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SYNTHESIS OF γ-KETOAMIDES VIA NUCLEOPHILIC ATTACK ON IRON TETRACARBONYL COMPLEXES OF α,β-UNSATURATED AMIDES

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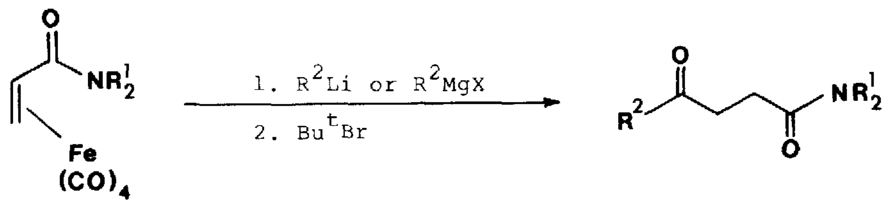
Summary : Organolithium and Grignard reagents react with the readily-formed iron tetracarbonyl complexes of α,β-unsaturated amides to give γ-ketoamides in good yield via acyl transfer from the metal to the β carbon of the α,β-unsaturated amide.

1,4-Addition of acyl anions or their equivalents to α,β-unsaturated carbonyl compounds is an important route to synthetically-useful 1,4-dicarbonyl compounds. Although there are numerous examples in the literature of such additions to α,β-unsaturated aldehydes, ketones, and esters, 1,4-additions of acyl anion equivalents to α,β-unsaturated amides are surprisingly under-represented.[1] This may reflect a neglect of 1,4-addition reactions of α,β-unsaturated amides in general.[2] Addition of an acyl anion equivalent to an α,β-unsaturated amide followed by unmasking of the carbonyl group to reveal a γ-ketoamide has been employed, however, in syntheses of the 1-aryltetralin lignans galcatin and isogalcatin,[3] and in preliminary studies for a synthesis of the alkaloid camptothecin.[4] These isolated examples suggest that an efficient method for converting α,β-unsaturated amides to γ-ketoamides would be synthetically attractive.

We are currently investigating the effect of nucleophilic attack on iron tetracarbonyl complexes of α,β-unsaturated carbonyl compounds.[5] In this Letter, we report that addition of organolithium or Grignard reagents to the readily-formed iron tetracarbonyl complexes of α,β-unsaturated amides 1 leads to the production of γ-ketoamides 2 in good yield.

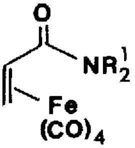
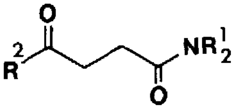


1

2

Complex 1a (R^1_2 = Me_2)[6] and the novel complexes[7] 1b (R^1_2 = Ph_2), 1c (R^1_2 = $-(CH_2)_4-$), and 1d (R^1_2 = $-(CH_2)_2O(CH_2)_2-$) were prepared by heating the appropriate N,N-disubstitutedacrylamide with $Fe_2(CO)_9$ in diethyl ether at 35 °C for 0.5 - 1.5 h under a nitrogen atmosphere. After chromatography, the complexes were isolated as yellow air-stable crystalline solids in 97, 58, 60, and 78% yields respectively.

TABLE Synthesis of γ-ketoamides 2 from iron tetracarbonyl complexes 1

Entry	Complex 1  	R^2Li or R^2MgX	γ-Ketoamide 2[a]  	Yield%
1	1a (R^1_2=Me_2)	MeLi	2a (R^1_2=Me_2, R^2=Me)	82
2	1a (")	BnMgCl	2b (" , R^2=Bn)	69
3	1a (")	PhLi	2c (" , R^2=Ph)	74
4	1a (")	EtMgBr	2d (" , R^2=Et)	53
5	1a (")	BuLi	2e (" , R^2=Bu)	63
6	1b (R^1_2=Ph_2)	MeLi	2f (R^1_2=Ph_2, R^2=Me)	60
7	1b (")	BnMgCl	2g (" , R^2=Bn)	63
8	1c (R^1_2=$-(CH_2)_4-$)	MeLi	2h (R^1_2=$-(CH_2)_4-$, R^2=Me)	60
9	1c (")	BnMgBr	2i (" , R^2=Bn)	52
10	1d (R^1_2=$-(CH_2)_2O(CH_2)_2-$)	MeLi	2j (R^1_2=$-(CH_2)_2O(CH_2)_2-$, R^2=Me)	70
11	1d (")	BnMgBr	2k (" , R^2=Bn)	67

[a] All products gave satisfactory spectroscopic and analytical data.

A range of organolithium and Grignard reagents were then added to complexes 1a-d. After quenching with a proton source and chromatography, γ-ketoamides 2a-k were isolated from the reactions in good yield (see Table).

Typical Experimental Procedure

Benzylmagnesium chloride (1.29 mmol) was added to a solution of complex 1a (0.86 mmol) in diethyl ether (10 ml) at -78 °C under a nitrogen atmosphere. After stirring the mixture for 1.5 h at -78 °C, it was quenched with t-butyl bromide (8.6 mmol), allowed to warm to room temperature, and filtered through a plug of alumina. Chromatography of the crude product (SiO_2, 30-40 petroleum ether : ethyl acetate, 3:2) led to the isolation of pure 2b (Entry 2, Table).

Treatment of the iron tetracarbonyl complex of N,N-dimethylcrotonamide with methyl-lithium gave N,N-dimethylcrotonamide as the major product and only a low yield of the expected γ-ketoamide. The relative instability of the N,N-dimethylcrotonamide complex may account for this result.

The results presented here demonstrate that hard nucleophiles attack iron tetracarbonyl complexes of N,N-disubstitutedacrylamides at one of the carbonyl ligands rather than at the β carbon of the organic ligand. Transfer of the acyl group thus formed to the β carbon of the acrylamide ligand and protonation lead to the product γ-ketoamide.

Acknowledgement

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7. All novel complexes and compounds gave satisfactory spectroscopic and analytical data.

8. N,N-disubstitutedacrylamides were prepared from acryloyl chloride and the appropriate secondary amine with the exception of commercially-available N,N-dimethylacrylamide.

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