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Preliminary communication

COBALT-CATALYZED LOW PRESSURE DOUBLE CARBONYLATION OF ARYL AND SECONDARY BENZYL HALIDES

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Summary

α-Ketoacids can be easily synthesized with satisfactory yields and selectivities by carbonylation of aryl halides and secondary benzyl halides under very mild conditions. The reactions are catalyzed by $Co_2(CO)_8$ in alcoholic solvents; the presence of a methyl source (dimethyl sulfate or methyl iodide) is necessary for the carbonylation of the aryl halides. Base, temperature and solvent have large effects on the course of the reaction.

The one step synthesis of α-ketoacids or their derivatives from organic halides is one of the most promising developments of the carbonylation reaction. While the cobalt-catalyzed double carbonylation of benzyl halides has been known for several years [1,2], use of phosphine-palladium complexes in the presence of amines is required to extend the reaction to aryl and vinyl halides [3].

We report here our preliminary results on the synthesis of α-ketoacids by cobalt-catalyzed double carbonylation of aromatic and heteroaromatic halides (eq. 1).

$$\mathrm{ArX + CO + ROH} \xrightarrow[\mathrm{CH_3Z}]{\mathrm{Co_2(CO)_8/Ca(OH)_2}} \mathrm{ArCOCOOH + ArCOOH} \qquad (1)$$

(T 15—20°C; P(CO) 1 atm; X = Cl, Br; Z = I, (CH_3OSO_3))

We have also found a new route to α-keto-β-arylbutanoic acids, which is easier and more efficient than that previously reported (eq. 2) [2].

$$\mathrm{ArCH(CH_3)X + CO} \xrightarrow[\mathrm{Base/Co(CO)_4^-}]{\mathrm{R'OH/H_2O}}$$

$$\mathrm{ArCH(CH_3)CO\ COOH + ArCH(CH_3)COOH + Ar(CH_2)_2COOH} \qquad (2)$$

(T 10—25°C; P(CO) 1—1.8 atm; X = Cl, Br; Base = $Ca(OH)_2$, NaOH, LiOH)

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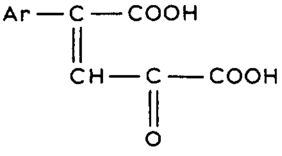
Both reactions occur very readily in aqueous alcoholic media under atmospheric pressure of CO at room temperature or below, using catalytic amounts of $Co_2(CO)_8$. The main requirements for formation of aromatic α-ketoacids are: (1) the presence of at least a stoichiometric amount of dimethyl sulfate or methyl iodide; (2) the use of $Ca(OH)_2$ as base and of linear C_2—C_4 alcohols as solvents.

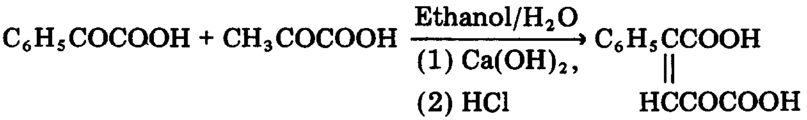
Alkaline hydrolysis at the end of the reaction is essential to liberate the α-ketoacids, which are mainly present as compounds of type I.



$$\begin{array}{l} \mathrm{Ar-C-COOH} \\ \qquad \| \\ \qquad \mathrm{CH}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{COOH} \end{array}$$

(I)

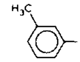
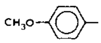
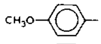
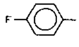
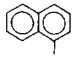
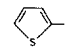
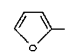
These products were identified by GC/MS and by comparison with the product obtained by reaction of phenylglyoxylic with pyruvic acid in aqueous ethanol (eq. 3).



$$\mathrm{C_6H_5COCOOH + CH_3COCOOH} \xrightarrow[\mathrm{(1)\ Ca(OH)_2,\ (2)\ HCl}]{\mathrm{Ethanol/H_2O}} \underset{\mathrm{HCCOCOOH}}{\underset{\|}{\mathrm{C_6H_5CCOOH}}} \qquad (3)$$

TABLE 1

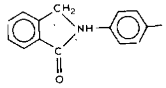
CARBONYLATION OF ARYL HALIDES ArX [a]

Entry	Ar	X	Solvent	Total yield (%)	ArCOCOOH/ArCOOH
1	Ph	Br	Ethanol	70.0	6.1
2 [b]	Ph	Br	Ethanol	98.3	0.1
3	Ph	Br	Methanol	78.2	0.2
4	Ph	Br	n-Propanol	29.0	>90
5	Ph	Br	n-Butanol	30.5	>90
6	Ph	Br	t-Butanol	traces	n.d.
7 [c]	Ph	Br	Ethanol	70.4	0.82
8		Br	Ethanol	62.6	5.2
9		Br	Ethanol	43.2	1.6
10 [d]		Br	Ethanol	21.9	5.5
11		Br	Ethanol	82.5	1.9
12		Cl	Ethanol	76.4	2.8
13		Cl	Ethanol	96.0	1.3
14 [e]		Cl	Ethanol	74.5	1.2

[a] Unless otherwise indicated all reactions were carried out in alcohol (25 ml)/water (2 ml) with $Ca(OH)_2$ (5 g), dimethyl sulfate (30—40 mmol), ArX (25 mmol), $Co_2(CO)_8$ (1 mmol) at 20°C under 1 atm of CO. [b] T 40°C. No α-ketoacid was detected in a reaction at 55°C. [c] Methyl iodide (5.7 g) was used instead of dimethyl sulfate. [d] T 10°C. [e] T 10°C in ethanol (50 ml)/water (4 ml).

TABLE 2

DOUBLE CARBONYLATION OF α-HALO ARYLETHANES $ArCH(CH_3)X^a$

Entry	Ar	X	Solvent	T (°C)	P(CO) (Atm)	$ArCH(CH_3)COCOOH^b$		Monocarbonylation products. Yield (%)[d]
						Yield (%)[c]	Selectivity (%)	
1	Ph	Br	t-Butanol	25	1.0	71.6	89.5	8.4
2	Ph	Br	t-Butanol	25	1.8	72.2	91.4	6.8
3	Ph	Br	t-Butanol	55	1.0	40.0	61.6	25.0
4	Ph	Br	Ethanol	55	1.0	—	—	70.0
5	Ph	Br	t-Amyl alcohol	25	1.8	84.0	90.0	9.0
6	Ph	Cl	t-Amyl alcohol	40	1.8	38.5	96.2	1.5
7	i-BuC_6H_4	Br	t-Butanol	10	1.8	64.6	92.3	5.4
8	i-BuC_6H_4	Cl	t-Butanol	16	1.8	61.9	91.7	5.6
9	i-BuC_6H_4	Cl	i-Propanol	16	1.0	41.6	64.0	23.4
10[e]	i-BuC_6H_4	Cl	t-Butanol	16.	1.0	49.7	71.0	20.3
11[f]	i-BuC_6H_4	Cl	t-Butanol	16	1.0	42.0	60.0	28.0
12		Cl	t-Butanol	25	1.0	40.9	87.0	6.1

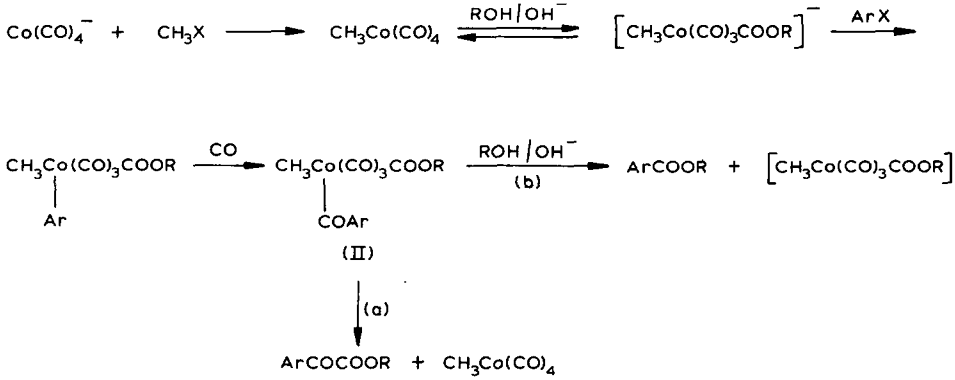
[a] Unless otherwise indicated all reactions were carried out using $ArCH(CH_3)X$ (16 mmol), $Co_2(CO)_8$ (1 mmol), $Ca(OH)_2$ (25 mmol), alcohol (40 ml), H_2O (5 ml). [b] The linear isomer was never detected. [c] Determined by g.l.c. and ^1H NMR of the crude acid fraction. [d] Mixture of linear and branched acids in entries 1-6,12; only the branched isomer was found in cases 7-11. [e] Base = NaOH. [f] Base = LiOH.

The presence of compounds such as I among the reaction products shows that double carbonylation of dimethyl sulfate or methyl iodide takes place under the conditions used. Some unoptimized results are listed in Table 1.

As far as the double carbonylation of secondary benzyl halides is concerned, it is noteworthy that: (1) no addition of a methyl source is required; (2) branched alcohols are the best solvents; $Ca(OH)_2$ is the most effective base, but NaOH and LiOH can also be used. Some preliminary results are summarized in Table 2. Two α-keto-β-arylbutanoic acids of pharmaceutical interest were synthesized by use of this reaction (entries 7—12) [4,5].

For both reactions the nature of the solvent and the temperature strongly affect the yields and selectivities, and it was therefore possible to achieve good selectivities towards either carboxylic acids, or α-ketoacids simply by changing

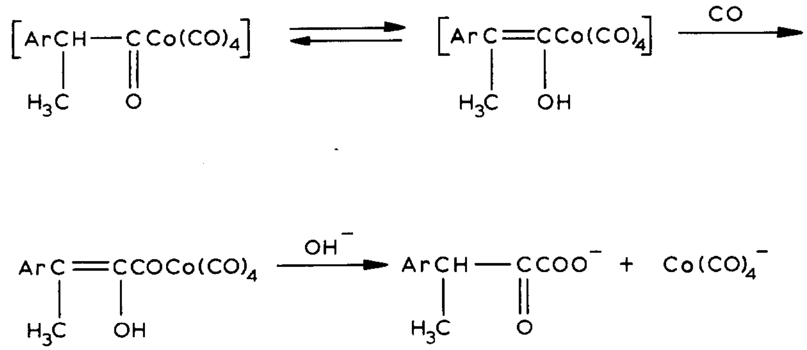
SCHEME 1



the reaction conditions. This suggests to us that the same catalytic complexes are responsible for both mono and double carbonylation. On the basis of the mechanism proposed for the monocarbonylation of aryl halides [6], Scheme 1 can be suggested for the double carbonylation of these substrates.

The ArCOCOOH/ArCOOH ratio is accounted for by the relative importance of reductive elimination from an aroyl complex of $\mathrm{Co^{III}}$ (II) (path a) compared with that of the nucleophilic attack of base on the same intermediate (path b) [7].

As previously reported [2,8], we believe the mechanism is completely different in the case of secondary benzyl halides, the enolization of the acylcobalt carbonyl intermediate then probably being the key step (eq. 4).



$$\left[\mathrm{Ar}\underset{\underset{\mathrm{H_3C}}{|}}{\mathrm{CH}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{Co(CO)_4}\right] \rightleftharpoons \left[\mathrm{Ar}\underset{\underset{\mathrm{H_3C}}{|}}{\mathrm{C}}=\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}\mathrm{Co(CO)_4}\right] \xrightarrow{\mathrm{CO}} \qquad (4)$$

$$\mathrm{Ar}\underset{\underset{\mathrm{H_3C}}{|}}{\mathrm{C}}=\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}\mathrm{COCo(CO)_4} \xrightarrow{\mathrm{OH^-}} \mathrm{Ar}\underset{\underset{\mathrm{H_3C}}{|}}{\mathrm{CH}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{COO^-} + \mathrm{Co(CO)_4^-}$$

The stabilization of the enol form arising from the presence of the methyl group could account for the surprising ease of this double CO insertion.

References

1 (a) R. Perron, U.S. Patent 4,152,352, 1979; (b) M. Foa', A. Moro, A. Gardano and L. Cassar, Ital. Pat. Appl. 28288, 1978 and U.S. Patent 4,351,952, 1982; (c) M. El Chahawi, Belgian Patent 877,229, 1979; (d) J.Y. Lee, J.W. Wolfram, PCT Int. Appl. WO 84 02,699, 1984; Chem. Abstr., 102 (1985) 78371r; (e) H. Des Abbayes and A. Buloup, J. Chem. Soc. Chem. Commun., (1978) 1090.

2 (a) F. Francalanci and M. Foa', J. Organomet. Chem., 232 (1982) 59 and ref. therein; (b) F. Francalanci, A. Gardano, L. Abis, T. Fiorani and M. Foa', ibid., 243 (1983) 87.

3 (a) F. Ozawa, H. Soyama, T. Yamamoto and A. Yamamoto, Tetrahedron Lett., 23 (1982) 3383; (b) T. Kobayashi and M. Tanaka, J. Organomet. Chem., 233 (1982) C64; (c) F. Ozawa, N. Kawasaki, T. Yamamoto and A. Yamamoto, Chem. Lett., (1985) 567; (d) M. Tanaka, T. Kobayashi, T. Sakakura, H. Itatani, S. Danno and K. Zushi, J. Mol. Catal., 32 (1985) 115.

4 K. Kigasawa, M. Hiiragi, H. Ishimaru, S. Haga and K. Shirayama, U.S. Patent 4,166,125, 1979.

5 Jpn. Kokai Tokkyo Koho JP 57,200,338; Chem. Abstr., 99 (1983) 5365b.

6 M. Foa', F. Francalanci, E. Bencini and A. Gardano, J. Organomet. Chem., 285 (1985) 293.

7 The presence of small amounts of methyl aryl ketones in several reaction mixtures suggests that a methyl and an aroyl group must be simultaneously bonded to the same metal atom.

8 L. Cassar, Ann. N.Y. Acad. Sci., 33 (1980) 208.