Novel, Mild and Chemoselective Dehydrogenation of 2-Imidazolines with Trichloroisocyanuric Acid

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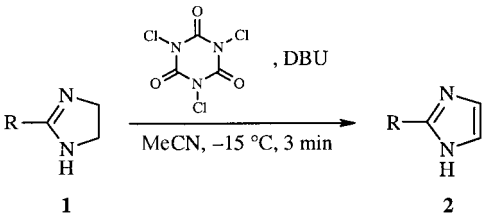
Abstract: A rapid, mild and high-yielding method for dehydrogenation of a variety of structurally diverse 2-imidazolines to imidazoles using trichloroisocyanuric acid (TCCA) in the presence of DBU is reported. Chemoselective oxidation of 2-imidazolines can be achieved in the presence of sulfide and alcohol. The mild conditions of this procedure and the absence of any transition metal make this reaction suitable for safe laboratory use.

Key words: 2-imidazolines, imidazoles, trichloroisocyanuric acid, dehydrogenation

The dehydrogenation of 2-imidazolines to imidazoles is of importance from both biological and synthetic considerations, due to antiinflammatory, antihypertensive, antibacterial and antidiabetic activities of many imidazole derivatives.[1] Several reagents such as Zn-Al_2O_3,[2] Ni,[3] Se,[4] Pd/C,[5] manganese dioxide,[6] barium manganate,[7] potassium permanganate[8] and DMSO[9] have been previously reported for the oxidation of 2-imidazolines. However, this transformation remains capricious because these compounds are very sensitive to oxidizing agents and reaction conditions. Moreover, the reported reagents suffer from disadvantages such as very long reaction times, low yields of the products, harsh reaction conditions and the use of large excess of the reagents. Another major drawback of the older procedures is either high toxicity or serious disposal problems of the reagents.

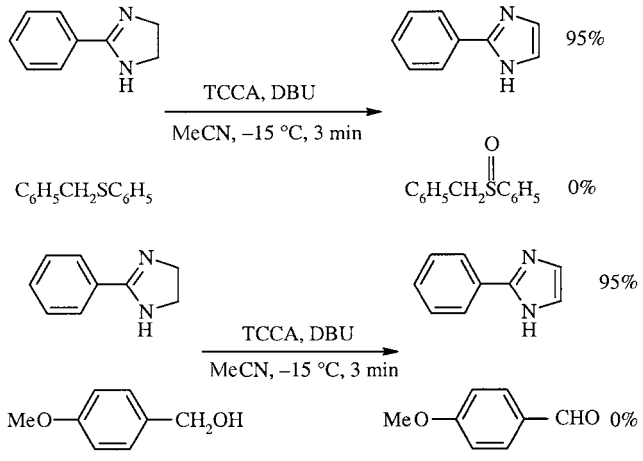
Our objective in this work was focused on some interesting features such as: (a) to achieve rapid reaction rates, higher yields and milder reaction conditions; (b) to overcome the limitations of the reported methods such as tedious work-up and presence of toxic transition metal within the molecular structure of the reagents; (c) to introduce a new and chemoselective method for the preparation of imidazoles using a safe commercially available reagent.

Trichloroisocyanuric acid is a very cheap commercially available reagent, which is used as disinfectant, deodorant, cleaning, sterilizing and bleaching agent.[10] Recently, several synthetically useful organic transformations using this reagent have been also reported.[10,11] Along this line, we now report a very mild, simple, cheap and convenient method for the effective oxidation of 2-imidazolines to imidazoles with trichloroisocyanuric acid in the presence of DBU (Scheme 1).



Scheme 1

As shown in Table 1, a range of structurally different 2-imidazolines are rapidly and cleanly oxidized to their corresponding imidazoles with trichloroisocyanuric acid in the presence of DBU in acetonitrile at –15 ºC.[12] The reactions are very fast (3 min) and furnish high yields of imidazoles. It is important to note that the waste cyanuric acid is environmentally non-hazardous.[13] Although trichloroisocyanuric acid has been used for chlorination of aromatic systems and benzylic positions,[10] no chlorinated derivatives were detected in the present method. The optimum molar ratio of 2-imidazoline:TCCA:DBU for complete conversion of 2-imidazolines to imidazoles was found to be 1:0.4:1.8. It is also worth mentioning that the method can be selectively applied for the chemoselective oxidation of 2-imidazolines in the presence of sulfide and alcohol, which was previously reported to be effectively oxidized using trichloroisocyanuric acid[11a,b] (Scheme 2).



Scheme 2

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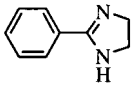
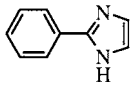
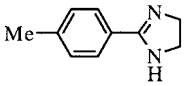
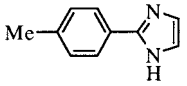
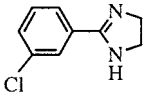
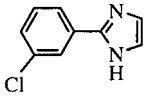
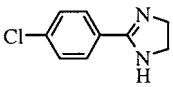
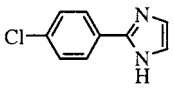
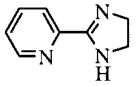
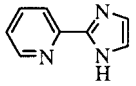
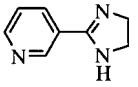
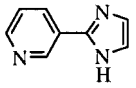
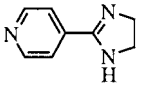
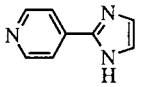
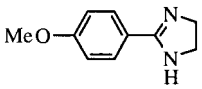
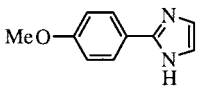
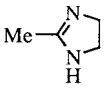
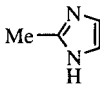
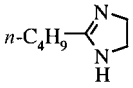
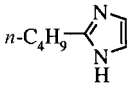
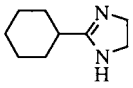
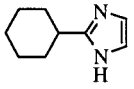
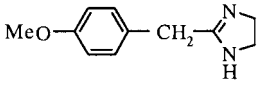
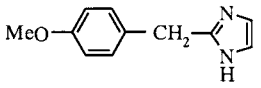
Table 1 Dehydrogenation of 2-Imidazolines using TCCA–DBU

2-Imidazoline (**1**)	Imidazole[a] (**2**)	Time (min)	Yield (%)[b]
 **1a**	 **2a**	3	93
 **1b**	 **2b**	3	94
 **1c**	 **2c**	3	88
 **1d**	 **2d**	3	85
 **1e**	 **2e**	3	94
 **1f**	 **2f**	3	95
 **1g**	 **2g**	3	89
 **1h**	 **2h**	3	84
 **1i**	 **2i**	3	90
 **1j**	 **2j**	3	90
 **1k**	 **2k**	3	92
 **1l**	 **2l**	3	77

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.[7–9,14]
[b] Isolates yields.

These observations clearly suggest that the method can be applied for the chemoselective oxidation of 2-imidazolines in the presence of other oxidizable functional groups such as sulfide and alcohol in multifunctional molecules.

In summary, we have demonstrated that trichloroisocyanuric acid–DBU is an excellent reagent system for rapid oxidation of 2-imidazolines. In addition, safe and mild reaction conditions, very short reaction times, high yields of the products, cheapness and commercial availability of the reagent, transition metal absence, nontoxic by-products and excellent chemoselectivity make this method ideal for both laboratory and large scale.

Acknowledgment

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(12) **Typical Experimental Procedure:** 2-(4-Methylphenyl)imidazoline (**1b**, 2.0 mmol) was dissolved in MeCN (40 mL) and DBU (0.54 g, 3.6 mmol) was added. The solution was cooled to –15 °C and a solution of TCCA (0.185 g, 0.8 mmol) in MeCN (10 mL) was added dropwise. The reaction mixture was stirred for 3 min. After completion of the reaction (as monitored by TLC), the mixture was allowed to warm up to r.t. and passed through a short pad of alumina. The solvent was evaporated and the resulting crude material was purified by column chromatography on alumina with appropriate eluent to afford the pure 2-(4-methylphenyl)imidazole (**2b**, 94%), mp 218–220 °C (lit.[9] mp 223 ºC). IR (KBr): 3435, 3150, 2985, 1658, 1610, 1575, 1514, 1435, 1100, 815, 725 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 2.31 (s, 3 H), 6.99 (br s, 1 H), 7.18 (br s, 1 H), 7.23 (d, *J* = 7.5 Hz, 2 H), 7.81 (d, *J* = 8 Hz, 2 H), 12.39 (s, 1 H).

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