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A New Method for the Preparation of Tetrazoles From Nitriles Using Trimethylsilylazide/Trimethylaluminum

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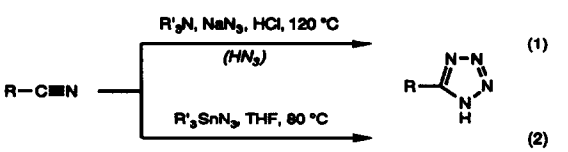
Summary: Tetrazoles are prepared in good yields from alkyl and aryl nitriles by treatment with equimolar trimethylaluminum and trimethylsilylazide. Yields, substrate compatibility, and reaction temperature are comparable with the use of other metal azides such as Al(N3)3 and n-Bu3SnN3. The reactions are run in toluene or with added THF at 80 °C.

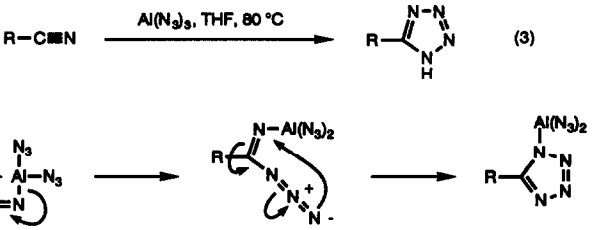
Tetrazoles are commonly used in medicinal chemistry as isosteric carboxylic acid pharmacophores.[1] Their preparation from nitriles typically involves the use of hydrazoic acid (HN_3) formed *in situ* from mineral acids and sodium azide.[2] HN_3 is typically complexed as its amine salt by the addition of ammonium chloride or tertiary amines (eqn 1). Care must be taken to monitor the concentration of HN_3 in the head space of the reactor to avoid explosive levels of hydrazoic acid.[3] Alternatively, tetrazoles are prepared from nitriles using tributyltinazide, prepared from NaN_3 and *n*-Bu_3SnCl (eqn 2).[4,5] This is an excellent general method for the lab-scale preparation of tetrazoles. However, removal and disposal of stoichiometric (highly toxic) residual organotin at the end of the reaction is a major drawback of this method. We sought to develop a method for tetrazole preparation that would offer the general applicability of *n*-Bu_3SnN_3 without the toxicity, stench, and isolation difficulties associated with the tin reagent. The value of developing methods that avoid the use of stoichiometric organotin was recently demonstrated with the report of a tetrazole preparation using catalytic dialkyltin oxide.[6] In this letter, we report the reaction of nitriles with commercially available trimethylaluminum (toluene solution) and trimethylsilylazide to conveniently prepare a variety of tetrazoles.



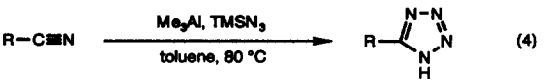
(1)

(2)

Based on an interesting metal azide reaction reported by Wiberg and Michaud in a 1957 German patent we envisioned that aluminum azides might be a practical alternative to tin azides.[7] These workers prepared $Al(N_3)_3$ by treatment of $AlCl_3$ with 3 equivalents of NaN_3 in THF at reflux (eqn 3). This reagent was excellent for the preparation of vinyl tetrazole and 3-chloroethyltetrazole. However, during the HCl quench of the reaction, 2 moles of HN_3 were formed for every mole of product. Wiberg and Michaud proposed that the reaction proceeds through intramolecular delivery of N_3^- from $Al(N_3)_3$ complexed with the nitrile (Scheme).



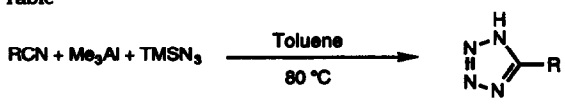
However, to make this method practical and safe, elimination of the excess azide was necessary. We proposed that a trialkylaluminum would provide the necessary Lewis acidity to activate the nitrile towards azide addition while allowing for the use of only one equivalent of azide. Trimethylsilylazide was seen as a convenient (syringeable) form of azide (an HN_3 equivalent)[8] which would be compatible with trialkylaluminum. Treatment of nitriles at 80 °C with premixed 2 M trimethylaluminum in toluene and *equimolar* trimethylsilylazide resulted in very good yields of tetrazoles (eqn 4).

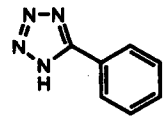
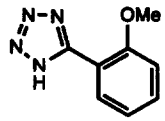
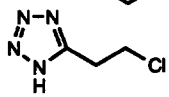
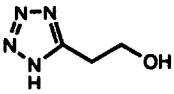
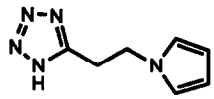
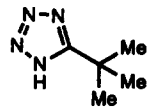
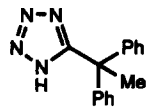
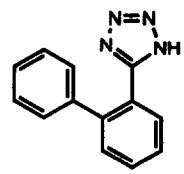
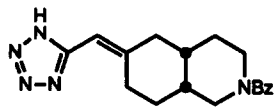


The Table lists a variety of tetrazoles that were prepared according to these new reaction conditions. The method is general for alkyl as well as aryl nitriles. Highly hindered nitriles resulted in poor conversion; However, the results are similar to those obtained using *n*-Bu_3SnN_3. For example, the yield of 5-(2,2-diphenylethyl) tetrazole using *n*-Bu_3SnN_3 was 12%. The biphenyl system exemplified in entry 8 is of interest as a pharmacophore in nonpeptidic A2 receptor antagonists.[1b,4,6] Surprisingly, the reaction works quite well in the presence of a free hydroxyl to give 5-(2-hydroxyethyl) tetrazole.

General Procedure*: Trimethylaluminum (2.0 M in toluene, 67.0 mmol, 33.5 mL) was added to an oven-dried three-neck flask equipped with a magnetic stirrer, reflux condenser, electronic thermocouple, and septum inlet. To this was added trimethylsilylazide (67.0 mmol, 8.9 mL) while keeping the temperature of the reaction ≤ 5 °C. To the resulting clear solution was added 4.3 mL of chloropropionitrile (55.8 mmol), again keeping the temperature ≤ 5 °C (gas evolution can often be observed during the nitrile addition). The homogeneous solution was warmed to room temperature then 80 °C (oil bath temperature) and allowed to stir overnight. After cooling to 0 °C the light yellow reaction mixture was added by cannula to a 0 °C quench mixture of 50 mL of 6 M HCl and 50 mL of EtOAc (Caution! Quench may be exothermic with vigorous gas evolution). The quench solution was added to a separatory funnel and the pH of the aqueous layer adjusted to ≤ 3 with HCl. The aqueous layer was extracted with 2 x 25 mL of EtOAc and the combined extracts washed with 1 x 50 mL of brine and dried over Na_2SO_4. Rotary evaporation afforded the tetrazole as a light yellow solid that was recrystallized from EtOAc to give the product (6.6 g, 89%) as light yellow needles (entry 3, Table). *Accelerated Rate Calorimetry study of the reaction mixture showed a small exotherm which occurred at 40 °C (0.04 °C/min self heat rate). A smaller exotherm occurred at 96 °C. While neither of these exotherms points to any particular hazard, one should use due caution in the preparation of all tetrazoles.

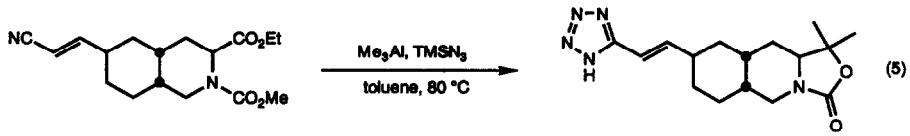
Table[10]



Entry	Product	Yield[a]
1		98%
2		71%
3		89%
4		65%
5		87%
6		38%
7		10%[b]
8		72%[c]
9		85%[d]

[a]Yields are unoptimized and refer to crystallized or chromatographed products.
[b]The yield using *n*-Bu_3SnN_3 under identical conditions was 12%.
[c]Reaction was carried out over 72 h.
[d]Stoichiometry, except in entry 9, is 1.5 eq $TMSN_3$, 1.5 eq Me_3Al.
Entry 9 stoichiometry is 5.0 eq $TMSN_3$, 5.0 eq Me_3Al.

The mechanism of the current reaction has not been determined. Roeder and Dehnicke[9] reported that trimethylaluminum when treated with trimethylsilylazide formed a 1 : 1 complex at temperatures less than 120 °C. However, at temperatures greater than 120 °C the initially formed complex $Me_3Al{\cdot}TMSN_3$ reacts to give $(Me_2AlN_3)_3$. Therefore, it is likely that trimethylaluminum simply acts as a Lewis acid in these reactions and does not form $(Me_2AlN_3)_3$. Circumstantial evidence for the presence of free trimethylaluminum was found in the reaction of the nitrile-containing protected amino acid shown in eqn 5. Under the reaction conditions (5 equivalents of $TMSN_3$ and 5 equivalents of Me_3Al) two methyl groups were added to the ester during the reaction. The tertiary carbinol then cyclizes to form the oxazolidinone. The tetrazole was also formed during the reaction. The overall yield for the process was about 50% (unoptimized).



In summary, this new method offers a versatile alternative to traditional preparations of tetrazoles using either trialkyltin reagents or hydrazoic acid. This chemistry offers the advantage of using two commercially available, syringeable reagents and does not require solvent beyond that in the trimethylaluminum solution. Reactions are readily carried out at about 80 °C and in most cases do not require excess azide. Very pure tetrazoles may simply be extracted from the acidic aqueous workup since all the aluminum byproducts are water soluble.

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1. a) For a general review see, Singh, H. *et al* in *Progress in Medicinal Chemistry*, Ellis, G. P. and West, G. B. Eds.; Elsevier/North Holland Biomedical Press, Amsterdam, 1980; Vol. 17, pp. 151-184. b) For a recent example see Bradbury, R. H.; Allott, C. P.; Dennis, M.; Girdwood, A. J.; Kenny, P. W.; Major, J. S.;Oldham, A. A.; Ratcliffe, A. H.; Rivett, J. E.; Roberts, D. A..; Robins, P. J. *J. Med. Chem.* 1993, *36*, 1245-1254. See also reference 4.
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8. The reaction of $TMSN_3$ without added Lewis acid requires elevated temperatures and often gives poor yields: a) Ettenhuber, E.; Rühlmann, K. *Ber.* 1968, *101*, 743-750. b) Washburne, S.S.; Peterson, W. R. *J. Organometal. Chem.* 1970, *21*, 427-430. c) See also reference 6.
9. a) Roeder, N.; Dehnicke, K. *Chimia* 1974, *28*, 349-351. See also, b) Müller, J.; Dehnike, K. *J. Organometal. Chem.* 1968, *12*, 37-47. c) Müller, J. *J. Organometal. Chem.* 1973, *51*, 119-123. d) Atwood, J. L.; Hrncir, D. C. *J. Organometal. Chem.* 1973, *61*, 43-48.
10. All compounds were characterized with acceptable ^1H NMR, ^{13}C NMR, IR spectra and MS or elemental analysis.

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