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Carbon–Carbon and Carbon–Heteroatom Bond Formation on Solid Phase Using Cationic Iron Carbonyl Complexes

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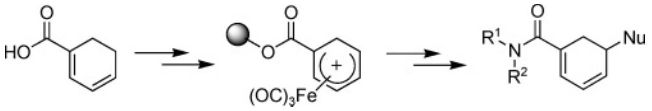
ABSTRACT



Iron-mediated methodology for the formation of carbon–carbon and carbon–heteroatom sp^3 bonds on solid phase has been developed. Treatment of a polymer-bound cationic iron cyclohexadienyl complex with carbon, oxygen, nitrogen, and phosphorus nucleophiles, followed by cleavage with amines and subsequent decomplexation, yielded 18 different cyclohexadienoic acid amides of high purity.

Despite the rapid development of new organometallic methods for solid-phase carbon−carbon bond formation,[1] in particular palladium-catalyzed cross-coupling,[2] available methodology for the formation of carbon−carbon bonds involving sp^3-hybridized carbons is still limited. Iron carbonyl complexes of alkenes, dienes, and arenes are versatile intermediates for the formation of carbon−carbon bonds,[3] but there are as yet few examples of their application in solid-phase synthesis. An early study by Pittman describes the addition of nucleophiles to polymer-bound π-allyliron tetracarbonyl cations, using triphenylphosphine or ethyl acetoacetate anion as the nucleophiles.[4] Kane-Maguire and Pyne report the preparation and characterization of polymer-supported dicarbonyl(dienyl)(triphenylphosphine) iron complexes, where the complex is linked to the solid support via the phosphine ligand,[5] and also describe the reactions of these complexes with hydrogen, amine, and phosphine nucleophiles. Knölker has used polymer-bound tricarbonyl(η^4-1-aza-1,3-butadiene)iron complexes as iron tricarbonyl transfer reagents,[6] and Wrighton and Pittman investigated the use of polymer-bound iron carbonyl complexes in the photocatalyzed isomerization of alkenes and the reaction of alkenes with trialkylsilanes.[7] Recently, Ruhland and co-workers have developed an efficient method for S$_N$Ar-type reactions with iron arene complexes using a wide scope of nucelophiles.[8] Our interest lies in the study of cationic iron dienyl complexes and their reaction with nucleophiles. Despite the early report by Pittman, such complexes have not been used for the formation of carbon−carbon bonds, nor have they been applied in a combinatorial sense, i.e., combined with a different reaction in order to increase the number of possible

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(1) For some recent reviews, see: (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549. (b) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, 101, 137−202. (c) Reginato, G.; Taddei, M. *Farmaco* **2002**, *57*, 373−384.

(2) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885−939.

(3) For a review on iron carbonyl diene and dienyl complexes, see: Pearson, A. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 637−683.

(4) Pittman, C. U. *Macromolecules* **1974**, *7*, 396−397.

(5) Siu, A. F. H.; Kane-Maguire, L. A. P.; Pyne, S. G.; Lambrecht, R. H. *J. Chem. Soc., Dalton Trans.* **1996**, 3747−3754.

(6) Knölker, H. J.; Gonser, P. *Synlett* **1992**, 517−520.

(7) Sanner, R. D.; Austin, R. G.; Wrighton, M. S.; Honnick, W. D.; Pittman, C. U. *Inorg. Chem.* **1979**, *18*, 928−932.

(8) Ruhland, T.; Bang, K. S.; Andersen, K. *J. Org. Chem.* **2002**, *67*, 5257−5268.

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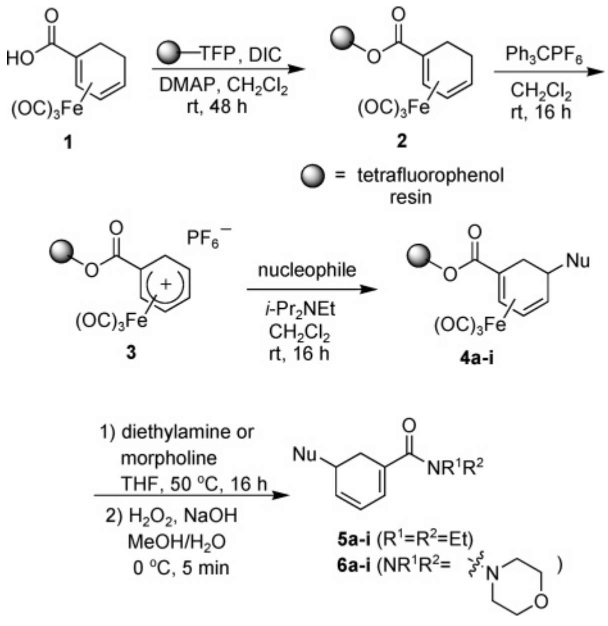
products. The advantages of the use of iron chemistry as compared to the more widely used palladium-catalyzed reactions are not only that no functionality in the form of a halide or pseudohalide is needed on the carbon undergoing nucleophilic substitution but also that a plethora of different nuclophiles can be used, enabling the formation of both carbon–carbon and carbon–heteroatom bonds using *the same methodology*, i.e., compounds of high diversity can be prepared in the same library. Examples of nucleophiles reported in solution-phase reactions with cationic iron dienyl complexes are alcohols, amines, electron-rich aromatics, enolates, silyl enol ethers, activated methylene compounds, allyl silanes, hydrides, phosphines, and phosphites as well as dialkylzinc, dialkylcadmium, and alkylcuprate reagents.[9] In this report we describe the application of some of these types of nucleophiles, including the use of carbon nucleophiles, in the solid-phase synthesis of cyclohexadienoic acid amides using iron carbonyl cation methodology.

Iron carbonyl complex **1** was prepared according to an earlier published procedure[10] and subsequently attached to commercially available tetrafluorophenol resin (Scheme 1).[11]

Scheme 1. Solid-Phase Synthesis of Cyclohexadienoic Acid Amides via Polymer-Bound Iron Carbonyl Complex **3**



IR analysis verified the presence of C≡O vibrations at 2060 and 1979 cm^{-1}. Hydride abstraction and subsequent cation formation was accomplished via treatment of **2** with triphenylcarbenium hexafluorophosphate to yield polymer-bound iron dienyl complex **3**. Treatment with carbon, oxygen, nitrogen, or phosphorus nucleophiles in the presence of an amine yielded complexes **4a–i**.

Cleavage with diethylamine or morpholine at 50 °C was followed by rapid decomplexation with alkaline hydrogen peroxide yielding the desired substituted cyclohexadienoic acid amides **5a–i** and **6a–i** (Figure 1). The results are displayed in Table 1. The documented yields are the overall yields for the five-step sequence.

Table 1. Overall Yields and Purities of **5** and **6** in the Solid-Phase Reaction of Nucleophiles with Polymer-Bound Iron Carbonyl Cation **3**

entry	nucleophile	product[a]	overall yield[b] (%)	purity[c] (%)
1	*N*-methylindole	**5a**	30	100
2	*N*-methylindole	**6a**	56	92
3	trimethoxybenzene	**5b**	19	95
4	trimethoxybenzene	**6b**	50	93
5	3-phenylpropanol	**5c**	30	100
6	3-phenylpropanol	**6c**	47	91
7	cyclopentanol	**5d**	12	87[d]
8	cyclopentanol	**6d**	24	100
9	*t*-butanol	**5e**	9	37[d]
10	*t*-butanol	**6e**	18	19[d]
11	*p*-toluidine	**5f**	14	87
12	*p*-toluidine	**6f**	23	86
13	*p*-anisidine	**5g**	15	100
14	*p*-anisidine	**6g**	31	86
15	diethylamine	**5h**	35	54
16	diethylamine	**6h**	15	85
17	triethyl phosphite	**5i**	33	85
18	triethyl phosphite	**6i**	27	100

[a] **5**, R^1 = R^2 = Et; **6**, NR^{1}R^2 = morpholinyl. [b] Yield after silica gel filtration for the five-step sequence in Scheme 1, calculated from the intial loading of the TFP resin. [c] Purity of product after silica gel filtration, determined by HPLC (ELS). [d] Purity in this case determined by HPLC (DAD).

The carbon nucleophiles indole and trimethoxybenzene gave the desired products in high purity. Cleavage with morpholine (entries 1 and 3) gave a higher yield than the corresponding reaction with diethylamine (entries 2 and 4), with yields in the former case of 50–56%, indicating average yields of 87–89% for the individual steps in the reaction sequence. Noteworthy is that unactivated nucleophiles can be used in these types of transformations, i.e., anionic carbon nucleophiles are not needed.

Three different oxygen nucleophiles of varying degrees of steric hindrance were tried in the coupling reactions. 3-Phenylpropanol gave the desired ether adducts of high purities in yields similar to those obtained for the carbon nucleophiles, with a better yield for the morpholinyl amide in this case as well (entries 5 and 6). For cyclopentanol the yields dropped, although the desired products were still formed (entries 7 and 8) and for the more bulky *tert*-butyl alcohol, the steric hindrance of the nucleophile lowered the overall yields to 9–18%. According to analysis by MS, the main byproducts in these cases are the corresponding unsubstituted benzamides.

Amine nucleophiles performed somewhat poorer than the carbon and oxygen nucleophiles, probably because of some

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(9) Pearson, A. J. *Iron Carbonyl Compounds in Organic Synthesis*; Academic Press Inc.: New York, 1994; pp 97–164.

(10) Graden, H.; Hallberg, J.; Kann, N.; Olsson, T. *J. Comb. Chem.* **2004**, *6*, 783–788.

(11) Tetrafluorophenol resin is available from Argonaut Technologies.

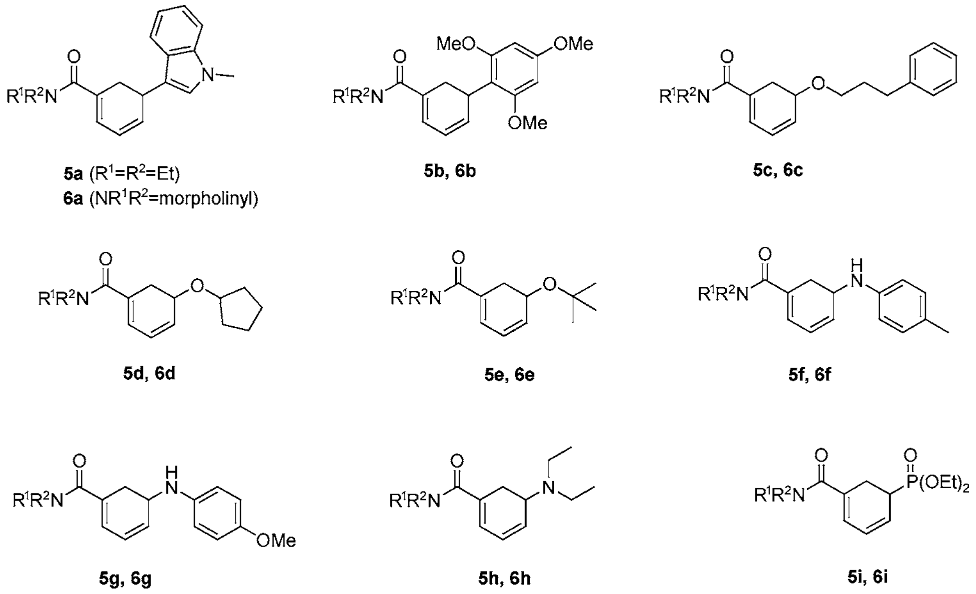

Figure 1. Structures of product cyclohexadienoic acid amides **5a**−**i** and **6a**−**i**.

extent of nucleophilic attack by the amine on the activated ester moiety, resulting in premature cleavage from the resin. Both aliphatic and aromatic amines were used, i.e., two different aniline derivatives (entries 11−14) as well as the more nucleophilic dimethylamine (entries 15 and 16), yielding the desired products in overall yields of 14−35% and somewhat lower purities than earlier. One reason for the lower purities in this case could be side reactions during the oxidative removal of the iron carbonyl moiety due to facile oxidation of the amine functionality.

One phosphorus derivative was also tried, triethyl phosphite. Despite the unreactive nature of such a nucleophile, the corresponding diethylphosphonate were formed in high purities, with the cleavage using diethylamine giving a slightly higher yield in this case.

In summary, we have developed methodology for the solid-phase synthesis of carbon-, oxygen-, nitrogen-, and phosphorus-substituted cyclohexadienoic acid amides amenable to the preparation of combinatorial libraries. It should be noted that the same reaction conditions are used for all substrates despite the different nature of the nucleophiles and that no extra functional group is needed on the substrate carbon undergoing reaction. The methodology thus forms a complement to already existing methods for carbon−carbon and carbon−heteroatom bond formation on solid phase.

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Supporting Information Available: Experimental procedures for the preparation of polymer-supported intermediates **2**−**4** and cyclohexadienoic acid amides **5a**−**i** and **6a**−**i**, and characterization data for products **5a**−**i** and **6a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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