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2-Benzyloxymethyl-5-(tributylstannyl)tetrazole. A reagent for the preparation of 5-aryl- and 5-heteroaryl-1*H*-tetrazoles via the Stille reaction†

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Abstract

2-Benzyloxymethyl-5-(tributylstannyl)tetrazole (**2**) is a useful reagent for the conversion of aryl- and heteroaryl-halides (bromides and iodides) to 5-aryl- and 5-heteroaryl-1*H*-tetrazoles. The conversion entails a copper(I) iodide co-catalyzed Stille palladium-catalyzed cross-coupling reaction and a *N*-benzyloxymethyl deprotection step. Coupling was possible with electron neutral and electron poor substrates in yields ranging from 35–93%. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: tetrazoles; palladium and compounds; biaryls; coupling reactions.

The tetrazole functionality is an increasingly popular replacement or isostere for the carboxylic acid group in drug discovery research.[1] The tetrazole group, which is metabolically stable, has a similar pK_a to CO_2H and as part of a drug molecule it offers the potential of a longer in vivo half life. Its negative charge can be delocalized over all four nitrogens which translates into derivatives with a higher log P and thus better oral bioavailablity and cell penetration. Additionally, the four nitrogen atoms offer a greater opportunity for H-bond donor/acceptor interactions and the π-electron system of the aromatic ring can have additional hydrophobic interactions, both of which can provide strong receptor binding. One example where some of these effects resulted in tetrazole being the preferred CO_2H mimetic is the angiotensin II receptor antagonist Losartan (**1**).[2–4]

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† Dedicated to Professor Ernest Wenkert on the occasion of his 75th birthday.

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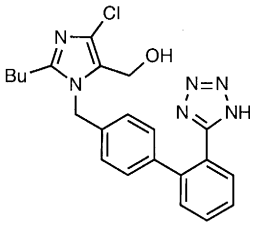
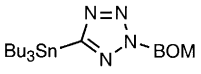


1, Losartan



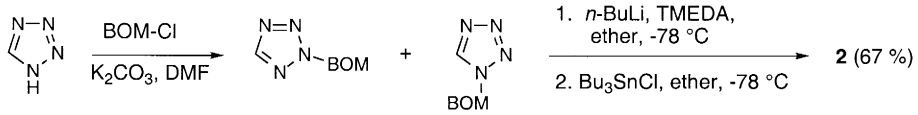
2

BOM = $PhCH_2OCH_2$

Standard methods for 1*H*-tetrazole synthesis require the use of a toxic azide reagent and a cyano or carboxamide precursor.[1,5] A few methods have been published which allow the preparation of 5-alkyl- or 5-acyl-1*H*-tetrazole derivatives from simple *N*-protected tetrazole precursors using organolithium or organomagnesium techniques.[6] This report focuses on defining a method for the synthesis of 5-aryl- and 5-heteroaryl-1*H*-tetrazoles which does not involve azide-based reagents or highly reactive carbanion chemistry and can be used at virtually any point in a synthetic protocol.

Palladium-catalyzed biaryl synthesis methods meet these requirements.[7,8] Prior work by Yi and Yoo demonstrated that 1-benzyl-5-bromotetrazole was a useful coupling partner in the Suzuki reaction with various phenyl boronic acids.[9] However, this method does not produce free 1*H*-compounds and it is limited in scope by the availability of arylboronic acids. Herein is reported the preparation and successful use of stannane **2** as a reagent for the preparation of 5-aryl-1*H*-tetrazoles. Use of this reagent with the neutral reaction conditions of the Stille reaction[7] should provide for a high degree of flexibility in the structure of the aryl coupling partner.

The required stannane **2** can be prepared in two steps from tetrazole (**3**) (Scheme 1). Alkylation of tetrazole (**3**) with benzyl chloromethyl ether (BOM-Cl) produced a separable 1:1 mixture of N2- and N1-isomers **4** and **5**, respectively.[10] The 5-lithio species of **4**, generated by treatment with *n*-BuLi and TMEDA in ether at −78°C, was trapped with Bu_3SnCl using inverse addition to produce the desired stannane **2** (67%).[11]



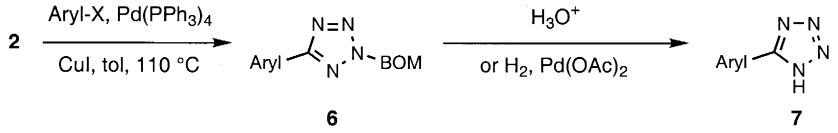
3 **4** (41 %) **5** (40 %)

Scheme 1.

In contrast, addition of *n*-BuLi to the N1-isomer (**5**) under the same reaction conditions resulted in instantaneous gas evolution (N_2) from the reaction mixture, a result of ring-opening fragmentation, even at temperatures as low as −100°C.[12] Examination of prior literature seems to indicate a trend in this fragmentation process of 5-lithio-1-substituted tetrazoles which is dependent on the N1-substituent. Electron withdrawing N1-substituents (Ph,[12] BOM) lower the thermal barrier to fragmentation while neutral substituents (CH_3,[12] Bn,[9,6b] *p*-methoxybenzyl[6b]) appear to stabilize the 5-lithio species.

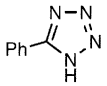
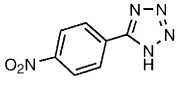
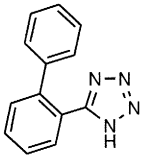
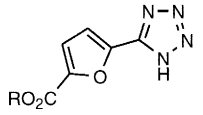
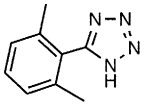
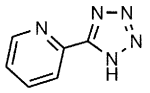
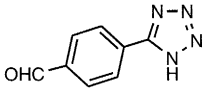
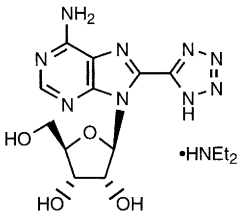
Scheme 2 shows the process adopted for converting aryl- and heteroarylhalides (bromides and iodides) to 5-aryl- and 5-heteroaryl-1*H*-tetrazoles by way of the 5-stannyltetrazole **2**.[13] When 10 mol% CuI and 5 mol% tetrakis(triphenylphosphine)palladium(0) were combined with the stannane **2** and an arylhalide in refluxing toluene, the desired coupled products **6** were obtained in good to excellent yield as shown in Table 1.[14] The reaction was effective with a range of electron neutral and electron poor aryl halides

(entries a–c and f–j) as well as sterically hindered substrates (entries b and c). Entries d and e failed to produce coupled products which may be related to the electron rich character of these aryl halides.



Scheme 2.

Table 1

Entry	Aryl-X [a]	Coupling product (yield)[b]	Deprotection product (yield)[b]	Entry	Aryl-X[a]	Coupling product (yield)[b]	Deprotection product (yield)[b]
a	**8**	**6a** (63 %)	 **7a** (83 %)[c]	g	**14**	**6g** (91 %)	 **7g** (91 %)[d]
b	**9**	**6b** (91 %)	 **7b** (83 %)[c]	h	**15**	**6h** (68 %)	 **7h**, R = H (52 %)[c] **7h'**, R = Me (43 %)[e]
c	**10**	**6c** (76 %)	 **7c** (76 %)[c]	i	**16**	**6i** (93 %)	 **7i** (57 %)[f]
d	**11**	nd[g]					
e	**12**	nd[g]					
f	**13**	**6f** (80 %)	 **7f** (91 %)[d]	j	**17**	**6j** (35 %)[h]	 **7j** (73 %)[i]

[a] **8** = bromobenzene; **9** = 2-iodobiphenyl; **10** = 2-iodo-*m*-xylene; **11** = 4-iodoanisole; **12** = 4-iodoaniline; **13** = 4-bromobenzaldehyde; **14** = 1-iodo-4-nitrobenzene; **15** = methyl 5-bromo-2-furoate; **16** = 2-bromopyridine; **17** = 8-bromoadenosine. [b] Products showed satisfactory CHN analyses and/or 200 MHz ^{1}H NMR spectra. [c] Deprotection: 6 M HCl, MeOH, 65 °C, 3 h. [d] Deprotection: 6 M HCl, dioxane, 75 °C, 3 h. [e] Deprotection: H_2, $Pd(OAc)_2$, MeOH/EtOAc, 96 h. [f] Deprotection: 90:10 TFA:water, 80 °C, 3 h. [g] Product not detected. [h] DMF substituted for toluene during coupling. [i] Deprotection: H_2, $Pd(OAc)_2$, DMF, 96 h; $HNEt_2$, C-18 RP SiO_2.

Deprotection was conducted in acidic media or by hydrogenolysis. The latter was a useful alternative when other acid labile groups were present in the molecule (entries h and j). For example, hydrogenolysis was necessary to convert **6j** to 8-(tetrazol-5-yl)adenosine (**7j**) since 8-substituted purine nucleosides are susceptible to deglycosylation in acid.[15]

This two-step method for the installation of tetrazole rings onto aryl and heteroaryl halides should be useful to medicinal and other areas of chemistry desiring to explore the utility of this nitrogen-dense, carboxylate-mimicking aromatic-ring.

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3. The total 1998 annual sales worldwide of Losartan-based products COZAAR® and HYZARR® was >US$1 billion. Private comm. from Paul Chusid, Executive Consultant, Public Affairs, Human Health, Merck & Co., Inc, One Merck Drive, PO Box 100, WS1A-10A, Whitehouse Station, NJ 08889-0100, USA.
4. A survey of the MDL Comprehensive Medicinal Chemistry database (CMC) reveals 33 FDA approved drugs incorporate the 1*H*-tetrazole functionality. MDL Information Systems, Inc, 14600 Catalina Street, San Leandro, CA 94577, USA. Tel: 510-352-2870.
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11. 2-Benzyloxymethyl-5-(tributylstannyl)tetrazole (**2**): To a mixture of tetrazole (**3**) (2.00 g, 28.5 mmol) and powdered K_2CO_3 (5.90 g, 42.7 mmol) in 30 mL DMF cooled to 0°C was added benzyl chloromethyl ether (5.36 g, 34.2 mmol) and the resulting mixture stirred for 30 min at 0°C and then for 16 h at rt. Dilution with water and extraction with ether (2×), drying ($MgSO_4$) and evaporating the combined ether extracts followed by chromatography of the residue eluting with 2.5:1 hexane:EtOAc provided 2.22 g (41%) of compound **4**[10] as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 4.64 (s, 2), 6.13 (s, 2), 7.2–7.4 (m, 5), 9.10 (s, 1). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.92; H, 5.31; N, 29.74. To a solution of compound **4** (2.00 g, 10.5 mmol) and TMEDA (3.2 mL, 21 mmol) in 30 mL diethyl ether at −78°C was added 4.2 mL of a 2.5 M solution of *n*-BuLi in hexanes (10.5 mmol) and a dark red solution resulted. This was left to stir for 5 min at −78°C and then added via cannula needle to a precooled (−78°C) solution of (n-Bu)$_3$SnCl (3.42 g, 10.5 mmol) in 20 mL of diethyl ether. The resulting pale yellow solution was stirred at −78°C for 30 min and then diluted with water and diethyl ether. The ether layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was subjected to chromatography on SiO_2 eluting with hexane:EtOAc mixtures of 100:1, 50:1 and 25:1 which provided 3.35 g (67%) of the stannane **2** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 9, J=7 Hz), 1.0–1.8 (m, 18), 4.61 (s, 2), 6.11 (s, 2), 7.2–7.4 (m, 5). Anal. calcd for $C_{21}H_{36}N_4OSn$: C, 52.63; H, 7.57; N, 11.69. Found: C, 52.74; H, 7.65; N, 11.82.
12. Early work by Raap identified N1-substituted C5-anions as being susceptible to decomposition by an N_2-elimination, electrocyclic ring-opening fragmentation: Raap, R. *Can. J. Chem.* **1971**, *49*, 2139–2142. This fragmentation route was confirmed when **5** was treated with *t*-BuLi in THF/DMPU at −78°C followed by benzyl bromide to produce *N*-benzyloxymethyl-*N*-benzylcyanamide (67%): mp 51–53°C; ^{1}H NMR ($CDCl_3$) δ 4.29 (s, 2), 4.58 (s, 2), 4.65 (s, 2), 7.2–7.5 (m, 10). Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.93; H, 6.35; N, 11.03.
13. A typical procedure: 5-Phenyltetrazole (**7a**): A mixture of bromobenzene (**8**) (63 mg, 0.4 mmol), stannane **2** (230 mg, 0.48 mmol), tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol) and copper(I) iodide (8 mg, 0.04 mmol) in 2 mL of toluene was refluxed at 110°C for 2 h. The resulting mixture was filtered over Celite and the filtrate evaporated. The residue

was subjected to chromatography on SiO_2 eluting with hexane:EtOAc mixtures of 100:1, 50:1 and 25:1 which provided 67 mg (63%) of the compound **6a** as an oil contaminated with approximately 5 mol% tributyltin iodide by ^{1}H NMR: ^{1}H NMR (DMSO-d_6) δ 4.69 (s, 2), 6.12 (s, 2), 7.3–7.4 (m, 5), 7.5–7.6 (m, 3), 8.0–8.2 (m, 2). A solution of compound **6a** (60 mg, 0.23 mmol) in 2 mL of methanol and 0.2 mL of 6 M HCl was refluxed at 65°C for 3 h and then the solvent evaporated. The residue was dissolved in 1 M NaOH and extracted with EtOAc (2×) and these organic extracts discarded. The aqueous layer pH was lowered to 1 with 6 M HCl and then extracted with EtOAc (4×). This EtOAc extract was dried ($MgSO_4$) and evaporated to provide 28 mg (83%) of compound **7a** as a white solid. It was recrystallized with water/ethanol: mp 214–216°C (Aldrich cat. No. 34,774-4 mp 216°C). ^{1}H NMR (DMSO-d_6) δ 7.5–7.6 (m, 3), 8.0–8.1 (m, 3). Anal. calcd for $C_7H_6N_4 \cdot 0.1H_2O$: C, 56.83; H, 4.22; N, 37.87. Found: C, 57.04; H, 3.87; N, 37.54.

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