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THE SELECTIVE REDUCTIVE ACYLATION OF α-KETO IMINES

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Summary: Reaction of α-keto imines with the *in situ* generated acetylcobalt tetracarbonyl occurs only at the carbon-nitrogen double bond to give β-keto amides. An unexpected by-product was formed in several instances.

The acylation of dienes, trienes[2], and fulvenes[3] by the *in situ* generated acetylcobalt tetracarbonyl is a useful synthetic transformation. In addition, the use of allenes as substrates results in hydroxyacylation[4]. These reactions are all regiospecific.

Although simple olefins do not react with $CH_3COCo(CO)_4$, it seemed conceivable that the organometallic compound would add to the carbon-nitrogen double bond of an imine since there is polar character in such a bond. Chosen as the substrates for this investigation were α-keto imines, easily prepared in high yields by reaction of α-diketones with an appropriate amine[5]. The use of these carbon-nitrogen double bond systems as reactants would also provide information on the selectivity of the process.

Triethylborohydrides are useful reagents in organometallic synthesis, one example being the formation of metal carbonyl anions from neutral precursors[6,7]. Gladysz has noted that, in addition to the organometallic anions, "only the volatile by-products H_2 and $(C_2H_5)_3B$ are produced" in these reactions[6]. We used this method $[Na(C_2H_5)_3BH, Co_2(CO)_8]$ to form $Co(CO)_4^{\ominus}$, and subsequently $CH_3COCo(CO)_4$ [by adding methyl iodide under a CO atmosphere].

Treatment of the *in situ* generated $CH_3COCo(CO)_4$ with 1, $R=4-CH_3C_6H_4$ or $4-CH_3OC_6H_4$, at 60°C in tetrahydrofuran (THF), afforded the β-keto amides 2 in 74-88% yield, 3 being obtained as low yield by-products (Table 1). We were surprised to observe the formation of the ethyl amide 4 (R=Ph) in 32% yield when 1, R=Ph, was used as the reactant [2, R=Ph, was obtained in 40% yield]. The yield of 4, R=Ph, increased to 40% when the reaction was repeated in the absence of methyl iodide. Furthermore, 4, $R=p-CH_3OC_6H_4$, was isolated in 20-25% yield when 1, $R=p-CH_3OC_6H_4$, was treated (CO atm.) with the solution obtained from $Na(C_2H_5)_3BH$ and

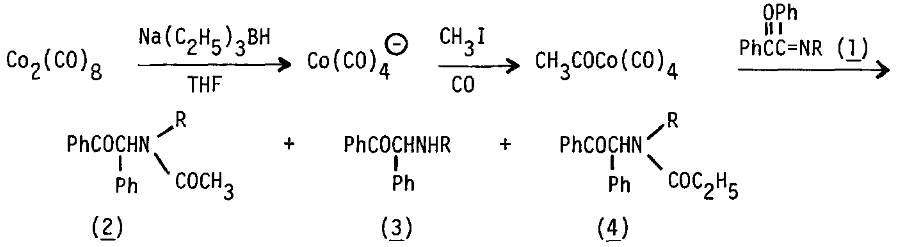

TABLE 1 Conversion of 1 to 2-4 at 60°C [a]

1, R=	Reaction time (hr)	Product	Yield (%) [b]	Mp (°C)
4-$CH_3C_6H_4$	10	2	74	144-145
		3	12	
4-$CH_3OC_6H_4$	7	2	88	125-126
		3	11	
Ph [c]	24	2	40	151-152
		4	32	118-119
2,4-$(CH_3)_2C_6H_3$	120 [d]	2	21	125-126
		3	<2	
2,6-$(CH_3)_2C_6H_3$	120 [e]	2	6	103-105
		3	8	

[a] The structures of the products were determined on the basis of analytical (C,H,N) and spectral [ir, nmr (^{13}C, ^1H), ms] data. [b] Yields are of pure materials. [c] Reaction at room temperature (5 days) gave 2(44%), 3(12%), 4(10%), and a product resulting from ring-opening of THF. [d] 1 was recovered in 68% yield. [e] 1 was recovered in 67% yield.

and $Co_2(CO)_8$. Recovered starting material and small amounts of 3 were formed in the reactions run without CH_3I.

Steric effects are probably important in the reductive acylation reaction. Although 1, R=2,4- and 2,6-$(CH_3)_2C_6H_3$- did afford 2 and 3, large quantities of starting materials were recovered from these reactions.

Several other observations merit recording here. In all reactions, 2.5 equivalents of triethylborohydride was used for reaction with $Co_2(CO)_8$ (as Gladysz used)[7]. Use of a 2:1 ratio of $Na(C_2H_5)_3BH/Co_2(CO)_8$ resulted in the recovery of substantial amounts of 1. No reaction occurs in the absence of $Na(C_2H_5)_3BH$.

In conclusion, selective reductive acylation of the carbon-nitrogen double bond of sterically unencumbered derivatives of 1 can be achieved in 40-88% yields by the use of $Co_2(CO)_8$, $Na(C_2H_5)_3BH$,CH_3I, and CO. What this means is that one can effect the overall conversion of α-diketones to β-keto amides. The isolation of ethyl amides (4) is intriguing, and suggests the participation of triethylborane in the reaction process.

The following general procedure was used: $NaCo(CO)_4$ was formed by stirring a mixture of $Co_2(CO)_8$ [2.0 mmol] and 5.0 ml. of $Na(C_2H_5)_3BH$ [1M in THF] in THF (50 ml.) for 15 min. Methyliodide [1.0 ml. - CO atm.] was added, the reaction mixture was warmed to 60°C and, after 15 minutes, 1[2.0 mmol] was added. The reaction was monitored by thin-layer chromatography and when complete, the solution was cooled to room temperature and to it was added 5N NaOH[20 ml.]. Ether was then added to the separated organic phase, the solution was acidified (pH 6), washed with water, dried ($MgSO_4$), and concentrated. Silica gel column chromatography [hexane/ether] was used to obtain analytically pure 2-4.

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