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Research Article

Trichloroisocyanuric acid: Novel, ecofriendly and efficient catalysts for the one-pot synthesis of Pyrano [2, 3-d] pyrimidine dione derivatives in aqueous media

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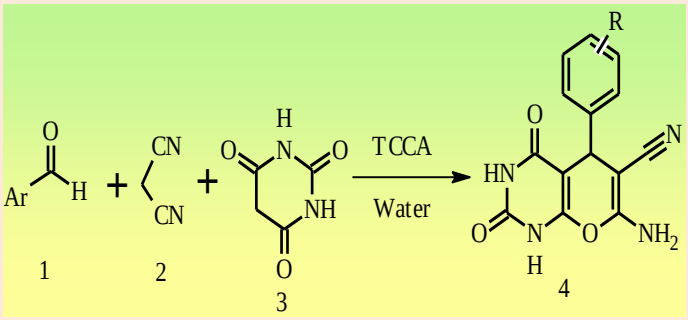
Abstract

An efficient one-pot synthesis of pyranopyrimidine derivatives was developed by using novel ecofriendly Trichloroisocyanuric acid as a catalyst in water as a green solvent at reflux temperature. The attractive features of this protocol is environmentally benign Mild reaction conditions, cost effective easily available catalyst, low toxic effects to the environment, shorter reaction time, easy isolation of product without use of chromatographic separation and excellent yields.



Keywords: Trichloroisocyanuric acid (TCCA), Pyrano [2, 3-d] pyrimidine dione derivatives, Barbituric acid, Solvent- Water, Multi-component reaction

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Introduction

The development of environmentally benign, safe and clean synthetic procedures in today's life has become the prime imperative objective of organic chemist. Synthesis of organic compounds in the nature occurs very efficiently in water. Organic chemists have traditionally been taught that water is not generally a good solvent for carrying out synthetic reactions. Nevertheless, in recent years reports have appeared in increasing number describing use of water as a solvent for various organic reactions. [1-3] The organic reactions in aqueous media have attracted great attention in organic synthesis, not only because water it is one of the most abundant, cheapest and environmentally benign solvent, but also exhibits unique reactivity and selectivity, which is different and, in most cases, higher than those in conventional organic solvents [4]. Reactions in aqueous media are environmentally safe, devoid of any malign carcinogenic effects, have a simple work up procedure and especially important in industries. Thus, there is a need for developing multicomponent reactions (MCRs) in water and without the use of any harmful organic solvents.

Pyrano [2, 3-d] pyrimidine derivatives are annulated uracils that have received great attention during the past years because of their wide range of biological activities. Compounds with these ring systems have various pharmacological activities such as antitumor, cardiotonic, hepatoprotective, antihypertensive, antibronchitic and antifungal activities [5-8]. Numerous methods have been reported for the synthesis of pyrano [2, 3-d] pyrimidine derivatives [9-11]. Although most of these protocols offer distinct advantages, at the same time they suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, high costs of solvent and the catalyst, harsh reaction conditions, use of a large quantity of volatile organic solvents, expensive metal precursors, and environmentally toxic catalysts. Considering these reports, the development of new, simple, and efficient synthetic methods for the preparation of heterocycles containing pyran ring fragments will be beneficial and an interesting challenge.

Experimental

All of the chemicals used were purchased from Sigma Aldrich and used as such. All the synthesized compounds are reportedly herein are known, and were identified by the comparison of spectral and physical data with the literature. Thin layer chromatography was used to monitor the reaction progress. Compounds were purified by crystallization from water: ethanol (1:1) solvent mixture. Melting points were determined using a melting point apparatus. IR (KBr) spectra were recorded on JASCO FTIR 4600 spectrophotometer and the values are expressed as ν max cm^{-1}. Mass spectral data were recorded on a Waters micro mass LCT Mass Spectrometer and on JEOL-AccuTOF JMS-T100 mass spectrometer having a DART source. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer and Jeol JNM ECX-400P at 300 MHz and 400 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) in hertz.

Catalyst

Trichloroisocyanuric acid (TCCA) is an inexpensive, water-soluble, non-toxic, and commercially available compound that can be used in the laboratory without special precautions. This reagent has been used in important manufacturing processes, such as water purification, paper and pharmaceutical industries etc. This reagent is also used as an industrial disinfectant, bleaching agent and a reagent in organic synthesis [12, 13]. There are few reports regarding the applications of TCCA in the synthesis of organic compounds. As a part of our current studies on the development of efficient methods for the synthesis of pyrano [2, 3-d] pyrimidine heterocyles, we herein report an environmental friendly and straightforward protocol for the synthesis of pyrano [2, 3-d] pyrimidine derivatives by using a Trichloroisocyanuric acid (TCCA) in water at a reflux temperature.

General procedure for the synthesis of pyrano [2, 3-d] pyrimidine dione derivatives.

A mixture of an appropriate aromatic aldehyde (1 mmol), malononitrile (1.2 mmol), barbituric acid (1 mmol) and trichloroisocyanuric acid [TCCA] (10 mole %) in water (3 ml) was stirred magnetically in a round-bottomed flask under reflux conditions. The progress of the reaction was monitored by thin-layer chromatography (TLC) using chloroform methanol (9:1) as an eluent system. Upon the completion of the reaction, the reaction mixture was cooled to room temperature. The precipitated solid was collected by filtration. All the products were obtained in an excellent yield as summarized in Table 3.

Result and discussion

Trichloroisocyanuric acid catalyzed synthesis of pyran annulated heterocyles, are obtained through one-pot three-component condensation reaction of aldehydes, malononitrile and barbituric acid as shown in (**Scheme 1**).

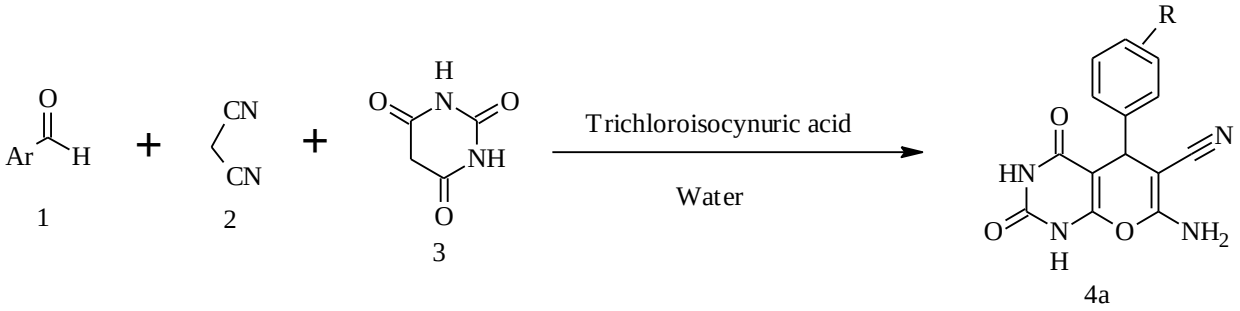
The reaction was optimized using different moles of the catalysts for obtaining the best yield of 4a summarized in **Table 1**. It was noted that 10 mole % of the Trichloroisocyanuric acid in water provides the best result in terms of yield and time.

After the optimization of the reaction conditions, the reaction of benzaldehyde with malononitrile and barbituric acid was carried out under the same reaction conditions using different solvents afford with different yields. It is observed that reaction with water as solvent gave 95% yield. Therefore the reactions of diversely substituted aromatic aldehydes were attempted with malononitrile and barbituric acid in water under reflux in the presence of 10 mole % of trichloroisocyanuric acid (TCCA). All the reactions yielded corresponding to pyrano [2, 3-d] pyrimidine dione (**Table 3**, entries) in excellent yields.

Conclusion

In summary, we have developed a novel synthetic methodology for the synthesis of pyran annulated heterocyclic systems using 10 mole % trichloroisocyanuric acid as a green nontoxic, inexpensive efficient catalyst. This methodology not only offers great advantages like substantial reaction conversions, high yields and easy isolation

which avoids use of column chromatography but also avoids use of hazardous solvent media and the catalysts helping in to protect environment and safeguards mankind.



Scheme 1

Table 1 Effect of the catalyst Pyrano [2, 3-d] pyrimidine dione derivatives

Entry	Catalyst (mole %)	Time/hrs	%Yield
1	Catalyst(10)	3	92
2	Catalyst(5)	4	85
3	Catalyst(3)	5	79
4	No catalyst	10	<20
5	Morpholine	3	80 [14]
6	Tetrabutylammonium bromide (TBAB)	6	80 [15]
7	Ammonium, acetate	5	82 [16]
8	Zn[(L)proline]	6	80 [17]

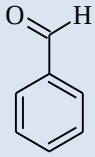
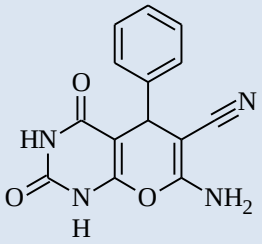
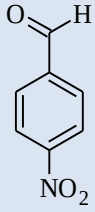
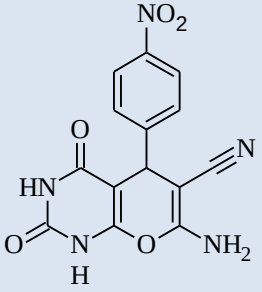
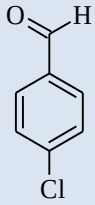
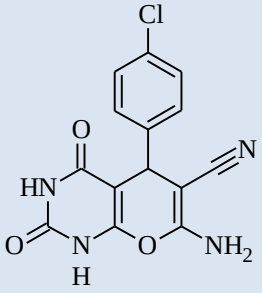
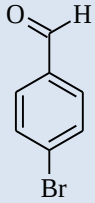
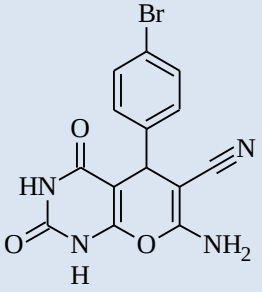
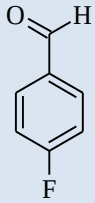
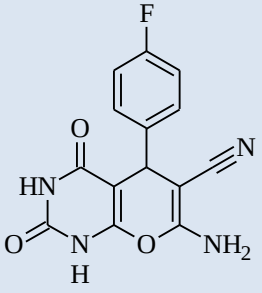
The yields are referred to isolated products.

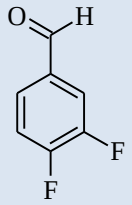
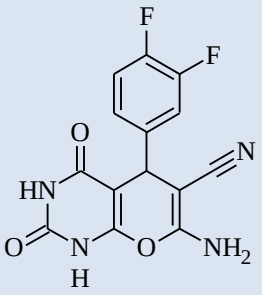
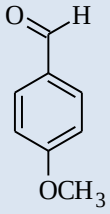
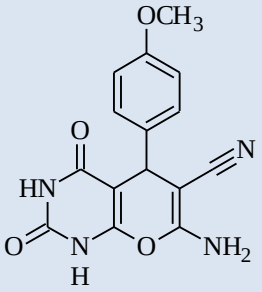
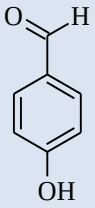
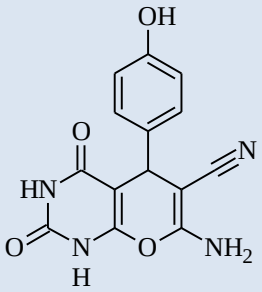
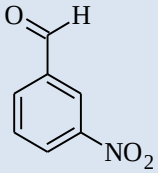
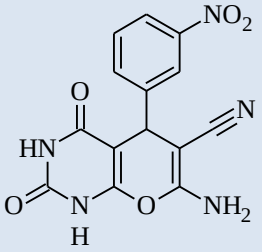
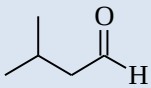
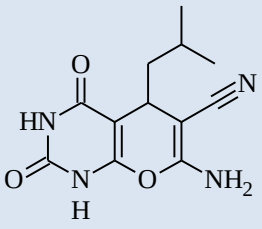
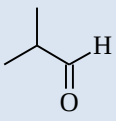
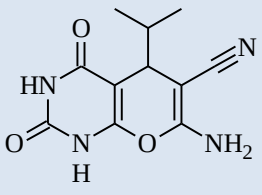
Table 2 Effect of solvent on the reaction of benzaldehyde, malononitrile and barbituric acid

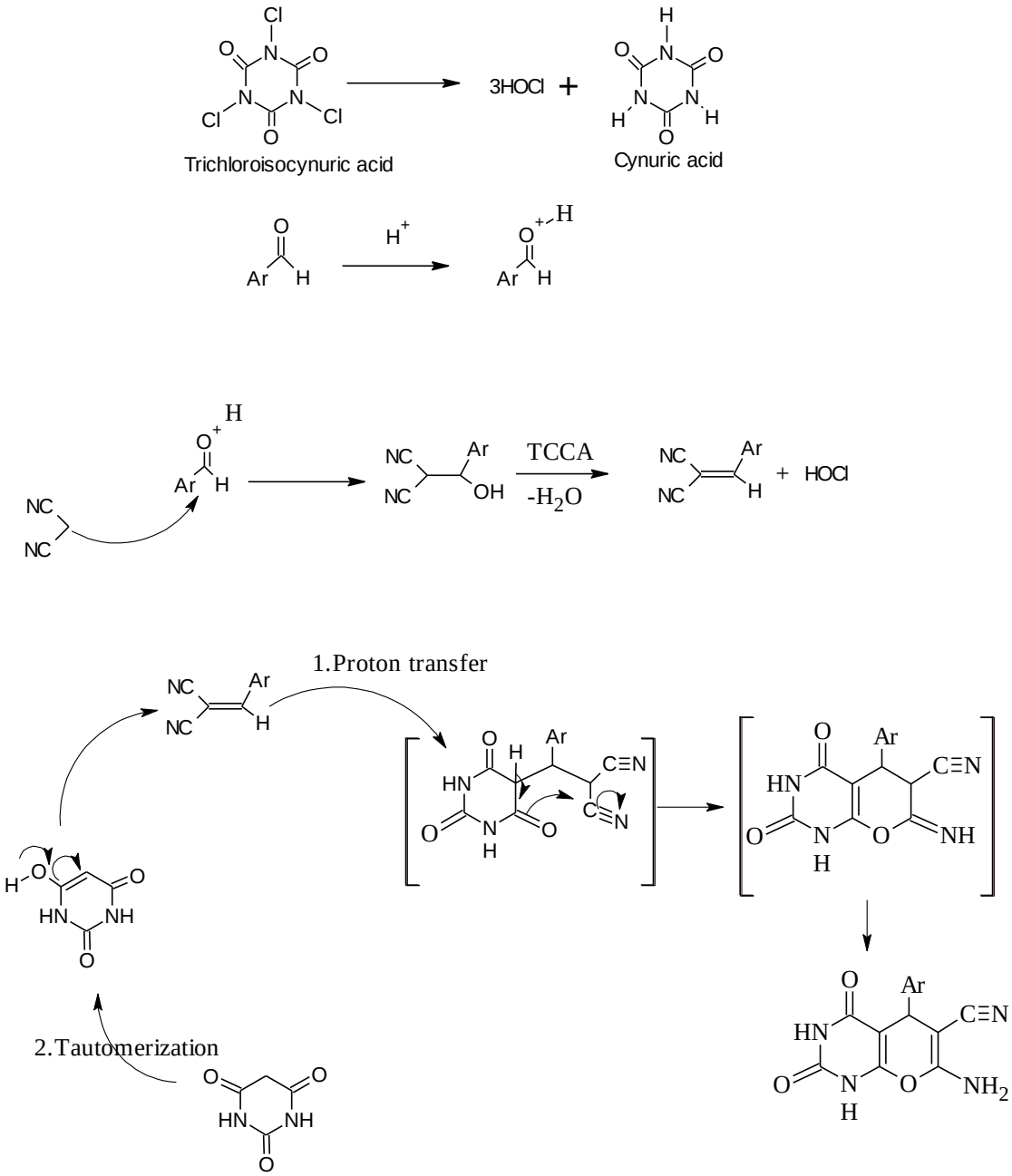
Entry	Solvent	Temp/°C	Time/hrs	%Yield
1	Ethanol	Reflux	10	80
3	Acetonitrile	Reflux	8	60
4	Water	Reflux	3	95
5	Tetrahydrofuran	Reflux	10	30
6	DMSO	100°C	8	55
7	MTBE	Reflux	10	<10

The yields are referred to isolated products.

Table 3 Trichloroisocyanuric acid catalyzed three-component synthesis of substituted pyrano [2, 3-d] pyrimidine dione derivatives

Entry	Aldehyde	Product	Time(hrs)	Yield	M.P./°C	
					Found	Lit
1			2	93	228-230	230-231 [18]
2			3	95	236-238	239-240 [18]
3			1.5	93	242-245	244-246 [19]
4			2	90	226-234	230-231 [20]
5			1.5	95	225-227	225-226 [21]

6			2	94	234-238	--
7			4	89	281-282	280-281 [23]
8			5	85	155-158	--
9			2	93	272-274	268-270 [18]
10			5	90	190-195	--
11			4.5	91	180-185	--



Scheme 2 Plausible synthetic mechanism

Spectral data of some representative products given below

7-Amino-6-cyano-5-(phenyl)-5H-pyrano [2, 3-d] pyrimidine-2, 4(1H, 3H)-diones (1) : Off-white color powder; yield 93 %; mp 228-230° C, IR (ν max): 3380, 3300, 3268, 3085, 2179, 1710, 1671,1633 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 4.25(s, 1H, CH), 7.14 (s, 2H, NH2), 7.55–7.78 (m, 5H, ArH), 11.19 (1H, NH), 12.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 50.89, 58.66, 118.21, 127.61, 128.49, 128.68, 145.92, 151.36, 153.91, 155.61, 160.39 ppm; Mass (*m/z*): 282(M^+); anal. calcd. for $C_{14}H_{10}N_4O_3$: C, 59.52; H, 3.54; Found: C, 59.70; H, 3.60%.

7-Amino-6-cyano-5-(4-nitrophenyl)-5H-pyrano [2, 3-d] pyrimidine-2, 4(1H, 3H)-diones (2). Yellow color powder; yield 95 %; mp 236-238° C, IR (ν max): 3380, 3291, 3181, 2198, 1711, 1675, 1628 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 4.42 (s, 1H, CH), 7.16 (s, 2H, NH_2), 7.47–8.14 (m, 4H, ArH), 11.01 (s, 1H, NH), 12.07 (s, 1H,

NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 35.4, 58.2, 79.9, 119.3, 123.5, 125.9, 143.8, 150.5, 150.8, 159.0, 160.1, 163.8; Mass (*m/z*):327(M^+); anal. calcd. for $C_{14}H_9N_5O_5$: C, 51.33; H, 2.75; Found: C, 51.40; H, 2.80%.

7-Amino-6-cyano-5-(4-chlorophenyl)-5H-pyrano [2, 3-d] pyrimidine-2, 4(1H, 3H)-diones (3). Cream color powder; yield 93 %; mp 242-245° C, IR (ν max):3458, 3354, 3190,2925, 2199, 1664, 1594, 1516 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 4.55 (s, 1H, CH), 7.17(s, 2H, NH2), 7.30–7.78 (m, 4H, ArH), 11.09 (1H, NH), 12.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 35.8, 59.3, 80.1, 119.1, 127.9, 130.0, 131.1, 142.6, 150.4, 159.3,160.3, 163.1; Mass (*m/z*):317 (M^+); anal. calcd. for $C_{14}H_9N_4O_3Cl$: C, 53.05; H, 2.84; Found: C, 53.0; H, 2.80%.

7-Amino-6-cyano-5-(4-bromophenyl)-5H-pyrano [2, 3-d] pyrimidine-2, 4(1H, 3H)-diones (4). Off-white color powder; yield 90 %; mp 226-234° C, IR (ν max), 3385, 3300, 3251, 3178, 2195, 1720, 1674,1636 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 4.41 (s, 1H, CH), 7.03 (s, 2H, NH2), 7.16(d, 2H, J= 7.0 Hz, ArH), 7.25 (d, 2H, J= 7.0 Hz, ArH), 10.96 (s, 1H, NH),11.97 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.10, 69.60, 105.25, 121.28, 124.03, 129.69(2C), 131.97(2C), 138.53, 145.91, 153.89, 160.34, 173.47; Mass (*m/z*):361 (M^+); anal. calcd. for $C_{14}H_9N_4O_3Br$: C, 46.52; H, 2.49; Found: C, 46.50; H, 2.50%.

7-Amino-6-cyano-5-(4-fluorophenyl)-5H-pyrano [2, 3-d] pyrimidine-2, 4(1H, 3H)-diones (5). Off-white color powder; yield 95 %; mp 225-227° C IR (ν max)3380, 3291,3249, 3180, 2197, 1716, 1674, 1635 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) d: 4.17 (s, 1H, CH), 7.04 (s, 2H, NH2), 7.09-7.44(m, 4H, ArH), 10.93(s, 1H, NH), 11.92 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) 35.8, 59.3, 80.1, 119.1, 127.9, 130.0, 131.1, 142.6, 150.4, 159.3,160.3, 163.1; Mass (*m/z*):300 (M^+); anal. calcd. for $C_{14}H_9N_4O_3F$: C, 55.95; H, 2..99; Found: C, 55.90; H, 3.00%.

Acknowledgements

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