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The Mitsunobu Reaction: An Alternative Synthesis of 1-(Primary Alkyl)benzotriazoles

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THE MITSUNOBU REACTION: AN ALTERNATIVE SYNTHESIS OF 1-(PRIMARY ALKYL)BENZOTRIAZOLES

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Abstract - 1-(Primary alkyl)benzotriazoles are obtained in convenient yields by treating the corresponding alcohol with triphenylphosphine, *N*-bromosuccinimide and benzotriazole. Under these conditions, the alcohols gave exclusively the corresponding 1-alkyl-benzotriazoles. Allyl and propargyl alcohols also reacted regiospecifically in a typical S_N2 manner, and no products derived from prototropic rearrangement were found.

Displacement of the hydroxy group of alcohols under Mitsunobu conditions is a highly versatile synthetic procedure[1] as demonstrated by the abundance of applications reported over the last twenty years. The reaction has been sparsely utilized in heterocyclic chemistry, but it has recently gained attention as an alternative to condensations of nitrogen nucleophiles bearing acidic N-H protons, being employed to functionalize imides,[2] purines and imidazoles,[3] and to alkylate tetrazoles.[4] Conversion of hydroxy groups into primary amino groups is

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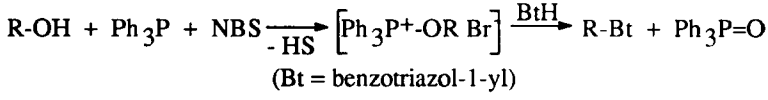
conveniently achieved *via* azides by a one-pot Mitsunobu protocol.[5] Moreover, primary amines can be further converted into secondary and secondary into tertiary amines, *via* sulfonamides,[6] or by using preformed alkylphosphonium salts.[7]

A reported alkylation of amines using an alternative Mitsunobu procedure, in which the alcohols were activated by *N*-bromosuccinimide (NBS)[8] instead of diethyl azodicarboxylate (DEAD), prompted us to attempt a corresponding easy route to 1-alkylbenzotriazoles. 1-Alkylbenzotriazoles are valuable intermediates used in benzotriazole-mediated syntheses.[9-11] They are normally obtained by reacting the corresponding bromoderivatives with benzotriazole in basic conditions.[11-13] Two other methods: the thermal decarboxylation of 1-(alkoxycarbonyl)benzotriazoles[14] and the reaction of 1,1'-sulfonyldibenzotriazole with sodium alkoxides[15] have seldom been used for preparative purposes.

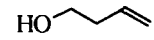
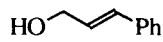
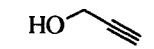
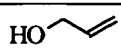
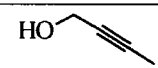
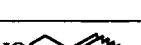
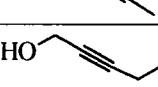
The Mitsunobu reaction proceeds with low yields for secondary and rarely for tertiary alcohols,[1] therefore the limitations of our new method are *a priori* defined. The procedure described below provides an easy way to react primary alcohols with benzotriazole to afford 1-(primary alkyl)benzotriazoles, and offers a useful alternative for the synthesis of these versatile compounds. The abovementioned general limitation does not impede its usefulness as, provided 1-(primary alkyl)benzotriazoles are available, a higher substitution at the α-carbon leading to 1-(1-substituted)alkylbenzotriazoles can be easily achieved, by lithiation and subsequent alkylation of the 1-(primary alkyl)benzotriazole congeners.[9,11]

Results and Discussion

The reaction between an alcohol and benzotriazole in the presence of triphenylphosphine and *N*-bromosuccinimide probably occurs *via* the alkoxyphosphonium salt **2**, which subsequently reacts with the acidic N-H bond in benzotriazole. Only the 1-benzotriazole isomer was obtained.



(Bt = benzotriazol-1-yl)

1		2	3
1a	MeOH	**1f**	
1b	$nC_6H_{13}OH$	**1g**	
1c		**1h**	
1d		**1i**	
1e		**1j**	

No alcohol was detected in the reaction mixture after 5 min, which implies that this first step was quantitative. Secondary alcohols reacted in low yields, while tertiary alcohols did not react at all. 2-Propanol and borneol gave the expected products in very low yields, as shown by the NMR analysis of the reaction mixtures (less than 10% of the expected products, and isolations were not attempted). Allyl alcohol and 3-buten-1-ol reacted in good yields without any of the prototropic rearrangement which reportedly occured during some Mitsunobu reactions.[16,17] Acetylene alcohols **1h-j** formed only 1-(2-acetylene)-methyl-benzotriazoles **3h-j** and did not isomerize to the corresponding allene derivatives,

as reported to occur during the synthesis of compound **3h** from propargyl bromide and benzotriazole.[18]

The low yields for secondary alcohols and the absence of the isomerization for alcohols with double and triple bonds led to the conclusion that benzotriazole attacks the alkylphosphonium ion by an SN_2 mechanism, similar to the Mitsunobu esterification.[19]

In conclusion, the method presented above is an efficient way of preparing 1-(primary alkyl)benzotriazoles from the corresponding alcohols.

Experimental

^1H And ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, on a Varian Gemini 300 spectrometer with tetramethylsilane or $CDCl_3$ as the internal standards. TLC was carried out on pre-coated plates (silica gel G60) purchased from Fisher using as solvent a mixture $CHCl_3$:Et_2O (95:5). Column chromatography separations were carried out on silica gel G60 (200-450 mesh) purchased from Fisher. Melting points were determined on a Koefler hot-stage microscope and are uncorrected. Yields were not optimized.

General Procedure for the Preparation of Compounds 3a-h. To a stirred solution of triphenylphosphine (10 mmol, 2.62 g) and alcohol (10 mmol) in anhydrous THF (8 mL), at -18 °C, was added *N*-bromosuccinimide (10 mmol, 1.78 g) over 2-4 min in small portions. After about 5 min, solid benzotriazole (24 mmol, 2.86 g) was added in one portion, and stirring was continued until the reaction mixture reached room temperature. The mixture was heated at reflux for

12-24 hr (the reaction was monitored by GC and ^{1}H NMR, and was stopped when the ratio between the free benzotriazole and the product became constant). The solvent was removed by distillation under vacuum, the residue dissolved in methylene chloride and subsequently washed with an aqueous solution of sodium carbonate 5% (50 mL) and a saturated aqueous solution of ammonium chloride (50 mL). The organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. The product was separated from triphenylphosphin oxide and benzotriazole by dry flash vacuum chromatography or by flash column chromatography, using as solvent gradient mixtures of methylene chloride:hexanes (from 1:2 to 2:1).

1-(Methyl)benzotriazole (3a). Yield 60 % (lit.[12] yield 55 %). White crystals (ethanol), m.p. 64-65 °C (lit.[12] m.p. 65 °C). ^{1}H NMR ($CDCl_3$) δ (ppm) 4.26 (s,3H), 7.40-7.50 (m, 1H), 7.50-7.60 (m, 2H), 8.12 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 33.9 (Bt-$\underline{CH_3}$), 110.0, 119.5, 123.6, 127.0, 133.2, 145.6.

1-(*n*-Hexyl)benzotriazole (3b). Yield 60 % (lit.[11] yield 43 %). Oil (lit.[11] oil). ^{1}H NMR ($CDCl_3$) δ (ppm) 0.72 (t, 3H, *J* = 7.3 Hz), 1.10-1.30 (m, 6H), 1.80-1.95 (m, 2H), 4.48 (t, 2H, *J* = 7.2 Hz), 7.21 (t, 1H, *J* = 8.3 Hz), 7.32 (t, 1H, *J* = 8.3 Hz), 7.40 (d, 1H, *J* = 8.3 Hz), 7.91 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.8, 22.3, 26.3, 29.6, 31.1, 48.2 (Bt-$\underline{CH_2}$), 109.3, 119.9, 123.8, 127.1, 132.9, 145.8.

1-(Benzyl)benzotriazole (3c). Yield 85 % (lit.[13] yield 65 %). White crystals (ethanol), m.p. 115-116 °C (lit.[13] m.p. 115-116 °C). ^{1}H NMR ($CDCl_3$) δ (ppm)

5.80 (s, 2H), 7.20-7.30 (m, 6H), 7.30-7.40 (m, 2H), 8.05 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 51.9 (Bt-$\underline{CH_2}$), 109.6, 119.7, 123.7, 127.2, 127.3, 128.2, 128.7, 132.6, 134.6, 146.0.

1-(Prop-2-enyl)benzotriazole (3d). Yield 75 % (lit.[9] yield 50 %). Oil (lit.[9,13] oil). ^{1}H NMR ($CDCl_3$) δ (ppm) 5.19-5.38 (m, 4H), 5.96-6.14 (m, 1H), 7.37 (t, 1H, J = 8.3 Hz), 7.47 (t, 1H, J = 8.3 Hz), 7.52 (d, 1H, J = 8.3 Hz), 8.06 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 50.4 (Bt-$\underline{CH_2}$), 109.4, 118.8, 119.5, 123.5, 126.9, 130.9, 132.5, 145.7.

1-(But-2-enyl)benzotriazole (3e). Yield 65 %. Oil. Mixture of *cis* and *trans* isomers 1:5. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.70 (dd, 3H, J = 6.7, 2.0 Hz, *cis+trans*), 5.31 (*trans*) [5.20 (*cis*)] (dd, 1H, J = 7.0, 1.5 Hz), 5.69 (dtq, 1H, J = 17.0, 7.0, 2.0 Hz), 5.83 (dtq, 1H, J = 17.0, 6.7, 1.5 Hz), 7.35 (t, 1H, J = 8.3 Hz), 7.46 (t, 1H, J = 8.3 Hz), 7.53 (d, 1H, J = 8.3 Hz), 8.05 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) for the *trans* isomer: 17.5, 50.4 (Bt-$\underline{CH_2}$), 109.7, 119.8, 123.8, 124.0, 127.1, 131.2, 132.7, 145.9. HRMS m/e (M+1) POS FAB Calcd for $C_{10}H_{12}N_3$ 174.1031. Found 174.1030.

1-(But-3-enyl)benzotriazole (3f). Yield 70 %. Oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 2.74 (q, 2H, J = 7.0 Hz), 4.65 (t, 2H, J = 7.0 Hz), 5.01 (d, 1H, J = 9.3 Hz), 5.03 (d, 1H, J = 17.0 Hz), 5.77 (ddt, 1H, J = 17.0, 9.3, 7.0 Hz), 7.40-7.60 (m, 3H), 8.03 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 33.6, 47.3 (Bt-$\underline{CH_2}$), 109.1, 117.9, 119.6, 123.5, 126.9, 132.7, 133.1, 145.6. HRMS m/e (M+1) POS FAB Calcd for $C_{10}H_{12}N_3$ 174.1031. Found 174.1033.

1-(3-Phenyl-prop-2-enyl)benzotriazole (3g). Yield 80 % (lit.[20] yield 32 %). White crystals (ethanol), m.p. 78°C (lit.[20] m.p. 75-76 °C). ^{1}H NMR ($CDCl_3$) δ (ppm) 5.37 (dd, 2H, *J* = 6.2, 1.4 Hz), 6.34 (dt, 1H, *J* = 15.8, 3.2 Hz), 6.68 (dt, 1H, *J* = 15.8, 1.4 Hz), 7.20-7.35 (m, 6H), 7.41 (t, 1H, *J* = 8.3 Hz), 7.52 (d, 1H, *J* = 8.3 Hz), 8.05 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 50.3 (Bt-$\underline{CH_2}$), 109.6, 119.7, 122.0, 123.7, 126.4, 127.1, 128.1, 128.4, 132.7, 134.1, 135.4, 146.0.

1-(Prop-2-ynyl)benzotriazole (3h). Yield 80 % (lit.[11] yield 60 %). Yellow crystals (ethanol), m.p. 57 °C (lit.[11] m.p. 57-58 °C). ^{1}H NMR ($CDCl_3$) δ (ppm) 2.53 (t, 1H, *J* = 2.6 Hz), 5.47 (d, 2H, *J* = 2.6 Hz), 7.45 (t, 1H, *J* = 8.2 Hz), 7.54 (t, 1H, *J* = 8.2 Hz), 7.73 (d, 1H, *J* = 8.2 Hz), 8.10 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 38.0 (Bt-$\underline{CH_2}$), 75.0, 75.2, 109.7, 120.1, 124.2, 127.7, 132.4, 146.2.

1-(But-2-ynyl)benzotriazole (3i). Yield 84 %. White crystals (ethanol), m.p. 81 °C. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.82 (t, 3H, *J* = 2.5 Hz), 5.40 (q, 2H, *J* = 2.5 Hz), 7.39 (t, 1H, *J* = 8.5 Hz), 7.51 (t, 1H, *J* = 8.5 Hz), 7.71 (d, 1H, *J* = 8.5 Hz), 8.08 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 3.4, 38.5 (Bt-$\underline{CH_2}$), 70.8, 82.9, 109.9, 119.9, 123.9, 127.3, 132.4, 146.1. (Found: C, 69.97; H, 5.31; N, 24.89. Calc. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54).

1-(Pent-2-ynyl)benzotriazole (3j). Yield 80 %. White-yellow crystals (ethanol), m.p. 71-72 °C. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.13 (t, 3H, *J* = 6.7 Hz), 2.21 (qt, 2H, *J* = 6.7, 2.2 Hz), 5.41 (t, 2H, *J* = 2.2 Hz), 7.39 (t, 1H, *J* = 8.3 Hz), 7.51

(t, 1H, J = 8.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 8.08 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 12.2, 13.3, 38.5 (Bt-$\underline{CH_2}$), 71.0, 88.7, 110.0, 119.8, 123.9, 127.3, 132.4, 146.1. (Found: N, 22.46. Calc. for $C_{11}H_{11}N_3$: N, 22.69).

References

1. Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.
2. Qü, J.; Ishimura, Y. and Nagato, N. *Nippon Kagaku Kaishi* **1996**, 525.
3. Mitsunobu, O. *Synthesis* **1981**, 1.
4. Purchase, C. F. II and White, A. D. *Synth. Commun.* **1996**, *26*, 2687.
5. Fabiano, E.; Golding, B. T. and Sadeghi, M. M. *Synthesis* **1987**, 190.
6. Edwards, M. L.; Stemerick, D. M. and McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417.
7. Castro, B. and Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 4368.
8. Frøyen, P. and Juvvik, P. *Tetrahedron Lett.* **1995**, *36*, 9555.
9. Katritzky, A. R.; Li, J. and Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843.
10. Katritzky, A. R. and Lan, X. *Chem. Soc. Rev.* **1994**, 363.
11. Katritzky, A. R.; Wu, J.; Kuzmierkiewicz, W. and Rachwal, S *Liebigs Ann. Chem.* **1994**, 1.
12. Krollpfeiffer, F.; Rosenberg, A. and Mühlhausen, C. *Liebigs Ann. Chem.* **1935**, *515*, 113.
13. Krollpfeiffer, F.; Pötz, H. and Rosenberg, A. *Chem. Ber.* **1938**, *71*, 596.
14. Katritzky, A. R.; Zhang, G.-F.; Fan, W.-Q.; Wu, J. and Pernak, J. *J. Phys. Org. Chem.* **1993**, *6*, 567.

15. Katritzky, A. R.; Zhang, G.-F.; Pernak, J. and Fan, W.-Q. *Heterocycles* **1993**, *36*, 1253.

16. Burke, S. D.; Pacofsky, G. J. and Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228.

17. Koreeda, M. and Visger, D. C. *Tetrahedron Lett.* **1992**, *33*, 6603.

18. Katritzky, A. R.; Li, J. and Gordeev, M. F. *J. Org. Chem.* **1993**, *58*, 3038.

19. Hughes, D. L.; Reamer, R. A.; Bergan, J. J. and Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

20. Arnau, N.; Arredondo, Y.; Moreno-Mañas, M.; Pleixats, R. and Villarroya, M. *J. Heterocycl. Chem.* **1995**, *32*, 1325.

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