Lithiation-Functionalisation of Triazoles Bearing Electron-Withdrawing *N*-Substituents: Challenges and Solutions

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Abstract: The regioselective lithiation of 1,2,3-triazoles provides an opportunity to introduce additional functionality, however this simple functionalisation strategy using triazoles bearing electron-withdrawing *N*-substituents has not been investigated until now. Herein, we demonstrate that the lithiated triazole intermediates can readily decompose, even at −78 °C. In addition, lithiation-deuteration studies reveal lithiation can take place competitively on both the triazole and the electron-withdrawn aryl ring. Careful control of reaction conditions is therefore required to i) minimise decomposition pathways; and ii) facilitate regioselective functionalisation of the triazole.

Introduction

1,2,3-Triazoles are incredibly popular molecular motifs that have found widespread application in a diverse range of fields, including material science, bioconjugation, drug design, catalysis and supramolecular chemistry.[1] One reason for the use of 1,2,3-triazoles in these fields is their high chemical, thermal and biological stability, however they can also perform important functions. For example, 1,2,3-triazoles have been applied as metabolically-stable bioisosteres for amides, esters, carboxylic acids, alkenes and other heterocycles;[2] whilst their hole transport and H-bond donor properties have led to applications in electronics and anion recognition, respectively.[3]

The immense range of applications of 1,2,3-triazoles can be also attributed to the ease of their synthesis through the Nobel Prize winning Cu-catalysed azide-alkyne cycloaddition reaction.[4] In contrast to the thermal Huisgen azide-alkyne cycloaddition,[5] the Cu-catalysed variant provides excellent yield and regioselectivity for 1,4-substituted triazoles, and can be performed at room temperature in a range of solvents, including water, allowing its use in bioconjugation applications.[1c]

Bis-triazole/triazolium scaffolds as halogen/chalcogen bond donors in anion binding and catalysis have recently received significant attention and application.[6] As part of an on-going program into the design of new chalcogen bond donors, we were interested in the synthesis and functionalisation of related bis-triazoles bearing electron-withdrawing *N*-substituents (Figure 1A). Using conditions developed by Huber,[6h] the literature synthesis of selenated bis-triazole **3** bearing *N*-octyl substituents was replicated in an excellent 77% yield (Figure 1A); however, applying these conditions to a bis-triazole bearing *N*-bis(trifluoromethyl)phenyl groups resulted in a complex mixture, with none of the expected product **4**, or starting material **2**, present. Only a small number of studies have previously focused on the lithiation-functionalisation of triazoles (Figure 1B).[7] This is surprising considering 1,4,5-functionalised triazoles are bioactive motifs,[1e–h] and post-functionalisation of 1,4-triazoles in the 5-position provides a useful new vector to add or improve function in any of the myriad of applications for which triazoles find use. In 1971, Raap reported the lithiation of 1,4-diphenyl-1,2,3-triazole, followed by reaction with methyl iodide or carbon dioxide.[7a] Rapp also demonstrated that the lithiated triazole intermediate was prone to decomposition above 10 °C, resulting in extrusion of N_2 and formation of an *N*-phenylketenimine anion. Ohta subsequently demonstrated an expanded electrophile scope for the lithiation-functionalisation of *N*-methyl-1,2,3-triazole,[7b] whilst Holzer and Begtrup have reported directed lithiations using *N*-alkoxymethyl- and *N*-benzyloxy-1,2,3-triazole,

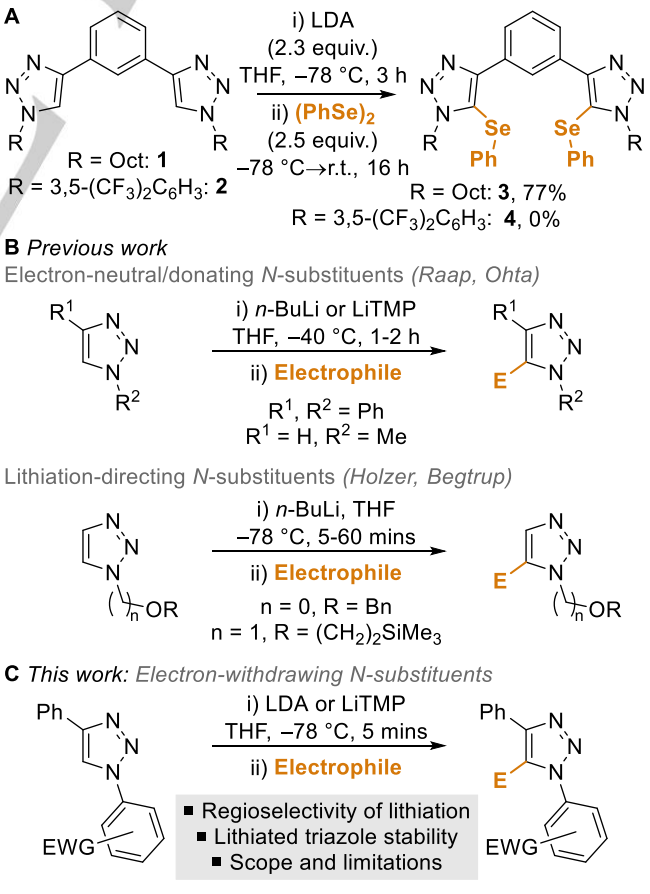

Figure 1. Lithiation-functionalisation of 1,2,3-triazoles. LDA = lithium diisopropylamide; LiTMP = lithium tetramethylpiperidide.

respectively.[7c,d] The synthesis of 1,4,5-functionalised triazoles can also be achieved through 'interrupted' Cu-catalysed azide-alkyne cycloaddition reactions,[8] however these methods add complexity by requiring alignment of the relative rates of various processes and therefore can restrict substrate scope. Due to the lack of studies on the lithiation-functionalisation of 1,2,3-triazoles bearing electron-withdrawn *N*-substituents,[9] we focused our efforts on understanding and optimizing this process. Herein, we report the lithiation-deuteration of a selection of 1,2,3-triazoles bearing electron-withdrawing groups to assess the regioselectivity of lithiation and understand the stability of the lithiated intermediates. The optimised lithiation conditions were then applied in lithiation-functionalisation reactions using a range of electrophiles (Figure 1C).

Results and Discussion

Initial investigations aimed to determine the origin of the issues encountered during the lithiation-selenation of bis-triazole **4**, by studying the lithiation of *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5** (Figure 2A). Triazole **5** was treated with lithium diisopropylamide (LDA) at −78 °C and allowed to warm to room temperature over 3 hours. Upon addition of LDA, a deep red solution was produced, which upon warming quickly turned black. Analysis of the crude reaction product mixture by ^{19}F NMR spectroscopy revealed that >15 different compounds were present, none of which were the starting triazole **5**. Of these compounds, only the major product was successfully isolated and identified as amidine **6**. Formation of this compound can be explained based on a combination of mechanistic pathways proposed in related work by Raap, Chang and Fokin (Figure 2B).[7a,10] Following deprotonation by LDA, the lithiated triazole **7** undergoes nitrogen extrusion to form lithium propargyl amide **8**. Protonation (possibly by diisopropylamine) gives ketenimine **9**, which can undergo nucleophilic attack from LDA to give, following protonation, the amidine product **6**.[10a,11] Further studies showed that ~5% amidine forms within 5 minutes, even when the reaction is maintained at −78 °C.[12] This highlights the instability of this lithiated triazole relative to those previously reported.[7] Of interest, Cu-catalysed azide-alkyne cycloaddition reactions using *N*-sulfonyl azides have been shown to spontaneously undergo a similar nitrogen extrusion process from the cuprated triazole intermediate at room temperature (Figure 2C).[10] Our work demonstrates that whilst the cuprated triazole bearing an *N*-bis(trifluoromethyl)phenyl substituent is sufficiently stable for the synthesis of triazole **5**, the lithiated species is unstable, even at −78 °C. These results indicate that the stability of metalated triazoles are a function of both the electron-withdrawing nature of the *N*-substituent[13] and the electropositivity of the associated metal.

The lithiation of a range of triazoles was investigated through treatment with LDA at −78 °C, followed by the addition of D_2O, where %D incorporation was used as a proxy for the extent of lithiation that had taken place (Figure 3). A standard lithiation time of 5 mins was chosen as only trace levels of decomposition were observed when using *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5** under these conditions. Lithiation-deuteration of triazoles **11** and **12** bearing electronically-neutral *N*-octyl and *N*-phenyl substituents was achieved with 88%D and 84%D incorporation, respectively (Figure 3A). The repeatability

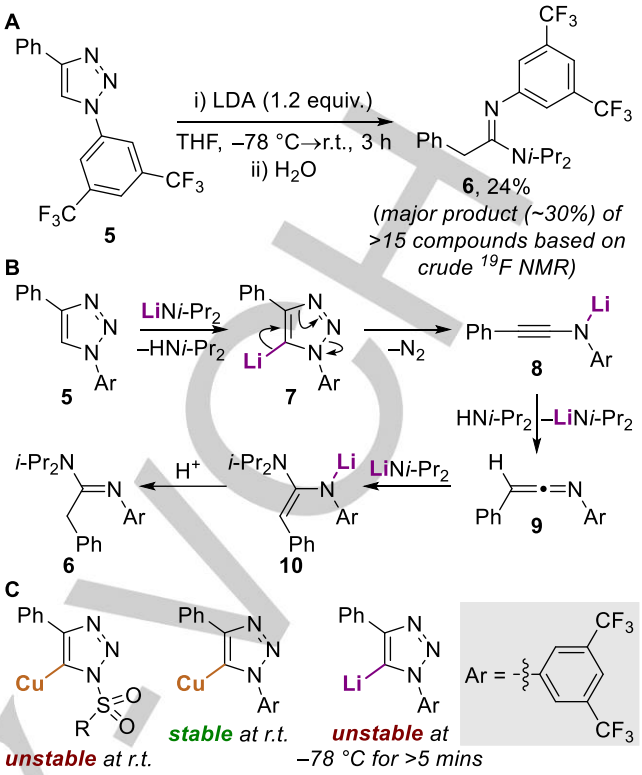

Figure 2. Lithiation-decomposition of *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5**. LDA = lithium diisopropylamide.

of lithiation-deuteration of *N*-octyl triazole **11** was assessed through 3 repeat experiments and provided a standard deviation of ±3%D.[14] A similar level of error was assumed for all other entries. Lithiation-deuteration of *N*-bis(trifluoromethyl)phenyl-substituted triazole **5** resulted in 90% deuteration at the 5-position of the triazole, in addition to 15%D in each of the *ortho*-positions of the bis(trifluoromethyl)phenyl ring.[15] To investigate this result further, the regioisomeric triazole **18**, with an *N*-phenyl substituent and a bis(trifluoromethyl)phenyl group at C(4), was subjected to the lithiation-deuteration procedure (Figure 3B). Exclusive deuteration of the triazole was observed with 87%D incorporation. This suggests that lithiation of the aryl ring is not purely due to the moderate directing effect of the CF_3 groups,[16] but also due to directing and acidifying effects of the triazole. Further variation of electron-withdrawing *N*-aryl substituents demonstrated there was also competition between deuteration at the triazole and aryl C-H when an *N*-2,4,6-trichloro- (**13**) or *N*-3,4,5-trifluorophenyl substituent (**14**) was used (Figure 3A). Lithiation-deuteration of *N*-pentafluorophenyl triazole **15** required the use the more sterically-hindered lithiating agent, LiTMP (lithium tetramethylpiperidide), to provide deuterated triazole **15** with 92%D incorporation (Figure 3A). In contrast, when LDA was used, a mixture of compounds was produced (Figure 3A, red box). Triazole **15** constituted ~60% of the reaction product mixture (80%D), with the next largest constituent (~30%) identified as aniline **16**. This product presumably arises from nucleophilic aromatic substitution (S_NAr) of the pentafluorophenyl substituent by LDA, directed through coordination of LDA to N(2) of the triazole. Whilst S_NAr reactions of pentafluorophenyl groups generally take place in the *para*-position,[17] examples of *ortho*-alkylation, amination and

alkoxylation have been reported using oxazinyl and oxazolinyl directing groups.[18,19] In contrast, when the regioisomeric triazole **19** was subjected to the lithiation-deuteration conditions using LDA, no S_NAr products were obtained, despite the potential for this process to be directed through coordination of LDA to the N(3) position (Figure 3B). This suggests that the S_NAr process is not only directed through proximal coordination of LDA, but also promoted through connection of the pentafluorophenyl group to the triazole at the electron-withdrawing N(1) atom. Finally, the attempted lithiation-deuteration of *N*-trifluoromethyltriazole **17** resulted in no detectable deuterium incorporation and significant (~80%) decomposition (Figure 3A)). This result implies that once lithiated, the triazole undergoes rapid decomposition, and is in line with the expected reduction in stability of this metalated triazole, as predicted computationally by Ariafard.[13]

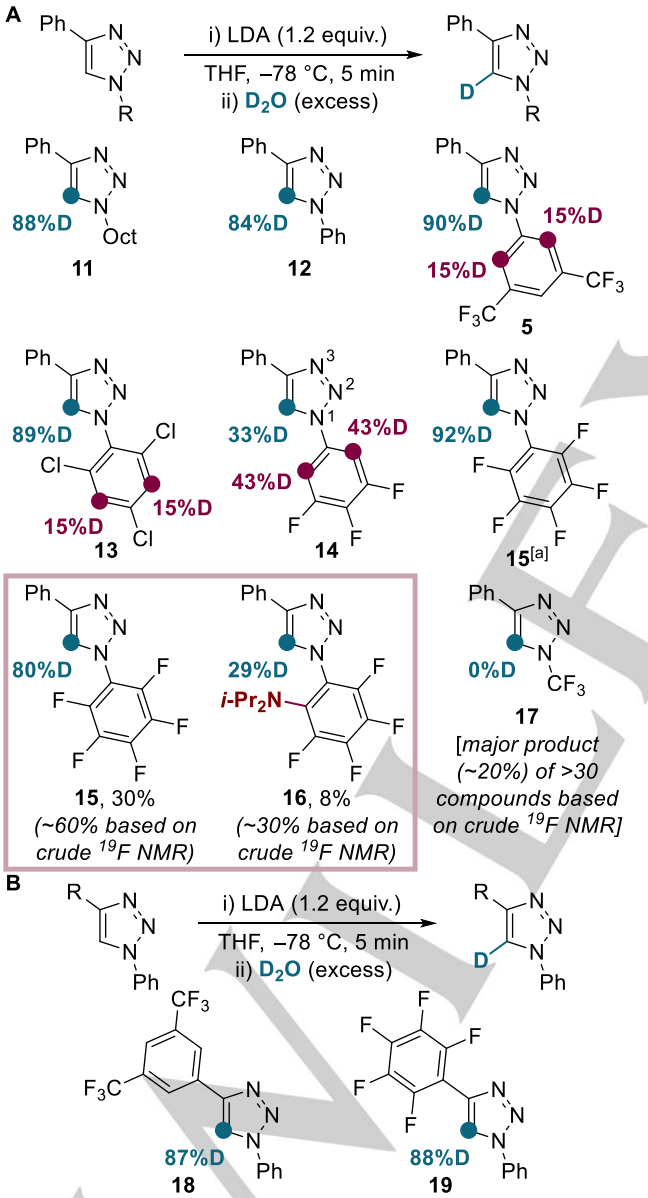

Figure 3. Lithiation-deuteration of triazoles. Error in %D value estimated as ±3. All triazoles obtained in >95% purity, except where specified. LDA = lithium diisopropylamide. [a] LiTMP used in place of LDA.

The utility of the developed lithiation conditions was investigated through lithiation-functionalisation of two selected triazoles (Figures 4, 5). *N*-Pentafluorophenyl triazole **15** was chosen due to the potential sensitivity of the pentafluorophenyl group; whilst *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5** was chosen to assess if regioselective functionalisation could be achieved despite the imperfect regioselectivity of lithiation (as shown by the lithiation-deuteration studies). Preparative isolation of deuterated triazole **15** was achieved in 67%, despite a 99% yield determined by ^{1}H NMR using an internal standard. This demonstrates that although no side-products were formed, isolation of these triazoles can pose a challenge. Halogenation was also successful, with iodo- and bromotriazoles **20** and **21** obtained in 57% and 50%, respectively. Alkylation, ethoxycarbonylation and sulfenylation were also achieved to give **22**–**24** in low to moderate yields. Selenation using diphenyldiselenide gave selenated triazole **25** in 13%, in addition to diselenated product **26** in 22%. This side-product presumably arises following S_NAr of product **25** by the phenylselenide anion released during triazole selenation.[20] In line with this proposal, side-product **26** could be completely supressed by using phenylselenyl bromide as the selenating agent. Alternative orders of addition and *in situ* trapping strategies were also investigated,[21] however the yield of the selenated product could not be further improved.[14] Finally, the use of either benzaldehyde or benzophenone led to cyclised products **27** and **28**.[22] These products presumably form through intramolecular S_NAr of the pentafluorophenyl ring by the oxyanion intermediate.[23] These results further highlight the sensitivity of the pentafluorophenyl ring to nucleophilic attack. Whilst electrophiles containing halogen and sulfinate leaving groups are compatible, more nucleophilic leaving groups (and intermediates) such as alkoxides and selenides can result in competitive S_NAr processes.

Next, lithiation-functionalisation of *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5** was investigated to determine if regioselective functionalisation could be achieved despite lithiation taking place on both the triazole and the bis(trifluoromethyl)phenyl ring (Figure 5). First, selenation using diphenyldiselenide at −78 °C and warming to room temperature over 2 hours resulted in a mixture of selenated triazole **29** and diselenated triazole **30** in 22% and 37% yield, respectively. Improved selectivity for the mono-selenated product **29** could be achieved by maintaining the reaction temperature at −78 °C for 1 hour, followed by quenching with water at this temperature (**29**: 53%; **30**: 4%). These conditions were then applied for further functionalisations using benzaldehyde and benzophenone, to give triazoles **31** and **32** in 43% and 57%, respectively. No evidence of functionalisation on the aryl ring was observed in either case. These examples demonstrate that although lithiation takes place on both the triazole and the aryl ring, careful control of the reaction conditions can allow selective functionalisation of the triazole and expand the range of products that can be accessed.

Finally, the optimised lithiation-selenation conditions were applied to bis-triazole **2**, leading to the formation and isolation of bis-selenated product **4** in 5% yield (Figure 6). This low yield was in part due to challenges associated with isolation; however it still provides a significant improvement upon the literature conditions initially applied (Figure 1A). Further work, and

alternative approaches, are currently being investigated to provide more efficient access to these novel architectures.

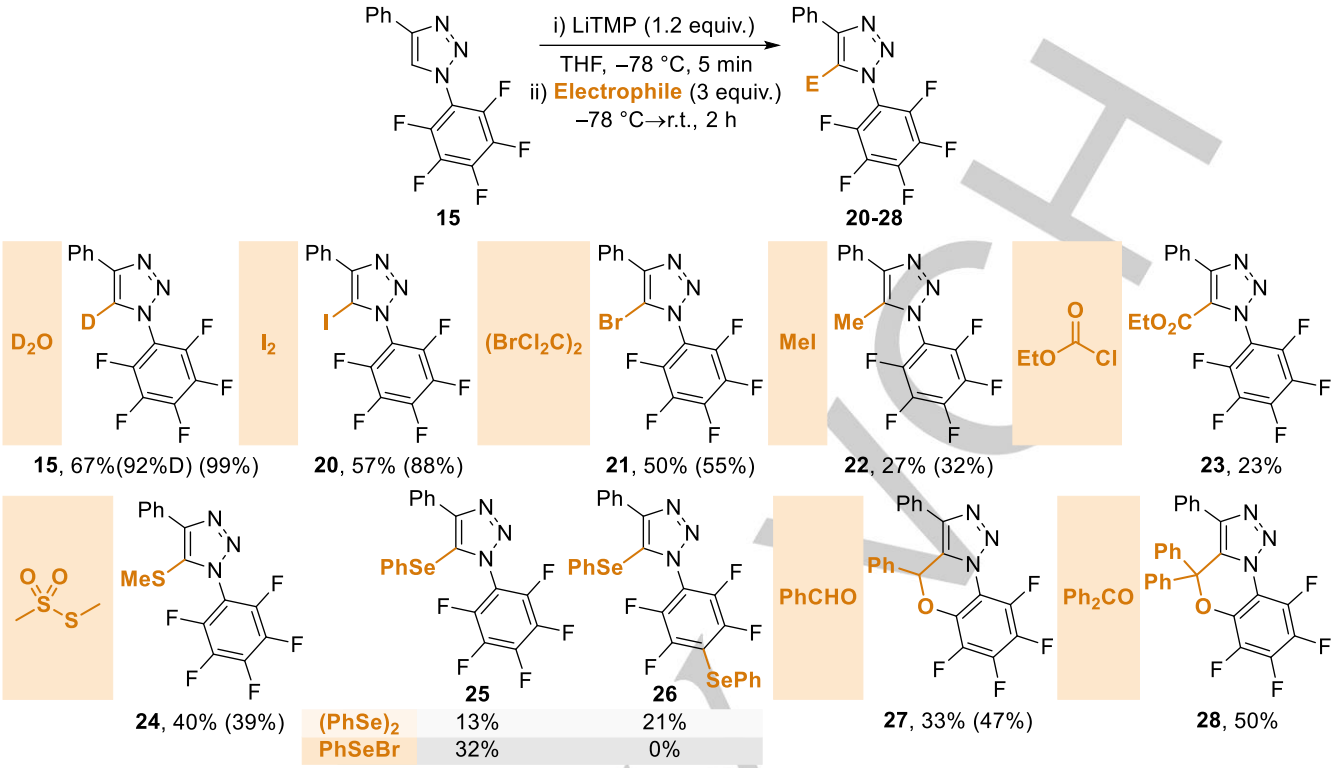

Figure 4. Lithiation-functionalisation of *N*-pentafluorophenyl-4-phenyl-1,2,3-triazole **15**. Yields in parentheses based on ^{1}H NMR using an internal standard. LiTMP = lithium tetramethylpiperidide.

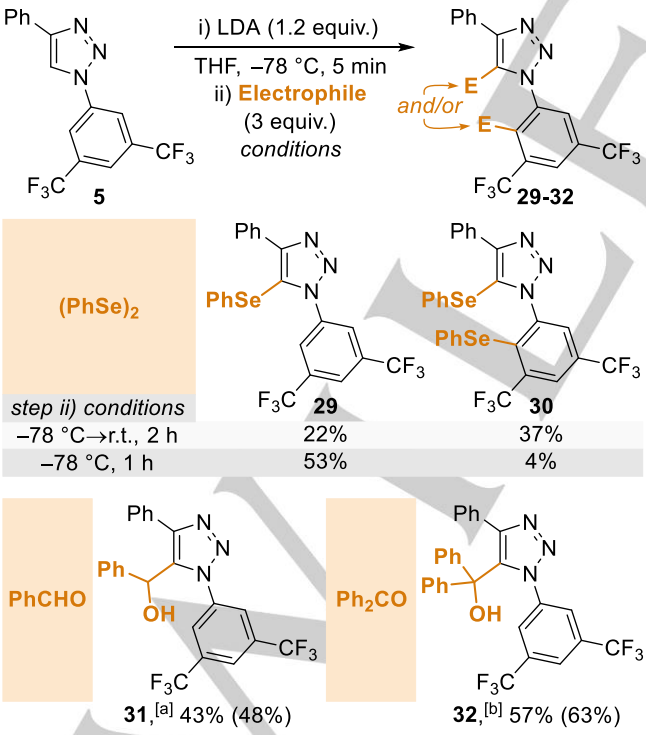

Figure 5. Lithiation-functionalisation of *N*-bis(trifluoromethyl)phenyl-4-phenyl-1,2,3-triazole **5**. Yields in parentheses based on ^{1}H NMR using an internal standard. LDA = lithium diisopropylamide. [a] step ii conditions: −78 °C, 1 h. [b] step ii conditions: −78 °C, 5 h.

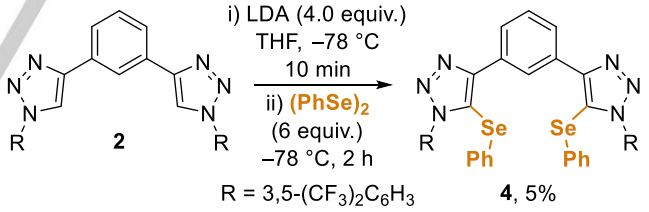

Figure 6. Lithiation-selenation of *N*-bis(trifluoromethyl)phenyl-substituted bistriazole **2**. LDA = lithium diisopropylamide.

Conclusion

In conclusion, we have demonstrated that 5-lithiated 1,2,3-triazoles with *N*-aryl substituents bearing electron-withdrawing groups are susceptible to decomposition, even at −78 °C. In addition, lithiation can take place competitively on both the triazole and the electron-withdrawn *N*-aryl ring. To achieve successful and regioselective lithiation-functionalisation processes, short reaction times and low reaction temperatures are essential. In total, the lithiation of 9 triazoles and the use of 9 different electrophiles was demonstrated, giving 5-functionalised triazoles in 23-67% yield. Whilst LDA was used for the lithiation of the majority of triazoles, the lithiation of an *N*-pentafluorophenyl triazole resulted in competitive *ortho*-amination, presumably through directed nucleophilic aromatic

substitution. The use of the more sterically-hindered LiTMP was therefore required in this case. Furthermore, we have demonstrated that even at −78 °C lithiated triazoles bearing an *N*-trifluoromethyl substituent are not sufficiently stable to be utilised. This experimentally-determined trend of lithiated triazole intermediate stability is in line with computational predictions made by Ariafard on an analogous series of cuprated triazole intermediates in Cu-catalysed azide-alkyne cycloaddition reactions.[13] Overall, this work provides insight into the stability of metalated triazole intermediates and presents cautionary information and suggested solutions for the successful functionalisation of triazoles bearing electron-withdrawn *N*-substituents.

Experimental Section

All experimental details are provided in the supporting information, including details on i) reaction set-up and work-up; ii) analytical characterisation data, including melting points, ^{1}H, ^{2}H, ^{13}C and ^{19}F NMR spectroscopy, IR spectroscopy and high-resolution mass spectrometry; and iii) NMR traces for all novel compounds.

Acknowledgements

This research was funded in whole or in part by the EPSRC, Grant number EP/R513374/1. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission. Research data underpinning this manuscript can be accessed at http://wrap.warwick.ac.uk/170069/.

Keywords: lithiation • substituent effects • heterocycles • fluorine • deuterium

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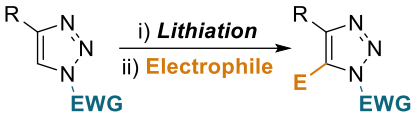

Presence of **Electron-withdrawing group** promotes side-reactions

Assessment of:

☑ Lithiated triazole stability
☑ Regioselectivity of lithiation
☑ Scope and limitations

Lithiated 1,2,3-triazoles bearing electron-withdrawing *N*-substituents are susceptible to decomposition, even at −78 °C. In addition, lithiation of *N*-aryl triazoles can take place at either the triazole or the *N*-aryl ring. Careful control of reaction conditions is therefore required to i) minimise decomposition pathways; and ii) facilitate regioselective functionalisation of the triazole.

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