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On the relative strength of the 1*H*-tetrazol-5-yl- and the 2-(triphenylmethyl)-2*H*-tetrazol-5-yl-group in directed *ortho*-lithiation

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Abstract—*ortho*-Lithiation followed by electrophilic trapping of *N*-unsubstituted and N2-triphenylmethyl substituted 5-aryltetrazoles, further substituted with another *ortho*-director at the *para* position of the aryl ring, resulted in the formation of regioisomers of which the ratio depended on the competing *para*-substituents. By such intramolecular competition experiments, the *ortho*-directing strength of these tetrazol-5-yl groups in comparison to some commonly employed *ortho*-directors were found to be: OMe<1*H*-tetrazol-5-yl<$CONEt_2$<2-(triphenylmethyl)-2*H*-tetrazol-5-yl<$NHCOCMe_3$, $OCONEt_2$.

In one of our medicinal chemistry programs we desired a set of compounds of the general structure **1**. The employment of the tetrazole-group—a well known carboxylic acid bioisostere[1]—as an *ortho*-director for the introduction of R^1 via directed *ortho*-lithiation,[2,3] was appealing because of the high structural diversity this methodology allows for. Possible electrophiles acting as carriers of R^1 are numerous and subsequent transformations via transition metal catalyzed cross-couplings further expands the possible diversity of the derivatives.[3–5] In addition, starting 5-aryltetrazoles are within easy reach from the corresponding nitriles[6] or halides.[7]

The literature covering the use of the tetrazole-group as an *ortho*-director in *ortho*-metalations applicable to the disconnection depicted in Fig. 1, is scarce but inspiring.

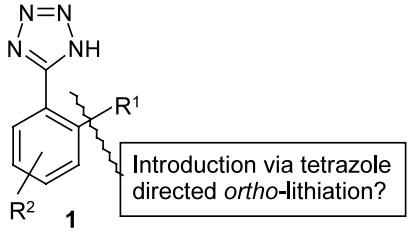

Figure 1. Strategy considered for the synthesis of compounds **1**.

Flippin[8] was the first to report on the use of 1*H*-tetrazole for this purpose, followed by Larsen et al.[5] who employed 2-(triphenylmethyl)-2*H*-tetrazole as *ortho*-director for the introduction of a boronic acid substituent. Additional reports from the patent literature include the *ortho*-lithiation[9] and the *ortho*-magnesiation[10] of *N*-unsubstituted and N2-triphenylmethyl-, or *N*-*t*-butyl-substituted, 5-aryl-tetrazoles. To our knowledge, little is known about the relative strength of the tetrazole as *ortho*-director when compared to other groups commonly used to direct metalations, or of the importance of the *N*-substituent attached to the tetrazole-nucleus. As this had implications for our synthetic strategy, we initiated a study; the results from which are summarized in this communication.

Initially, we subjected **2a–d** to standard *ortho*-lithiation conditions in order to study the influence of the *N*-substituent attached to the tetrazole-nucleus on the outcome of the reaction (Table 1). We observed high yields when the *N*-unsubstituted **2a** and the N2-triphenylmethyl substituted **2b** tetrazole was reacted with methyl iodide as electrophile (entries 1 and 2). The less reactive isopropyl iodide did not, however, give any product from either **2a** or **2b** under these conditions (entries 5 and 6). *N*-Benzyloxymethyl substituted tetrazoles are known to undergo lithiation at position 5,[7,11] but surprisingly, the corresponding 5-phenyl analogues **2c–d** (entries 7 and 8) failed to give any of the desired *ortho*-substituted products using a variety of conditions

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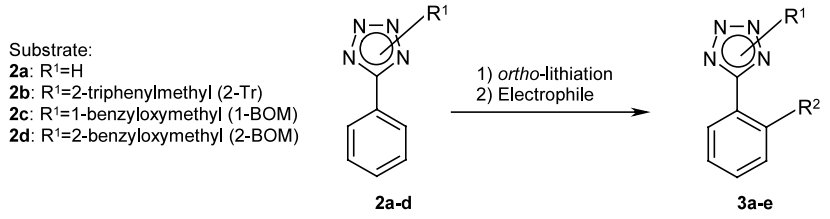
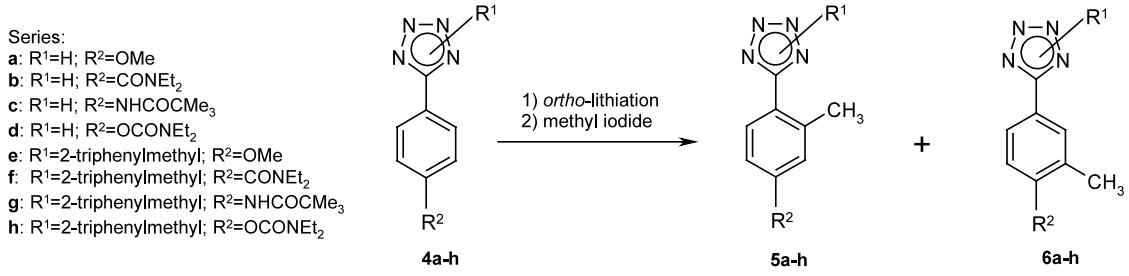
Table 1. *ortho*-Lithiation and electrophilic trapping of differently *N*-substituted 5-phenyltetrazoles[a]



Entry	Substrate/product	Electrophile	R^1	R^2	Temperature (°C)	Yield (%)[b]
1[f]	**2a**/**3a**	MeI	H	Me	−30	83
2	**2b**/**3b**	MeI	2-Tr	Me	−30	88
3	**2b**/**3c**	BnBr	2-Tr	Br	−30	38
4	**2b**/**3c**	BnBr	2-Tr	Br	−78	42
5	**2b**/**3d**	*i*PrI	2-Tr	*i*Pr	−30	[c]
6	**2a**/**3e**	*i*PrI	H	*i*Pr	−78	[c]
7	**2c**/–	[e]	1-BOM	–	[e]	[d]
8	**2d**/–	[e]	2-BOM	–	[e]	[d]

[a] General procedure: To a stirred solution of the substrate (2 mmol) and TMEDA (2 mmol) in dry THF at −78°C, was added *sec*-BuLi (6 mmol for **2a** and 4 mmol for **2b**–**d**). The mixture was kept at the indicated temperature for 1 h before addition of the electrophile (6 mmol), and then allowed to reach room temperature. Workup was done with aqueous satd ammonium chloride or 1 M HCl (for $R^1 = H$)/DCM, followed by purification by chromatography. All products showed spectroscopic data in accordance with the assigned structures.
[b] Isolated yields.
[c] Substrate recovered unchanged.
[d] Substrate recovered unchanged or a complex mixture was obtained.
[e] See text.
[f] See Ref. 8 for comparison.

Table 2. *ortho*-Lithiation of 5-aryltetrazoles carrying a competing *ortho*-director at the *para*-position[a]



Entry	Substrate/product	R^1	R^2	Temperature (°C)	Yield 5+6 (%)[b]	Conversion (%)[b]	Ratio[b,c] **5**:**6**
1	**4a**/**5a**,**6a**	H	OMe	−78	62	86	85:15
2	**4a**/**5a**,**6a**	H	OMe	−30	53	99	90:10
3	**4e**/**5e**,**6e**	2-Tr	OMe	−78	88	97	90:10
4	**4f**/**5f**,**6f**	2-Tr	$CONEt_2$	−78	53	98	95:5
5	**4b**/**5b**,**6b**	H	$CONEt_2$	−78	10	30	<5:>95
6	**4c**/**5c**,**6c**	H	$NHCOCMe_3$	−78	Trace	–	–
7[f]	**4c**/**5c**,**6c**	H	$NHCOCMe_3$	−30	Trace	–	–
8	**4g**/**5g**,**6g**	2-Tr	$NHCOCMe_3$	−30	25	96	<5:>95
9	**4g**/**5g**,**6g**	2-Tr	$NHCOCMe_3$	−78	12	71	<5:>95
10	**4h**/**5h**,**6h**	2-Tr	$OCONEt_2$	−78	26	>99	<5:>95
11	**4d**/**5d**,**6d**	H	$OCONEt_2$	−78	[d]	[d]	<5:>95[e]

[a] General procedure: see Table 1. Methyl iodide was used as the electrophile.
[b] As estimated by integration of the UV-trace (254 nm) from the RPHPLC-chromatogram of the crude products.
[c] Qualitative analysis by RPHPLC-MS and NMR.
[d] Insufficient separation on RPHPLC.
[e] As estimated from ^1H NMR integrals.
[f] 8 mmol (4 equiv.) of *sec*-BuLi was used.

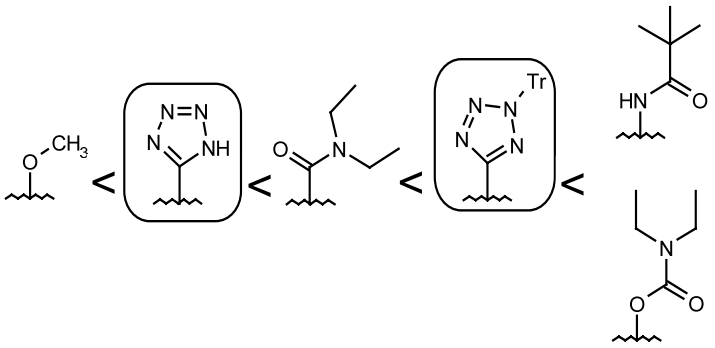


Figure 2. *ortho*-Directors arranged in the order of increasing strength.

[with or without TMEDA; temperature (−78 to 25°C); electrophile (MeI and DMF)]. As indicated by the comparable yields, lithiation of **2b** is as effective at −78°C as it is at −30°C (entries 3 and 4). This was further confirmed by HPLC-analysis of aliquots, followed by methyl iodide quench, taken from a solution of **2b** in THF after the addition of TMEDA and *sec*-BuLi. Full conversion of **2b** was achieved already at −78°C in less than 30 min.

Thereafter, the *para*-substituted 5-aryltetrazoles **4a**–**h** were used as substrates in intramolecular competition experiments (Table 2). The *N*-unsubstituted tetrazoles **4a**–**d** were conveniently obtained from the corresponding nitriles by treatment with trimethylsilyl azide and dibutyltin oxide in toluene at 100°C.[6] Subsequent tritylation yielded the corresponding N2-triphenylmethyl substituted derivatives **4e**–**h**. The *para*-substituents were chosen from the groups of moderate (OMe; **4a**,**e**) and strong ($OCONEt_2$; **4d**,**h**>$NHCOCMe_3$; **4c**,**g**, $CONEt_2$; **4b**,**f**) *ortho*-directors as classified by Snieckus.[2] From the ratio of the regioisomeric products **5a**–**h** and **6a**–**h**, resulting from *ortho*-lithiation followed by methyl iodide trapping of **4a**–**h**, respectively, an estimate of the *ortho*-directing strength of the *N*-(un)substituted tetrazole as compared to the *para*-substituent of the same molecule, was obtained. Thus, 2-(triphenylmethyl)-2*H*-tetrazole was found to be a stronger *ortho*-director than OMe and $CONEt_2$ (entries 3 and 4, respectively), but weaker than $NHCOCMe_3$ and $OCONEt_2$ (entries 8, 9 and 10, respectively), regioselectivities in these cases being equal to 9:1 or better.

In the same way, 1*H*-tetrazole was found to be stronger than OMe (entries 1 and 2), but weaker than $CONEt_2$ and $OCONEt_2$ (entries 5 and 11, respectively). The failure of **4c** to give more than trace amounts of either **5c** or **6c** may be due to the reluctance of the molecule to formally carry three negative charges after *ortho*-lithiation (entries 6 and 7). Overall, higher yields and conversions were obtained for N2-triphenylmethyl substituted, as compared to *N*-unsubstituted derivatives (entries 1 and 3, 4 and 5, 7 and 8).

In summary, we have estimated the relative strengths of the N2-triphenylmethyl substituted, and of the *N*-unsubstituted tetrazole nucleus, in comparison to some commonly employed *ortho*-lithiation directors through intramolecular competition experiments. The results are summarized in Fig. 2, where the tetrazoles are drawn together with the competing *ortho*-directors used in this study in the order of increasing strength. We believe that this information will serve as a useful guideline in the design of syntheses of 5-aryltetrazoles carrying additional substituents on the benzene-ring.

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