Iron(iii) catalysis of the Michael reaction of 1,3-dicarbonyl compounds and enones

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Iron(III) chloride hexahydrate catalyses the Michael reaction of β-dicarbonyl compounds and enones under mild and neutral conditions with excellent yields and product selectivity.

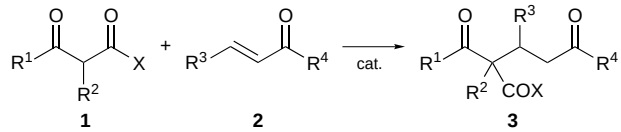
The reaction of enolates with α,β-unsaturated carbonyl compounds (Michael reaction) is a fundamental C–C bond forming methodology, which classically is a high yielding base catalysed process, and can even be performed with high stereoselection.[1] However, there are some disadvantages of base catalysis, *e.g.* incompatibility with base sensitive or acidic functionalities, ester solvolysis, reverse and other side reactions. In these terms it seems interesting that the Michael reaction is known to be catalysed under neutral conditions by transition metal compounds, in particular by Group VIII 1,3-dionato complexes.[2] Also, some lanthanide catalysts have been reported to be efficient under neutral and mild conditions.[3]

Although the strong tendency of Fe^{III} to form 1,3-dionato complexes is well known,[4] catalysis of the Michael reaction by $FeCl_3·6H_2O$ has not yet been reported to the best of our knowledge,† despite the fact that in terms of economical and ecological considerations iron should be the transition metal of choice.

Iron(iii) chloride hexahydrate is an extraordinarily efficient catalyst for the Michael reaction shown in Scheme 1. We have been investigating the catalytic activity of several transition metal halides on the reaction of **1a** with **2a**, and some did show activity, but only with $FeCl_3·6H_2O$ did we observe complete conversion at room temperature. For about the first 30% conversion the turn over number was *ca*. 2 min^{-1}, and using 1 mol% Fe^{III} the reaction was quantitative within 3 h. It has to be pointed out that as the product and starting materials are liquid at room temp. and no solvents needed to be used, and since no side reactions have been observed, workup is very simple: filtration using a small column of silica gel removes all iron-containing materials.

The best results were obtained with cyclic ketoesters and methyl vinyl ketone (**2a**; products **3a**, **b**,‡ **d**, **e**§). With only 1 mol% $FeCl_3·6H_2O$ full conversion within a few hours is observed, even if bulkier ester functions are present (**3b**). Although starting from a methyl ester **1e**, some hydrolysis and subsequent decarboxylation reactions, presumably resulting from hydrate water, are noticed. This is negligible if 1 mol% Fe^{III} is applied, but with 5 mol% yield drops significantly to 72%. Using β-diketones or other species other than cyclic ketoesters, conversion is a little slower, but with 5 mol% catalyst results are still satisfying (in Table 1 some optimized examples are listed).

While Fe^{III} catalysis seems to be effective with **2a**, some restrictions have to be made in the use of other enones: although even bulkier *E*-enones like **2b** or **2c** form Michael products (the higher reaction temperature might be due to steric effects; solvent had to be applied in these cases), no reaction was observed with enones with a *Z*-substituent like cyclopentenone or mesityl oxide. This might give some insight into a possible mechanism of the Fe^{III} catalysis (actually, chloride does not play a role, because the same results have been observed using



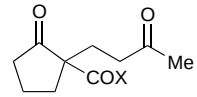
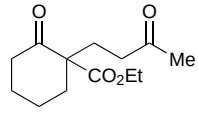
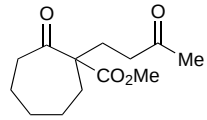
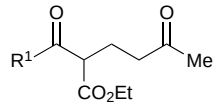
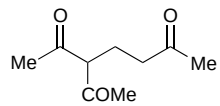
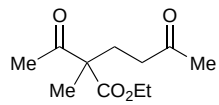
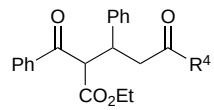
1 **2** **3**

1a X = OEt, R^1, R^2 = –$(CH_2)_3$–
b X = OBu^i, R^1, R^2 = –$(CH_2)_3$–
c X = Me, R^1, R^2 = –$(CH_2)_3$–
d X = OEt, R^1, R^2 = –$(CH_2)_4$–
e X = OMe, R^1, R^2 = –$(CH_2)_5$–
f X = OEt, R^1 = Me, R^2 = H
g X = OEt, R^1 = Ph, R^2 = H
h X = Me, R^1 = Me, R^2 = H
i X = OEt, R^1 = R^2 = Me

2a R^3 = H, R^4 = Me
b R^3 = Ph, R^4 = Me
c R^3 = R^4 = Ph

Scheme 1 Iron(iii) catalysed Michael reactions, (cat. = $FeCl_3·6H_2O$).

Table 1 Reaction of **1** and **2** to give **3**

Product			Conditions[a]	Yield (%)[b]
	X = OEt	**3a**	1, room temp.	97
	X = OBu^i	**3b**	1, toom temp.	95
	X = Me	**3c**	5, room temp.	86
		**3d**	1, room temp.	94
		**3e**	1, room temp.	91[c]
	R^1 = Me	**3f**	5, room temp.	90
	R^1 = Ph	**3g**	5, room temp.	87
		**3h**	5, room temp.	77[d]
		**3i**	5, room temp.	78
	R^4 = Me	**3j**	5, 50[e]	84[f]
	R^4 = Ph	**3k**	5, 50[e]	90[f]

[a] Mol% $FeCl_3·6H_2O$, reaction temp./°C, no solvent. [b] Isolated yields. [c] Use of 5 mol% catalyst resulted in 72% yield. [d] Chromatographic separation from byproducts was necessary. [e] Solvent ($CHCl_3$) was used. [f] Isolated as a mixture of two diastereoisomers.

Fe^{III} nitrate or sulfate). Starting from a diketonato complex **4**, in which the ligand is planar and particularly stabilized by π-delocalization, the enone **2** is proposed to coordinate in a vacant coordination site to form species **5** (Scheme 2). Subsequently, the central carbon centre of the dionato ligand is thought to be alkylated by the coordinated enone, but only if the enone is in the S-*cis* conformation, which is obviously impossible for cyclopentenone and strongly disfavoured in mesityl oxide. In complex **6**, the central carbon centre of the dione ligand is tetrahedral, thus π-delocalization is impossible, and the compound is destabilized. Product **3** is liberated and complex **4** reformed *via* ligand exchange. All together, Fe^{III} catalysis of the Michael reaction seems to show a classic template effect,[6] where both reactants are coordinated at the same time and activated by a metal centre. And in fact $Fe(acac)_3$, which offers no vacant coordination site to an enone, does not catalyse the Michael reaction at all, that means a dionato ligand like acac can not be alkylated by non-coordinated **2a**, which was proved by a stoichiometric experiment. Also, it was impossible to achieve bis-substitution by converting, *e.g*. **3g** with **2a**, at even higher temperatures. This fits into the outlined picture of the mechanism, if we assume that the oxobutyl side chain of **3g** is donating itself to the centre metal and blocking a possibly vacant coordination site.

In summary, catalysis of the Michael reaction of β-dicarbonyl compounds and enone by $FeCl_3 \cdot 6H_2O$ is a very effective alternative to the classic base catalysis. The selectivity of this method is excellent in most cases, reaction conditions are mild and neutral, and performance is reasonably easy (no anhydrous or inert conditions, simple workup procedure), although it seems not to be appliable for enones bearing a *Z*-substituent.

Supplementary Information containing experimental details and characterization data for **3a**–**k** is available from the author on request.

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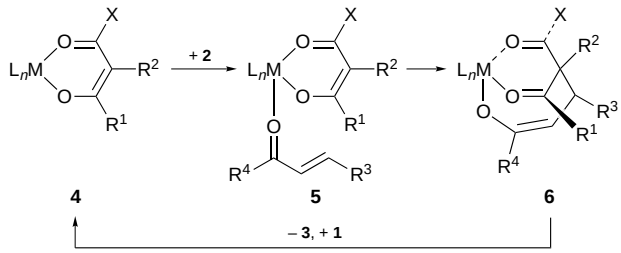

Scheme 2 Proposed mechanism for the iron(iii) catalysed Michael reaction

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Footnotes

† In one case the application of a combination of $Ni(acac)_2$ and $FeCl_3$ was reported, but the authors ascribe the role of Fe^{III} to be a Lewis acid (activation of the enone).[5]

‡ *2-(3-Oxobutyl)cyclopentanone-2-carboxylic acid 2-methylpropyl ester* (**3b**): A mixture of oxo ester **1b** (1.03 g, 5.60 mmol), enone **2a** (0.500 ml, 6.00 mmol), and $FeCl_3 \cdot 6H_2O$ (15 mg, 0.055 mmol) was stirred overnight at room temp., then chromatographed on silica gel [hexane–methyl *tert*-butyl ether (MTB) 1 : 5, R_f = 0.45] to afford 1.35 g (5.32 mmol, 95%) of **3b** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.84–2.15 (m, 6 H, CH, CH_2), 2.13 (s, 3 H, CH_3), 2.25–2.52 (4 H, CH_2), 2.70 (ddd, *J* = 18, *J* = 9.1, *J* = 6.2 Hz, 1 H, CH*H*), 3.84–3.92 (m, 2 H, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.72 (2 CH_3), 19.37 (CH_2), 26.79 (CH_2), 27.47 (CH), 29.62 (CH_3), 34.08 (CH_2), 38.62 (CH_2), 58.73 (C), 71.08 (OCH_2), 171.13 (C=O), 207.38 (C=O), 214.42 (C=O).

§ *2-(3-Oxobutyl)cycloheptanone-2-carboxylic acid methyl ester* (**3e**): A mixture of oxo ester **1e** (929 mg, 5.46 mmol), enone **2a** (0.500 ml, 6.00 mmol), and $FeCl_3 \cdot 6\ H_2O$ (15 mg, 0.055 mmol) was stirred overnight at room temp., then chromatographed on silica gel (hexane–MTB 1 : 5, R_f = 0.45) to give 1.20 g (4.99 mmol, 91%) of **3e** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.55 (m, 2 H, CH_2), 1.58–1.75 (m, 5 H, CH_2), 1.79–1.92 (m, 1 H, CH*H*), 1.88 (ddd, *J* = 14, *J* = 10, *J* = 5.6 Hz, 1 H, C*H*H), 2.10 (s, 3 H, CH_3), 2.15 (ddd, *J* = 14, *J* = 10, *J* = 5.6 Hz, 1 H, CH*H*), 2.39 (ddd, *J* = 18, *J* = 10, *J* = 5.6 Hz, 1 H; C*H*H), 2.45–2.65 (m, 3 H, CH_2), 3.70 (s, 3 H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.49 (CH_2), 24.99 (CH_2), 28.82 (CH_2), 29.34 (CH_2), 29.38 (CH_3), 33.48 (CH_2), 38.57 (CH_2), 41.68 (CH_2), 51.69 (OCH_3), 61.32 (C), 172.39 (C=O), 206.99 (C=O), 208.87 (C=O).

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