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Homogeneous Catalysis

Iron-Catalyzed Carbonylation: Selective and Efficient Synthesis of Succinimides**

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Dedicated to Professor Hans Jürgen Wernicke on the occasion of his 60th birthday

The development of sustainable, efficient, and selective catalysis is a fundamental goal in chemistry. During the last decades, manifold transition metal catalyzed reactions have been uncovered which have significantly improved organic synthesis. Notably, most of the applications are based on complexes of precious metals such as palladium, rhodium, iridium, and ruthenium. The limited availability of these metals and their high price makes it highly desirable to search for more economical and environmentally friendly alternatives.[1] Among the various biorelevant metals, iron is an especially attractive alternative compared to precious metals. Iron is the second most abundant metal in the earth's crust (4.7 wt %), it is cheap, benign, readily available, and ecological friendly.[2] Obviously, numerous iron salts and complexes are commercially accessible on a large scale[3] or are easy to synthesize.[4] In contrast to man-made precious-metal catalysts, iron takes part in various biological systems as an essential key element, for example, in metalloproteins for the transport or metabolism of small molecules (oxygen, nitrogen, methane, etc.) and electron-transfer reactions.[5]

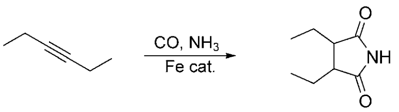
Despite these many advantages, until recently, iron-catalyzed processes were underrepresented in the field of organic synthesis. One reason for this might be the fact that most of the known catalytic reactions with iron are either limited in scope or do not qualify for practical applications.

In 2004, Bolm et al. summarized the achievements in iron catalysis until that time.[6] Since then, a number of impressive examples have demonstrated the increased potential of iron catalysis in the field of reduction, oxidation, and coupling reactions.[7,8] However, to the best of our knowledge, there are no modern examples of iron-catalyzed carbonylation reactions known,[9] even though such reactions would allow for the most efficient way to prepare carboxylic acid derivatives.[10] Clearly, the main problem of such catalytic reactions is the formation of stable iron–carbonyl complexes, which are kinetically relatively inert. To achieve catalytic carbonylations based on iron, we started to investigate the reaction of alkynes with carbon monoxide and different nucleophiles. Herein, we report the first iron-catalyzed synthesis of succinimides by carbonylation of different terminal and internal alkynes with ammonia or amines to give good selectivity and high activity. This new catalytic reaction is based on the double carbonylation of alkynes and intramolecular nucleophilic attack.

Initially, the carbonylation of 3-hexyne with ammonia was investigated as a model system. First attempts were performed with and without the use of a metal. Such blank tests are important when using high pressure equipment in order to exclude a possible contamination of the autoclave by previous reactions that were carried out in the presence of precious metal catalysts. As shown in Table 1, entry 1 no activity was seen without iron present.

In contrast, when 10 mol % of ironpentacarbonyl [$Fe(CO)_5$] was used at a CO pressure of 20 bar and 120 °C,

Table 1: Iron-catalyzed carbonylation of 3-hexyne: catalysts and ligands.[a]



Entry	c(Cat.) [mol %]	Ligand (Fe/L 1:2)	p(CO) [bar]	Conv. [%][b]	Yield [%][b]
1	–	$(t\mathrm{Bu})_2\mathrm{P}(n\mathrm{Bu})$	50	0	0
2[c]	10	–	50	97	96
3[c]	10	$(t\mathrm{Bu})_2\mathrm{P}(n\mathrm{Bu})$	50	46	26
4[c]	10	PPh_3	50	20	15
5[c]	5	–	50	85	79
6	5	–	50	79	66
7	2	–	50	60	40
8	2	–	25	79	79
9	2	–	20	100	93 (84)
10	2	–	10	96	92
11	1	–	20	95	92
12[d]	1	–	20	19	14
13	0.5	–	20	79	74
14[e]	0.5	–	20	94	85
15[f]	0.5	–	20	93	87
16[g]	0.5	–	20	32	18
17[h]	0.5	–	20	94	36

[a] Reaction conditions: 20 mL of THF, 10 mmol of 3-hexyne, Fe ([$Fe_3(CO)_{12}$]), 5 g of NH_3, 120 °C, 16 h. [b] Determined by GC analysis with bis(2-methoxyethyl)ether as the internal standard. Yield of isolated product in parenthesis. [c] $Fe(CO)_5$ as catalyst. [d] $T = 100$ °C. [e] $T = 140$ °C. [f] Reaction with 10 g of NH_3. [g] Reaction with 2 g of NH_3. [h] Reaction with toluene as solvent.

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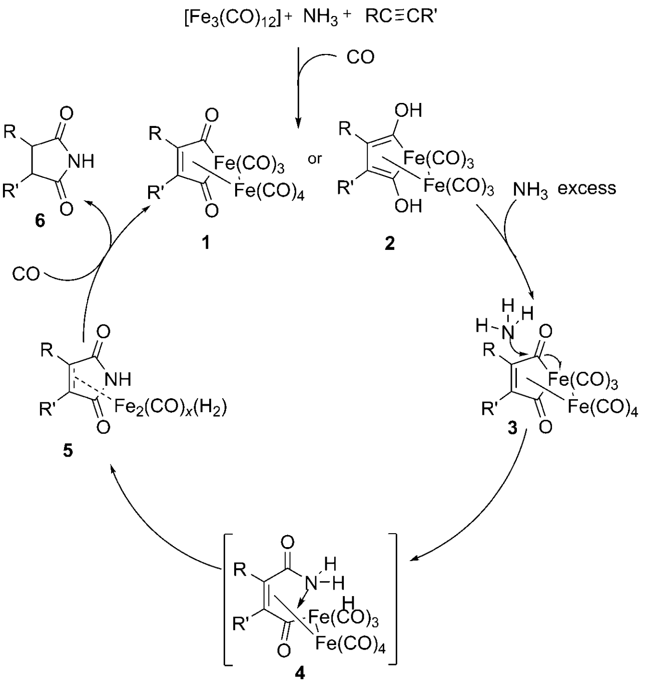
almost quantitative conversion along with excellent yield (96 %) and selectivity was obtained without any ligand present (Table 1, entry 2). The addition of basic alkylphosphine or triphenylphosphine both significantly decreased the activity of the catalyst (Table 1, entries 3 and 4). Therefore, we used no ligand in the following experiments. Next, different sources of iron were used. Beside ironpentacarbonyl, triirondodecacarbonyl $[Fe_3(CO)_{12}]$ was used as a catalyst precursor (Table 1, entries 6–17), which is less toxic and easier to handle as it is a solid.

The CO pressure had an important influence on the product yield (Table 1, entries 7–10): When using a CO pressure of 50 bar only 40 % yield of 3,4-diethylsuccinimide was observed, while the yield increased up to 93 % when a CO pressure of 20 bar was used. Apparently, the metal centre becomes inaccessible for the substrate as a result of the increased CO pressure. A further lowering of the pressure led to decreased yields.

Notably, at a CO pressure of 20 bar the iron concentration can be as low as 0.5 mol % to still afford good yields (74–84 %) and high selectivity (Table 1, entries 13–15). In addition, the reaction temperature has a major influence on the catalysis. At 100 °C (Table 1, entry 12) the yield was negligible, whereas at 120 °C (Table 1, entry 11) the yield increased to 92 %.

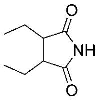
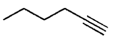
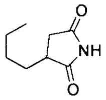
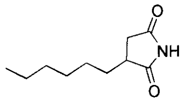
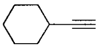
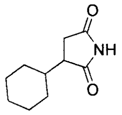
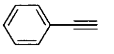
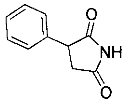
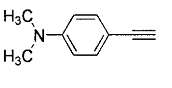
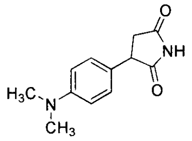
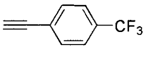
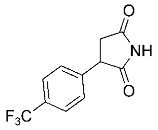
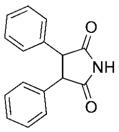
With respect to the mechanism, we believe that our catalytic reaction proceeds in a similar way to the stoichiometric studies reported by Periasamy et al., who worked intensively on the carbonylation of alkynes.[11,12] The formation of the cyclic imides can be tentatively explained by the sequence of reactions and intermediates shown in Scheme 1. According to Periasamy et al. the amine reacts with $[Fe_3(CO)_{12}]$ to form an "amine–$[Fe(CO)_4]$" and an $[Fe_2(CO)_8]$ species, which on further reaction with alkynes leads to complexes **1** or **2**. In the presence of an excess amount of amine the corresponding cyclic imides **6** are obtained via intermediates **3**–**5**. The order of adding the reagents is significant. Notably, when the amine is added to the catalyst solution before the alkyne the yield increases by about 10 %. We assume that double carbonylation and not a stepwise reaction via acryl amide is responsible because the product yield decreases upon the addition of acryl amide to the model system. Obviously, ironpentacarbonyl shows a completely different reaction behavior compared to $[Co_2(CO)_8]$, which reacts with acryl amides to give the corresponding succinimides.[13]



Scheme 1. Proposed mechanism for the iron-catalyzed carbonylation of alkynes.

Next, the scope of the catalyst system was demonstrated in the carbonylation of various simple alkynes, including terminal and internal alkynes (Table 2). Terminal alkynes such as phenylacetylene and 1-hexyne showed lower reactivity compared to 3-hexyne (Table 2, compare entry 1 with entries 2 and 5). However, when the reaction mixture was more diluted

Table 2: Carbonylation of various substituted alkynes with ammonia.[a]

Entry	Alkyne	Succinimide		Conv. [%]	Yield [%][b]
1[c]			**1**	100	84 (93)
2[d]			**2**	100	68 (79)
3[d]	C_6H_{13}—≡		**3**	100	68
4[d]			**4**	100	83
5[d]			**5**	100	– (92)
6[d]			**6**	100	55 (86)
7[d]			**7**	100	37 (50)
8			**8**	100	82 (98)

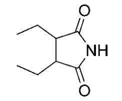
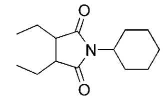
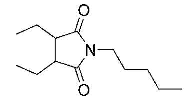
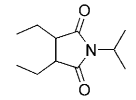
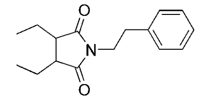
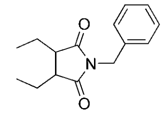
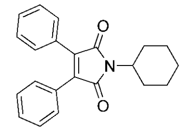
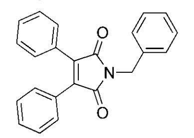
[a] Reaction conditions: 20 mL of THF, 10 mmol of alkyne, 10 mol % of Fe ($[Fe_3(CO)_{12}]$), 5 g of NH_3, CO pressure of 20 bar, 120 °C, 16 h. [b] Yield of isolated product. Yield determined by GC analysis, using isooctane as the internal standard, in parenthesis. [c] Reaction with 2 mol % of Fe. [d] Reaction with 2 mmol of alkyne.

in the presence of a higher iron catalyst concentration products **1**–**8** were obtained in good to excellent yields (50–98 %). Both symmetrical and nonsymmetrical aliphatic-substituted (Table 2, entries 1–3) as well as cyclic aliphatic-substituted succinimides (Table 2, entry 4) were successfully synthesized. Also, the preparation of aromatic-substituted succinimides proceeded smoothly in good to very good yields (Table 2, entries 5–8).

When comparing the reactions of substituted phenylacetylenes it is evident that electron-donating substituents (Table 2, entry 6) seem to have no influence on the product yield, whereas electron-withdrawing substituents like the CF_3 group (Table 2, entry 7) led to lower yields. This observation might be explained by the lower nucleophilicity of acceptor-substituted alkynes. The corresponding symmetrical aromatic derivative 3,4-diphenylsuccinimide was obtained almost quantitatively in 98 % yield (Table 2, entry 8).

Finally, we investigated the use of various amines (Table 3). Thus, 3-hexyne was carbonylated in the presence of different amines under the optimized reaction conditions. Notably, the concentration of the nucleophilic primary amines was lower compared to the reactions with ammonia.

Table 3: Reaction of various substituted alkynes with different amines.[a]

Entry	Amine	Succinimide		Conv. [%]	Yield [%][b]
1[c]	ammonia		**1**	100	84 (93)
2	cyclohexylamine		**9**	100	56 (63)
3	pentylamine		**10**	82	44 (48)
4	isopropylamine		**11**	95	79
5	phenethylamine		**12**	100	88
6	benzylamine		**13**	100	71
7[d,e]	cyclohexylamine		**14**	100	60 (92)
8[e]	benzylamine		**15**	71	48 (66)

[a] Reaction conditions: 20 mL of THF, 10 mmol of 3-hexyne, 2 mol % of Fe ($[Fe_3(CO)_{12}]$), 13 equiv of amine, CO pressure of 20 bar, 120°C, 16 h. [b]] Yield of isolated product. Yield determined by GC analysis, using isooctane as the internal standard, in parenthesis. [c] Reaction with 5 g of NH_3. [d] Reaction with 10 mol % of Fe. [e] Reaction with 10 mmol of diphenylacetylene.

In most cases, the corresponding N-substituted succinimides were obtained in good to very good yields (Table 3). Interestingly, when diphenylacetylene was the substrate that was treated with various amines, the reaction gave N-substituted maleinimides. This result can be explained by the facile aromatization of this fully conjugated system (Table 3, entries 7 and 8).

In conclusion, we have developed a convenient one-pot method for the synthesis of various substituted succinimides.[14] By starting from commercially available amines (or ammonia) and alkynes a range of interesting succinimides were obtained selectively in the presence of catalytic amounts of either $[Fe(CO)_5]$ or $[Fe_3(CO)_{12}]$. For this novel environmentally friendly reaction, no expensive catalyst was required. Currently, we are expanding this chemistry to the monocarbonylation of alkynes.

Experimental Section

General procedure: $[Fe(CO)_5]$ or $[Fe_3(CO)_{12}]$ was dissolved in THF under an argon atmosphere in a 50 mL schlenk flask. The alkyne and amine were added to this solution before being transferred into an autoclave. When ammonia was required, it was condensed from a small bomb into the autoclave. Afterwards the autoclave was pressurized with carbon monoxide and heated to 120 °C. The reaction was carried out for 16 h before the reaction mixture was cooled to room temperature. The pressure was then released and isooctane (internal standard) was subsequently added to the mixture. After removal of the solvent in vacuo, the crude succinimide product was purified by column chromatography on silica gel (heptane/ethyl acetate 10:1→1:1). The yield was measured by GC analysis.

Synthesis of 3,4-diethylsuccinimide (**1**): $Fe_3(CO)_{12}$ (0.07 mmol, 35 mg, 2 mol % Fe) was dissolved in THF (20 mL) under an argon atmosphere in an 50 mL schlenk flask before 3-hexyne (10 mmol, 1.15 mL) was added and the mixture was stirred. The solution was transferred into a 100 mL Parr autoclave, then ammonia (5 g) was condensed into the ice-cooled autoclave. Afterwards the autoclave was pressurized with carbon monoxide (20 bar) and heated to 120 °C for 16 h. The reaction mixture was then cooled to room temperature, the pressure was then released, and isooctane (0.5 mL, internal standard) was added to the mixture. After removal of the solvent in vacuo, the crude product was purified by column chromatography on silica gel (heptane/ethyl acetate 10:1→1:1) to afford **1** in 84 % yield as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.93$ (brs, 1 H, NH), 2.54–2.48 (m, 2 H, CH), 1.93–1.65 (m, 4 H, CH_2), 1.02 ppm (t, $^{3}J_{CH_2,CH_2} = 7.5$ Hz, 6 H, CH_3). ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 179.3$ (s, 2 × CO), 47.5 (s, 2 × CH), 24.1 (s, 2 × CH$_2$), 10.9 ppm (s, 2 × CH$_3$). MS (GC-MS): 155 (14), 127 (100), 112 (26), 99 (26), 98 (76), 84 (11), 69 (21), 56 (22), 55 (46), 42 (20), 41 (24), 39 (19). HRMS (EI): calcd for $C_8H_{13}O_2N_1$: 155.09408; found: 155.094054. IR (ATR): $\tilde{\nu} = 3177$ (m), 3067 (m), 2964 (m), 2941 (m), 2909 (m), 2879 (m), 2758 (w), 1773 (w), 1693 (s), 1459 (m), 1436 (w), 1385 (m), 1361 (m), 1335 (m), 1313 (m), 1258 (w), 1227 (w), 1183 (s), 11232 (w), 1077 (m), 1053 (w), 1036 (w), 953 (m), 884 (m), 830 (m), 786 (m), 738 (m), 674 cm^{-1} (m).

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