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Calcite and fluorite as catalyst for the Knövenagel condensation of malononitrile and methyl cyanoacetate under solvent-free conditions

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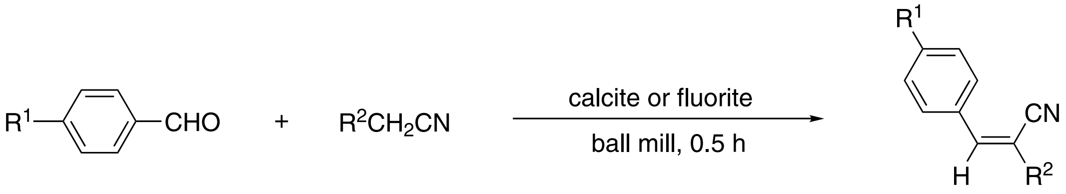
Abstract—When milled together with calcite or fluorite, malononitrile and methyl cyanoacetate readily underwent Knövenagel condensation with aromatic aldehydes, giving the corresponding arylidenemalononitriles and (*E*)-α-cyanocinnamic esters in good to excellent yield. © 2002 Elsevier Science Ltd. All rights reserved.

The Knövenagel condensation has been an important tool for constructing the α,β-unsaturated structure unit from a carbonyl and an active methylene components.[1] The reaction is usually carried out in the presence of a weak base, which includes aliphatic amines such as ethylenediamine and piperidine or corresponding ammonium salts,[2] amino acids such as glycine and β-alanine,[3] and potassium fluoride.[4] The reaction is strongly dependent on solvents and the solvents of choice are benzene, ethanol and *N*,*N*-dimethylformamide (DMF). In recent years, soft Lewis acids,[5] modified inorganic solids,[6] resins,[7] and phase-transfer agents[8] have been introduced as new catalysts. Microwave and infrared irradiation have also shown its utility in Knövenagel condensation under solvent-free conditions.[9,10]

Alkaline earth carbonate and fluoride are found as limestone (calcite) and fluorspar (fluorite) in Nature. They occur in huge quantities and serve as sources for calcium- and fluorine-based products. These rock minerals are intrinsically basic substances, but they cannot be used as inorganic base in solution chemistry due to the insolubility in organic solvents and water. Herein, we wish to report that these minerals can work as a mild catalyst for the Knövenagel condensation of malononitrile and methyl cyanoacetate with aromatic carbonyl compounds under ball-milling conditions, i.e. *dry and neutral* conditions. In these two decades, solvent-free organic synthesis has received considerable attention due to growing worldwide concerns over chemical wastes and future resources. From these points of view, the present methodology offers advantage over traditional ones that have been performed in organic solvents (Scheme 1).

Iceland spar (Mohs hardness, **3**), a transparent variety of natural calcium carbonate, and colorless fluorspar (Mohs hardness, **4**) were purchased in the form of crystalline block and hammered into pieces of 1–3 mm in size before use. The mineral reagent thus obtained was placed, together with small stainless balls of 7 mm



Scheme 1.

Keywords: Knövenagel condensation; solid phase synthesis; nitriles; catalysts.

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diameter, in a stainless cylinder (1.2×4 cm) with a screw cap and a 1:2-molar mixture of an aromatic aldehyde and malononitrile was introduced. The reaction vessel was closed and shaken using a laboratory ball-mill apparatus at a rate of 30 Hz for 0.5 h at room temperature. The resulting pale yellow to light brown powder or pasty solid was extracted with ethyl acetate by trituration. The extract was filtered on a thin bed of a Celite and evaporated to leave the expected product.[11] As can be seen from Table 1, the yields obtained were good to excellent. Even in the presence of excess mineral, neither the telomerization of malononitrile nor the polymerization of condensation products was observed.

Aldehydes bearing an electron-withdrawing group afforded the highest yields relative to other ones, while aldehydes bearing an electron-donating group led to lower yield. The reaction vessel was not airtight, so benzaldehyde and *p*-tolualdehyde suffered extensive oxidation during milling, lowering the yield of condensation products (entries 5 and 7). However, the Michael addition reaction of the initial product with a second molecule of active methylene component to form a 1:2-addition product was not observed under the conditions employed. The reaction appears to be subject to considerable steric effect. Thus, in the case of aromatic ketones, acetophenone was quite sluggish to react, giving the expected product only in 23% yield under the same conditions. As expected, benzophenone failed to react.

Table 1. Calcite/fluorite-mediated Knövenagel reaction of aromatic aldehydes with malononitrile and methyl cyanoacetate

Run	Mineral reagent	R^1	R^2	Yield (%)[a]
1	Iceland spar	NO_2	CN	96
2	($CaCO_3$)	CN		92
3	from Kansu, China[b]	Br		81
4		Cl		84
5		Me		97 (66)[c]
6		OH		93
7		H		58 (36)[c]
8		NO_2	CO_2Me	100
9		CN		100
10		Br		94
11		Cl		56[d]
12		H		26[c]
13		NO_2		100
14		CN	CN	87
15		Br		99
16	Fluorspar	Cl		99 (30)[c]
17	(CaF_2)	Me		93 (38)[c]
18	from Hunan, China[b]	H		100 (30)[c]
19		NO_2	CO_2Me	82
20		CN		51[d]
21		Br		82[d]

[a] Yield is based on aldehyde and refers to isolated compound. No effort was made to optimize the milling conditions.

[b] Purchased from Nichika Corporation, Nakagyo-ku, Kyoto 604-0943, Japan.

[c] A catalytic amount of hydroquinone was added. Numeral in parenthesis refers to the yield obtained in the absence of antioxidant.

[d] Determined by ^1H NMR.

When methyl cyanoacetate was similarly allowed to react with aldehydes, the reaction occurred with the stereoselective formation of (*E*)-cyanocinnamic esters. However, oxidative loss of aldehydes became serious. The addition of a small amount of hydroquinone as antioxidant was found to solve the problem (entries 16–18).

Reagent-grade calcium carbonate and fluoride are commercially available in the form of fine powder which, however, proved to be unsatisfactory for the Knövenagel condensation under milling conditions. Thus, it may be pertinent to speculate on the role of calcite and fluorite employed. When the minerals are mechanically crushed, the newborn solid surface should be highly activated with the naked ionic species in situ generated. The naked carbonate and fluoride anions act as a strong base capable of deprotonating the active methylene compounds, with the consequent formation of a carboanion stabilized via the coordination with calcium cation, which combines with a carbonyl compound, eventually leading to the Knövenagel product.

In summary, we have developed an attractive alternative to the classical Knövenagel condensation. The reaction proceeds on the mechanically crushed mineral surface under completely solvent-free and neutral conditions. It is fast, clean and of low cost, work-up procedure is simple, and yield is good to excellent. The present methodology was also found to be applicable to the aldol-type condensation between active methylene and carbonyl compounds,[13] the details of which will appear in a forthcoming paper.

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11. Typical experimental procedure for the mineral-mediated Knövenagel condensation: Malononitrile (33.7 mg; 0.510 mmol), 4-nitrobenzaldehyde (38.5 mg, 0.255 mmol), calcite grains (19.5 mg, 1–4 mm in size), and two stainless balls of 7 mm diameter were placed in a stainless cylinder (1.2×4 cm; 5 ml vol.) with a screw cap. The cap was tightened and the reaction vessel was shaken using a ball mill apparatus (Retsch mixer mill, MM200; Retsch GmbH, Haan, Germany) at a rate of 30 Hz. The vessel warmed slightly by mechanical friction. After 0.5 h, milling was stopped and the resulting slightly yellow solid was extracted with ethyl acetate by trituration. The extract was filtered on a thin Celite bed and evaporated to leave a pale yellow solid, which was recrystallized from ethanol to give pure 4-nitrobenzylidenemalononitrile (48.8 mg, 96%) as pale yellow crystals, mp 160–162°C (lit.[12] 159–160°C).
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13. Under similar conditions, dimethyl malonate and methyl nitroacetate underwent the aldol-type condensation with aromatic aldehydes to give the corresponding β-hydroxy esters in low to good yield.