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Is a Catalyst Always Needed? The Case of the Knoevenagel Reaction with Malononitrile

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Dedicated to Professor Renato Noto on the occasion of his 76th birthday

The aim of this Perspective is to start a discussion about the real usefulness of more or less sophisticated catalytic systems for the Knoevenagel reaction with malononitrile, a reaction that can take place under mild conditions without the need of a catalyst. From a sustainable viewpoint the questions are: Is it useful to increase the rate of a reaction that already occurs under mild conditions? Is it useful to spend resources and time in designing, characterizing and realizing complex catalytic systems for such reaction? Does it make sense to carry out the reaction under conditions such as to have a slower reaction rate and therefore to find a catalyst that is able to increase it?

Introduction

The aim of this Perspective is to start a discussion about the question in the title: is a catalyst always needed? As we know, a catalyst is needed to increase the rate of a chemical reaction, especially important when such increase make the difference between the success and the complete failure of a synthetic transformation, then making the process much more efficient with respect to the non-catalysed reaction. In this sense, a catalytic process is certainly sustainable if in the absence of a catalyst the product is practically not obtained whichever are the conditions adopted. In every case, we must know the rate of the non-catalysed reaction.

The Knoevenagel condensation reaction[1] is an important and well-explored strategy for the formation of C=C bonds. It is a condensation reaction between aldehydes or ketones with active methylene compounds and it is a very useful synthetic approach that has been employed in a plethora of examples, in the total synthesis of biologically active natural products and their synthetic analogues,[2] for electroluminescent compounds,[3] for organic solar cells,[4] polymers, cosmetics,[5] anticancer agents and in medicinal chemistry in general among other applications.[6]

Due to the easy way to realize Knoevenagel reaction and its importance, many studies have been reported. Almost 6300 papers deal with this topic (Figure 1) especially in the last fifteen years. It is interesting to note that although the reaction has been known for over 100 years the 87% of papers have been published in the last 20 years. From a mechanistic standpoint the reaction may take place through several pathways and the simplest way is the deprotonation of the active methylene compound, depending on the presence of a proper base and solvent. Given its synthetic utility, a very large array of catalysts has been synthetized and tested.[7]

A complete list of catalysts employed for the above reaction will be very long and, it is out of the scope of this Perspective. Nevertheless, such list ranges from very simple base such as hydroxide ions, simple amines, or amino acids, to ionic liquid-based catalysts, to a huge number of examples of heterogeneous materials and even nanomaterials.[8] In many cases, catalysts used are either complex, expensive, heavy metal-based, or rare-earth-metal-based (see Table 4). In addition, in many examples, reactions are performed in non-green solvents (see Table 3).[9]

Discussion

The question raised in the title is of particular significance in the Knoevenagel reaction. Indeed, non-catalysed reactions may take place.[10] As already observed by Patai, ethanol behaves as
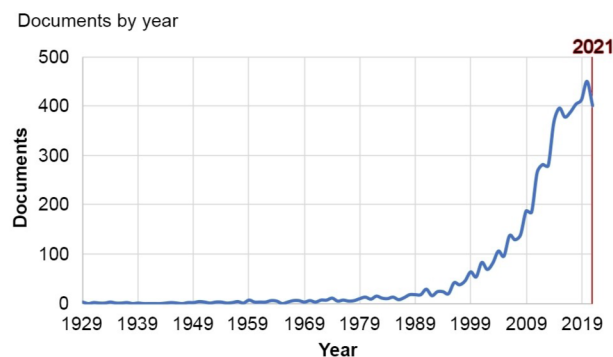
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Figure 1. Number of papers with Knoevenagel in title, abstract or keyword present in the literature (from SCOPUS).

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a stronger base than water; they reported that upon the dissociation of the carbon-hydrogen bond of the active methylene group, the concentration of the carbanion reaches equilibrium practically instantaneously on dissolution in ethanol. In addition, weak bases (acetamide, pyridine, and aniline) had a very slight effect, whereas stronger bases, such as piperidine and piperidinium salts (acetate and benzoate), benzylamine, and ammonia catalysed the reaction strongly whereas addition of acid had a very large inhibiting effect on the reaction rates. During the years, some reports were dealing with the non-catalysed Knoevenagel reaction between benzaldehydes and malononitrile. In 2005 it was reported that such reactions can take place in water at room temperature without catalyst. As a simple check, however, we tried the reaction of malononitrile and benzaldehyde in water but were not able to get the 95% yield reported after 5 min.[13] The paper was a communication without an exhaustive experimental section, then we do not know the exact procedure for product isolation. Indeed, it should be taken into consideration that this reaction can take place in the absence of solvent simply by drying the reaction mixture or leaving the solid reaction mixture and then dissolving it in deuterated solvent for ^{1}H-NMR analysis.[14] In 2012 the same reaction was reported at 65 °C for 1 h in water to give a 94% yield when benzaldehyde was used and 98% yield for 4-nitrobenzaldehyde (Table 1, entries 1–2).[11] In 2018 another paper reported that non-catalysed reaction takes place in ethanol:water 3:7 at 75 °C; as examples, 2-benzylidenemalononitrile was obtained in 82% after 4 minutes whereas 2-(4-nitrobenzylidene) malononitrile in 93% yield in 1 minute (Table 1, entries 3–4).[12] As already reported, the reaction can proceed by drying the reaction mixture or leaving it in the flask or by mixing the reactants in PEG-600 with vigorous grinding using a mortar and pestle at room temperature, until TLC showed complete disappearance of the starting materials.[15] We checked the synthesis of 2-benzylidenemalononitrile and 2-(4-nitrobenzylidene) malononitrile in very mild conditions without catalyst obtaining excellent yields (Table 1, entries 5–10), con-

firming what Patai reported in 1960 and observed in other papers.

Nevertheless, as already introduced, a very large number of structurally different catalytic systems are reported for these reactions. The first impression could be that accelerating such reactions seems more like an exercise in style than a real necessity. Moreover, we must keep in mind that, for this reaction, the use of other solvents slows down the reaction, for example in toluene the reaction becomes much slower but this depends on the nature of the reaction as already pointed out by Patai in 1960. Hence some questions arise. First, is it useful to increase the rate of a reaction that already occurs under very mild conditions? The other question is: does it make sense to carry out the reaction under different conditions such as to have a slower reaction rate and therefore to find a catalyst that is able to increase the reaction rate?

On these questions we would like to start a discussion with the scientific community. Regarding the first point, our opinion is that it certainly does not appear strictly necessary. In addition, there is a point that is very often overshadowed and it is, in fact, the comparison between catalysed and non-catalysed reaction, or the so-called "blank test" or "control test". Any reaction must be compared with its own "blank test". For the present discussion, taking into consideration that since the Patai's observation these reactions take place even without a catalyst, this comparison should be done for each substrate or, at least, for the more reactive ones under the conditions adopted. Actually, in many papers such comparison is missing or done for a single substrate, not for the more reactive substrates. The next step is a cost analysis. A catalyst, whatever it is, has a cost due to its synthesis, characterization, use, recovery and, sometimes, to its regeneration and/or disposal. This overall cost must be lower than the cost of the non-catalysed reaction.

Regarding the second question, our opinion is that this approach is not sustainable. It does not make sense to investigate a costly catalytic system working under well-known unfavourable condition. The only reason could be if someone

Table 1. Non catalysed and catalysed Knoevenagel reaction in sustainable solvents.

Entry	R	Reaction condition t [min], solvent, T [°C]	Conv./Yield [%]	Ref.
1	H	120, H_2O, 65 °C	94	[11]
2	NO$_2$	120, H_2O, 65 °C	98	[11]
3	H	4, EtOH/H_2O 3/7 (v/v), 75 °C	82	[12]
4	NO$_2$	1, EtOH/H_2O 3/7 (v/v), 75 °C	93	[12]
5[a]	H	120, H_2O, 50 °C	>99	This work
6[a]	H	20, EtOH/H_2O 3/7 (v/v), 50 °C	>99	This work
7[b]	H	120, EtOH, 60 °C	>99	This work
8[a]	NO$_2$	15, H_2O, 50 °C	>99	This work
9[a]	NO$_2$	60, H_2O, 25 °C	99	This work
10[a]	NO$_2$	5, H_2O or EtOH, 25 °C	97 or 98	This work

[a] Reactions were carried out with 1 mmol of aldehyde and 1.2 equiv. of malononitrile in 1 mL of solvent, [b] Reaction was carried out with 1 mmol of aldehyde and 1.5 equiv. of malononitrile in 2 mL of EtOH. Products were isolated by simple filtration or after EtOH removal or after extraction and solvent removal.
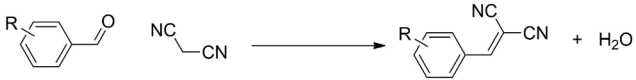
wanted to use the title reaction as a probe to investigate the availability of catalytic moieties on surface of a new heterogeneous catalytic material, not as new catalyst for the reaction.[8c, 16]

During the years many papers have dealt with the use of more or less sophisticated catalysts in order to improve the title reaction. In this Perspective we would like to discuss some examples with the aim to show that, especially in the case of sophisticated materials, though well synthesized and characterized, their use for the title reaction could be considered questionable in terms of cost/benefit. To do this, we have selected some examples from the literature, and we have divided them into four tables. In Table 1 are reported non-catalysed examples, including some reactions checked by us. In

Table 2 some reactions performed with simple catalysts or simple heterogeneous catalysts under aqueous and/or alcoholic solution under mild temperature are reported. In Table 3 examples of reactions carried out in harmful solvents, mainly with metal-based catalysts, that, in principle, could add the problem of metal contamination of the product, are reported. In Table 4 reactions carried out in green solvents but in the presence of sophisticated catalysts are reported. For the sake of brevity, we decided to make the discussion only with two substrates, benzaldehyde and 4-nitrobenzaldehyde.

The use of quinine in 15 mol% loading (Table 2, entries 1–2)[17] gave 2-benzylidenemalononitrile and 2-(4-nitrobenzylidene)malononitrile in 89% and 76% yield, respectively, in solvent-free condition, but quinine was recovered by column

Table 2. Knoevenagel reactions catalysed by simple catalysts or simple heterogeneous catalysts under aqueous/alcoholic solution or solvent-free conditions.

Entry	R	Catalyst	Reaction condition t [min], solvent, T [°C]	Conv./Yield [%]	Ref.
1	H	Quinine (15 mol%)	15, solvent-free, rt	89	[17]
2	NO$_2$	Quinine (15 mol%)	10, solvent-free, rt	76	[17]
3	NO$_2$	Hydroquinone/benzoquinone 0.5/0.5 eq.	360, H$_2$O, rt	73	[18]
4	H	Taurine (20 mol%)	14, H$_2$O, reflux	86	[19]
5	NO$_2$	Taurine (20 mol%)	15, H$_2$O, reflux	94	[19]
6	H	Chitosan (25 mg/mmol)	360, EtOH, 40°C	96	[20]
7	NO$_2$	Chitosan (25 mg/mmol)	360, EtOH, 40°C	90	[20]
8	H	cSiO$_2$-NH$_2$ (10 mg/mmol)	15, EtOH, rt	95	[21]
9	NO$_2$	cSiO$_2$-NH$_2$ (10 mg/mmol)	5, EtOH, rt	99	[21]
10	NO$_2$	S-4 (20 mol%)	20, H$_2$O, rt	91	[22]
11	H	BPEI-CD (5 mg/mmol)	120, EtOH, 60°C	>99	[23]
12	4-OMe	9 (1 mg/mmol)	60, EtOH, 30°C	>99	[24]

Table 3. Catalysed Knoevenagel reaction in less sustainable solvents.

Entry	R	Catalyst	Reaction condition t [min], solvent, T [°C]	Conv./Yield [%]	Ref.
1	H	No catalyst	60, [bmim]PF$_6$, rt	99	[26]
2	H	Mg-Al HT (24 mg/mmol)	30, [bmim]PF$_6$, rt	99	[26]
3	NO$_2$	No catalyst	180, [bmim]PF$_6$, rt	>99	[26]
4	NO$_2$	Mg-Al HT (24 mg/mmol)	20, [bmim]PF$_6$, rt	95	[26]
5	H	[Zn(κN-H$_3$L)(H$_2$O)$_3$]·3H$_2$O (3 mol%)	300, THF, 50°C	94	[27a]
6	H	[Zn$_2$dobdc]$_n$ (1 mol%)	24 h, toluene, 70°C	77	[27b]
7	H	{[Ni$_4$(μ6-MTB)$_2$(μ2-H$_2$O)$_4$(H$_2$O)$_4$]·10DMF·11H$_2$O}$_n$ (4 mol%)	360, p-xylene, 130°C	78	[27c]
8	H	[Tb(BTATB)(DMF)$_2$(H$_2$O)]$_n$ (4 mol%)	24 h, CH$_3$CN, 60°C	99	[27d]
9	H	{[Eu(TATMA)(H$_2$O).2H$_2$O]$_n$ (100 mg/mmol)	180, toluene, 80°C	98	[27f]
10	NO$_2$	{[Y$_2$(TDP)(H$_2$O)$_2$]·5H$_2$O·4DMF}$_n$ (NUC-53) (0.35 mol%)	6 h, DMSO, 70°C	99	[28]
11	H, NO$_2$	Au@Cu(II)-MOF (3 mol%)	7 h, toluene/MeOH, rt	99	[8e]
12	H, NO$_2$	Si-MCM-41-PEI-GO (10 wt%)	30, THF/benzene, rt	>99	[30]
13	H, NO$_2$	MPU (5 mol%)	14 h, THF, 50°C	98, 99	[31]
14	H	MOF-NH$_2$ (13 mol%)	270, DMF, 80°C	98	[32]
15	NO$_2$	MOF-NH$_2$ (13 mol%)	240, DMF, 80°C	97	[32]
16	H	Fe$_3$O$_4$@DETA@GO (2 mg/mmol)	60, THF, 50°C	55	[33]
17	NO$_2$	Fe$_3$O$_4$@DETA@GO (2 mg/mmol)	30, THF, 50°C	99	[33]
18	NO$_2$	SiO$_2$-L-proline (10 mol%)	7 h, CH$_3$CN, 80°C	90	[34]
19	NO$_2$	Cage@FDU-ED (10 mol%)	5, CH$_3$CN, 60°C	96	[35]
20	H	cG@-700-SZ10 (50 mg/mmol)	24 h, CH$_3$CN, 70°C	99	[36]

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Table 4. Sophisticated catalysts for Knoevenagel reaction in sustainable solvents.

Entry	R	Catalyst	Reaction condition t [min], solvent, T [°C]	Conv./Yield [%]	Ref.
1	H	Zn-Bp-BTC MOF (9 mol%)	180, MeOH, 60 °C	99	[41]
2	NO$_2$	Pd@MOF-3 (0.4 mol%)	210, H$_2$O/toluene, rt	95	[42]
3	2- NO$_2$	Pd@MOF-3 (0.4 mol%)	210, H$_2$O/toluene, rt	91	[42]
4	H	Fe$_3$O$_4$@CFR-S-PNIPAM@Pd/CDs (0.2 mol%)	7 h, H$_2$O, 50 °C	99.5	[43]
5	NO$_2$	Fe$_3$O$_4$@CFR-S-PNIPAM@Pd/CDs (0.2 mol%)	24 h, H$_2$O, rt	72	[43]
6	H	Fe$_3$O$_4$@SiO2@NH-NH$_2$-PW (30 mg/mmol)	12, H$_2$O, reflux	93	[44]
7	NO$_2$	Fe$_3$O$_4$@SiO$_2$@NH-NH$_2$-PW (30 mg/mmol)	6, H$_2$O, reflux	96	[44]
8	H	Fe$_3$O$_4$@SiO$_2$@CuO-Fe$_2$O$_3$MNPs (30 mg/mmol)	4, H$_2$O, reflux	90	[45]
9	NO$_2$	Fe$_3$O$_4$@SiO$_2$@CuO-Fe$_2$O$_3$MNPs (30 mg/mmol)	40, H$_2$O, reflux	93	[45]
10	H	Fe$_3$O$_4$@SiO$_2$-3N (50 mg/mmol)	12, H$_2$O, 75 °C	93	[47]
11	NO$_2$	Fe$_3$O$_4$@SiO$_2$-3N (50 mg/mmol)	10, H$_2$O, 75 °C	94	[47]
12	H	L-proline-Cu/TCT@NH$_2$@Fe$_3$O$_4$ (10 mg/mmol)	50, H$_2$O, rt	95	[48]
13	NO$_2$	L-proline-Cu/TCT@NH$_2$@Fe$_3$O$_4$ (10 mg/mmol)	15, H$_2$O, rt	94	[48]
14	H	MOF-PIL-AM (20 mg/mmol)	60, H$_2$O, reflux	97	[49]
15	NO$_2$	MOF-PIL-AM (20 mg/mmol)	50, H$_2$O, reflux	95	[49]
16	H	PdNi@GO (2 mg/mmol)	8, H$_2$O/EtOH, rt	95	[50]
17	NO$_2$	PdNi@GO (2 mg/mmol)	5, H$_2$O/EtOH, rt	94	[50]
18	H	RhPt/TC@GO NPs (8 mg/mmol)	10, H$_2$O/MeOH, rt	>99	[9a]
19	NO$_2$	RhPt/TC@GO NPs (8 mg/mmol)	8, H$_2$O/MeOH, rt	>99	[9a]
20	NO$_2$	NiCu@MWCNT (4 mg/mmol)	15, H$_2$O/MeOH, rt	96	[51]
21	H, NO$_2$	KGCN-RGO (5 wt%)	5, EtOH, rt	>99	[52]
22	H	SDS/[bmim]Br (3.5 mol%/10 mol%)	15, H$_2$O, 80 °C	90	[53]
23	NO$_2$	SDS/[bmim]Br (3.5 mol%/10 mol%)	15, H$_2$O, 80 °C	96	[53]
24	H	JLU-MOF112 (0.25 mol%)	120, EtOH, 60 °C	98	[54]
25	NO$_2$	JLU-MOF112 (0.25 mol%)	120, EtOH, 60 °C	>99	[54]
26	H	NH-Cu(II)@MNP (20 mg/mmol)	5 h, EtOH, 80 °C	92	[55]

chromatography. The hydroquinone/benzoquinone catalytic system afforded a 73% yield of 2-(4-nitrobenzylidene)-malononitrile after 360 min at rt (entry 3)[18] using a very large excess of malononitrile (40 equiv.). Taurine was used in 20 mol% in refluxing water in short reaction times (entries 4–5),[19] but in the same time, at least, 4-nitrobenzaldehyde will react without catalyst (compare Table 2, entry 5 *vs* Table 1, entry 8). High yields of 2-benzylidenemalononitriles were achieved using chitosan as catalyst after 6 h at 40 °C in ethanol (entries 6–7).[20] Recycling experiments claimed no loss in catalytic activity. Actually, under these conditions, reactions can take place without catalyst, moreover the catalyst was dried at 60 °C overnight, adding in this manner an additional cost. The amine functionalized cubic mesoporous silica nanoparticles (cSiO$_2$-NH$_2$) allows the synthesis at rt in ethanol in a short reaction time (entries 8–9),[21] the blank test was carried out in the presence of silica (25 mg/mmol) which being acidic could slow down the reaction. Blank test with 4-nitrobenzaldehyde in ethanol carried by us gave 98% of product after 5 min (Table 1, entry 10). On the other hand, blank test on benzaldehyde showed low conversion of the product within this short reaction time. Sevelamer, a copolymer of epichlorohydrin and allylamine, was used as catalyst in water at rt in 20 mol% loading (entry 10).[22] Polyamine-functionalized carbon dots were used at 60 °C in EtOH, a condition that furnish the final product without the need of the catalyst (Table 2, entry 11 *vs* Table 1, entry 7).[23] Even us reported a cross-linked polyamine-based material **9** that was used in two examples. The less reactive 4-

methoxy derivative was obtained in 99% yield in 1 h (entry 12)[24] whereas after the same time the non-catalysed reaction gave the product in 85% yield in EtOH/H$_2$O at 75 °C.[12]

The use of other solvents can be also questionable. In many cases, reactions are carried out in solvents that display major issues based on GSK Solvent Sustainable Guide.[25] Reactions were also carried out in expensive and toxic ionic liquid [bmim]PF$_6$ without catalyst or in the presence of hydrotalcite (HT) at rt to give 2-benzylidenemalononitrile in 99% yield after 60 or 30 min respectively at rt (Table 3, entries 1–2).[26] The presence of Mg-Al HT increased also the rate in the case of 2-(4-nitrobenzylidene)malononitrile but it is clear that the usefulness of both the ionic liquid and Mg-Al HT is very limited (Table 3, entries 3–4).[26] Other selected examples are based on the use of different poor sustainable solvents and/or at high temperature with long reaction times and metal-based catalysts (Tables 3, entries 5–9).[27] A binuclear 3D framework of {[Y$_2$(TDP)(H$_2$O)$_2$]·5H$_2$O·4DMF}$_n$ was reported to be a good catalytic system in the deacetalization-Knoevenagel condensation reactions in DMSO for 6 h at 70 °C (Table 3, entry 10).[28] Actually, the reaction with 4-nitrobenzaldehyde and malononitrile is complete in a few minutes under these conditions, then the blank experiment reported demonstrated that catalyst works in the deacetalization step. There are other examples concerning one-pot transformations in which one step is the Knoevenagel condensation (Table 4, entries 2–3, 26). This step does need catalysis and it could be catalysed even by the basic aqueous conditions as in the sequential Suzuki-Knoevenagel

reactions.[29] Another example of tandem reactions (oxidation-Knoevenagel) was reported by using a Au@Cu(II)-MOF catalyst in toluene/MeOH at rt for 7 h (Knoevenagel step, entry 11).[8e] The blank experiment was reported only for the first step (alcohol oxidation).

In other examples metal-free catalysts are used but still with toxic solvents such as THF/benzene mixture. This is the case of the complex system polyethylenimine functionalized Si-MCM-41 grafted on surface modified graphene oxide (Table 3, entry 12).[30] Microporous polyurethane material with sponge like morphology was used in THF with a very long reaction time of 14 h (entry 13).[31] MOF-NH$_2$ was used in DMF at 80°C for long reaction times (entries 14–15).[32] Diethylenetriamine (DETA)-functionalized graphene oxide decorated with Fe$_3$O$_4$ nanoparticles were used in THF at 50°C (entries 16–17).[33] L-Proline adsorbed on silica was used in CH$_3$CN at 80°C for several hours (entry 18).[34] Metal-organic cages within amino-functionalized mesoporous carbon containing TEMPO moieties (Cage@FDU-ED) was used as bifunctional heterogeneous catalyst for one-pot alcohol oxidation-Knoevenagel reactions. The second step was carried out in the presence of malononitrile at 60°C in CH$_3$CN. (entry 19).[35] Reaction with benzaldehyde was used as test to analyse the basic character of cG@-700-SZ10 material, among others, that has been prepared via direct condensation, up to 700°C, of guanine in the presence of an inorganic salt melt as structure directing agent to give a C1N1 sp^2-conjugated material. After degassing at 150°C for 20 h, a 99% conversion was obtained after 24 h at 70°C in acetonitrile (entry 20).[36]

Other examples of costly materials are ordered mesoporous carbon nitrides with C3N5 or C3N4 structure that were tested in toluene at 60°C for up 4 h with the aim to investigate their basicity, but bearing in mind that the easiness of the proton abstraction by the catalysts does not control the catalysis in the series malononitrile, ethylcyanoacetate, diethylmalonate.[37] Other examples are SBA-15 supported carbon nitride catalysts (CH$_3$CN, 90°C)[38] or strongly oxidised graphitic carbon nitride treated with NaOH (CH$_3$CN, 70°C)[39] or carbon doped hexagonal boron nitride (toluene, 80°C).[40] These materials are examples of the second question we have raised. Actually, they have an effective catalytic role, since in their absence no reaction take place, but the question is: are they actually sustainable for the Knoevenagel reaction?

The last set of examples of catalytic materials is reported in Table 4. The metal organic framework Zn-Bp-BTC MOF (Bp: 4,4′-bipyridine; BTC: 1,3,5-benzene tricarboxylic acid) was used in MeOH at 60°C for 3 h with benzaldehyde and even a longer reaction time was used with 4-bromobenzaldehyde (Table 4, entry 1),[41] conditions that allow the synthesis without the need of the catalyst. Pd@MOF-3 catalyst was prepared via grafting of poly[2-(diethylamino)ethyl methacrylate)] (PDEAEMA) chains onto UiO-66-type NPs via a post synthetic approach to generate PDEAEMA-g-UiO-66 NMOF (termed as MOF-3), then the Pd NPs-loaded Pd@MOF-3 was synthesized via solution impregnation. Pd@MOF-3 catalyst was used in a cascade reaction Knoevenagel-hydrogenation. However, it is possible that the catalyst was operative only in the second step. Indeed, in our hand, non-

catalysed reactions with 2-nitro and 4-nitrobenzaldehyde in water/toluene at rt gave quantitative yields (Table 4, entries 2–3).[42]

The Fe$_3$O$_4$@catechol-formaldehyde resin core-shell nanosphere stabilized carbon dots/PdNP (Fe$_3$O$_4$@CFR-S-PNIPAM@Pd/CDs) was reported to catalyse the reaction of benzaldehyde and malononitrile in 24 h at rt in about 99% conversion while the non-catalysed reaction afforded, under the same condition, a 38% conversion. The same reaction carried out at 50°C for 7 h gave an almost quantitative conversion (entry 4).[43] Actually, in our hand a complete conversion (and yield) was obtained in 2 h without catalyst (Table 1, entry 5). In addition, reaction with 4-nitrobenzaldehyde gave an almost complete conversion (and yield) in 1 h at rt (Table 1, entry 8) whereas, strangely, Fe$_3$O$_4$@CFR-S-PNIPAM@Pd/CDs afforded the Knoevenagel product in 72% conversion in 24 h at rt (entry 5).[43] The Pd-based catalyst was used in a cascade reaction Knoevenagel-hydrogenation but it could be possible that the catalyst was operative only in the second step.

The diamine-modified silica-coated magnetite-polyoxometalate material Fe$_3$O$_4$@SiO$_2$@NH-NH$_2$-PW was used in refluxing water (Table 4, entries 6–7) that is a condition that allow the non-catalysed pathway to 2-benzylidenemalononitrile compounds.[44] Binary copper and iron oxides immobilized on silica layered magnetite was also used for the reaction. In this case, a blank experiment was carried out in water at reflux giving only traces of the final compound after 60 min. Actually, we obtained an almost quantitative yield at 50°C in 120 min. Nevertheless, under this condition Knoevenagel products were obtained in a short reaction time, for instance, 4 min in the case of benzaldehyde (90% yield) and 40 min for 4-nitrobenzaldehyde (93% yield) (entries 8–9).[45] In the latter case, it is evident that the reaction can proceed without the need of the catalyst. It is important, in this example, to highlight that the data of TON and TOF reported have been calculated based on the basis of the amount of CuO contained. However, as authors reported, even unmodified silica plays a catalytic role, then the TON and TOF values could be overestimated. We think that these values should reflect only the main catalysed pathway not the contribution of other catalysed or non-catalysed pathways.[46] Reactions catalysed by amine compounds-tethered to Fe$_3$O$_4$@SiO$_2$ nanoparticles were carried out in water at 75°C in high yields. A blank test was performed only in THF, then, the role of the catalyst in some of the reported reactions could be negligible (entries 10–11).[47] Proline-Cu complex based 1,3,5-triazine coated on Fe$_3$O$_4$ magnetic nanoparticles (L-proline-Cu/TCT@NH$_2$@Fe$_3$O$_4$) was used in water at rt (entries 12–13).[48] 1-Butyl-3-vinylimidazolium chloride was polymerized with acrylamide to furnish an ionic liquid-containing polymer, which was then used for the formation of a composite with iron-based metal-organic framework. This material was used in water under reflux (entries 14–15).[49] The recyclability was tested with benzaldehyde under this condition. Palladium-nickel nanoparticles on graphene oxide (PdNi@GO) was used in water/ethanol at rt (entries 16–17).[50] A bimetallic catalyst based on monodisperse Rh-Pt nanoparticles onto thiocarbamide functionalized graphene oxide (RhPt/TC@GO NPs) was used in short

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reaction times in water/methanol at room temperature (entries 18–19).[9a] The blank test with 4-chlorobenzaldehyde under the adopted condition gave only traces of the product. Recycling procedures were also carried out with 2-nitrobenzaldehyde. However, under the adopted condition, after 8 min at rt in water/methanol we obtained a precipitate which was filtered and collected indicating that this substrate gave complete conversion without catalyst. Another example of bimetallic catalyst was monodisperse nickel/copper nanohybrids (NiCu@MWCNT) based on multi-walled carbon nanotubes (MWCNT) that was used at rt in water/methanol (1/1) in short reaction times (entry 20).[51] Recycling procedure was also performed with 4-nitrobenzaldehyde. Under these conditions, this reaction gave complete conversion when carried out in the absence of a catalyst. A nanocomposite of potassium-functionalized graphitic carbon nitride and reduced graphene oxide (KGCN-RGO) was used in ethanol at rt to give Knoevenagel products in high yields (entry 21).[52] This paper is another interesting example about cost/benefits, indeed, the catalysts allows the synthesis of the benzylidene malononitrile derivatives at rt by using 5 wt% of catalyst but the KGCN-RGO catalyst is prepared from dicyanamide and KCl that must be heated at 500 °C for 4 h, then, after stirring for 6 h and centrifugation, there is another synthetic step at 70 °C for 12 h followed by a final treatment at 180 °C for 12 h. It appears clear that it could be less expensive to carry out the reaction at 50 °C without catalyst. The combined use of SDS and [bmim]Br in 3.5 mol% and 10 mol% loading respectively gave benzylidene malononitrile derivatives when reactions were carried out in water at 80 °C (entries 22–23).[53] Recycling experiments were carried out with 4-nitrobenzaldehyde that, actually, reacts completely at 50 °C or at rt in water in the same reaction time. A Y(III)-based amide-functionalized MOF (JLU-MOF112) was used in ethanol at 60 °C for 120 min. Under these conditions a 20 % yield was reported in the blank test with benzaldehyde whereas a 98 % yield in the presence of the catalyst. Actually, in our hand this reaction performed under the same condition and then evaporating the solvent at reduced pressure at rt. gave a complete conversion (Table 1, entry 7). A quantitative yield was reported with 4-nitrobenzaldehyde (entries 24–25).[54] It appears clear that almost no contribution of the catalyst was operative. The TON and TOF values claimed should be much lower since a great contribution of the non-catalysed reaction was operative and, as already stated, the contribution of the non-catalysed reaction should be taken into account. A bifunctional catalyst for Knoevenagel condensation and 1,3-dipolar cycloaddition domino reactions was reported working in ethanol at 80 °C for 5 h. In our opinion, also in this example the catalyst plays its role in the second step (entry 26).[55] As final example, a 3s–3d {CaZn}-organic framework (NUC-21) was used under solvent free condition at 60 °C using 2 equivalents of malononitrile. As already stated, the reaction takes place using water and/or ethanol that is a condition more sustainable than performing the reaction with a catalyst under solvent-free condition with an excess of a reagent and then washing the catalyst with N,N-dimethylformamide.[56] Finally, for the sake of completeness, as suggested by a reviewer, another crucial point that is interesting to emphasise is the question of whether the reaction under investigation can be considered a true Knoevenagel reaction or not. Indeed, a Knoevenagel condensation can only be named if the catalyst has an effect on the used carbonyl compound (i.e. benzaldehyde) forming reactive/catalytic intermediate that is demonstrable.[57] A classic example is the use of a tertiary amine as a catalyst, which does not give rise to any catalytic intermediate, so the reaction cannot be classified as a Knoevenagel reaction, but rather as a base-catalysed aldol condensation.

Conclusion

The Knoevenagel reaction is a very useful reaction and it is also an interesting way to test new catalytic materials. Nevertheless, we must bear in mind, as already observed by Patai in 1960, that in the case of the reaction with malononitrile the non-catalysed pathway in green solvent such as water and/or ethanol can give the final products in very mild conditions avoiding any costs for less expensive or highly expensive catalysts. We also must bear in mind that each catalytic reaction should be compared with the "blank test" and due to the high reactivity of malononitrile, this test should be carried out for each substrate. This point is compulsory if we are investigating the recycling of the catalytic system. Finally, as we are moving towards increasingly sustainable synthetic approaches, we must consider that the cost related to the life cycle of the catalyst (design, synthesis, use, recovery, reuse, regeneration, disposal of the spent catalyst) must be affordable compared to the non-catalysed reaction. Although the catalytic systems here reported are very well synthesized and characterized, many of them could be useful for other applications than the Knoevenagel reaction with malononitrile.

Conflict of Interest

The authors declare no conflict of interest.

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