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PAPER

A selective solvent-free self-condensation of carbonyl compounds utilizing microwave irradiation†

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An environmentally benign microwave-assisted solvent-free self-condensation of carbonyl compounds was developed using catalytic amounts of triethylamine and lithium perchlorate. Changing the amount of lithium perchlorate helps in controlling the ratio of the single-condensation and double-condensation products. The effect of other additives and microwave activation was also investigated. The optimized conditions were then applied to various cyclic/acyclic ketones and aldehydes, with selectivity observed in many cases.

Introduction

The aldol reaction is one of the most powerful tools for the construction of carbon–carbon bonds, both in nature and synthetic chemistry.[1] The reaction involves the addition of an enol or enolate of a carbonyl compound to another aldehyde or ketone. The product of this reaction is a β-hydroxycarbonyl compound, which, on dehydration, generates the corresponding α,β-unsaturated carbonyl moiety. This bifunctional moiety is present in various synthetic intermediates and provides a usefully functionalized platform, which can be further elaborated.[2] The α,β-unsaturated carbonyl functionality is particularly important due to its widespread occurrence in biologically important compounds.[3]

Self-condensation of aldehydes is a well known process,[4] but self-condensation of ketones is limited to a few examples.[5] Steric compression accounts for the poor reactivity of ketones. Special reagents and reaction conditions are required for their practical conversion, especially for non-activated cyclic and higher molecular weight ketones.[5–10] Ketones being moderate carbonacids require strong bases, like lithium diisopropylamide (LDA) and sodium hydride, for their self-condensation.[5] These strong bases are incompatible with protic solvents, therefore tetrahydrofuran is frequently used as a solvent for these reactions, which is not preferable from an environmental perspective.[5b] Also, the reaction conditions require the complete exclusion of moisture under an inert atmosphere. Strong acids, like hydrochloric acid[6a] and polyphosphoric acid[6b] are also known to promote the self-condensation of ketones, but the reaction usually requires 2–3 equivalents of acid. Alternative methods reported for the self-aldol condensation of aromatic and aliphatic ketones require organometallic[7,8] or titanium alkoxides,[9] while cyclic ketone self-condensation has been reported using a $W(CO)_6/CCl_4$/UV system.[11] The cationic rhodium complex $[Cp^*Rh(\eta^6\text{-}C_6H_6)](BF_4)_2$ is also known to promote the self-condensation of ketones.[10] While efficient, some of these methods produce a significant quantity of hazardous metals and noxious solvents.

The lack of a general strategy for the selective self-condensation of non-activated ketones under mild conditions limit its application in organic synthesis.[5] Increasing environmental concern around energy efficiency and waste management provides an opportunity to develop even more powerful and greener methods for well known organic transformations. This paper describes a general strategy for the self-condensation of cyclic/acyclic ketones and aldehydes under mild solvent-free conditions using microwave irradiation.

Results and discussion

Interestingly, during process development for the synthesis of arylidene and alkylidene carbonyl compounds, Arnold *et al.* observed a very slow self-condensation of cyclopentanone (**1**) over a period of 11 days at room temperature.[12] The reaction required two molar equivalents of anhydrous lithium perchlorate and catalytic triethylamine. Since the application of microwave irradiation as an alternative heating source provides an efficient and environment-friendly procedure to accelerate organic transformations, we decided to investigate the microwave–assisted self-condensation using cyclopentanone as a model substrate under solvent-free conditions (Scheme 1).

First, the self-condensation of cyclopentanone was investigated in the absence of lithium perchlorate. No product

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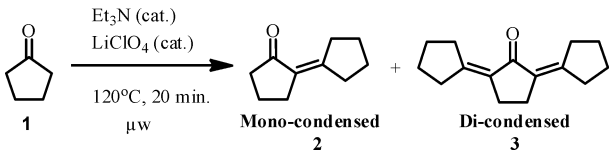


Scheme 1

was obtained, even with an equivalent of triethylamine. In order to investigate the effect of lithium perchlorate, the self-condensation was carried out using different amounts of lithium perchlorate. It was found that as the mol% of lithium perchlorate increased, more di-condensed product **3** was formed (Fig. 1). When the effect of triethylamine was investigated, surprisingly, we observed no effect on the yield or ratio of the two products, even with the addition of extra equivalents of triethylamine relative to lithium perchlorate. It is noteworthy that no product was obtained when the reaction was performed in the absence of triethylamine. The best yield for 2-cyclopentylidene-cyclopentanone (**2**) was observed when equal molar quantities of lithium perchlorate and triethylamine were used. We found that 40 mol% of each triethylamine and lithium perchlorate provide the best yield (80%) with good selectivity (Table 1, entry 5). Importantly, distillation was used to obtain the enone **2**, while the remaining solid was crystalized to yield **3**. Additionally, the reaction to form compound **2** was accomplished on a 100 mmol scale without loss in yield or selectivity.

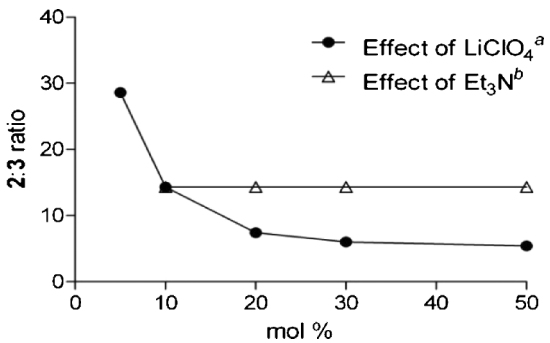


Fig. 1 The effect of $LiClO_4$ and Et_3N on the ratio of mono-condensed (**2**) and di-condensed (**3**) products. [a] mol% of $LiClO_4$ was increased, keeping the concentration of Et_3N at 20 mol%. [b] mol% of Et_3N was increased, keeping the concentration of $LiClO_4$ at 10 mol%.

Table 1 Optimization of the self-condensation of **1**

Entry	$LiClO_4$ (mol%)	Et_3N (mol%)	Ratio (**2** : **3**)[a]	Yield of **2** (%)[b]
1	10	10	93 : 7	50
2	20	20	88 : 12	69
3	25	25	86 : 14	72
4	30	30	86 : 14	77
5	40	40	90 : 10	80
6	50	50	88 : 12	75
7	60	60	86 : 14	71
8	70	70	85 : 15	75
9	100	100	88 : 12	61

[a] Ratio based on the peak integration of ^{1}H NMR (500 MHz). Entries 2–6 are the average of two runs. [b] Isolated yield. Entries 2–6 are the average of two runs.

Table 2 Reaction using conventional heating[a]

Entry	Time	Ratio (**2** : **3**)[b]	Yield of **2** (%)[c]
1	20 min	95 : 5	17
2	1 h	85 : 15	46
3	2 h	80 : 20	68
4	4 h	70 : 30	54

[a] Reactions were carried out with 40 mol% of $LiClO_4$ and 40 mol% of Et_3N at 120 °C. [b] Ratio based on the peak integration of ^{1}H NMR (500 MHz). [c] Isolated yield.

Table 3 Investigation of other additives[a]

Entry	Additive	Ratio (**2** : **3**)[b]	Yield of **2** (%)[c]
1	Li_2SO_4	—	0
2	LiCl	—	0
3	$LiCF_3SO_3$	92 : 8	71
4	$LiClO_4 \cdot 3H_2O$	94 : 6	51
5	$NaClO_4$	—	0
6	$KClO_4$	—	0

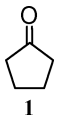
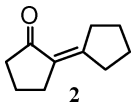
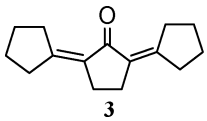
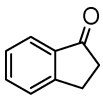
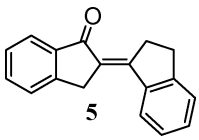
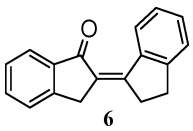
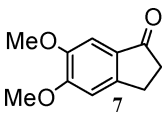
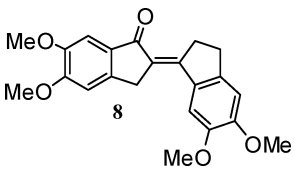
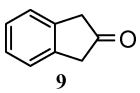
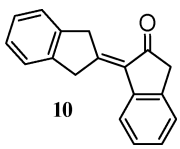
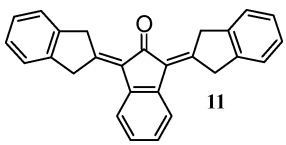
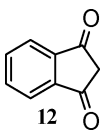
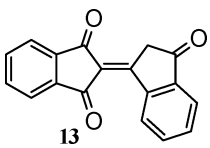
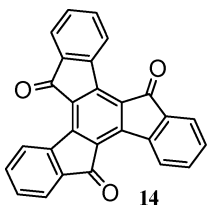
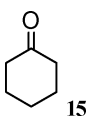
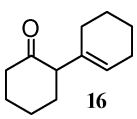
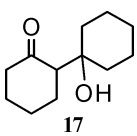
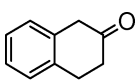
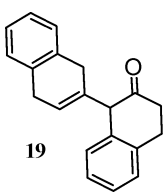
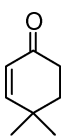
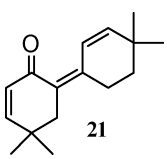
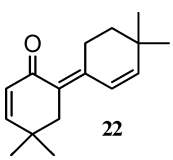
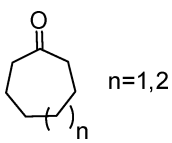
[a] Reactions were carried out with 40 mol% of $LiClO_4$ and 40 mol% of Et_3N at 120 °C. [b] Ratio based on the peak integration of ^{1}H NMR (500 MHz). [c] Isolated yield.

To elucidate the importance of microwave irradiation, similar reactions were performed using conventional heating. When the reaction was performed in a pre-heated oil bath at 120 ± 0.5 °C using the optimal conditions observed for microwave irradiation (Table 1, entry 5), only 17% of the desired cyclic enone **2** was obtained (Table 2, entry 1). An increase in yield was observed when the reaction was carried out for longer periods of time; however, selectivity for the monosubstituted enone **2** dropped 4-fold, with a 3-fold increase in reaction time (Table 2, entry2).

In order to investigate the mechanism of self-condensation, we examined the ability of other additives to catalyze the reaction. We found that the reaction worked with lithium trifluoromethanesulfonate in comparable yield (Table 3, entry 3). The reaction proceeded even in the presence of hydrated lithium perchlorate (Table 3, entry 4). We also observed that lithium perchlorate, lithium perchlorate trihydrate, and lithium trifluoromethanesulfonate are soluble in cyclopentanone at 120 °C.[13] The other additives, which are not soluble in cyclopentanone at 120 °C, did not work for this reaction. Therefore, it can be concluded that the lithium ion acts as a mild Lewis acid due to solvation, and that the Lewis acidity of the lithium ion is a major factor for the reaction to proceed. Also, anhydrous lithium perchlorate acts as a dehydrating agent, thus helping in aldol dehydration.

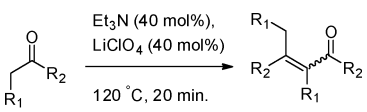
To explore the substrate scope of this reaction, the self-condensation of a series of cyclic ketones was attempted under optimized conditions (Table 4). NOE experiments showed that the solvent-free condensations of 1-indanone **4** and 5,6-dimethoxy-1-indanone **7** exclusively gave the *E*-isomers (Table 4, entries 2 and 3). The same reaction of 2-indanone **9** afforded the monoalkylated compound **10** as the major product. Importantly, the self-condensation of 1,3-indandione was completed in 5 min giving dione **13** as the major product. An extended reaction time helped in increasing the yield of truxenequinone **14**, an interesting compound used for the synthesis of compounds

Table 4 Substrate Scope[a]

Entry	Substrate	Major product	Minor product	Ratio[b] (major : minor)	Yield of major (%)[c]
1	 1	 2	 3	90 : 10	80
2	 4	 5	 6	99 : 1	73
3[d]	 7	 8	—	NA[e]	70
4	 9	 10	 11	75 : 25	71
5[f]	 12	 13	 14	99 : 1	92
6	 15	 16	 17	98 : 2	50
7	 18	 19	—	NA	61
8	 20	 21	 22	50 : 50	40
9	 n=1,2	—	—	NA	No reaction

[a] Reactions were carried out with 40 mol% of $LiClO_4$ and 40 mol% of Et_3N at 120 °C. [b] Ratio based on the peak integration of ^1H NMR (500 MHz). [c] Isolated yield. [d] Reaction temperature was 150 °C. [e] Not applicable. [f] Reaction time was 5 min.

Table 5 Self-condensation of acyclic aldehydes and ketones



Entry	R_1	R_2	Yield (%)[a]	$E:Z$[b]
1	C_5H_{11}	H	95	98 : 2
2	C_4H_9	H	93(0)[c]	97 : 3
3	C_3H_7	H	90	95 : 5
4	C_2H_5	H	90	98 : 2
5	$(CH_3)_2CHCH_2$	H	85	94 : 6
6	$PhCH_2$	H	92	98 : 2
7	$PhCH_2CH_2$	H	89	97 : 3
8	H	4-Me-C_6H_4	15	>99 : 1
9	H	4-Me-C_6H_4	42[d]	50 : 50

[a] Isolated yield. [b] Ratio based on the peak integration of ^{1}H NMR (500 MHz). [c] Reaction without $LiClO_4$. [d] Reaction was done at 200 °C for 4 h.

related to fullerenes.[14] Notably, when applying this process to cyclohexanone **15** and beta-tetralone **18**, we obtained the β,γ-unsaturated isomer. It was also possible to apply the reaction to α,β-unsaturated ketone **20**. Unlike previous substrates, larger ring systems, such as cycloheptanone and cyclooctanone (Table 4, entry 9), did not undergo self-condensation.

To establish the generality and scope of the method, the procedure was successfully applied to various aldehydes and afforded the desired self-condensation products in excellent yields, with high selectivity towards the *E*-isomer[15] (Table 5, entries 1–7). In addition, we found that the reaction does not proceed in the absence of lithium perchlorate, even with aldehydes (Table 5, entry 2). Also, in contrast to aldehydes and cyclic ketones, which require relatively low temperatures and shorter reaction times, acyclic ketones require higher temperatures and longer reaction times for their practical conversion to the required products (Table 5, entries 8–9).

Conclusion

In summary, we have developed a mild and effective method for the self-condensation of carbonyl compounds using catalytic triethylamine and lithium perchlorate. The process takes place under solvent-free conditions utilizing microwave irradiation. The present methodology has clear green credentials judging from the following: (1) the reactions are solvent free, (2) catalytic amounts of both triethylamine and lithium perchlorate are used, (3) the reaction time is very short, (4) small amounts of aqueous waste are produced, (5) distillation or crystallization can be employed to purify the products in most cases, and (6) it is possible to scale up the reactions without much loss in yield or selectivity.

Experimental

General experimental procedures

All microwave reactions were carried out in sealed tubes in a Biotage Initiator™ Microwave Synthesizer using the standard mode of operation at the specified temperature. All reagents were obtained from commercial sources and used without further purification with the exception of triethylamine and aldehydes, which were distilled under reduced pressure.

Optimized Reaction Procedure

To a 0.2–0.5 mL microwave vial containing substrate (1 mmol) was added anhydrous $LiClO_4$ (0.043 g, 40 mol%) and Et_3N (0.056 mL, 40 mol%). The vial was sealed and the reaction mixture was stirred for 20 min at 120 °C (or as specified conditions) in the microwave reactor. After cooling in the reactor, the microwave vessel was uncapped and 15 mL of sat. NH_4Cl was added. The product was extracted with (2 × 20) mL ethyl acetate (diethyl ether was used in the case of aldehydes). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure, obtaining an almost pure product. All liquid products were purified using distillation, while the solid products were purified either by crystallization or by silica gel column, as further described in the ESI.†

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