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

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ABSTRACT

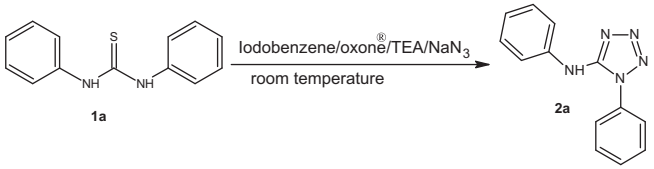
A novel and expedient regioselective method for the synthesis of 5-aminotetrazoles and 3-amino-1,2,4-triazoles through oxidative desulfurization of corresponding 1,3-disubstituted thioureas has been discovered and optimized for the process conditions. The process is broadly applicable to structurally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

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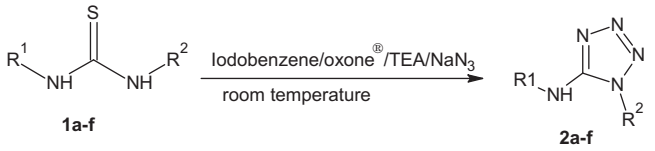
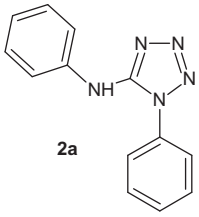
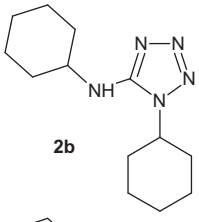
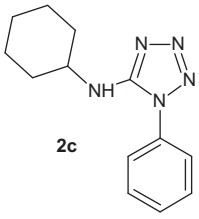
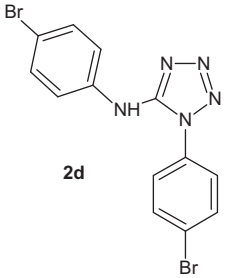
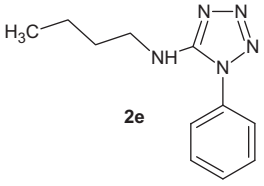
First, the method to synthesize 5-aminotetrazoles from corresponding 1,3-disubtituted thioureas via oxidative desulfurization was developed using iodobenzene and oxone® (Scheme 1).

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