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Silica Gel Catalysed Knoevenagel Condensation in *Dry Media* under Microwave Irradiation

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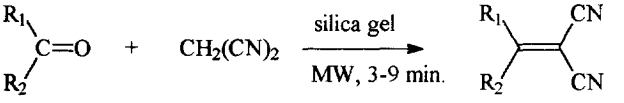
Abstract: *Neutral silica gel catalysed efficiently the Knoevenagel condensation of carbonyl compounds on malononitrile in dry media under microwave irradiation. Synergy between dry media and microwaves is shown.*

Knoevenagel condensation of carbonyl compounds on compounds containing an active methylene group is one of the most important preparation method of substituted alkenes. Reactions are generally catalysed using bases or Lewis acids.[1] Recently, use of inorganic solid supports as catalysts, resulting in higher selectivity, milder conditions and easier work-up, has rapidly increased and has been reported as a useful condition for Knoevenagel reaction. Thus, aluminium oxide,[2] xonotlite,[3] $AlPO_4$-Al_2O_3, [4] clays as KSF[5] and K10-$ZnCl_2$ [6] or Cadmium Iodide [7] have been reported mainly for aldehydes and scarcely for ketones.

Application of microwave heating technique is currently under intensive examination since the early articles of Gedye and Giguere[8] and has been recently reviewed.[9] The effects usually observed were: decreasing reaction times (up to 3 orders of magnitude) and in some cases, cleaner reactions with easier work-up. Especially interesting was the coupling with *dry media* conditions which allowed reactions on a preparative scale and opened vessels (avoiding the risk of high pressures and explosions).[10] Recently, Knoevenagel condensation has been reported to proceed efficiently under microwave irradiation without solvent and with piperidine as a base[11] and in acid media with Montmorillonite K10.[12]

Although silica gel functionalized with amino groups is an efficient heterogeneous catalyst for the Knoevenagel condensation,[13] the authors note that silica gel alone failed to catalyse the reaction under continuous-flow conditions with toluene as an eluent.

In this article, we would like to report that silica gel,[14] without any functionalization, could be used as an useful catalyst for the Knoevenagel condensation in *dry media* coupled with microwave irradiation. Malononitrile reacted with several aldehydes and ketones (see table 1) under the former conditions affording the desired alkene in good yields.



1 **2** **3**

Table 1. Knoevenagel reaction of carbonyl compounds **1a-k** and malononitrile **2** on silica gel in *dry media* under microwave irradiation[a]

Entry 1	R_1	R_2	Power (W)	Time (min)	Yield %,[b,c]	mp (solvent) or bp (mm Hg), °C	Ref.
a	C_6H_5	H	150	3	79[d]	83 (n-BuOH)	15
b	p-NO_2-C_6H_4	H	780	5	68	159 (EtOH)	16
c	p-MeO-C_6H_4	H	450	9	54	114 (AcOH)	15
d	p-Cl-C_6H_4	H	450	3	69	163 (EtOH)	16
e	PhCH(CH_3)	H	450	6	75	150 (1)	17
f	$(CH_3)_2$-CH	H	450	7	33[e]	100 (1)	18
g	-$(CH_2)_5$-		450	3	64	150 (15)	4
h	-$(CH_2)_4$-CH(CH_3)-		150	6	67	100 (1)	19
i	- CH(CH_3)-$(CH_2)_3$-CH(CH_3)-		780	7	0	-	-
j	C_6H_5	CH_3	450-780	7[g]	28	92[f]	2
k	C_6H_5	C_6H_5	450-780	7[g]	6	138[f]	20

[a] Irradiations were carried out in a domestic microwave oven (Miele M-310) operating at 2450 MHz, for an optimised time and power. The temperature of reactions reached 90-110° C.
[b] Evaluated by weight of isolated alkene after purification.
[c] All products are known compound and exhibit satisfactory spectroscopic data (^{1}H NMR and I.R.).
[d] Reaction were carried out with 5 g of silica gel.
[e] Low yield is probably due to the high volatility of the aldehyde.
[f] Isolated and purified by column chromatography with Hexane-Ethyl Acetate (9:1) for entry **j** and (4:1) for entry **k** as an eluent.
[g] Irradiation was carried out for 5 min at 450 W plus 2 min at 780 W.

The ability of silica gel as a neutral catalyst in Knoevenagel condensations was demonstrated using various aldehydes and ketones with malononitrile; results are summarised in Table 1. The aromatic aldehydes were

converted to the corresponding olefins in good yields (entries **a-d**) as well as the non aromatic aldehyde **1e**; only isobutyraldehyde (entry **f**) afforded **3** in low yield, probably due to the evaporation (low boiling point of this aldehyde). In the case of ketones, the condensation of cyclohexanone and 2-methylcyclohexanone readily occurred (entries **g-h**) but the hindered 2,6-dimethylcyclohexanone failed to react (entry **i**). Reactions were more difficult with aromatic ketones (acetophenone reacted in moderate yield, entry **j**); the less reactive benzophenone was also found to condense with malononitrile (entry **k**).

In order to evaluate the synergy between *dry media* and microwave irradiation in this reaction, several experiments were tried. As described in table 2, the irradiation of benzaldehyde and malononitrile without silica gel was unsuccessful and the aldehyde remained practically unchanged after irradiation (entry 2); similarly, when silica gel was used as catalyst in methylene chloride solution (1h, reflux), the alkene **3a** was not obtained (entry 4). Although silica gel in *dry media* catalysed the reaction at room temperature, yield was only 41% after 1 h of reaction (entry 3); increase in temperature using classical heating (30 min, 120°C) in the absence of solvent gave a moderate yield (entry 5). Only in the case of *dry media* coupled with microwave irradiation, taking advantage of synergy between both methodologies, the Knoevenagel condensation proceeded efficiently (entry 1).

Table 2. Condensation of benzaldehyde with malononitrile.

Entry	Catalyst	Temp (°C) or MW Power (W)	Time (min)	Solvent	3a (%)[a]
1	silica gel	150 W	3	none	79
2	none	150 W	3	none	0
3	silica gel	r.t.	60	none	41
4	silica gel	40 °C	240	CH_2Cl_2	0
5	silica gel	120 °C	30	none	48

[a] Evaluated by weight of isolated alkene after purification.

To the best of our knowledge, this is the first example for neutral catalysis of this reaction. In conclusion, the reported procedure is an attractive methodology for the Knoevenagel condensation, because reactions were fast, the procedure was simple and of low cost and it was possible to work under mild neutral conditions.

Standard procedure:

In a typical experiment, the carbonyl compound (1 g) was intimately mixed with an equimolar amount of malononitrile and 3 g of silica gel.[14] The glass vessel (Pyrex) was irradiated in a domestic microwave oven during appropriate time at the indicated power (see table). After cooling down, the reaction product was isolated by extraction of the silica gel with CH_2Cl_2 in a continuous extraction-apparatus and the alkene was purified by recristallization or *via* Kugelrohr distillation.

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