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

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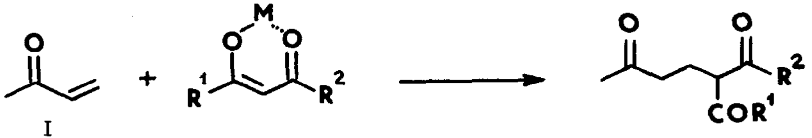
Abstract: (2,4-Pentanedionato)copper(I) and bis(2,4-pentanedionato)copper(II) together with boron trifluoride etherate catalyze Michael addition of β-dicarbonyls to cyclohexenone, cyclopentenone, 2-methylcyclopentenone, and 3-thienylidenemalonaldehyde.

Carbon-carbon bond formation is of prime importance in synthetic organic chemistry. One of the most efficient tools is the conjugated 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 some drawbacks, namely retro-addition, bis-addition, subsequent condensations and other reactions leading to formation of considerable amounts of by-products in numerous instances[1]. Although some of the problems have been circumvented by application of phase-transfer catalysis[2], it was still desirable to seek novel catalytic systems.

Recently, Nelson and co-workers[3] reported on $(acac)_2Ni$ catalysis in addition of β-dicarbonyls to methylvinylketone (I) and related electrophiles. This reaction proceeds analogously to traditional basic catalysis (Scheme 1) via Ni-chelated species (M = Ni/2)[3]. Although the addition was fairly smooth with I, in our hands it completely failed with 2-cyclohexen-1-one (II), probably due to the presence of another carbon at β-position that imposes some steric hindrance[4]. We speculated that other transition-metal complexes might, possibly, be more reactive and catalyze the addition to cyclohexenone. A brief screening of acetylacetonates of a number of transition metals[5] under varying conditions revealed, however, that none of them could induce the addition of ethyl acetoacetate or diethyl malonate to cyclohexenone.

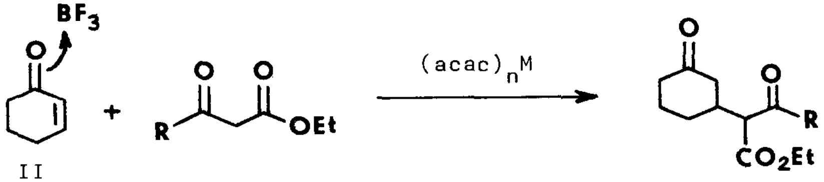


I

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 $RCu.BF_3$ reacts much faster than the ordinary R_2CuLi[6]. This finding was attributed to a coordination of BF_3 to carbonyl oxygen increasing thus the electrophilicity of the β-carbon[6]. Hence, we ran another screening, now with $BF_3.Et_2O$

as a co-catalyst (Scheme 2). Although (acac)$_2$Ni and several other acetylacetonates turned out to be nearly or completely ineffective, we could detect the reaction products in some instances.



II

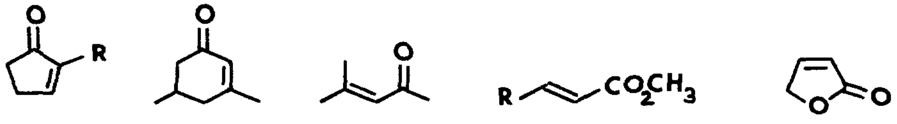
Scheme 2

After much experimentation with a variety of transition and other metals, solvents, and reaction conditions we were able to achieve fair to good results particularly with (acac)$_3$Fe^{III}, (acac)$_2$Cu^{II}, and (acac)Cu^{I} as shown in Table I (entries 1, 5, 7, 15)^7. The experiments were run in dioxane either at 25^{o}C/48 h (method A) or at 60^{o}C/2 h (method B). Elevated temperature had beneficial effect especially on the reaction catalyzed by copper acetylacetonates (entries 5, 7, 15 in the Table I).

In a representative procedure, cyclohexenone (960 mg, 10 mmol) and ethyl acetoacetate (1.43 g, 11 mmol) were dissolved in dioxane (4 mL), (2,4-pentanedionato)copper(I) (5 mol%) and BF$_3$.Et$_2$O (5 mol%)^{13} were added and the mixture was stirred at 60^{o}C for 2 h under argon. The blue-green mixture was then diluted with ether, washed with water, 5% aqueous HCl, 5% aqueous KHCO$_3$, brine, and dried. Concentration at the rotary evaporator gave a dark residue that was chromatographed on silica gel (Light petroleum/ether 9:1) to give the pure product (1.96 g, 88%)^{14}.

Since the copper catalysis appeared to be the most promising, we tested other solvents, namely CH$_3$NO$_2$, CH$_3$CN and AcOH (entries 8-10)^8. Nitromethane and AcOH were particularly good. Furthermore, we found that BF$_3$ could be replaced by p-toluenesulfonic acid if the reaction was carried out in acetic acid^9 (entry 10). Of other copper compounds, the complex of CuCl with (EtO)$_3$P^{10} (entry 11) turned out to be nearly as effective as (acac)$_2$Cu. Even copper(II) acetate in the presence of TsOH as an electrophilic co-catalyst induced the reaction in acetic acid (entry 12)^{11}.

Having thus worked out catalytic conditions for the Michael addition of β-dicarbonyls to cyclohexenone we attempted to carry out the addition of ethyl acetoacetate to other β-substituted α,β-unsaturated ketones and esters (Scheme 3). Whereas ketones III and IV gave reasonable results, β,β-disubstituted compounds V and VI proved to be non-reactive under a variety of conditions. The same resistance to react was detected with β-substituted α,β-unsaturated esters



III, R = H
IV, R = CH$_3$

V

VI

VII, R = CH$_3$
VIII, R = C$_6$H$_5$

IX

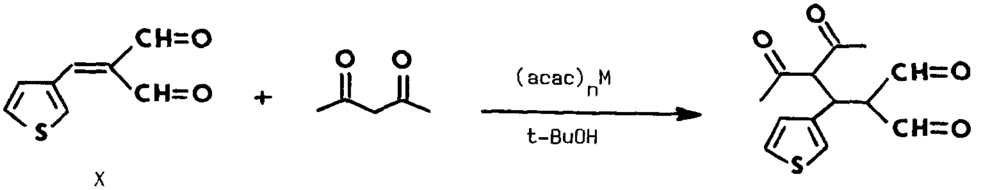
Scheme 3

TABLE I. Transition-Metal Catalyzed Michael Addition of β-Dicarbonyls to α,β-Unsaturated Ketones II-IV (Scheme 2)

Entry	Ketone	R	Catalyst[a]	Solvent	%Yield (%Recovered)[b]	
					Method A[c]	Method B[d]
1	II	CH_3	$(acac)_3Fe^{III}$	dioxane	57 (41)	63 (34)
2	II	CH_3	$(acac)_3Co^{III}$	dioxane	14 (84)	10 (89)
3	II	CH_3	$(acac)_2VO$	dioxane	26 (72)	45 (51)
4	II	CH_3	$(acac)_2Mn^{II}$	dioxane	-	16 (82)
5	II	CH_3	$(acac)_2Cu^{II}$	dioxane	23 (76)	86 (0)
6	II	CH_3	$(CH_3COCHCO_2Et)_2Cu^{II}$	dioxane	38 (60)	61 (37)
7	II	CH_3	$(acac)Cu^{I}$	dioxane	15 (83)	96 (0)
8	II	CH_3	$(acac)Cu^{I}$	CH_3NO_2	77 (22)	-
9	II	CH_3	$(acac)Cu^{I}$	CH_3CN	18 (77)	-
10	II	CH_3	$(acac)Cu^{I}$ [e]	CH_3CO_2H	72 (27)	-
11	II	CH_3	$(EtO)_3P.CuCl$	dioxane	-	79 (17)
12	II	CH_3	$(AcO)_2Cu^{II}$ [e]	CH_3CO_2H	64 (35)	-
13	II	C_2H_5O	$(acac)_2Ni^{II}$	dioxane	21 (76)	
14	II	C_2H_5O	$(acac)_2Cu^{II}$	dioxane	43 (52)	-
15	II	C_2H_5O	$(acac)Cu^{I}$	dioxane	9 (74)	89 (7)
16	II	C_2H_5O	$(EtO)_3P.CuCl$	dioxane	9 (81)	-
17	III	CH_3	$(acac)Cu^{I}$	dioxane	48 (43)	-
18	IV	CH_3	$(acac)Cu^{I}$	dioxane	22 (76)	-

[a] 5 mol% of the catalyst has been used together with 5 mol% of $BF_3.Et_2O$ as a co-catalyst unless stated otherwise. [b] Established by capilary gas chromatography; products were characterized by NMR, IR, and mass spectra. [c] 25°C/48 h. [d] 60°C/2 h. [e] p-TsOH (5 mol%) used instead of $BF_3.Et_2O$

VII-IX. On the other hand, activation of the conjugated double bond by another carbonyl group as in X results in a fast reaction with various acetylacetonates at 25°C even without electrophilic co-catalysis (Scheme 4, Table II)[15].



X

Scheme 4

TABLE II. Transition-Metal Catalyzed Michael Addition of 2,4-Pentanedione to X (Scheme 4)

Entry	Catalyst[a]	Time	% Conversion[b,c]
1	$(acac)_2Co^{II}$	5 min	73
2	$(acac)_3Co^{III}$	60 min	15
3	$(acac)_2Ni^{II}$	5 min	58
4	$(acac)_2Cu^{II}$	60 min	42
5	$(acac)Cu^{I}$	60 min	75
6	Et_3N	60 min	88

[a] 5 mol%. [b] The yields were established by HPLC on silica gel, n-hexane/AcOEt (3:1) with Ph_3COH as an internal reference. [c] The structure of the product was deduced from NMR, IR, and mass spectra.

In light of the above results we are confident that this catalytic procedure represents a useful modification of the Michael addition. The methods' value is particularly apparent from the purity of the reaction products, high yields achieved with selected substrates, and the irreversibility of the reaction. In this respect it expands the applicability of Nelson's protocol[3] and complements the palladium catalyzed "Michael reaction equivalent" developed by Godleski[16]. The observed chemoselectivity may also be of value in synthesis of polyfunctional molecules.

References and Notes

1. Bergman E.D., Ginsberg D., Rappo R.: Org. React. 10, 179 (1959).
2. Krychtal G.V., Kulhanek V.V., Kucherov V.F., Yanovskaya L.A.: Synthesis 1979, 107.
3. Nelson J.H., Howells P.N., DeLullo G.C., Landen G.L.: J.Org.Chem. 45, 1246 (1980).
4. 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 matter (see ref.[1]).
5. Acetylacetonates of Fe(III), Co(II), Co(III), Ni(II), Mn(II), Cr(III), Zn(II), Cd(II), VO, and Mg(II) have been used as well as $(EtO)_3P.CuCl$ and Py_4NiCl_2.
6. (a) Maruyama K., Yamamoto Y.: J.Am.Chem.Soc. 99, 8068 (1977); (b) Yamamoto Y., Maruyama K.: J.Am.Chem.Soc. 100, 3240 (1978); (c) Yamamoto Y., Yamamoto S., Yatagai H., Ishihara Y., Maruyama K.: J.Org.Chem. 47, 119 (1982); (d) Lipshutz B.H., Parker D.A., Kozlowski J.A., Nguyen S.L.: Tetrahed.Lett. 25, 5959 (1984); (e) Kang J., Cho W., Lee W.K.: J.Org.Chem. 49, 1838 (1984); (f) Oppolzer W., Moretti R., Godel T., Meunier A., Löhler H.: Tetrahed. Lett. 24, 4971 (1983).
7. Less than 10% conversion in the reaction of ethyl acetoacetate has been achieved with $(acac)_2Co$ (3%), $(acac)_2Ni$ (1%), Py_4NiCl_2 (0%), $(acac)_3Cr$ (2%), $(salen)_2Cu$ (0%), $(acac)_2Cd$ (1%), $(acac)_2Mg$ (5%) at 60°C/2h.
8. Other solvents tried unsuccessfully include DMF, DMSO, HMPA.
9. In aprotic solvents (dioxane, $MeNO_2$, MeCN) the addition of TsOH induces precipitation of the copper salt.
10. For preparation see: Nishizawa Y.: Bull.Chem.Soc.Japan 34, 1170 (1961).
11. However, $CuSO_4$, the most ordinary copper compound, is completely ineffective.
12. For preparation see: Emmert B., Gsottschneider W., Stanger H.: Chem.Ber.69B, 1319 (1936).
13. Using only 2 mol% of the catalysts doubles the reaction time.
14. Identical with the compound prepared by traditional route.
15. For similar example see ref.[3]
16. Godleski S.A., Villhauer E.B.: J.Org.Chem. 49, 2246 (1984), and 51, 486 (1986).

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