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Trichloroisocyanuric acid as a novel oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazolines under both heterogeneous and solvent free conditions

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Abstract—Trichloroisocyanuric acid is used as an effective oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles under both heterogeneous and also solvent free conditions with good yields at room temperature.

Some of five-membered heterocyclic compounds are used commercially as pharmaceuticals, pesticides, and dyestuffs. These compounds are also important constituents in many biologically active natural products and synthetic compounds of medicinal interest.[1,2] The conversion of 1,3,5-trisubstituted pyrazolines with sensitive functional groups to their corresponding pyrazole derivatives are a tricky step. A variety of reagents such as Pd/C/acetic acid,[3] cobalt soap of fatty acids,[4] lead tetraacetate,[5] mercury or lead oxide,[6] manganese dioxide,[7] potassium permanganate,[8] silver nitrate,[9] iodobenzene diacetate,[10] and zirconium nitrate[11] are all capable of effecting the pyrazoline oxidation. However, this transformation remains capricious because these compounds are very sensitive to oxidizing agents and the reaction conditions. Moreover, most of the reported reagents produce some by-products, which either destroy, or are difficult to remove from the sensitive pyrazoles.[4] Another major drawback to the older procedures is their use of reagents, which are either highly toxic, or produce serious disposal problems (or both).

Our goals, in undertaking this work, were (a) to overcome the limitations and drawbacks of the reported methods such as tedious work-up, acidic media,[3] and safety problems (presence of toxic transition metal cations such as Co(II),[4] Pb(IV),[5] Hg(II),[6] Mn(IV and VII),[7,8] Ag(I),[9] Zr(IV)[11] within the molecular structure of the reagents); (b) to devise a solvent free synthesis especially, useful for industry, with many advantages: reduced pollution, low costs, and simplicity in processing and handling;[12–14] (c) to develop a high-yielding synthesis of pyrazoles by using a commercially available reagent. Therefore, we were interested to find a heterogeneous system for pyrazoline oxidation. In continuation of our studies in this regard,[15–18] we have found that trichloroisocyanuric acid, a cheap commercially available reagent used primarily as a disinfectant and deodorant, has found little application in organic chemistry.[18–21] Therefore, we wish to report a simple, cheap, and convenient method for the effective conversion of 1,3,5-trisubstituted pyrazolines **1** to their corresponding pyrazoles **2** using trichloroisocyanuric acid both under heterogeneous and also solvent free conditions (Table 1).

A good range of 1,3,5-trisubstituted pyrazolines were subjected to oxidation in the presence of trichloroisocyanuric acid in CCl_4 or solvent free conditions (Table 1). The oxidation reactions were performed under mild conditions at room temperature with good yields. The 1,3,5-trisubstituted pyrazoles **2** were obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are given in Table 2.[22–24]

In conclusion, a practical and efficient oxidation of 1,3,5-trisubstituted pyrazolines has been achieved by the new methodology described. This reagent could be used for the oxidation of a wide variety of pyrazoline derivatives under safe conditions.

Keywords: Trichloroisocyanuric; 1,3,5-Trisubstituted pyrazolines; Pyrazoles; Solvent free conditions.
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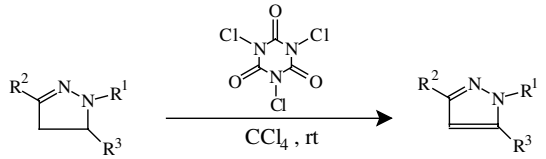
Table 1



1 2

Substrate	Product	R^1	R^2	R^3
1a	**2a**	Ph	2-Naphthyl	2-$CH_3C_6H_4$
1b	**2b**	Ph	2-Naphthyl	Ph
1c	**2c**	Ph	Ph	Ph
1d	**2d**	Ph	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$
1e	**2e**	Ph	3-$CH_3C_6H_4$	2-ClC_6H_4
1f	**2f**	Ph	4-$CH_3OC_6H_4$	3-$CH_3C_6H_4$
1g	**2g**	Ph	4-$CH_3OC_6H_4$	2-$CH_3C_6H_4$
1h	**2h**	Ph	4-$CH_3OC_6H_4$	Ph
1i	**2i**	Ph	4-$CH_3OC_6H_4$	4-ClC_6H_4
1j	**2j**	Ph	3-$CH_3C_6H_4$	4-ClC_6H_4
1k	**2k**	Ph	2-Naphthyl	3-$CH_3C_6H_4$
1l	**2l**	Ph	2-Naphthyl	4-ClC_6H_4
1m	**2m**	Ph	2-Naphthyl	2-ClC_6H_4
1n	**2n**	Ph	3-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$
1o	**2o**	Ph	2-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$
1p	**2p**	Ph	4-$CH_3OC_6H_4$	4-ClC_6H_4

Table 2. Oxidation of 1,3,5-trisubstituted pyrazolines **1** to their corresponding pyrazoles **2** with trichloroisocyanuric acid both in CCl_4 (**I**) and solvent free conditions (**II**) at room temperature

Substrate	Product[a]	Reagent/substrate[b]		Time (h)	Yield[c] (%)
		I	**II**	**I (II)**	**I (II)**
1a	**2a**	1.25	3.5	0.8 (1.3)	90 (80)
1b	**2b**	1.25	3.25	0.75 (1.5)	92 (80)
1c	**2c**	1.25	3.25	0.75 (1.3)	85 (80)
1d	**2d**	2.25	4.25	0.8 (1.75)	85 (75)
1e	**2e**	2.5	4.25	0.8 (1.3)	74 (70)
1f	**2f**	2.75	4.25	0.5 (1)	92 (80)
1g	**2g**	3.25	4.75	0.5 (1.3)	90 (78)
1h	**2h**	2	3.75	0.6 (1.5)	92 (70)
1i	**2i**	2.25	4	0.6 (1.75)	70 (70)
1j	**2j**	3.25	4.75	0.9 (1.5)	85 (72)
1k	**2k**	2.25	4.75	0.9 (1.3)	85 (80)
1l	**2l**	3.5	5.25	0.8 (1.5)	82 (75)
1m	**2m**	3.25	5.25	0.8 (1.5)	78 (65)
1n	**2n**	2.5	4.75	0.5 (1.2)	82 (70)
1o	**2o**	2.5	5.25	0.5 (1.5)	85 (68)
1p	**2p**	2.5	4	0.5 (1)	90 (75)

[a] All of the isolated products are known compounds and their spectra and physical data have been reported in the literature.[2–11]

[b] Molar ratio of trichloroisocyanuric acid in CCl_4 (**I**) mmol and under solvent free conditions (**II**) mmol.

[c] Isolated yields.

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22. Chemicals were purchased from Fluka, Merck, Riedeldehaen AG, and Aldrich chemical companies. Yields refer to isolated pure products. The oxidation products were characterized by comparison of their spectral (IR, and ^1H NMR) and physical data with authentic samples. All 1,3,5-trisubstituted pyrazolines were synthesized according to our previously reported procedure.[1]
23. General procedure for oxidation of pyrazoline: A suspension of trichloroisocyanuric acid (the molar ratios of trichloroisocyanuric acid to the substrate **1** are given in Table 2), pyrazoline **1** (2 mmol) and CCl_4 (10 mL) were stirred vigorously at room temperature. The progress of the reaction was followed by TLC. Reactions were

completed after 0.5–1.75 h (Table 2). After the reaction was completed, dry silica gel (1 g) was added to the reaction mixture, the solid materials were removed by filtration and washing with dichloromethane (10 mL). The solvent was evaporated and the pyrazoles **2** were obtained (Table 2). If further purification is needed, flash chromatography on silica gel (eluent: acetone/petroleum ether 1:5) was used to give highly pure **2**.

24. General procedure for oxidation of pyrazoline under solvent free conditions: A mixture of trichloroisocyanuric acid (the molar ratio of trichloroisocyanuric acid to the substrate **1** are given in Table 2), pyrazoline **1** (2 mmol) was shaken at rt for 1–1.75 h (the progress of the reaction was monitored by TLC), followed by CH_2Cl_2 (20 mL) addition and filtration of the resulting mixture. Dichloromethane was finally removed by heating (35–40 °C)[18] simple distillation, and the pyrazoles **2** were obtained (Table 2). If further purification is needed, flash chromatography on silica gel (eluent: acetone/petroleum ether 1:5) was used to give highly pure **2**.