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Melamine trisulfonic acid as an efficient and reusable catalyst for the crossed-Aldol condensation of ketones and aldehydes under solvent-free conditions

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ABSTRACT

Various types of aldehydes undergo crossed-Aldol condensation with ketones in the presence of melamine trisulfonic acid (MTSA) under solvent-free conditions. The reported method is mild, efficient and has the advantages such as using heterogeneous catalysis, short reaction times, high yields of the products and the recyclability of the catalyst.

***Keywords**: Melamine trisulfonic acid, Aldehydes, Ketones, Crossed-Aldol condensation, Solvent-free conditions.*

1. Introduction

Crossed-Aldol condensation is one of the most important methods for the carbon-carbon bond formation and the synthesis of α,β-unsaturated carbonyl compounds. Among the α,β-unsaturated carbonyl compounds, α,α′-bis (substituted benzylidene) cycloalkanones are very important precursors to potentially bioactive pyrimidine derivates [1], intermediates of agrochemicals, pharmaceuticals, and perfumes [2], new organic materials for nonlinear optical applications [3], cytotoxic analogous [4] and the units of liquid-crystalline polymers [5].

Crossed-Aldol condensation is classically carried out using strong acid or base [6]. However, this process suffers from reverse and side reactions resulting in low yields of the products. Several methods for the promotion of this type of reactions have been developed. Various complexes of metal (II) ions, such as Mn(II), Fe(II), Co(II), Ni(II), and Zn(II), were used as catalysts [7], but all the reported yields were less than 38%. In other cases, bis (*p*-ethoxyphenyl) telluroxide (BOMPTO) [8], $RuCl_3$ [9], SmI_3 [10], Cp_2TiPh_2 [11], $TiCl_3(SO_3CF_3)$ [12], KF-Al_2O_3 [13, 14], $FeCl_3$ [15], $BF_3.OEt_2$ [16], $InCl_3$ [17, 18], $LiClO_4$ [19], silica sulfuric acid [20], I_2 [21], $Yb(OTf)_3$ [22], SiO_2-Pr-SO_3H [23], polymer supported sulphonic acid (NKC-9) [24], perfluoroalkylated-pyridine [25], carbon based solid acid [26], $Mg(HSO_4)_2$ [27] and $LiOH.H_2O$ [28] have also been used to catalyze this reaction. These procedures, although effective, have various drawbacks such as requirement of long reaction times (for example in the case of perfluoroalkylated-pyridine reactions completed after 8-24 hour), use of solvent, potential hazards (nickel compounds are toxic, perchlorates are potentially explosive, silica sulfuric acid is corrosive etc.), difficulty in the preparation of the catalyst (e.g., preparation of SiO_2-Pr-SO_3H involves reflux of the starting materials in toluene for 24 h and then oxidation of the obtained intermediate with H_2O_2 at another 24 h) and formation of side-products. Therefore, the search for new reagents and methods is still of practical importance.

2. Experimental

2.1. General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. All yields refer to the isolated products. The purity of the substrate and reaction monitoring were accomplished by thin-layer chromatography (TLC) on a silica-gel polygram SILG / UV 254 plates. Melamine trisulfonic acid (MTSA) was prepared according to the reported procedure [29]. Products were characterized by comparison of their spectroscopic data (^{1}HNMR, IR) and physical properties with those reported in the literature [22-25].

2.2. Instrumentation

IR spectra were run on a Perkin–Elmer bio-spectrometer. The reaction conversions were measured by GC on a

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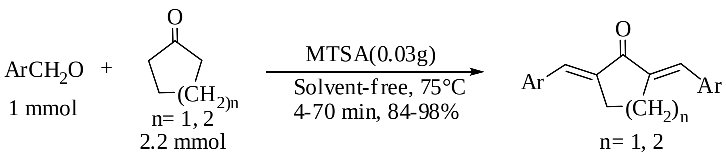


Fig. 1. Crossed-Aldol condensation catalyzed by MTSA.

Shimadzu model GC- 16A instrument. The ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). Microanalyses were performed on a Perkin- Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.3. General procedure

A mixture of ketone (1 mmol), aromatic aldehyde (2.2 mmol), and melamine trisulfonic acid (MTSA) (0.082 mmol, 0.03 g) was heated in an oil bath (75 °C) for an appropriate time (Table 2). After complete conversion of the ketone, as indicated by thin-layer chromatography (TLC), the mixture was cooled to room temperature. Dichloromethane (10–15 mL) was added, and the mixture was heated for few minutes. The catalyst was separated by filtration. The filtrate was concentrated, and the solid obtained was recrystallized from ethanol to give the pure product. The products were characterized by comparing their spectroscopic data (^{1}H NMR and IR) and physical properties with those reported in the literature.

The selected spectral data

a) 2,6-Di(*p*-chlorobenzylidene)cyclohexanone (Table 2, Entry 2): m.p. 145-146 °C. IR (KBr, cm^{-1}): 2930, 1660, 1606, 1576, 1262, 828. ^{1}H NMR (400 MHz, TMS, $CDCl_3$, ppm): δ: 1.76–1.84 (m, 2H), 2.90 (t, *J* = 6.0 Hz, 4H), 7.36–7.43 (m, 8H), 7.73 (s, 2H).

b) 2,6-Di(*p*-methoxybenzylidene)cyclopentanone (Table 2, Entry 14): m.p. 211-212 °C. IR (KBr, cm^{-1}): 2962, 2841, 1649, 1595, 1506, 1253, 1020, 834. ^{1}H NMR (400 MHz, TMS, $CDCl_3$, ppm) δ: 3.09 (t, 4H), 3.86 (s, 6H), 6.96–7.56 (m, 8H), 7.58 (s, 2H).

c) 4′-Nitrochalcone (Table 2, Entry 17): m.p. 156-157°C. IR (KBr, cm^{-1}): 3010, 2896, 1705, 1680, 1643, 1470, 921, 845. ^{1}H NMR (400 MHz, TMS, $CDCl_3$, ppm) δ: 6.32 (d, *J* = 16.1 Hz, 1H), 7.36 (d, *J* = 16.1 Hz, 1H), 7.15–7.36 (m, 5H), 7.52–8.26 (m, 4H).

3. Results and discussion

Recently we have reported the preparation of melamine trisulfonic acid and its application as a new, efficient and versatile catalyst in organic transformations that need acidic reagents to accelerate the reaction rate [29-33]. Also Ma *et al*. used this reagent for the synthesis of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6] pyrano-[3,2-c]chromen-6-ones [34]. Herein, and in continuation of these research, we wish to report the applicability of this reagent in the promotion of the crossed-Aldol condensation reaction specially in the synthesis of α,α'-bis(substituted benzylidene)cycloalkanones in a one-pot condensation reaction of ketones with aldehydes under solvent-free conditions (Fig. 1).

In order to optimize the reaction conditions, we conducted the condensation of 4-chloro benzaldehyde (2.2 mmol), cyclohexanone (1mmol) and melamine trisulfonic acid (MTSA) (0.082 mmol, 0.03g) by stirring at 75 °C without solvent, which was completed after 13 min. Addition of the amount of MTSA and temperature did not affect the result of the reaction, but after reduction of the amount of the aldehyde to 2.1 and/or 2 mmol the reaction was not completed after 30 min. To illustrate the efficiency of MTSA in these reactions, preparation of 2,6-di (*p*-chlorobenzylidene) cyclohexanone, was also carried out in the absence of the catalyst and the reaction was not completed after 4h. Obviously, the use of MTSA is necessary for the reaction to proceed (Table 1).

After optimization of the reaction conditions various aldehydes were subjected to condensation with ketones under the selected conditions. The results are summarized in Table 2.

Aromatic aldehydes having various substituents (such as F, Cl, Br, NO_2, OMe) and cinnamaldehyde were converted to their α,α'-bis(substituted benzylidene) cycloalkanone derivatives efficiently (Table 2, entries 1-15). As seen in Table 2, the condensations of aromatic aldehydes with ketones yielded the corresponding α,α'-bis(substituted benzylidene) cycloalkanone derivatives and the reaction times were remarkably affected by the substituent groups of aromatic aldehydes: reactants having electron-withdrawing substituents gave the products in lower times related to those having electron-donating ones. The crossed-Aldol condensations were finished within 4–74 min and excellent yields (84–98%). We have found that this method is also very useful for the condensation of aldehydes with acetophenone and 1,3-indandione. All reactions were performed in the absence of solvent at 75 °C using 1.1 mmol of the aldehyde (Table 2, entries 16-21).

In order to ascertain the scope and limitations of this catalyzed condensation, the method was further applied to the condensation of acetone with propionaldehyde as an aliphatic aldehyde (Table 2, entry 22) and the desired product obtained in 16% yield after 24 h in the reflux

Table 1. Condensation of cyclohexanone and 4-chlorobenzaldehyde over MTSA under different reaction conditions.

Entry	Catalyst loading (mg)	Temperature (°C)	Time (min)	Yield (%) [a]
1	0	75	240	Trace
2[b]	20	75	30	90
3[b]	30	75	13	98
4[b]	40	75	13	97
5[c]	30	75	30	65
6[d]	30	75	30	50
7[e]	750	80	150	90 [20]
8[f]	50	80	30	100 [23]
9[g]	750	70	100	90 [26]
10[h]	1740	60	420	93 [27]

[a] Isolated yield.
[b] Reaction condition: 1 mmol cyclohexanone, 2.2 mmol 4-chlorobenzaldehyde.
[c] Reaction condition: 1 mmol cyclohexanone, 2.1 mmol 4-chlorobenzaldehyde.
[d] Reaction condition: 1 mmol cyclohexanone, 2 mmol 4-chlorobenzaldehyde.
[e] Using Silica sulfuric acid as the catalyst.
[f] Using SiO_2-Pr-SO_3H as the catalyst.
[g] Using Carbon based solid acid as the catalyst.
[h] Using $Mg(HSO_4)_3$ as the catalyst.

conditions. Therefore this method is not useful for the condensation of the aliphatic aldehydes with ketones.

After performing one reaction under the conditions described in Table 2, the catalyst was recovered by filtration, washed with n-hexane (10 mL), dried at room temperature, and reused for a consecutive run under the same reaction conditions. Thus, after the first run, which gave the corresponding α,β-unsaturated compound from 4-chlorobenzaldehyde and cyclohexanone with 98% yield in 13 min, and after recovery, the catalyst was subjected to the second condensation reaction which also gave 2,6-di(*p*-chlorobenzylidene) cyclohexanone with 97% yield in 15 min. these observations clearly demonstrate the practical recyclability of this catalyst. MTSA was recyclable for three times without any decrease in its catalytic activity (Fig. 2).

The possible mechanism for the crossed-Aldol condensation in the presence of MTSA as a promoter is shown in Fig. 3. On the basis of this mechanism, MTSA catalyzes the reaction by the nucleophililic activation of ketone to form an enol tautomer, the formation of enol is slow, and the reaction rate depends on this step. As shown in Scheme 2, condensation of enol **2** with aldehyde **3** gives Aldol **4**, which then is dehydrated to give the product **5**. In the case of cyclic ketones the resulting product reacts with the second aldehyde molecule to form α,α'-bis(substituted benzylidene) cycloalkanone (6) [23].

The efficiency of the present method is illustrated by the comparison of some of our results to some of those reported in the literature (Table 3) [20, 21, 23, 24].

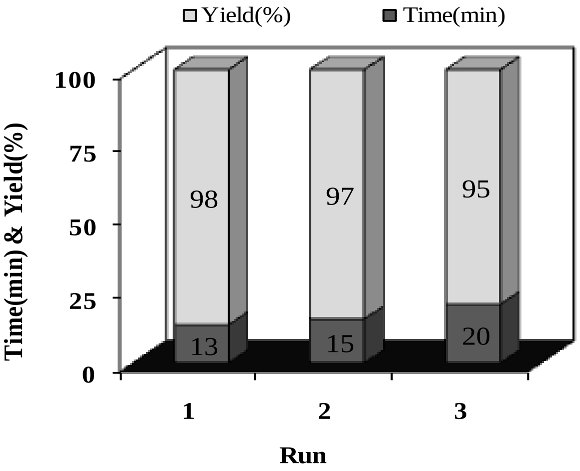


Fig. 2. Recyclability of MTSA for the synthesis of 2,6-di(*p*-chlorobenzylidene) cyclohexanone (Table 1, entry 2).

Table 2. Crossed-Aldol condensation of ketones with aldehydes in the presence of melamine trisulfonic acid (MTSA) under solvent-free conditions at 75°C.

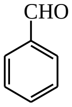
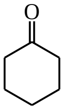
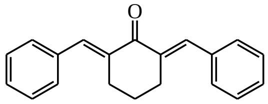
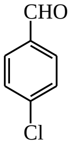
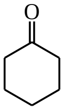
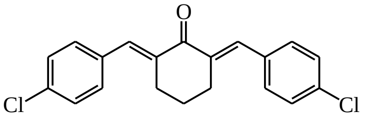
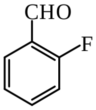
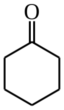
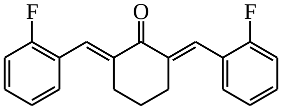
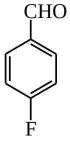
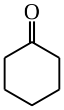
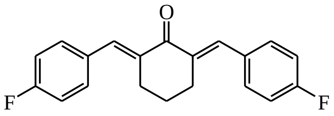
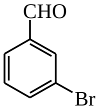
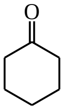
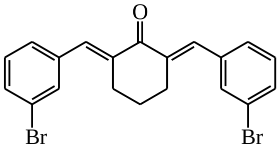
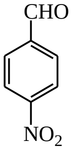
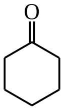
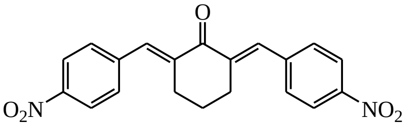
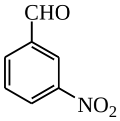
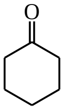
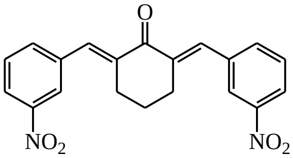
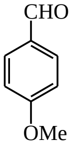
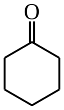
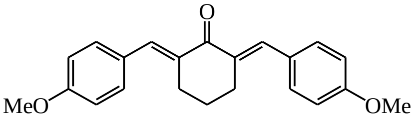
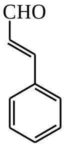
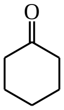
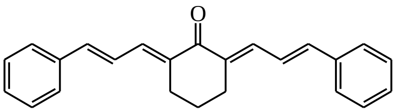
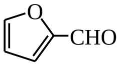
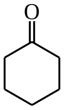
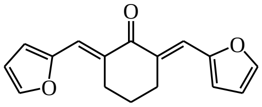
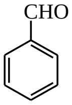
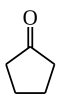
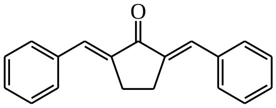
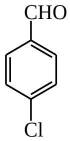
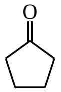
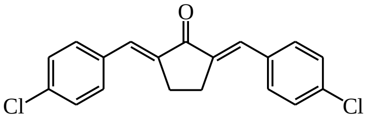
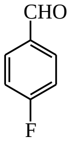
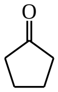
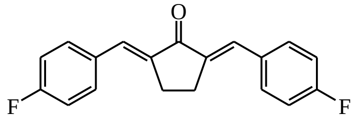
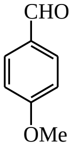
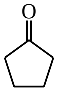
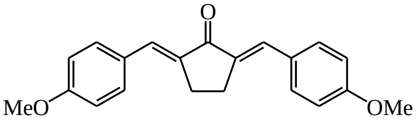
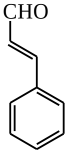
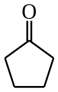
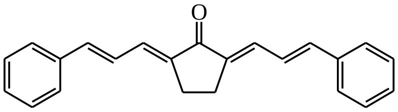
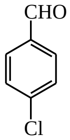
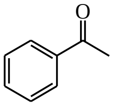
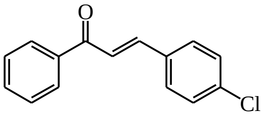
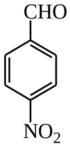
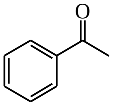
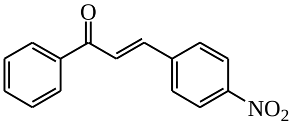
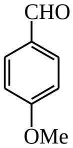
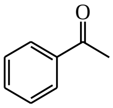
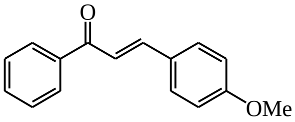
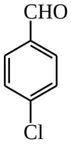
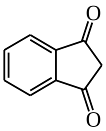
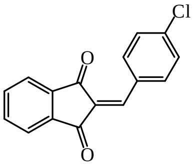
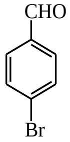
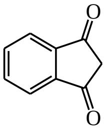
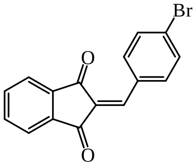
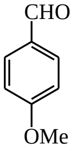
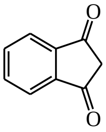
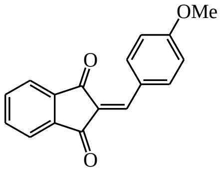
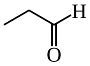
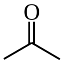
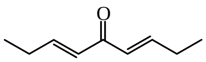
Entry	Aldehyde	Ketone	Product	Time(min)	Yield [a] (%)	m.p.(°C) [ref.]
1				36	93	115-116 [21]
2				13	98	145-146 [21]
3				70	95	199-202 [21]
4				35	92	156-157 [21]
5				70	98	119-120 [21]
6				13	95	186-187 [22]
7				6	95	189-191 [23]
8				30	92	148-149 [21]
9				6	91	177-178 [21]
10				70	87	[28]
11				5	90	187-189 [21]
12				10	95	219-220 [21]

Table 2. *(continued)*

13				22	84	237-239 [21]
14				15	90	211-212 [21]
15				4	89	227-228 [21]
16[b]				74	93	109-110 [25]
17[b]				15	90	156-157 [25]
18[b]				70	94	74-75 [25]
19[b]				5	90	175-176 [35]
20[b]				8	92	171-173 [35]
21[b]				6	94	156-157 [35]
22[c]				24 h	16[d]	liquid [9]

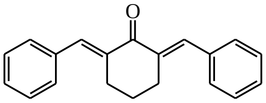
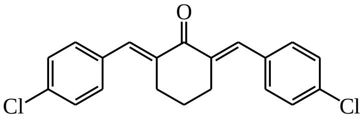
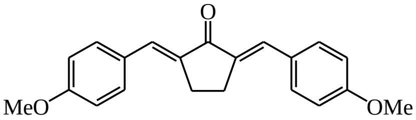
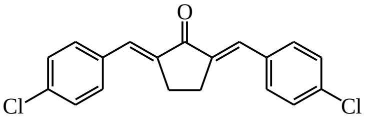
[a] Isolated yield. Products were characterized by comparison of their spectroscopic data (^{1}H-NMR and IR) and mps with those reported in the literature.

[b] 1.1 mmol of the aldehyde was used.

[c] Reaction conditions: 1 mmol propionaldehyde, reflux in 3 mL acetone, 0.03 g MTSA.

[d] GC yield.

Table 3. Comparison of some of the results obtained by the present method (**I**) with some of those reported by silica sulfuric acid (**II**) [20], I_2 (**III**) [21], SiO_2-Pr-SO_3H (**IV**) [23], and NKC-9 (**V**) [24].

Entry	Product	Time (h)/Yield (%)				
		(**I**)	(**II**) [a]	(**III**) [b]	(**IV**) [c]	(**V**) [d]
1		0.6/93	2.5/91	4.5/92	2/100	4/86
2		0.22/98	3/90	4.5/94	0.5/100	6/87
3		0.25/90	2/95	4.5/92	0.3/98	6/89
4		0.17/95	2.5/94	—	0.17/95	6/85

[a] Reaction conditions: Solvent-free, 80 °C.
[b] Reaction conditions: CH_2Cl_2, r.t.
[c] Reaction conditions: Solvent-free, 80 °C.
[d] Reaction conditions: $CHCl_3$, reflux.

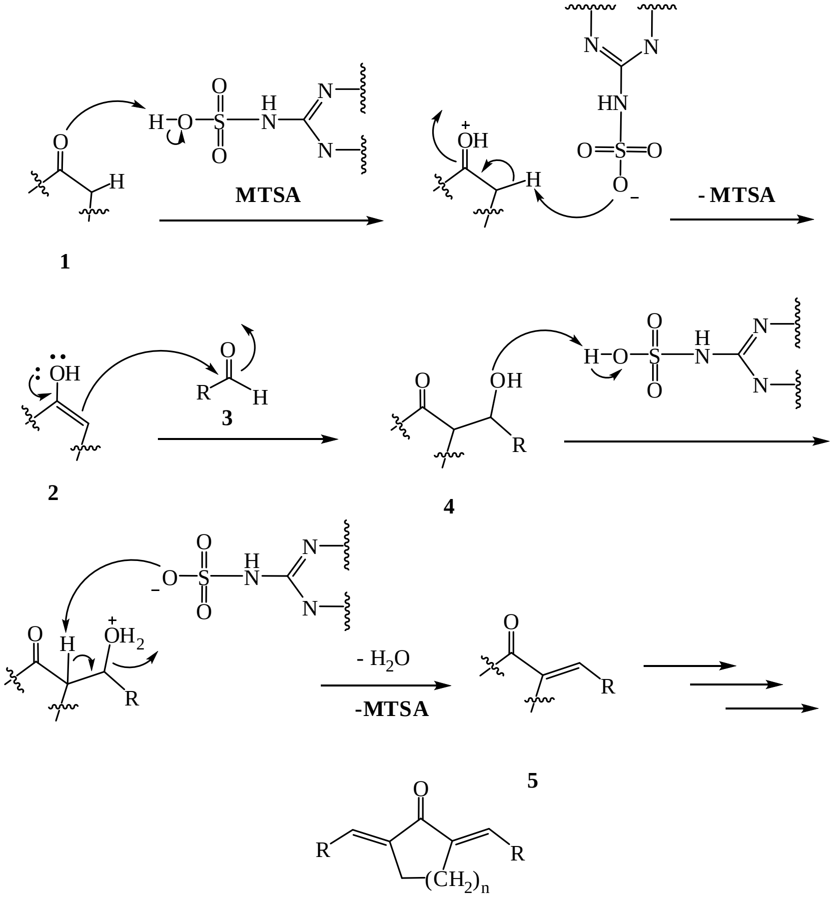


Fig. 3. The plausible mechanism of the reaction.

4. Conclusion

In conclusion, we have developed an easy and efficient method for the cross-Aldol condensation of aldehydes and ketones to form, α,α′-bis(substituted-benzylidene) cycloalkanones and chalcone derivatives using MTSA at 75°C. The mild reaction conditions, shorter reaction times, high yields and application of an inexpensive and readily available catalyst are the great advantages of the method.

Acknowledgment

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