Lithiation Substitution of Unprotected Benzyltetrazoles

Lithiation-Substitution of Unprotected Benzyltetrazoles

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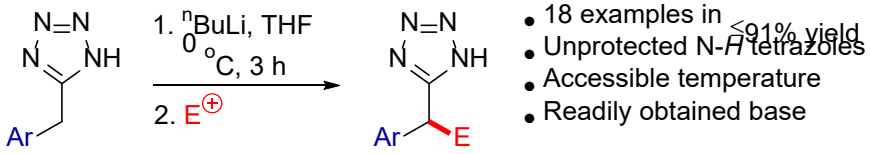
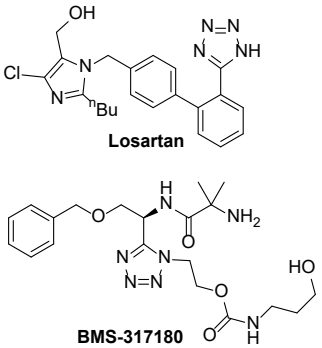
Supporting Information Placeholder



ABSTRACT: 1*H*-Tetrazoles occupy an important role in modern medicinal chemistry, but few methods for their modification exist. Many extant protocols require the use of a difficult to remove *N*-alkyl protecting group, precluding the products from use as carboxylate bioisosteres, the major role of tetrazoles in pharmaceuticals. We herein report a convenient, protecting group-free lithiation-substitution protocol for benzylic tetrazoles. Metalation with *n*-BuLi at 0 °C followed by electrophilic trapping gave a range of α-functionalised benzyltetrazoles in up to 91% yield.

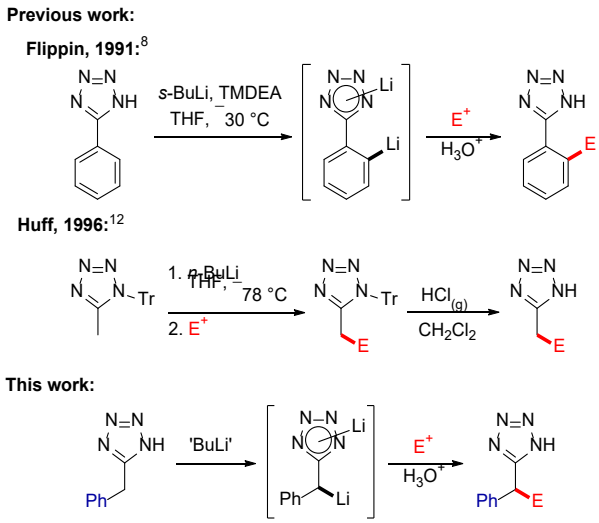
Tetrazoles occupy a privileged position in pharmaceutical chemistry, and appear in multiple blockbuster drugs,[1] most famously the angiotensin II receptor antagonist family typified by the first example, losartan.[2] Other bioactive examples include amide-mimetic tetrazoles such as BMS-317180 (figure **1**).[3] A recent survey of 1175 drug structures listed in the FDA Orange Book showed tetrazole as the 6th most common heteroaryl ring system.[4] Most frequently, they are employed as bioisosteres of carboxylates[5] displaying a similar size, shape, electronic distribution and pK_a.[6] *N*-H tetrazoles do not occur in nature, and bioactive tetrazoles display considerable metabolic stability compared with the analogous carboxylate.[7]

Figure 1



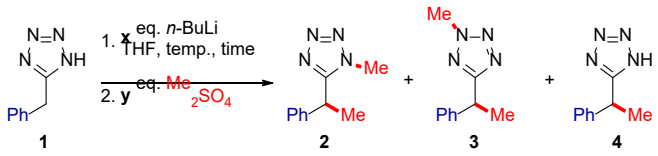
Despite this ubiquity in medicinal chemistry, the metalation-substitution of tetrazoles remains relatively unexplored. In 1991, Flippin reported that an unprotected 5-phenyltetrazole underwent ready *ortho*-metalation in the presence of *s*-BuLi, and subsequent electrophilic trapping afforded the *o*-functionalized products in good yields (scheme **1**).[8] Other protocols rely on preliminary tetrazole *N*-alkylation before metalation of the 5-substituent.[9-11] A major limitation of these methods is difficulty of deprotecting *N*-alkyltetrazole products, rendering them unsuitable for use as carboxylate bioisosteres. Huff and co-workers reported the metalation of 2-trityl-5-methyltetrazole, however subsequent deprotection was inconvenient, accomplished by passing gaseous HCl through a solution of the product in CH_2Cl_2.[12] Transition metal-catalysed tetrazole functionalizations also rely on protecting group strategies.[13, 14] In this context, we report a ready lithiation-substitution procedure for unprotected 5-benzyltetrazoles, allowing ready access to functionalized *N*-H tetrazolyl products.

Scheme 1



We were motivated by the observation that many naturally occurring carboxylate protein ligands are derived from α-amino acids and feature adjacent stereocentres, making α-stereogenic tetrazoles an important target (e.g. figure **1**).[3, 15-19] To begin, we decided to investigate conditions for the lithiation-substitution of the parent 5-benzyltetrazole **1**, followed by electrophilic trapping with Me_2SO_4 (table **1**). We proposed that trapping would occur preferentially at the more nucleophilic carbanion *vs*. N1 or N2. To our surprise, metalation using *n*-BuLi in THF at 0 °C (a temperature convenient for use on an industrial process chemistry scale) for 1 h then trapping with 1.0 equivalent of Me_2SO_4, dimethylated benzyltetrazoles **2** and **3** were isolated in 19% and 24% respectively (43% in total yield) with no evidence of monomethylated product **4** observed (entry 1). Neither increasing the amount of electrophile nor reducing the reaction temperature gave an increase in product yields (entries 2 and 3). It was found that yields could be increased by increasing the amount of electrophile further and metalating using 3.0 equivalents of base (entry 4), and slightly increasing the reaction time gave us our optimal conditions (entry 5).

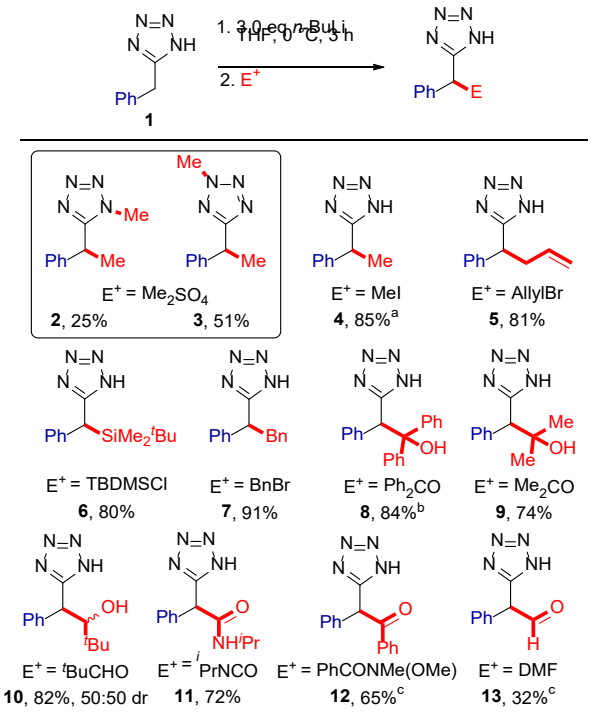
Table 1.



Entry	x	y	Temp. /°C	Time /h	Yield of **2**	Yield of **3**	Yield of **4**
1	2.2	1.0	0	1	19%	24%	0%
2	2.2	3.0	0	1	6%	20%	0%
3	2.2	3.0	–35	1	4%	37%	0%
4	3.0	4.0	0	1	27%	43%	0%
5	3.0	4.0	0	3	25%	51%	0%

With optimized conditions in hand, we explored the electrophile scope (scheme **2**), and proposed that other electrophiles than Me_2SO_4 would be less likely to facilitate *N*-alkylation. To our delight, this proved to be the case, and the mono-substituted desired products were obtained in good yield after trapping with MeI to give **4** in 85% yield, allyl bromide to give **5** (81% yield) and BnBr (**7**, 91%). Silylation was accomplished using TBMDSCl to give **6** in 80% yield. Other electrophiles included benzophenone (**8**, 84%), acetone (**9**, 74%), pivaldehyde (**10**, 82%), an isocyanate (**11**, 72%) and a Weinreb amide (**12**, 65%). A more modest yield was obtained after trapping with DMF to give **13** in 32%. Finally, we confirmed that 3.0 equivalents of base are required when trapping with electrophiles other than Me_2SO_4 – after metalation of **1** using 2.2 equivalents of *n*-BuLi under our standard conditions followed by trapping with Ph_2CO, only a 71% yield of **8** was obtained, compared with 84% when using 3.0 equivalents of base.We note that this requirement for 3.0 equivalents of base has also been observed by Flippin during *ortho*-metalation of 5-phenyltetrazole (scheme **1**).[8]

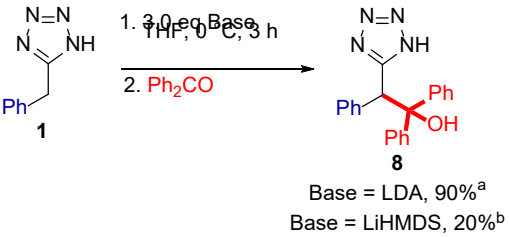
Scheme 2.



[a] Using 1.1 equivalents of MeI. [b] 71% after metalation with 2.2 equiv. *n*-BuLi. [c] As determined by ^{1}H NMR spectroscopy in the presence of Me_2SO_2.

Having demonstrated the electrophile scope and overcome the potential problem of *N*-substitution, we wondered whether less nucleophilic bases than *n*-BuLi might also effect the desired metalation. Thus, under our optimized conditions, metalation of **1** with LDA followed by trapping with benzophenone gave **8** in 90% yield, while a similar procedure using LiHMDS gave **8** in only 20% yield (scheme **3**). While using LDA may be more compatible with substrates bearing electrophilic motifs, we note that LDA is both more expensive (£49.90 for 100 mL of a 2.0 M solution in THF/hexanes/ethylbenzene *vs.* £43.60 for 100 mL of a 2.0 M solution of *n*-BuLi in hexanes, Sigma-Aldrich 2019) and usually obtained from reaction of *n*-BuLi and diisopropylamine; we thus propose that our optimized *n*-BuLi conditions are more convenient in most cases.

Scheme 3

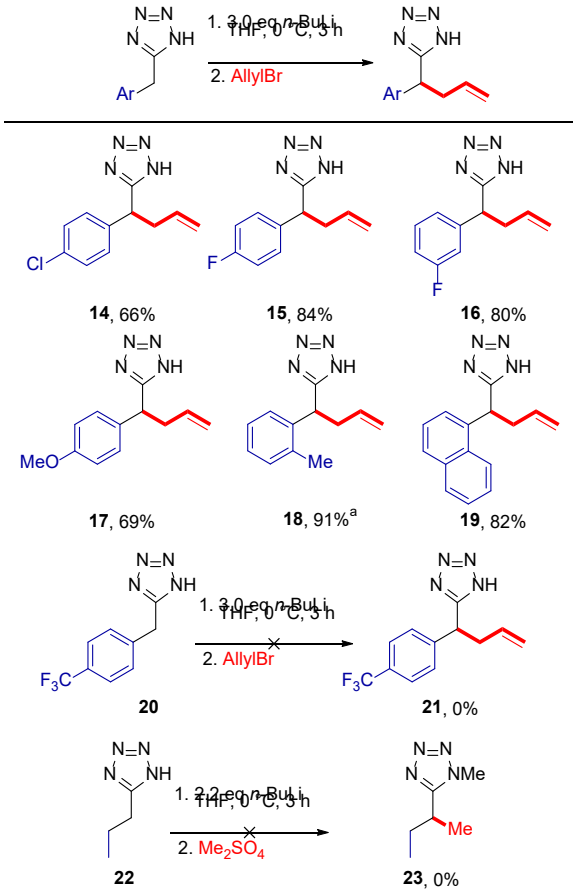


[a] Isolated yield. [b] Conversion determined by ^{1}H NMR spectroscopy.

Next, we turned our attention to exploring the benzyltetrazole substrate scope (scheme **4**). Haloaryl substrates were well tolerated with chlorinated product **14** being obtained in 66% yield after trapping with allyl bromide. Electron poor fluorinated products **15** and **16** were isolated in 84% and 80% yield, respectively, while electron rich **17** was afforded in 69%. We also explored sterically hindered substrates; 1-naphthyl product **19** (82% yield) was readily obtained, as was *ortho*-

methyl **18** (91%) after lengthening the lithiation reaction time from 3 to 4 h. After attempted lithiation-trapping of trifluoromethyl substrate **20**, expected product **21** was not obtained; inspection of the ^{1}H NMR spectrum of the crude reaction mixture suggested a mixture of polymeric products, presumably arising from the elimination of fluoride to give cyclohexadienyl species observed by Schlosser during the metalation of *para*-trifluoromethyltoluene, followed by polymerization as reported by Aitken.[20, 21] Attempted substitution of an alkyltetrazoles substrate was similarly unsuccessful, with no product **23** (or its 2-methyl isomer) obtained from 5-*n*-propyltetrazole **22**. Further attempts to metalate **23** using *s*-BuLi and longer reaction times yielded only modest amounts of α-substituted products (see ESI for details).

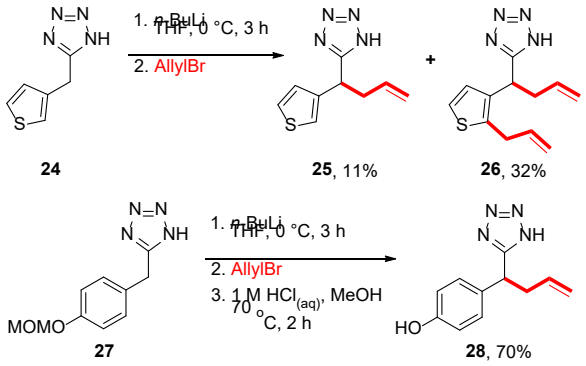
Scheme 4.



[a] After lithiation for 4 h

We next wished to explore heterocyclic examples. Attempted lithiation-substitution of thiophenyl example **24** gave an 11% yield of the expected product **25** and 32% of the disubstituted product **26** (scheme **5**), indicating that heterocyclic ring metalation was competitive with the desired reaction.

Scheme 5



Instead, we turned our attention to attempting to lithiate a protected phenol-bearing tetrazole. Thus, **27** was subjected to our standard reaction conditions and inspection of the crude reaction mixture suggested that substitution had taken place, but that partial MOM deprotection had also occurred. To remedy this, a deliberate one-pot MOM deprotection step was included in our standard reaction protocol. Thus, lithiation and electrophilic trapping was carried out as per our standard conditions, followed by evaporation and deprotection using $HCl_{(aq)}$ in MeOH at 70 °C for 2 h.[22] After work-up and purification, we were furnished with phenolic tetrazole **28** in 70% yield (scheme **5**). Finally, we investigated the possibility of developing an enantioselective lithiation-substitution protocol. After investigating the use of multiple chiral diamine alkyllithium ligands we were unable to obtain enantioenrichments better than 60:40 er (see ESI for full details) – optimization of stereoselective proceedures as well as α-functionalisation of unprotected 5-alkyltetrazoles remains a focus of research in our group.

To conclude, we have developed a convenient, general and high-yielding protocol for the α-lithiation-substitution of unprotected 5-benzyltetrazoles using a readily obtained base, *n*-BuLi at an industrially convenient temperature. Functionalised tetrazoles were obtained in up to 91% yield. Expansion of this methodology to generalized 5-alkyltetrazoles as well as enantioselective examples remains a focus of our ongoing research.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no conflict of interest.

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