Tetrahedron Letters 54 (2013) 101–105

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

An expedient route to the azoles through oxidative desulfurization using iodine reagent

Nikhil C. Jadhav, Prashant B. Jagadhane, Kavitkumar N. Patel, Vikas N. Telvekar *

Department of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Matunga, Mumbai 400 019, India

ARTICLE INFO

Article history:
Received 21 September 2012
Revised 23 October 2012
Accepted 25 October 2012
Available online 2 November 2012

Keywords:
Iodobenzene
Oxone®
Tetrazole
Triazole
Desulfurization

ABSTRACT

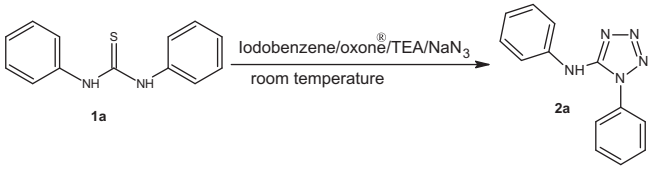
A novel and expedient regioselective method for the synthesis of 5-aminotetrazoles and 3-amino-1,2,4-triazoles through oxidative desulfurization of corresponding 1,3-disubstituted thioureas has been discovered and optimized for the process conditions. The process is broadly applicable to structurally diverse 1,3-disubstituted thioureas.

The synthesis of azoles has emerged as one of the most important topic in the field of heterocyclic chemistry due to the fact that azoles are the key features of pharmaceutical intermediates and bioactive molecules.[1,2] Among various azoles, aminotetrazole and aminotriazole skeletons are vital synthetic motifs in organic and medicinal chemistry.

Aminotetrazoles are the non-classical isosteric substituents of carboxylic acid functional group thus they play a vital role in drug discovery.[3] Aminotetrazoles constitute a crucial part of many biologically active pharmacophores and exhibit pharmaceutical activities such as antiviral,[4] anti-allergic,[5] and antibiotics.[6]

Aminotriazoles may serve as 'urea mimics' and thus, may be exploited for the design of new bioactive compounds. They have shown antiviral,[7] antibacterial,[8] anti-inflammatory,[9] and antifungal activities.[10]

Though some methods are available to synthesize aminotetrazoles and aminotriazoles, most of them have drawbacks like toxic reagents, higher temperatures, and harsh reaction conditions.[11] Thus novel reactions with metal-free conditions at ambient temperature are highly desirable. Hypervalent iodine(III) reagents have captivated organic chemists in recent years. Our lab has sparked interest in development of novel and simple methodologies using hypervalent iodine(III) reagents. Previously we have utilized this reagent system for the construction of oxadiazole and thiadiazole ring.[12] We herein describe expedient routes to synthesize aminotetrazoles and aminotriazoles through oxidative desulfurization using hypervalent iodine(III) reagent.



Scheme 1. Synthesis of 5-aminotetrazoles from 1,3-disubstituted thioureas.

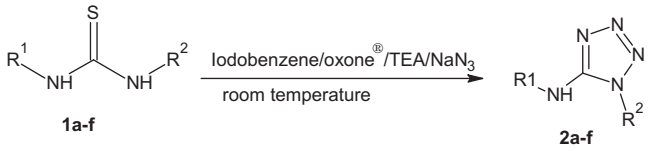
* Corresponding author.
E-mail address: vikastelvekar@rediffmail.com (V.N. Telvekar).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.114

First, the method to synthesize 5-aminotetrazoles from corresponding 1,3-disubtituted thioureas via oxidative desulfurization was developed using iodobenzene and oxone® (Scheme 1).

For the initial study, 1,3-diphenylthiourea was chosen as a model substrate to optimize the reaction conditions. To evaluate the effect of the reagents' concentration, reaction was carried out with different combinations of iodobenzene, oxone®, triethylamine (TEA), and sodium azide at room temperature. The best result was obtained when iodobenzene, oxone®, TEA, and sodium azide were used in 2, 3, 3, and 3 equiv, respectively. Very minor reaction was observed in the absence of TEA. We next compared various solvents such as MDC, ACN/water, ACN, and methanol. Superior results were observed with ACN/water affording 88% yield. Subsequently, various 1,3-disubstituted thioureas were investigated under the optimized conditions to study the scope of the system (Table 1).[13] The symmetrical thioureas containing electron donating as well as electron withdrawing groups smoothly underwent the reaction and produced corresponding products in moderate to good yields. A noteworthy aspect is that the reaction was regioselective in case of the unsymmetrical 1,3-disubstituted thio-

Table 1
Synthesis of 5-aminotetrazoles from 1,3-disubstituted thioureas[a]



1a-f 2a-f

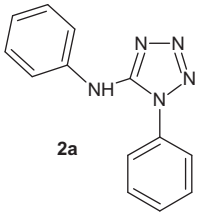
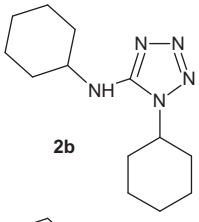
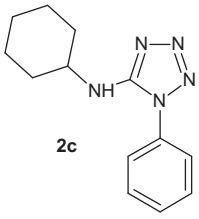
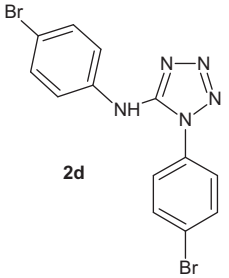
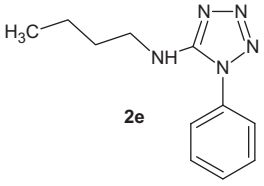
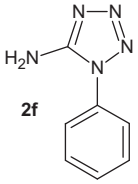
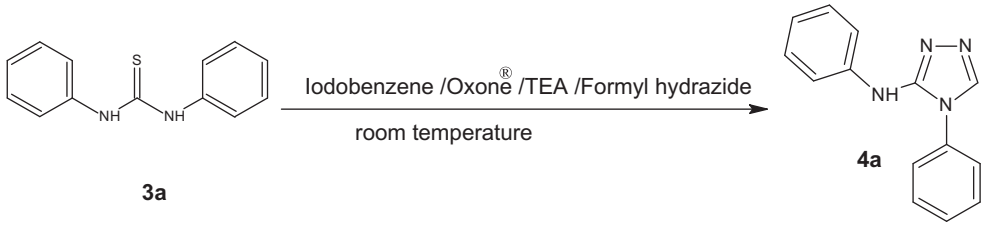
Sr. no.	Substrate	Product[b]	Yield[c] (%)
1	**1a**	 **2a**	88
2	**1b**	 **2b**	75
3	**1c**	 **2c**	80
4	**1d**	 **2d**	85
5	**1e**	 **2e**	78

Table 1 (*continued*)

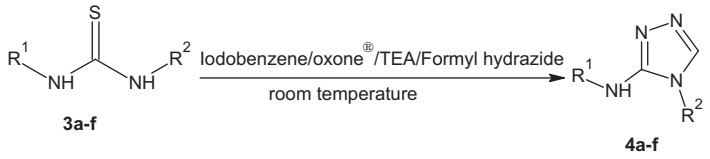
Sr. no.	Substrate	Product[b]	Yield[c] (%)
6	**1f**	 **2f**	72

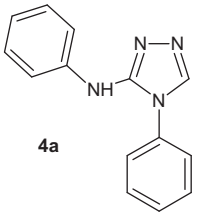
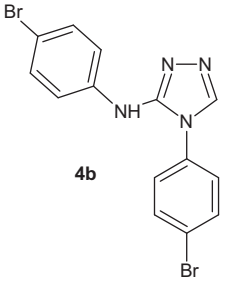
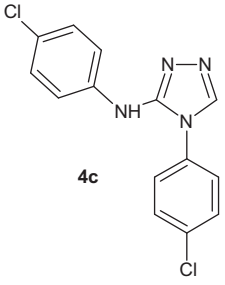
[a] All reactions of 1,3-disubstituted thioureas (1 mmol) were performed at room temperature in the presence of iodobenzene (2 equiv), oxone® (3 equiv), TEA (3 equiv), and sodium azide (3 equiv) in ACN/water (1:1, v/v) (10 mL).
[b] All previously reported products were identified by comparison of their NMR spectra, Mass spectra, and melting points with literature data.
[c] Isolated yields of analytically pure products.



Scheme 2. Synthesis of 3-amino-1,2,4-triazoles from 1,3-disubstituted thioureas.

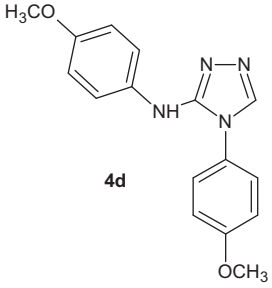
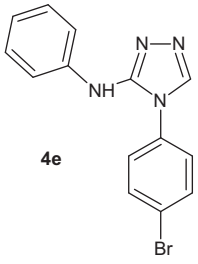
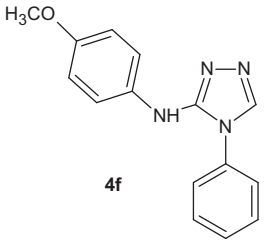
Table 2
Synthesis of 3-amino-1,2,4-triazoles from 1,3-disubstituted thioureas[a]



Sr.no.	Substrate	Product[b]	Yield[c] (%)
1	**3a**	 **4a**	80
2	**3b**	 **4b**	85
3	**3c**	 **4c**	78

(*continued on next page*)

Table 2 (*continued*)

Sr.no.	Substrate	Product[b]	Yield[c] (%)
4	**3d**	 **4d**	75
5	**3e**	 **4e**	68
6	**3f**	 **4f**	70

[a] All reactions of 1,3-disubstituted thioureas (1 mmol) were performed at room temperature in the presence of iodobenzene (2 equiv), oxone® (4 equiv), TEA (3 equiv), and formyl hydrazide (3 equiv) in methanol (10 mL).
[b] All previously reported products were identified by comparison of their NMR spectra, Mass spectra, and melting points with literature data.
[c] Isolated yields of analytically pure products.

ureas. The amine having lower pK_a was attached to the ring nitrogen and the amine having higher pK_a contributed to exocyclic amino group.

Subsequently, we extended this study to prepare 3-amino-1,2,4-triazoles using 1,3-disubstituted thioureas with formyl hydrazide (Scheme 2). The reaction was first explored in previously affirmed condition, however the result was unsatisfactory. Thus, reaction parameters such as stoichiometry of reagents, concentration, time, and temperature were studied using 1,3-diphenylthiourea as the model substrate for optimization of the process. Optimization afforded 2 equivalence of iodobenzene, 4 equivalence of oxone®, 3 equivalence of TEA, and formyl hydrazide as the best combination of reagents for this transformation. Examinations of various solvents confirmed the use of methanol as solvent.

In this case also with unsymmetrical 1,3-disubstituted thioureas, the product formed having lower pK_a amine get attached to the ring nitrogen and amine having higher pK_a contributed to exocyclic amino group.

As summarized in Table 2, various substrates of 1,3-disubstituted thioureas were subjected to optimized conditions.[14]

In summary, we have successfully developed a novel, simple, and highly efficient regioselective method for the synthesis of aminotetrazoles and aminotriazoles from corresponding 1,3-disubstituted thioureas. The procedure is broadly applicable to 1,3-disubstituted thioureas containing electron-rich as well as electron-deficient functional groups.

Acknowledgments

N.C.J. and K.N.P. acknowledge the University Grant Commission (UGC) India and P.B.J. thanks the Rajiv Gandhi National Fellowship (RGNF) for financial support.

References and notes

1. Upadhayaya, R. S.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R.; Arora, S. K. *Eur. J. Med. Chem.* **2004**, *39*, 579.
2. Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R. *J. Med. Chem.* **1991**, *34*, 2525.
3. Yella, R.; Khatun, N.; Rout, S.; Patel, B. K. *Org. Biomol. Chem.* **2011**, *9*, 3235.
4. Poonian, M. S.; Nowoswiat, E. F.; Blount, J. F.; Kramer, M. J. *J. Med. Chem.* **1976**, *19*, 1017.
5. Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538.
6. Andrus, A.; Partridge, B.; Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1984**, *25*, 911.
7. De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115.
8. Papakonstantinou-Garoufalias, S.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. *Farmaco* **2002**, *57*, 973.
9. Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **1976**, *2007*, 15.
10. Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Le Baut, G.; Marchand, P.; Le Borgne, M. *Tetrahedron Lett.* **2006**, *47*, 6479.
11. Katritzky, A. R.; Rogovoy, B. V.; Kovalenko, K. V. *J. Org. Chem.* **2003**, *68*, 4941. and references cited therein.
12. Patel, K. N.; Jadhav, N. C.; Jagadhane, P. B.; Telvekar, V. N. *Synlett* **2012**, *23*, 1970.
13. *Typical experimental procedure to synthesize 5-aminotetrazoles:* A mixture of iodobenzene (2 equiv) and Oxone® (3 equiv) in ACN/water was stirred at rt for 20 min followed by the addition of TEA (3 equiv) and substrate (1 equiv) and

after 5 min NaN_3 was added at rt and stirred for 3 h. The reaction mixture was diluted with H_2O and then extracted twice with EtOAc. The organic layer was washed successively with 10% $NaHCO_3$ (2×20 mL) and H_2O (2×20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The product was purified using silica gel column chromatography (20% EtOAc–hexane).

14. *Typical experimental procedure to synthesize 3-amino-1,2,4-triazoles:* A mixture of iodobenzene (2 equiv) and Oxone® (4 equiv) in methanol was stirred at rt for 20 min followed by the addition of TEA (3 equiv) and substrate (1 equiv) and after 5 min formyl hydrazide (3 equiv) was added at rt and stirred for 3 h. The reaction mixture was diluted with H_2O and then extracted twice with EtOAc. The organic layer was washed successively with 10% $NaHCO_3$ (2×20 mL)and H_2O (2×20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The product was purified using silica gel column chromatography (20% EtOAc–hexane).