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From rare reagents to rare products: regiospecific silver-catalyzed [3+2] cycloaddition of aryl-, alkyl- and aminosulfonyl diazomethanes with arenediazonium tosylates

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ABSTRACT

The scope of silver nitrate-catalyzed cycloaddition of arenediazonium salts has been expanded to include aryl- and alkylsulfonyl diazomethanes as well as the recently introduced diazomethyl sulfonamides. The reliance on these two classes of diazo compounds led to a new synthetic approach to the rare 2-aryltetrazol-5-yl sulfones as well as to the synthesis of hitherto not described 2-aryltetrazol-5-yl sulfonamides.

Introduction

Diazo compounds are distinctly versatile reagents with multiple reactivity modes.[1] However, some types of diazo reagents are either scarce (owing perhaps to the difficulties associated with their synthesis) or have not been investigated in preparative chemistry context.[2] The scarcity or absence of every such type of diazo reagent in the current arsenal of diazo reagents essentially deprives us from access to entire domains of the druglike chemical space.[3] Thus, developing new types of diazo reagents or alleviating synthetic hurdles to rare ones through new methodology findings is a worthy goal on its own which may immediately impact the outlook of synthetically accessible compounds for biotarget interrogation.[4]

Recently, we discovered a convenient, one-pot synthetic route to various α-diazo-β-ketosulfones **1**[5] which had been accessed *via* more cumbersome approaches. It occurred to us that acetyl variants of these compounds (**1**, R^2 = Me) could be deacetylated,[6] which would give rise to sulfonyl diazomethanes **2**. The latter represent a scarcely populated class of 'terminal' diazo compounds[7] which have been accessed predominantly by entirely different strategies.[8] Another class of diazo compounds which had been completely absent from the synthetic chemistry toolbox were the recently reported [9] CH-diazomethanesulfonamides **3**. Both **2** and **3**

appeared suitable partners for a [3+2] cycloaddition reaction with arenediazonium salts. As reported recently by us[10] and others[11] such a reaction, catalyzed by silver(I) salts, provides a facile and regiospecific entry into medicinally important[12] 2,5-disubstituted tetrazoles. We reasoned that this cycloaddition, if successfully applied towards **2** and **3**, would deliver 2-aryl tetrazol-5-yl sulfones **4** and sulfonamides **5** (Figure 1). Considering the significance of tetrazoles in general as amide bond replacements[13] as well as scaffolds with favorable physicochemical characteristics for drug design,[14] we noted that tetrazol-5-yl sulfones analogous to **4**[15] had been constructed in such a convenient and atom-economical manner. Moreover, preparation of 2-substituted tetrazol-5-yl sulfonamides in general (and of **5** in particular) have not been reported in the literature, which is a significant void to fill considering the importance of sulfonamides in drug design.[16] Thus, we set off to investigate this approach and would like to report our findings herein.

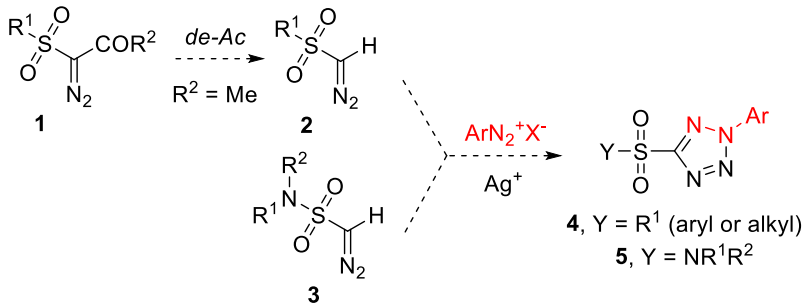
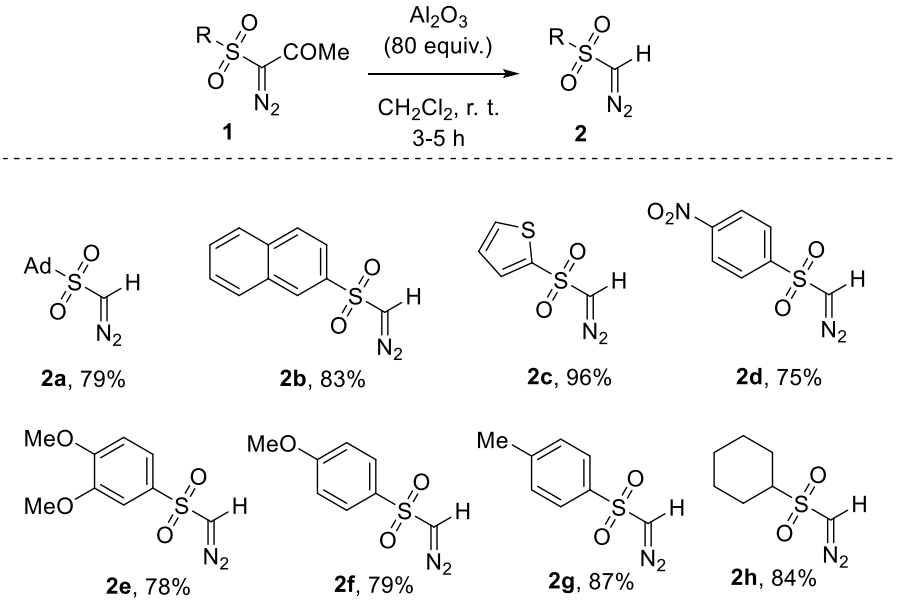


Figure 1. New approach to 2-aryl tetrazol-5-yl sulfones **4** and sulfonamides **5** investigated in this work.

Results and discussion

There are reports in the literature on the use of α-diazo-β-ketosulfones **1** (R^2 = Me) in the cycloaddition reactions with nitroolefins leading to pyrazoles.[17] In these reactions, substrates **1** were deacetylated *in situ* with sodium alkoxide in the respective alcohol as the reaction medium to give diazomethyl sulfones **2**. Unfortunately, such an *in situ* protocol was not found applicable to subsequent silver(I)-catalyzed cycloaddition with arenediazonium salts and we resorted to the preparation and isolation of reagents **2** prior to their subsequent use. A selection of eight α-diazo-β-ketosulfones **1a-h** prepared as described previously[5] was treated with excess alumina in dichloromethane at r. t. The deacetylation proceeded smoothly over 3-5 h and produced diazomethyl sulfones **2a-h** in good to excellent yields (Scheme 1).



Scheme 1. Preparation of diazomethyl sulfones **2a-h** (Ad = 1-adamantyl).

Sulfonyl diazomethanes **2a-h**, along with three sulfamoyl diazomethanes **3a-c** prepared as described recently,[9] were employed in the cycloaddition reactions with a series of arenediazonium tosylates **6a-k** (Figure 2) which had been earlier found[18] to be stable and easy to handle non-hygroscopic solid reagents and, importantly, proven efficient partners in similar cycloaddition reactions with acyl diazomethanes.[10]

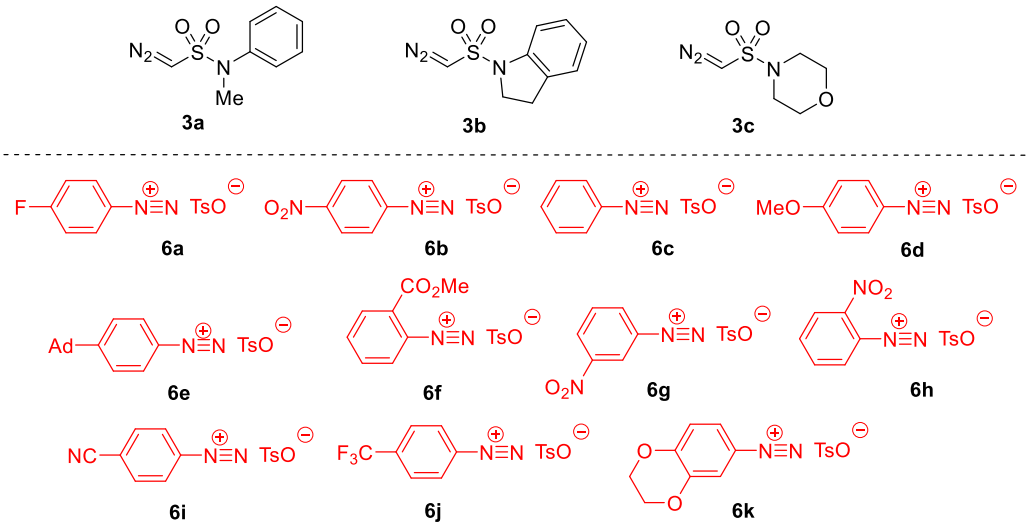


Figure 2. Selection of reagents for the tetrazole synthesis scope exploration.

Reaction conditions identified earlier for the cycloaddition of arenediazonium tosylates **6a-k** with acyl diazomethanes (1.1 equiv. **6**, 10 mol% $AgNO_3$, DABCO, 10% DMF in THF, 0 °C to r. t., 18 h)[10] were found to give high yields of the desired cycloaddition products and, therefore, were not optimized further. These conditions were employed throughout the scope investigation the results of which are presented in Scheme 2.

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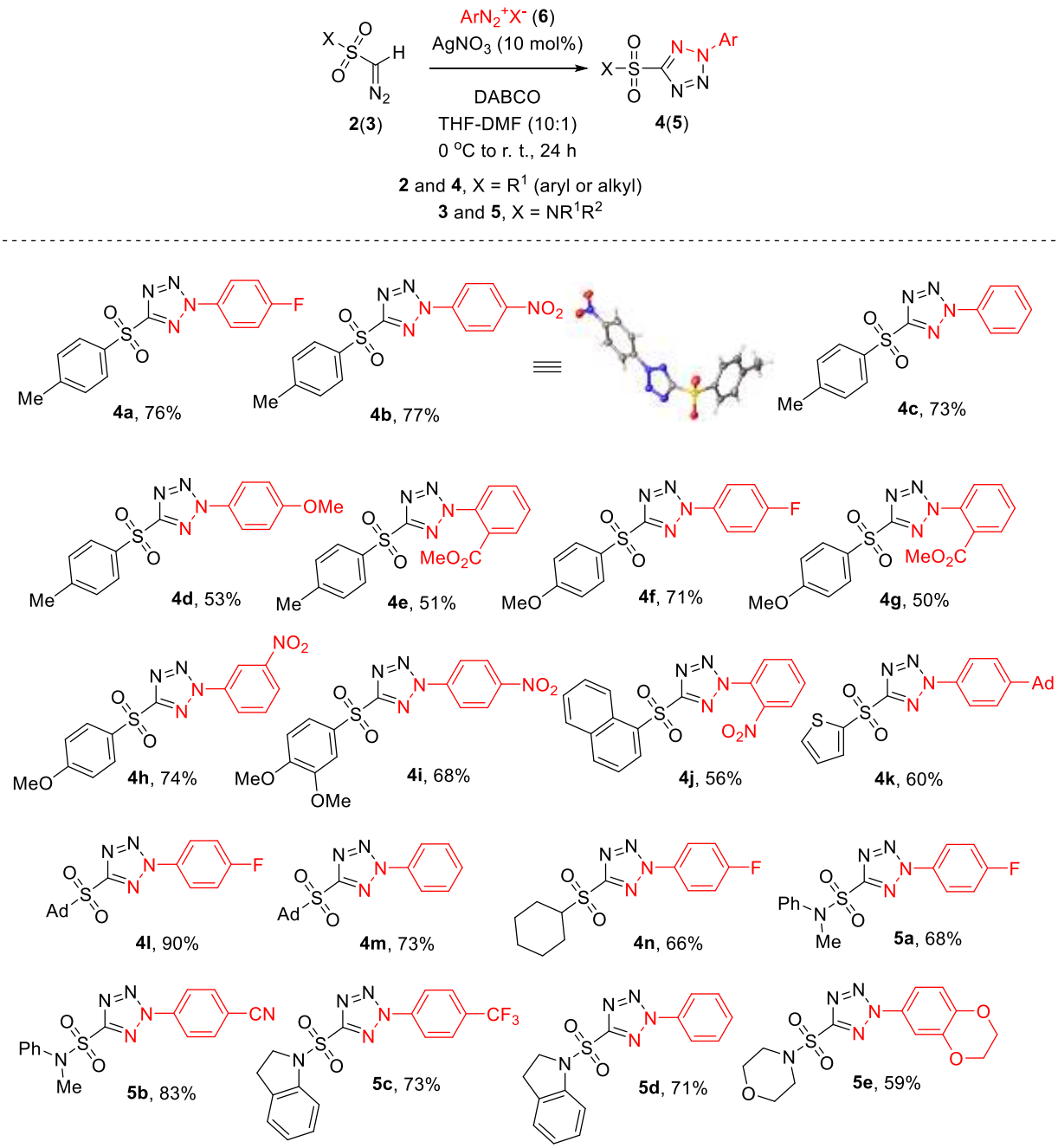
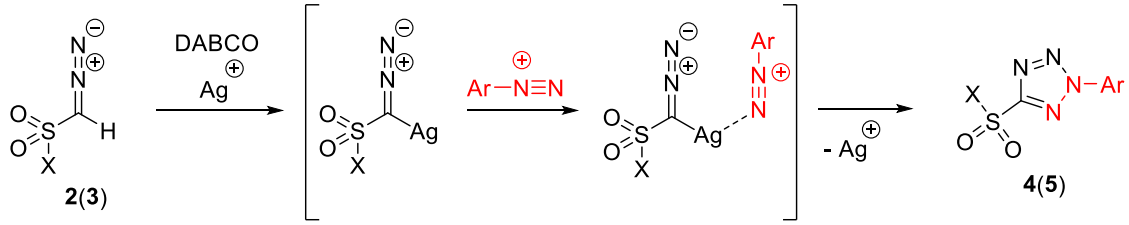


Scheme 2. Synthesis of 2,5-disubstituted tetrazoles **4** and **5**. The reactions were conducted on a 0.3 mmol scale, in the mixture of dry DMF (0.2 mL) and dry THF (1.8 mL).

The yields of products **4a-n** and **5a-e** are generally good throughout. However, the yields were noticeably lower for the diazonium partners with electron-donating groups (**4d**, **5e**) or *o*-substituents (**4e**, **4g**, **4j**). The structures of the tetrazoles thus obtained were consistent with the ^{1}H and ^{13}C NMR data, high-resolution mass-spectrometry. For a representative compound (**4b**), single-crystal X-ray crystallography confirmed the anticipated regiochemistry.

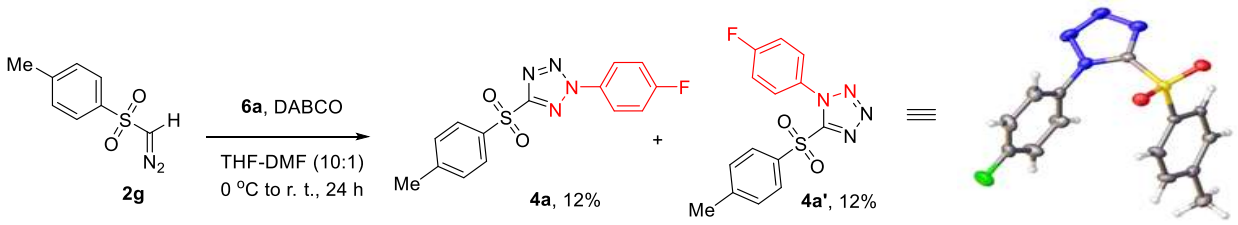
The high regiospecificity of the reaction is thought to be due to the silver(I) catalyst employed.[10] A plausible mechanism may include deprotonation of the starting diazomethyl

sulfone or sulfonamide and coordination of the reacting substrates with the silver cation. The latter event likely activates the partners towards the cycloaddition (which liberates the catalyst) and ensures the observed regiochemical outcome (Scheme 3).



Scheme 3. Plausible mechanism of the tetrazole formation involving a silver(I) catalyst.

Much in line with this mechanistic consideration, the reaction between **2g** and **6a** conducted under identical conditions in the absence of the silver(I) catalyst proved not only less efficient but also turned out to be completely non-regiospecific and afforded a 1:1 mixture of tetrazoles **4a** and **4a′** in combined 40% yield (both regioisomers were isolated by preparative HPLC in 12% yield each). The structure of **4a′** was unequivocally confirmed by single-crystal X-ray analysis (Scheme 4).



Scheme 4. Non-catalyzed cycloaddition reaction.

Conclusion

Based on two rare classes of diazo compounds – diazomethyl sulfones and sulfonamides – we developed a [3+2] cycloaddition approach to the respective 2,5-disubstituted tetrazoles *via* $AgNO_3$-catalyzed reaction with arenediazonium tosylates. While only four tetrazol-5-yl sulfones with the same substitution pattern have been reported so far in the literature as prepared in entirely different manner, preparation of tetrazol-5-yl sulfonamides has not been described to-date. These findings expand the methodologically enabled toolbox of synthetic diazo chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical and crystallographic data, copies of the NMR spectra. CCDC 1994531 (**4b**) and 1994532 (**4a'**) contain the supplementary crystallographic data for this

paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

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Notes

The authors declare no competing financial interest.

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KEYWORDS: sulfonyl diazomethanes; sulfamoyl diazomethanes; deacetylation; cycloaddition; arenediazonium tosylate; regiospecificity; silver(I) catalysis.

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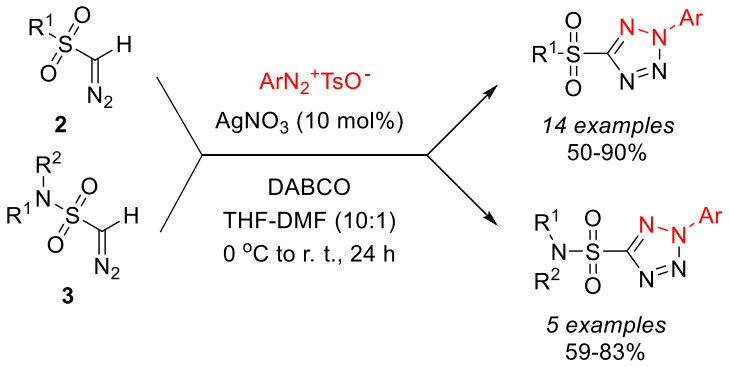
Graphical abstract



TOC text

Ag(I)-catalyzed [3+2] cycloaddition between diazomethyl sulfones and sulfonamides with arenediazonium tosylates provides regiospecific access to novel tetrazoles.

Key topic

Diazo compounds