Tetrahedron Letters 54 (2013) 4645–4648

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Haixuan Liu, Yunyang Wei *

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, PR China

ARTICLE INFO

Article history:
Received 18 February 2013
Revised 31 May 2013
Accepted 13 June 2013
Available online 21 June 2013

Keywords:
Heterocycles
Hydrazones
Hypervalent iodine
Nitrile imide
Tetrazines

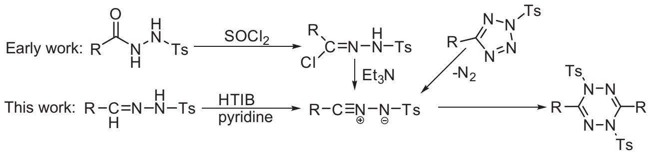
ABSTRACT

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



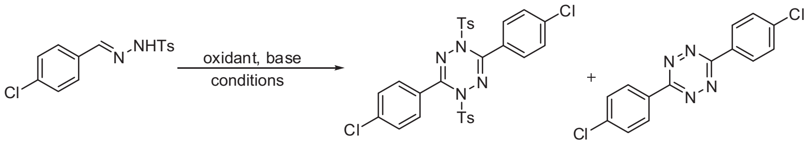
Scheme 1. Methods to prepare *N*-*p*-toluenesulfonyl protected 1,4-dihydro-1,2,4,5-tetrazines.

---

* Corresponding author. Tel./fax: +86 (25)84317078.
E-mail address: ywei@mail.njust.edu.cn (Y. Wei).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.06.053

Table 1
Optimization of reaction conditions

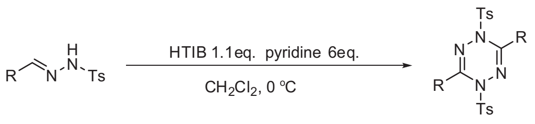


1a **2a** **3a**

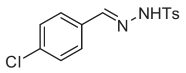
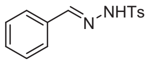
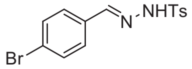
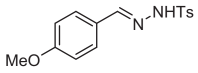
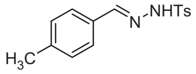
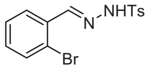
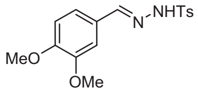
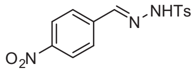
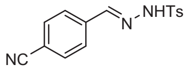
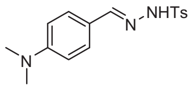
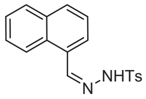
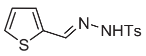
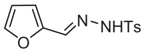
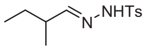
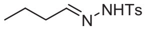
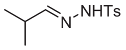
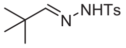
Entry	Oxidant[a]	Base	Conditions	Yield[b] (%)
1	HTIB	/	CH_2Cl_2, rt	Mixture
2	/	DMAP 5 equiv	CH_2Cl_2, rt	0
3	HTIB	DMAP 5 equiv	CH_2Cl_2, rt	45; 40[c]
4	HTIB	DMAP 5 equiv	EtOAc, 70 °C	0
5	HTIB	Pyridine 6 equiv	CH_2Cl_2, rt	87
6	HTIB	Pyridine 6 equiv	CH_2Cl_2, 0 °C	93[d]
7	HTIB	Pyridine 3 equiv	CH_2Cl_2,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



1 **2**

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
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