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Facile synthesis of novel ferrocene α-ketoamides via homogeneous catalytic carbonylation

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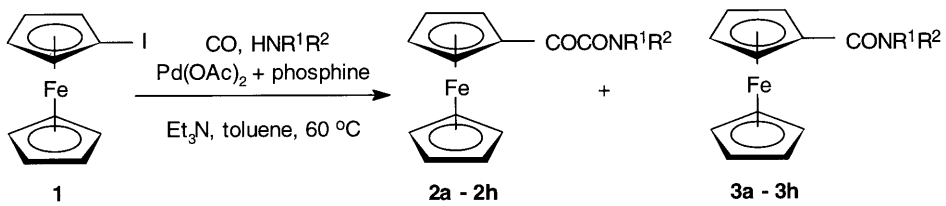
Abstract—An efficient synthesis of novel ferrocene α-ketoamides is described. They were synthesised in good yields via a palladium-catalysed carbonylation reaction. The ratio of the main products and the ferrocene amides, obtained as minor compounds in most cases, depends on the catalyst and on the structure of the amine reagent.

In recent years a considerable amount of research has been devoted to the synthesis of various substituted ferrocenes.[1] Such compounds can effectively be used in asymmetric catalysis[2] and enantioselective synthesis.[3] Ferrocene-based systems can serve as redox sensors,[4] redox-active self-assembled monolayers[5] or redox

Table 1. Carbonylation of iodoferrocene in the presence of various secondary amines



(1)

Entry	HNR^1R^2	Phosphine	Conv.%	Ratio of products	Isolated yield of **2**%
1	Morpholine	PPh_3	95	**2a**:**3a** = 79:21	70
2	Morpholine	dppp	91	**2a**:**3a** = 77:23	68
3	Morpholine	dppb	95	**2a**:**3a** = 79:21	69
4	Morpholine	PBu_3	95	**2a**:**3a** = 41:59	–
5	Piperidine	PPh_3	89	**2b**:**3b** = 70:30	57
6	2-Ethylpiperidine	PPh_3	98	**2c**:**3c** = 27:73	–
7	2,6-Dimethylpiperidine	PPh_3	99	**2d**:**3d** = 0:100	–
8	3,5-Dimethylpiperidine	PPh_3	94	**2e**:**3e** = 82:18	72
9	Et_2NH	PPh_3	97	**2f**:**3f** = 69:31	63
10	nBu_2NH	PPh_3	97	**2g**:**3g** = 73:27	67
11	$cHex_2NH$	PPh_3	91	**2h**:**3h** = 6:94	–

Keywords: ferrocene α-ketoamides; homogeneous catalysis; carbonylation; Pd-catalysts.

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switches.[6] Substituents will influence the redox behaviour of the ferrocene moiety by changing the energy level of the HOMO.[7] Ferrocenecarboxylic acid derivatives represent a group of such compounds. In the synthesis of these systems the commonly used intermediates are ferrocenecarboxylic acid,[8] chlorocarbonylferrocene[9] or fluorocarbonylferrocene.[10]

In the past few years we turned our attention to the homogeneous catalytic carbonylation of alkenyl or aryl halides/triflates.[11] During our research we have found that using iodoferrocene as substrate, novel ferrocene α-ketoamides can be synthesised by this method. Although ferrocene α-diones have been produced before,[12] to the best of our knowledge, this is the first report concerning the synthesis of α-ketoamides.

Iodoferrocene (**1**)[13] was reacted with various secondary amines in the presence of a Pd-catalyst in an autoclave under CO pressure (Eq. (1)). The formation of two types of products, ferrocene α-ketoamides (**2a**–**2h**) and ferrocene amides (**3a**–**3h**) was observed. The ratio of dicarbonylated and monocarbonylated products (**2**/**3**) was mainly influenced by the phosphine ligands of the catalyst and by the structure of the secondary amines (Table 1).

Yamamoto and his co-workers observed in their paper dealing with double carbonylation of simple aryl halides that mainly basic and less bulky amines were suitable for the predominant formation of α-ketoamides.[14] Surprisingly, with iodoferrocene as substrate, contrary to their results, dicarbonylated products were obtained as major products not only with Et_2NH (entry 9), but also with morpholine (entry 1) and piperidine (entry 5) as the amine reagent. At the same time more bulky and sterically hindered amines like 2,6-dimethylpiperidine or dicyclohexyl amine gave the corresponding amides almost exclusively (entries 7, 11).

In the presence of triaryl- or bidentate alkyldiaryl phosphines [dppb:1,4-bis(diphenylphosphino)butane or dppp: 1,3-bis(diphenylphosphino)propane] the ketoamide **2a** was formed with the same selectivity (entries 1-3). The use of the basic ligand PBu_3 led to a decrease in the selectivity towards **2a** (entry 4).

In summary we have found that novel ferrocene α-ketoamides can be synthesised in fair yields via palladium-catalysed double carbonylation. Research concerning the optimisation of the reaction conditions to increase selectivity is in progress.

In a typical experiment 1 mmol iodoferrocene, 0.05 mmol $Pd(OAc)_2$, 0.1 mmol PPh_3, 5 mmol amine, 0.5 ml Et_3N and 15 ml toluene were transferred under an inert atmosphere into a stainless steel autoclave. It was charged with carbon monoxide (40 bar at room temperature) and heated with stirring in an oil bath at 60°C for 8 h. Then the volatile components were removed in vacuo. The residue was dissolved in 30 ml of $CHCl_3$, washed with 30 ml 5% HCl, 30 ml of saturated aqueous $NaHCO_3$ and 30 ml of brine and dried over Na_2SO_4. The conversion and product ratios were determined by GC. The evaporation of the solvent and chromatography (aluminum oxide, benzene/EtOAc = 14/1) resulted in the products in good isolated yields.

Selected spectroscopic data for **2a**: ^1H NMR: δ 4.83 (s, 2H), 4.62 (s, 2H), 4.31 (s, 5H), 3.70 (m, 6H), 3.41 (m, 2H). ^{13}C NMR: δ 197.3 (CO), 165.3 (CO), 74.9, 73.6, 70.7, 70.2, 66.8, 66.5, 46.4, 41.6. MS m/e 327(M^+)/98, 213/100, 185/70, 129/44, 91/40, 56/15. IR (cm^{-1}): 1610, 1630 (C=O).

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