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Protection, Metalation, and Electrophilic Substitution of 5-Methyl Tetrazole

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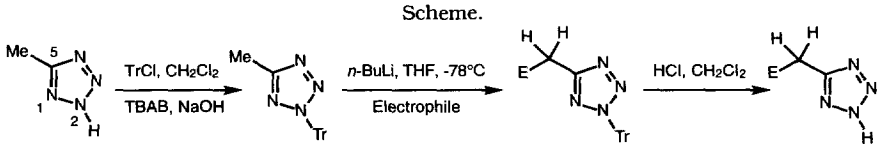
Abstract: 5-Methyl tetrazole was N-protected with the trityl group and deprotonated using *n*-BuLi. The resulting 5-methyl anion was trapped with a variety of electrophiles to provide 5-substituted tetrazoles in good yields. The trityl protecting group was readily removed using HCl in methylene chloride. Copyright © 1996 Elsevier Science Ltd

Tetrazoles have been widely used as carboxylic acid pharmacophores, especially in the design of angiotensin II antagonists.[1] Generally, the tetrazole ring is prepared by the cycloaddition reaction of azide with nitriles.[2] A method for incorporation of the tetrazole ring into compounds by reaction of a 5-alkyl tetrazole anion with an electrophile was necessary for our work. However, few reports describe the functionalization of tetrazoles by reaction of their anions with electrophiles. In one example, 1-phenyl-5-tetrazole acetic acid was prepared from 1-phenyl-5-methyl tetrazole by reaction of PhLi followed by CO_2.[3] Thomas reported the regiochemical outcome of the metalation and electrophile trapping reaction of 1(2)-methyl-5-ethyl tetrazole.[4] Those experiments showed that selective functionalization of the 5-alkyl position can occur *only* on the 1,5 regioisomer. Furthermore, the free tetrazole is inaccessible since an N-1 alkyl group is present. A potential solution to this problem was suggested by the work of Andrus.[5] In that report, tetrazole acetic acid ester was N-protected with ((((*p*-nitrobenzyl) oxy)carbonyl)oxy)methyl chloride to provide a 1:1.3 ratio of N-regioisomers. The 1,5-regioisomer was treated with $LiOCEt_3$, the resulting anion trapped with an acid chloride, and the protecting group removed by hydrogenolysis. This strategy suffers from a lack of regioselectivity in the protection step and does not use a readily available protecting group. We report here a protection, metalation and deprotection process which allows for the reaction of 5-methyl tetrazole with a wide variety of electrophiles. The overall sequence utilizes inexpensive, commercially available reagents and allows for the isolation of free 5-alkyl tetrazoles in high yield.

Scheme.

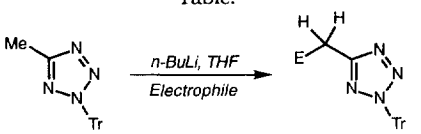


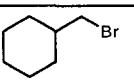
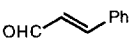
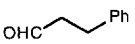
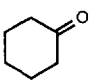
We selected the trityl group to protect the acidic N-H of 5-methyl tetrazole[6] for several reasons: crystalline N-trityl-5-methyl tetrazole was prepared in high yield, the bulky trityl group provided *exclusively* the 2,5-regioisomer, it was inert to the metalation conditions, and deprotection occurred

readily in high yield (Scheme). Significantly, only a single regioisomer is formed in the protection step; this simplifies subsequent synthetic operations which might be carried out prior to tetrazole deprotection.

Commercially available 5-methyl-tetrazole[7] was reacted under phase transfer conditions[8] with trityl chloride[9] to provide the product in 75% recrystallized yield as a single regioisomer. 2-Trityl-5-methyl tetrazole was then treated with *n*-BuLi (THF, -78 °C) followed by an electrophile to provide a variety of 5-methyl substituted tetrazoles (Table). Most electrophiles reacted in satisfactory yield including aldehydes[10], ketones, alkyl halides and benzyl halides.[11] Two of the cases that we examined, DMF and benzoyl chloride, did not provide the desired product. Generally, reactions with acyl chlorides resulted in complex reaction mixtures. We did not observe overalkylation in any of the reactions. Regiochemistry of the trityl position was confirmed by single-crystal X-ray of the product resulting from the reaction of 2-trityl-5-methyl tetrazole and benzyl bromide.

Table.[12]



Electrophile	Yield	Electrophile	Yield
PhCHO	76%		53%
	72%	TMSCl	62%
	74%	*n*-C_4H_9Br	65%
n-$C_6H_{13}CHO$	71%	Br_2	50%
	45%		—
DMF	—		42%
	73%		

The trityl group was removed by treatment of the products with HCl (gas).[13] The desired 5-alkylated tetrazoles were readily separated from residual trityl chloride by extraction of the reaction mixture with base, taking the tetrazole into the aqueous layer. Subsequent washing of the aqueous layer with Et_2O removed the trityl by-products. Finally, reacidification and extraction with EtOAc provided the desired products free from trityl contamination.

In summary, we have described the selective preparation of 2-trityl-5-methyl tetrazole which was metalated with *n*-BuLi and trapped with a variety of electrophiles. The trityl group was readily

removed under acidic conditions. This method should provide a useful alternative to the reaction of nitriles and amides with azide for the incorporation of free tetrazoles into organic molecules.

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7. 5-Methyl tetrazole [4076-36-2] was purchased from Aceto Corporation.

8. For a report on the reaction of 5-methyl terazole with MeI under PTC conditions see: Osipova, T. F.; Ostrovskii, V. A.;, Koldobskii, G. I.; Erusalimskii, G. B. *Zh. Org. Khim.* **1984**, *20*, 398.

9. **Procedure for the tritylation of 5-methyl tetrazole:** To a 200 mL round bottom flask was charged 5-methyl tetrazole (3.00 g, 36 mmol, 1.0 eq), trityl chloride (10.0 g, 36 mmol, 1.0 eq), 1 N NaOH (37.5 mL, 1.05 eq), tetrabutylammonium bromide (catalytic), and CH_2Cl_2 (50 mL). The resulting mixture was stirred vigorously at room temperature for 18 hours, after which it was diluted with water (50 mL) and transferred to a separatory funnel. After layer separation, the aqueous layer (upper) was back extracted with CH_2Cl_2 (25 mL). The combined organic portions were washed with water (2 x 50 mL), 5% $NaHCO_3$ (25 mL), and brine (25 mL). The solution was dried over Na_2SO_4, filtered and concentrated in vacuo to afford 11.0 g of off-white solids (99% crude yield). The crude

solids were purified by recrystalliztion from EtOAc (8 mL/g) to afford white crystals in 75% recovery (mp 177.9 °C). ^{1}H NMR (500 MHz, DMSO): δ 2.51 (s, 3H); 7.01-7.03 (m, 6H); 7.39-7.40 (m, 9H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 162.5, 141.8, 130.4, 129.0, 128.7, 82.0, 10.6; Anal. Calc'd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.16. Found: C, 77.34; H, 5.45; N, 17.26.

10. Organocopper or organocerium reagents did not provide any yield enhancement in the reaction of 2-trityl-5-methyl tetrazole with cyclohexanecarboxaldehyde.

11. **Procedure for reaction of N-trityl-5-methyl tetrazole with benzaldehyde:** To a dry 10 mL round bottomed flask was charged 2-trityl-5-methyl tetrazole (0.20 g, 0.64 mmol, 1.0 eq) and 3.2 mL of dry THF (0.2 M) under an N_2 atmosphere. The reaction was cooled to -78 °C and 0.44 mL of 1.6 M *n*-BuLi (0.70 mmol, 1.1 eq) was added dropwise at a rate which maintained the temperature below -70 °C. The reaction was stirred at -78 °C for 45 minutes whereupon benzaldehyde (0.090 mL, 0.89 mmol, 1.4 eq) was added dropwise at such a rate to maintain the temperature below -70 °C. After stirring for 30 minutes at -78 °C the bath was removed and the reaction warmed to ambient temperature. The reaction mixture was poured into 100 mL of EtOAc and washed with 25 mL of saturated ammonium chloride solution followed by 25 mL of brine. The EtOAc layer was dried over sodium sulfate, filtered and evaporated to provide 0.264 g (98% crude recovery). The product was purified by flash chromatography using 25:75 EtOAc/ hexane as the eluent (R_f = 0.27). The product was isolated a white solid (0.197 g, 73%, mp 167 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (bs, 1H); 3.31 (d, 2H, J = 6.3 Hz); 5.1 (t, 1H, J = 6.3 Hz); 7.00 (d, 6H, J = 7.0 Hz); 7.24 (m, 14H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 35.31, 72.21, 83.15, 125.91, 127.78, 127.88, 128.43, 128.52, 130.23, 141.28, 142.70; Anal. Calcd for $C_{28}H_{24}N_4O$: C, 77.75; H, 5.59; N, 12.95. Found: C, 77.53; H, 5.66; N, 13.14.

12. All products provided satisfactory ^{1}H NMR, ^{13}C NMR, and elemental analyses.

13. **Deprotection of 2-trityl-5-(2-hydroxy-2-phenyl)ethyltetrazole:** Dry hydrogen chloride was passed through a solution of the trityl tetrazole (700 mg, 1.62 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) for 10 min at room temperature, producing a yellow slurry. The slurry was treated with methanol (0.5 mL) and the resulting colorless solution was concentrated. The residue was partitioned between Et_2O (5 mL) and 1N NaOH (2.5 mL) and the organic phase extracted with 1N NaOH (3 X 2.5 mL). The combined aqueous portions were acidified to a pH of 1 with conc HCl and extracted with EtOAc. The combined EtOAc portions were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated in a small amount of CH_2Cl_2 to provide the product as a white solid (260 mg, 84%). An analytically pure sample was obtained by recrystallization from EtOAc/hexane, mp 141 °C: ^{1}H NMR (500 MHz, DMSOd_6): δ14.0 (br. s, 1H, N**H**), 7.25-7.37 (m, 5H, aryl **H**), 5.72 (br. s, 1H, O**H**), 4.99 (m, 1H, C**H**OH), 3.16-3.25 (m, 2H, C**H$_2$**); ^{13}C NMR (126 MHz, DMSOd_6): δ145.2, 129.0, 128.1, 126.5, 71.4, 34.3: FDMS m/e 191 (M+1); Anal. Calc'd for $C_9H_{10}N_4O$: C, 57.08; H, 5.16; N, 29.55. Found: C, 56.83; H, 5.30; N, 29.46.

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