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Wet 2,4,6-trichloro-1,3,5-triazine (TCT) as an efficient catalyst for the synthesis of 2,4,6-triarylpyridines under solvent-free conditions

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Abstract

An efficient one-pot synthesis of 2,4,6-triarylpyridines has been described. This involves the three-component reaction of aldehydes, ketones and ammonium acetate in the presence of a catalytic amount of wet 2,4,6-trichloro-1,3,5-triazine (TCT) under solvent-free condition at 130 °C.

Keywords: 2,4,6-Triarylpyridines; 2,4,6-Trichloro-1,3,5-triazine; Aldehydes; Ketones; Ammonium acetate

Pyridines have attracted considerable attention due to their wide range biological and pharmacological actives. Pyridines have been found wide applications in various fields such as in supramoleular chemistry [1–4], in pharmacology as antimalarial, anesthetic, anticonvulsant, vasodilator and antiepileptic, and in agrochemistry as fungicides, pesticides and herbicides [5–8]. In addition, pyridines have been used in many natural products including NAD nucleotides, vitamine B_6 and alkaloids [9]. As a result, a continuous interest has been drawn towards the development of various methods for the synthesis of 2,4,6-triarylpyridines.

The most direct synthetic methods reported so far have been accomplished by reactions that are promoted with ammonium acetate as a benign source of ammonia. The methods used for the synthesis of these compounds in the presence of NH_4OAc include the reaction of *N*-phenancylpyridinium [10] or *N*-phenacylisoquinolinium salts with α,β-unsaturated ketones [11,12], one-pot reaction of ketones with aldehydes [13–17], michael addition and solid phase condensation of chalcones [18], reaction of α-benzotriazolylketone with 1,5-diketones [19] and addition reaction of lithiated β-enaneinophosphonatest to chalcones [20]. Other methods involve the conversion of 2,4,6-triarylpyrylium salts into 2,4,6-triarylpyridines using aqueous ammonia [21], reaction of ω-pyrrolidinoacetophenine with chalcone using $BF_3.OEt_2$ and urea as a benign source of ammonia [22].

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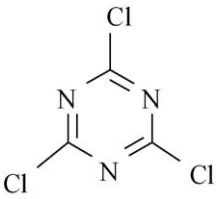
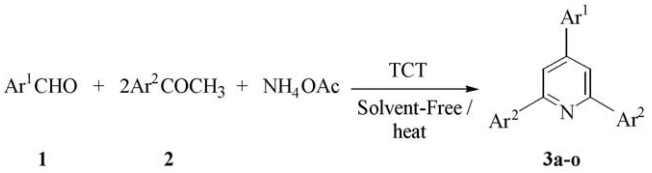


Fig. 1. The structure of cyanuric chloride.



Scheme 1.

Table 1
Optimizing the reaction conditions.

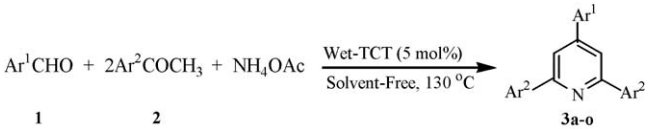
Entry	TCT (mol%)	Temperature (°C)	Time (h)	Yield[a] (%)
1	10	130	5.5	62
2	5	130	5.5	64
3	3	130	6	42
4	5	110	6.5	36
5	5	120	5.5	52
6	5	140	5	53
7	–	130	7	–
8	5 (+2 drops of H_2O)	130	4	70

[a] Isolated yields.

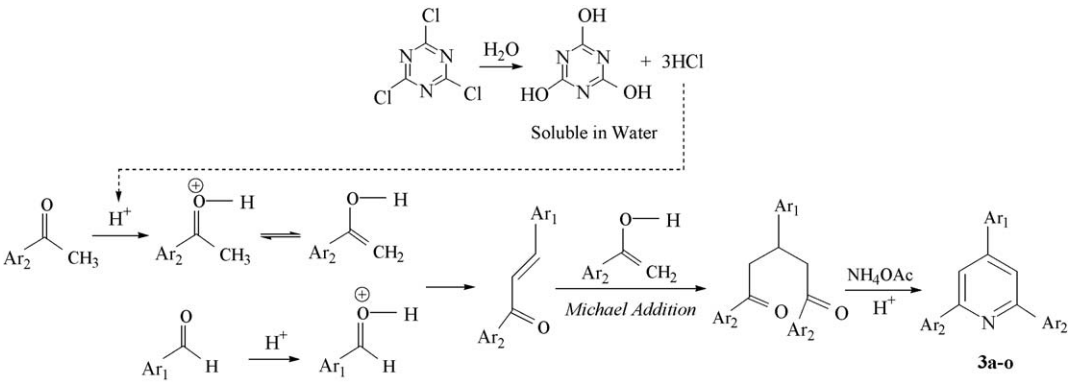
In recent years, 2,4,6-trichloro-1,3,5-triazine called cyanuric chloride (Fig. 1) has been widely used in organic synthesis because it is stable, non-volatile, inexpensive and commercially available reagent [23–27].

In continuation of our ongoing research on the development of more efficient and environmentally friendly procedures for some important transformations in organic synthesis [28–30], herein we wish to describe a new and convenient protocol for the synthesis of 2,4,6-triarylpyridines *via* a multicomponent reaction of aldehydes and ketones with ammonium acetate in the presence of wet-TCT under solvent-free condition (Scheme 1).

First of all, we tested the efficiency of our method by choosing the reaction between benzaldehyde (1 mmol), acetophenone (2 mmol) and ammonium acetate (1.3 mmol) as model reaction in the presence of a catalytic amount of TCT under solvent-free condition. The effects of temperature and the amount of TCT as the catalyst on the reaction to achieve suitable reaction conditions in terms of the reaction time and yield were investigated as summarized in Table 1. As shown in this table, the reaction worked out best (70%) at 130 °C in 4 h when 5 mol% of TCT moisturized with two drops of water was used as the catalyst compared with dry TCT (Scheme 2). Our attempts to study and optimize the reaction conditions showed that carrying out the reaction in H_2O met with failure; whereas using minute amounts of H_2O to moisten the media gave satisfactory results. It is note worthy that the reaction did not go to complication in completely dry media. This probably implies that the *in situ* generation of HCl probably occurs [23–27] in the course of the reaction along with cyanuric acid as indicated in the mechanism given as Scheme 3. This generated HCl acts as an efficient protic acid catalyst by activating the carbonyl group of the aldehyde or ketone to undergo rapid



Scheme 2.



Scheme 3.

condensation to yield the expected products **3a–o**. It was also observed that, increasing the reaction time or the amount of the catalyst did not bring about any improvement in the yield. The importance of the catalyst on the reaction was evaluated by conducting the reaction in the absence of TCT under the same reaction conditions and no formation of the respective product was detected after 7 h (entry 7). In order to verify the role of HCl which is probably generated upon moisturizing the TCT with water, we conducted the reaction under the similar conditions with directly using HCl in the absence of TCT. A test reaction was performed between 4-chlorobenzaldehyde (1 mmol), acetophenone (2 mmol) and ammonium acetate (1.3 mmol) in the presence of HCl (one drop) at 130 °C without solvent. It was found that the generation of 4-(4-chlorophenyl)-2,6-bisphenylpyridine (**3b**) occurred in 48% after 5 h.

In conclusion, we have developed a convenient, highly efficient and benign synthetic procedure for the synthesis of 2,4,6-triarylpyridines in high yields.

1. Experimental

IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr). ^{1}H NMR spectra were obtained using Jeol FT NMR 90 MHz spectrometer using TMS as an internal reference.

Table 2
TCT-catalyzed solvent-free synthesis of 2,4,6-triarylpyridines.

Products[a]	Ar^1	Ar^2	Time (h)	Yields (%)[b]	Mp (°C)	
					Found	Reported
3a	C_6H_5	C_6H_5	4	70	133–134	134–135 [14]
3b	4-ClC_6H_4	C_6H_5	5	80	125–126	122–124 [14]
3c	C_6H_5	4-$CH_3C_6H_4$	5	72	153–155	159–160 [14]
3d	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	5.5	64	178–179	176–177 [14]
3e	4-HOC_6H_4	C_6H_5	7	58	195–196	197 [14]
3f	2-$CH_3C_6H_4$	C_6H_5	6	74	119–120	120–122 [18]
3g	4-$MeOC_6H_4$	4-$CH_3C_6H_4$	7	76	154–156	155–157 [18]
3h	4-$N(CH_3)_2C_6H_4$	C_6H_5	7	86	136–138	138–140 [18]
3i	4-ClC_6H_4	4-$CH_3C_6H_4$	7.5	80	198–200	199–201 [18]
3j	4-ClC_6H_4	4-$MeOC_6H_4$	6	70	112–114	115–116 [18]
3k	4-$MeOC_6H_4$	C_6H_5	5.5	82	99–100	100–103 [18]
3l	2-Furyl	C_6H_5	6	80	164–165	165–166 [18]
3m	2-ClC_6H_4	C_6H_5	5.5	78	112–114	113–114 [18]
3n	2-Thienyl	C_6H_5	6	76	172–174	168–170 [18]
3o	4-BrC_6H_4	C_6H_5	6	79	164–166	166–167 [15]

[a] All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H and ^{13}C NMR spectral analysis and by direct comparison with authentic materials.

[b] Isolated yields.

1.1. General procedure for the synthesis of 2,4,6-triarylpyridines

To a stirred mixture of the aldehydes **1** (1 mmol), ketones **2** (2 mmol) and ammonium acetate (1.3 mmol) at room temperature were added TCT (5 mol%) and H_2O (2 drops) and then temperature was raised to 130 °C and maintained for the appropriate time (Table 2). After the completion of the reaction (as monitored by TLC), the reaction mixture was diluted with EtOH (96%, 5 mL) and stirred for 2 min at 130 °C. The solvent was evaporated; the remaining solid products were collected and washed with water to give the crude products. Then, recrystallization from EtOH (96%, 5 mL) provided pure 2,4,6-triarylpyridines.

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