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AN IMPROVED AND HIGHLY EFFICIENT ONE-POT THREE-COMPONENT SYNTHESIS OF 2,4,6-TRIARYLPYRIDINES CATALYZED BY MELAMINE TRISULFONIC ACID UNDER SOLVENT-FREE CONDITION**

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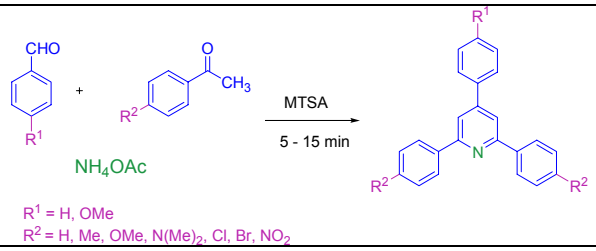
A facile one-pot synthesis of triarylpyridines as valuable products is reported *via* three-component condensation reaction in the presence of environmentally benign melamine trisulfonic acid (MTSA) under solvent-free condition. The present protocol offers several advantages including simple work-up procedure, high yields and ease of catalyst isolation with suitable recyclability.



INTRODUCTION

The substitution of conventional stoichiometric methodologies by catalytic processes, combined with the possibility of intensifying processes by combining several catalytic steps into a one-pot catalytic system, provides a means to improve the economical and environmental aspects of chemical processes. Moreover, the fact that the same catalyst can catalyze different consecutive steps in a single reaction vessel under the same reaction conditions decreases the operating time and the amount of waste produced.[1] In this way, heterogeneous catalysts containing various active sites on their surface are promising candidates for promoting multiple reactions in a single pot. So, designing new ways for the synthesis of fine chemicals through this category is important. Synthesis of biologically significant heterocyclic molecules under solvent-free conditions is very promising and challenging.

Pyridine ring system, especially triaryl substituted ones (Krohnke pyridines) has widely been utilized for biological, biochemical, pharmaceutical, and antitumor chemo-therapeutics.[2-5] Due to the aforementioned chemical and pharmacological significance, much effort has been devoted to developing more efficient methods for the synthesis of Krohnke pyridines.[6-9] Among all these methods, one pot reaction between acetophenones, aryl aldehydes, and NH_4OAc is the well established protocol for the synthesis of triarylpyridines using various catalyst such as cyanuric chloride,[10] $HClO_4$–SiO_2,[11] NaOH in PEG-400,[12,13] PEG-300 along with NaOH,[14] catalytic amount of acetic acid,[15] Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$,[16] H_2SO_4-SiO_2[17]and 3-methyl-1-(4-sulfonylbutyl) imidazolium hydrogen sulfate $[HO_3S(CH2)_4MIM][HSO_4]$.[18] The main drawbacks of mentioned protocol using these catalysts are, long reaction times, low yields, harsh reaction conditions, non reusability of the catalyst, use of excess amounts of the reagent, strictly reactive conditions (N_2 atmosphere), special efforts required to prepare the catalyst and tedious work-up procedures. Thus, the search for finding new

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catalyst in the synthesis of 2,4,6-triarylpyridine which are not associated with the above-mentioned disadvantages is still of growing importance.

Melamine trisulfonic acid (MTSA) has recently received considerable attention as acid-containing catalysts and effectively used in some organic transformations including synthesis of coumarins,[19] and 3,4-dihydropyrimidin-2(1*H*)-ones/thiones,[20] acetylation of alcohols, phenols, and amines,[21] chemoselective methoxymethylation of alcohols,[22] regioselective nitration of aromatic compounds,[23] N-formylation of amines,[24] aryldithienylmethanes[25] and spiro [pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives.[26]

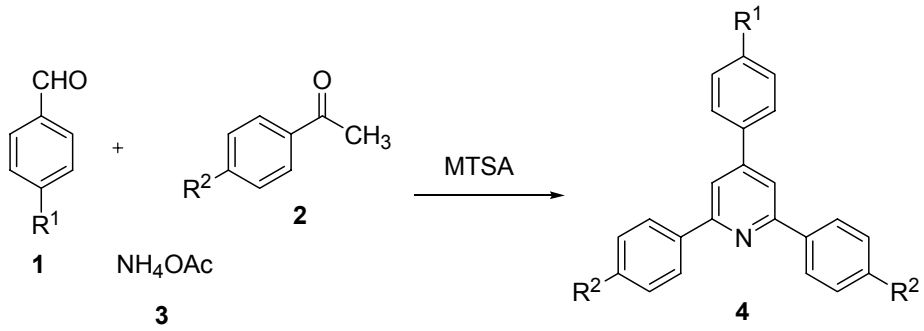
However, to the best of our knowledge there are no reports on the use of MTSA as a catalyst in the synthesis of Krohnke pyridines. As a part of our endeavor aimed at the development of novel, simple and efficient synthesis and transformation of biologically active heterocyclic molecules[27-33] and also in continuation of our ongoing investigation on design and using new catalyst,[34-39] we now wish to introduce an efficient procedure for the preparation of 2,4,6-triarylpyridines **4** through a one-pot three-component reaction including aldehydes **1**, acetophenones **2** and NH_4OAc **3** in the presence of MTSA under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

To investigate the possible catalytic properties of MTSA, the three-component condensation of benzaldehyde, acetophenone, and ammonium acetate was selected as a model reaction. Under solvent-free conditions in the absence of the catalyst no product was obtained even after 12 h. However, in the presence of MTSA the reaction leads to the formation of triphenylpyridine. So, comparative results led us to introduce MTSA as an effective catalyst system in the mentioned reaction.

Further experiments were arranged to determine the effect of temperature and the catalyst amount on the rate of the reaction (Table 1). The results clearly revealed that, at 120 °C and in the presence of 10 mol% of the MTSA, the reaction preceded toward the formation of triphenylpyridine in short reaction time and high yield. It was also found that, increasing temperature leads to a decrease in yields due to probable undesirable side-reactions. However, increase in amount of MTSA did not have any significant effect on reaction time and yield.

The generality of the three-component reaction was explored with respect to various substituted aromatic aldehydes and ketones (Table 2). It is noteworthy to mention that very clean condensation reactions at optimized conditions were observed irrespective of the nature of the substituents on the aromatic ring. As shown in Table 2, in all cases of aromatic aldehydes, either bearing electron-withdrawing groups (such as NO_2 and halides entries 2,5 and 7) or electron-donating groups (such as CH_3, NMe_2 and OCH_3 in entries 3,4,6 and 8), corresponding products were obtained at high yields in relatively short reaction times.



Scheme 1 – Synthesis of one-pot three-component 2,4,6-triarylpyridine derivatives in the presence of MTSA under solvent-free conditions.

Table 1

Effect of MTSA amount and temperature on the synthesis of 2,4,6-triphenylpyridine (model reaction)

Entry	Catalyst (mol%)	T (°C)	Time	Yield (%)
1	None	r.t	12 h	-
2	None	80	12 h	-
3	None	120	12 h	Trace

Table 1 (continued)

4	5	r.t	12 h	23
5	5	80	1.5 h	45
6	5	120	20 min	59
7	8	120	20 min	76
8	10	120	5 min	92
9	10	135	5 min	84
10	12	120	5 min	91
11	15	120	5 min	92

Table 2

MTSA catalyzed synthesis of 2,4,6-triarylpyridines 4a–h

Entry	**R^1**	**R^2**	**Product**	**Time (min)**	**Yield (%)**	**Observed mp (°C)**	**Reported mp (°C)**
1	H	H	4a	5	97	132-134	134-135
2	NO_2	H	4b	10	89	193-195	192-193
3	CH_3	H	4c	10	94	125-127	127-128
4	$N(CH_3)_2$	H	4d	15	88	134-136	138-140
5	Cl	H	4e	10	95	124-126	122-124
6	OCH_3	H	4f	10	90	98-100	100-101
7	Br	H	4g	10	92	164-166	166-167
8	H	OCH_3	4h	10	93	132-134	-

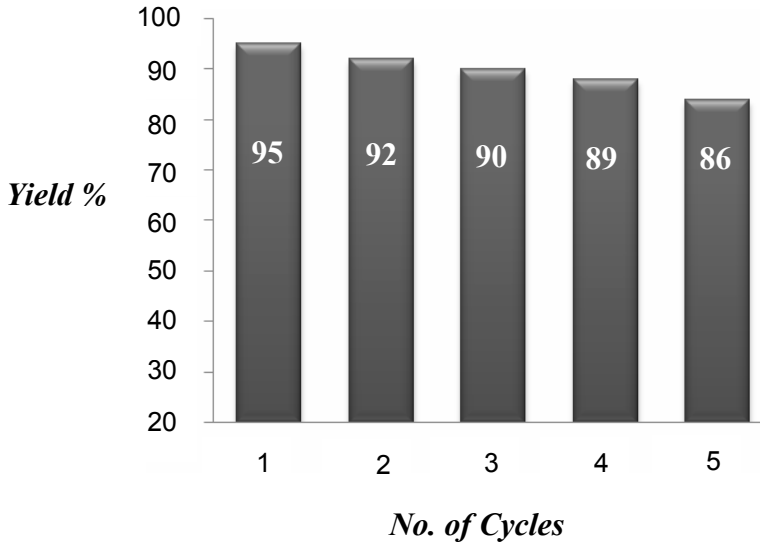


Fig. 1 – Reusability of MTSA catalyst.

It should also be noted that, the catalyst could be recovered by simple filtration and reused for five additional times without a considerable change in the reaction times and yields (Fig. 1).

Summery, compared to other procedures reported for the synthesis of 2,4,6-triarylpyridines *via* one-pot reaction, the present method has a short reaction time, good yield and solvent-free conditions.

EXPERIMENTAL

General

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. All yields refer to isolated products unless otherwise stated. Monitoring of the reactions was accomplished by TLC. IR spectra were obtained on a Bomen MB:102 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ with tetramethylsilane as an

internal standard. MS spectra were measured on an agilent 5975 Mass Spectrophotometer.

Preparation of melamine trisulfonic acid (MTSA)

Melamine trisulfonic acid was prepared according to the previously reported method by Shirini *et al.*[40] A 250 mL suction flask charged with chlorosulfonic acid (5 mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas overran adsorbing solution *i.e.* water. Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After completion of the addition of melamine, the mixture was shaken for 30 min, meanwhile, the residual HCl was exhausted by suction. The mixture was triturated with *n*-hexane (10 mL) and then filtered. The solid residue was washed with *n*-hexane (10 mL) and dried under vacuum. Melamine trisulfonicacid (7.6 g, 84%) was obtained as a white solid.

General experimental procedure for the synthesis of compounds 4a-h

A mixture of aldehydes **1** (1 mmol), ketones **2** (2 mmol), ammonium acetate **3** (1.5 mmol) was stirred and heated in an oil bath (120 °C) in the presence of MTSA (10 mol%) for the appropriate time and monitored by TLC (eluent 8:2 of *n*-hexane:ethyl acetate). After completion of the reaction, 20 mL of boiled EtOH was added into the reaction mixture and the MTSA was filtered off and washed with ethanol for reuse. The filtrate was evaporated under reduced pressure by rotary and the residues were purified by crystallization from ethanol to afford triarylpyridines **4** as products.

The structure of products were settled from their physical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data (Supplementary Material).

CONCLUSIONS

In conclusion, we have developed a convenient and nontoxic method for the one-pot synthesis of 2,4,6-triarylpyridinesfrom three-component reaction using MTSA as an inexpensive organocatalyst. The reactions were carried out under thermal solvent-free conditions with short reaction time and produce the corresponding products in excellent yields. Also the metal-free catalyst could be successfully recovered and reused at least for five runs without significant loss in activity. We believe that this method is a useful alternative to many other protocols reported earlier.

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