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Study of an *in situ* carbocationic system formed from trityl chloride (Ph_3CCl) as an efficient organocatalyst for the condensation of dimedone with arylaldehydes

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ABSTRACT

Organocatalyst trityl chloride (Ph_3CCl), by *in situ* formation of trityl carbocation with inherent instability, efficiently catalyzes the condensation of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (2 equiv.) with arylaldehydes (1 equiv.) under solvent-free conditions to afford 9-aryl-1,8-dioxo-octahydroxanthenes in high to excellent yields and in relatively short reaction times. Formation of the carbocationic system is confirmed by studying IR, ^1H NMR and UV spectra according to the literature. Moreover, a plausible mechanism based on the literature and observations is proposed for the reaction.

Keywords*: Trityl chloride (Ph_3CCl), Trityl carbocation, Organocatalyst, Dimedone (5,5-Dimethyl-1,3-cyclohexanedione), Arylaldehyde, 9-Aryl-1,8-dioxo-octahydroxanthene.*

1. Introduction

The use of small-molecule organocatalysts in organic synthesis has flourished over the past decade [1-10]. However, the concept of organocatalysis has emerged as a discrete strategy for addressing modern day challenges in chemistry. It has become widely appreciated that small-molecule organic catalysts can hold a wide range of practical advantages relative to macromolecular, precious metal or protic acidic catalysts, including air stability, low cost, commercial availability, relative non-toxicity, green nature and simple reaction conditions, and can promote a chemical reaction through different activation modes [1-10]. With the dramatic recent expansion of research efforts in organocatalysis throughout the world, synthetically useful transformations based on new reactivity concepts have been identified, often with no counterpart in the more established catalysis regimens [1-10]. Triarylmethyl chlorides (Ar_3CCl) are an attractive and unusual class of small-molecule organocatalysts which have been utilized to promote a few organic transformations by *in situ* formation of triarylmethyl carbocations [5-10].

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It is noteworthy that the inherent instability of carbocations has precluded up to now their use in catalysis with decent turnover numbers [6].

The condensation reaction of dimedone (2 equiv.) with arylaldehydes (1 equiv.) is of importance as this reaction provides a useful and appealing synthetic route toward 9-aryl-1,8-dioxo-octahydroxanthenes [11-17]. Xanthene derivatives have different biological and industrial applications [18-23]. For example, they have been applied as anti-inflammatory [18], antibacterial [19], and antitumor [20] agents, as positive allosteric modulators of metabotropic (mGlu) receptors [21] as pH sensitive fluorescent materials for visualization of biomolecules [22], and as dyes in laser technology [23]. Although some catalysts (mostly Brønsted and Lewis acids) for the condensation of dimedone with arylaldehydes are known, newer catalysts continue to attract attention for their difference with the others, high novelty and effectiveness.

In most of the existing processes in organic synthesis, the use of toxic and volatile organic solvents as reaction media is inevitable, and these are environmentally unacceptable from green chemistry view point. One of the most effective techniques to solve this problem is solvent-free conditions which

makes synthesis simpler, saves energy, and prevents solvent waste, hazards, and toxicity [24-28].
In this work, we introduce a high novelty in the condensation reaction between dimedone and arylaldehydes leading to 9-aryl-1,8-dioxo-octahydroxanthene derivatives, and perform the reaction using trityl chloride (Ph_3CCl) as an efficient, homogeneous and unusual small-molecule organocatalyst under solvent-free conditions at 110 °C. It is attractive that trityl chloride, by *in situ* formation of trityl carbocation, promoted the reaction, and this subject has confirmed by studying IR, ^1H NMR and UV spectra according to the literature.

2. Experimental

2.1. General

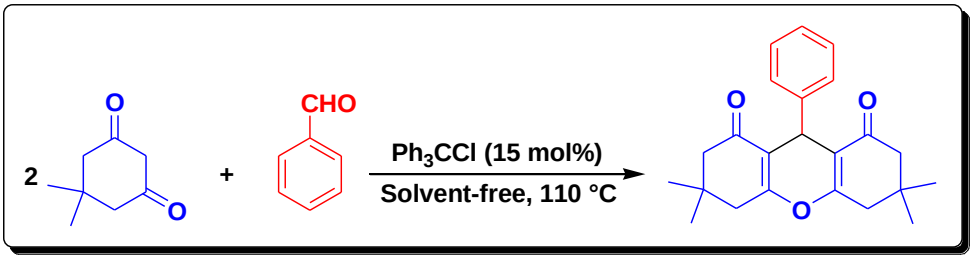
All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^1H NMR (300, 400 or 500 MHz) and ^{13}C NMR (75, 100 or 125 mhz) were run on a Bruker Avance DPX, FT-NMR spectrometer. UV spectra were run on a T8 UV-VIS spectrometer, PG instruments Ltd. Elemental analysis was performed on a PerkinElmer 240B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2. General procedure for the condensation of dimedone with arylaldehydes

A mixture of dimedone (0.28 g, 2 mmol) and arylaldehyde (1 mmol) in a test tube was heated and stirred at 110 °C, and then trityl chloride (0.042 g, 0.15 mmol) was added. The resulting mixture was stirred magnetically at this temperature for about 15-20 min (after this time, the reaction mixture was solidified). Subsequently, the solid reaction mixture was stirred with a small rod at 110 ºC. After completion of the reaction, as monitored by TLC, the mixture was cooled to room temperature, petroleum ether (10 mL) was added to it, refluxed with stirring for 3 min, and filtered to separate the catalyst. The solid residue was recrystallized from EtOH (95%) to give the pure 9-aryl-1,8-dioxo-octahydroxanthene.

3. Results and Discussion

We have previously applied trityl chloride (Ph_3CCl) as an efficient organocatalyst in a few organic transformations [5-10]. This subject combined with the high importance of the reaction of dimedone with arylaldehydes encouraged us to examine the efficacy of Ph_3CCl to promote this transformation. For this purpose, at first, as a model reaction, the condensation of dimedone with benzaldehyde (Scheme 1) was examined in the absence of catalyst and solvent at 110 °C in which the product was obtained in trace yield after 180 min. Afterward, the reaction was studied in the presence of different molar ratios of triarylmethyl chlorides (Ar_3CCl) under solvent-free and solution conditions at range of 90-115 °C. The results are summarized in Table 1. As Table 1 indicates, 15 mol% of the three triarylmethyl chlorides afforded the desired product in high yield and short reaction time under solvent-free conditions at 110 °C (Table 1, entries 3, 8 and 9). Nevertheless, trityl chloride (Ph_3CCl) was selected as catalyst for the reaction (Table 1, entry 3), because it was cheaper and more available in comparison with the two other triarylmethyl chlorides. No improvement in the reaction results was observed by increasing the amount of Ph_3CCl and the temperature (Table 1, entries 4 and 7). The reaction was also examined in the presence of trityl alcohol (Ph_3COH) under solvent-free conditions at 110 °C wherein the yield was low even after long reaction time (Table 1, entry 10).
After optimization of the reaction conditions, the efficiency, the generality and the scope of the organocatalyst in the preparation of 9-aryl-1,8-dioxo-octahydroxanthenes were assessed by the reaction of dimedone with different arylaldehydes including benzaldehyde as well as aldehydes containing electron-releasing substituents, halogens or electron-withdrawing substituents (Table 2).



Scheme 1. The condensation of dimedone with benzaldehyde catalyzed by Ph_3CCl.

Table 1. The reaction of dimedone with benzaldehyde in the presence of different amounts of Ph_3CCl at various temperatures.

Entry	Catalyst	Mol% of Catalyst	Solvent	Temp. (°C)	Time (min)	Yield[a] (%)
1	-	-	-	110	180	Trace
2	Ph_3CCl	10	-	110	70	90
3	Ph_3CCl	15	-	110	50	95
4	Ph_3CCl	17.5	-	110	50	95
5	Ph_3CCl	15	-	90	60	80
6	Ph_3CCl	15	-	100	60	88
7	Ph_3CCl	15	-	115	50	95
8	MMTCl[b]	15	-	110	50	95
9	DMTCl[c]	15	-	110	50	95
10	Ph_3COH	15	-	110	180	Trace
11	Ph_3CCl	15	CH_3CN	Reflux	120	43
12	Ph_3CCl	15	DMSO	110	60	71

[a]Isolated yield.
[b]Monomethoxytrityl chloride [Ph_2(*p*-$MeOC_6H_4$)CCl].
[c]Dimethoxytrityl chloride [Ph(*p*-$MeOC_6H_4)_2$CCl].

As it can be seen in Table 2, all reactions proceeded efficiently and the desired products were obtained in high to excellent yields and in relatively short reaction times. Thus, in this reaction, Ph_3CCl was efficient and general catalyst. The results showed that most of the arylaldehydes bearing electron-releasing as well as electron-withdrawing substituents and halogens decreased the reaction times (in comparison with benzaldehyde). Moreover, most of these functional groups had negligible effect on the reaction yields.

In a proposed reaction mechanism, we suggest that aldehyde and trityl chloride produce intermediate **I** in a reversible reaction (Scheme 2) [5-10].

To prove the formation of **I**, benzaldehyde was reacted with trityl chloride, and then IR, ^{1}H and UV spectra of the aldehydic functional group in the reaction mixture was compared with those in benzaldehyde as follow:

IR (nujol): ν_{max} (cm^{-1}) of C=O in benzaldehyde (1705.5) decreased to 1697.3 in the reaction mixture (Fig. S1, Supplementary Information) [5,6,9,10].

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) of the aldehydic hydrogen (9.78) increased to 10.04 in the reaction mixture (Fig. S2, Supplementary Information) [5,6,9,10].

UV (*n*-Hexane): λ_{max} (nm) of absorption of benzaldehyde and trityl chloride appears in 240 and 222, respectively; however, λ_{max} of the absorbtion of the complexes of benzaldehyde and trityl cation was observed in 245 (Fig. S3, Supplementary Information) [9,10].

These results confirm that intermediate **I** is present in the reversible reaction media. Moreover, the cationic intermediate **I** has been introduced by Oikawa *et al* for the first time [29]. These complex acts as activated carbonyl compound and then react with dimedone providing **II**, which converts to **III** by proton transfer. Intermediate **III** can convert to **IV** by removing Ph_3COH in a reversible reaction. Afterward, **IV** reacts with another dimedone to obtain **V**, which is in equilibrium with **VI**. Nucleophilic attack of the hydroxy group of **VI** to the activated carbonyl group of this intermediate gives **VII**, and **VII** converts to **VIII** by proton transfer. In the last step, elimination of one molecule H_2O from intermediate **VIII** accompanied with Ph_3COH (which produced previously during the reaction) affords the corresponding 9-aryl-1,8-dioxo-octahydroxanthene and Ph_3CCl.

Table 2. The condensation of dimedone and aromatic aldehydes, leading to 9-aryl-1,8-dioxo-octahydroxanthenes, using Ph_3CCl at 110 °C in the absence of solvent.

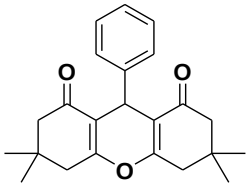
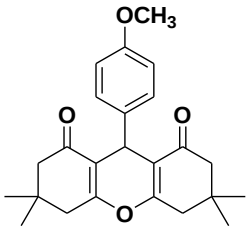
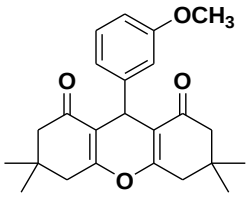
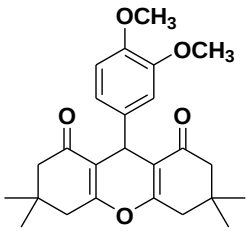
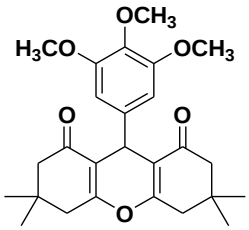
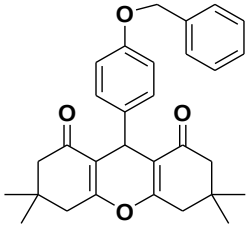
Entry	Product	Time (min)	Yield[a] (%)	M.p. (°C)	
				Found	Reported
1		50	95	200-202	201-202 [14]
2		30	94	243-245	242-244 [14]
3		30	91	161-163	161-162 [15]
4		30	93	178-180	175-176 [15]
5		30	96	190-192	186-188 [14]
6		80	90	153-155	145-147 [17]

Table 2. *(Continued).*

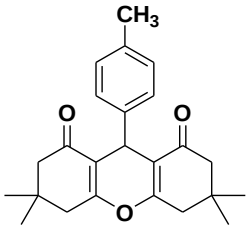
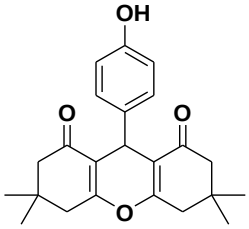
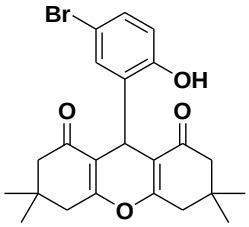
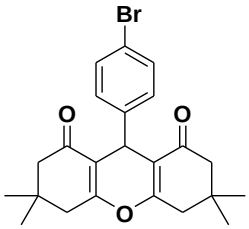
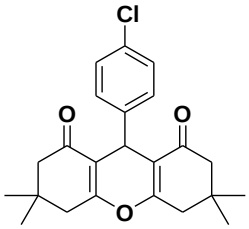
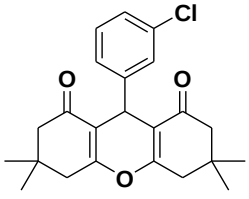
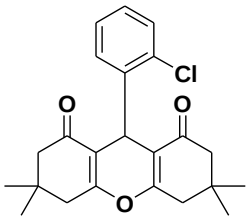
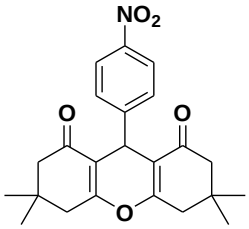
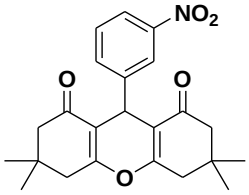
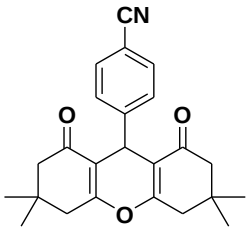
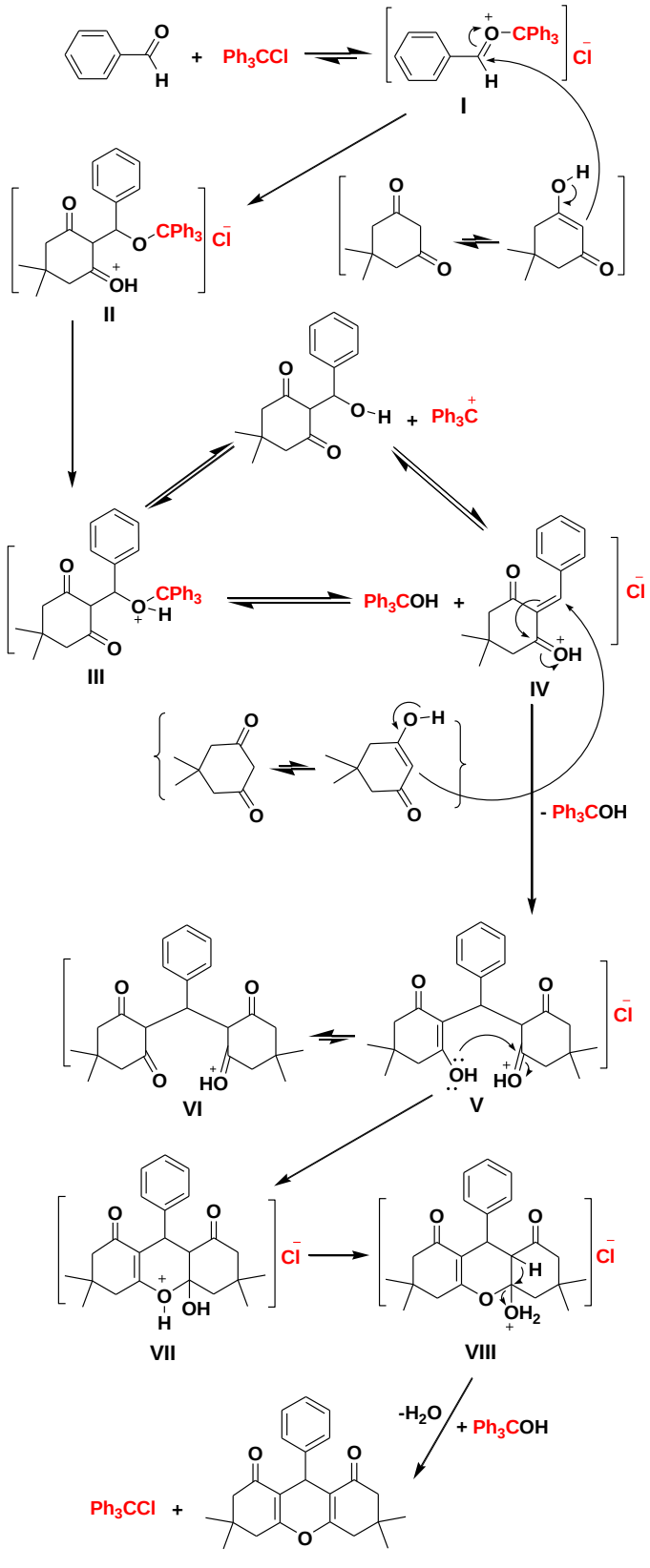
7		35	95	217-219	220-222 [17]
8		30	94	252-254	250-251 [14]
9		50	86	250-252	250-252 [11]
10		20	98	239-241	233-235 [16]
11		30	95	231-233	236-237 [17]
12		40	89	186-187	183-185 [15]

Table 2. *(Continued).*

13		50	84	223-225	226-227 [15]
14		30	94	225-227	229-230 [17]
15		45	87	164-166	168-170 [16]
16		40	91	220-222	217-218 [15]

[a]Isolated yield.

The suggested mechanism is confirmed based the literature [5-10,12,14,29], and also by the fact that Ph_3CCl was completely recovered unchanged and Ph_3COH couldn't be identified after the completion of the reaction as it could be observed on TLC by comparison with pure authentic samples. In another study, to demonstrate that Ph_3CCl can not convert to Ph_3COH and HCl by the water produced during the reaction, and consequently HCl is not the real catalyst of the process, the solvent-free condensation of dimedone with benzaldehyde was examined in the presence of the expected amount of HCl produced by the reversible reaction of Ph_3COH with H_2O, at 110 °C, in which the product was obtained in 62% within 120 min. The reaction was also tested using a base (pyridine); in these conditions, the reaction yield progressed in trace yield after 180 min. Moreover, the reaction was checked in the presence of Ph_3CCl (15 mol%) and pyridine (15 mol%) as acid scavenger wherein the reaction was performed successfully and the desired product was obtained in 95% within 60 min (the base didn't affected the reaction results significantly). It is clear that in these conditions, pyridine can absorb one H^+ from the intermediates containing H^+, and produce pyridinium chloride. But pyridinium chloride reacts with Ph_3COH (that produces in the conversion of intermediate III to V) and forms Ph_3CCl. To prove this, in a separate reaction, pyridinium chloride was reacted with Ph_3COH in which Ph_3CCl was obtained, and some starting materials remained. Finally, the reaction was studied in the presence of pyridinium chloride



Scheme 2. The proposed mechanism for the Ph_3CCl-catalyzed condensation of dimedone with arylaldehydes.

(15 mol%) in which the reaction yield was 36% (after 150 min). These evidences showed that HCl hasn't produced from Ph_3CCl in these conditions, and Ph_3CCl really has catalyzed the reaction.

4. Conclusion

In summary, we have developed a new protocol with high novelty for the condensation of dimedone with arylaldehydes, leading to 9-aryl-1,8-dioxo-octahydroxanthenes, using Ph_3CCl as a green, efficient and homogenous organocatalyst. Clean reaction, simple purification, short reaction times, high yields, and economic availability of the catalyst are some advantages of in this work.

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