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Directed Metalation and New Synthetic Transformations of 5-Aryltetrazoles

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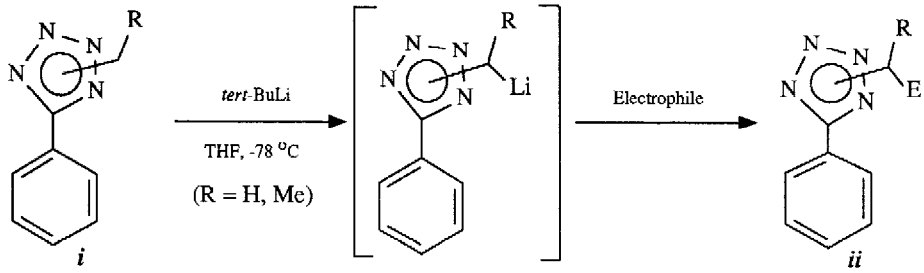
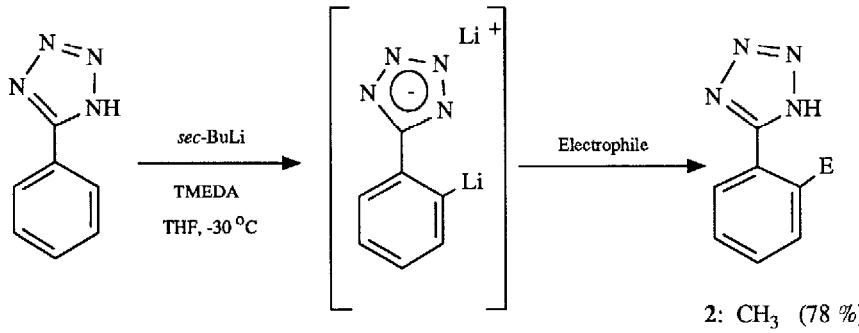
Summary: The tetrazole moiety is a useful directing group for the lithiation of 5-aryl substituents. Dilithiated 5-aryltetrazoles generally react with alkyl halides and aldehydes to give substitution and addition products, respectively.

The broad functional analogy between 5-alkyl or 5-aryl substituted 1(H)-tetrazoles and structurally related carboxylic acids has attracted considerable interest in recent years. Nevertheless, synthetic methods that are useful for the efficient assembly of complex tetrazoles are relatively few in number and limited in scope.[1] In view of the burgeoning interest in heteroatom-directed metalation reactions of aromatic compounds we decided to explore the tetrazole moiety as a potentially stable activating group under reaction conditions typically employed for the directed lithiation and subsequent functionalization of benzamides, 2-aryl oxazolines, and BOC-protected anilines.[2] It was first reported a century ago that 5-phenyltetrazole is stable toward strong base (dry NaOH at 250 °C)[3] ; however, it does not appear that ortho metalation of 5-aryltetrazoles or benzylic metalation of 5-(2-alkylaryl)tetrazoles have been reported to date. A recent study by Moody and co-workers concerning the reactivity of 1-alkyl and 2-alkyl-5-phenyltetrazoles, ***i***, demonstrated that lithiation gives exclusive formation of 1-lithioalkyl and 2-lithioalkyl-5-phenyltetrazole intermediates, respectively, which react with electrophiles to give 5-phenyltetrazoles, ***ii***:[1b]



The results of dilithiation and subsequent functionalization of 5-phenyltetrazole and 5-(2-methylphenyl)tetrazole are described in this communication. 5-Phenyltetrazole, **1**, was readily prepared in 83 - 88 % yield by treatment of benzonitrile for 7 days with NaN_3 in refluxing 1-butanol-glacial AcOH.[4] 5-(2-Alkylphenyl)tetrazoles were obtained in very low yields by this method; in the best example of this type o-tolunitrile gave 5-(2-methyphenyl)tetrazole, **2**, in only 11 - 15 % yield. However, **2** could be prepared in satisfactory yield by the thermal addition of Bu_3SnN_3 to o-tolunitrile in

refluxing xylenes followed by decomposition of the intermediate 2-tributyltin-5-(2-methylphenyl)tetrazole with anhydrous HCl.[5] Treatment of 5-phenyltetrazole with 3 equivalents of *sec*-butyllithium and one equivalent of tetramethylethylenediamine (TMEDA) in THF generated a yellow solution of dianion **3** which reacted immediately at -35 to -30 °C with methyl iodide, acetaldehyde, or acrolein to give products **2**, **4**, and **5** respectively (Equation 1).[6]



(Eq 1)

1 **3**

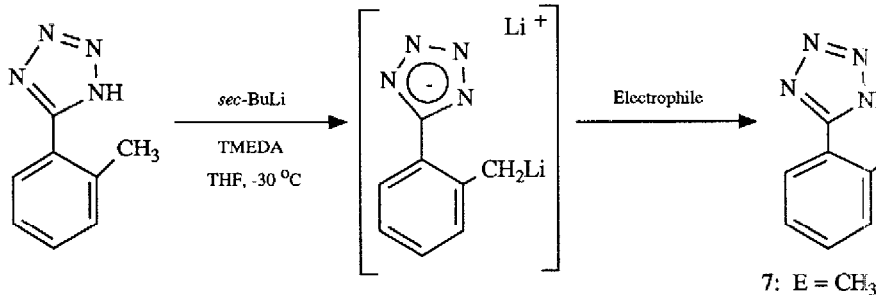
2: CH_3 (78 %)

4: $CH_3CH(OH)$ (95 %)

5: CH_2=CHCH(OH) (51 %)

Unfortunately, dianion **3** did not afford substitution products from its reaction with alkyl halides more complex than methyl iodide. Thus, reaction of **3** with 1-iodopentane and 1-chloro-3-iodopropane led to nearly complete recovery of the starting tetrazole while benzyl bromide reacted with **3** to give exclusively 5-(2-bromophenyl)tetrazole[4a] and bibenzyl.

When 2.2 equivalents of *sec*-butyllithium was added to 5-(2-methylphenyl)tetrazole and 1 equivalent of TMEDA in THF a bright orange solution of dianion **6** was generated. Dianion **6** reacted with methyl iodide to give 5-(2-ethylphenyl)tetrazole, **7**, in excellent yield (Eq 2).



(Eq 2)

2 **6**

7: E = CH_3 (71 %)

8: E = $CH_3(CH_2)_4$ (92 %)

9: E = $PhCH_2$ (73 %)

However, in contrast to the behavior of **3**, dianion **6** also reacted smoothly with 1-iodopentane and benzyl bromide to afford good yields of the substitution products 5-(2-hexylphenyl)tetrazole, **8**, and 5-(2-phenylethyl)phenyl)tetrazole, **9**, respectively.[7]

All of the compounds described in this Letter (except for putative intermediate dianions **3** and **6**) have

been satisfactorily characterized.[8]

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References and Notes

1) (a) Duncia, J. V.; Pierce, M. E.; Santella, J. B. *J. Org. Chem.*, **1991**, *56*, 2395. (b) Moody, C. J.; Rees, C. W.; Young, R. G. *J. Chem. Soc, Perkin Trans. I*, **1991**, 323. (c) Huff, L.; Henry, R. A. J. Med. Chem., 1970, 13, 777. (d) Morely, J. S. J. Chem. Soc. (C) 1969, 809. (e) Hayao, S.; Havera, H. J.; Stryker, W. G.; Leipzig, T. J.; Rodriguez, R. J. Med. Chem., 1967, 10, 400. For reviews of the synthesis, properties and transformations of tetrazoles see: (f) Benson, F. R. in "The High Nitrogen Compounds", John Wiley and Sons: New York (1984) (g) Grimmet, M. R. in "Comprehensive Organic Chemistry", Vol. 4, Barton, D., ed., Pergamon Press: Oxford (1979) (h) Butler, R. N. *Adv. Heterocycl. Chem.*, **1977**, *21*, 323.

2) For a recent comprehensive review of heteroatom-directed metalation reactions of aryl rings see: Snieckus, V. *Chem. Rev.*, **1990**, *90*, 879.

3) (a) Lossen, W. *Ann.*, **1891**, *263*, 73. (b) Lossen, W. *Ann.*, **1897**, *298*, 54.

4) (a) Herbst, R. M.; Wilson, K. R. *J. Org. Chem.*, **1957**, *22*, 1142. (b) Mihina, J. S.; Herbst, R. M. *J. Org. Chem.*, **1950**, *15*, 1082.

5) This procedure is a minor modification of a previously described tetrazole synthesis: Sisido, K.; Nabika, K.; Isida, T.; Kozima, S. *J. Organometal. Chem.*, **1971**, *33*, 337. Tributyltin azide and its precursor, tributyltin chloride, are highly toxic and potentially can be absorbed through the skin; therefore these compounds should be handled in a hood with protective gloves.

6) The optimized preparation of **2** from **1** is typical: A three-neck round bottom flask equipped with low temperature thermometer, nitrogen inlet, septum and magnetic stirrer was charged with 0.34 g (2.3 mmol) of **1**, 0.35 mL (2.3 mmol) of TMEDA and 20 mL of dry THF. The solution was cooled to -35 °C and 5.4 mL of 1.3 M sec-butyllithium in cyclohexane was added over 2 min. The yellow solution was maintained at -35 to -30 °C for 45 min and 0.43 mL (6.9 mmol) of freshly distilled CH_3I was added in one portion. The cooling bath was removed; the reaction mixture was adjusted to pH = 2 with dilute aqueous HCl and concentrated with a rotary evaporator. The residue was taken up in 50 mL of EtOAc, washed with 3 x 20 mL portions of water, dried ($MgSO_4$), filtered and concentrated to give 0.35 g of a white amorphous solid. Recrystallization of the crude material from abs EtOH gave 0.29 g (78 %) of analytically pure **2**.

7) A nearly identical procedure to that described in note 6 was used; however, dianion **6** was generated efficiently with only a 5 % excess of sec-butyllithium. Satisfactory yields of products **7** - **9** were obtained from reaction of **6** with 2.1 eq of the appropriate electrophile; however, when a solution of dianion **6** was quenched with a 30-fold excess of 99.9% D_2O and washed with several portions of water to effect N-D → N-H exchange the recovered product (90% yield) contained only 9.7% excess deuterium. The significance of this result, as well as deuterium incorporation experiments with dianion **3**, are under continuing investigation.

8) NMR spectra were recorded on $CDCl_3$ solutions except in the case of **1** (DMSO-d_6). 5-Phenyltetrazole **1**: mp = 215 - 216 °C [lit.[4a] 217 - 218 °C]. ^{13}C NMR δ 155.3, 131.3, 129.4, 127.1, 124.2.; 5-(2-methylphenyl)tetrazole **2**: mp = 156 - 158 °C [lit.[4b] 157 - 158 °C] ^1H NMR δ 7.60 (d, J = 7.6 Hz, 1 H), 7.45 (m, 3 H), 2.50 (s, 3 H). Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.04; N, 34.98. Found: C, 60.04; H, 5.21; N, 34.92. 5-(2-(1-hydroxyethyl)phenyl)tetrazole **4**: mp = 163 - 165 °C. ^1H NMR δ 7.82 (dd, J = 7.5, 1.5 Hz, 1 H), 7.60 (m, 2H); 7.44 (m, 1 H), 5.21 (q, J = 6.3 Hz, 1 H), 1.30 (d, J = 6.3 Hz, 3 H). ^{13}C NMR δ 147.0, 130.8, 129.3, 129.0, 126.8, 126.3, 121.3, 64.3, 25.5. Anal. Calcd for $C_9H_9N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.90; H, 5.46; N, 29.86. 5-(2-(1-hydroxyprop-2-enyl)phenyl)tetrazole **5**: Colorless oil. ^1H NMR δ 8.08 (dd, J = 7.9, 1.6 Hz, 1 H); 7.6 - 7.4 (m, 3 H), 6.1 - 5.95 (m, 1 H), 5.90 (m, 1 H), 5.3 - 5.15 (m, 2 H). ^{13}C NMR δ 143.6, 140.9, 130.8, 129.2, 127.4, 127.2, 122.1, 113.0, 69.1. Anal. Calcd for $C_{22}H_{33}N_5O$ (dicyclohexylamine salt): C, 68.89; H, 8.68; N, 18.26. Found: C, 68.70; H, 8.75; N, 18.38. 5-(2-ethylphenyl)tetrazole **7**: mp = 141-142 °C. ^1H NMR δ 7.64 (dd, J = 7.6, 1.1 Hz, 1 H); 7.55 - 7.35 (m, 3 H), 2.85 (q, J = 7.5 Hz, 2 H), 1.11 (t, J = 7.6 Hz, 3 H). Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 62.05; H, 5.84; N, 32.55. 5-(2-hexylphenyl)tetrazole **8**: mp = 109 - 110 °C. ^1H NMR δ 7.57 (dd, J = 7.5, 1.0 Hz, 1 H), 7.44 (m, 1 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.25 (m, 1 H), 2.83 (t, J = 7.8 Hz, 2 H), 1.49 (pentet, j = 7.7 Hz, 2 H), 1.3 - 1.1 (m, 6 H), 0.83 (t, J = 7.8 Hz, 3 H). ^{13}C NMR δ 142.7, 131.0, 130.4, 129.6, 126.1, 122.7, 33.4, 31.4, 31.0, 28.9, 22.4, 13.9. Anal. for $C_{13}H_{16}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.83; H, 7.91; N, 24.31. 5-(2-(2-phenylethyl)phenyl)tetrazole **9**: mp = 124 - 125.5 °C. ^1H NMR δ 7.53 (d, J = 7.7 Hz, 1 H), 7.45 (td, J = 7.7, 1 Hz, 1 H), 7.36 (d, J = 7.0 Hz, 1 H), 7.3 - 7.1 (m, 4 H), 7.00 (dd,, J = 7.7, 1.8 Hz, 2 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.87 (t, J = 7.2 Hz, 2 H). ^{13}C NMR δ 141.4, 141.1, 131.3, 130.9, 129.7, 128.7, 128.5, 126.6, 126.3, 123.3, 37.8, 35.5. Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.89; H, 5.72; N, 22.66.

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