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JSCS–4343 *Original scientific paper*

Trichloroisocyanuric acid as an efficient homogeneous catalyst for the chemoselective synthesis of 2-substituted oxazolines, imidazolines and thiazolines under solvent-free condition

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Abstract: Trichloroisocyanuric acid, as a commercially available and inexpensive catalyst, was used in a new, facile and efficient procedure for the synthesis of 2-oxazolines, 2-imidazolines and 2-thiazolines through the reaction of nitriles with 2-aminoethanol, ethylenediamine or 2-aminoethanethiol under solvent-free conditions.

Keywords: trichloroisocyanuric acid; oxazoline; imidazoline; thiazoline; solvent-free condition.

INTRODUCTION

Developing new and efficient methods for the synthesis of heterocyclic biologically active natural compounds has received considerable attention in organic chemistry. This importance is due to their great applications in medicine. Oxazolines, imidazolines and thiazolines are important substructures in a large number of biologically active natural products.[1,2] Many derivatives of these heterocycles have shown antihypertensive,[3,4] antidepressive,[5] antihypercholesterolemic,[6] antidiabetic,[7] antitumor[8] and anti-inflammatory[9] properties. In addition to these serious affairs, they are also known as valuable intermediates in organic transformations.[10,11] Furthermore, optically active mono- and bis-derivatives of these heterocycles have been widely used as both auxiliaries and ligands in asymmetric syntheses.[12–14]

Numerous methods have been reported for the synthesis of 2-oxazolines, 2-imidazolines and 2-thiazolines from various precursors.[15–25] Although some of these procedures have been successfully used for the synthesis of these heterocycles, most of them suffer from disadvantages such as: strong acidic conditions, long reaction times, low yields of products, use of complex and expensive re-

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agents and toxic solvents. Therefore, the introduction of a new efficient method for the synthesis of these useful moieties is still in demand.

Trichloroisocyanuric acid (1,3,5-trichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione or TCCA) is an *N*-halo compound which has been known since 1902 (Fig. 1). It has been used primarily as a disinfectant in swimming pools and water treatment.[26] Recently, TCCA has become attractive candidate as a homogeneous catalyst in organic transformations[27–35] due to its lack of volatility, commercial availability, low cost and ease of handling.

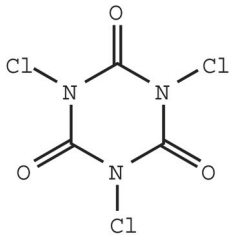
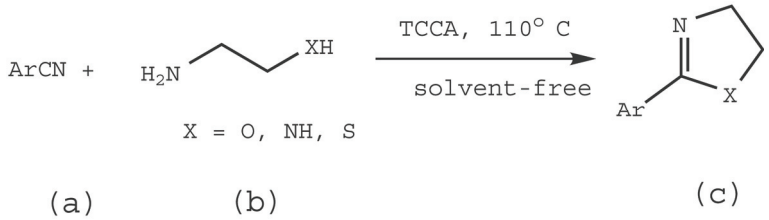


Fig. 1. Structure of trichloroisocyanuric acid.

Consequently, in continuation of our interest in the synthesis of 2-oxazoline, 2-imidazoline and 2-thiazoline derivatives,[36–38] the catalytic activity of TCCA in this field was investigated (Scheme 1).



Scheme 1. Synthesis of 2-oxazoline, 2-imidazoline and 2-thiazoline derivatives using TCCA as catalyst.

EXPERIMENTAL

General procedure for the conversion of nitriles to 2-oxazolines, 2-imidazolines and 2-thiazolines

A mixture of a nitrile (l mmol), 2-aminoethanol (6 mmol), ethylenediamine (4 mmol) or 2-aminoethanethiol (1.2 mmol) and TCCA (0.03 mmol for oxazoline, 0.1 mmol for imidazoline and 0.01 mmol for thiazoline synthesis) was stirred at 110 °C for an appropriate time, according to Table I. The reaction was performed under solvent-free conditions. After completion of the reaction, monitored by TLC (eluent: *n*-hexane:EtOAc, 2:1 for oxazolines and thiazolines, EtOAc:methanol, 10:1 for imidazolines), the reaction mixture was cooled to room temperature and the crude product (**1c**–**24c**) was purified by column chromatography to afford the pure products in high yields (Table I).

TABLE I. Synthesis of 2-oxazolines, 2-imidazolines and 2-thiazolines from nitriles catalyzed by TCCA

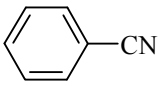
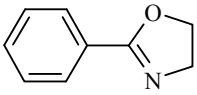
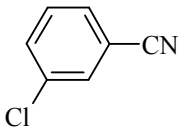
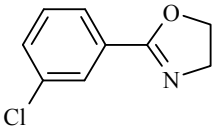
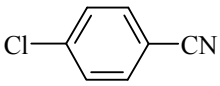
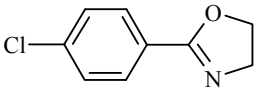
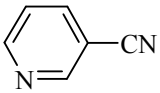
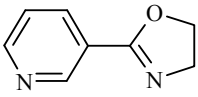
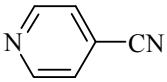
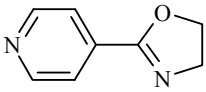
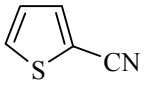
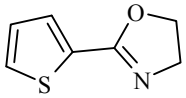
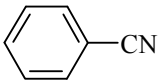
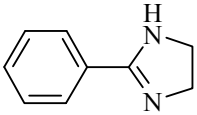
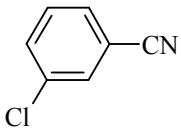
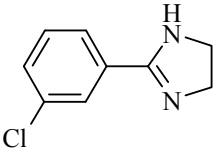
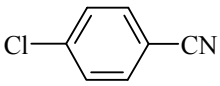
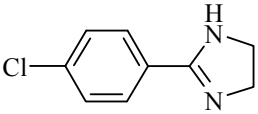
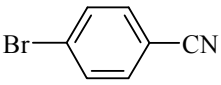
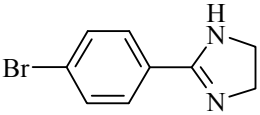
No.	Nitrile (a)	Product (c)[a]	Time, min	Yield[b], %
1c			60	95
2c			30	90
3c			120	98
4c			60	90
5c			20	94
6c			140	93
7c			240	90
8c			120	85
9c			180	93
10c			150	93

TABLE I. Continued

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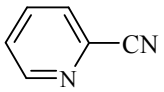
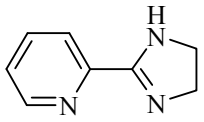
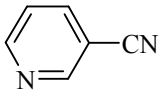
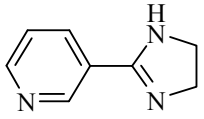
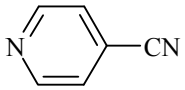
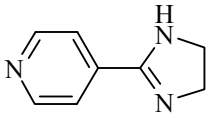
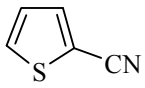
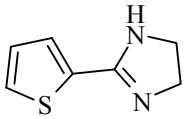
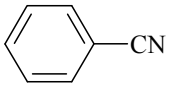
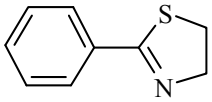
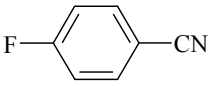
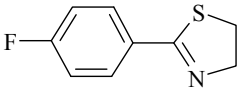
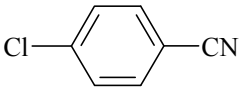
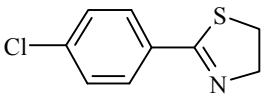
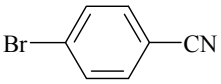
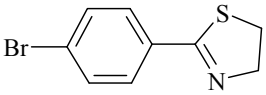
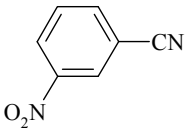
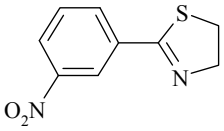
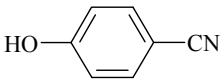
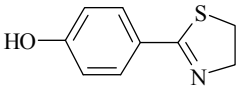
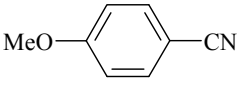
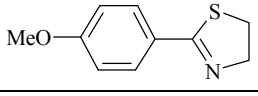
11c			8	98
12c			150	95
13c			15	94
14c			120	90
15c			2	95
16c			1	96
17c			5	97
18c			2	80
19c			2	98
20c			3	60
21c			2	50

TABLE I. Continued

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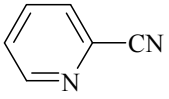
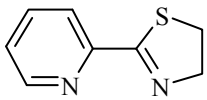
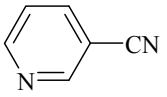
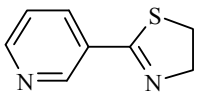
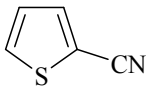
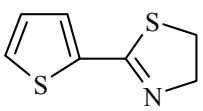
22c			1	98
23c			3	97
24c			2	98

[a]The products were identified by comparison of their physical and spectral data with those of authentic samples; [b]isolated yield

General method for the conversion of dinitriles to mono- and bis-oxazolines, mono-imidazolines and bis-thiazolines

To a mixture of a dinitrile (1 mmol) and 2-aminoethanol (10 mmol), ethylenediamine (8 mmol) or 2-aminoethanethiol (2.5 mmol), TCCA (0.06 mmol for oxazoline, 0.15 mmol for imidazoline and 0.02 mmol for thiazoline synthesis) was added. The reaction mixture was stirred at 110 °C without solvent. The progress of the reaction was followed by TLC (eluent: *n*-hexane:EtOAc, 2:1 for mono- and bis-oxazolines and bis-thiazolines, EtOAc:methanol, 10:1 for mono-imidazolines). After the appropriate time according to Table II, the pure products (**1f**–**8f**) were gained by column chromatography.

RESULTS AND DISCUSSION

In continuation of our work to recommend new catalysts for organic syntheses,[36–42] now TCCA as a highly efficient homogeneous catalyst for the preparation of 2-oxazolines, 2-imidazolines and 2-thiazolines from nitriles is presented (Scheme 1).

In order to find the optimum reaction conditions, benzonitrile was reacted with 2-aminoethanol in the presence of TCCA. The model reaction was performed using different molar ratios of substrates and catalyst, at various temperatures and in different polar and non-polar solvents. With the goal of performing the synthesis in the absence of solvent as a special advantage of the method, the model reaction was also investigated under solvent-free conditions. The best result was obtained in the reaction of benzonitrile (1 mmol), 2-aminoethanol (6 mmol) and TCCA (0.03 mmol) at 110 °C under solvent-free conditions (Table I, entry 1). Using these optimized conditions, a variety of aromatic and heteroaromatic nitriles were reacted with 2-aminoethanol and corresponding 2-oxazolines were generated in high yields (Table I, entries 1–6).

Similarly, the model reaction of benzonitrile with ethylenediamine was performed in the presence of TCCA for optimization of 2-phenylimidazoline syn-

thesis. After several experiments, 1:4:0.1 molar ratio of benzonitrile: ethylenediamine: catalyst at 110 °C in the absence of solvent was selected as the best reaction conditions (Table I, entry 7). Subsequently, heterocyclization of a great variety of aromatic and heteroaromatic nitriles with ethylenediamine were performed to prepare the corresponding 2-imidazoline products (Table I, entries 7––14).

Furthermore, cyclocondensation of benzonitrile with 2-aminoethanethiol was performed in the presence of different amounts of TCCA. The effects of temperature and solvent were also investigated. The best result was obtained with 1:1.2:0.01 molar ratios of benzonitrile:2-aminoethanethiol:TCCA at 110 °C under solvent-free conditions. Various aromatic and heteroaromatic nitriles were reacted with 2-aminoethanethiol in the presence of TCCA under the optimum reaction conditions. The corresponding 2-substituted thiazolines were generated in good to excellent yields (Table I, entries 15–24).

Extensive applications of both chiral and achiral bis-oxazolines, bis-imidazolines and bis-thiazolines as ligands in various complex structures promoted the use of the present method for the synthesis of these useful ligands from dinitriles. Therefore, dicyanobenzene derivatives were reacted with 2-aminoethanol, ethylenediamine or 2-aminoethanethiol in the presence of TCCA at 110 °C under solvent-free conditions (Table II). As given in Table II, the conversion of dinitriles to mono-oxazolines (10–20 min) and bis-oxazolines (300–390 min) is a special time-dependent chemo-selective procedure. It is also important to note that the synthesis of mono-imidazolines and bis-thiazolines is a chemo-selective, but not a time-dependent reaction (Table II). Mono-imidazolines were satisfactorily produced after 20–30 min (Table II, **5f** and **6f**) and prolonging the reaction time did not lead to the production of the corresponding bis-imidazolines. Whereas, bis-thiazolines were exclusively obtained from the reactions of dinitriles with 2-aminoethanethiol after 7–10 min (Table II, **7f** and **8f**).

TABLE II. Synthesis of mono- and bis-derivatives of oxazolines, imidazolines and thiazolines from dinitriles catalyzed by TCCA

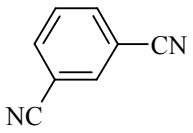
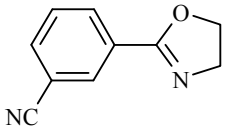
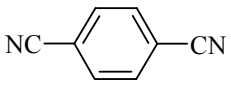
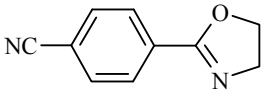
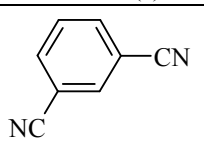
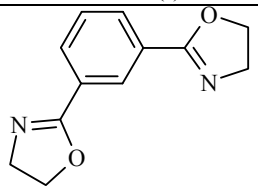
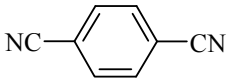
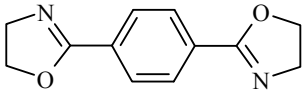
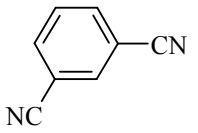
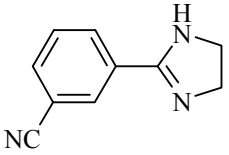
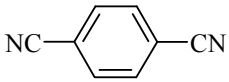
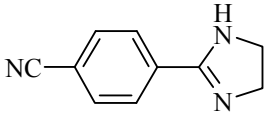
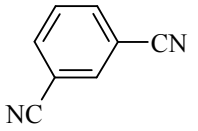
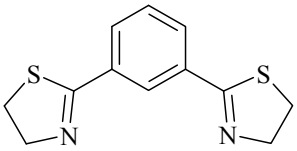
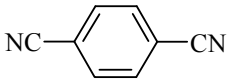
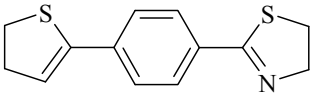
Entry	Dinitrile (e)	Product (f)[a]	Time, min	Yield[b], %
1f			10	95
2f			20	92

TABLE II. Continued

Entry	Dinitrile (e)	Product (f)[a]	Time, min	Yield[b], %
3f			300	80
4f			390	97
5f			20	92
6f			30	95
7f			7	95
8f			10	92

[a]The products were identified by comparison of their physical and spectral data with those of authentic samples; [b]isolated yield

It is noteworthy that the method is selective for the reaction of aromatic nitriles as aliphatic nitriles are unreactive under these conditions.

In order to show the superiority of TCCA over other catalysts, the results obtained in the present study for the synthesis of 2-phenyloxazoline are compared with some other results reported in the literature in Table III. It is note-

TABLE III. Comparison of some other procedures with the present method for the synthesis of 2-phenyloxazoline (**1c**)

Entry	Catalyst amount, mol %	Temperature, °C	Time, h	Yield, %	Ref.
1	TCCA (3)	110	1	95	–
2	$Bi(OTf)_3$ (5)	100	3.5	88	31
3	$ZrOCl_2.8H_2O$ (10)	100	5	90	33
4	$H_3PW_{12}O_{40}$ (1)	100	3.5	85	–
5	$ZnCl_2$ (1.25)	130, under N_2	12	74	34

worthy that the catalytic activity of TCCA was greater than those of some active Lewis acids or solid acids, as given in Table III.

CONCLUSIONS

In summary, TCCA was employed as a novel and highly efficient catalyst for the synthesis of 2-oxazolines, 2-imidazolines and 2-thiazolines from nitriles in high yields. This homogeneous catalyst is commercially available, inexpensive and non-volatile and is a chemical commonly found in organic laboratories. Furthermore, the efficiency and chemoselectivity of the protocol was also investigated in the selective preparation of aromatic and heteroaromatic mono- and bis-oxazolines, mono-imidazolines and bis-thiazolines. In addition, the absence of hazardous and non-green solvents, easy work-up and approximately short reaction times are another noteworthy advantage of the reported protocols.

SUPPLEMENTRY MATERIAL

The physical and spectral data of the prepared compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ТРИХЛОРИЗОЦИЈАНУРНА КИСЕЛИНА КАО ЕФИКАСАН ХОМОГЕНИ КАТАЛИЗАТОР У ХЕМОСЕЛЕКТИВНОЈ СИНТЕЗИ 2-СУПСТИТУИСАНИХ ОКСАЗОЛИНА, ИМИДАЗОЛИНА И ТИАЗОЛИНА У РЕАКЦИЈАМА БЕЗ РАСТВАРАЧА

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Трихлоризоцијанурна киселина је комерцијално доступан и приступачан реагенс, који је употребљен као катализатор у синтези 2-оксазолина, 2-имидазолина и 2-тиазолина, у реакцији 2-аминоетанола, етилендиамина или 2-аминоетантиола у одсуству растварача.

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