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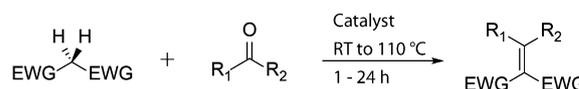
Base-free Knoevenagel condensation catalyzed by copper metal surfaces†

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For the first time Knoevenagel condensation has been catalyzed by elemental copper with unexpected activity and excellent isolated yields. Inexpensive, widely available copper powder was used to catalyze the condensation of cyanoacetate and benzaldehyde under mild conditions. To ensure general applicability, a wide variety of different substrates was successfully reacted.

Copper has been a fascinating element in catalysis for decades.[1] In the early days of copper catalysis, famous name reactions such as the Ullmann coupling,[2] the Sandmeyer reaction and the Chan–Evans–Lam coupling have emerged.[3] Around the millennium, Sharpless and coworkers developed the extremely important "click chemistry", in which the copper catalyzed azide–alkyne Huisgen cycloaddition (CuAAc) plays the most essential role.[4] However, much more expensive noble metals such as platinum, palladium and gold have received most attention in the field of catalysis, while the inexpensive yet semi-noble copper has been more or less neglected.[5] Knoevenagel condensation (Scheme 1) is a widely used reaction in research and industry and has been of importance for several pharmaceutical products.[6] Generally this reaction is catalyzed by organo-bases, such as pyridine or piperidine. But using these homogeneous base catalysts often leads to time consuming work-up procedures. Additionally, undesired side-reactions such as oligomerizations can occur, high temperatures are necessary, and catalyst recovery is difficult.[7] Thus, numerous accounts on heterogeneous Knoevenagel catalysts, for example modified zeolites, ionic liquids or magnetic base analogues, have been reported.[8] This leads to cleaner products while complex neutralization procedures can be avoided.[4b] Moreover, these catalysts can be recovered and regenerated. Within one of these studies it was shown that carbon-coated

cobalt nanoparticles (C/Co)[9] showed some activity in the Knoevenagel condensation if compared to the uncatalyzed reaction (entries 1 and 2, Table 1).[8e] As a consequence of these results, several other carbon coated nanoparticles were tested; amongst which carbon-coated copper nanoparticles (C/Cu)[10] showed the highest activity. As reference, we compared the nanoparticles with pure metal powders. These experiments afforded the insight that commercially available, dendritic copper powder Cu(D) catalyses the Knoevenagel condensation of benzaldehyde 1

Scheme 1   Knoevenagel condensation of an active methylene compound with an aldehyde or ketone.

Table 1   Activity of different catalysts for the Knoevenagel reaction of benzaldehyde and ethyl cyanoacetate[a]
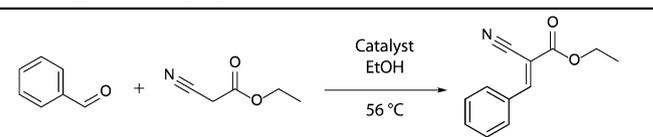
Entry	Catalyst	Time (h)	Yield[b] (%)
1	None	2	3
2	C/Co	2	8
3	Co powder	2	9
4	C/Fe	4	4
5	FeCl$_3$	4	4
6	Fe powder	4	6
7	C/Cu	4	12
8	Cu powder	2	32
9	Brass alloy 260	2	5
10	Ag powder	4	7
11	Au powder	4	6
12	ZnCl$_2$	6	4

[a] Reaction conditions: catalyst (4 mg), benzaldehyde (0.12 mmol) and ethyl cyanoacetate (0.1 mmol) in 1 mL of EtOH for 2 h. [b] Only the *E*-isomer was detected, yield determined *via* HPLC-UV (MS) using commercial product 3 as the reference standard.

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Table 2 Optimization of the reaction conditions[a]

Entry	Solvent	Loading (mg)	t (h)	Cu[b] (ppm)	Yield[c] (%)
1	EtOH	0.4	2	3	6
2	EtOH	2	2	38	14
3	EtOH	4	2	44	32
4	EtOH	10	2	216	96 (95)[d]
5	EtOH	40	2	114	99 (85)[d]
6	EtOH	4	6	44	99 (95)[d]
7	Acetone	4	20	18	1
8	Cyclohexane	4	20	32	3
9	Toluene	4	20	30	3
10	DMF	4	6	17	99 (98)[d]
11	DMSO	4	2	241	99
12	MeCN	4	2	230	99 (98)[d]

[a] Reaction conditions: copper (4 mg), benzaldehyde (0.12 mmol) and ethylcyanoacetate (0.1 mmol). [b] Cu leaching measured by ICP-OES. [c] Determined *via* HPLC-UV using commercial product **3** as the reference standard. [d] Isolated yield.

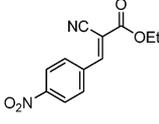and cyanoacetate **2** in ethanol to **3** (entry 8, Table 1) with enhanced yields. Compared to other heterogeneous catalysts for the Knoevenagel condensation, the unmodified, commercially available copper does not need any special treatment, synthesis procedure or sophisticated storage and is the base stock in many laboratories. Notable is the fact that silver, gold, ZnCl$_2$ and brass showed only low activities compared to elemental copper (entries 9–12). To optimize the reaction conditions the catalyst loading was varied, and as expected higher loading resulted in higher yields (up to 99%; entries 1–5, Table 2). It should be noted that an equivalent amount of copper compared to the reagents is not imperative to result in full conversion (entry 6). Optimization tests with different solvents clearly favoured aprotic, polar solvents over non-polar solvents (entries 7–12). These results are in line with the general literature on Knoevenagel condensation, namely with the first step in the reaction mechanism which is the generation of an anion at the α-position of the carbonyl group followed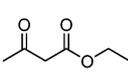 by enolate formation.[7] After optimizing the reaction conditions with the model substrates, a variety of different aldehydes and active methylene compounds were reacted (Table 3). As already summarised by Tietze *et al.*, all condensations using **2** as the substrate exclusively yielded the *E*-isomer.[7] Other active methylene compounds were tested, such as Meldrum's Acid (entry 6) and analogues (yielding the bis-adduct, entry 5), the very reactive malononitrile (99% yield in 1 h, entry 8) and the less reactive ethylacetoacetate (23% yield after 15 h, entry 9). The different reactivities of these compounds are well known and correlate with their ability of stabilizing the corresponding anion.[7] To gain more detailed insight into the reaction mechanism, further experiments concerning the nature of the copper catalyst have been conducted.

A possible first hypothesis was that copper leaching, *i.e.* soluble Cu(I) or Cu(II) species, could be the reason for catalytic activity. Several Cu(I/II) compounds have been tested (entries 1–5, Table 4) to investigate the activity of copper ions in solution. None of these copper species showed substantial activity, instead of a high measured solvated Cu amount (entries 2 and 3). Also, there are reports of metal-alkoxide catalysed Knoevenagel condensations, and activity of *in situ* generated CuOMe may also be

Table 3 Scope of the condensation[a]

Entry	Reactant	Reactant	Product	Yield[b] (%)
1	2	4-methoxybenzaldehyde	ethyl (E)-2-cyano-3-(4-methoxyphenyl)acrylate	99[c] (98[d])
2	2	4-nitrobenzaldehyde	ethyl (E)-2-cyano-3-(4-nitrophenyl)acrylate	99 (87[d])
3	2	cinnamaldehyde (Ph-CH=CH-CHO)	ethyl (E)-2-cyano-5-phenylpenta-2,4-dienoate	90[c] (86[d])
4	2	4-R-benzaldehyde; R$_1$= Cl, R$_2$= Br, R$_3$= I	ethyl (E)-2-cyano-3-(4-R-phenyl)acrylate	R$_1$ 85 (73[d]); R$_2$ 90 (68[d]); R$_3$ 98 (93[d])
5	1	5,5-R-cyclohexane-1,3-dione (2 eq.); R$_a$=H,H; R$_b$=Me,Me	bis-adduct	R$_a$ 98[e] (97[d]); R$_b$ 93[e] (89[d])
6	1	Meldrum's acid	benzylidene Meldrum's acid	57[e]
7	2	cyclohexanone	ethyl 2-cyano-2-cyclohexylideneacetate	87[e]
8	1	malononitrile	2-benzylidenemalononitrile	99[f] (99[d])
9	1	ethyl acetoacetate	ethyl 2-acetyl-3-phenylacrylate	23[g]
10	1	2-cyanoacetamide	(E)-2-cyano-3-phenylacrylamide	87[c] (85[d])

[a] Reaction conditions: Cu (20 mg), aldehyde (0.21 mmol) and active methylene (0.2 mmol) in EtOH for 6 h at 56 °C. [b] Yield determined *via* HPLC-UV or GC-FID. [c] Stirred for 16 h. [d] Isolated yield, only the *E*-isomer was detected. [e] 6 h in DMF. [f] Stirred for 1 h at RT. [g] Stirred for 15 h in DMSO at 70 °C, $E/Z = 65\% : 35\%$.

possible.[11] However, if the solid catalyst is filtered (Fig. 1), conversion stops immediately. This leads to the conclusions that either there is a very unstable homogeneous reactive species formed on the surface of Cu or leaching is not the reason for catalytic activity. Hence, a second hypothesis can be formulated around Cu surface based catalysis, where the yield is expected to correlate with the specific surface area (SSA) of the catalyst. Cu(D) has dendritic structures between 0.5–1 μm (see Fig. S4, ESI†) and thus a relatively low BET surface area of 0.2 m^2 g^{-1}. While a tenfold larger amount of Cu(D) resulted in a tenfold

Table 4 Copper containing reference substances as catalysts for the Knoevenagel condensation[a]

Entry	Catalyst	Time (h)	SSA (m^2 10^{-4})	Cu (ppm)	Yield[b] (%)
1	$Cu(II)_2(OH)_2CO_3$	2	—	6	2
2	$Cu(II)Cl_2$	16	—	740	1
3	$Cu(I)Cl$	16	—	460	3
4	$Cu(II)O$	20	—	6	4
5	$Cu(I)_2O$	20	—	12	14
6	Cu(D)	2	8	44	32
7[c]	Cu(D)	2	80	114	99
8	Cu(Hol)	2	84	62	65
9	Cu(NPA)	2	168	176	96
10	Cu(NPB)	2	636	197	99

[a] Reaction conditions: catalyst (4 mg), benzaldehyde (0.12 mmol) and ethyl cyanoacetate (0.1 mmol) in EtOH at 56 °C. [b] Yield determined *via* HPLC-UV (MS) using commercial product **3** as the reference standard. [c] 40 mg of Cu(D) used.
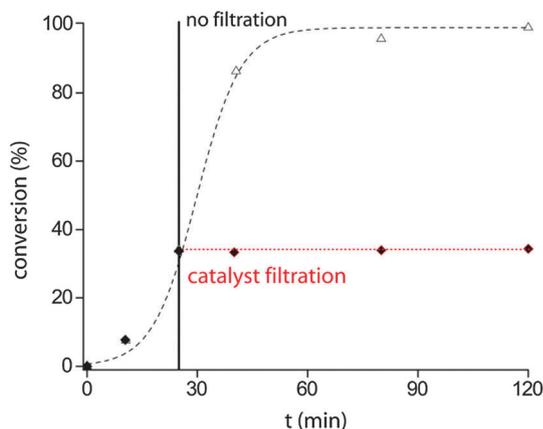

Fig. 1 Knoevenagel condensation of benzaldehyde (0.12 mmol) and ethyl cyanoacetate (0.1 mmol) with copper Cu(D) (4 mg) at 56 °C in DMSO: after 20 minutes half of the reaction volume was extracted and filtered and further subjected to the reaction conditions without a solid catalyst (black diamonds).

larger surface area, leaching was only increased by factor 2.5 (entries 6 and 7), yet the yield substantially changed from 32% to 99%. This is another argument against a mechanism based on solvated Cu species, since the relatively small amount of additional leached species, for example in the case of Copper hollow-spheres (Cu(Hol), entry 8, Table 4), can hardly be responsible for the large increase in yield. Thus, a Cu surface based mechanism can be assumed. However, the nature of the surface state required for catalytic action is still unknown. Thus, surface activation experiments were done: the copper catalyst was pre-treated under different reducing conditions, in order to reduce copper oxide species. This resulted in higher yields, most obviously for toluene, where the pre-treated copper yielded 53% product after 20 h, while the untreated copper did not catalyze the reaction at all (entries 4 and 5, Table 5). This finding leads to the conclusion that a non-oxidized Cu(0) surface reacts with the substrates. Kinetic measurements support the surface catalyzed mechanism too, as a zero-order kinetic model fits well in the beginning of the reaction (see Fig. S1 and S2 in the ESI†). An initial TOF of 0.88 s^{-1} was calculated using optimal

Table 5 Effect of surface activation of Cu(0) on the reaction rate[a]

Entry	Pretreatment	t_P (h)	T_P (°C)	t_{cat} (h)	Solvent	Yield[b] (%)
1	—	—	—	2	EtOH	32
2	Reduction w/FA[c]	1	RT	2	EtOH	49
3	Reduction w/H_2	2	60	2	EtOH	52
4	—	—	—	20	Toluene	3
5	Reduction w/H_2	2	110	20	Toluene	53

[a] Reaction conditions: pre-treated catalyst (4 mg), benzaldehyde (0.21 mmol) and ethyl cyanoacetate (0.2 mmol) at 56 °C. [b] Yield determined *via* HPLC-UV (MS) using commercial product **3** as the reference standard. [c] In 2% formic acid.

conditions (Fig. 1, 41% yield after 30 min) and the conservative assumption that every Cu(0) atom on the surface is an active site. Further mechanistic studies are a subject of ongoing research. Moreover, similar copper(0) species with different BET surface areas (see Table S1 in the ESI†), such as copper hollow spheres Cu(hol),[12] copper nanoparticles A Cu(NPA) and copper nanoparticles B Cu(NPA) were tested (entries 8–10). A correlation between the surface area and conversion could be confirmed. Also, an experiment was conducted to prove the reusability of the catalyst. The standard setup in DMSO afforded constant high yields after 1 h for 5 consecutive cycles (Fig. S1, ESI†).

To illustrate the practical synthetic utility of our method, a 100 gram scale experiment was performed (Scheme 1). Benzaldehyde **1** (81.2 mL, 0.8 mol) was reacted with ethyl cyanoacetate **2** (84.8 mL, 0.8 mol) and 16.00 ± 0.001 g of Cu(D) in EtOH at 56 °C for 16 h. After filtration through aluminum oxide and recrystallization, 91% (146 g) pure isolated yield was obtained and almost all of the solid catalyst (15.94 ± 0.001 g) could be recovered. This satisfying result highlights the simplicity of both catalyst and work-up and hence is of interest for industrial scale Knoevenagel reactions. It should be noted that this kind of upscale experiment is difficult to perform with soluble base catalysts as large amounts of solvent and neutralization agent have to be used.

In summary, we have developed a simple and mild method for the Knoevenagel condensation using commercially available semi-noble copper. In this catalysis, tedious separation procedures are not necessary and no traces of base remain. Further experiments revealed that a Cu(0) surface is necessary to catalyze the condensation and, surprisingly, other noble metals such as gold and silver were not active. Moreover, a substantial scale up (>100 g) experiment demonstrated simple applicability.

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