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Novel synthesis of 3,6-disubstituted-1,2,4,5-tetrazine derivatives from hydrazones by using [hydroxyl(tosyloxy)iodo]benzene

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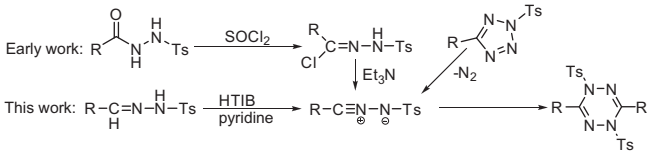
ABSTRACT

A mild and efficient protocol for the construction of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines from *p*-toluenesulfonyl hydrazones mediated by [hydroxyl(tosyloxy)iodo]benzene in the presence of pyridine has been developed. This protocol affords the products in good to excellent yields. The corresponding 3,6-disubstituted-1,2,4,5-tetrazines can be easily obtained through one-step N-deprotection of *p*-toluensulfonyl groups and aromatization by tetrabutyl ammonium fluoride in THF. A mechanism has been proposed.

1,2,4,5-Tetrazine derivatives are of considerable interest because of their unique role in constructing diverse aza-containing heterocycles.[1] Moreover, they exhibit versatile applications in coordination chemistry,[2] protein and live cell labeling,[3] and as raw materials or intermediates for the manufacture of organic solar cells,[4] high energetic materials,[5] and pharmaceuticals including antitumor,[6] insecticidal, and acaricidal drugs.[7,8] The most common way to access these molecules involves treating aromatic nitriles with hydrazine to give dihydro-1,2,4,5-tetrazines followed by oxidation.[6,9] Recently, Devaraj and co-workers utilized divalent nickel and zinc salts as catalysts in this method and broadened the substance to unreactive aliphatic nitriles.[10]

On the other hand, hypervalent iodine reagents have been extensively used in organic synthesis and were proved to be effective to simplify the construction of heterocyclic frames.[11,12] [Hydroxyl (tosyloxy)iodo]benzene (HTIB), known as Koser's reagent, is one of the most investigated hypervalent iodine reagents and has been established as a powerful reagent in many kinds of transformations.[13] In continuation of our efforts to develop new applications of hypervalent iodine reagents,[14–18] recently, we focus on the synthesis of heterocycles. Here, we would like to report an HTIB-mediated mild and efficient procedure for one step synthesis of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines from easily accessible *N*-tosylhydrazones. The key process of this reaction is the generation of nitrile imide 1,3-dipoles (Scheme 1). According to early reports, such intermediates are difficult to acquire, examples involve either the use of hydrazonoyl halides to react with triethylamine or extruding nitrogen from tetrazole precursors, which have several drawbacks such as harsh reaction conditions, long reaction time, low yield, and extra synthetic steps.[19,20] Moreover, the N-deprotection and aromatization of 1,4-dihydro-3,6-disulstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines serve an alternative and promising way for the synthesis of 3,6-disubstituted-1,2,4,5-tetrazines. We were delighted to find that the known procedure initiated by tetrabutyl ammonium fluoride (TBAF) is quite competent for this goal. To our knowledge, there are no reports to exploit hypervalent iodine reagents on the construction of tetrazines before.

The initial experiments were carried out in CH_2Cl_2 with 4-chlorobenzaldehyde tosylhydrazone **1a** as the model substrate. HTIB (1.1 equiv) was used as oxidant and 4-dimethylaminopyridine (DMAP, 5 equiv) was used as base. The reaction was performed at room temperature. It was found by TLC plate that the starting material was consumed completely after 5 min reaction and two new spots generated. One of the new spots was identified as the spot of 1,4-dihydro-3,6-bis(4-chlorophenyl)-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines **2a**. The other spot was purple in



Scheme 1. Methods to prepare *N*-*p*-toluenesulfonyl protected 1,4-dihydro-1,2,4,5-tetrazines.

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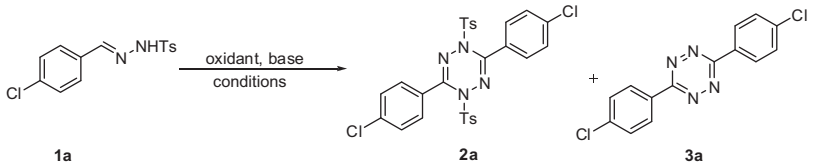
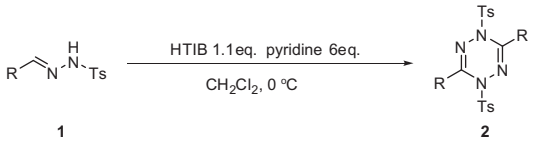
Table 1
Optimization of reaction conditions



Entry	Oxidant[a]	Base	Conditions	Yield[b] (%)
1	HTIB	/	CH_2Cl_2, rt	Mixture
2	/	DMAP 5 equiv	CH_2Cl_2, rt	0
3	HTIB	DMAP 5 equiv	CH_2Cl_2, rt	45; 40[c]
4	HTIB	DMAP 5 equiv	EtOAc, 70 °C	0
5	HTIB	Pyridine 6 equiv	CH_2Cl_2, rt	87
6	HTIB	Pyridine 6 equiv	CH_2Cl_2, 0 °C	93[d]
7	HTIB	Pyridine 3 equiv	CH_2Cl_2, 0 °C	75[d]
8	DIB	Pyridine 6 equiv	CH_2Cl_2, 0 °C	55[d]

[a] 1.1 equiv of oxidant was used for the reaction.
[b] The yield represents isolated yield of **2a**.
[c] The yield represents isolated yield of **3a**.
[d] The reaction time was 15 min.

Table 2
Synthesis of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines



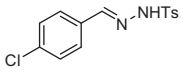
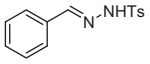
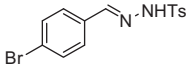
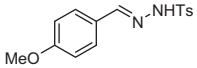
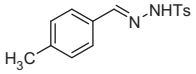
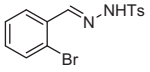
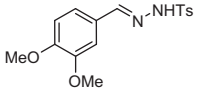
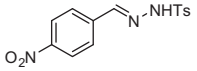
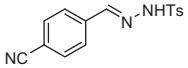
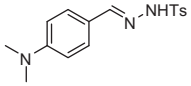
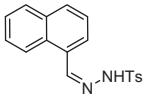
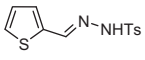
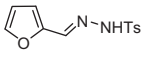
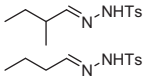
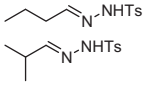
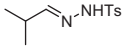
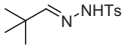
Entry	Hydrazones	Product	Yield[a] (%)
1		**2a**	93
2		**2b**	95
3		**2c**	96
4		**2d**	85
5		**2e**	90
6		**2f**	87
7		**2g**	80
8		**2h**	58
9		**2i**	15
10		**2j**	75[b]
11		**2k**	68

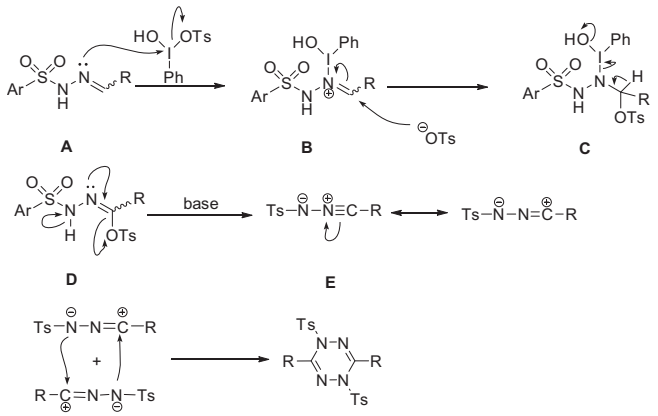
Table 2 (*continued*)

Entry	Hydrazones	Product	Yield[a] (%)
12		**2l**	84
13		**2m**	65
14		**2n**	39
15		**2o**	28
16		**2p**	34
17		**2q**	42[c]

[a] The yield represents isolated yield and the reaction times were between 15 min and 2 h.
[b] Isolated as *p*-dimethylaminobenzaldehyde.
[c] The product identified as 4-methyl-N′-pivaloylbenzenesulfonohydrazide.

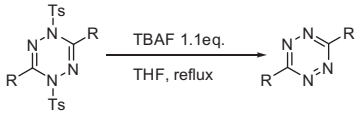
color, which was proved to be 3,6-bis(4-chlorophenyl)-1,2,4,5-tetrazine **3a** after separation and NMR spectra analyses. The ratio of **2a** and **3a** isolated was approximately 1:1 and **2a** was stable enough to be separated and dried, but converted into **3a** slowly in the solvent. Given the initial success, a survey of reaction parameters was then conducted with the aim to suppress the formation of **3a** (Table 1).

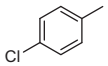
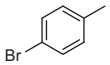
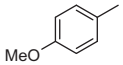
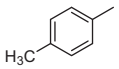
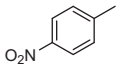
The control experiments were first examined and it was found that DMAP alone did not induce this transformation (Table 1, entry 2). While HTIB was used in the absence of base, the reaction gave complex mixture of byproducts (Table 1, entry 1). So both HTIB and base were indispensable for this reaction. Changing the solvent to EtOAc, albeit heated to 70 °C led to no reactions probably due to the poor solubility of HTIB in EtOAc (Table 1, entry 4). Using pyridine instead of DMAP successfully suppressed the generation of **3a**, and a great increase in the yield of **2a** was observed (Table 1, entry 5). When the reaction proceeded at 0 °C instead of room temperature, the yield of **2a** also increased (Table 1, entry 6). Decreasing the dosage of base to 3 equiv, the reaction became sluggish and was not completed in 15 min (Table 1, entry 7). When (diacetoxyiodo)benzene (DIB) was utilized as oxidant, inferior result was obtained (Table 1, entry 8). Therefore, the following reaction conditions were selected for further experiments, that is, using



Scheme 2. Plausible mechanism.

Table 3
Deprotection/aromatization of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines



Entry	R	Product	Yield[a] (%)
1		**3a**	93
2		**3b**	96
3		**3c**	90
4		**3d**	98
5		**3e**	97
6		**3f**	<5
7		**3h**	92[b]
8		**3l**	99
9		**3m**	<5; 85[c]
10		**3n**	99
11		**3o**	92
12		**3p**	94

[a] The yield represents isolated yield and the reaction times were between 30 min and 4 h.
[b] Ethanol was used as solvent.
[c] 0.5 mmol substrate was dissolved in 5 ml of ethanol at 80 °C, and 1 ml of concd H_2SO_4 dropped in.

HTIB (1.1 equiv) as oxidant and pyridine (6 equiv) as base and carrying out the reaction in CH_2Cl_2 at 0 °C.[23]

With the reaction conditions screened, the scope and generality of the reaction were then investigated. The results are depicted in Table 2.

It was observed that this protocol was generally feasible with aryl, heteroaryl, and alkyl substituted *N*-tosylhydrazones. Benzaldehyde and halo, methoxy or methyl functionalized benzaldehyde derived hydrazones gave the target products in good to excellent yields (Table 2, entries 1–7). In case of hydrazones bearing highly electron-withdrawing groups on the aromatic ring, such as the nitro group and cyano group, the yield of isolated products declined (Table 2, entries 8, 9). When *p*-dimethylaminobenzaldehyde tosylhydrazone was used as reactant, only dehydrazone product was obtained (Table 2, entry 10). α-Naphthaldehyde derived hydrazone and heteroaryl *N*-tosylhydrazones also underwent the reaction smoothly and afforded the desired products in moderate to good yields (Table 2, entries 11–13). To our delight, the alkyl *N*-tosylhydrazone can take part in the reaction (Table 2, entries 14–16). However, with pivaldehyde derived *N*-tosylhydrazone as substrate, 4-methyl-N'-pivaloylbenzenesulfonohydrazide, an oxidative product of the *N*-tosylhydrazone, was formed in 42% yield and no corresponding tetrazine was detected (Table 2, entry 17).[21]

On the basis of the above results, a plausible mechanism was proposed (Scheme 2). Initially, *N*-tosylhydrazones **A** was oxidized to nitrenium ion **B**. The addition of tosyloxy anion to **B** followed by elimination of iodobenzene and water afforded α-tosyloxy substituted *N*-tosylhydrazone **D**. Base catalyzed 1,3-elimination of p-toluenesulfonic acid afforded nitrilesulfonimide **E**. This 1,3-dipole intermediate readily dimerized to form the desired products.

The ready synthesis of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines aroused our interest to examine methods to get synthetically more important 3,6-disubstituted-1,2,4,5-tetrazines through deprotection of *p*-toluensulfonyl groups and presumably aromatization at the same time.

Among the methods we tested, we found the known procedure using TBAF was suitable. According to the literature,[22] 1.1 equiv of TBAF was used in refluxing THF and the results are summarized in Table 3.[24] Most of the examined 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines gave corresponding deprotection/aromatization products in high yields by this mild protocol (Table 3). *p*-Nitrophenyl substituted substrate can get a satisfied result by changing the reaction solvent to ethanol (Table 3, entry 10). However, *o*-bromophenyl and 2-furyl substituted substrates were inert under the reaction conditions (Table 3, entries 6, 9). We found 2-furyl substituted substrate can be N-deprotected and aromatized by 40 equiv of conc. H_2SO_4 to get the desired product in 85% yield (Table 3, entry 9).[25] But for *o*-bromophenyl substrate, still no deprotection/aromatization product was observed using this method.

In summary, we have found a novel way of constructing 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines starting from *N*-tosylhydrozones. This general protocol can apply to aryl, heteroaryl, and alkyl substituted *N*-tosylhydrazones. A [hydroxyl(tosyloxy)iodo]benzene mediated generation of nitrile imide mechanism was proposed. Meanwhile, 3,6-disubstituted-1,2,4,5-tetrazines can be afforded in high yields by deprotection/aromatization of the dihydro products. We believe that this reaction route with metal-free and mild conditions will provide an alternative method to construct 1,2,4,5-tetrazines especially diheteroaryl and dialkyl substituted 1,2,4,5-tetrazines and make these heterocycles more accessible.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.053.

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23. *Typical procedure for the synthesis of 1,4-dihydro-3,6-disubstituted-1,4-bis(p-toluenesulfonyl)-1,2,4,5-tetrazines*: To a stirred solution of *N*-tosylhydrazone (1.00 mmol) in CH_2Cl_2 (10 ml) at 0 °C were added pyridine (0.480 ml, 6.00 mmol) and HTIB (0.431 g, 1.10 mmol) sequentially. The stirring was then continued until TLC monitored the full consumption of hydrazone. Upon completion, the reaction was quenched with aqueous HCl (1.0 M, 20 ml). The mixture was stirred for an additional 10 min and extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were concentrated in vacuum. The crude residue was purified by column chromatography (EtOAc/petroleum ether, 1:4) to give the pure product.
24. *Typical procedure for the synthesis of 3,6-disubstituted-1,2,4,5-tetrazines*: A mixture of 1,4-dihydro-3,6-disubstituted-1,4-bis(*p*-toluenesulfonyl)-1,2,4,5-tetrazines (0.500 mmol), TBAF 1.0 M solution in THF (0.550 ml, 0.550 mmol), and THF (5 ml) was refluxed until TLC monitored the full consumption of the starting material. Then, the reaction mixture was concentrated in vacuum to get a purple solid and washed with methanol (10 ml × 3), or directly filtered through a pad of silica gel to remove the catalyst and followed by rotary evaporation. For isolation of aliphatic 1,2,4,5-tetrazines, because of its highly volatile property, low-boiling petroleum ether or CH_2Cl_2 was used for column chromatography.
25. *Typical procedure for the synthesis of 3,6-di(furan-2-yl)-1,2,4,5-tetrazine*: 3,6-Di(furan-2-yl)-1,4-bis(tosyl)-1,4-dihydro-1,2,4,5-tetrazine (0.263g, 0.500 mmol) was added in 5 ml ethanol and was heated to 80 °C. Then, conc. H_2SO_4 (1.09 ml, 20.0 mmol) was dropped in slowly. Keep stirring until TLC monitored the full consumption of the substrate. Then, the reaction mixture was washed with aqueous $NaHCO_3$ (1.0 M, 10 ml) and extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were concentrated in vacuum. The crude residue was purified by column chromatography (EtOAc/petroleum ether, 1:10) to give the pure product.