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One-Pot Reactions for Synthesis of 2,5-Substituted Tetrazoles from Aryldiazonium Salts and Amidines

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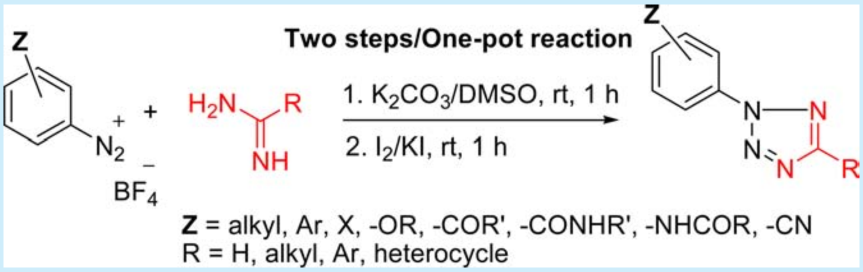
Supporting Information



ABSTRACT: One-pot sequential reactions of aryldiazonium salts with amidines followed by the treatment of I_2/KI under basic conditions provide 2,5-disubstituted tetrazoles in moderate to excellent yields. This one-pot synthesis has several advantages such as mild reaction conditions, short reaction time, convenient workup, and high yields, making this methodology practical.

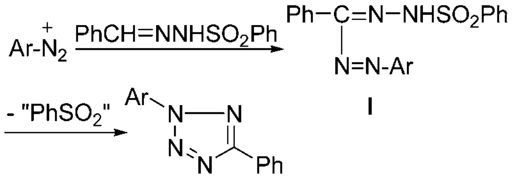
Among various *N*-heterocycles, tetrazoles are one of the most stable, nitrogen-rich heterocyclic compounds and have been studied extensively owing to the biological, pharmaceutical, and material uses.[1−5] Both 1,5- and 2,5-disubstituted tetrazoles are the most notable members of the tetrazole family. In particular, 2,5-substituted tetrazoles are often used as key pharmacophores[3] and photosensitive materials.[4] In addition, some 2,5-disubstituted tetrazoles are convenient precursors for the preparation of a variety of *N*-heterocycles.[5]

1,3-Dipolar cycloaddition reactions of azides with nitrile compounds,[6] or sodium azide with imidoylbenzotriazoles,[7] are typical synthetic routes to yield 1,5-disubstituted tetrazoles. Pd-catalyzed Suzuki−Miyaura coupling[8] and Baylis−Hillman reaction[9] have also been reported to prepare this scaffold. For the synthesis of 2,5-substituted derivatives, multistep procedures based on various cyclization protocols have been reported.[10] Alternatively, approaches involving the metal-catalyzed arylation of readily available 5-substitued 2*H*-tetrazoles have been documented.[11] However, some of these synthetic potentials rely on C−N bond formation with a regioselective arylation.

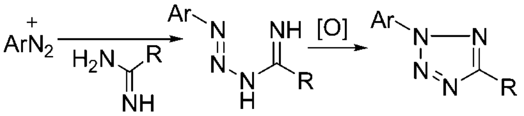
Aryldiazonium salts, a class of inexpensive and readily available chemicals, are useful precursors in a variety of organic transformations.[12] In this context, the reaction of aryldiazonium chloride with phenylsulfonylhydrazone to yield 2,5-substituted tetrazoles was reported by Kakehi and co-workers.[10b,c] In this reaction, formazan (**I**) is the initial product, which then undergoes the cyclization with the elimination of benzenesulfinic acid to yield the product (Scheme 1a). However, this protocol still suffers from some drawbacks such as limited substrate scope, preparation of starting materials, and the generation of waste molecules. Thus, further development is needed to enable a new method for the preparation of 2,5-substituted tetrazoles in terms of atom economy and environmental impact. We herein report a facile method for the synthesis of 2,5-disubstituted tetrazole from the reaction of aryladiazonium salts with amidines, followed by oxidative ring closure (Scheme 1b).

Scheme 1. Preparation of Tetrazoles from Diazonium Salts

(a) Kakehi tetrazole synthesis



(b) This work



1-(Iminophenylmethyl)-3-phenyltriazene (**2a**), prepared by the treatment of phenyldiazonium tetrafluoroborate (**1a**) with phenylamidine under aqueous basic conditions, was used as a model compound to screen the optimum conditions for the ring closure (Scheme 2). With 1.5 equiv of iodosobenzene diacetate (IBDA) at both ambient and refluxing temperatures using acetonitrile as the solvent, no desired product was observed; instead, the starting material was consumed to

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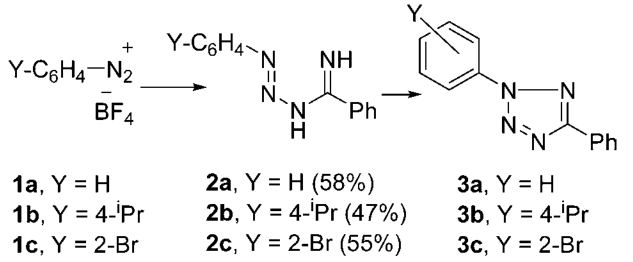
Scheme 2. Preparation of 2 and N−N Coupling Leading to 3



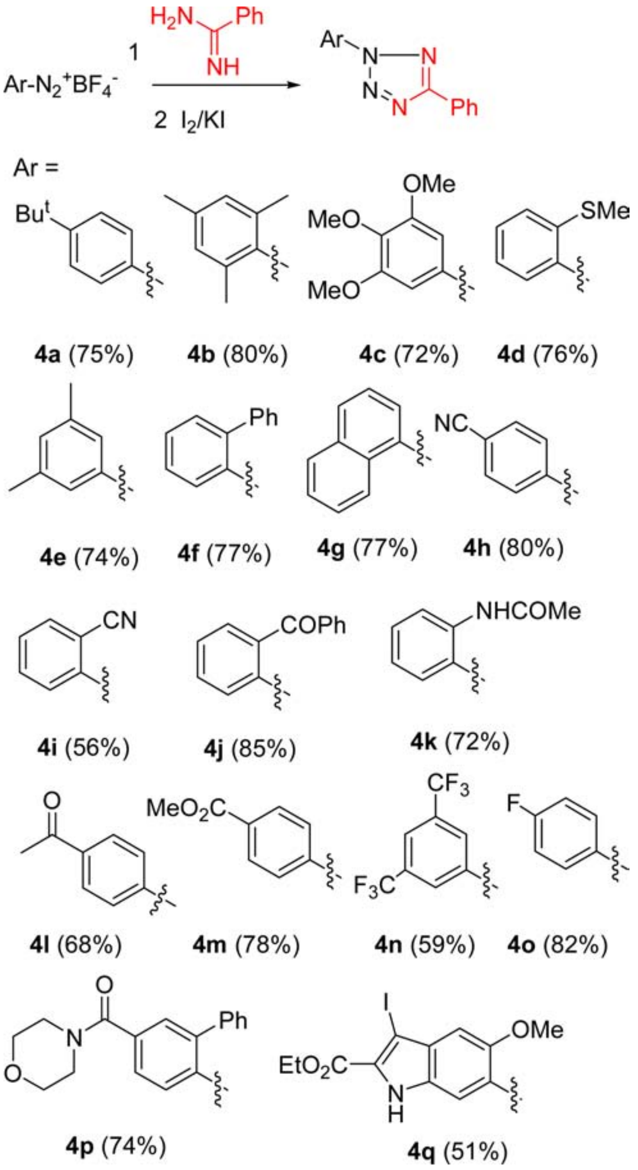
unidentified compounds (Table 1, entries 1, 2). Similar inferior results were observed with variety of copper sources such as $Cu(OAc)_2$, Cu_2O with O_2 (Table 1, entries 3−4). Although a mixture of $CuBr/ZnI_2$ under aerobic conditions is known to be an effective system for the tandem oxidative synthesis of 1,2,4-triazoles,[13] in our case it led to a complicated result (Table 1, entry 5). To our delight, 2,5-disubstituted tetrazole was isolated as the sole product in 94% yield under $I_2/KI/K_2CO_3$ in DMSO at 100 °C for 1 h (Table, 1 entry 6). Further investigation on modification of reaction conditions allowed learning that the cyclization proceeded smoothly at room temperature (Table 1, entry 7). At this point of the investigation, we speculated the oxidative N−N bond formation can be carried out in situ after generation of **2a**. In addition, the isolations of imino-triazene **2a**−**2c** were difficult to obtain in high yields. These prompted us to explore the feasibility of a sequential one-pot synthesis by combining aryldiazonium salt, amidine, and then an I_2/KI mixture in the presence of a base. Indeed, **3a** was isolated in 81% yield in a sequential one-pot reaction (Table 1, entry 8). This one-pot approach was also applicable to the substrate **1b** and **1c** (Table 1, entries 9−10). It is noteworthy that this oxidative transformation is insensitive to moisture and air, allowing the reaction to be carried out in an open flask.

Table 1. Optimization of the Oxidative Ring Closure of 2

entry	compd[a]	reagents	conditions	yield (%)[c]
1	**2a**	$PhI(OAc)_2$	THF/Δ/12 h	dec.
2	**2a**	$PhI(OAc)_2$	THF/rt/12 h	dec.
3	**2a**	$Cu(OAc)_2/O_2$	CH_3CN/Δ/12 h	SM
4	**2a**	Cu_2O (cat)/O_2	CH_3CN/Δ/24 h	dec.
5	**2a**	$CuBr/ZnI_2$/Air	DMSO/130 °C/5 h	dec.
6	**2a**	$I_2/KI/K_2CO_3$	DMSO/100 °C/1 h	**3a** (94)
7	**2a**	$I_2/KI/K_2CO_3$	DMSO/rt/2 h	**3a** (89)[d]
8[b]	**1a**	$I_2/KI/K_2CO_3$	DMSO/rt/2 h	**3a** (81)
9[b]	**1b**	$I_2/KI/K_2CO_3$	DMSO/rt/2 h	**3b** (82)
10[b]	**1c**	$I_2/KI/K_2CO_3$	DMSO/rt/2 h	**3c** (87)

[a] **2** (0.22 mmol). [b] One-pot reaction; **1** (1.04 mmol), benzamidine(HCl) (1.04 mmol), and K_2CO_3 (5.21 mmol) in DMSO at rt for 1 h, and then I_2 (1.25 mmol) and KI (1.56 mmol) were added and stirred at rt for another 1 h. [c] Isolated yields dec = decomposition. [d] NMR yield.

Scheme 3. Tetrazoles from Various Diazonium Salts[a]



[a] Reaction conditions: diazonium salt (1.04 mmol), benzamidine(HCl) (1.04 mmol) and K_2CO_3 (5.21 mmol) in DMSO at rt for 1 h, then I_2 (1.25 mmol) and KI (1.56 mmol) were added and stirred at rt for another 1 h. Isolated yields given in parentheses.

With suitable reaction conditions in hand, we next explored the generality of these reaction conditions for variously substituted diazonium salts (Scheme 3). Aryldiazonium salts with common substituents such as 4-^{t}Bu, 2,4,6-trimethyl, 3,4,5-trimethoxy, 2-methylthio, 3,5-dimethyl, and 2-phenyl groups (Scheme 3, entries **4a**−**4f**) readily reacted with phenylamidine followed by the oxidative ring closure to give the corresponding tetrazoles as a single product in good isolated yields. It is noted that 2,4,6-trimethylbenzenediazonium salt reacted with phenylamidine to yield **4b** in 80% yield. However, 2,6-diisopropylbenzenediazonium salt did not undergo such a coupling with amidine presumably due to the steric hindrance. This one-pot synthesis is also applicable for the reaction of 1-naphthylenediazonium tetrafluoroborate with phenylamidine to produce **4g** in 77% yield. It is noted that the reaction also succeeded with aryldiazonium salts bearing ortho substituents in decent yields (Scheme 3, entries **4b**−**d**, **4f**, **4g**). In addition, this protocol was found to tolerate a wide range of functional groups such as halo, cyano, carbomethoxy, carbonyl, and 2-acetamido functionalities and furnished the corresponding tetrazoles in good yields (Scheme 3, entries **4h**−**4m**). Furthermore, tetrazoles with F− and CF_3− substituents could be accessed by this transformation in good to excellent yields (Scheme 3, entries **4n**−**o**). Finally, to extend the applicability of this method in more complicated molecules, we tested this methodology for a heteroaromatic

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framework embedded with an aryldiazonium moiety. Thus, 4-benzoylmorpholine substituted tetrazole **4p** was efficiently obtained in 74% yield, which is notoriously difficult to achieve with the existing routes and suitable for further functionalization.[14] X-ray crystallographic determination confirms the structure of **4p**, and the ORTEP plot of **4p** is shown in Figure 1. It is documented that iodination of an indole molecule can be easily achieved via the treatment of iodine under basic conditions.[15] Indeed, the iodinated product **4q** was obtained under the conditions described above.

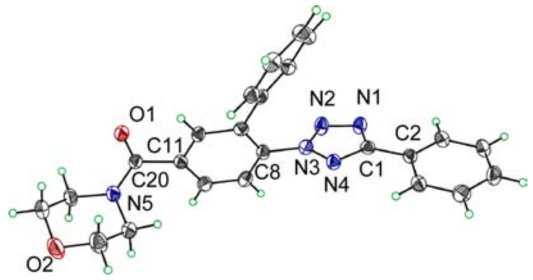


Figure 1. ORTEP plot of **4p** (30% probability ellipsoids).

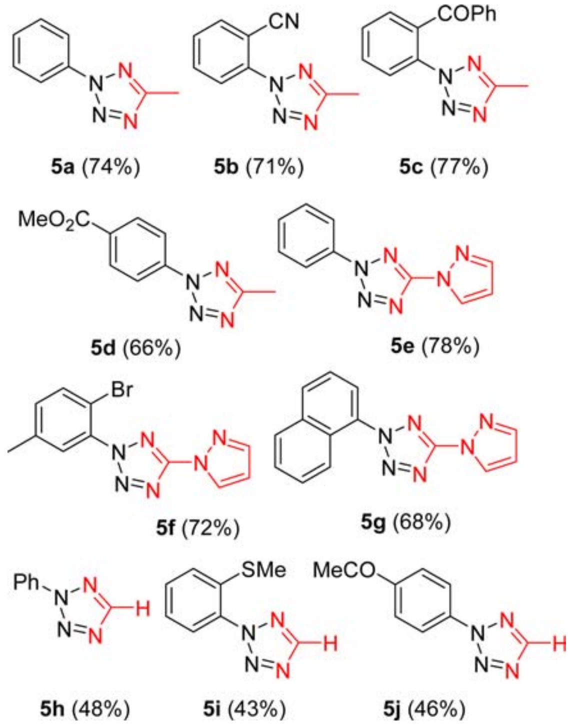
This protocol represents an easy-to-handle and versatile method for a wide variety of tetrazoles, and hence we checked the scalability. Phenyldiazonium tetrafluoroborate **1a** on a 2 g scale was treated with benzamidine hydrochloride under the optimized conditions yielding the tetrazole **3a** in 83% yield (1.81 g), comparable to the small-scale experiment.

We next examined various amidines against functionalized aryldiazonium salts under the standard conditions. Aliphatic, heteroaryl, and formamidines smoothly participated in the one-pot transformation to afford the corresponding 2,5-disubstituted tetrazoles in moderate to good yields (Scheme 4). The reaction was amenable with functional groups such as cyano (**5b**), benzoyl (**5c**), and ester (**5d**) in the ortho- and para-positions of the aryldiazonium salts, delivering the corresponding tetrazoles in 66%−77% yields. Reaction of 1*H*-pyrazole-1-carboximidamide with various diazonium salts yielded the corresponding 2,5-functionalized tetrazoles in good isolated yields (Scheme 4, entries **5e**−**5g**). It is worth noting that polynitrogenated tetrazoles with structural diversity of this kind are previously unknown by any other method. Moreover, formamidine is also a viable substrate, providing the desired products. A variety of 2-aryl-2*H*-tetrazoles with various functional groups were obtained in acceptable yields (Scheme 4, entries **5h**−**5j**).

A possible mechanistic pathway is depicted in Scheme 5. Initial reaction of amidine with diazonium salt results in the formation of imino-triazene **II**. Further interaction with iodine and deprotonation resulted in the formation of iodide **III**. An intramolecular nucleophilic attack gives the quaternary ammonium ion with a new N−N bond. Finally, subsequent deprotonation and rearomatization furnishes the desired product.

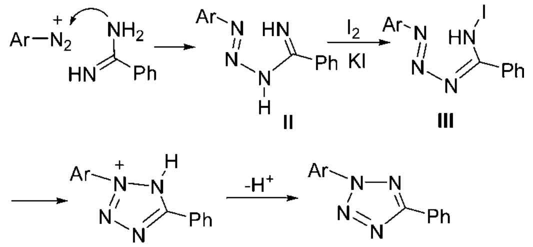
In summary, a diverse array of 2,5-difunctionalized tetrazoles were prepared from the reactions of aryldiazonium salts with amidines, followed by an oxidative N−N bond formation with the use of inexpensive and easy-to-handle starting materials and reagents. This convenient one-pot approach tolerates various functional groups and represents a facile, atom-efficient, and easy-to-handle synthesis of tetrazoles. The desired products were obtained in high yields, even on gram scale, with no requirements of inert or anhydrous reaction conditions. Further developments of aryldiazonium salt based novel synthesis of N-heterocycles are currently in progress in our laboratory.

Scheme 4. Tetrazoles from Various Amidines[a]



[a]Reaction conditions: diazonium salt (1.04 mmol), amidine(HCl) (1.04 mmol), and K_2CO_3 (5.21 mmol) in DMSO at rt for 1 h, and then I_2 (1.25 mmol) and KI (1.56 mmol) were added and stirred at rt for another 1 h. Isolated yields given in parentheses.

Scheme 5. A Possible Mechanism for N−N Bond Coupling



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03068.

Experimental procedures and details of the characterization of all of the new compounds (PDF)
ORTEP plot of **4p**, tables of atomic positional parameters, bond distances and angles, and anisotropic thermal parameters of **4p** (PDF)
Crystallographic data for **4p** (CIF)

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Notes

The authors declare no competing financial interest.

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