduced with diborane generated externally from sodium borohydride and boron trifluoride

etherate. This reaction gave a mixture of three products which were resolved by chromatography on a silica gel column and characterized as **4**–**6** from their spectroscopic characteristics. The presence of a vinyl group in **4** was indicated by the appearance of three one-proton signals at $\delta = 5.07$, 5.11, and 6.02 ppm in its ^{1}H NMR spectrum, and two signals at $\delta = 113.21$ and 142.19 ppm in its ^{13}C NMR spectrum (cf. Ref. [13]).

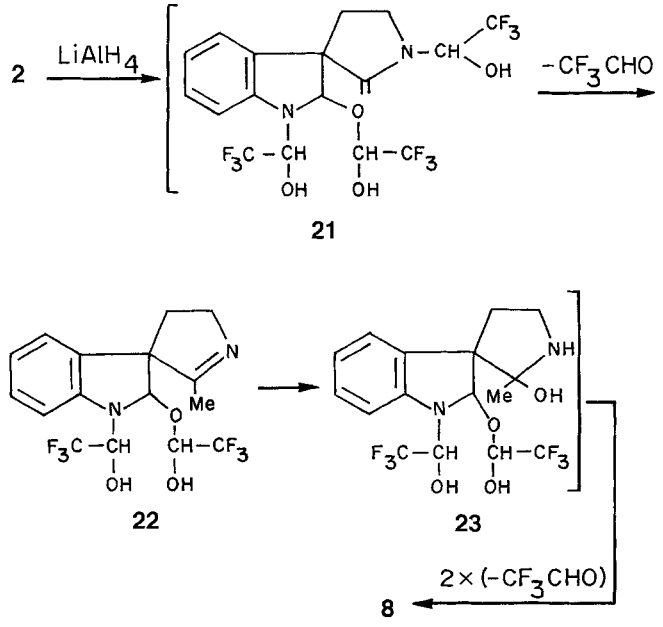
The sodium borohydride reduction of **2** gave tryptamine **7** only. However, its reduction with lithium aluminum hydride afforded an interesting product which has tentatively been assigned structure **8** from spectroscopic evidence. The resonance of its methyl protons and H-2 as two singlets at $\delta = 1.73$ and 1.78 ppm and two other singlets at $\delta = 8.64$ and 8.94 ppm, respectively, in its ^{1}H NMR spectrum indicated it to be a mixture (3:1) of two possible diastereoisomers. However, all attempts to separate them either as such or *via* derivatives were unsuccessful. Finally, catalytic hydrogenation of **2** afforded indoline **9** [2] with the enamine function still intact.



Scheme 1



Scheme 2



Scheme 3

The mechanisms of the reactions leading to **4–8** are suggested briefly in Schemes 1–3. These have some analogy to those reported in the literature [10–12].

Experimental

Melting points are uncorrected. UV spectra were recorded in aldehyde free 95% ethanol on a Varian Techtron Series 634 spectrophotometer, IR spectra as KBr pellets or as thin films on a Perkin Elmer 782 instrument, and NMR spectra in $CDCl_3$ on a Varian CFT-20 (80 MHz) or Bruker AM 300L (300 MHz) instrument using *TMS* (^1H and ^{13}C) as internal and CCl_3F (^{19}F) as external standard. Mass spectra were recorded on an AEIMS 30 or Jeol D-300 machine. Trifluoroacetic anhydride (*TFAA*) was prepared and diglyme, tetrahydrofuran (*THF*), and boron trifluoride etherate were purified just before use [14]. Petroleum ether indicates the fraction boiling from 60–80°C. Silica gel (60–120 mesh) was used for column chromatography.

Diborane reduction of **2**

To a cold solution of **2** (0.7 g, 0.0014 mol) in dry *THF* (20 ml), diborane (0.01 mol) generated externally from $NaBH_4$ (0.567 g, 0.015 mol) in dry diglyme (20 ml) and $BF_3 \cdot OEt_2$ (4.72 ml, 5.286 g, 0.037 mol) in dry diglyme (15 ml) was added in an oxygen-free dry nitrogen atmosphere. The reaction mixture was allowed to stand overnight at room temperature. Excess diborane was destroyed by slow addition of methanol (25 ml). The sample was then refluxed for 2 h and evaporated to dryness under reduced pressure. The residue was taken up in chloroform. The chloroform solution was successively washed with 5% $NaHCO_3$ solution and water and then dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on a silica gel column. Elution of the column with a mixture of petroleum ether–ether (9:1) gave **4**. Continued elution with a mixture of petroleum ether–ether (3:1) furnished **6**. Further elution of the column with a mixture of petroleum ether–ether (1:1) afforded **5**.

1-Trifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)-3-vinylindoline (**4**)

Colourless viscous liquid; yield: 110 mg (22%); IR: $\nu = 3300$–3400 (N–H), 1605 (C=C), 995, 920 ($CH{=}CH_2$) cm^{-1}; UV: $\lambda_{max} = 249$, 293 nm (characteristic of an indoline moiety); ^1H NMR ($CDCl_3$): $\delta = 1.82$–2.02 (2H, m, 1′-H_2), 2.54–2.81 (2H, m, 2′-H_2), 3.05 (2H, q, $J = 9.4$ Hz, NH-CH_2-CF_3), 3.35–3.81 (4H, m, 1-CH_2 and 2-H_2), 5.07 (1H, d, $J_{trans} = 17.2$ Hz, 2″-H_A), 5.11 (1H, d, $J_{cis} = 10.8$ Hz, 2″-H_B), 6.02 (1H, dd, $J = 17.2$ and 10.8 Hz, 1″-H_X), 6.47–7.13 (4H, m, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 38.83$ (C-1′), 45.32 (C-2′), 49.32 (C-3), 50.38 (NH-CH_2CF_3), 51.04 (1-CH_2CF_3), 64.89 (C-2), 106.74 (C-7), 113.21 (C-2″), 118.90 (C-5), 123.63 (C-4), 128.21 (C-6), 133.35 (C-8), 142.19 (C-1″), 149.75 (C-9) ppm; MS (EI): m/z (%) = 352 (60, M^+), 226 (100, M–$CH_2CH_2NHCH_2CF_3$), 225 (25), 156 (17, M–$CH_2CH_2NHCH_2CF_3$–H–CF_3), 143 (24, M–$CH_2CH_2NHCH_2CF_3$–CH_2CF_3), 127 (33, $CH_3CH_2NHCH_2CF_3$), 83 (40, $CF_3CH_2^+$); $C_{16}H_{18}F_6N_2$ (352.30); calcd.: C 54.55, H 5.14, N 7.95; found: C 54.80, H 5.00, N 8.15.

1-Hydroxytrifluoroethyl-3-(2′-(trifluoroethylamino)ethyl)indole (**5**)

M.p.: 136°C; pinkish prisms (petroleum ether); yield: 5.5 mg (1.14%); IR: $\nu = 3280\,cm^{-1}$ (OH and NH); UV: $\lambda_{max} = 222$, 269, 291 nm; ^1H NMR ($CDCl_3$): $\delta = 2.47$–2.67 (2H, br s, exchangeable with D_2O, NH and OH), 2.87–3.02 (4H, m, 3-CH_2-CH_2-NH), 3.10 (2H, q, $J = 9.37$ Hz, NH-CH_2CF_3), 6.10 (1H, q, $J = 4.9$ Hz, 1-C*H*OHCF_3), 7.15 (1H, s, 2-H), 7.18–7.43 (3H, m, Ar-H), 7.54–7.58 (1H, m, 7-H) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -72.42$ (3F, t, $J = 10$ Hz, NH-CH_2-CF_3), -82.37 (3F, d, $J = 6$ Hz, 1-CHOHCF_3) ppm; MS (FD): m/z (%) = 340 (100, M^+); MS (EI): m/z (%) = 340 (18, M^+),

242 (23, M–CF_3CHO), 229 (87, M–$CH_2=NCH_2CF_3$), 228 (86, M–$CH_2=NCH_2CF_3$–H), 131 (80, M–CF_3CHO–$CH_2=NCH_2CF_3$), 130 (100, M–CF_3CHO–$CH_2=NCH_2CF_3$–H), 112 (88, $CH_2=N^+H$-CH_2CF_3); $C_{14}H_{14}F_6N_2O$ (340.25); calcd.: C 49.42, H 4.14, N 8.23; found: C 49.20, H 4.25, N 8.37.

1-Methyl-2-trifluoroethyl-1,2,3,4-tetrahydro-β-carboline (**6**)

M.p.: 130°C; colourless needles (petroleum ether); yield: 4 mg (1.04%); IR: $\nu = 3380\,cm^{-1}$ (NH); UV: $\lambda_{max} = 226$, 274.5 nm; ^1H NMR ($CDCl_3$): $\delta = 1.48$ (3H, d, $J = 6.6$ Hz, 1-CH_3), 2.75 (2H, t, $J = 5.2$ Hz, 4-H_2), 3.01–3.42 (4H, m, 3-H_2 and N-CH_2CF_3), 3.97 (1H, q, $J = 6.6$ Hz, 1-H), 7.07–7.55 (4H, m, Ar-H), 7.66 (1H, br s, exchangeable with D_2O, NH) ppm; MS (EI): m/z (%) = 268 (25, M^+), 253 (100, M–CH_3), 157 (22, M–$CH_2=NCH_2CF_3$), 156 (16, M–$CH_2=NCH_2CF_3$–H), 144 (13); $C_{14}H_{15}F_3N_2$ (268.27); calcd.: C 62.68, H 5.63, N 10.44; found: C 62.49, H 5.71, N 10.31.

Sodium borohydride reduction of **2**

To a stirred solution of $NaBH_4$ (0.375 g, 0.01 mol) in absolute alcohol, a solution of **2** (0.49 g, 0.001 mol) in the same solvent was added, and stirring was continued for 30 min. After diluting with water, the mixture was extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The crude product thus obtained was chromatographed on a silica gel column. Elution with ethyl acetate-methanol (1:1) gave **7**.

N-Ethyltryptamine (**7**)

M.p.: 81°C (Ref. [15]: m.p.: 81–82°C); colourless needles (petroleum ether); yield: 20 mg (10.63%).

Lithium aluminum hydride reduction of **2**

To a stirred suspension of lithium aluminum hydride (1.5 g, 0.04 mol) in dry tetrahydrofuran (150 ml), a solution of **2** (1.495 g, 0.003 mol) in the same solvent (150 ml) was added, and stirring was continued for 8 h. After standing overnight, the mixture was treated cautiously with water followed by saturated *Rochelle* salt solution and filtered. The filtrate was extracted with ether and the extract dried (Na_2SO_4). The crude product obtained after removal of the solvent was chromatographed over a silica gel column. Elution with benzene and ethyl acetate (4:1) gave **8**.

Hydroxyspiroindolenine **8**

Light brown oil; yield: 450 mg (73%); IR: $\nu = 3240$–3360 (NH and OH), 1460 (C=N) cm^{-1}; UV: $\lambda_{max}^{EtOH}(\log \varepsilon) = 230$ (3.90), 236 (3.91), 252 (3.86), 283 (3.30), 292 (3.30) nm; $\lambda_{max}^{EtOH+2N\,HCL}$ ($\log \varepsilon$) = 231 (3.91, shoulder), 235 (3.90), 247 (3.81, shoulder), 268 (3.49, shoulder), 287 (3.33) nm; ^1H NMR ($CDCl_3$): $\delta = 1.73$ (0.75H, 2′-CH_3), 1.78 (2.25H, 2′-CH_3), 2.15–2.38 (1H, m, 4′-H_B), 2.69–2.86 (1H, m, 4′-H_A), 3.03–3.10 (2H, m, exchangeable with D_2O, NH and OH), 3.37 (1H, d, $J = 9.9$ Hz, 5′-H_B), 3.48 (1H, d, $J = 9.2$ Hz, 5′-H_A), 7.04–7.27 (3H, m, 4,5,6-H), 8.11 (1H, d, $J = 7.86$ Hz, 7-H), 8.64 (0.25H, s, 2-H), 8.94 (0.75H, s, 2-H) ppm; MS (FD): m/z (%) = 203 (17), 202 (100, M^+); MS (EI): m/z (%) = 202 (7, M^+), 199 (11), 187 (11, M–CH_3), 186 (38, M–CH_3–H), 174 (4, M–$CH_2=CH_2$), 173 (7, M–$CH_2=CH_2$–H), 159 (11, M–$COCH_3$), 158 (6), 146 (11), 145 (24), 144 (24, M–$CH_3C(OH)=NH+H$), 143 (28, M–$CH_3C(OH)=NH$), 131 (10), 130 (60, protonated quinolinium ion), 120 (9), 118 (12), 117 (100, indole), 116 (6), 115 (11), 103 (6, $C_6H_5CH=CH^+$); $C_{12}H_{14}N_2O$ (202.25); calcd.: C 71.26, H 6.98, N 13.85; found: C 71.03, H 7.15, N 13.96.

Catalytic hydrogenation of **2**

A solution of **2** (200 mg, 0.41 mmol) in ethyl acetate (75 ml) was hydrogenated with hydrogen and 10% palladium on charcoal at room temperature for 12 h and filtered. The solvent was removed under reduced pressure. The residue was chromatographed over a silica gel column. Elution with benzene afforded **9**.

Hydroxy-bis(trifluoroacetyl)enaminospiroindoline **9**

M.p.: 148°C (Ref. [2]: m.p.: 148–149°C); colourles needles (benzene); yield: 129 mg (80%).

Acknowledgements

The authors thank the *Central Drug Research Institute*, Lucknow, India, for the mass spectra. *H.M.* and *S.H.* are grateful to the U.G.C. and C.S.I.R., New Delhi, respectively, for the award of a fellowship.

References

[1] Biswas KM, Dhara RN, Mallik H, Halder S, Sinha-Chaudhuri A, De P, Brahmachari AS, Saha A (1997) Indian J Chem **36B**: 318
[2] Biswas KM, Jackson AH, Kobaisy MM, Shannon PVR (1992) J Chem Soc Perkin Trans 1, 461
[3] Biswas KM, Jackson AH, Tehrani M (1982) J Chem Soc Chem Commun 765
[4] Biswas KM, Dhara RN, Halder S, Mallik H, Sinha-Chaudhuri A, De P, Brahmachari AS (1993) Synthetic Commun **23**: 379
[5] Biswas KM, Jackson AH (1989) J Chem Soc Perkin Trans 1, 1981
[6] Biswas KM, Jackson AH (1983) J Chem Soc Chem Commun 85
[7] McKay AF, Vavasour GR (1954) Canad J Chem **32**: 639
[8] Bissell ER, Finger M (1959) J Org Chem **24**: 1256
[9] Weygand F, Frauendorfer E (1970) Chem Ber **103**: 2437
[10] Reduction (1991) In: Trost BM (ed) Comprehensive Organic Synthesis, vol 8. Pergamon Press, New York, pp 938–939
[11] Singaram B, Goralski CT, Rangaishenvi MV, Brown HC (1989) J Am Chem Soc **111**: 384
[12] Goralski CT, Singaram B, Brown HC (1987) J Org Chem **52**: 4014 and references cited therein
[13] Wenkert E, Buckwalter BL (1972) J Am Chem Soc **94**: 4367
[14] Brown HC (1975) Organic Synthesis via Boranes. Wiley, New York, pp 251–261
[15] Biswas KM, Jackson AH (1968) Tetrahedron **24**: 1145

Received June 25, 1997. Accepted July 7, 1997