Supporting Information

Base-free Knoevenagel condensation catalyzed by copper metal surfaces

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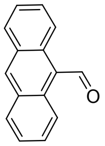
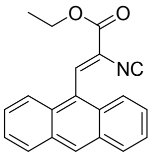
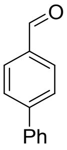
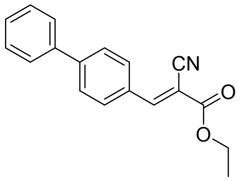
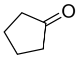
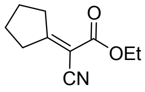
1. General information

Commercially available reagents were used as received from Sigma-Aldrich. Nanoparticles A were purchased from Sigma-Aldrich. Nanoparticles B were purchased from Alfa-Aesar. All air-sensitive reactions were carried out under an argon atmosphere. HPLC measurements were conducted on an AGILENT 1100 (WATERS Column C18, particle size, 5 μm; column size, 2.1 × 150 mm2) to determine the yield of the catalytic reactions. GC−MS measurements were performed (capillary, 30 m × 250 × 0.5 μm2) with split injection (250 °C; ratio = 10:1; injection volume, 1 μL) and a temperature program (80 °C for 2 min; increase at 20 °C min−1 until 300 °C). The copper concentration present in solution was measured by inductively coupled plasma−atomic emission spectroscopy (ULTIMA ICPOES). ^{1}H NMR (200 MHz) were recorded on a Bruker AMX-200 spectrometer and reported in ppm (δ). NMR spectroscopy abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. XRD measurements were performed on a X'Pert Pro-MPD diffractometer (PANalytical), using Cu-Kα radiation (λ = 1.54060 Å), generally over a range of 70° 2θ with a step size of 0.05°. Scanning electron microscopy (SEM) micrographs were measured on a FEI Nova NanoSEM 450, 5 kV. Brunauer–Emmett–Teller (BET) measurements were done on a Micromeritics TRISTAR surface analyzer.

2. Experimental procedures

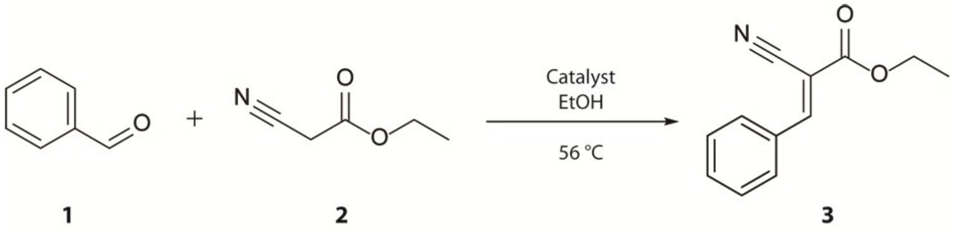
2.0 Additional substrate scope

Table 1. Additional Substrate scope[a]

Entry	Reactant	Reactant	Product	Yield (%)[b]
1[c]	2a			54 (32)[d]
2[c]	2a			64 (55)[d]
3	2a			42

[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.

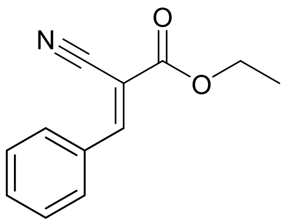
2.1 General procedure for the Cu(0) catalyzed Knoevenagel condensation



A mixture of solvent (1 mL) and catalyst (4 mg) was prepared in an Eppendorf-tube. Aldehyde or ketone (0.11 mMol) and active methylene compound (0.1 mMol) were added and the whole reaction mixture was shaken at 56 °C for 2 h. The residue was filtrated using a standard frit and 3 g of aluminum oxide (removing solvated Cu(II) ions) and the solvent was removed under reduced pressure. The resulting solid was dissolved in hot EtOH and recrystallized at 8 °C.

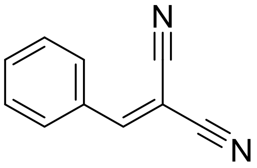
2.2 Characterization of Knoevenagel products

2.2.1 Ethyl-2-cyano-3-phenylacrylate



Ethyl (Z)-2-cyano-3-phenylacrylate was prepared from benzaldehyde (0.12 mmol) and cyano 2-ethylacetate (0.1 mmol) following the general procedure and was obtained as a white solid (19.1 mg, 0.095 mmol, 95 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.19 (s, 1H), 7.9 (m, 2H), 7.47 – 7.43 (m, 3H), 4.37 – 4.27 (q, 2H), 1.37 – 1.30 (t, 3H). ESI-MS: $[M+H]^+$ 202.08 m/z.

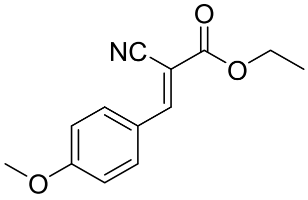
2.2.2 Benzylidenemalononitrile



Benzylidenemalononitrile was prepared from benzaldehyde (0.12 mmol) and malononitrile (0.1 mmol) following the general procedure and was obtained as a yellowish solid (15.2 mg, 0.099 mmol, 99 %).

^{1}H NMR (CDCl$_3$, 200 MHz, 25°C): δ 7.86 – 7.82 (m, 2H), 7.71 (s, 1H), 7.57 – 7.43 (m, 3H). ESI-MS: [M+H]$^+$ 155.03 m/z.

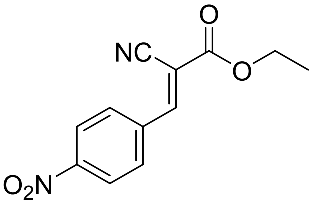
2.2.3 Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate



Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate was prepared from anisaldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 16 h in EtOH at 56 °C and was obtained as a white solid (45.3 mg, 0.196 mmol, 98 %).

^{1}H NMR (CDCl$_3$, 200 MHz, 25°C): δ 8.10 (s, 1H), 7.95 – 7.91 (m, 2H), 6.94 – 6.90 (m, 2H), 4.35 – 4.25 (q, 2H), 3.82 (s, 3H), 1.37 – 1.30 (t, 3H). ESI-MS: [M+H]$^+$ 232.07 m/z.

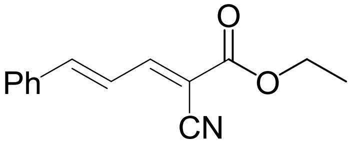
2.2.4 Ethyl (2-cyano-3-(4-nitrophenyl)acrylate



Ethyl (2-cyano-3-(4-nitrophenyl)acrylate was prepared from 4-nitrobenzaldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 16 h in EtOH at 56 °C and was obtained as a white solid (42.8 mg, 0.174 mmol, 86 %).

^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.31 (s, 1H), 8.24 (m, 2H), 8.09 – 8.04 (m, 2H), 4.41 – 4.30 (q, 2H), 1.39 – 1.32 (t, 3H). ESI-MS: $[M]^-$ 246.03 m/z.

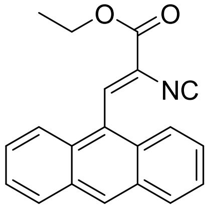
2.2.5 Ethyl 2-cyano-5-phenylpenta-2,4-dienoate



Ethyl 2-cyano-5-phenylpenta-2,4-dienoate was prepared from cinnamic aldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 16 h in EtOH at 56 °C and was obtained as a yellow solid (39.4 mg, 0.174 mmol, 86 %).

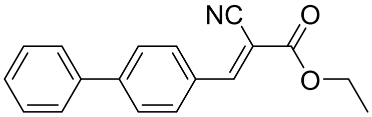
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 7.95 (m, 1H), 8.24 (m, 2H), 7.50 (m, 2H), 7.37-7.22 (m, 5H), 4.33 – 4.22 (q, 2H), 1.34 – 1.27 (t, 3H). ESI-MS: $[M+Na]^+$ 250.09 m/z.

2.2.6 Ethyl 3-(anthracen-9-yl)-2-cyanoacrylate



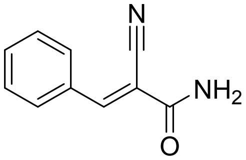
Ethyl 3-(anthracen-9-yl)-2-cyanoacrylate was prepared from anthracene aldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 15 h in DMSO at 70 °C and was obtained as a yellow solid (19.3 mg, 0.064 mmol, 32 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 9.24 (s, 1H), 8.51 (s, 1H), 8.02-7.87 (m, 4H), 7.46 (m, H), 4.49 – 4.38 (q, 2H), 1.45 – 1.38 (t, 3H). ESI-MS: $[M+Na]^+$ 324.01 m/z.

2.2.7 Ethyl 3-([1,1'-biphenyl]-4-yl)-2-cyanoacrylate



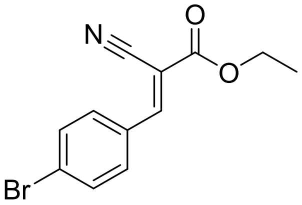
Ethyl 3-([1,1'-biphenyl]-4-yl)-2-cyanoacrylate was prepared from biphenyl aldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 16 h in EtOH at 56 °C and was obtained as a yellow solid (30.5 mg, 0.11 mmol, 54 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.21 (s, 1H), 8.00 (s, 1H), 7.59-7.34 (m, 8H), 4.39 – 4.28 (q, 2H), 1.38 – 1.31 (t, 3H). ESI-MS: $[M+H]^+$ 278.04 m/z.

2.2.8 2-cyano-3-phenylacrylamide



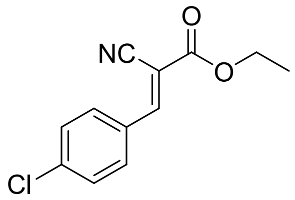
2-cyano-3-phenylacrylamide was prepared from benzaldehyde (0.22 mmol) and cyano acetamide (0.2 mmol) using 20 mg of Cu powder, stirring 16 h in EtOH at 56 °C and was obtained as a yellow solid (29.2 mg, 0.17 mmol, 85 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.25 (s, 1H), 7.88 (m, 2H), 7.47 (m, 3H), 6.29 – 6.05 (br, 2H). ESI-MS: $[M+H]^+$ 173.06 m/z.

2.2.9 ethyl-3-(4-bromophenyl)-2-cyanoacrylate



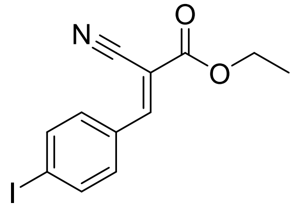
Ethyl-3-(4-bromophenyl)-2-cyanoacrylate was prepared from 4-bromobenzaldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 6 h in EtOH at 56 °C and was obtained as a white solid after recrystallization in EtOH (38.2 mg, 68 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.11 (s, 1H), 7.81 – 7.77 (m, 2H), 7.60 – 7.55 (m, 2H), 4.37 – 4.25 (q, 2H), 1.37 – 1.30 (t, 3H). ESI-MS: $[M+H]^+$ 280.01, 282.03 m/z.

2.2.10 ethyl-3-(4-chlorophenyl)-2-cyanoacrylate



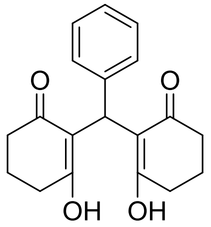
Ethyl-3-(4-chlorophenyl)-2-cyanoacrylate was prepared from 4-chlorobenzaldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 6 h in EtOH at 56 °C and was obtained as a off-white solid after recrystallization in EtOH (34 mg, 72 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.13 (s, 1H), 7.89 – 7.85 (m, 2H), 7.44 – 7.39 (m, 2H), 4.38 – 4.28 (q, 2H), 1.37 – 1.30 (t, 3H). ESI-MS: $[M+H]^+$ 236.04 m/z.

2.2.11 ethyl-3-(4-iodophenyl)-2-cyanoacrylate



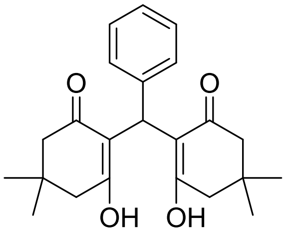
Ethyl-3-(4-iodophenyl)-2-cyanoacrylate was prepared from 4-iodobenzaldehyde (0.22 mmol) and ethyl cyanoaceate (0.2 mmol) using 20 mg of Cu powder, stirring 6 h in EtOH at 56 °C and was obtained as a white solid after recrystallization in EtOH (61.1 mg, 93 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 8.09 (s, 1H), 7.77 – 7.64 (m, 2H), 7.60 – 7.55 (m, 2H), 4.37 – 4.26 (q, 2H), 1.36 – 1.29 (t, 3H). ESI-MS: $[M+H]^+$ 328 m/z.

2.2.12 2,2'-(phenylmethylene)bis(3-hydroxycyclohex-2-en-1-one)



2,2'-(phenylmethylene)bis(3-hydroxycyclohex-2-en-1-one) was prepared from 4-benzaldehyde (0.22 mmol) and cyclohexa-1,3-dione (0.4 mmol) using 20 mg of Cu powder, stirring 6 h in DMF at 56 °C and was obtained as a off-white solid after recrystallization in EtOH (60.6 mg, 97 %). This solid product was not soluble anymore, so no NMR-spectra could be obtained.
ESI-MS: $[M+H]^+$ 313 m/z.

2.2.13 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one)



2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) was prepared from benzaldehyde (0.2 mmol) and 5,5-dimethylcyclohexane-1,3-dione (0.4 mmol) using 20 mg of Cu powder, stirring 6 h in DMF at 56 °C and was obtained as a white solid after recrystallization in EtOH (66 mg, 89 %).
^{1}H NMR ($CDCl_3$, 200 MHz, 25°C): δ 7.23 – 7.00 (m, 5H), 5.47 (s, 1H), 2.33 – 2.07 (m, 8H), 1.16 – 1.03 (m, 12H).
ESI-MS: $[M+H]^+$ 369.2 m/z.

3. Copper catalyst properties

Table 2. Overview of the copper(0) containing catalysts and their properties.

Entry	Catalyst	Abbreviation	Colour	Size (nm)	Shape	BET SA (m^2 g^{-1})
1	copper powder dendritic	Cu(D)	red	500-1000	dendritic	0.2
2	copper nanoparticles A	Cu(NPA)	brown	40-60	spherical	4.2
3	copper nanoparticles B	Cu(NPB)	black	20-50	spherical	15.9
4	carbon-coated-copper nanoparticles	Cu(C)	black	5-50	spherical	61.1
5	copper hollow spheres	Cu(Hol)	black	1000-1500	hollow sphere	2.1

4. Catalytic cycles and kinetic figures

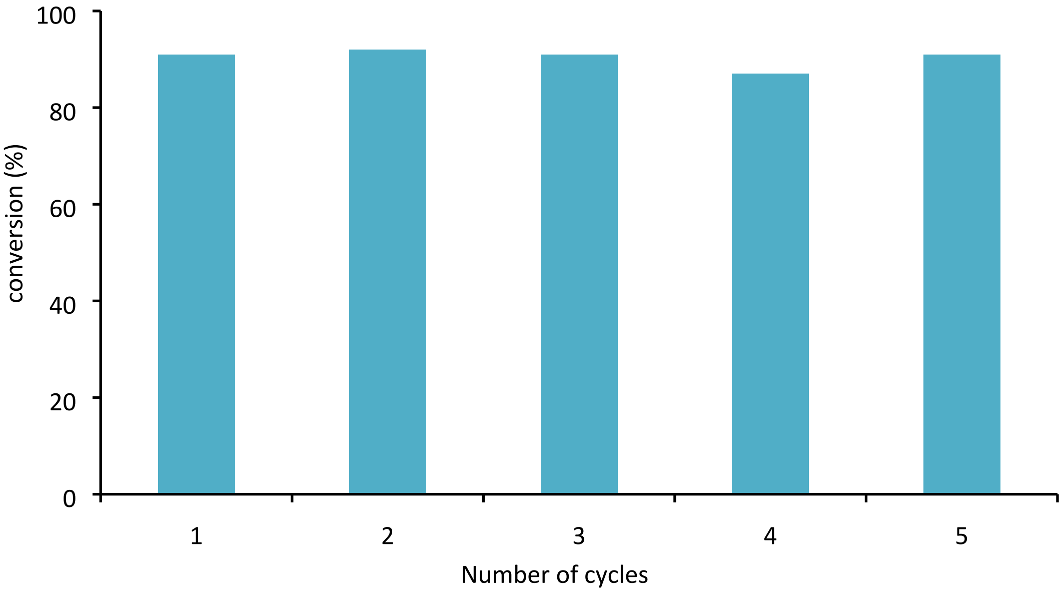


Figure 1. Conversion of the condensation between benzaldehyde (0.1 mMol) and ethyl-cyanoacetate (0.1 mMol) in 1 ml DMSO with 4 mg Cu @56 °C after 1 h. 5 successive cycles using the same catalyst.

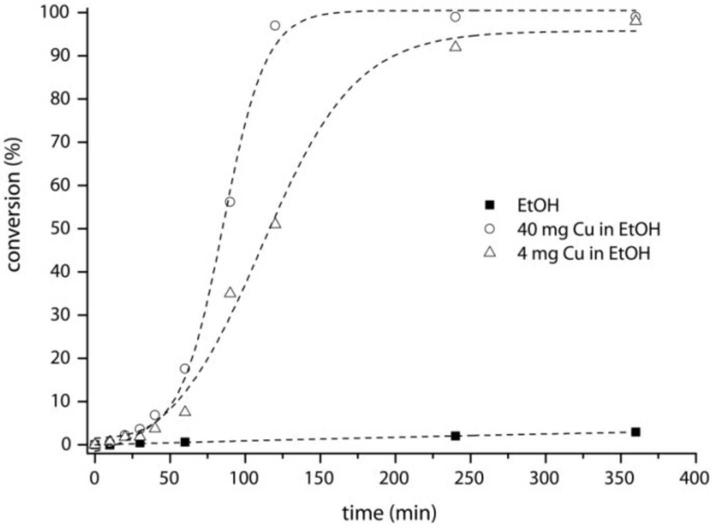


Figure 2. Knoevenagel condensation of benzaldehyde (0.2 mmol) and ethyl cyanoacetate (0.1 mmol) with dendritic copper powder at 56 °C: No visible reaction without catalyst was detected.

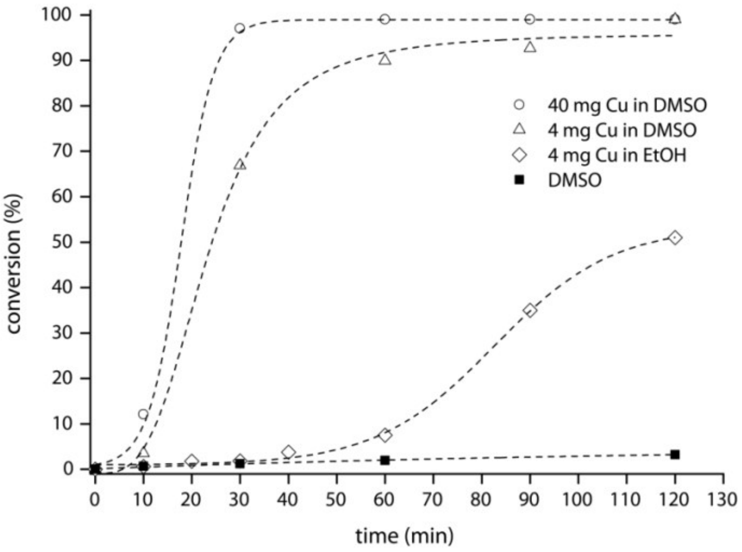
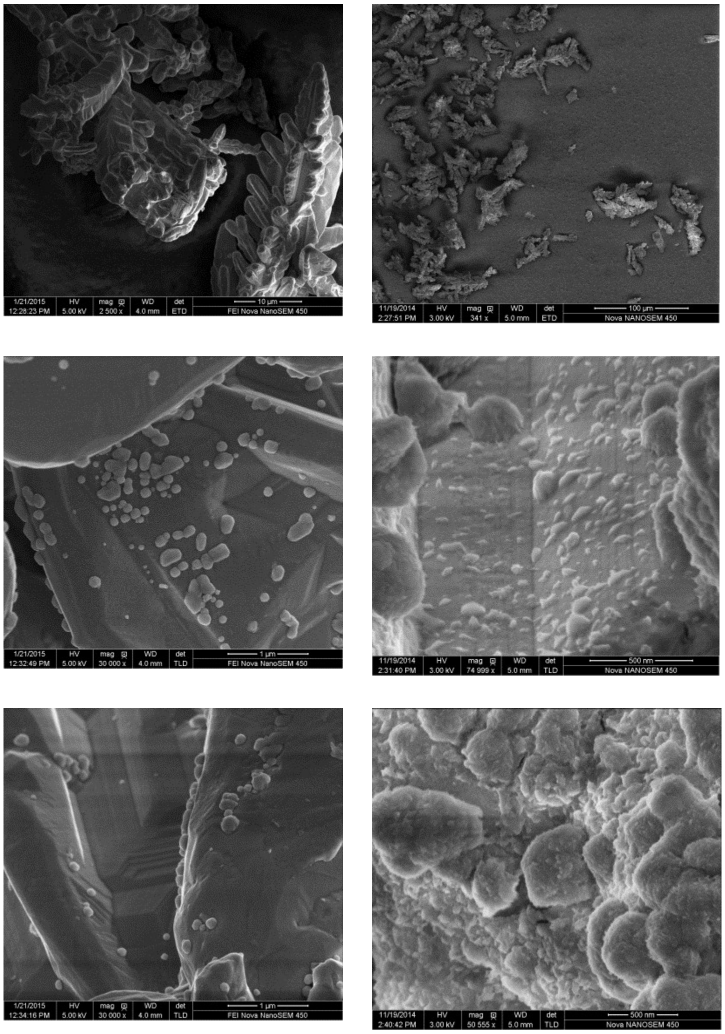
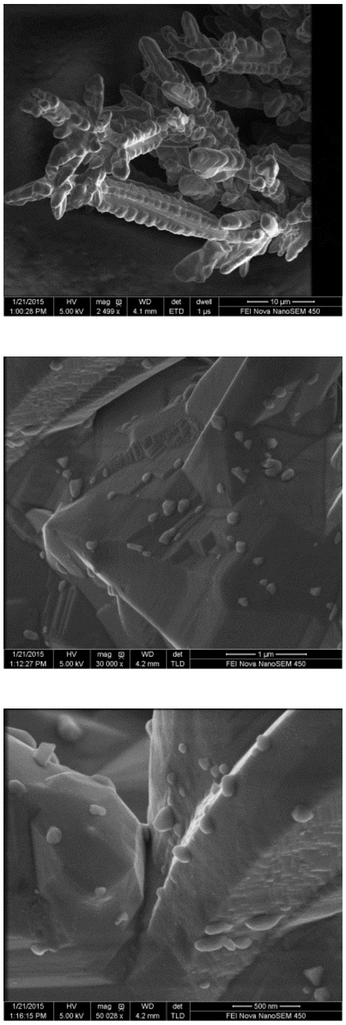


Figure 3. Knoevenagel condensation of benzaldehyde (0.2 mmol) and ethyl cyanoacetate (0.1 mmol) with dendritic copper powder at 56 °C. Nearly linear conversion with Ethanol, zero order kinetics fit.

5. SEM micrographs





Untreated Cu(0) powder

Cu(0) after catalysis (washed)

Cu(0) after 16 h at 56°C in EtOH

Figure 4. SEM micrographs showing Cu(0) powder at different stages of the catalysis.

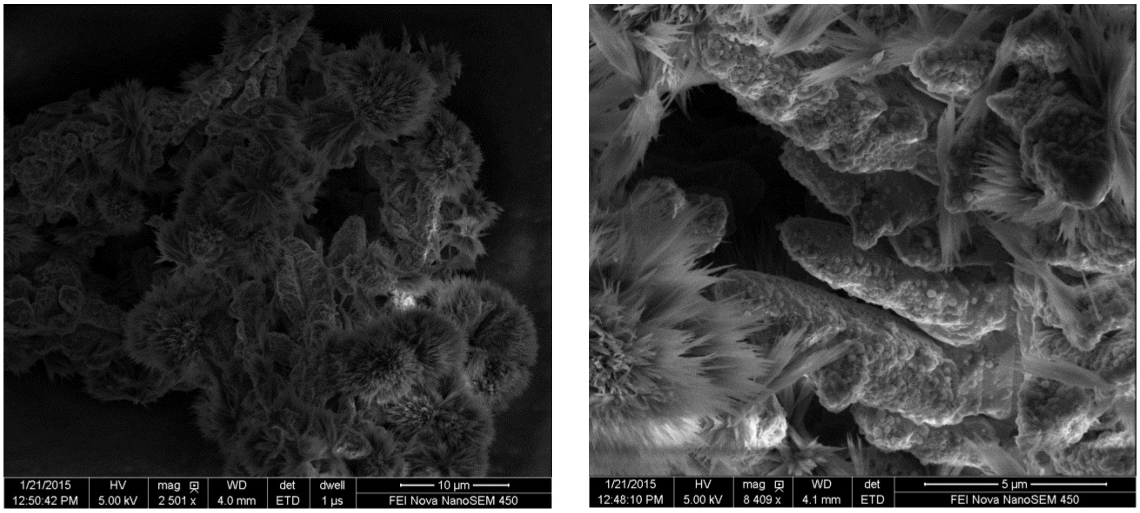


Figure 5. Cu(0) powder after catalysis in cold ethanol: product crystal formation visible on copper surface

6. Scale up documentation

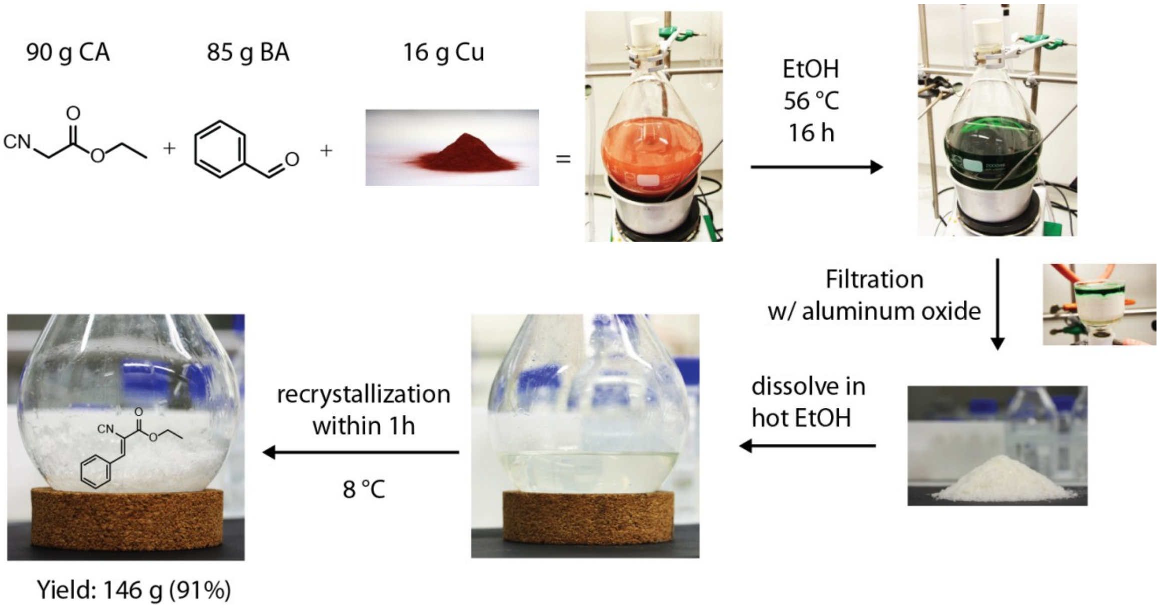


Figure 6. Scale up experiment: Knoevenagel condensation of benzaldehyde (81.2 mL, 0.8 mol) and ethyl cyanoacetate (84.8 mL, 0.8 mol) in 1000 mL EtOH with 16 g copper catalyst . Yield after recrystallization : 146 g (91 %).

7. XRD Measurement

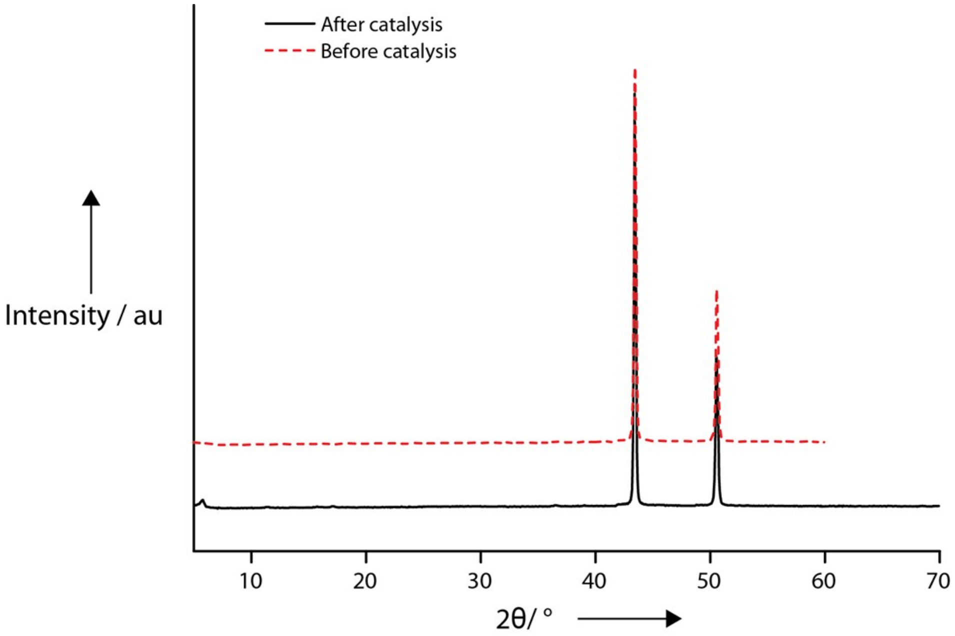
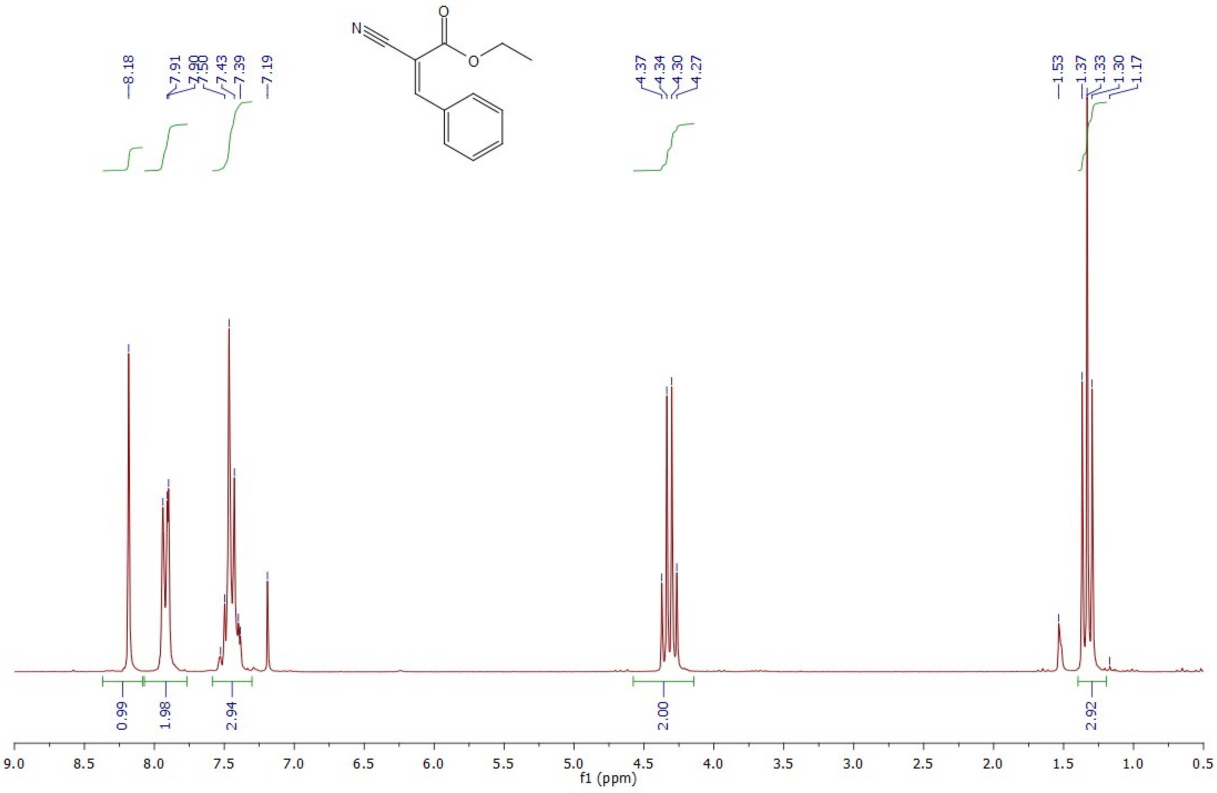


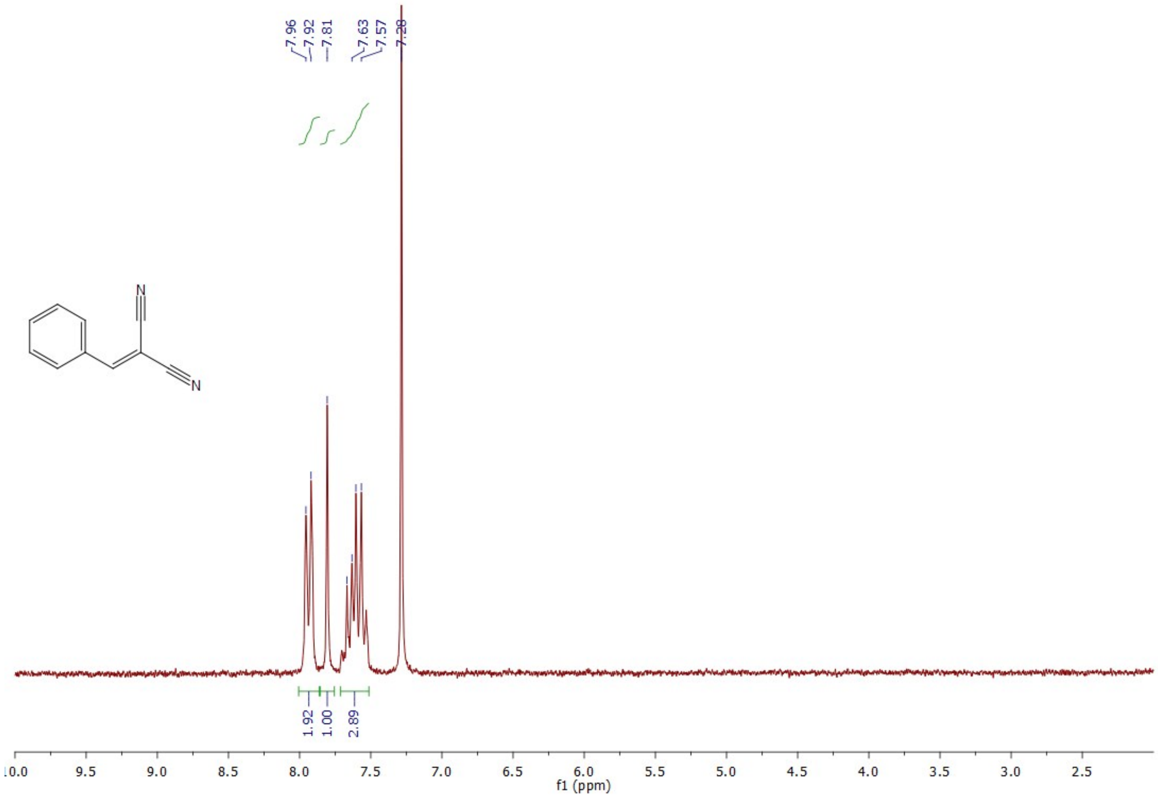
Figure 7. XRD measurement of the Cu powder used in the scale up experiment before (red, dashed line) and after (black, solid line).

8. NMR spectra

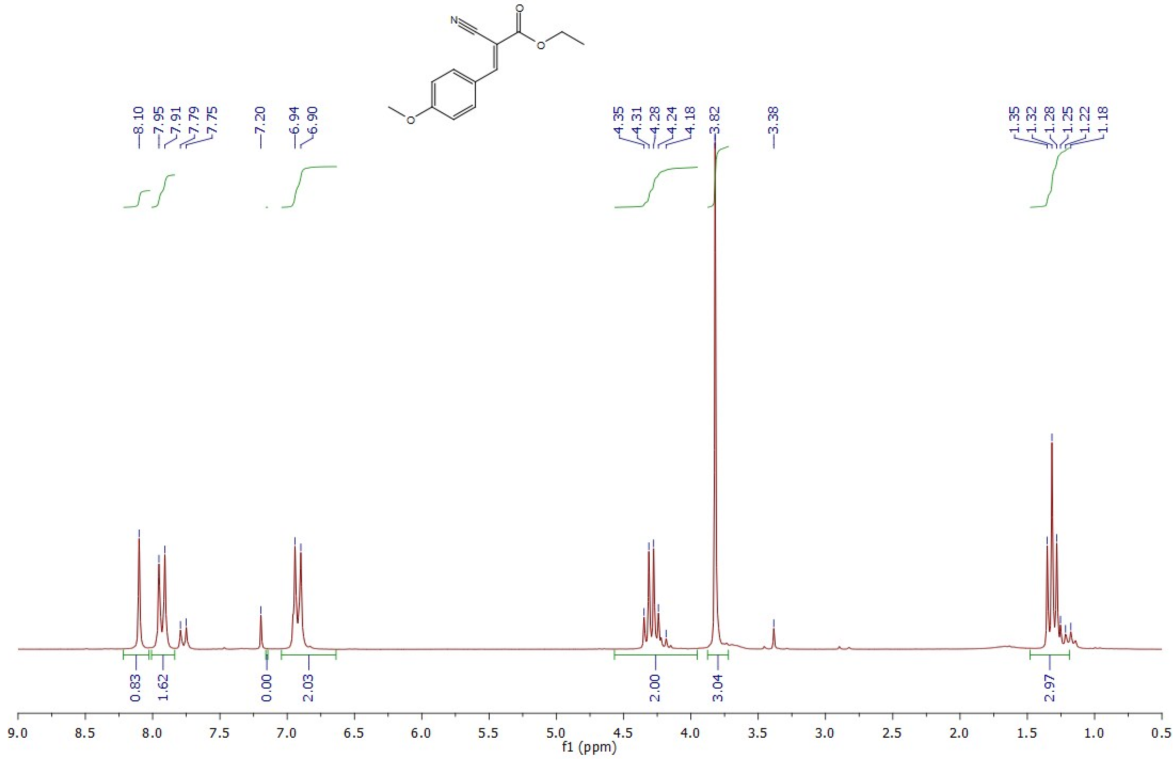
8.1 Ethyl (Z)-2-cyano-3-phenylacrylate in CDCl3



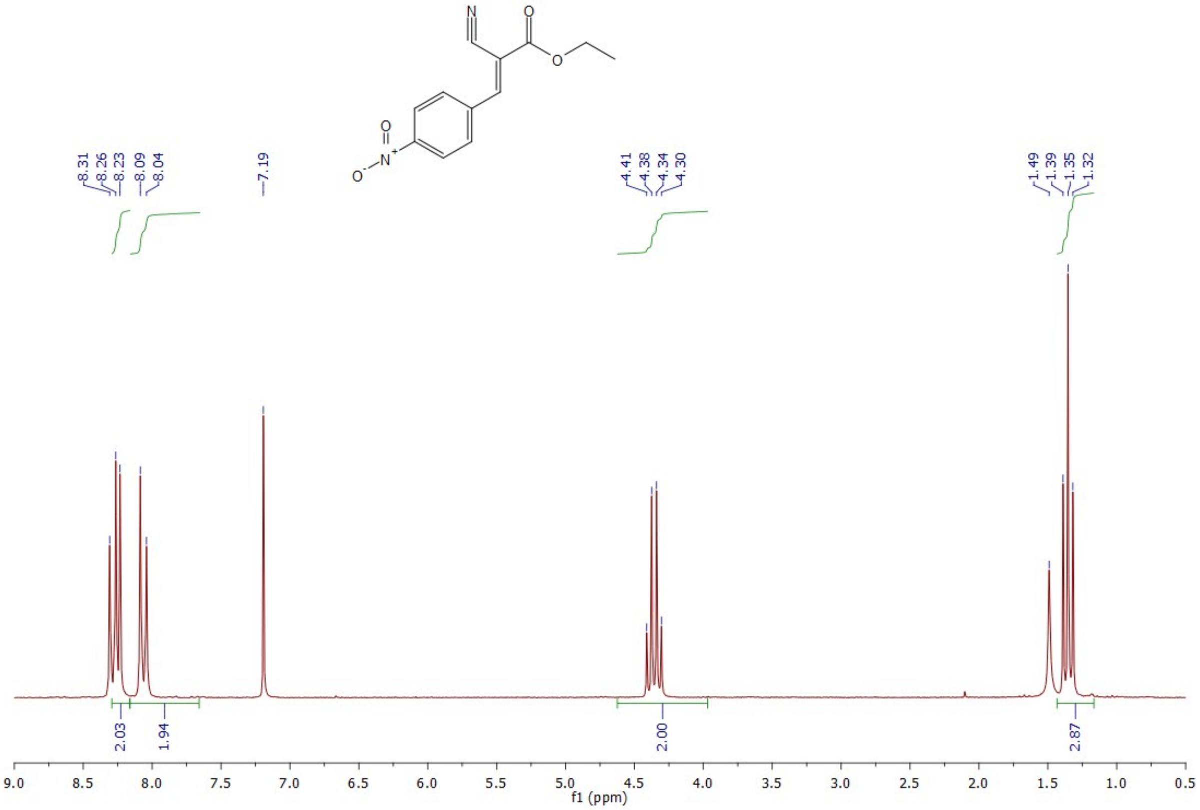
8.2 Benzylidenemalononitrile in $CDCl_3$



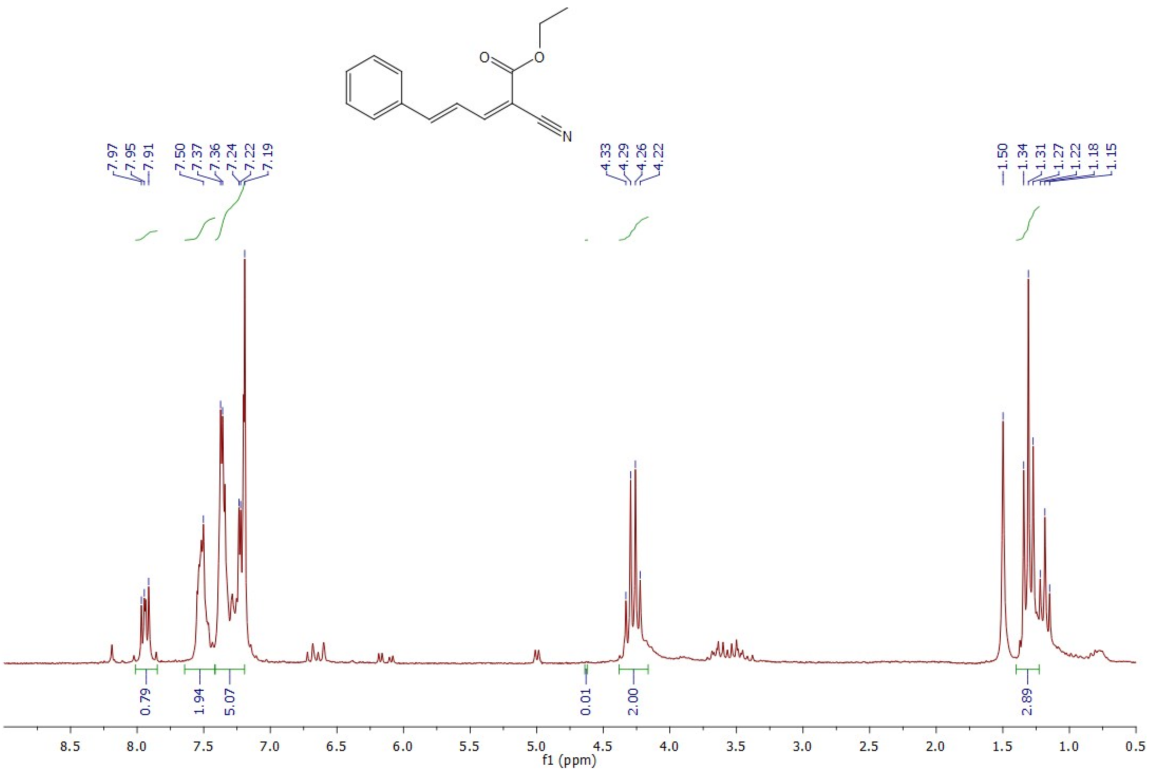
8.3 Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate



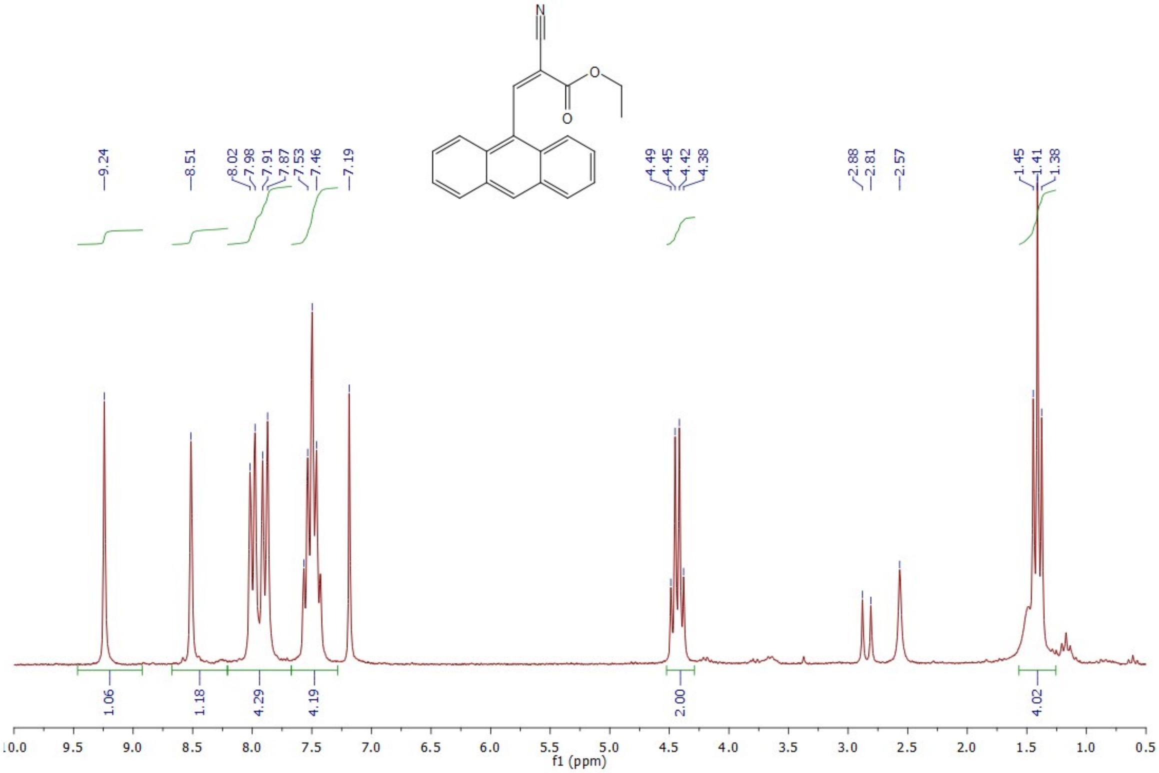
8.4 Ethyl (2-cyano-3-(4-nitrophenyl)acrylate



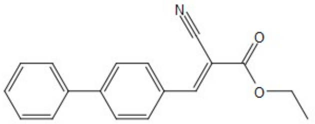
8.5 Ethyl 2-cyano-5-phenylpenta-2,4-dienoate

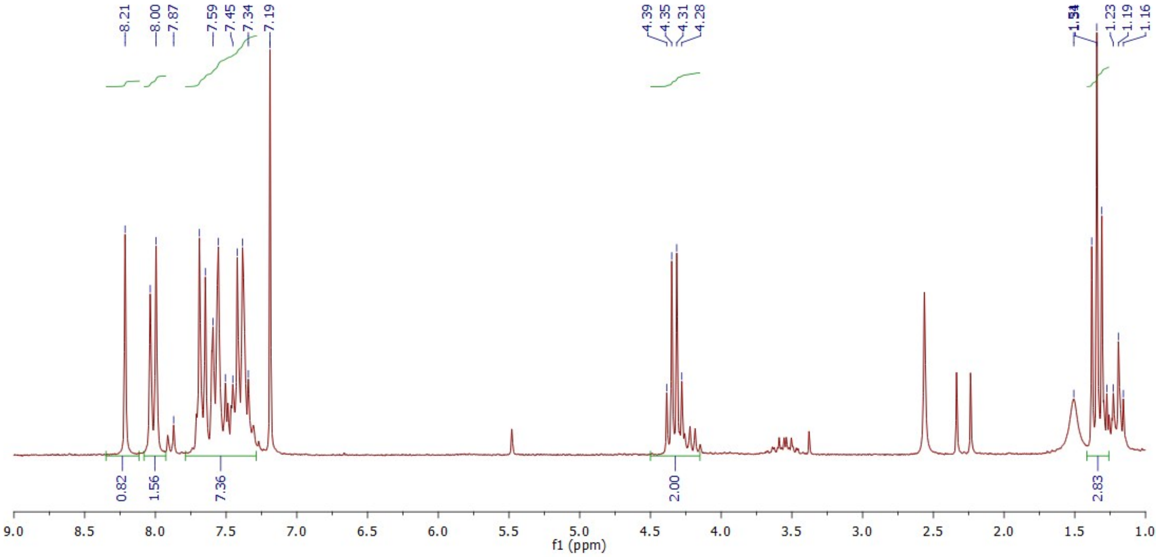


8.6 Ethyl 3-(anthracen-9-yl)-2-cyanoacrylate

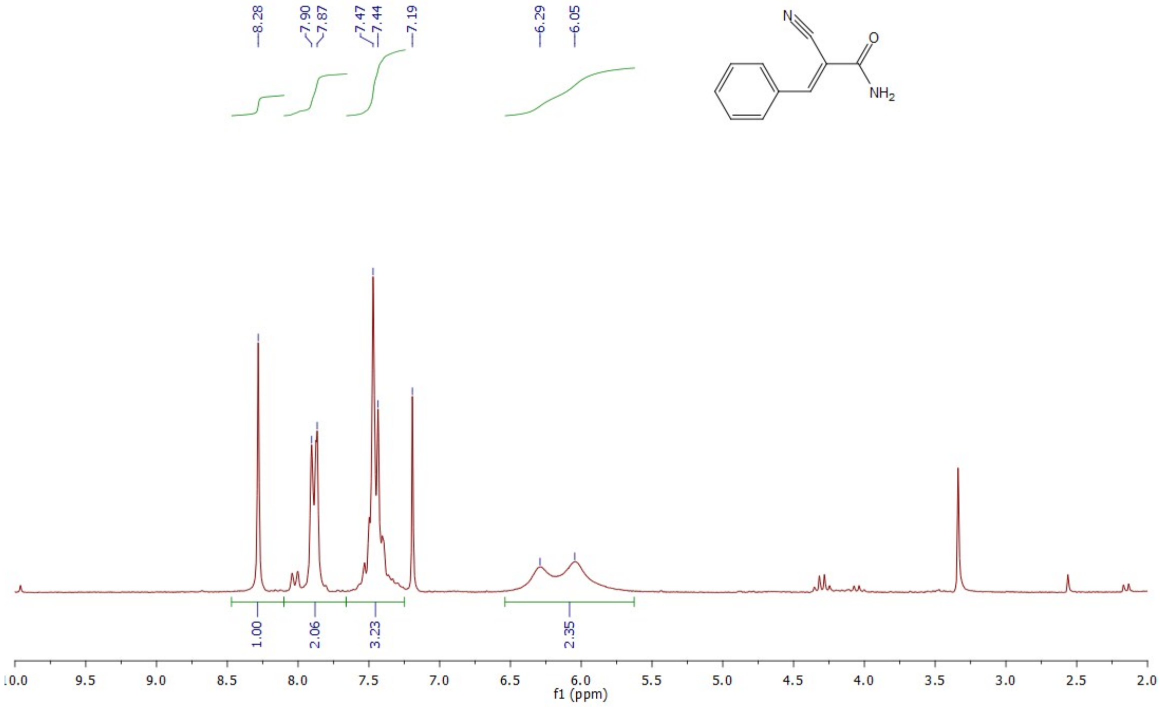


8.7 Ethyl 3-([1,1'-biphenyl]-4-yl)-2-cyanoacrylate

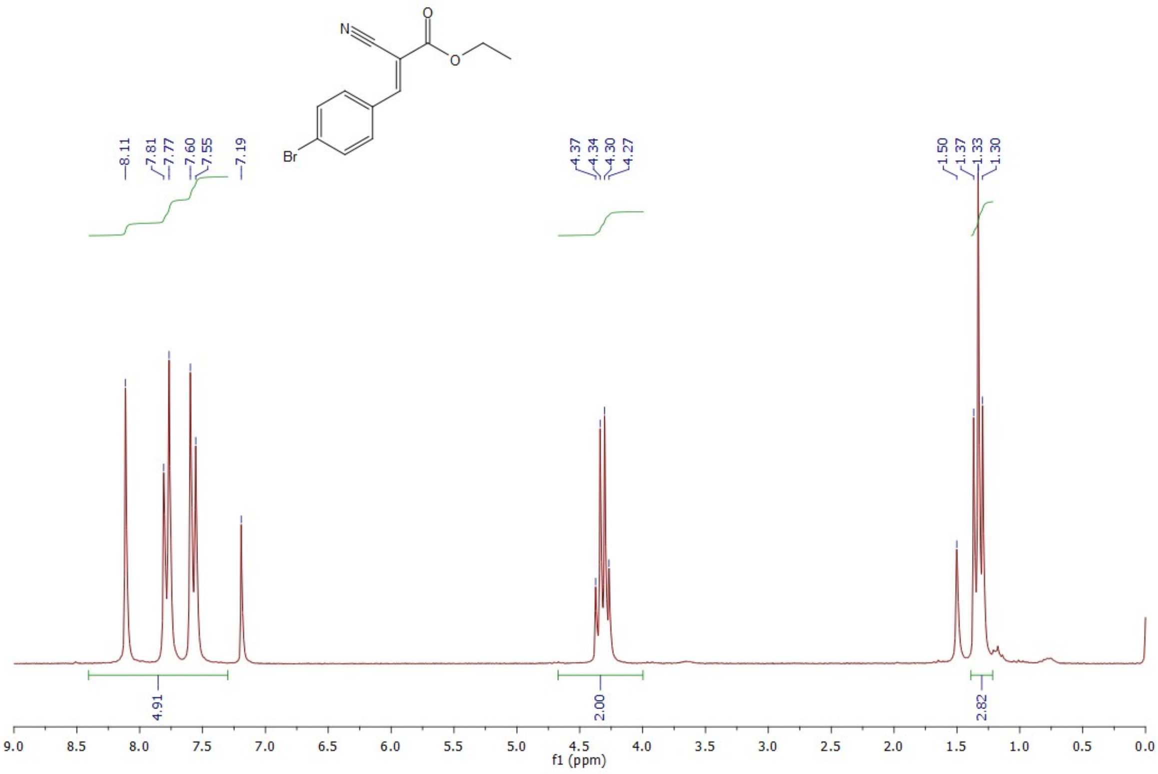




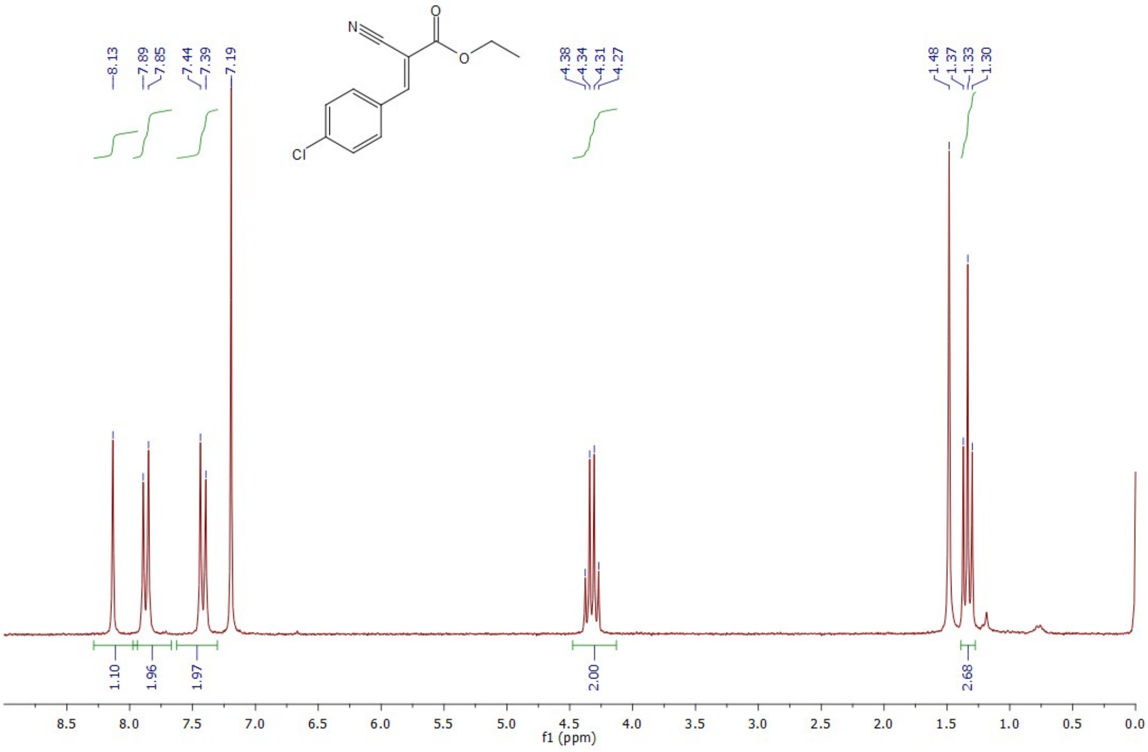
8.8. 2-cyano-3-phenylacrylamide



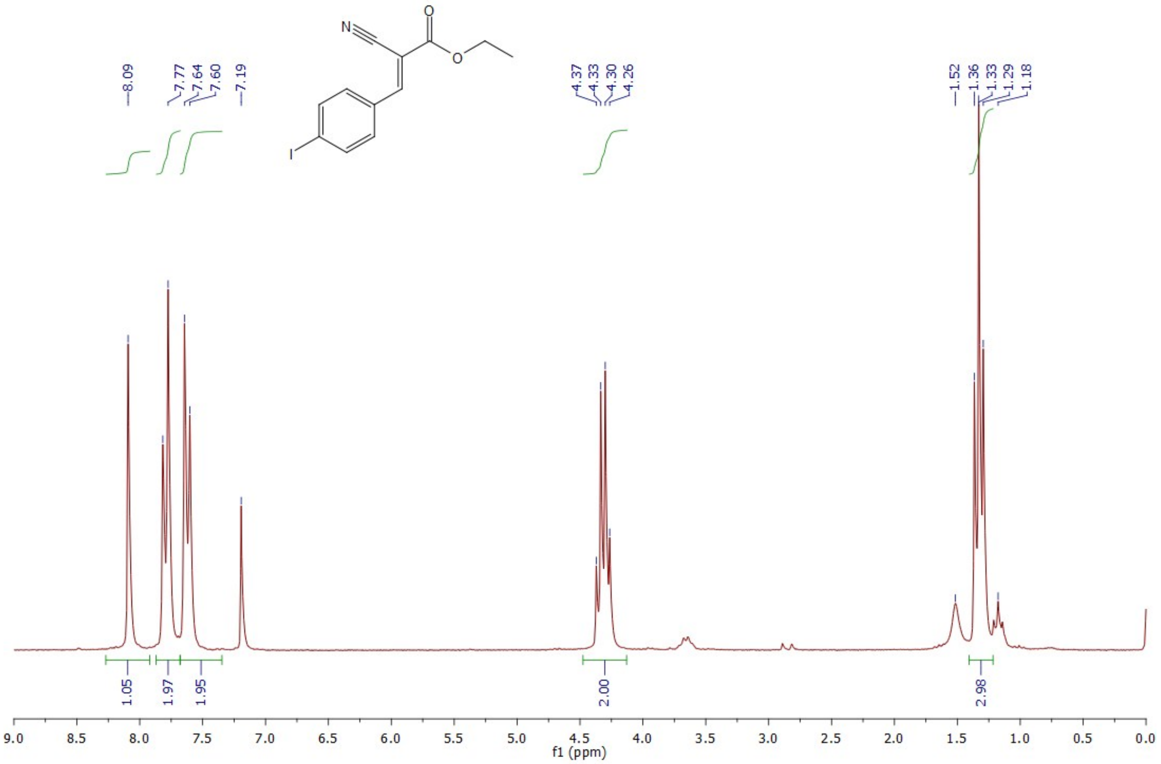
8.9. ethyl-3-(4-bromophenyl)-2-cyanoacrylate



8.10. ethyl-3-(4-chlorophenyl)-2-cyanoacrylate



8.11 ethyl-3-(4-iodophenyl)-2-cyanoacrylate



8.12 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one)