Metal- *vs.* Base-catalysis in the Reactions of β-Ketoamides with Cyanogen: Synthesis of Multifunctional Olefins and Related Heterocycles

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Received September 13, 1984

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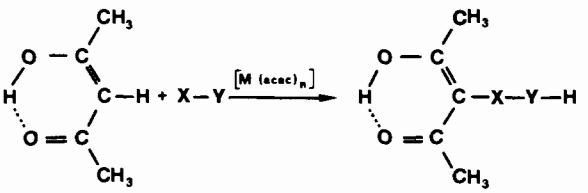
It is known that acetylacetone can be effectively added to various electrophiles in the presence of catalytic amounts of the $[M(acac)_n]$ complexes, Scheme 1 [1, 2].



XY = R–N=C=O; $COOCH_3$–C≡C–$COOCH_3$; $COOCH_3$–N=N–$COOCH_3$; CCl_3–C=N; CCl_3–C(O)H.

Scheme 1

This synthetic procedure was recently extended to the addition of acetylacetone, ethylacetoacetate, and dimethylmalonate to cyanogen [3–5] and to typical Michael acceptors [6].

TABLE I. Addition of Cyanogen to β-Ketoamides Catalyzed by 1 mol% $[M(acac)_2]$ (M = Cu, Zn) or EtO^-.[a]

$CH_3COCH_2CON(R')(R) + C_2N_2 \rightarrow$ **1** or **2**

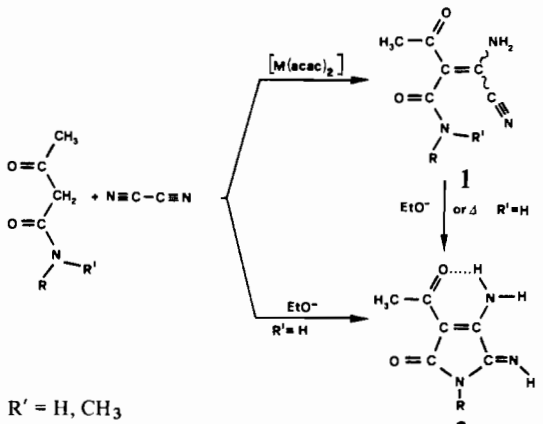
R′	R	Catalyst	(Solvent)[b]	Product	Yield	Time (h)[c]
H	H	$[Zn(acac)_2]$	(A)	**1**	91	72
H	$CH_2C_6H_5$	$[Cu(acac)_2]$	(B)	**1**	85	168
H	$CH_2C_6H_5$	$[Zn(acac)_2]$	(A)	**1**	92	72
H	$CH_2C_6H_5$	EtO^-	(C)	**2**	54	48
H	p-Cl–C_6H_4	$[Zn(acac)_2]$	(D)	**1**	53	24
H	p-Cl–C_6H_4	$[Zn(acac)_2]$	(A)	**1**	94	24
H	p-Cl–C_6H_4	$[Cu(acac)_2]$	(B)	**1**	87	168
H	p-Cl–C_6H_4	EtO^-	(C)	**2**	70	72
H	Ph	$[Zn(acac)_2]$	(A)	**1**	96	72
H	Ph	$[Cu(acac)_2]$	(B)	**1**	81	168
H	Ph	EtO^-	(C)	**2**	48	124
H	CH_3	$[Zn(acac)_2]$	(A)	**1**	76	96
H	CH_3	$[Cu(acac)_2]$	(B)	**1**	80	144
H	CH_3	EtO^-	(C)	**2**	16	24
–CH_2–CH_2–CH_2–CH_2–		$[Zn(acac)_2]$	(B)	**1**	94	48
–CH_2–CH_2–CH_2–CH_2–		$[Cu(acac)_2]$	(B)	**1**	92	168
CH_3	$CH_2C_6H_5$	$[Cu(acac)_2]$	(B)	**1**	40	48
CH_3	C_6H_5	$[Cu(acac)_2]$	(B)	**1**	55	72
CH_3	CH_3	$[Cu(acac)_2]$	(B)	**1**	77	72
CH_3	CH_3	EtO^-	(C)	no addition		72

[a]All products are novel compounds and gave satisfactory elemental analyses. Typical condition: $[C_2N_2]$ = 0.9 M; [reagent] = 0.5 M; [cat] = 5×10^{-3} M. [b]Solvents were of reagent grade and were used as received. A = toluene, B = dichloroethane, C = ethanol, D = dichloromethane. [c]Reaction time at *ca.* 20 °C.

0020-1693/85/$3.30

We report here on the addition of various acetoacetamides to C_2N_2 at room temperature, using as catalysts $[Zn(acac)_2]$ or $[Cu(acac)_2]$ in dichloromethane, dichloroethane and toluene or EtO^- in ethanol, Table I.

The results obtained indicate that the metal catalyst plays a determinant role in influencing the regioselectivity of the overall reaction towards compounds **1**, Scheme 2, whereas a typical 'aspecific' catalyst such as the ethoxyde ion drives the reaction towards compounds **2**.



R′ = H, CH_3
R = CH_3, C_6H_5, p-Cl–C_6H_4, CH_2–C_6H_5
RR′ = $(CH_2)_4$

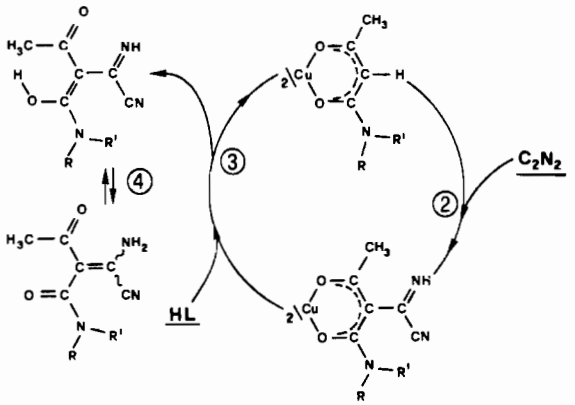
Scheme 2

Multifunctional olefins **1** were isolated in the presence of soluble metal catalysts in all cases investigated; they were characterized* by elemental analysis, NMR, IR, UV–Vis and mass spectrometry. When EtO^- was employed as the catalyst, compounds **2** were directly obtained from the secondary amides at room temperature. Compounds **1** could be quantitatively converted to compounds **2** when R′ = H by refluxing in $C_2H_4Cl_2$ for some hours or by treatment with catalytic amounts of EtO^- (1 mol % catalyst) in ethanol at room temperature.

The structures of compounds **2** were determined by single crystal X-ray analysis for R = p-Cl–C_6H_4 [7].

The reason for the strict control by the metal center on the selective formation of species **1** lies on the mechanistic proposal depicted in Scheme 3.

$$[Cu(acac)_2] + 2HL \underset{①}{\overset{K}{\rightleftharpoons}} [CuL_2] + 2Hacac$$



ACTIVATION HL = β-ketoamide

Scheme 3

The proposed mechanism is based on the following facts:

(i) $[M(acac)_n]$ complexes are known to undergo substitution reactions [8, 9] such as that depicted in stage 1;

(ii) [M(β-carbonylenolate)$_2$] complexes easily add C_2N_2 to give cyanoimino-β-carbonylenolate complexes [10–12], and we have found that some [Cu(β-acetoacetamidate)$_2$] complexes react quantitatively with cyanogen to give the corresponding addition–insertion products**.

(iii) The complex [Cu(N-phenylacetoacetamidate·C_2N_2)$_2$] effectively catalyzes the addition of N-phenylacetoacetamide to C_2N_2 to give the expected type **1** product.

*All compounds have been isolated as single isomers. The ^1H NMR spectra in DMSO-d_6 show that one isomer is normally predominant in solution and further work is in progress to elucidate the configuration. We report some data for representative compounds of type **1** and **2** (R = CH_2–C_6H_5). **1**: IR, 3170, 3270, 3340 (N–H); 2230 (C≡N); ^1H NMR, 2.00 ($COCH_3$), 8.77 (NH_2, NH), 4.35 (CH_2, d, J = 6 Hz), 7.32 (C_6H_5); mass spectrum: 243(100) M^+, 91(87), 43(18). **2**: IR, 3200, 3320, 3280 (N–H), 1720 (C=N?); ^1H NMR, 2.33 ($COCH_3$), 4.63 (CH_2), 7.23 (C_6H_5), 9.78 (=N–H); mass spectrum: identical to 1 (at 220 °C).

**The complex [Cu{(CH_3–C(O)–C(H)–C(O)–N(H)(pCl–C_6H_4)}$_2$], [CuL_2], is obtained from copper acetate monohydrate and the acetoacetamide in a water/ethanol mixture (10:1) as a green microcrystalline powder (yield 85%). *Anal.* Calcd.: C, 49.55; H, 3.74; N, 5.78. Found: C, 49.82; H, 3.72; N, 5.90. M.p. 215 °C. IR (cm^{-1}): ν_{N-H} amide = 3300(m). The complex reacts with C_2N_2 in $C_2H_4Cl_2$ at ambient temperature to give the cyanoimino yellow–green derivative [Cu(L·C_2N_2)$_2$] (yield 80%). *Anal.* Calcd.: C, 48.95; H, 3.08; N, 14.27. Found: C, 48.33; H, 3.08; N, 14.01. M.p. >270 °C. IR (cm^{-1}): ν_{N-H} amide = 3320(m); ν_{N-H} imine = 3340(m); $\nu_{C\equiv N}$ = 2230(vw); $\nu_{C=N}$ = 1640(m). IR data are in full agreement [9–12] with the structure of the intermediate at 6 o'clock in Scheme 3.

The metal-controlled chemoselectivity towards the synthesis of compounds **1** is the consequence of the appropriate inability of the catalyst to promote the hydrogen transfer from the amide to the nitrile nitrogen in compounds **1**. On the contrary, EtO^- not only catalyzes the addition of acetoacetamides to cyanogen, but is also effective in the catalysis of the cycloisomerization **1** → **2**.

In conclusion, $[Cu(acac)_2]$ and $[Zn(acac)_2]$ prove quite convenient catalysts for the selective preparation of a group of cyanoenaminediones, which are in fact *thermodynamically unstable* with respect to their pyrrolinic isomers.

Acknowledgement

This work was partially supported by C.N.R., Progetto Finalizzato Chimica Fine e Secondaria.

References

1 K. Uehara, Y. Ohashi and M. Tanaka, *Bull. Chem. Soc. Jpn., 49,* 1447 (1976).
2 R. P. Eckberg, J. H. Nelson, J. W. Kenney, P. N. Howells and R. A. Henry, *Inorg. Chem., 16,* 3128 (1977).
3 B. Corain, M. Basato and H.-F. Klein, *Angew. Chem., Int. Ed. Engl., 20,* 982 (1981).
4 B. Corain, M. Basato, E. Mori and G. Valle, *Inorg. Chim. Acta, 76,* L263 (1983).
5 M. Basato, B. Corain, A. Marcomini, G. Valle and G. Zanotti, *J. Chem. Soc., Perkin Trans., 2,* 965 (1984).
6 J. H. Nelson, P. N. Howells, G. C. DeLullo and G. L. Landen, *J. Org. Chem., 45,* 1246 (1980).
7 G. Valle, to be published.
8 R. C. Mehrotra, R. Bohra and D. P. Gaur, 'Metal β-Diketonates and Allied Derivatives', Academic Press, 1978, p. 48.
9 B. Corain, M. Basato, G. Visentin and G. Zanotti, *J. Chem. Soc., Dalton Trans.,* 1217 (1983).
10 B. Corain and M. Basato, *J. Organomet. Chem., 232,* C59-61 (1982).
11 B. Corain, M. Basato, A. Del Zotto and G. Zanotti, *Inorg. Chem., 22,* 2744 (1983).
12 B. Corain, M. Basato, C. Ballotta and M. Ahmed, *Inorg. Chim. Acta, 87,* 105 (1984).