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Diversity-Oriented Synthesis of 1,2,4-Triazols, 1,3,4-Thiadiazols, and 1,3,4-Selenadiazols from *N*-Tosylhydrazones

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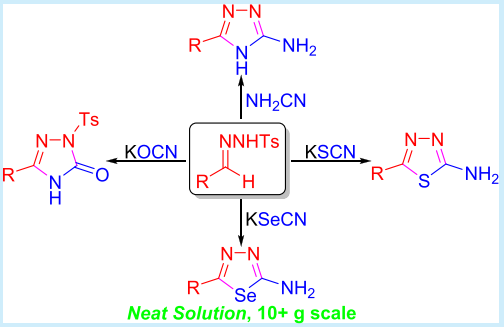
ABSTRACT: The diversity-oriented synthesis of 1,2,4-triazols, 1,3,4-thiadiazols, and 1,3,4-selenadiazols from *N*-tosylhydrazones was developed, and the reactions were general for a wide range of substrates, in which NH_2CN, KOCN, KSCN, and KSeCN were used as odorless sources. Two different pathways were proposed, and *N*-tosylhydrazonoyl chlorides were formed *in situ* in the presence of NCS.



Nitrogen-containing five-membered aromatic heterocycles with three heteroatoms, such as 1,2,4-triazol, 1,3,4-thiadiazole, and 1,3,4-selenadiazole, have been extensively studied due to their widespread existence in natural products, materials, and biologically active synthetic compounds.[1] Many drugs containing these nuclei such as alprazolam, trapidil, and furidiazine are commercially available, and they display a broad spectrum of pharmaceutical and biological activities. Impressive developments have been achieved, and a variety of powerful strategies have been developed for their construction.[2−4] However, for some reactions, the starting materials are not readily commercially available, and most of the sulfur sources and selenium sources are odorous; meanwhile, somewhat harsh reaction conditions greatly reduce the attractiveness of these methods. Therefore, the development of facile strategies and chemical reactions continues to be a major challenge for researchers.

As a readily accessible and useful reagent,[5] *N*-tosylhydrazones have been used in the preparation of 1,2,4-triazoles and 1,3,4-thiadiazoles. The synthesis of 1,2,4-triazoles from *N*-tosylhydrazones and imines via formal 1,3-dipolar cycloaddition reactions has been developed by Maiti et al. and Kalita et al.;[6] the $B(C_6F_5)_3$-catalyzed dehydrogenative cyclization of *N*-tosylhydrazones and anilines to 1,2,4-triazoles has been disclosed by Koley et al. in 2019;[7] Cheng et al. and Okuma et al. reported the three-component reactions between two *N*-tosylhydrazones and different sulfur sources leading to 1,3,4-thiadiazoles, respectively.[8] Recently, Yan et al. reported an I_2 promoted synthesis of 1,3,4-thiadiazoles from *in situ* *N*-tosylhydrazones and KSCN, in which KSCN as an odorless sulfur source was used in the construction of 1,3,4-thiadiazoles for the first time, but the reactions were conducted in a sealed tube at higher temperature for 12 h, and aliphatic aldehyde was unsuitable for the transformation.[9]

In the past decade, we have developed a series of methods for the synthesis of heterocyclic compounds from *N*-tosylhydrazones, including pyrazoles,[10] indazoles,[11] and 1,4-dihydropyridines.[12] Herein, we present a facile diversity-oriented synthesis of 1,2,4-triazols, 1,3,4-thiadiazols, and 1,3,4-selenadiazols from *N*-tosylhydrazones.

The investigation was initiated by a reaction of *N*-tosylhydrazone (**1a**) with cyanamide, and the results were summarized in Table 1. Initially, we performed the reaction in DCE without using any additive, and no reaction was detected. Then, the reaction was conducted in the presence of 0.5 equiv of $BF_3{\cdot}OEt_2$; after 20 h, 1,2,4-triazol-3-amine **2a** could be isolated in 39% yield (entry 1). To our delight, increasing the amount of $BF_3{\cdot}OEt_2$ could improve the yields apparently (entries 2, 3), and 1.5 equiv of $BF_3{\cdot}OEt_2$ resulted in 93% yield of **2a** within 9 h. $FeCl_3$ gave moderate yield (entry 4); other Lewis acids, such as $AlBr_3$, $TiCl_4$, and $Sc(OTf)_3$, resulted in lower yields (entries 5−7). Of the solvents screened, CH_2Cl_2, $CHCl_3$, CH_3CN, CH_3NO_2, and toluene could give moderate yields (entries 8−12) (for details, see Supporting Information, Table S1).

Under the above optimized conditions, various *N*-tosylhydrazones **1** were applied to the reaction to test the generality

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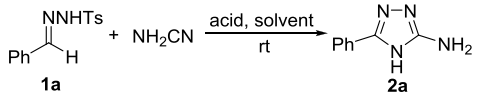
Table 1. Screening the Reaction Conditions of 1a with Cyanamide[a]

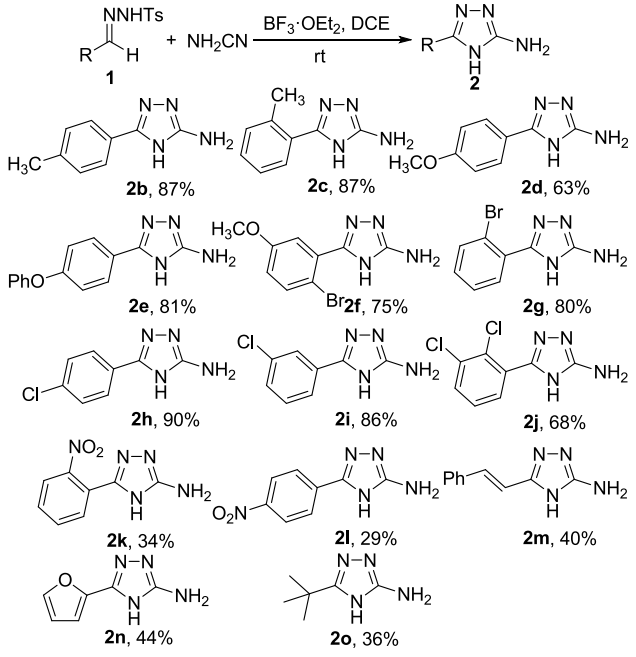


entry	acid (equiv)	solv	time (h)	yield (%)[b]
1	$BF_3{\cdot}OEt_2$ (0.5)	DCE	20	39
2	$BF_3{\cdot}OEt_2$ (1.25)	DCE	20	75
3	$BF_3{\cdot}OEt_2$ (1.5)	DCE	9	93
4	$FeCl_3$ (1.5)	DCE	20	58
5	$AlBr_3$ (1.5)	DCE	20	31
6	$TiCl_4$ (1.5)	DCE	20	19
7	$Sc(OTf)_3$ (1.5)	DCE	20	18
8	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	20	68
9	$BF_3{\cdot}OEt_2$ (1.5)	$CHCl_3$	20	55
10	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	20	56
11	$BF_3{\cdot}OEt_2$ (1.5)	CH_3NO_2	20	37
12	$BF_3{\cdot}OEt_2$ (1.5)	toluene	20	38
13[c]	$BF_3{\cdot}OEt_2$ (1.5)	DCE	9	68

[a]Unless noted otherwise, the reactions were conducted with **1a** (0.1 mmol), NH_2CN (0.2 mmol), and acid (0.15 mmol) in 2 mL solvent at room temperature under an argon atmosphere. [b]Isolated yields. [c]0.2 mmol NCS was added.

and scope of the method. First, we examined the electronic effect on the aromatic ring of *N*-tosylhydrazones. As shown in Scheme 1, *N*-tosylhydrazones derived from benzaldehyde

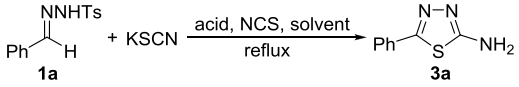
Scheme 1. Synthesis of 1,2,4-Triazol-3-amines 2



featuring ortho-, meta-, and para- electron-donating substituents and halogen had little influence on the reaction; products **2b**–**2j** were prepared in good yields. However, lower yields were observed with nitro (**2k**, **2l**). To our delight, *N*-tosylhydrazone derived from cinnamaldehyde, 2-furaldehyde, and trimethylacetaldehyde was also appropriate in the reaction; products **2m**–**2o** were given in moderate yields.

Encouraged by the above results, we tried to apply other cyanates to the reaction. However, to our disappointment, it was tried rigorously and failed many times in a row. For example, we used KSCN instead of cyanamide in the reaction under similar conditions to prepare 1,3,4-thiadiazol-2-amine **3a**, and different solvents were screened even at higher temperature, but no reaction could be detected by TLC (Table 2, entries 1, 2). Referring to the results reported in the

Table 2. Screening the Reaction Conditions of 1a with KSCN[a]



entry	acid (equiv)	solv	time/h	yield (%)[b]
1[c]	$BF_3{\cdot}OEt_2$ (1.5)	DCE	5	N. R.
2[c]	$BF_3{\cdot}OEt_2$ (1.5)	*t*-BuOH	5	N. R.
3[d]	$BF_3{\cdot}OEt_2$ (1.5)	*t*-BuOH	9	20
4	$BF_3{\cdot}OEt_2$ (1.5)	*t*-BuOH	9	29
5	$BF_3{\cdot}OEt_2$ (1.25)	*t*-BuOH	6	54
6	$BF_3{\cdot}OEt_2$ (0.5)	*t*-BuOH	0.5	87
7	$BF_3{\cdot}OEt_2$ (0.25)	*t*-BuOH	1	64
8[e]	$BF_3{\cdot}OEt_2$ (0.5)	*t*-BuOH	30	83
9	$AlCl_3$ (0.5)	*t*-BuOH	0.5	59
10	$TiCl_4$ (0.5)	*t*-BuOH	0.5	73
11	H_2SO_4 (0.5)	*t*-BuOH	3	59
12	HCl (0.5)	*t*-BuOH	0.5	62
13	$BF_3{\cdot}OEt_2$ (0.5)	*t*-AmOH	3	37
14	$BF_3{\cdot}OEt_2$ (0.5)	EtOH	3	trace
15[f]	$BF_3{\cdot}OEt_2$ (0.5)	*t*-BuOH	0.5	52
16[g]	$BF_3{\cdot}OEt_2$ (0.5)	*t*-BuOH	2	30

[a]Unless noted otherwise, the reactions were conducted with **1a** (0.1 mmol), KSCN (0.2 mmol), NCS (0.2 mmol), and acid in 2 mL solvent at reflux temperature under an argon atmosphere. [b]Isolated yields. [c]Without using NCS. [d]0.11 mmol NCS was used. [e]The reaction was conducted at room temperature. [f]0.2 mmol NBS was used instead of NCS. [g]0.2 mmol NIS was used instead of NCS.

literature, in which *in situ* *N*-thiocyanatosuccinimide has better reactivity in C–S bond formation,[13] we added 1.1 equiv of NCS to the reaction. As we envisaged, product **3a** could be isolated in 20% yield in *t*-BuOH after 9 h, even though the *N*-tosylhydrazone **1a** could not be fully consumed (entry 3). Increasing the amount of NCS could not improve the transformation (entry 4). Fortunately, we found that decreasing the amount of $BF_3{\cdot}OEt_2$ resulted in better yields (entries 5–7), and 0.5 equiv of $BF_3{\cdot}OEt_2$ gave 87% yield within 0.5 h. Furthermore, the reaction could be performed at room temperature (entry 8). Then, some acids were screened (entries 9–12): $AlCl_3$ and $TiCl_4$ gave moderate yields, while H_2SO_4 and concentrated HCl could promote the reaction. Next, a variety of different solvents were also evaluated; *t*-AmOH led to lower yields and EtOH gave disappointing results (entries 13, 14). NBS and NIS could also promote the reaction, but the yields were lower (entries 15, 16). (For details, see Supporting Information, Table S2.)

Then, we attempted to synthesize a variety of 1,3,4-thiadiazol-2-amine derivatives. As shown in Scheme 2, the electronic effect on the aromatic ring of *N*-tosylhydrazones had little influence on the transformation; *N*-tosylhydrazones derived from benzaldehyde featuring ortho-, meta-, and para-substituents as well as electron-donating (**3b**–**3e**) or electron-withdrawing (**3f**–**3k**) substituents worked well to furnish the corresponding products, and the yield was not affected when R

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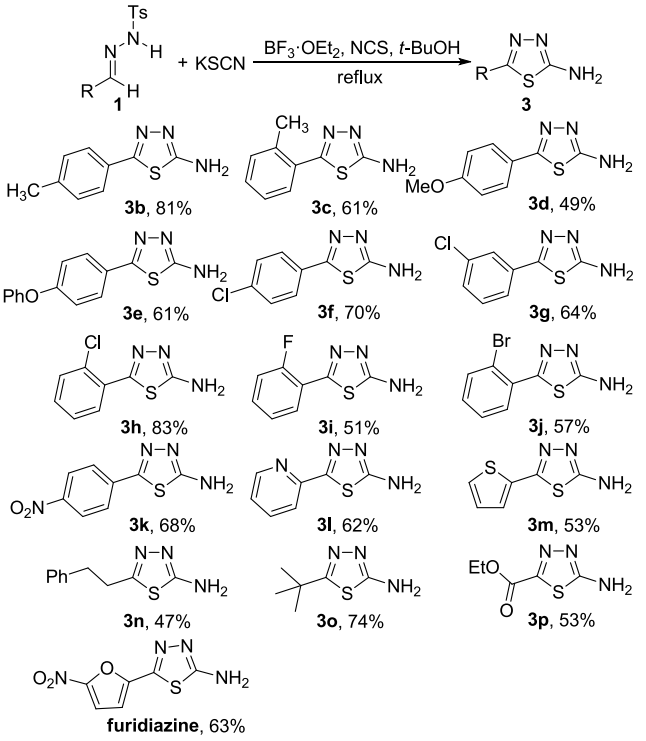
Scheme 2. Synthesis of 1,3,4-Thiadiazol-2-amines 3

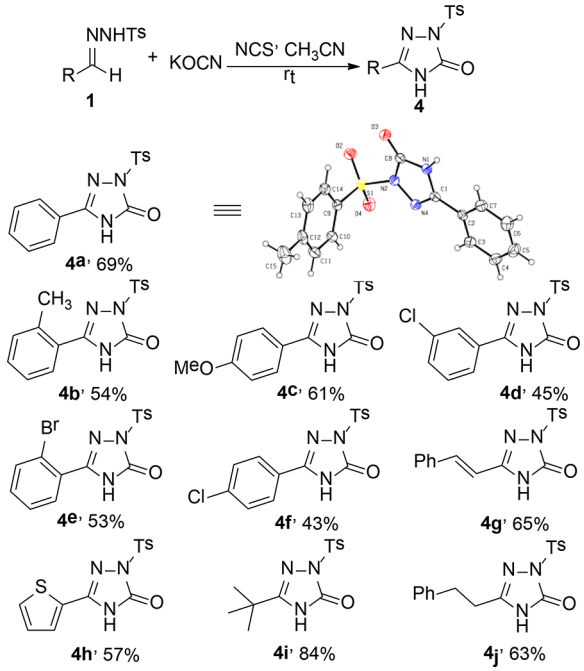


contained a nitro (**3k**). Additionally, *N*-tosylhydrazones derived from 2-pyridinecarboxaldehyde, 2-thenaldehyde, and aliphatic aldehydes were all suitable for the transformation; products **3l**−**3o** were given in good yields. Furthermore, product **3p**, which has been used widely in the design and synthesis of biologically active compounds,[14] could be prepared in a 53% yield; and furidiazine, which has antibacterial activity in animals after oral or intramuscular administration,[15] was obtained in 63% yield. To demonstrate the synthetic utility of the protocol, we conducted the reaction with 100 mmol **1a**, and 10.8 g of **3a** could be isolated in 61% yield by recrystallization. Furthermore, *N*-methylsulfonylhydrazone and *N*-phenylsulfonylhydrazone were applicable to the reaction and gave products **3a** in 76% and 72% yields, respectively, whereas *N*-phenylhydrazone was unsuitable, and no product could be confirmed in the current state.

Next, we used KOCN in the reaction. By screening the reaction conditions, we found that 2-tosyl-1,2,4-triazol-3-one **4a** could be isolated in 69% yield in CH_3CN at room temperature in the presence of 1.1 equiv of NCS. The structure of **4a** was confirmed by NMR and single-crystal X-ray analysis (Scheme 3). Acid was not essential, but it could accelerate the reaction. The reaction could be conducted at reflux temperature. (For details, see Supporting Information, Table S3.) Meanwhile, we noticed that a small amount of compound **12** (Scheme 5) could be isolated as byproduct. The procedure was applicable for *N*-tosylhydrazones with both electron-donating (**4b**, **4c**) and electron-withdrawing (**4d**−**4f**) groups, provided the desired 2-tosyl-1,2,4-triazol-3-ones in good yields. Additionally, *N*-tosylhydrazones derived from cinnamaldehyde, 2-thenaldehyde, and aliphatic aldehydes were all suitable for the reaction; products (**4g**−**4j**) could be prepared in good yields.

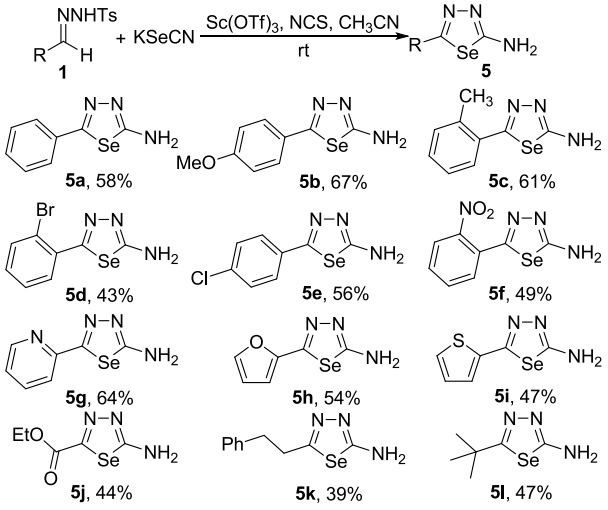
To our delight, KSeCN was also suitable for the reaction. 1,3,4-Selenadiazol-2-amine **5a** could be isolated in 58% yield in CH_3CN at room temperature in the presence of 0.5 equiv of

Scheme 3. Synthesis of 2-Tosyl-1,2,4-triazol-3-ones 4



$Sc(OTf)_3$ and 1.1 equiv of NCS (for details, see Supporting Information, Table S4). As shown in Scheme 4, the electronic

Scheme 4. Synthesis of 1,3,4-Selenadiazol-2-amine 5



effect on the aromatic ring of *N*-tosylhydrazones had little influence on the reaction; products **5b**−**5f** were prepared in moderate yields. Meanwhile, *N*-tosylhydrazones derived from 2-furaldehyde, 2-pyridinecarboxaldehyde, 2-thenaldehyde, ethyl 2-oxoacetate, and aliphatic aldehydes were appropriate in the reaction, and gave products **5g**−**5l** in moderate yields.

To elucidate the reaction mechanism, some control experiments were designed with **1a**. We found that product **11** (Scheme 5) could be isolated in the presence of NCS in *t*-BuOH in about 30% yield. We believed that *N*-tosylhydrazonoyl chloride **8** was formed, although it could not be detected and isolated in the current. It could be confirmed by the formation of byproduct **12** in the reaction to prepare **4a**. Then, two different pathways were proposed. In the absence of NCS, the reaction was initiated by the nucleophilic addition of

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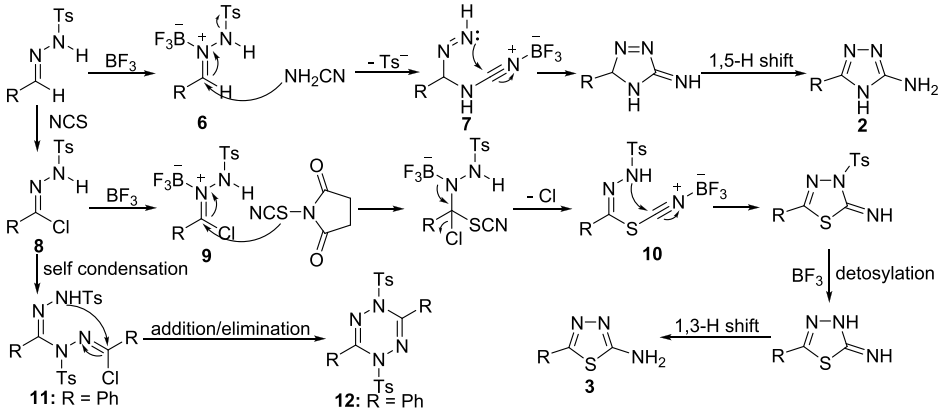
Scheme 5. Proposed Pathway for 1,2,4-Triazols and 1,3,4-thiadiazols Formation



NH_2CN to *N*-tosylhydrazone iminium salt **6** resulting in **7**, which subsequently went through an intramolecular cyclization, and 1,5-H shift led to 1,2,4-triazol-3-amine **2**. In the presence of NCS, *N*-tosylhydrazonoyl chloride **8** was formed. An addition elimination reaction of *in situ* *N*-thiocyanatosuccinimide and *N*-tosylhydrazone iminium salt **9** produced intermediate **10**, followed by intramolecular cyclization, detosylation, and 1,3-H shift resulting in 1,3,4-thiadiazol-2-amine **3**. In certain cases, self-condensation and cyclization of *N*-tosylhydrazonoyl chloride **8** gave byproduct **12**. 2-Tosyl-1,2,4-triazol-3-ones **4** and 1,3,4-selenadiazol-2-amine **5** were formed by the similar process from *N*-tosylhydrazonoyl chloride **8**. (For details, see Supporting Information, Scheme S1.)

The mechanism explained the inequable dosage of NCS in different reactions. Due to the formation of *N*-tosylhydrazonoyl chloride **8** and *N*-thiocyanatosuccinimide, 2 equiv of NCS was necessary for the preparation of **3**. However, in the preparation of **4** and **5**, no compounds similar to *N*-thiocyanatosuccinimide were formed, so 1.1 equiv of NCS was enough. In the preparation of **2**, probably due to the better nucleophilicity of NH_2CN, the formation of **8** was unnecessary; NCS was not required. We also tried to add NCS in the reaction, but it did not improve the yield; on the contrary, there were more byproducts like **12**, resulting in lower yield (Table 1, entry 13).

In summary, we have established a neat solution for the preparation of 1,2,4-triazols, 1,3,4-thiadiazols, and 1,3,4-selenadiazoles, and it was effective for a wide scope of substrates. NH_2CN, KOCN, KSCN, and KSeCN were used as odorless sources. *N*-Tosylhydrazonoyl chlorides were formed *in situ* in the presence of NCS, and further studies on their reactivity are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01379.

Experimental procedures, characterization data, copies of NMR spectra for all products, and crystal data and structure refinement for **11** (CCDC 2055756) and **4a** (CCDC 2055757) (PDF)

Accession Codes

CCDC 2055756−2055757 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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