Notes

Dialkyltin Oxide Mediated Addition of Trimethylsilyl Azide to Nitriles. A Novel Preparation of 5-Substituted Tetrazoles†

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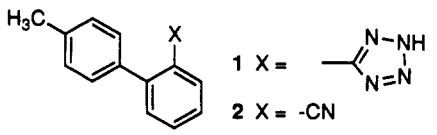
Angiotensin II (AII) is the octapeptide responsible for the peripheral effects of the renin-angiotensin system.[1] These effects include the regulation of blood pressure, volume homeostasis, and salt retention. Activity has been intense in the area of developing novel nonpeptide AII antagonists, spurred initially by the discovery of Furukawa et al.[2,3] and recently accelerated by reports from workers at DuPont–Merck detailing their structure–activity relationship studies that have resulted in the clinical candidate DUP 753.[4,5] The 5-(4′-methyl-1,1′-biphenyl-2-yl)-1*H*-tetrazole subunit (1) has become ubiquitous in the most potent and bioavailable antagonists disclosed to date.[6] The tetrazole moiety functions as a carboxylic acid



isostere that imparts greater metabolic stability and increased absorption relative to the carboxylic acid.[7] With the discovery of a series of novel AII antagonists by our medicinal chemistry team,[8] we sought to develop a method to prepare the tetrazole containing subunit that would be amenable to large-scale synthesis. In this paper, we report a novel method for the preparation of 5-substituted tetrazoles from nitriles utilizing trimethylsilyl azide in the presence of catalytic dialkyltin oxide.

Existing methods for the preparation of 5-substituted tetrazoles caused concern.[9] Typically, they were prepared by the reaction of a hydroazoic acid source (e.g., sodium azide and ammonium chloride) with an acceptor group, such as a nitrile, in an inert solvent at high temperature.[10] Hydroazoic acid itself is poisonous, extremely explosive, and has a low boiling point (37 °C). Trialkyltin azide, a stoichiometric reagent typically prepared *in situ* from a trialkyltin chloride (volatile and toxic) and sodium azide, has been shown to be effective in the synthesis of 5-substituted tetrazoles at somewhat lower temperatures.[11,12] Alternatively, 5-aryl 1*H*-tetrazoles have been prepared by bromination of the related tolyl compound, converting the dibromide to the diazido compound with sodium azide and then cyclization by heating in refluxing dimethylformamide to produce the tetrazole.[13] Due to safety considerations, we required a method that did not rely on the use of hydroazoic acid or an azide source that produced hydroazoic acid *in situ* because of the associated hazards.

Trimethylsilyl azide has been reported to react with aryl and alkyl nitriles to give 5-substituted 1*H*-tetrazoles.[14] It is an attractive azide source due to its stability, relatively high boiling point (105 °C) and commercial availability. In our hands, however, benzonitrile reacted with only very low conversion and ortho-substituted benzonitriles failed to undergo the reaction. More recently, a new method of tetrazole preparation has appeared.[15] *N*-(2-Cyanoethyl)-amides were treated with triphenylphosphine, diethyl azodicarboxylate, and trimethylsilyl azide to give the *N*-(2-cyanoethyl)-protected tetrazole in one step. Base hydrolysis of the cyanoethyl protecting group yielded the 5-substituted tetrazole.

We focused our efforts toward discovering a reagent that in combination with trimethylsilyl azide would produce tetrazoles from ortho-substituted aryl nitriles. Initially, we investigated the reaction of 4′-methyl-1,1′-biphenyl-2-carbonitrile **2** with trimethylsilyl azide in the presence of tributyltin acetate. Tributyltin acetate was chosen because of its low volatility and low cost. The reaction could be forced to completion (i.e., tetrazole 1) with excess trimethylsilyl azide (ca. 4–5 equiv) and tributyltin acetate (1.2 equiv) in toluene at 110 °C over 7 days. In the presence of catalytic tributyltin acetate (ca. 0.1 equiv) and several equivalents of trimethylsilyl azide in toluene at 110 °C, partial conversion was observed though the reaction could not be taken to completion. This indicated that tin ligand exchange, azide for acetate, had occurred. It seemed likely that liberation of tributyltin azide (or acetate) from the intermediate *N*-tributyltin tetrazole was the point at which the potential catalytic cycle was breaking down.

† Dedicated to the memory of James E. Leonard.

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(13) Jpn. Kokai Tokkyo Koho JP 59 98,023.

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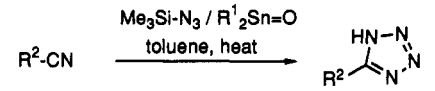
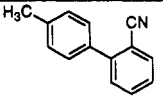
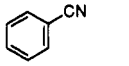
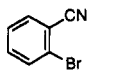
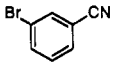
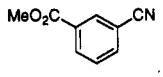
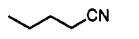
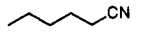
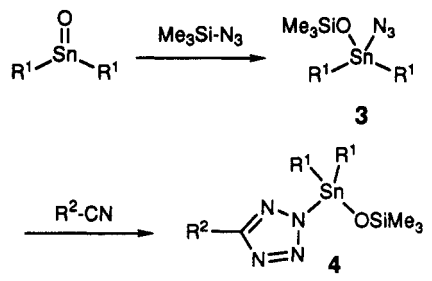
Table I. Yields for the Conversion of Nitriles into Tetrazoles



R^2CN	Me_3SiN_3 (equiv)	$R^1_2Sn{=}O$ (equiv) (R^1)[a]	time (h)	R^2CN_4H % yield[b]
	5.4	0.18 (Bu)	70[c]	86
	2.0	0.10 (Me)	72[d]	60
	2.0	0.10 (Me)	72[d]	74
	2.0	0.10 (Me)	72[d]	80
	2.0	0.10 (Bu)	24[c]	98
	2.0	0.10 (Bu)	25[c]	85
	2.0	0.10 (Bu)	25[c]	70

[a] Dibutyltin oxide or dimethyltin oxide catalyst used as indicated. [b] Yields unoptimized. [c] Reaction temperature 110 °C. [d] Reaction temperature 93 °C.

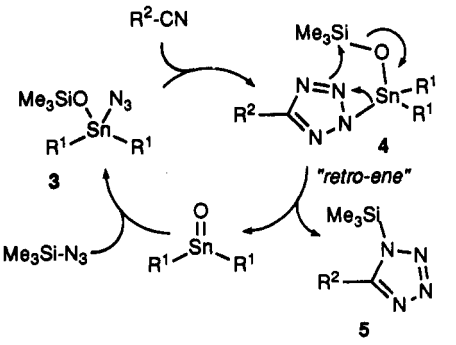
Dialkyltin oxides are known to undergo condensation with diols to form dioxastannolanes,[16] much like ketones react with diols to give ketals. Ketones are also known to react with trimethylsilyl azide to give *O*-trimethylsilyl azidohydrins.[17] We wondered if the reactivity of trimethylsilyl azide could be extended from the C=O case to Sn=O. We expected that a tetracoordinate dialkyl(*O*-trimethylsilyl)azidostannylhydrin **3** would be produced and would react with the nitrile to give the *N*-(dialkyl(trimethylsiloxy)stannyl)tetrazole **4** in analogy to the known trialkyltin azides. Dibutyltin oxide (1.1 equiv) was



suspended in a toluene solution of the nitrile **2** and trimethylsilyl azide (2.7 equiv). Upon warming the suspended solids quickly dissolved,[18] and after heating 91 h, a 95% yield of the tetrazole **1** was isolated along with 1% recovered nitrile **2**. More importantly, in the presence of catalytic dibutyltin oxide (0.18 equiv) the tetrazole **1** was obtained in 86% yield.

The procedure can be applied to a variety of substrates (Table I). Both aryl as well as aliphatic nitriles give good yields of 5-substituted tetrazoles. Reaction conditions have not been optimized for any of these substrates. The reaction proceeds well in cases of ortho-substituted aryl nitriles where steric hindrance might be anticipated to reduce the yield. This is especially important in the context of preparing nonpeptide AII antagonists that feature the 5-(4′-methyl-1,1′-biphenyl-2-yl)-1*H*-tetrazole subunit **1**.

Scheme I



We have been able to observe the putative dialkyl(*O*-trimethylsilyl)azidostannylhydrin **3** spectroscopically. The results were disappointing with both carbon-13 and proton NMR, but we were partially successful observing the tin-119 NMR spectrum. Dibutyltin oxide is insoluble in d_8-toluene, and we were unable to detect a signal in the tin-119 NMR spectrum (+450 to −440 ppm, Me_4Sn internal standard). To a suspension of dibutyltin oxide in d_8-toluene was added trimethylsilyl azide (500 mol %), and after several minutes at rt the remaining suspended solids were filtered off. This sample exhibited a sharp signal in the tin-119 NMR spectrum (+7.67 ppm) that we have assigned to the dibutyl(*O*-trimethylsilyl) azidostannylhydrin **3** (R^1 = Bu).

Although we have not attempted to rigorously establish the mechanistic details, it is likely that an intermediate *N*-(dialkyl(trimethylsiloxy)stannyl)tetrazole **4** is formed as described. This intermediate is proposed to break down into an *N*-(trimethylsilyl)tetrazole **5** and a tin species that carries on the catalytic cycle (Scheme I). This presents the intriguing possibility of an intramolecular retro-ene process wherein all six of the participating centers are heteroatoms. The driving force for this process would presumably be the expulsion of dialkyltin oxide resulting in the aforementioned *N*-(trimethylsilyl)tetrazole **5**. We are unaware of a report describing a similar example of a retro-ene reaction though there is precedent for the collapse of tetracoordinate α-(acyloxy)-ω-alkoxydialkyltin intermediates to lactones driven by the generation of dialkyltin oxide.[19] Another possibility for the identity of the chain-carrying tin species is the dialkyl(*O*-trimethylsilyl)azidostannylhydrin **3**. Intermolecular reaction of the intermediate *N*-(dialkyl(trimethylsiloxy)stannyl)tetrazole **4** with trimethylsilyl azide would produce the *N*-(trimethylsilyl)tetrazole **5** and regenerate the dialkyl(*O*-trimethylsilyl)azidostannylhydrin **3** (Scheme II). At this point we are unable to distinguish between the proposed mechanisms.

In conclusion, we have described a novel method for the transformation of nitriles into 5-substituted tetrazoles. This new process offers several advantages over many of

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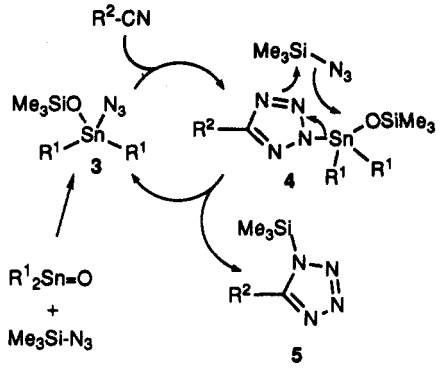
(17) (a) Birkofer, L.; Müller, F.; Kaiser, W. *Tetrahedron Lett.* **1967**, 2781–2783. (b) Nishiyama, K.; Yamaguchi, T. *Synthesis* **1988**, 106–108.
(18) A sample of dibutyltin oxide in toluene did not dissolve upon warming to 105 °C over several minutes. Upon addition of trimethylsilyl azide, the solid rapidly dissolved.
(19) Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578–7579.

Scheme II



the previously published procedures. The use of trimethylsilyl azide as the azide source greatly reduces the hazard posed by *in situ* generation of hydroazoic acid (especially on large scale). The use of catalytic dialkyltin oxide eliminates the possibility of exposure to the volatile, noxious, and toxic trialkyltin chloride used for the preparation of trialkyltin azide. The dialkytin oxide/trimethylsilyl azide reaction is a one-step method that is useful for the preparation of tetrazoles, a functional group that has recently become more important in medicinal chemistry as a carboxylic acid isostere.[7]

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with tetramethylsilane as an internal standard. ^{119}Sn NMR spectra were measured at 111.85 MHz with tetramethyltin as an internal standard.

General Procedure for Conversion of Nitriles to Tetrazoles. To a solution of the nitrile (5.5 mmol) and trimethylsilyl azide (11 mmol, 2.0 equiv) in toluene (11 mL) was added dibutyltin oxide (0.55 mmol, 0.10 equiv), and the mixture was heated for 24–72 h until the nitrile was consumed (TLC analysis). The reaction mixture was concentrated *in vacuo*. The residue was dissolved in methanol and reconcentrated. The residue was partitioned between ethyl acetate (25 mL) and 10% sodium bicarbonate solution (25 mL). The organic phase was extracted with an additional portion of 10% sodium bicarbonate solution (25 mL). The combined aqueous extracts were acidified to pH 2 with 10% hydrochloric acid solution and then extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the 5-substituted tetrazole.

5-(4′-Methyl-1,1′-biphenyl-2-yl)-1*H*-tetrazole: mp 144 °C; ^{1}H (CD_3OD, 300 MHz) δ 2.32 (s, 3H), 6.95–7.05 (m, 2H), 7.1–7.15 (m, 2H), 7.45–7.55 (2H), 7.6–7.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 124.4, 128.6, 129.9, 130.1, 131.6, 131.8, 132.4, 137.7, 138.8, 143.6, 157.0; MS (DCI/NH_3) *m/z* 237 (M + H^+, 100), 254 (M + NH_4^+, 40); IR (KBr) 3440 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_4 \cdot {}^1/_2H_2O$: C, 68.56; H, 5.34; N, 22.84. Found: C, 68.90; H, 5.17; N, 22.78.

5-Phenyltetrazole: mp 215 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.55–7.65 (m, 3H), 8.0–8.1 (m, 2H); HRMS (DCI/NH_3) *m/z* calcd for $C_7H_7N_4$ 147.0671, found 147.0688; IR (KBr) 3440 cm^{-1}. Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.27; H, 3.99; N, 38.25.

5-(2-Bromophenyl)tetrazole: mp 181–183 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.48–7.6 (m, 2H), 7.70 (dd, J = 2, 7 Hz, 1H), 7.84 (dd, J = 1, 6 Hz, 1H); HRMS (DCI/NH_3) *m/z* calcd for $C_7H_6N_4{}^{79}Br$ 224.9776, found 224.9762; IR (KBr) 3440 cm^{-1}. Anal. Calcd for $C_7H_6N_4Br$: C, 37.36; H, 2.24; N, 24.90. Found: C, 37.44; H, 2.25; N, 24.77.

5-(3-Bromophenyl)tetrazole: mp 150–152 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.50 (t, J = 8 Hz, 1H), 7.75 (ddd, J = 1, 2, 8 Hz, 1H), 8.02 (dt, J = 8, 1 Hz, 1H), 8.23 (t, J = 1 Hz, 1H); HRMS (DCI/NH_3) *m/z* calcd for $C_7H_6N_4{}^{79}Br$ 224.9776, found 224.9765; IR (KBr) 3450 cm^{-1}. Anal. Calcd for $C_7H_5N_4Br \cdot 0.3H_2O$: C, 36.48 H, 2.45; N, 24.31. Found: C, 36.13; H, 2.11; N, 24.09.

5-(3-(Methoxycarbonyl)phenyl)tetrazole: mp 186–187 °C; ^{1}H NMR (d^6-DMSO, 300 MHz) δ 3.0–4.5 (br, 1H), 3.92 (s, 3H), 7.75 (t, J = 8 Hz, 1H), 8.11 (d, J = 8 Hz, 1H), 8.32 (d, J = 8 Hz, 1H), 8.54 (s, 1H); MS (DCI/NH_3) *m/z* 205 (M + H^+, 10), 222 (M + NH_4^+, 100).

5-*n*-Butyltetrazole: mp 46–47 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7 Hz, 3H), 1.43 (sextet, J = 7 Hz, 2H), 1.87 (p, J = 7 Hz, 2H), 3.12 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.4, 22.0, 23.1, 29.6, 156.9; IR ($CDCl_3$) 2900 cm^{-1}; MS (DCI/NH_3) *m/e* 127 (M + H^+, 25), 144 (M + NH_4^+; 100). Anal. Calcd for $C_5H_{10}N_4 \cdot {}^1/_{10}H_2O$: C, 46.93; H, 8.03; N, 43.78. Found: C, 47.14; H, 7.99; N, 43.75.

5-*n*-Pentyltetrazole: mp 41–42 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7 Hz, 3H), 1.30–1.45 (m, 4H), 1.90 (p, J = 7 Hz, 2H), 3.12 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 22.1, 23.4, 27.3, 31.1, 156.9; IR ($CDCl_3$) 2900 cm^{-1}; MS (DCI/NH_3) *m/e* 141 (M + H^+, 15), 158 (M + NH_4^+; 100). Anal. Calcd for $C_6H_{12}N_4$: C, 51.41; H, 8.63; N, 39.97. Found: C, 51.25; H, 8.59; N, 39.93.

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