

TRANSITION-METAL CATALYSIS IN MICHAEL ADDITION OF β -DICARBONYLS: TUNING OF THE REACTION CONDITIONS*

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Received March 29th, 1988

Accepted May 4th, 1988

Dedicated to the memory of Dr Karel Bláha.

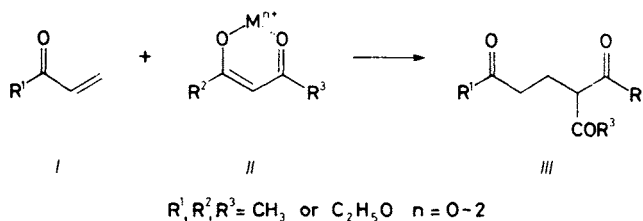
(2,4-Pentanedionato)copper(I), bis(2,4-pentanedionato)copper(II), and tris(2,4-pentanedionato)iron(III) together with boron trifluoride etherate catalyze Michael addition of β -dicarbonyls *V* and *VI* to 2-cyclohexen-1-one (*IV*), 2-cyclopenten-1-one (*IX*), 2-methyl-2-cyclopenten-1-one (*X*), and 3-thienylidenemalonalddehyde (*XIX*).

Carbon-carbon bond formation is of prime importance in synthetic organic chemistry. One of the most efficient tools is the conjugate addition of nucleophiles to activated double bonds (Michael addition, addition of organometallics to α,β -enones, etc.). The classical Michael addition of β -dicarbonyls to α,β -unsaturated ketones catalyzed by strongly basic alkoxides suffers from several drawbacks, namely retro-addition, bis-addition, subsequent condensations and other reactions leading to formation of considerable amounts of by-products in numerous instances¹. Although some of the problems have been circumvented by application of phase-transfer catalysis², it was still desirable to seek novel catalytic systems.

Recently, Nelson and co-workers³ reported on (2,4-pentanedionato)-nickel(II), (acac)₂Ni, catalysis in addition of β -dicarbonyls to 1-buten-3-one (*I*, R = CH₃) and related electrophiles. This reaction proceeds analogously to traditional basic catalysis (Scheme 1) via Ni-chelated species *II* (M = Ni/2)³. Although the addition was fairly smooth with 1-buten-3-one (*I*), in our hands it completely failed with 2-cyclohexen-1-one (*IV*), probably due to the presence of another carbon at β -position that imposes some steric hindrance. In traditional base-catalysis, the β -substituted α,β -unsaturated ketones are also much less prone to act as the Michael acceptors, while α -substitution does not

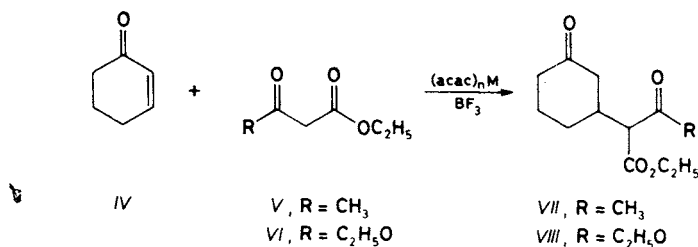
* For preliminary publication see: Kočovský P., Dvořák D.: *Tetrahedron Lett.* 27, 5015 (1986).

matter¹. We speculated that other transition metal complexes might, possibly, be more reactive and catalyze the addition to 2-cyclohexen-1-one. A brief screening of acetylacetonates of a number of transition metals including Fe(III), Co(II), Co(III), Ni(II), Mn(II), Cr(III), Zn(II), Cd(II), VO, and Mg(II) as well as $(C_2H_5O)_3P.CuCl$ and $(C_5H_5N)_4.NiCl_2$ under varying conditions revealed, however, that none of them could induce the addition of ethyl acetoacetate (V) or diethyl malonate (VI) to 2-cyclohexen-1-one (IV).



SCHEME 1

We thus arrived at the conclusion that an electrophilic co-catalysis was needed. It has been known that, for example, the presence of Lewis acids considerably improves organocuprate additions to α,β -unsaturated ketones and that $RCu.BF_3$ react much faster than the ordinary R_2CuLi (refs⁴⁻¹⁰). Hence, we run another screening, now with boron trifluoride etherate as a co-catalyst (Scheme 2). Although $(acac)_2Ni$ and several other acetylacetonates turned out



SCHEME 2

to be nearly or completely ineffective, we could detect the reaction products in some instances.

After much experimentation with wide variety of transition and other metals, solvents, and reaction conditions we were able to achieve fair to good

results particularly with $(\text{acac})_3\text{Fe}^{\text{III}}$, $(\text{acac})_2\text{Cu}^{\text{II}}$, and $(\text{acac})\text{Cu}^{\text{I}}$ as shown in Table I (entries 1, 5, 7, and 15). The standard experiments were run in dioxane either at 25 °C for 48 h (Method A) or at 60 °C for 2 h (Method B) with 5 mole% of the catalyst (acetylacetonate of metal) and 5 mole% of the co-catalyst (boron trifluoride etherate). Elevated temperature had beneficial effect especially on the reaction catalyzed by copper acetylacetonates (entries 5, 7, 15 in the Table I). While the Fe(III) catalyst gave up to 63% yield of VII and Cu(II) and Cu(I) up to 86–96% on reaction of 2-cyclohexen-1-one (IV) with ethyl acetoacetate (V), less than 10% conversion has been achieved with $(\text{acac})_2\text{Mg}$ (5%), $(\text{acac})_2\text{Co}$ (3%), $(\text{acac})_3\text{Cr}$ (2%), $(\text{acac})_2\text{Ni}$ (1%), $(\text{acac})_2\text{Cd}$ (1%), $(\text{C}_5\text{H}_5\text{N})_4\text{NiCl}_2$ (0%), and $(\text{salen})_2\text{Cu}$ (0%) at 60 °C for 2 h.

Since the copper catalysis appeared to be the most promising one, we tested other solvents, namely nitromethane, acetonitrile, and acetic acid (entries 8–10

TABLE I

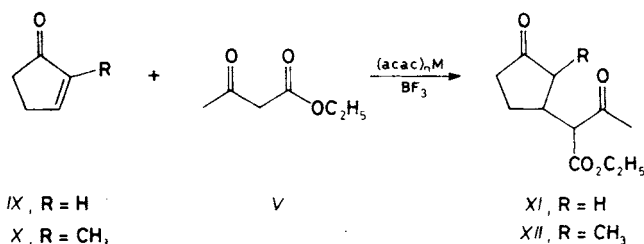
Transition-metal catalyzed Michael addition of β -dicarbonyls V and VI to α,β -unsaturated ketones IV, IX, and X (Schemes 2 and 3)

Entry	Ketone	R	Catalyst ^a	Solvent	% Yield (% Recovered) ^b	
					Method A ^c	Method B ^d
1	IV	CH ₃	$(\text{acac})_3\text{Fe}^{\text{III}}$	dioxane	57 (41)	63 (34)
2	IV	CH ₃	$(\text{acac})_3\text{Co}^{\text{III}}$	dioxane	14 (84)	10 (89)
3	IV	CH ₃	$(\text{acac})_2\text{VO}$	dioxane	26 (72)	45 (51)
4	IV	CH ₃	$(\text{acac})_2\text{Mn}^{\text{II}}$	dioxane	—	16 (82)
5	IV	CH ₃	$(\text{acac})_2\text{Cu}^{\text{II}}$	dioxane	23 (76)	86 (0)
6	IV	CH ₃	$(\text{CH}_3\text{COCHCO}_2\text{C}_2\text{H}_5)_2\text{Cu}^{\text{II}}$	dioxane	38 (60)	61 (37)
7	IV	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	dioxane	15 (83)	96 (0)
8	IV	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	CH ₃ NO ₂	77 (22)	—
9	IV	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	CH ₃ CN	18 (77)	—
10	IV	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	CH ₃ CO ₂ H ^e	72 (27)	—
11	IV	CH ₃	$(\text{C}_2\text{H}_5\text{O})_3\text{P}\cdot\text{CuCl}$	dioxane	—	79 (17)
12	IV	CH ₃	$(\text{AcO})_2\text{Cu}^{\text{II}}$	CH ₃ CO ₂ H ^e	64 (35)	—
13	IV	C ₂ H ₅ O	$(\text{acac})_2\text{Ni}^{\text{II}}$	dioxane	21 (76)	—
14	IV	C ₂ H ₅ O	$(\text{acac})_2\text{Cu}^{\text{II}}$	dioxane	43 (52)	—
15	IV	C ₂ H ₅ O	$(\text{acac})\text{Cu}^{\text{I}}$	dioxane	9 (74)	89 (7)
16	IV	C ₂ H ₅ O	$(\text{C}_2\text{H}_5\text{O})_3\text{P}\cdot\text{CuCl}$	dioxane	9 (81)	—
17	IX	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	dioxane	48 (43)	—
18	X	CH ₃	$(\text{acac})\text{Cu}^{\text{I}}$	dioxane	22 (76)	—

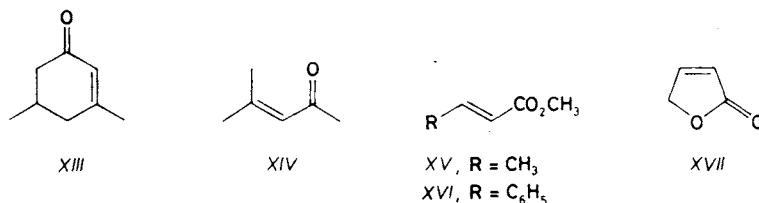
^a 5 mole% of the catalyst has been used together with 5 mole% of $\text{BF}_3\cdot\text{O}(\text{C}_2\text{H}_5)_2$ as a co-catalyst unless stated otherwise. ^b Established by capillary gas chromatography. ^c 25°C/48 h. ^d 60°C/2 h. ^e *p*-TsOH (5 mole%) used instead of $\text{BF}_3\cdot\text{O}(\text{C}_2\text{H}_5)_2$.

in Table I). Nitromethane and acetic acid were particularly good. Other solvents tried unsuccessfully include dimethylformamide, dimethylsulfoxide, and hexamethylphosphoric triamide. Furthermore, we found that boron trifluoride could be replaced by *p*-toluenesulfonic acid if the reaction was carried out in acetic acid (entry 10). However, in aprotic solvents (dioxane, nitromethane, and acetonitrile) the addition of *p*-toluenesulfonic acid induces precipitation of the copper salt. Of other copper compounds the complex of copper(I) chloride with triethyl phosphite (for the complex preparation see ref.¹⁰) turned out to be nearly as effective as (acac)₂Cu (entry 11). Even copper(II) acetate in the presence of *p*-toluenesulfonic acid as an electrophilic co-catalyst induced the reaction in acetic acid (entry 12). On the other hand, copper(II) sulfate, the most ordinary copper compound, is completely ineffective, probably due to its poor solubility in organic solvents.

Having worked out catalytic conditions for the Michael addition of β -dicarbonyls *V* and *VI* to cyclohexenone (*IV*) we attempted to carry out the addition of ethyl acetoacetate to other β -substituted α,β -unsaturated ketones and esters (Scheme 3 and 4). Whereas cyclopentenones *IX* and *X* gave



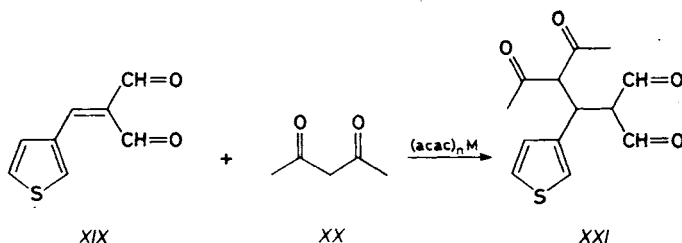
SCHEME 3



SCHEME 4

reasonable results (Table I, entries 17 and 18), β,β -disubstituted compounds *XIII* and *XIV* proved to be inert under a variety of conditions. The same

resistance to react was observed with β -substituted α,β -unsaturated esters *XV-XVII*. On the other hand, activation of the conjugated double bond by another carbonyl group as in *XIX* (Scheme 5) results in a fast reaction with



SCHEME 5

various acetylacetonates at 25°C even without the electrophilic co-catalysis (Table II). For a similar example of activation by another electron withdrawing group in the classical Michael addition see ref.¹¹.

The addition of ethyl acetoacetate or diethyl malonate catalyzed by metal acetylacetonates is accompanied by addition of 2,4-pentanedione originating from the catalyst and hence by formation of the corresponding by-product. This can be avoided in tailored preparative reactions by employing a metal chelate that corresponds to the β -dicarbonyl compound to be added. Thus copper(II) chelate of ethyl acetoacetate in co-operation with etherate of boron trifluoride has been found to catalyze the Michael addition of ethyl acetoacetate to cyclohexenone fairly well (Table I, entry 6) being thus comparable with the acetylacetonate.

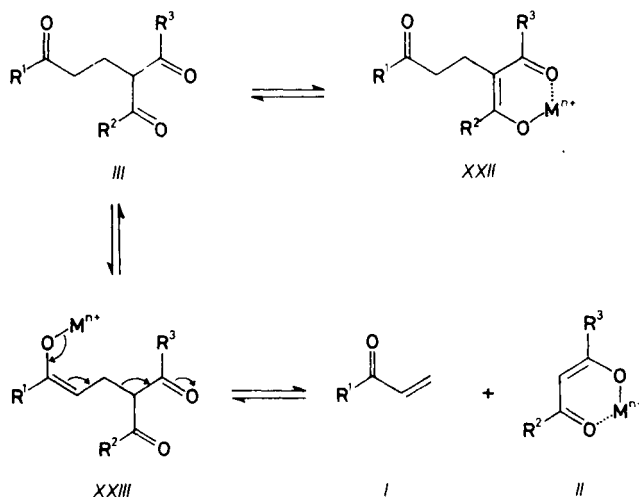
TABLE II

Transition-metal catalyzed Michael addition of 2,4-pentanedione (*XX*) to 3-thienylidenemalonaldehyde (*XIX*) (Scheme 5)

Entry	Catalyst ^a	Time, min	% Conversion ^b
1	(acac) ₂ Co ^{II}	5	73
2	(acac) ₃ Co ^{III}	60	15
3	(acac) ₂ Ni ^{II}	5	58
4	(acac) ₂ Cu ^{II}	60	42
5	(acac)Cu ^I	60	75
6	(C ₂ H ₅) ₃ N	60	88

^a 5 mole%. ^b The yields were established by HPLC on silica gel using 1-hexane-ethyl acetate (3:1) with (C₆H₅)₃CHOH as an internal reference.

In light of the above results we are confident that this catalytic procedure represents a useful modification of the Michael addition. The method's value is particularly apparent from the purity of the reaction products and high yields achieved with selected substrates. Moreover, unlike the classical, base-catalyzed procedure, our catalytic method is irreversible. This can be rationalized as follows (Scheme 6): In the classical, thermodynamically controlled Michael



SCHEME 6

addition the product *III* can form two enolates *XXII* and *XXIII*. Retrogression of the latter leads back to the starting compounds *I* and *II* while the former does not undergo further reaction. Although *XXIII* is less populated than *XXII* due to the different acidity of the competing sites in *III*, consuming of *XXIII* by subsequent retrogression to *I* and *II* drives the reaction to the undesired equilibrium. In contrast, with our transition metals only the chelate *XXII* can be formed, since the reagent is not basic enough to generate the isomeric enolate *XXIII*. We believe that this precludes the retrogression.

The transition-metal catalysis further allows for distinguishing the reactive sites if the potential molecule had several Michael-acceptor sites. Thus simple catalysis with $(\text{acac})_n\text{M}$ will lead only to addition to conjugated vinyl groups, while co-catalysis with Lewis acid would enable the β -mono-substituted α,β -unsaturated ketones to react. β,β -Disubstituted α,β -unsaturated ketones, as well as α,β -unsaturated esters and lactones will be inert.

Our mild, clean, high-yielding, and chemoselective method thus expands the applicability of the Nelson's protocol³, surpasses the classical methodology, and complements the palladium-catalyzed "Michael reaction equivalent" developed by Godleski^{12,13}. The observed chemoselectivity may also be of value in synthesis of polyfunctional molecules.

EXPERIMENTAL

Product purity and yields were established by capillary gas chromatography and/or by HPLC on silica gel using hexane-ethyl acetate (3:1) as eluant. The products were characterized by ¹H NMR, IR, and mass spectra. The ¹H NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz) in deuteriochloroform at 30 °C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The identity of the samples prepared by different routes was checked by thin-layer and gas chromatography.

Typical Experiment

2-Cyclohexen-1-one (960 mg, 10 mmol) and ethyl acetoacetate (1.43 g, 11 mmol) were dissolved in dioxane (4 ml). (2,4-pentadionato)copper(I)¹⁴ (5 mole%) and etherate of boron trifluoride (5 mole%) were added and the mixture was stirred at 60 °C for 2 h under argon. The blue-green mixture was then diluted with ether, washed with water, 5% aqueous hydrochloric acid, 5% aqueous potassium hydrogen carbonate, brine, and dried with anhydrous sodium sulfate. Concentration at the rotary evaporator gave a dark residue that was chromatographed on silica gel using a mixture of light petroleum and ether (9:1) to elute the pure product *VII* (1.96 g, 88%), identical with the compound prepared by traditional route using sodium ethoxide as the catalyst. ¹H NMR: 1.10 t, 3 H (*J* = 7, CH₃CH₂); 2.22 s, 3 H (CH₃CO); 3.37 d, 1 H (*J* = 8, CH—COCH₃); 4.67 q, 2 H (*J* = 7, CH₃CH₂O).

The IR spectra were recorded by Mrs K. Matoušková and interpreted by Dr S. Vašíčková. The NMR spectra were recorded by Mrs J. Jelinková and M. Snopková. The capillary GC analyses were carried out by Miss J. Hodačová.

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Translated by the author (P.K.).