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Magnesium perchlorate as efficient Lewis acid for the Knoevenagel condensation between β-diketones and aldehydes

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Abstract

A new protocol for the Knoevenagel condensation between β-diketones and aliphatic and aromatic aldehydes promoted by $Mg(ClO_4)_2$ under mild conditions is reported.

Keywords: Knoevenagel condensation; Magnesium perchlorate; β-Diketones; Aldehydes; Mild reaction conditions

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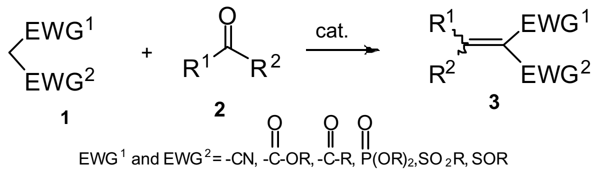
The Knoevenagel condensation is a well-known organic reaction largely employed in order to form C–C bonds for the synthesis of important derivatives in perfume, polymer, and pharmaceutical applications.[1] The Knoevenagel adducts, in fact, are useful intermediates for further transformations, such as Diels–Alder and Michael additions.[2]

The classical Knoevenagel condensation (Scheme 1) has been carried out by reacting a methylene active compound with an aldehyde or a ketone in the presence of a base.[1,3] Recently, alternative procedures employed heterogeneous catalysts, such as zeolites,[4] clays,[5] layered double hydroxides (LDHs),[6] and hydrotalcites.[7] Various protocols carried out in ionic liquids[8] have also been developed. On the contrary, relatively few examples of condensation mediated by Lewis acids such as $TiCl_4$,[9] $ZnCl_2$,[10] $CeCl_3{\cdot}7H_2O/NaI$, [11] and $HClO_4$–SiO_2[12] have been reported. Frequently, high reaction temperatures[4a,5,12,13] or microwave irradiation[12,14] are necessary to promote the reaction independently from the employed catalytic system.



Scheme 1.

Methylene active compounds carrying two electron-withdrawing groups, such as malononitrile, cyanoacetates, malonates, and β-ketoesters, are generally used in the known condensations. However, only few examples of β-diketones as starting materials are reported.[12,15] Very likely, such compounds are less reactive than the other ones since their attitude to form a stable cyclic enol.

Since our interest in the last years in the use of metal perchlorates as Lewis acids,[16] and since their ability to coordinate 1,3-bidentate substrates,[17] in order to extend their applicability we investigated the possibility to promote a Knoevenagel condensation between β-diketones with aldehydes in the presence of a perchlorate salt.

On the other hand, perchlorate salts of alkaline and alkaline earth metals showed to be very active in promoting a large variety of reactions,[18] in some cases being more powerful than metal triflates.[16b,17c,19] Concerning the risk connected with the use of such salts, it has been demonstrated that such perchlorates are not dangerous chemicals

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if not employed under highly acidic conditions and not exposed to high temperatures (>300–500 °C).[20]

To test the reactivity of β-diketones we chose the reaction of acetoacetone **4a** with benzaldehyde **5a** in the presence of various catalytic systems, under solvent free conditions at room temperature. We checked the conversion by NMR at maximum after 70 h, (Table 1).

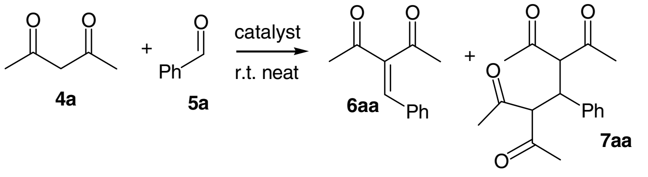
The best reaction conditions required the use of a 10 mol % of $Mg(ClO_4)_2$, and a 20 mol % of $MgSO_4$ (Table 1, entry 1) to obtain a 65% of conversion in the desired product without any traces of by-products. On the other hand, an increase in temperature (40 °C) led to the formation of the side product **7aa**, derived from the attack of acetoacetone on the Knoevenagel adduct, right after 30 h (Table 1, entry 2). The addition of $MgSO_4$ as a catalyst was necessary very likely to adsorb the water formed during the condensation. In fact the reaction carried out only in the presence of $Mg(ClO_4)_2$ was slower (55% vs 65% of conversion, Table 1, entries 1 and 3). As in other reactions,[16a,17d] $Mg(ClO_4)_2$ showed to be more effective than $Zn(ClO_4)_2{\cdot}6H_2O$ (Table 1, entries 1 and 4). The attempt to increase the conversion by the addition of a catalytic amount of Et_3N was unsuccessful: after 48 h the conversion in the desired product was 55% but a 5% of the side product **7aa** was also detected (Table 1, entry 5).

Notably, the reaction works well under neat conditions, the addition of a solvent slows the conversion rate.

The protocol was applied to other substrates.[21] Results are reported in Table 2. Acetoacetone **4a** smoothly reacted with both aromatic and aliphatic aldehydes **5a–h** (Table 2, entries 1–8). The presence of an electron-withdrawing group on the aromatic aldehyde, such as NO_2 and CN, increases the reactivity and very good yields in the desired product **6** were obtained (Table 2, entries 2–4).

Table 1

Reaction of acetoacetone **4a** with benzaldehyde **5a** (1.2 equiv) under various conditions



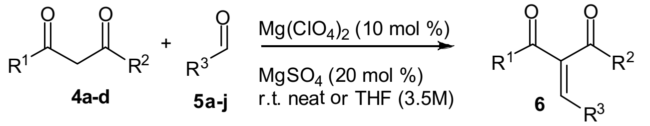
Entry	Catalyst	Time (h)	Conversion[a] in **6aa** (**7aa**)
1	$Mg(ClO_4)_2$ 10 mol % $MgSO_4$ 20 mol %	70	65 (0)
2	$Mg(ClO_4)_2$ 10 mol % $MgSO_4$ 20 mol %	30[b]	65 (3)
3	$Mg(ClO_4)_2$ 10 mol %	70	55 (0)
4	$Zn(ClO_4)_2{\cdot}6H_2O$ 10 mol % $MgSO_4$ 20 mol %	70	52 (0)
5	$Mg(ClO_4)_2$ 10 mol % $MgSO_4$ 20 mol % Et_3N 10 mol %	48	55 (5)

[a] Calculated from ^1H NMR.

[b] Reaction carried out at 40 °C.

Table 2

Reaction of dicarbonyl compounds **4** with aldehydes **5** (1.2 equiv) in the presence of $Mg(ClO_4)_2$ (10 mol %) and $MgSO_4$ (20 mol %) at rt



Entry	R^1	R^2	R^3	Time (h)	Yields[a] (%) (*E*/*Z* ratio)	Product
1	Me	Me	C_6H_4	70	55	**6aa**
2	Me	Me	p-NO_2–C_6H_4	70	86[b]	**6ab**
3	Me	Me	m-NO_2–C_6H_4	48	78[b]	**6ac**
4	Me	Me	p-CN–C_6H_4	24	70[b]	**6ad**
5	Me	Me	p-Br–C_6H_4	70	65	**6ae**
6	Me	Me	n-C_3H_7	48	70	**6af**
7	Me	Me	n-C_5H_{11}	48	67	**6ag**
8	Me	Me	$Ph(CH_2)_2$	90	73[c]	**6ah**
9	Et	Et	p-NO_2–C_6H_4	70	62[b]	**6bb**
10	Et	Et	p-CN–C_6H_4	90	80[b]	**6bd**
11	Et	Et	5-NO_2-2-furyl	24	81[b]	**6bi**
12	Et	Et	$Ph{-}C{\equiv}C$	24	63	**6bj**
13	*i*-Bu	Me	p-NO_2–C_6H_4	90	75 (1:7)	**6cb**
14	OEt	Me	p-NO_2–C_6H_4	54	88[b] (1:3)	**6db**
15	OEt	Me	p-CN–C_6H_4	70	76[b] (1:2.5)	**6dd**
16	Me	Me	*trans*-PhCH=CH	90	30	**6ak**

[a] Isolated yields.

[b] Reaction carried out in THF (3.5 M).

[c] A 5% of the isomer **8ah** was also detected.

The reaction with aliphatic aldehydes is generally faster than those with aromatic ones. In particular, despite the presence of α-protons in the aliphatic aldehydes only the α,β-unsaturated systems **6** are obtained and no isomerization to β,γ-unsaturated[22] ones was detected, (Table 2, entries 6 and 7). Only the reaction of 3-phenylpropanal **5h** required longer reaction times, and traces of by-product **8ah** (Fig. 1), an isomer of the desired product **6ah**, was observed.

Increasing the bulkiness of the diketone system ($R^1 = R^2 =$ Et, **4b**), the reactivity essentially did not change (Table 2, entries 9–12) and the expected products were obtained in good yields. The reaction of **4b** with the substituted heteroaromatic aldehyde **5i** was faster than those with an aromatic one giving **6bi** in very good yield. Moreover, the reaction of **4b** with an unsaturated aldehyde like **5j** gave only **6bj** as product, and no 1,4-addition product was detected. On the other hand, an asymmetric and bulkier system like 6-methylheptane-2,4-dione **4c** took longer time to give **6cb** in good yields even if two isomeric products are formed, the *Z*-isomer being predominant, (Table 2, entry 13).

The protocol works also with active systems generally used in classical Knoevenagel condensation different from diketones. Ethyl 3-oxobutanoate **4d** reacted with aromatic

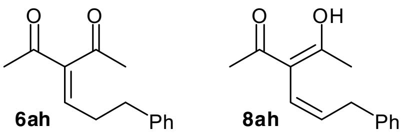


Fig. 1.

aldehydes to give a mixture of *Z*- and *E*-isomeric alkenes, (Table 2, entries 14 and 15).

We tried to extend the procedure to α,β-unsaturated aldehydes, but unfortunately not very satisfactory results were obtained, (Table 2, entries 16). In fact in the reaction of **4a** with cinnamaldehyde the desired product **6ak** was obtained in 30% yields, together with a mixture of starting materials and unidentified by-products.

In some cases, when the aldehyde is solid and does not dissolve in the diketone, the addition of a minimum amount of solvent is necessary to solubilize the reagents. THF proved to be the best choice, and the reactions were carried out under concentrated conditions (3.5 M).

In conclusion, we have demonstrated another interesting application of $Mg(ClO_4)_2$ to act as a Lewis acid in promoting the synthesis of trisubstituted functionalized alkenes via a Knoevenagel condensation between poorly reactive β-diketones and aliphatic and aromatic aldehydes. The protocol works also with more reactive systems like β-ketoesters. The reaction conditions are very mild, in fact the condensation works at room temperature, in the absence or with a minimum amount of solvent. Notably, this procedure led only to the Knoevenagel products, any side-product derived from a subsequent Michael addition of the β-diketone was never detected. In addition, the reaction with aliphatic aldehydes gave generally only the desired product, in contrast to other reported examples.

Acknowledgments

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21. *General procedure for the Knoevenagel condensation*: In a two necked flask equipped with a magnetic stirring bar, $Mg(ClO_4)_2$ (0.10 mmol), $MgSO_4$ (0.20 mmol), β-keto derivative **4** (1.0 mmol) and aldehyde **5** (1.2 mmol) were added. If the system was completely solid, THF (0.29 ml) was added to dissolve the reagents. The mixture was stirred at rt. CH_2Cl_2 was added to the crude reaction mixture. Filtration on Celite and removal of the solvent by rotary evaporation gave the crude product. The substituted olefin **6** was purified by flash chromatography on silica gel with the appropriate mixture of hexane/Et_2O.

    Spectroscopic data for selected compounds follow: *3-Butylidenepentane-2,4-dione* (**6af**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 0.90 (t, $J_{HH} = 7.4$, 3H), 1.42–1.51 (m, 2H), 2.11–2.18 (m, 2H), 2.25 (s, 3H), 2.26 (s, 3H), 6.63 (t, $J = 7.69$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 13.7 (CH_3), 21.8 (CH_2), 25.9 (CH_3), 31.4 (CH_2), 31.6 (Me), 145.2 (CH), 146.6 (C), 197.1 (C), 203.5 (C). MS (ESI+): $m/z = 177$.

    4-((5-Nitrofuran-2-yl)methylene)heptane-3,5-dione (**6bi**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 1.11 (t, $J_{HH} = 7.1$, 3H), 1.22 (t, $J_{HH} = 7.1$, 3H), 2.67–2.75 (m, 4H), 6.82 (d, $J_{HH} = 3.8$, 1H), 6.15 (s, 1H), 7.28 (d, $J_{HH} = 3.8$, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 7.1 (CH_3), 7.7 (CH_3), 32.0 (CH_2), 37.1 (CH_2), 112.7 (CH), 117.7 (CH), 121.5 (CH), 143.4 (C), 150.5 (C), 197.8 (C), 205.9 (C). MS (ESI+): $m/z = 274$.

    4-(3-Phenylprop-2-ynylidene)heptane-3,5-dione (**6bj**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 1.12 (t, $J_{HH} = 7.2$, 3H), 1.20 (t, $J_{HH} = 7.2$, 3H), 2.67 (q, $J_{HH} = 7.3$, 2H), 2.88 (q, $J_{HH} = 7.3$, 1H), 6.89 (s, 1H), 7.34–7.40 (3H, m), 7.43–7.46 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 7.6 (CH_3), 7.9 (CH_3), 32.6 (CH_2), 36.7 (CH_2), 85.0 (C), 105.4 (C), 120.2 (CH), 121.6 (C), 128.6 (CH), 129.9 (CH), 132.0 (CH), 149.8 (C), 198.1(C), 204.8(C). MS (ESI+): $m/z = 263$.
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