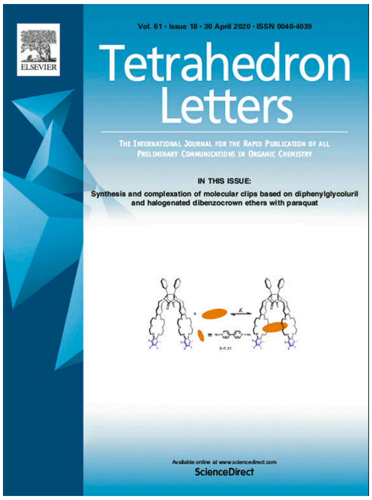

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Lewis Acid Catalyst System for Claisen-Schmidt Reaction under Solvent Free Condition

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ABSTRACT

$Ca(OTf)_2$ in combination with $NBu_4.BF_4$ was established to function as an efficient catalyst system for one-pot Claisen-Schmidt condensation under neat conditions. Substituted acetophenones and benzaldehydes were coupled *in situ* to afford their corresponding chalcones in excellent yields. The method, with a broad range of substrate tolerance and mild operational conditions can produce assorted chalcone derivatives in moderate to high yields from easily accessible starting materials.

1. Introduction

Chalcones which (1, 3- diphenyl-2-propene-1-one) are biphenyl compound have two aryl moieties connected through -α, β-unsaturated ketones. The -α, β-unsaturated carbonyl group is a good Michael acceptor and undergoes nucleophilic addition. They acquire multi-prolonged activities due to methylene and carbonyl moieties in their structures. Chalcones which is one of secondary metabolite compounds have gained the attention of researchers *due to their* therapeutic potential activities as antimicrobial[1a], antifungal[1b], antioxidant[1c], antitumor[1d], antimalarial[1g], anticancer[1f], anti-inflammatory[1e,] antidepressant[1h,] antituberculosis[1i]. Chalcones are also an imperative precursor for biosynthesis of flavonoids[2a] and isoflavonoids[2b] and numerous heterocyclic compounds such as benzodiazepine[2c], pirazoline[2d], flavones[2e] and aurone[2f]. Chalcones have two aromatic rings and are connected by three carbon α, β unsaturated in carbonyl compounds system[3].

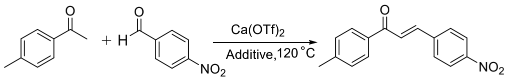
The carbon-carbon double bonds formation is essential reaction in organic chemistry. Numerous advances have been made for the synthesis of olefins while attempting to deal with the demands of chalcones from time to time.[4] Usually, chalcone and their derivatives were prepared by performing the reaction between an aromatic ketones and aldehydes under normal acidic or alkaline conditions. This method is most often known as Claisen-Schmidt condensation [5]. Plethora of efforts have, previously, been made for the synthetic strategies of chalcones and their derivatives in the past decades.[6] However, in the majority cases of these transformations, strong base, noble metal catalysts, ligands and harsh operations are always required. The catalysts frequently used for the synthesis of chalcones were HCl[6l], $SOCl_2$[6b], NaOH[6c], KOH[6d], Fly-ash: sulphuric acid[6e], anhydrous zinc chloride[6f], barium hydroxide[6g], anhydrous sodium bicarbonate[6-h-i], Fly-ash:water[6j], triphenylphosphite[6k], KF/Al_2O_3[6l], silica–sulphuric acid[6m-n]. Claisen-Schmidt condensations have been also reported using $Ca(OH)_2$ catalyst in aqueous ethanol.[7]

Recently, alkaline earth metal catalysts due to their broad natural abundance, low-cost and safe natures have been established as alternatives to transition metals and lanthanide based catalysts[8-9]. Among them, calcium salts holding a hard conjugate base such as triflate ions, was highly stable to moisture and air and demonstrated as an alternative to transition metals and lanthanide based catalysts. However, very few reports have been available about the applications of $Ca(OTf)_2$ in organic synthesis[10-11].

Claisen-Schmidt condensation methodology is widely used in organic synthesis ranging from the preparation of biologically active small molecules to the total synthesis of more complex natural products and there are a plethora of examples regarding synthesis in the literature[12]. Remarkably, the substituted chalcone structural moiety get applications in several biologically active compounds along with marketed and investigational drugs.[13] To the best of our knowledge, there are no reports describing chalcone synthesis in presence of $Ca(OTf)_2$-$NBu_4.BF_4$ catalyst system. Herein, we are reporting synthesis of a number of aromatic chalcones using Lewis acid based calcium catalyzed system under solvent free, base free, mild operational and wide substrate tolerance conditions to furnish corresponding products in moderate to good yields.

At the beginning of our strategy, a model reaction was performed using 4-methyl acetophenone and 4-nitrobenzaldehyde as a substrate, and 10 mol% of $Ca(OTf)_2$ as a catalyst in water at 110 °C (Table 1). Most pleasantly, the desired product 3c was obtained in modest yield (Table 1, entry 6) after 6h. Different Ca (II) sources such as $CaCl_2$, $CaCO_3$, $CaSO_4$, $Ca(OH)_2$ and $CaNTf_2$ were then examined, and we observed that Ca $(OTf)_2$ was found to be the most effective catalyst. We examined a number of va catalyst and mol % additive (Table 1).

Table 1: Optimizations of the conditions



Entry	[Ca(OTf)$_2$] (mol%)	Additive (mol%)	Solvents	Time (h)	Temp (°C)	Yield[a]
1	10	0	H_2O	6	120	25
2	10	0	CH_3CN	8	120	15
3	10	0	Toluene	8	120	NR
4	10	0	EtOH	8	120	NR
5	10	0	$CHCl_3$	8	120	NR
6	10	0	Neat	6	120	56
7	15	0	Neat	6	120	55
8	5	0	Neat	6	120	55
9	4	0	Neat	6	120	52
10	6	0	Neat	6	120	55
11	5	$NaPF_6$ (5%)	Neat	6	120	52
12	5	NaOTs (5%)	Neat	6	120	55
12	5	Py.OTs (5%)	Neat	6	120	50
13	5	Proline (5%)	Neat	6	120	45
14[b]	5	Bu_4NPF_6 (5%)	Neat	0.5	120	96
15	5	Bu_4NPF_6 (10%)	Neat	0.5	120	90
16	5	Bu_4NPF_6 (15%)	Neat	0.5	120	90
17	0	Bu_4NPF_6 (5%)	Neat	8	120	trace
18	0	Bu_4NPF_6 (10%)	Neat	8	120	trace
19	0	Bu_4NPF_6 (15%)	Neat	8	120	trace

a. Isolated Yields after crystallization; [b]. Optimum conditions; NR: no reaction

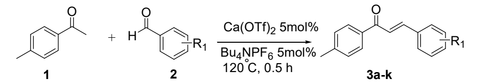
Initially the influence of solvent system was evaluated. To optimize the reaction conditions and find the right solvent, few experiments were carried out using 4-methyl acetophenone and 4-nitrobenzaldehyde as a model substrate with different solvents and 10 mol % of catalyst Ca(OTf)$_2$. Among the tested solvents CH_3CN, methanol, toluene, chloroform, water and neat system, the reaction proceeded most efficiently in neat system at 120 °C and afforded the desired product in good yield (Table 1, entry 6). Indeed, we used an extremely fundamental procedure and examined various solvent/base systems for the synthesis of representative compound 3c (Table 1).

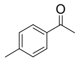
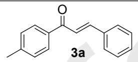
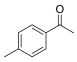
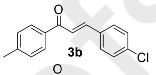
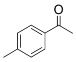
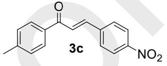
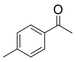
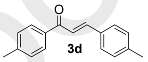
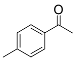
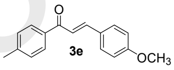
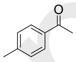
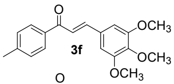
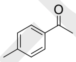
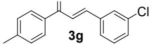
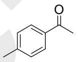
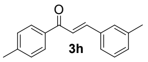
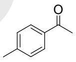
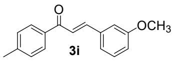
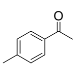
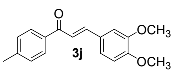
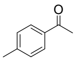
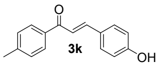
Further, in order to evaluate the correct catalyst Ca(OTf)$_2$ loading, a model reaction using 4-nitrobenzaldehyde and 4-methyl acetophenone was carried out using 4 mol%, 5 mol %, 10 mol % and 15 mol % of catalyst under neat system (Table 1, entries 6–10). It was found that 5 mol % of catalyst showed maximum yield in minimum time. Higher percentage of loading of the catalyst (10 to 15 mol %) neither increased the yield nor decreased the conversion time. The effective amount of the catalyst required for optimal yield was 5 mol % because on decreasing the amount of the catalyst from 5 mol% to 4 mol%, the yield was reduced (Table 1, entry 8 versus 9) while it did not change on using 6 mol% of the catalyst (Table 1, entry 8 versus 10). So, 5 mol % of catalyst was found to be the optimal quantity and sufficient to drive the reaction forward.

In order to scrutinize role of additive on reaction, initially, we examined the reaction with seven different additives $NaPF_6$, $NaBF_4$, Bu_4NPF_6, NaOTs, $NaNO_3$, CF_3SO_2Na, proline along with catalyst Ca(OTf)$_2$. Among these additives, the reaction with Bu_4NPF_6 gave the best results (Table 1, entry 14). The other six additives screened did not provide satisfactory yields of the desired product. When the same reaction was carried out in the absence of the additive Bu_4NPF_6 and the presence of catalyst 5 mol% of Ca (OTf)$_2$, 55% of chalcone (3c) was isolated. This

the catalyst Ca(OTf)$_2$, addition of the additive (Bu_4NPF_6) is imperative in reaction (Table 1, entry 14). *It is well observed that Bu_4NPF_6 helps in solubilizing the Ca(II) salts for the enhanced reactivity.*[14]

Table 2: Substrate scope in the Ca(II) catalyzed Claisen Schmidt reaction of 4-Methyl acetophenone with substituted aromatic aldehyde



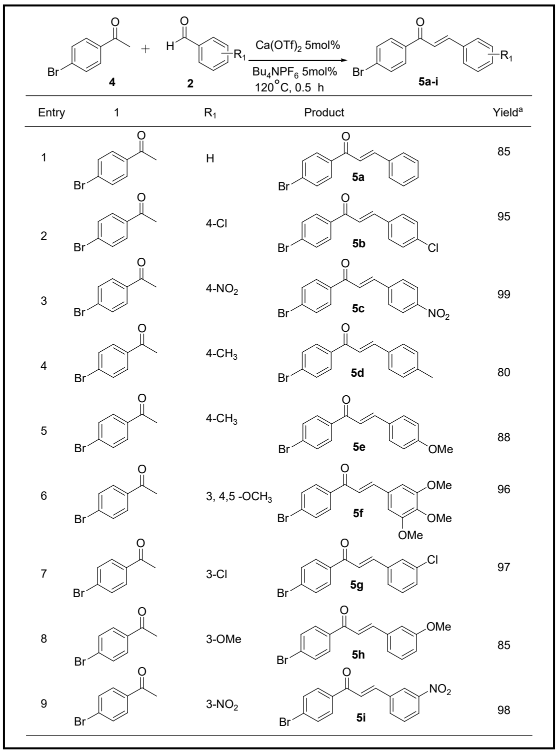
Entry	4	R$_1$	Product	Yield[a]
1		H	 3a	80
2		4-Cl	 3b	94
3		4-NO$_2$	 3c	98
4		4-CH$_3$	 3d	88
5		4-OCH$_3$	 3e	92
6		3, 4, 5-OCH$_3$	 3f	96
7		3-Cl	 3g	94
8		3-Me	 3h	85
9		3-OCH3	 3i	93
10		3,4-OCH3	 3j	95
11		4-OH	 3k	92

a. Isolated Yields after crystallization

Considering the importance of the additive Bu_4NPF_6 we also carried out the reaction with 5 mol% of Bu_4NPF_6 (without Ca(OTf)$_2$) and no product formation of chalcone product was observed after 8 h (Table 1, entry 17). Increase in the additive (Bu_4NPF_6) loading from 5 to 15 mol% has also not showed any remarkable effect on the reaction time and yield (Table 1, entries 17-19). These studies confirm that the additive (Bu_4NPF_6) alone does have even minor effect on the reactions. Interestingly, no product formation was detected in the absence of catalyst Ca(OTf)$_2$ (Table1, entries17-19). In order to establish the real effectiveness of the catalyst Ca(OTf)$_2$ and addition of the additive (Bu_4NPF_6) is imperative in reaction (Table 1, entry 14).

The reaction of the 4-Nitrobenzaldehyde with 4-methyl acetophenone gave excellent yields of the desired adduct in presence of 5 mol% of catalyst Ca(OTf)$_2$ and 5 mol % of additives Bu_4NPF_6 under neat condition at 120 °C (Table 1, entry 14).. Originally, we allowed the reaction to proceed for 4 h but later found the reaction to be complete within 30 min of at 120 °C. With this optimal reaction condition in hands the scope of this greener catalytic system was then studied, we extended our study with various substituted acetophenones and substituted benzaldehyde as reaction patterns (Table 2 and 3).[15]

Tab reaction of 4-Bromo acetophenone with substituted aromatic aldehyde



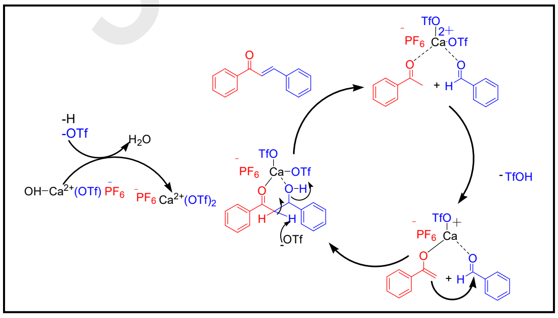
Entry	1	R$_1$	Product	Yield^a
1		H	5a	85
2		4-Cl	5b	95
3		4-NO$_2$	5c	99
4		4-CH$_3$	5d	80
5		4-CH$_3$	5e	88
6		3, 4,5 -OCH$_3$	5f	96
7		3-Cl	5g	97
8		3-OMe	5h	85
9		3-NO$_2$	5i	98

b. Isolated Yields after crystallization

We have performed reactions with $Ca(OH)_2$ and TfOH on a number of aromatic aldehydes, under the reaction conditions which were used in the case of $Ca(OTf)_2$/ $NBu_4.BF_4$ system but this did not work well . Neither the $Ca(OH)_2$ nor the TfOH could furnish the significant yield of chalcones even after 8 hrs at 120 ℃.

A plausible mechanism for the chalcone adducts of acetophenones and aldehydes in the presence of catalyst $Ca(OTf)_2/Bu_4NPF_6$ is depicted in Figure 1. In essence, the Ca(II) ions act in conjugation with the non-coordinating PF6¯ in order to activate the carbonyl groups. $Ca(OTf)_2/Bu_4NPF_6$ are anticipated to catalyze the reactions by activating the aldehydes via reversible coordination to Ca (II), resulting in a favorable transition state for driving the reaction forward. The presence of bulky anions likely increases the electrophilicity by leaving Ca(II) with unsaturated coordination sites.

Figure 1: Plausible mechanism for the chalcone synthesis using Ca (II) catalyst system



our study using $Ca(OTf)_2/Bu_4NPF_6$ (5 mol %) as catalyst system under solvent-free condition at 120 °C with different aromatic aldehydes to prepare a series of chalcones. Under the established optimized reaction conditions a series of aldehydes were reacted with acetophenones (1 and 4) respectively. The corresponding (3a-f and 5a-f) were obtained in good to excellent yields. The results are summarized in Table 2 and 3.

Subsequently, the reaction scope was evaluated by varying the aldehydes and the groups, attached to acetophenone ring (Table 2). When the reaction was performed using substituted aldehydes with the electron-withdrawing groups high to excellent results were achieved (88–99%) with full utilization of the starting materials within eight hours. The presence of the electron-donating groups on the substituted aldehydes slightly decreased the reactivity (Table 2 and 3, entries 1, 4). Subsequent to the completion of the reactions, the reaction mixtures were filtered to collect the precipitates and it was further purification by recrystallization to afford the pure chalcones 3a–k and 5a-i in 80–99% yield.

Here, we would like to conclude that we have presented a broad-spectrum and efficient method for the synthesis of Claisen Schmidt adducts (chalcones) of acetophenones and aromatic aldehydes in the presence $Ca(OTf)_2/Bu_4NPF_6$.The mild reaction conditions, no workup, easy purification, higher yield, and economic availability of the catalyst make this procedure an eco-friendly attractive alternative to the existing methods for the synthesis of chalcones. This catalyst may find application in organic synthesis.

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15. *General experimental procedure for the Ca(OTf)$_2$/Bu$_4$NPF$_6$ catalyzed Chalcone synthesis:* Suitable acetophenones (1mmol) and substituted benzaldehydes (1.1 mmol) were heated under solvent free condition at 120 °C for 0.5 h in the presence of Ca(OTf)$_2$ (5 mol%) and nBu$_4$NPF$_6$ (5 mol%). Progress of reactions was monitored by TLC. After completion, reaction mixtures were brought to room temperature and diluted with tates were, then, filtered through suction pump and washed with 20-30 mL of water. It afforded crude products. The crude products recrystallization from ethanol afforded pure products.

Supplementary Material

Supplementary data associated with this article are attached with this article

Conflicts of interest: The authors declare no conflict of interest.

Highlights

- Aryl-aryl chalcones were synthesized using Ca(OTf)$_2$/BuNPF$_6$ catalyst system under solvent free condition
- Better yields of the chalcones obtained
- Easy-workup procedure, environmentally solvent free synthetic method was adopted
- Purification through crystallization techniques

Graphical Abstract

Lewis Acid Catalyst System for Claisen-Schmidt Reaction under Solvent Free Condition

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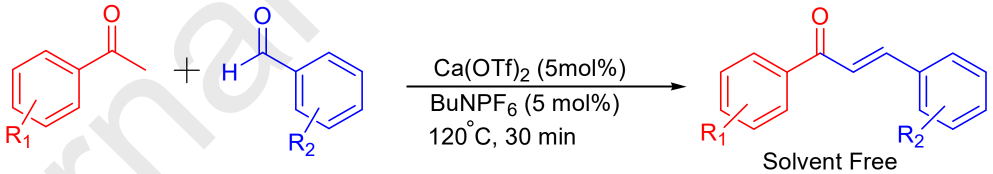
Chandni G Halpani[1] and Satyendra Mishra[1]*



Solvent Free
No workup
Purification via crystalization
Excellent Yield
20 examples