Malononitrile as Acylanion Equivalent

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Abstract: The oxidation of derivatives of malononitrile with peracid in methanol proceeds with loss of the cyano groups to yield methyl esters in high yield. The method was applied to a variety of malononitrile derivatives, some of which were prepared by Pd- or Ir-catalyzed asymmetric allylic substitution.

Key words: oxidations, cyanohydrins, allylations, iridium, asymmetric catalyses, Michael additions

Over the last few years, the Ir-catalyzed asymmetric allylic alkylation with stabilized carbanions has become a highly developed, reliable method. However, the range of C-nucleophiles is limited to malonic acid derivatives and β-ketoesters.[1] For further development it was desirable to implement C_1-nucleophiles, in particular acylanion equivalents,[2] in order to make vinyl-substituted α-stereogenic carboxylic acid derivatives accessible. Attempts with cyanide and nitromethane were not successful in our hands.

For Pd-catalyzed allylic substitutions several acylanion equivalents have been used successfully: phenylsulfonylmethylennitronate,[3] α-acetoxymalonate,[4] α-acetoxy- and silyloxymalononitrile (MAC reagents),[5] which gave methyl esters after methanolysis (Figure 1). Unfortunately, the requisite reagents are poorly available or the subsequent transformations are cumbersome.

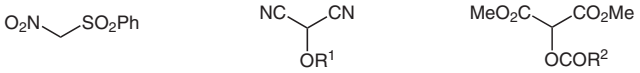
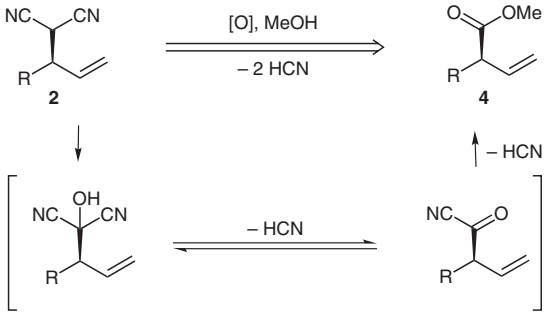


Figure 1 Important acylanion equivalents (R^1 = Ac, $SiMe_2t$-Bu)

Inspired by Nemoto's MAC reagents, we have now developed a new method, which solely requires readily available reagents (Scheme 1). The broadly applicable malononitrile is used as pronucleophile, which has proven useful, for example in allylic substitutions.[6] It was essential to find a method for oxidation of the malononitrile derivative yielding the corresponding cyanohydrin, which would decompose to the acyl cyanide to be transformed into a carboxylic acid derivative. Furthermore, epoxidation and migration of the double bond as well as racemization had to be avoided.

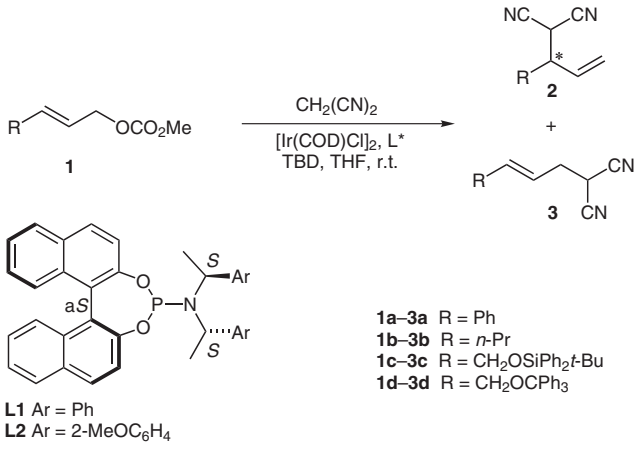
Oxidation of malononitrile derivatives has been reported twice. Patai and Dayagi oxidized α-tritylmalononitrile with aqueous H_2O_2–NaOH to give the corresponding carboxylic acid; the yield was not stated.[7] De et al. oxidized a heterocyclic malononitrile derivative with aqueous $KMnO_4$ under basic conditions to give a carboxylic acid in moderate yield.[8] Both procedures were unsuited for our purpose.



Scheme 1 Oxidative degradation of malononitrile derivatives

We prepared a series of the requisite malononitrile derivatives by Ir-catalyzed allylic alkylation with malononitrile under salt-free conditions (Scheme 2, Table 1).[6]

Malononitrile derivative **2c** ($R = CH_2OSiPh_2t$-Bu) was used as a test compound for the development of the oxidative degradation method. Initially, autoxidation of **2c** was attempted, using $CeCl_3$ or $Mn(OAc)_2$ as catalysts, which are successful with β-keto esters.[10] The product was isolated in only 16% yield (Table 2, entries 1 and 2). Then the combination H_2O_2 and Cs_2CO_3 was tested. The reaction was fast, however, the yield was low (entry 3). With t-BuO_2H as oxidant, side products were formed and the yield of the desired product was only 13% (entry 4).



Scheme 2 Iridium-catalyzed allylic alkylation with malononitrile as pronucleophile {TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene}

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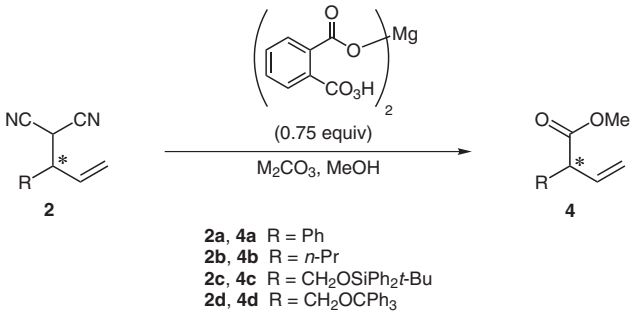
Table 1 Iridium-Catalyzed Allylic Alkylation with Malononitrile According to Scheme 2

Entry	Substrate	L*	Time (h)	Yield (%)[a]	Ratio **2**/**3**[b]	ee (%)[c]
1[d,e]	**1a**	**L1**	4	80	96:4	96
2[e]	**1a**	**L2**	3	87	97:3	98
3	**1b**	**L1**	10	73	87:13	96
4	**1b**	**L2**	2	89	90:10	96
5[f]	**1c**	**L1**	15	77	84:16	98
6[f]	**1c**	**L2**	5	70	73:27	96
7	**1d**	**L1**	24	68	89:11	97
8	**1d**	**L2**	5	78	89:11	94

[a] Isolated yield of **2a**, **3a** and **2b**, **3b** and isolated yield of **2c** and **2d**.
[b] Determined by ^{1}H NMR or GC of the crude products.
[c] Determined by HPLC or GC with chiral columns.[9]
[d] Reaction at 40 °C.
[e] Traces of the diallylation product were detected.
[f] These results were already reported and are given here for comparison.[6]

Despite of the possibility of epoxidation of the double bond of **2c**, percarboxylates were tested as oxidation agents. Complete conversion was obtained with MCPBA and Cs_2CO_3 at –20 °C in MeOH after three hours, and the methyl ester **4c** was isolated in 87% yield (Table 2, entry 5). Epoxidation products were not detected, but at temperatures higher than 0 °C isomerization of the double bond occurred yielding α,β-unsaturated methyl esters. This was not the case with Li_2CO_3 as base, although the reaction rate was only sufficient above 0 °C. Decrease of the enantiomeric excess, another problem, was negligable (0–2%). However, purification of the product was difficult because of the formation of methyl *m*-chlorobenzoate as side product. Therefore, peracetic acid, which was prepared in situ,



Scheme 3 Oxidative degradation of chiral malononitrile derivatives

was tested (Table 2, entry 6). With **2c** complete conversion was obtained at 0 °C after three hours, but the isolated yield was lower (62%) than that obtained with MCPBA.

Finally, the best results were achieved with magnesium monoperoxyphthalate as oxidant (Table 2, entry 7, Scheme 3). This oxidation agent is commercially available, and workup was very easy. Under the optimized conditions,[11] tests with other malononitrile derivatives (**2a**,**b**,**d**) also gave excellent results (Table 3).

Further malononitrile derivatives were probed in order to assess the scope of the new procedure. The simple compounds **5** and **7** were prepared via alkylation of malononitrile. The oxidative degradation gave the methyl esters **6** and **8** in high yield. Furthermore, the malononitrile derivative **9**, which was prepared via Pd-catalyzed asymmetric allylic alkylation, was transformed into the methyl carboxylate **10**. Again, neither racemization nor double-bond migration were observed.

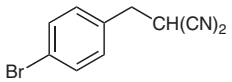
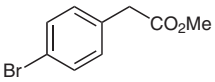
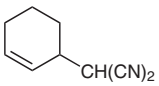
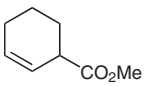
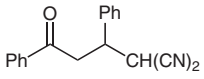
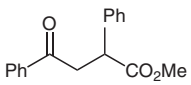
Another possibility to generate malononitrile derivatives is the 1,4-addition of enolates to 1,1-dicyanoethylenes, which are strong Michael acceptors. We have prepared racemic **11** by reaction of acetophenone with 2-benzylidenemalononitrile. The transformation into the γ-oxomethyl carboxylate **12** proceeded in 75% yield.

Table 2 Oxidation of **2c** under Various Conditions

Entry	Conditions	Time (h)	Temp (°C)	Comment	Yield (%)[a]
1	$CeCl_3$ (10 mol%), NaOMe (2 equiv), O_2 (1 atm), MeOH	240	r.t.	Slow reaction; removal of the protecting group	16
2	$Mn(OAc)_2$ (20 mol%), NaOMe (2 equiv), O_2 (1 atm), MeOH	0.1	r.t.	Decomposition	0
3	Cs_2CO_3 (1 equiv), H_2O_2 (1.2 equiv), MeOH	2.5	–20	Side products (not isolated)	39
4	Cs_2CO_3 (1 equiv), *t*-BuO_2H (1.3 equiv), MeOH	3	–20	Side products (not isolated)	13
5	Cs_2CO_3 (1.05 equiv), MCPBA (1.5 equiv), MeOH	3	–20	Formation of 3-$ClC_6H_4CO_2Me$[b]	87
6	Li_2CO_3 (1.5 equiv), $MeCO_3H$ (1.5 equiv), MeOH	3	0	Side products (not isolated)	62
7	Cs_2CO_3 (1.1 equiv), $Mg[o\text{-}(CO_2)C_6H_4CO_3H]_2$ (0.75 equiv), MeOH	3	–20	–	81

[a] Isolated yield.
[b] Removal of methyl *m*-chlorobenzoate required extensive column chromatography.

Table 3 Results of the Oxidative Degradation of Malononitrile Derivatives According to Scheme 3

Entry	Educt	Product	M[a]	Time (h)	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**2a**	**4a**	Cs	1.5	–20	80	98
2	**2b**	**4b**	Li	2	0	76	94.5
3	**2c**	**4c**	Cs	3	–20	81	96
4	**2d**	**4d**	Li	3	0	50	97
5	*n*-HeptCH(CN)$_2$	*n*-HeptCO$_2$Me	Li	3.5	0	81	–
	5	**6**					
6			Cs[d]	2	–20	84	–
	7	**8**					
7			Li	3	0	86	78
	9	**10**					
8			Li	3	0	75	0
	11	**12**					

[a] Cs_2CO_3 (1.1 equiv), Li_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Determined by HPLC or GC with chiral columns.
The Δee-value [ee(substrate) – ee(product)] was also determined: entry 2 Δee = 1.5%; entry 3 Δee = 2%; in all the other cases Δee = 0.[12]
[d] Cs_2CO_3 (1.5 equiv).

In conclusion, we have developed a versatile and convenient method for oxidation of malononitrile derivatives to give esters as degradation products under very mild conditions. Thus, we have established malononitrile as an acylanion equivalent.

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References and Notes

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(9) GC: Chiraldex γ-Trifluoracetyl (G-TA), 30 m × 0.25 mm × 0.125 μm; injector temperature: 200 °C, detector temperature: 250 °C; **2a** (column temperature: 140 °C, isothermal): t_R (–)-(*S*)-**2a** = 27 min, t_R (+)-(*R*)-**2a** = 28 min; **2b** (column temperature: 100 °C, isothermal), t_R (+)-(*S*)-**2b** = 25 min, t_R (–)-(*R*)-**2b** = 26 min.
HPLC: Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm, with precolumn 10 × 4 mm, 5 μm; **2c** [*n*-hexane–*i*-PrOH (99:1), flow = 0.5 mL min^{-1}, 20 °C, 210 nm], t_R (–)-(*S*)-**2c** = 18 min, t_R (+)-(*R*)-**2c** = 22 min; **2d** (*n*-hexane–*i*-PrOH (95:5), 20 °C, 220 nm, t_R (–)-(*S*)-**2d** = 20 min, t_R (+)-(*R*)-**2d** = 28 min.
(10) (a) Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668. (b) Werner, T.; Christoffers, J. *Synlett* **2002**, 119.
(11) **General Procedure for the Oxidative Degradation**
Magnesium monoperoxyphthalate hexahydrate (0.75 equiv, 80% technical grade from Sigma Aldrich, used as received) was added in small portions to a suspension of the substrate and M_2CO_3 (1.1 equiv/1.5 equiv) in MeOH (*c* 0.15 M) at the given temperature. The mixture was stirred for the given time and was then filtered through a short column of SiO_2, which was washed with PE–EtOAc. The solvent was

evaporated in vacuo, and the crude product was purified by bulb-to-bulb distillation or recrystallization.

(12) (a) The ester **4b** was treated with PhMgBr to give 1,1-diphenyl-2-propylbut-3-en-1-ol (**4b′**). Similarly, **10** was reacted with PhMgBr to produce cyclohex-2-en-1-yl-(diphenyl)methanol (**10′**), a known compound, see ref. 12b. GC: Chiraldex γ-Trifluoracetyl (G-TA), 30 m × 0.25 mm × 0.125 μm; injector temperature: 200 °C, detector temperature: 250 °C; **4a** (column temperature: 100 °C, isothermal), t_R (+)-(*S*)-**4a** = 24 min, t_R (–)-(*R*)-**4a** = 25 min; **9** (column temperature: 140 °C, isothermal), t_R (–)-**9** = 12 min, t_R (+)-**9** = 13 min. HPLC: Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm, with precolumn 10 × 4 mm, 5 μm; **4b′** [*n*-hexane–*i*-PrOH (99:1), flow = 0.5 mL min^{-1}, 20 °C, 210 nm], t_R (–)-(*S*)-**4b′** = 15 min, t_R (+)-(*R*)-**4b′** = 16 min); **4c** [*n*-hexane–*i*-PrOH (99.7:0.3), flow = 0.5 mL min^{-1}, 20 °C, 210 nm], t_R (+)-(*S*)-**4c** = 12 min, t_R (–)-(*R*)-**4c** = 14 min; Daicel Chiralcel AD-H, 250 × 4.6 mm, 5 μm, with precolumn 10 × 4 mm, 5 μm; **4d** [*n*-hexane–*i*-PrOH (99.4:0.6), flow = 0.5 mL min^{-1}, 20 °C, 210 nm), t_R (–)-(*R*)-**4d** = 22 min, t_R (+)-(*S*)-**4d** = 29 min; **10′** [*n*-hexane–*i*-PrOH (98:2), flow = 0.5 mL min^{-1}, 20 °C, 210 nm), t_R (+)-**10′** = 20 min, t_R (–)-**10′** = 22 min. (b) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587.