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STUDIES ON THE HYDROCARBOXYLATION OF N-ACETYLIMINES, ENAMINES AND ALLYLAMINES.

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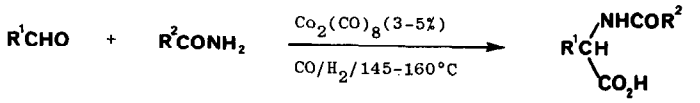
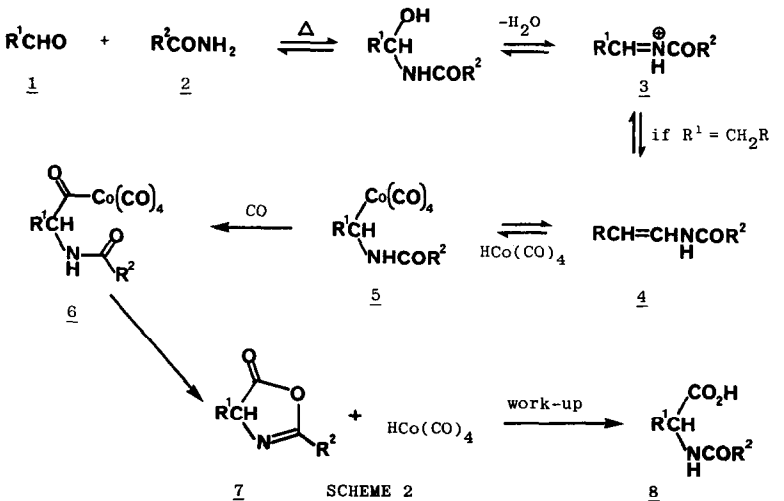
SUMMARY: Treatment of an amide with an aldehyde in the presence of $Co_2(CO)_8/CO/H_2$ results in N-acyl-α-amino acids. The scope and limitations of this reaction are explored.

In 1975 it was reported that N-acylamino acids are the products from the treatment of an aldehyde and an amide with $Co_2(CO)_8$(cat)/CO/H_2, SCHEME 1.[1] *For aldehydes that do not possess an α-hydrogen, such as benzaldehyde, the product is that of reductive amination, namely N-acylbenzylamine. It was later established*[2] *that (S)-2-methylbutanal did not result in enantiomerically enriched α-N-acylamino acids. Ojima*[3] *has also shown that epoxides and allylic alcohols can function as precursors to the aldehyde component, since they are isomerized by $Co_2(CO)_8$ under the reaction conditions.*



SCHEME 1

The mechanism proposed by Pino[2] *explains some of the above observations, in particular, the formation of carboxylic acids, rather than the usual aldehydes expected from a hydroformylation-type procedure.*[4] *Unfortunately, this mechanism does not account for the reductive amination or the racemization of (S)-2-methylbutanal. This suggests that the intermediate N acyliminium ion 3 can lose a proton (if available) to give an N-acylenamine 4, which is the species that adds $HCO(CO)_4$. The mechanism below accounts for these observations.*



SCHEME 2

Obviously, if $R^1 = Ph$, then 3 cannot lose a proton, and the N-acyliminium ion 3 is reduced by $HCo(CO)_4$. The racemization of (S)-2-methylbutanal is readily explained by the isomerization 3 ⇌ 4. The formation of N-acylaminocarboxylic acids is best accounted for by the regiospecific addition of $HCo(CO)_4$ to 4 to give 5, followed by CO insertion to form 6, which can undergo azlactone 7 formation, and on basic work-up gives 8.

In this paper we explore the scope and limitations of this potentially useful process for the synthesis of α-amino acid derivatives. N-Alkyl and α-methyl amino acids are valuable as conformationally restricted analogs, and have increased stability to enzymic degradation.[5] As a standard reaction, it should be noted that treatment of butanal (1.0 eq)/acetamide (2.0eq) with $Co_2(CO)_8$(3-5%)/CO/H_2/145-160°C gave N-acetylnorvaline 9a (72%).[6] If this procedure is conducted at 90-100°C, the only product is the bis-amide, $PrCH(NHCOMe)_2$.[7]

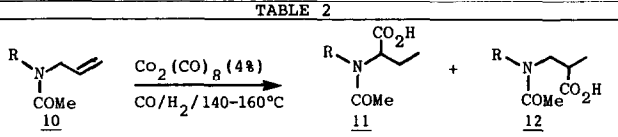
TABLE 1

	R^1	R^2	RATIO	SOLVENT	YIELD (%)
a.	Pr	H	1:2	EtOAc	72
b.	Me	Me	1:1	EtOAc	30
c.	Me	Et	1:2	EtOAc	20
d.	Me	Et	1:2	EtOAc	15
e.	Me	Et	1:1	Dioxane	13
f.	Me	Et	1:2	Dioxane	10
g.	Et	Me	1:1	EtOAc	∿2
h.	n-Pr	Me	1:2	EtOAc	5

$R^1CHO + R^2NHCOMe \xrightarrow[CO/H_2/145-160°C]{Co_2(CO)_8\,(3-5\%)} R^1CH(CO_2H)N(COMe)R^2$ (9)

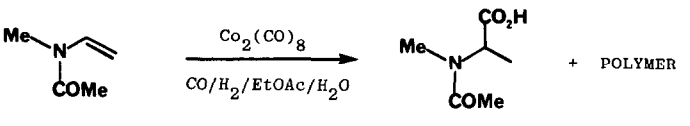
TABLE 1 clearly shows that N-substitution drastically reduces the yields of the N-Me and N-Et α-amino acid derivatives 9b-h. Murai[8] has demonstrated that $HSiEt_3$ can replace hydrogen in the $Co_2(CO)_8$ catalyzed process, and produces $Et_3SiCo(CO)_4$. Treatment of propanal with acetamide (2.0eq) in the presence of $Co_2(CO)_8$ (4%) and Et_3SiH (8%)/CO gave 9 (R^1=Et, R^2=H)(47%). This procedure did not improve the yield of N-alkyl systems. It appears that both N-substitution in the amide component, and C-substitution in the aldehyde, conspire to reduce the effective concentration of the acyliminium species 3. Another approach to 3 ⇌ 4, is to consider the transition metal catalyzed isomerization of allylamides to eneamides.[9] N-Acetyl allylamine, on treatment with $Co_2(CO)_8/Rh_6(CO)_{16}$ (11:1) in EtOAc/H_2O gave 2-acetamidobutyric acid 9 (R^1=Et, R^2=H)(40%). None of the isomeric β-acid was observed. TABLE 2 shows that the rhodium catalyst was not necessary. The carbonylation of a double bond to give a carboxylic acid is an unprecedented reaction.[10] It should be noted that the presence of water is necessary to hydrolyze the intermediate azlactones (see 7). The β-carboxylic acid is formed from 10 or its double bond isomer, as shown in SCHEME 3. N-vinyl-N-methylacetamide gave the α-carboxylic acid[11] 13 as the only acid product. For the examples 10g and 10h the major products are acetanilide and N-acetylcyclohexylamine respectively, and can be rationalized by β-elimination either from 10b or 10c to give 14. Finally, cyclic systems, which represent the intramolecular version of the original reaction depicted in SCHEME 1, resulted in reduction to the correspond-

TABLE 2

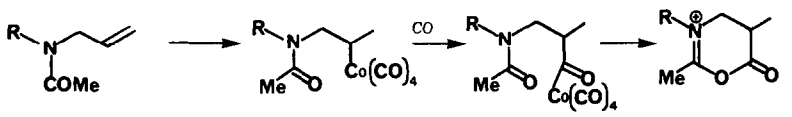


	R	SOLVENT	H_2O	$Rh_6(CO)_{16}$	YIELD	11/12
a.	H	EtOAc	1.0 eq	0.03%	40%	11 only
b.	H	EtOAc	1.0 eq	none	48%	11/12 (3.8:1)
c.	H[a]	EtOAc	1.0 eq	0.03%	5%	12 only
d.	H	EtOAc	4.0 eq	none	30%	11/12 (1:1)
e.	H	DME	1.5 eq	none	28%	11/12 (1:1)
f.	H	Et_2O	1.0 eq	none	10%	11/12 (4:1)
g.	Ph	EtOAc	1.5 eq	none	~2%	12 only
h.	C_6H_{11}	EtOAc	1.5 eq	none	trace	12 only

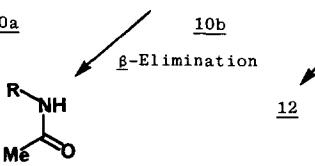
a. absence of $Co_2(CO)_8$



13 (17%)



10 10a 10b 10c

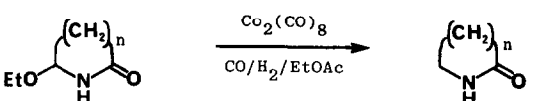


12

14

SCHEME 3

ing cyclic amide, SCHEME 4.



SCHEME 4

In conclusion, while the hydrocarboxylation of N-acetylenamines provides a direct route to N-acetyl-α-amino acids, it is evidently restricted to simple unsubstituted systems, otherwise the yields become impractical.

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6. *The work-up involved evaporation of the crude reaction mixture, extraction of the residue with EtOAc/10% aq Na_2Co_3, acidification of the aqueous phase with 85% H_3PO_4 at 0°C, and extraction of the product with EtOAc. Yields refer to crystalline material.*

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