Homologation of 1-(Benzyloxymethyl)-1*H*-tetrazole via Lithiation

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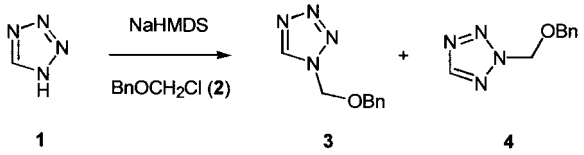
Abstract: Lithiation of 1-(Benzyloxymethyl)-1*H*-tetrazole, prepared by alkylation of 1*H*-tetrazole with benzyl chloromethyl ether, followed by treatement with a variety of electrophiles afforded its homologation products. Hydrogenation or acid hydrolysis gave the corresponding free tetrazoles.

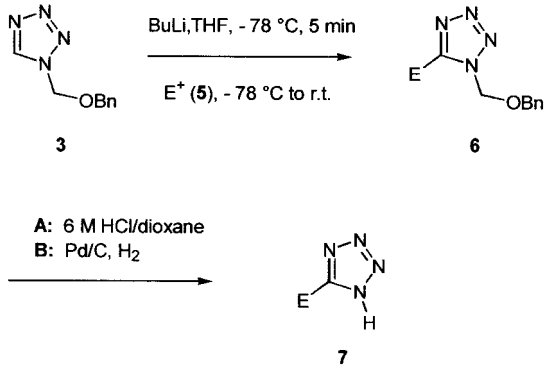
During the course of our studies on inhibitors of endothelin converting enzyme (ECE) based on the 5-aminomethyltetrazole template,[1] we developed a new method for the synthesis of N-protected 5-(1-hydroxylalkyl)-1*H*-tetrazoles by the reaction of 5-lithio-1-benzyl- or 1-p-methoxybenzyltetrazole with carbonyl compounds.[2] However, we encountered a number of cases where significant decomposition of the products was observed during the deprotection step. Identification of more versatile and easily removable protective groups of the tetrazole moiety for this application was therefore urgently needed to expand the scope of the methodology. In this Letter, we would like to disclose a successful lithiation and subsequent homologation of 1-benzyloxymethyl (BOM) protected tetrazole. The BOM group was removed under much milder conditions than the ones required for benzyl (Bn) or p-methoxybenzyl (PMB) groups.

The requisite BOM tetrazole **3** was prepared by condensation of tetrazole with BOM chloride. The use of NaHMDS in THF greatly improved the yield of **3**.[3]



Lithiation of **3** was successfully effected at -78 °C in THF, yielding a deep-purple solution typical of 5-lithiotetrazole. This is in a good contrast with 5-lithio derivatives of the Bn and PMB protected tetrazoles, which are stable only at -100 °C. We believe that improved stability of the lithiotetrazole in the current study is due to a decreased steric demand of the BOM group as compared to the corresponding benzylic counterparts.[4] Subsequent *in situ* condensation with electrophiles resulted in the formation of a variety of 1,5-substituted tetrazoles. As shown in the Table, the reaction proceeded well with aliphatic, aromatic, and unsaturated aldehydes and ketones (entries a - e). It should be noted that a good yield of the hydroxyalkyltetrazole (**6c**) was obtained even with cyclopentanone (**5c**), which often shows tendency for competitive enolization under basic conditions. The amino acid-based aldehyde required two full equivalents of the base (entry g) due to the presence of acidic NH. Little diastereoselection was observed in the reaction with **5g**. When a Weinreb amide was used, the most consistent results were obtained when three equivalents of the lithiotetrazole was utilized (entry h). Iodination afforded highly interesting iodide **6f**, which may be a good substrate for transition-metal catalyzed coupling reactions with organometallics.[5] In contrast, attempted lithiation of the N-2 regioisomer **4** and subsequent treatment with benzaldehyde afforded benzyl alcohol, a Cannizzaro product. The starting material **4** was also recovered unchanged; indicating that no lithiation took place under similar reaction conditions.

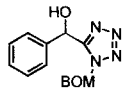
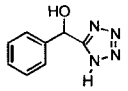
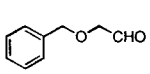
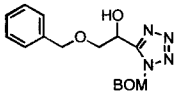
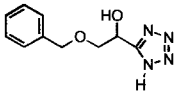
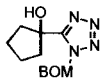
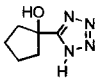
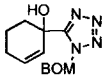
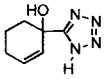
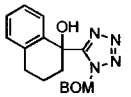
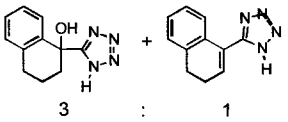
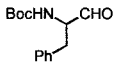
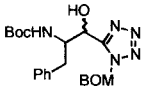
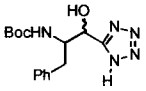
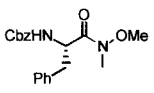
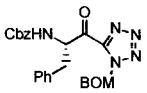
Attention was then focussed on the deprotection step. Under acidic conditions, warm aqueous hydrochloric acid in dioxane (55 °C, 2 h: Method A) was sufficient to effect deprotection of the BOM moiety (entries a, b, d-e, and g) while prolonged treatment with neat TFA was necessary for PMB.[2] The BOM deprotection, albeit in lower yields, took place with 20 eq. TFA in CH_2Cl_2 or with TMS-Br. It is interesting to note that, in the TMS-Br cleavage reaction, we observed partial regioisomerization of the BOM group from the N-1 position to N-2. Preparation of **7d** represents a pivotal case to demonstrate the superiority of the BOM derivatives. The corresponding PMB derivative could not be cleaved without decomposition. This method is only partly successful with the highly acid-sensitive substrate **6e** where we observed partial dehydration under the standard conditions (entry e). An acyltetrazole **6h** underwent extensive decomposition under the Method A (HCl) because of the concomitant Cbz cleavage. With the Bn and PMB groups, hydrogenolysis required the use of a full equivalent of palladium chloride in EtOH.[2] As expected, however, the BOM deprotection was performed under standard conditions (10% Pd/C, 1 atm. H_2, EtOH: Method B), affording the desired tetrazole in reasonable to good yields (entries c and h).



In summary, we have demonstrated facile deprotonation of N-1 BOM 1*H*-tetrazole by n-butyllithium, and subsequent reaction with a wide range of electrophiles. The BOM protective group was removed under mild conditions, allowing an easy entry to highly functionalized tetrazoles[6], which are otherwise inaccessible.

1-(Benzyloxymethyl)-1*H*-tetrazole (3) and 2-(Benzyloxymethyl)-*2H*-tetrazole (4): Sodium hexamethyldisilazide (360 mL, 1.0M in THF, 0.36 mol) was added to a stirred solution of tetrazole (Aldrich, 25.6 g, 0.36 mol) in 700 mL of dry THF over a period of 30 min at 0 °C. After 30 min, benzyl chloromethyl ether (Tokyo Kasei, 90% pure, 62 g, 0.36 mol) was added and the mixture was stirred for 2 h at room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (x2). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The oily residue was chromatographed on silica gel (4.0 kg, 43-60 μM) using 20% ether/ hexane as the eluent. The N-1 regioisomer **3** was obtained as a mobile, colorless oil (27.5 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (s, 2 H), 5.96 (s, 2 H), 7.3 - 4 (m, 5 H), 8.59 (s, 1 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 153.35, 135.51, 128.62, 128.45, 128.25, 79.37, 71.98 ppm. IR (film) 1496, 1325, 1283, 1110, 1023, 764, 702 cm^{-1}. MS (DCI/NH_3)

Table. Synthesis of 5-Substituted Tetrazoles

Entry	5	6[a]	Yield of 6, %[b]	7[a]	Yield of 7, %[c] (Method)[d]
a			71		56 (A)
b			65		90 (A)
c			56		60 (B)
d			60		42 (A)
e			57	 3 : 1	89 (A)
f	I_2		54	N. T.[e]	
g			27[f] (1 : 1)[g]		88 (B) (1 : 1)[g]
h			65[h]	Dec. (A)[i]	

[a] The product was fully characterized by spectral means. [b] Isolated yield based on **5**. [c] Isolated yield based on **6**. [d] Method A: 6N HCl in dioxane, 60 °C, 2 h. Method B: 10% Pd/C, H_2, (1 atm)EtOH. [e] Not Tried. [f] Using 2.0 eq. of the lithiotetrazole. [g] A 1:1 mixture of diastereomers was obtained. [h] Using 3.0 eq. of the lithiotetrazole. [i] Decomposed

191 (M+1), 208 (M + NH_4). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 57.05; H, 5.19; N, 29.66. Further elution with 30% ether/hexane afforded, after a small amount of impurity, **4** (19.6 g, 29%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 2 H), 5.82 (s, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.34 - 7.38 (m, 3 H), 8.76 (s, 1 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.68, 135.10, 128.77, 128.72, 128.30, 75.66, 71.92 ppm. IR (film) 1480, 1159, 1094, 750, 700 cm^{-1}. MS (DCI/NH_3) 191 (M+1), 208 (M + NH_4). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.62; H, 5.19; N, 29.74.

1-Benzyloxymethyl-5-(1-hydroxy-1-phenylmethyl)-1*H*-tetrazole (6a), Typical Procedure for the Synthesis of 6: To a stirred solution of **3** (300 mg, 1.58 mmol) in 10 mL of THF was added n-butyllithium (0.986 mL, 1.6 M in hexanes, 1.58 mmol) dropwise at -78 °C. After 5 min, benzaldehyde (152 mg, 1.43 mmol) was added and the mixture was stirred for 15 min. The mixture was then slowly allowed to reach room temperature over a period of 30min, quenched by addition of saturated aqueous ammonium chloride solution, and extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. Flash chromatography (silica gel, 30% ethyl acetate/hexane) gave 330 mg (71%) of the alcohol **6a** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (d, *J* = 5.6 Hz, 1 H), 4.65 (s, 2 H), 5.89 (s, 2 H), 6.18 (d, *J* = 5.6 Hz, 1 H), 7.28 - 7.52 (m, 10 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.56, 140.02, 135.52, 128.71, 128.57, 128.51, 128.38, 128.18, 126.61, 79.67, 72.10, 69.03 ppm. IR (film) 3420, 1602, 1494, 1454, 1110, 752, 698 cm^{-1}. MS (ES +) 297 (M+1). Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.88; H, 5.51; N, 18.78.

5-(1-Hydroxy-2-benzyloxyethyl)-1*H*-tetrazole (7b), a Typical Procedure for BOM Cleavage by Aqueous HCl (Method A): To a solution of **6b** (310 mg, 0.91 mmol) in dioxane (4 mL) was added 6 M HCl (2.0 mL, 13.2 mmol) and the mixture was heated at 55 °C for 2 h. The mixture was cooled, poured into diethyl ether (25 mL) and extracted with 1 M NaOH (x3). The combined basic extracts were washed with diethyl ether (x1), then made acidic with 1 M HCl, and extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated to give 180 mg (90%) of the title compound (**6d**) as a white solid: mp 98.5

- 100 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 - 3.81 (m, 2 H), 4.50 (s, 2 H), 5.17 (t, *J* = 5.3 Hz, 1 H), 6.3 (br s, 1 H), 7.23 - 7.34 (m, 5 H), 16.3 (br s, 1 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 157.36, 138.07, 128.24, 127.51, 72.65, 72.33, 63.95 ppm. IR (KBr) 3360, 2880, 1585, 1452, 1253, 1133, 734, 694 cm^{-1}. MS (ES +) 221 (M+1). Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.39; H, 5.70; N, 25.21.

5-(1-Hydroxycyclopentyl)-1*H*-tetrazole (7c), a Typical Procedure for BOM Cleavage by Hydrogenation (Method B): To a solution of **6c** (240 mg, 0.87 mmol) in EtOH (6 mL) was added 10% Pd/C (240 mg) at room temperature. The mixture was subjected to H_2 (1 atm) for 4 h. The catalyst was removed by filtration through a wad of celite, and the residue obtained upon evaporation was diluted with ether and extracted with 1 M NaOH (x2). The combined aqueous phase was acidified with conc. HCl to pH 2, and back-extracted with ethyl acetate (x3). The ethyl acetate layer was dried and evaporated. The solid residue was crystallized from ethyl acetate/hexane to give 80 mg (60%) of **7c** as a white crystalline solid: mp 112 - 114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.69 - 2.00 (m, 8 H), 5.40 - 6.10 (br s, 1 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 162.05, 76.42, 40.43, 23.32 ppm. IR (KBr) 1550, 1417, 1199, 1041, 1016 cm^{-1}. MS (ES +) 155 (M+1). Anal. Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.35. Found: C, 46.66; H, 6.44; N, 36.36.

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References and Notes

(1) De Lombaert, S.; Stamford, L. B.; Blanchard, L.; Tan, J.; Hoyer, D.; Diefenbacher, C. G.; Wei, D.; Wallace, E. M; Moscal, M.; Savage, P.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1059-64, and references cited therein.

(2) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759-62.

(3) Yokoyama, M.; Hirano, S.; Matsushita, M.; Hachiya, T.; Kobayashi, N.; Kubo, M.; Togo, H.; Seki, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1747-53. In this article, rigorous regiochemical assignment of **3** and **4** using a variety of NMR techniques was reported.

(4) The PMB protected 5-lithiotetrazole undergoes decomposition with concomitant loss of gaseous nitrogen to afford N-PMB-cyanamide. The temperature required for this irreversible process appears to be dependent upon the size of the N-1 substituent. See ref. 2, footnote 10. See also: Raap, R. *Can. J. Chem.* **1971**, *44*, 791-2. It is also possible that the ether oxygen of the BOM group may be stabilizing the lithiotetrazole through internal coordination. Studies clarifying these aspects are underway.

(5) Yi, K. Y.; Yoo, S-e. *Tetrahedron Lett.* **1995**, *36*, 1679-82.

(6) For a general review of synthesis and chemistry of tetrazoles, see: Butler, R. N. Comprehensive Heterocyclic Chemistry II; Storr, R. C. Ed.; Elsevier: Oxford, 1996, Vol. 4, pp 905-1006.