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Synthesis of 2-aryl-2H-tetrazoles via a regioselective [3+2] cycloaddition reaction

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ABSTRACT

A regioselective cycloaddition reaction of arenediazonium salts with trimethylsilyldiazomethane is reported. A series of 2-aryltetrazoles were obtained in good to moderate yields with wide functional group compatibility. Furthermore, this cycloaddition reaction opens the way to build up the versatile intermediate 2-aryl-5-bromotetrazole.

Introduction

Tetrazoles are an important class of five-membered ring heterocycles broadly used in pharmaceuticals, agrochemicals and material science. Surprisingly, the synthesis of simple unsubstituted 2-aryltetrazoles is almost non-existent in the literature. Lippmann *et al.* has developed a regioselective method for the construction of 2-aryl tetrazoles employing 2-(2-arylhydrazono)acetic acid and 1-azido-2,4,6-tribromobenzene[1]. Ito's synthesis employs arylsulfonylhydrazones and arene diazonium salts but both of these strategies afford 2-aryl-5-carboxylatetetrazole and must be decarboxylated at 160 °C[2]. Genin *et al.* and Kitazaki *et al.* reported a nucleophilic aromatic substitution between 4-nitrofluorobenzene or 3,4-difluoronitrobenzene and tetrazole but these non-regioselective transformations gave poor yields and require the nitro group for activation (10% to 25%)[3,4]. Very recently, Ramanathan *et al.* reported a cyclisation between an aryldiazonium salt and formamidine in the presence of iodide[5].

There are more examples of 2-aryl-5-substituted tetrazoles in the primary literature. This scaffold has recently acquired increasing attention from the medicinal chemistry community. For example, this substitution pattern has recently appeared in Breast Cancer Resistance Protein inhibitors[6], DNA methyltransferases 1 inhibitors[7], $\alpha_4\beta_2\alpha_5$ nicotinic acetylcholine receptors modulators[8], FAAH inhibitors[9] and MDR1 inhibitors[10]. In addition to Lippmann's and Ito's synthetic methods, Han and co-workers reported the synthesis of 2-aryl-5-substituted tetrazoles through the coupling of 5-substituted tetrazoles with arylboronic acids in the presence of copper(II)[11]. Onaka *et al.* also reported a regioselective 2-arylation of 5-substituted tetrazoles catalyzed by $[Cu(OH)(TMEDA)]_2Cl_2$.[12]

We recently had the need for the synthesis of substituted N-linked tetrazoles with versatility for substitution at the 5-position (H or aryl) wherein none of the current published methods proved useful. Therefore we embarked upon a search for a facile and robust method to generate these molecules. Chen *et al.* recently reported a cycloaddition between an arene-diazonium salt and 2,2,2-trifluorodiazoethane with a catalytic amount of silver salt[13]. This method was attractive, however the tetrazole products

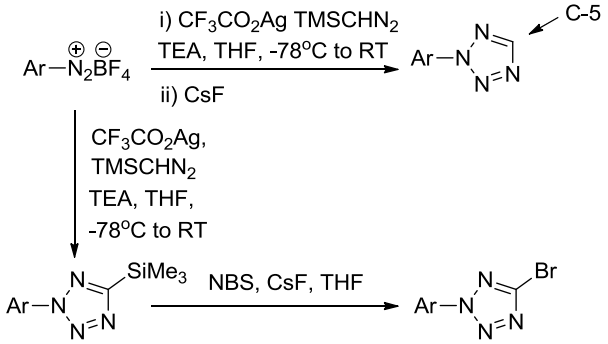


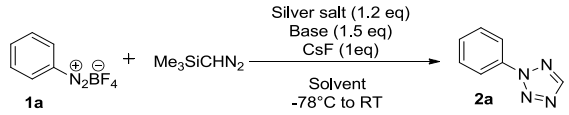
Figure 1. Tetrazole Formation

formed were CF_3-substituted at the 5-position wherein we needed a hydrogen atom or aryl ring. We envisioned that a silver salt might also be utilized to promote the cyclization of an arenediazonium salt with trimethylsilyldiazomethane. This would provide for TMS-substituted tetrazoles, which could either be desilylated to produce the unsubstituted tetrazole or converted to the bromo-tetrazole for further

functionalization (Figure 1). Herein, we report a [3+2] cycloaddition between an arenediazonium salt and trimethylsilyldiazomethane with a silver salt catalyst. This cycloaddition affords 2-aryl-5-trimethylsilyltetrazoles, a key intermediate which can be easily cleaved in one pot with CsF to provide 2-aryltetrazoles.

Results and discussion

Table 1. Optimization of reaction conditions[a]

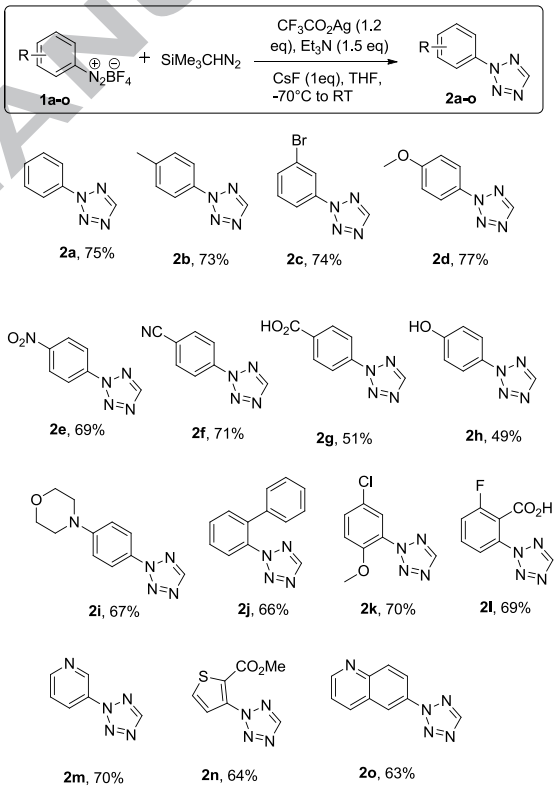


Entry	Catalyst	Base (equiv)	Solvent	Yield[b] (%)
1	CF_3CO_2Ag	Et_3N (1.5)	THF	82 (75)
2	$AgBF_4$	Et_3N (1.5)	THF	70 (61)
3	$AgNO_3$	Et_3N (1.5)	THF	69
4	AgOTf	Et_3N (1.5)	THF	70 (62)
5	AgOAc	Et_3N (1.5)	THF	42
6	Ag_2CO_3	Et_3N (1.5)	THF	<10
7	$Cu(OAc)_2$	Et_3N (1.5)	THF	<10
8	CF_3CO_2Ag	Cs_2CO_3 (1.5)	THF	36
9	CF_3CO_2Ag	Na_2CO_3 (1.5)	THF	<10
10	CF_3CO_2Ag	Lutidine (1.5)	THF	<10
11	CF_3CO_2Ag	DBU (1.5)	THF	71
12	CF_3CO_2Ag	DABCO (2.0)	THF	49
13	CF_3CO_2Ag	Et_3N (2.0)	THF	79
14	CF_3CO_2Ag	Et_3N (2.5)	THF	74
15[b]	CF_3CO_2Ag	Et_3N (3.0)	THF	77
16[c]	CF_3CO_2Ag	Et_3N (3.0)	THF	79
17[d]	CF_3CO_2Ag	Et_3N (1.5)	THF	<10
18[e]	CF_3CO_2Ag	Et_3N (1.5)	THF	<10
19[f]	CF_3CO_2Ag	Et_3N (1.5)	THF	23
20	CF_3CO_2Ag	Et_3N (1.0)	THF	54
21	—	Et_3N (1.5)	THF	<10
22	CF_3CO_2Ag	—	THF	<10
23	CF_3CO_2Ag	Et_3N (1.5)	CH_3CN	<10
24	CF_3CO_2Ag	Et_3N (1.5)	DCM	<10
25	CF_3CO_2Ag	Et_3N (1.5)	DMF	<10
26[g]	CF_3CO_2Ag	Et_3N (1.5)	THF/DMF	23
27	CF_3CO_2Ag	Et3N (1.5)	Toluene	77 (69)

[a]General reaction conditions: **1a** (0.2 mmol), Me_3SiCHN_2 (1.1eq), catalyst (1.2 eq), base (x equiv) in 2 mL of solvent under Ar at -78°C for 1 h. Yields were determined by HPLC with 3,5-Dimethoxybromobenzene as an internal standard. The values in parentheses represent the yields of isolated products. [b]2 eq CF_3CO_2Ag; [c]2 eq CF_3CO_2Ag and 1.5 eq Me_3SiCHN_2; [d]10 mol% of CF_3CO_2Ag was used; [e]reaction at 4°C; [f]reaction at -20°C; [g]THF/DMF = 10/1.

To optimize reaction conditions, phenyl diazonium tetrafluoroborate **1a** was employed as a substrate using trimethylsilyldiazomethane with various silver salts and one copper salt (widely used in click chemistry) in THF at -78 °C (entries 1-7, **Table 1**). To our delight, CF_3CO_2Ag was found to be optimal, and the cycloaddition proceeded smoothly to furnish the desired cycloadduct **2a** in 75% yield (entry 1).

The use of 2 equivalents of CF_3CO_2Ag did not improve the yield (entries 15 and 16). In sharp contrast, the reaction did not proceed without the silver catalyst or with only 10 mol% of CF_3CO_2Ag (entries 17 and 21). The control of the temperature is a critical parameter : a mixture of uncharacterized by-products is obtained when the reaction is conducted at 4°C and poor yield was obtained at -20°C (entries 18 and 19). Note that 1-aryl-1H-Tetrazole has never been detected. Next, we turned our attention to testing a range of mineral and organic bases. Triethylamine was found to be the base of choice for this cycloaddition reaction (entries 8-12). The yield substantially decreased with only 1 equivalent of trimethylamine (entry 20) and no reaction was observed without any base (entry 21), but 2.0 equivalents of Et_3N did not improve the yield when compared to that obtained with 1.5 equivalent of Et_3N (entries 1 and 13). A solvent screen was conducted in order to explore this parameter further (entries 23-27). THF was identified as the optimal solvent from those screened.

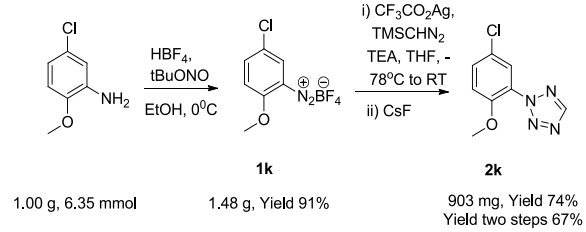


Scheme 1. Substrate scope of cycloaddition reaction of $TMSCHN_2$ with aryl diazonium salts

Having established optimal conditions, we set out to explore the scope of this silver-mediated cycloaddition reaction, and the results are summarized in **Scheme 1**. In the case of phenyl diazonium salts, the cycloaddition reaction tolerates various substitution patterns and a range of different substituents on the phenyl ring. Alkyl-, alkoxy-, amino-, cyano-, nitro-, acid-, halo- and phenyl-substituted phenyldiazonium salts all undergo the desired reaction to give the cycloadducts **2a-l** in moderate to good yields. It is worth noting that anilines bearing a free phenol group

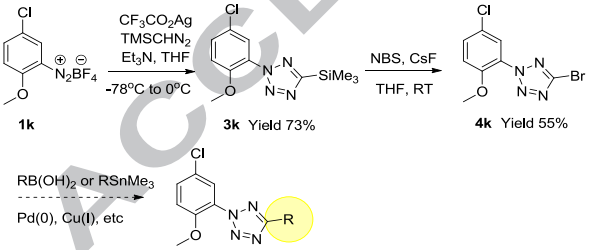
(**2h**) or carboxylic acid (**2g**) are tolerated as are electron poor (**2c**,**2e-f**,**2m**) or electron rich (**2d**,**2h-i**,**k**) aromatics. Note that in these reactions, only the 2-aryl tetrazole was formed and the 1-aryltetrazole was not observed.

To be synthetically useful, this new method also needed to scale well. Hence we conducted this reaction sequence on a 1g scale. As shown in **Scheme 2**, the diazotation step from the commercial aniline afforded **1k** in 91% yield which does not require purification. Intermediate **1k** reacted with $TMSCHN_2$ to give the corresponding 2-substituted tetrazole **2k** with a 67% yield in two steps.



Scheme 2. Gram scale reaction

Finally, we turned our attention to the key intermediate 2-aryl-5-trimethylsilyl tetrazole (**3k**, **Scheme 3**). This reaction could be carried out without the addition of CsF and, under these conditions, we were able to isolate the trimethylsilyl derivate **3k** in good yield. With this compound in hand, we demonstrated the versatile properties by substitution of the trimethylsilyl group with a bromine on the 5-position to afford **4k**. From this compound, introduction of many other groups and functionalities are possible via metal-mediated coupling reactions. This route offers an approach for rapid structure-activity relationship studies (SAR) of the 5-position of the tetrazole ring. This strategy complements that of Ramanathan *et al.* and offers a new synthetic method for the synthesis of functionalized tetrazoles.



Scheme 3. Access to the 2-aryl-5-bromo-tetrazole

Conclusions

In summary, we have successfully disclosed a quick and general method to synthesize 2-aryltetrazoles by a [3+2] regioselective cycloaddition reaction of trimethylsilyldiazomethane with various aryl and heteroaryl diazonium salts. A broad range of 2-substituted tetrazoles were obtained in moderate to good yields. The practicality of this methodology was further demonstrated by the facile synthesis of a gram scale sequence. We believe this motif has the potential for use in drug discovery programs as a valuable synthetic building block, which is now readily available via this methodology.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version, at.

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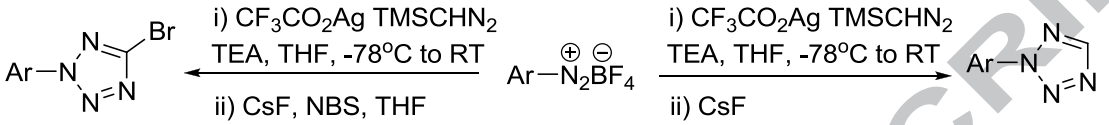

A regioselective cycloaddition reaction of arenediazonium salts with trimethylsilyldiazomethane is reported. A series of 2-aryltetrazoles were obtained in good to moderate yields with wide functional group compatibility. Furthermore, this cycloaddition reaction opens the way to build up the versatile intermediate 2-aryl-5-bromotetrazole.

Research highlights

► Regioselective cycloaddition reaction of arenediazonium salts with trimethylsilyldiazomethane.

►Best catalyst to perform this reaction was silver trifluoroacetate.

►A large set of diazonium salt was used under optimized conditions.

►Gram scale have been successfully accomplished