HETEROCYCLES, Vol.53, No.8, 2000, p.1783 - 1788, Received, 15th May, 2000

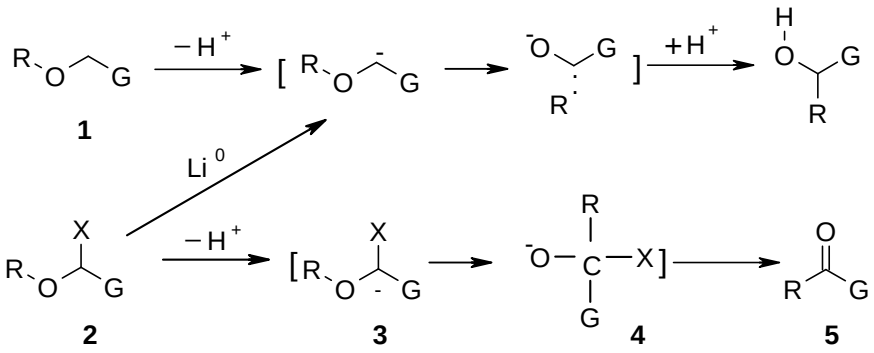
BENZOTRIAZOLE–MEDIATED [1,2]-WITTIG REARRANGEMENT. THE PREPARATION OF HOMOALCOHOLS FROM ETHERS

Alan R. Katritzky* and Yunfeng Fang

Center for Heterocyclic Compounds, Department of Chemistry,
University of Florida, Gainesville, FL 32611-7200, USA

Abstract - α-(Benzotriazol-1-yl)alkyl benzyl ethers (**6a-e**) undergo [1,2]-Wittig rearrangement upon treatment with 2 equiv of organolithium reagents.

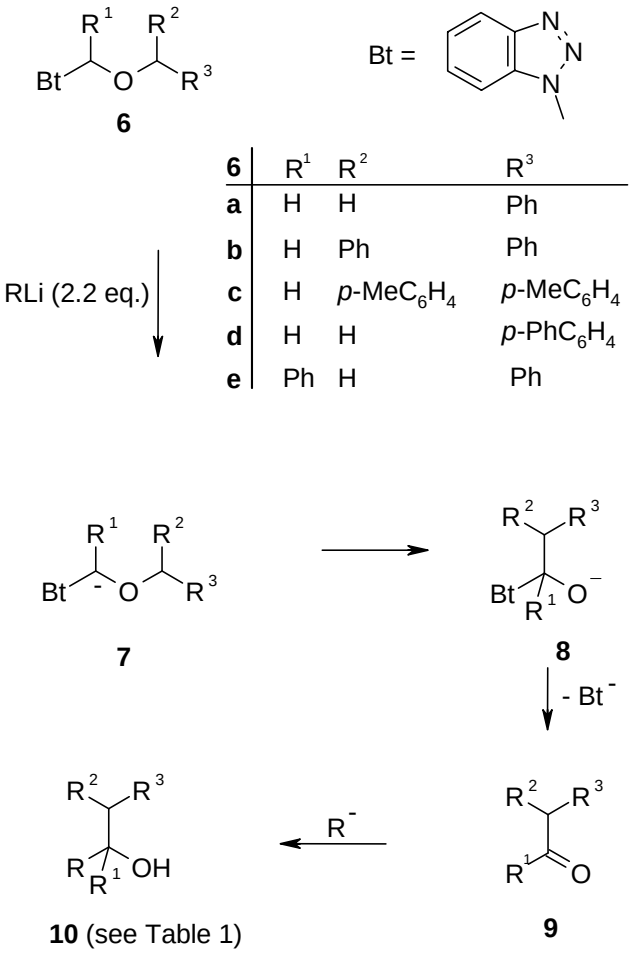
Georg Wittig and Lisa Löhmann described the [1,2]-alkyl shift of benzylic ethers by the action of phenyllithium in 1942.[1] Previous studies of this type of carbanion rearrangement, now called the [1,2]-Wittig rearrangement, have delineated its mechanism, stereochemistry, scope and limitations.[2a-f] Several mechanisms were considered, but it is now widely accepted that the [1,2]-Wittig rearrangement proceeds by homolysis of an ether α-anion intermediate and recombination of the radical and radical anion fragments (equation 1).[2b,c]



equation 1

The substrates which undergo [1,2]-Wittig rearrangements can be divided into three categories:
(1) CH_2 deprotonation is allowed in **1** when G is a CC-multiply bonded group (equation 1) (e.g., vinyl,[3a-d] ethynyl[2e,3c,4] or aryl[3b,c,5]).
(2) in **2**, X is a group that can be exchanged for a lithium atom by the action of RLi (equation 1) (e.g., SePh,[6a,b] SPh,[7a,b] $SnBu_3$[2d,8a,b] and $SiMe_3$[9]).

(3) Cyano,[10] imidazolium and benzimidazolium[11] groups X can function as both an electron-withdrawing and a leaving group in the rearrangement process **2→3→4** to furnish a carbonyl compound (**5**) (equation 1).



6	R^1	R^2	R^3
a	H	H	Ph
b	H	Ph	Ph
c	H	*p*-MeC_6H_4	*p*-MeC_6H_4
d	H	H	*p*-PhC_6H_4
e	Ph	H	Ph

Scheme 1

The benzotriazole group is both a good anion-stabilizing group and a good leaving group[12] and, indeed, acts as such in inducing [2,3]-Wittig rearrangements.[13] We now report that benzotriazole derivatives (**6**) can be readily lithiated and the resulting anions undergo [1,2]-Wittig rearrangement to afford homoalcohols (**10**) by subsequent carbanion addition to the initially formed carbonyl compounds (**9**).

Preparation of α-(Benzotriazol-1-yl)alkyl Ethers (6a-e). Alkylation of R^2R^3CHOH with *t*-BuOK and 1-(chloromethyl)benzotriazole in anhydrous DMSO gave the corresponding α-(benzotriazol-1-yl)alkyl ethers (**6a-d**) in 70–88% yields. 1-[(Benzyloxy)(phenyl)methyl)]-1*H*-1,2,3-benzotriazole (**6e**) was prepared following literature procedures in 40% yield.[14] Compounds (**6a-d)** were fully characterized by their NMR spectra and elemental analyses.

[1,2]-Wittig Rearrangement of α-(Benzotriazol-1-yl)alkyl Ethers (6a-f) under the Action of RLi. Treatment of compound (**6a**) with 2.2 equiv of *n*-BuLi (THF, -78 °C to rt) gave 11% (GC/MS) of product (**10a**). This transformation is envisaged to proceed *via* deprotonation of **6a** to **7a** followed by [1,2]-Wittig rearrangement to form intermediate (**8a**), which undergoes expulsion of the benzotriazole anion to form ketone (**9a**) and subsequent *in situ* nucleophilic addition of second molecule of the lithium reagent to give **10a**, albeit in low yield. Compounds (**6b-d**), with migrating groups which are more radical-stabilized, on exposure to 2.2 equiv. *n*-BuLi from –78 °C to rt gave in 30–43% yields **10b-d** which were fully characterized by NMR spectra and elemental analysis. Treatment of compounds (**6b**) and (**6d**) with 2.2 equiv PhLi gave products (**10e**) and (**10f**) in 50% and 54% yields, respectively. We further used compound (**6e**) to perform the rearrangement reaction by treating **6e** with *n*-BuLi. Compared to compound (**6a**), **6e** has a phenyl group in the benzotriazole terminus which will make the carbanion terminus generated by deprotonation more stable compared to the thus formed anion of **6a**. This will also help the rearrangement reaction. Indeed, the reaction went smoothly when compound (**6e**) was treated by *n*-BuLi and the desired product (**10g**) was obtained in 47% yield.

For all the successful rearrangements **6→10**, the migrating group was benzyl or substituted benzyl. In other cases, *o*-iminophenyl anions are formed by opening of the benzotriazole ring and subsequent nitrogen extrusion from starting materials of type (**6**) as previously reported.[15] Thus rearrangements **6→10** are preferred compared to the ring opening if the migrating group can stabilize a radical species.

Table 1. Reactions of α-(Benzotriazol-1-yl)alkyl Ethers (6a-e) with RLi.

entry	starting material	product R	R^1	R^2	R^3	yield (%)
10a	**6a**	*n*-Bu	H	H	Ph	11(GC/MS)
10b	**6b**	*n*-Bu	H	Ph	Ph	40
10c	**6c**	*n*-Bu	H	*p*-MeC_6H_4	*p*-MeC_6H_4	43
10d	**6d**	*n*-Bu	H	H	*p*-PhC_6H_4	30
10e	**6b**	Ph	H	Ph	Ph	50
10f	**6d**	Ph	H	H	*p*-PhC_6H_4	54
10g	**6e**	*n*-Bu	Ph	H	Ph	47

In conclusion, α-(benzotriazol-1-yl)alkyl ethers can undergo [1,2]-Wittig rearrangement under the action of RLi, which extends the type of starting materials that undergo [1,2]-Wittig rearrangement.

EXPERIMENTAL

General Comments. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using the solvent peak ($CDCl_3$, δ = 77.0 ppm) as reference. Microanalyses were carried out using a Carlo erba 1106 elemental analyzer. Tetrahydrofuran was freshly distilled from sodium-benzophenone.

General Procedure for the [1,2]-Wittig Rearrangements of α-(Benzotriazol-1-yl)alkyl Ethers (6a-f): To a solution of **6a-e** (1.0 mmol) in dry THF (10 mL) at – 78 °C was added dropwise RLi (2.2 mmol). The solution was allowed to reach rt overnight. The reaction was quenched by the addition of water (10 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed to furnish an oily residue which was subjected to column to yield the product (**10b-g**).

1-[(Benzhydryloxy)methyl]-1*H*-1,2,3-benzotriazole (6b): mp 104–106 °C (Hexanes / Ethyl acetate). Y = 88%. ^{1}H NMR δ 5.49 (s, 1H), 6.05 (s, 2H), 7.20–7.35 (m, 10H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 74.5, 80.9, 109.9, 120.0, 124.3, 127.3, 127.9, 128.4, 132.9, 140.1, 146.3. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.38; H, 5.71; N, 13.45.

1-{[Bis(4-methylphenyl)methoxy]methyl}-1*H*-1,2,3-benzotriazole (6c): mp 102–104 °C (Hexanes / Ethyl acetate). Y = 70%. ^{1}H NMR δ 2.29 (s, 6H), 5.39 (s, 1H), 6.02 (s, 2H), 7.05–7.16 (m, 8H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 21.1, 74.4, 80.6, 110.0, 119.9, 124.2, 126.4, 127.2, 127.8, 129.1, 132.9, 137.3, 137.5, 146.3. Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 77.32; H, 6.41; N, 12.33.

1-[([1,1'-Biphenyl]-4-ylmethoxy)methyl]-1*H*-1,2,3-benzotriazole (6d): mp 108–109 °C (Hexanes / Ethyl acetate). Y = 76%. ^{1}H NMR δ 4.55 (s, 2H), 6.08 (s, 2H), 7.32–7.50 (m, 6H), 7.50–7.64 (m, 5H), 7.70 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 70.5, 76.0, 109.9, 120.0, 124.4, 127.0,

127.2, 127.4, 128.0, 128.6, 128.7, 132.8, 135.0, 140.6, 141.1, 146.4. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.40; H, 5.65; N, 13.37.

1,1-Diphenyl-2-hexanol (10b): mp 54–56 °C (Hexanes / Ethyl acetate). Y = 40%. ^{1}H NMR δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.20–1.42 (m, 4H), 1.42–1.56 (m, 2H), 1.57 (d, *J* = 1.2 Hz, 1H), 3.88 (d, *J* = 8.4 Hz, 1H), 4.34 (br s, 1H), 7.19–7.44 (m, 10H); ^{13}C NMR δ 14.0, 22.6, 28.0, 34.7, 58.8, 73.7, 126.5, 126.8, 128.2, 128.5, 128.6, 128.8, 129.6. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.13; H, 9.10.

1,1-Bis(4-methylphenyl)-2-hexanol (10c): mp 76–78 °C (Hexanes / Ethyl acetate). Y = 43%.^{1}H NMR δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.20–1.40 (m, 4H), 1.40–1.56 (m, 2H), 1.58 (s, 1H), 2.28 (s, 3H), 2.29 (s, 3H), 3.80 (d, *J* = 8.3 Hz, 1H), 4.29 (br s, 1H), 7.03–7.20 (m, 6H), 7.20–7.30 (m, 2H); ^{13}C NMR δ 14.1, 21.0, 22.7, 28.1, 34.7, 58.0, 73.7, 127.9, 128.5, 129.2, 129.5, 135.8, 136.2, 138.6, 139.7. Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.82; H, 9.68.

1-(1,1'-Biphenyl)-4-yl-2-hexanol (10d): mp 72–74 °C (Hexanes / Ethyl acetate). Y = 30%. ^{1}H NMR δ 0.91 (t, *J* = 6.7 Hz, 3H), 1.25–1.40 (m, 4H), 1.40–1.60 (m, 2H), 1.73 (br s, 1H), 2.60–2.75 (m, 1H), 2.80–2.90 (m, 1H), 3.80 (br s, 1H), 7.20–7.32 (m, 2H), 7.32–7.46 (m, 2H), 7.46–7.70 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 27.9, 36.5, 43.6, 72.6, 126.9, 127.1, 128.6, 129.8, 137.7, 139.2, 140.8. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.16; H, 9.05.

1,2,2-Triphenyl-1-ethanol (10e): mp 76–78 °C (Hexanes / Ethyl acetate). Y = 50%. ^{1}H NMR δ 2.13 (d, *J* = 2.8 Hz, 1H), 4.25 (d, *J* = 8.9 Hz, 1H), 5.38 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.06–7.11 (m, 5H), 7.19–7.28 (m, 6H), 7.30–7.38 (m, 2H), 7.38–7.42 (m, 2H); ^{13}C NMR δ 60.3, 76.8, 126.3, 126.8, 126.9, 127.5, 128.0, 128.2, 128.5, 128.7, 128.9, 140.8, 141.4, 142.1. Anal. Calcd for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.29; H, 6.90.

2-(1,1'-Biphenyl)-4-yl-1-phenyl-1-ethanol (10f): mp 105–108 °C (Hexanes / Ethyl acetate). Y = 54%. ^{1}H NMR δ 2.05 (d, *J* = 2.3 Hz, 1H), 2.96–3.09 (m, 2H), 4.90 (br s, 1H), 7.20–7.50 (m, 10H), 7.50–7.70 (m, 4H); ^{13}C NMR δ 45.7, 75.3, 125.9, 127.0, 127.1, 127.6, 128.4, 128.7, 129.9, 137.1, 139.4, 140.8, 143.8. Anal. Calcd for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.45; H, 6.69.

1,2-Diphenyl-2-hexanol (10g): Oil. Y = 47%. ^{1}H NMR δ 0.81 (t, *J* = 7.1 Hz, 3H), 0.92–1.08 (m, 1H), 1.16–1.24 (m, 3H), 1.70–1.84 (m, 2H), 3.04, 3.15 (AB, *J* = 13.4 Hz, 2H), 6.90–7.00 (m, 2H), 7.10–7.40

(m, 8H); ^{13}C NMR δ 14.0, 23.0, 25.6, 41.8, 49.7, 76.7, 125.4, 126.3, 126.6, 127.9, 128.0, 130.6, 133.1, 136.3. HRMS (CI) *m/z* calcd for $C_{18}H_{21}$ $(M + 1)^+$-H_2O: 237.1643. Found $(M + 1)^+$-H_2O: 237.1625.

REFERENCES

1. G. Wittig and L. Löhmann, *Ann.*, 1942, **550**, 260.
2. (a) U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 763. (b) J. A. Marshall, 'Comprehensive Organic Synthesis,' Vol. 3, eds. by B. M. Trost, and I. Fleming, Pergamon Press, Oxford, 1991, pp. 975 – 1013. (c) K. Tomooka, H. Yamamoto, and T. Nakai, *Liebigs Ann. Chem.*, 1997, 1275. (d) R. E. Maleczka, Jr, and F. Geng, *J. Am. Chem. Soc.*, 1998, **120**, 8551. (e) K. Tomooka, M. Kikuchi, K. Igawa, P.-H. Keong, and T. Nakai, *Tetrahedron Lett.*, 1999, **40**, 1917. (f) J. C. Sheldon, M. S. Taylor, J. H. Bowie, S. Dua, C. S. B. Chia, and P. C. H. Eichinger, *J. Chem. Soc., Perkin Trans. 2*, 1999, 333.
3. (a) S. L. Schreiber and M. T. Goulet, *Tetrahedron Lett.*, 1987, **28**, 1043. (b) S. Kiyooka, T. Tsutsui, and T. Kira, *Tetrahedron Lett.*, 1996, **37**, 8903. (c) K. Tomooka, H. Yamamoto, and T. Nakai, *J. Am. Chem. Soc.*, 1996, **118**, 3317. (d) S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, and B. A. Keay, *J. Am. Chem. Soc.*, 1996, **118**, 10766.
4. P. Bertrand, J.-P. Gesson, B. Renoux, and I. Tranoy, *Tetrahedron Lett.*, 1995, **36**, 4073.
5. S. Superchi, N. Sotomayor, G. Miao, B. Joseph, M. G. Campbell, and V. Snieckus, *Tetrahedron Lett.*, 1996, **37**, 6061.
6. (a) R. Hoffmann and R. Brückner, *Chem. Ber.*, 1992, **125**, 1957. (b) R. Hoffmann, T. Rückert, and R. Brückner, *Tetrahedron Lett.*, 1993, **34**, 297.
7. (a) E. J. Verner and T. Cohen, *J. Am. Chem. Soc.*, 1992, **114**, 375. (b) E. J. Verner, and T. Cohen, *J. Org. Chem.*, 1992, **57**, 1072.
8. (a) K. Tomooka, T. Igarashi, and T. Nakai, *Tetrahedron Lett.*, 1993, **34**, 8139. (b) K. Tomooka, T. Igarashi, and T. Nakai, *Tetrahedron*, 1994, **50**, 5927.
9. (a) R. E. Maleczka, Jr. and F. Geng, *Org. Lett.*, 1999, **1**, 1115. (b) R. E. Maleczka, Jr. and F. Geng, *Org. Lett.*, 1999, **1**, 1111.
10. J. Cast, T. S. Stevens, and J. Holmes, *J. Chem. Soc.*, 1960, 3521.
11. A. Miyashita, Y. Matsuoka, Y. Suzuki, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*, 1997, **45**, 1235.
12. A. R. Katritzky, X. Lan, J. Z. Yang, and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
13. A. R. Katritzky, H. Wu, and L. Xie, *J. Org. Chem.*, 1996, **61**, 4035.
14. A. R. Katritzky, M. V. Voronkov, A. Pastor, and D. Tatham, *Heterocycles*, 1999, **51**, 1877.
15. A. R. Katritzky, G. Zhang, and J. Jiang, *J. Org. Chem.*, 1995, **60**, 7625.