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Synthesis of flavanones using nanocrystalline MgO

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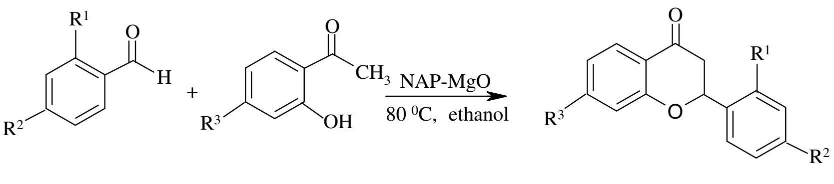
Abstract—The design and development of a truly nano heterogeneous catalyst for the Claisen–Schmidt condensation (CSC) of benzaldehydes with 2-hydroxyacetophenone to yield substituted chalcones followed by isomerization to afford flavanones with excellent yields and selectivity is described.

Flavanone and its derivatives are important intermediates in the synthesis of anticancer, anti-inflammatory, antibacterial, and anti-AIDS drugs.[1] Flavanones are commonly synthesized via the Claisen–Schmidt condensation between 2-hydroxyacetophenone and a benzaldehyde and subsequent isomerization of the 2′-hydroxychalcone intermediate.[2] Both reactions are catalyzed by acids or bases in homogeneous media, and also through electrochemical transformation, photochemical cyclization and, thermal isomerization.[3] There are many drawbacks under homogeneous conditions including catalyst recovery and waste disposal problems. Industry favors catalytic processes induced by heterogeneous catalysts over homogeneous processes in view of ease of handling, simple work-up and regenerability. Moving in this direction zeolites,[4] hydrotalcites,[4] hydroxyapatite,[5] silica,[6] the recently commercially available MgO, supported MgO[7a–d] and KF/natural phosphate[7e] have been employed in the synthesis of flavanones. Although a high selectivity for the desired product flavanone was achieved, there were limitations such as low conversions and the need for higher temperatures. We chose to use a microcrystalline and nanocrystalline form of MgO, since these materials have basic sites in high density. We recently reported Claisen–Schmidt condensations affording chalcones using nanocrystalline MgO in the presence of toluene with 100% conversion.[8] We herein report the use of recyclable, nanocrystalline MgO for the direct synthesis of flavanones in a single pot with high selectivity and conversions under mild conditions (Scheme 1).

Various types of magnesium oxide crystals [commercial MgO, CM-MgO SSA: 30 m^2/g), conventionally prepared MgO, NA-MgO (SSA: 250 m^2/g), aerogel prepared MgO, NAP-MgO (SSA: 590 m^2/g)] were evaluated for the synthesis of flavanones. All of them catalyzed both the CSC of benzaldehyde with 2-hydroxyacetophenone followed by cyclization to obtain flavanones in moderate to good yields in a single pot. However, nanocrystalline MgO (NAP-MgO) was found to be more active than CM-MgO and NA-MgO (Table 1).

When either of the benzaldehyde or the 2-hydroxyacetophenones carried electron-withdrawing groups at the



Scheme 1.

Keywords: Nanocrystalline MgO; Flavanone; Chalcone; 2-Hydroxyacetophenone; Isomerization.

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Table 1. Synthesis of flavanones using different crystallites of MgO[a]

Entry	Catalyst	Time (h)	Conversion (%)[b]	
			Flavanone	Chalcone
1	NAP-MgO	12	90, 60[c], 100[d]	10, 40[c]
2	NA-MgO	18	60	40
3	CM-MgO	36	50	50
4	Sil–NAP-MgO	40	85	15
5	Sil–NA-MgO	48	50	50

[a] Conditions: 2-hydroxyacetophenone (3.0 mmol), benzaldehyde (2.5 mmol), catalyst (0.100 g), solvent (ethanol, 5 mL).

[b] Conversions based on ^{1}H and G.C. according to Ref. 7b.

[c] Using toluene as a solvent.

[d] Using DMSO as a solvent.

Table 2. Synthesis of flavanones by nanocrystalline MgO[a]

Entry	R^1	R^2	R^3	Time (h)	Conversion (%)[b]	
					Flavanone	Chalcone
1	H	H	H	12, 20[c]	90, 90[c]	10, 10[c]
2	H	NO_2	H	18	95	5
3	H	Br	H	15	93	7
4	H	Cl	H	15	94	6
5	OH	H	H	18	86	14
6	H	OMe	H	18	60	40
7	H	CH_3	H	18	74	26
8	NO_2	H	H	20	60	40
9	Br	H	H	20	70	30
10	OMe	H	H	24	50	50
11	NO_2	OH	H	18	70	30
12	H	OH	H	15	80	20
13	H	H	NO_2	30	95	5
14	H	H	Cl	30	96	4
15	H	H	OMe	36	86	14
16	H	H	OH	32	80	20

[a] Reaction conditions: 2-hydroxyacetophenone (3.0 mmol), benzaldehyde (2.5 mmol), catalyst (0.100 g), solvent (ethanol, 5 mL).

[b] Conversions calculated based on ^{1}H NMR and GC according to Ref. 7b.

[c] After 4th cycle. (The catalyst can be regenerated at 250 °C under N_2 flow for 1 h).

4-position, conversion through to flavanone was higher than for substrates bearing electron-donating groups (Table 2, entries 2–4 and 5–7). When the benzaldehyde was substituted with either an electron-withdrawing group or donating group at the 2-position, the formation of flavanone was less efficient (Table 2, entries 5 and 8–11). The formation of flavanone was 100%, when the reaction was carried out in DMSO with total conversion of the benzaldehyde (Table 1, entry 1). All substituted starting materials gave lower yields than the unsubstituted reactants. The catalyst was activated by heating at 250 °C, under a nitrogen flow for 1 h (Table 2, entry 1) before being re-used. The NAP-MgO contains active Brønsted hydroxyl groups along with other active sites.[9] To examine the role of the OH group, Sil–NAP-MgO,[10] devoid of free OH groups was tested. It was found that for silylated MgO samples, longer reaction times were required than the corresponding MgO samples for the synthesis of flavanones (Table 1), indicating that the Bronsted hydroxyls are contributors in the cyclization reactions, to some extent, and that it is largely driven by Lewis basic O^{2-} ions. MgO is polyhedrally shaped, while NA-MgO has the shape of hexagonal platelets with the same average concentration of OH groups to that of NAP-MgO. A possible rationale for the display of the higher yields of flavanones using NAP-MgO is that the OH groups present on the corner sites of the NAP-MgO crystals are more accessible for the reactants. NAP-MgO has a single crystalline polyhedral structure, which a high surface concentration of edges/corners and various exposed crystal planes (such as 002, 001, 111), which leads to inherently high surface reactivity per unit area. Thus, NAP-MgO displayed the highest activity compared to NA-MgO and CM-MgO.[11]

To conclude, we have shown that the NAP-MgO is a highly active, reusable[12] catalyst for the synthesis of flavanones. Thus nanocrystalline MgO with its definite shape, size, and accessible OH groups, and higher density of Mg$^+$ at the edges/corner shows higher activity in the synthesis of flavanones.

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12. General experimental and reusability procedure: In a typical procedure, ethanol (5 ml), benzaldehyde (2.5 mmol), and 2-hydroxyacetophenone (3.0 mmol) were refluxed with stirring in the presence of NAP-MgO (0.100 g). The reaction was continued until completion, as monitored by TLC and also by GC according to the reference b. The catalyst was removed by filtration and the filtrate was concentrated to obtain the crude product, which was purified by column chromatography (hexane/ethyl acetate, 8/2, v/v) using silica gel. The yield of flavanone is 0. 4872 g. The reusability of the catalyst was assessed as follows using the experimental conditions described above after activating the catalyst at 250 °C for 1 h. After completion of the reaction, the catalyst was allowed to settle and the supernatant solution was pumped out from the reaction flask. The catalyst was washed with toluene and allowed to settle and the supernatant solution was pumped out. The NAP-MgO was then reused for four cycles with consistent activity.