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The Preparation of 1,5-Dioxygenated-pent-2-ynes

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Abstract: 1,5-Dioxygenated-pent-2-ynes were prepared *via* the reductive lithiations of 4-alkoxybut-2-ynylbenzotriazoles and subsequent condensations with ketones and aldehydes.

Functionalisation of dialkylacetylenes is of considerable importance in synthesis.[1a-e] In particular, α,α'-dioxygenated dialkylacetylenes have great utility.[2a-d] β,β'-Dioxygenated dialkylacetylenes have also been investigated, although to a lesser extent.[3a-b] The analogous α,β'-dioxygenated dialkylacetylenes are thus of interest; however, the only report that we could locate on such compounds is that of Nikitin *et al.* who prepared α,β,β'-trioxygenated dialkylacetylenes, some of which exhibited physiological activity.[4] We now report a versatile route to α,β'-dioxygenated dialkylacetylenes by the reductive debenzotriazolylation of readily available 4-alkoxybut-2-ynylbenzotriazoles, and subsequent trapping of the carbanions with carbonyl compounds. The present work was based on recent reports from our laboratory which demonstrated that *N*-allyl-[5a-b], *N*-benzyl-[5a,6] and *N*-(α-aminoalkyl)-benzotriazoles[7] could be converted into the corresponding carbanions *via* *C*-benzotriazole bond (a C-N type) scissions in reductive lithiations.

1-Propargylbenzotriazole (**1**) was prepared in 85% yield from benzotriazole and propargyl bromide, using sodium hydride as a base, at room temperature.[8] The lithiation of 1-propargylbenzotriazole (**1**) with butyllithium in THF was followed by reaction with either a ketone or an aldehyde and then with methyl iodide to give compounds **2a-e** in 35-50% yield. Compound **2a** was treated with lithium/lithium bromide in the presence of 3-pentanone in THF at -78 °C for 4 h. The development of a dark-green color indicated that the reaction had reached completion. After quenching the reaction with water at -78 °C, protected dihydroxy-acetylene **3a** was obtained in 60% yield. Aromatic and aliphatic aldehydes were also used as electrophiles to afford **3b-d** in 50-69% yield. Compound **1** was treated with lithium/lithium bromide in the presence of *p*-methylbenzaldehyde in THF at -78 °C for 4 h to give β-acetylenic alcohol **4** in 56% yield with the acetylenic proton remaining intact.

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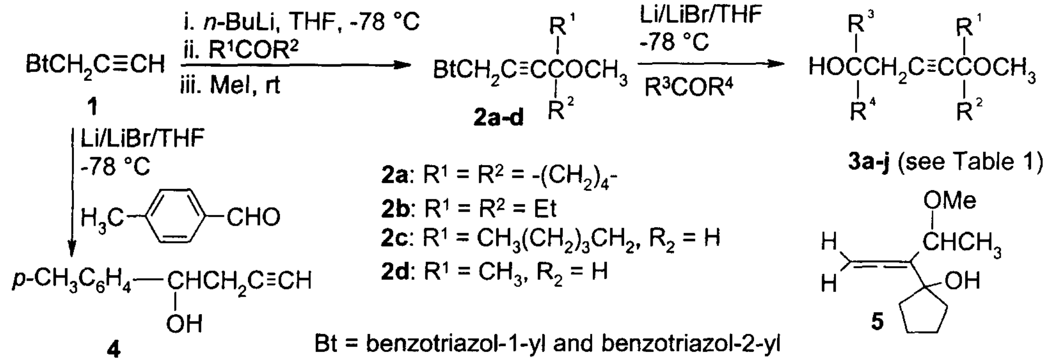


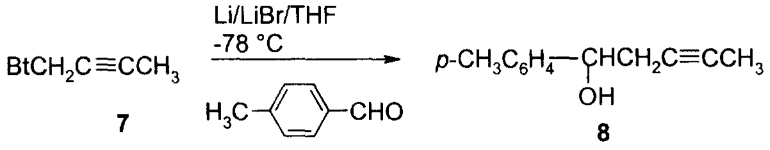
Scheme 1

Table 1. The Preparation of Functionally Substituted Acetylenes **3a-j**

Product	R^1	R^2	R^3	R^4	Yield (%)	CHN found (calcd) or HRMS found (calcd)	
						C	H
3a	$-(CH_2)_4-$		Et	Et	60	449.3634 (dimer) (224.1776)	
3b	$-(CH_2)_4-$		Ph	H	61	78.59 (78.65)	8.68 (8.25)
3c	$-(CH_2)_4-$		p-$CH_3C_6H_4$	H	69	78.81 (79.03)	8.60 (8.58)
3d	$-(CH_2)_4-$		n-Pent	H	50	239.1984 (M + 1) (238.1933)	
3e	Et	Et	p-$CH_3C_6H_4$	H	65	77.94 (78.42)	9.77 (9.29)
3f	n-Pent	H	p-$CH_3C_6H_4$	H	67	78.75 (78.79)	9.85 (9.55)
3g	n-Pent	H	Ph	H	72	78.56 (78.42)	9.04 (9.29)
3h	n-Pent	H	n-Pent	H	60	253.2051 (M - 1) (254.2246)	
3i	n-Pent	H	Et	Et	51	239.1882 (M - 1) (240.2089)	
3j	CH_3	H	$-(CH_2)_4-$		20[a]	182.1336 (182.1307)	

[a]Compounds **3j** and **5** were isolated from the same reaction as acetylenic and allenic products.

1-Benzotriazol-1-yl-2-butyne (**7**) was prepared from benzotriazole and 1-bromo-2-butyne using the same procedure as for the preparation of compound **1**. The treatment of compound **7** with lithium/lithium bromide in the presence of p-methylbenzaldehyde in THF at -78 °C for 4 h gave β-acetylenic alcohol **8** in 67% yield. The treatment of 1-benzotriazolyl-5-ethyl-5-methoxyhex-2-yne (**2b**) and an aromatic aldehyde with lithium/lithium bromide for 48 h gave compound **3e** in 65% yield. However, when 1-benzotriazolyl-4-methoxypent-2-yne (**2d**) was used as the starting material, allene **5** (40%) and acetylene **3j** (20%) were both isolated. Allene **5** was characterized by ^{1}H NMR and ^{13}C NMR. In the ^{1}H NMR spectrum, the methylene protons were shifted to 4.92 ppm in compound **5** as compared to 2.0-2.7 ppm in the other acetylenic products. The peak at 204.5 ppm in the ^{13}C NMR spectrum, which was assigned to the central carbon of the allenic compound, also supported the structure. Acetylene **3j** was characterized by ^{1}H NMR spectrum: the single peak at 2.65 ppm was assigned to the methylene protons which adjoin the triple bond.



Scheme 2

In conclusion, we have shown that 1,5-dioxygenated-pent-2-ynes can be efficiently prepared using benzotriazole methodology.

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9. ^{1}H NMR and ^{13}C NMR data of compounds **2a-d**: *1-[3-(Benzotriazol-1-yl)]-1-propynyl]cyclopentyl methyl ether* (**2a**): δ_H (300 MHz/CDCl$_3$) 1.60-1.75 (m, 4H), 1.75-1.90 (m, 2H), 1.90-2.05 (m, 2H), 3.24 (s, 3H),

5.52 (s, 2H), 7.36 (t, 1H, J = 7.5 Hz), 7.50 (t, 1H, J = 7.5 Hz), 7.72 (d, 1H, J = 8.2 Hz), 8.05)d, 1H, J = 8.2 Hz); δ_C (75 MHz/CDCl3) 22.9, 38.1, 38.6, 51.9, 75.0, 80.2, 88.0, 108.8, 120.0, 124.0, 127.8, 132.2, 146.0. *4-(Benzotriazol-1-yl)-1,1-diethyl-2-butynyl methyl ether* (**2b**): δ_H 0.88 (t, 6H, J = 7.4 Hz), 1.66 (q, 4H, J = 7.4 Hz), 3.25 (s, 3H), 5.55 (s, 2H), 7.40 (t, 1H, J = 7.5 Hz), 7.53 (t, 1H, J = 7.5 Hz), 7.73 (d, 1H, J = 8.2 Hz), 8.07 (d, 1H, J = 8.2 Hz). δ_C 7.8, 29.5, 38.2, 51.1, 77.1, 77.4, 87.7, 109.6, 119.8, 123.9, 127.3, 132.2, 146.1. *4-(Benzotriazol-1-yl)-1-pentyl-2-butynyl methyl ether* (**2c**): δ_H 0.86 (t, 3H, J = 6.5 Hz), 1.25-1.40 (m, 6H), 1.63-1.70 (m, 2H), 3.35 (s, 3H), 3.95 (t, 1H, J = 6.4 Hz), 5.53 (s, 2H), 7.41 (t, 1H, J = 7.6 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.73 (d, 1H, J = 8.2 Hz), 8.09 (d, 1H, J = 8.2 Hz); δ_C 13.4, 21.9, 24.3, 30.9, 34.8, 37.8, 55.9, 77.0, 85.3, 109.4, 119.3, 123.5, 126.9, 131.9, 145.7. *4-(Benzotriazol-1-yl)-1-methyl-2-butynyl methyl ether* (**2d**): 1.37 (d, 3H, J = 6.8 Hz), 3.31 (s, 3H), 4.07 (q, 1H, J = 5.0 Hz), 5.56 (s, 2H), 7.34 (t, 1H, J = 7.5 Hz), 7.48 (t, 1H, J = 7.5 Hz), 7.73 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.3 Hz); δ_C 20.9, 37.5, 55.5, 65.9, 76.3, 85.7, 109.2, 119.0, 123.3, 126.8, 131.7, 145.4.

10. Elemental analysis or HRMS data of compounds **4**, **5** and **8**: *4-(4'-Methylphenyl)-4-hydroxylbut-1-yne* (**4**): HRMS Calcd for $C_{11}H_{12}O$: 160.0888. Found: 160.0888. *1-[1-(Methoxyethyl)-1,2-propadienyl]cyclo pentanol* (**5**): HRMS Calcd for $C_{11}H_{18}O_2$: 182.1307. Found: (M^++1) 183.1393. *5-(4'-Methylphenyl)-5-hydroxypent-2-yne* (**8**): Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.50; H, 8.60.
11. General procedure: Lithium (10 mmol, 30% dispersion in mineral oil) was washed twice with THF under argon. THF (10 mL) was added, and the lithium suspension was treated with 1,2-dibromoethane (2 mmol) and then cooled to -78 °C. A solution of starting material **2** (2 mmol) and electrophile (4 mmol) in THF (10 mL) was added dropwise to the lithium suspension over 1 h and kept another 3-6 h before being quenched with water (15 mL) at the same temperature. After ether extraction, the crude product was purified by flash column chromatography on silica gel. All of the acetylene and allene compounds prepared gave satisfactory ^1H and ^{13}C NMR spectra, and all novel products gave satisfactory microanalyses or HRMS.