New Methodologies for the Oxidation of Fischer Carbene Complexes: Synthesis of Hydrazides

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ABSTRACT
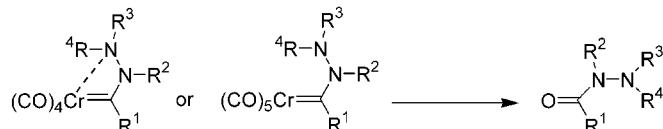
We report new, high-yield methodologies for oxidizing Fischer carbenes, particularly hydrazinocarbene complexes. The reagents traditionally used to oxidize Fischer carbenes have failed because of the stability of hydrazinocarbene complexes and the easy oxidation of formed hydrazides in the reaction conditions. The three newly developed methodologies are very mild, fast, efficient, and complementary. Differently functionalized hydrazinocarbene complexes can be oxidized to afford new hydrazides.

Many examples of synthetic applications of Fischer-type carbene complexes have so far been reported.[1] In general, the synthetic strategy consists of functionalizing the complexes (also in a stereoselective manner) and then converting them into organic compounds. Among the reported procedures for the recovery of the organic ligand as a stable organic molecule, oxidation is the easiest and most efficient and converts the metal–carbon into the O=C bond.

We have recently developed two complementary synthetic methodologies to obtain hydrazinocarbene complexes[2] and studied their reactivity.[3] In particular, we have shown that they are suitable substrates for metathesis reactions.[4] In connection with the last study, we became interested in the recovery of the organic ligand as hydrazide by means of the oxidation of hydrazinocarbene complexes.

Several methods have been reported to oxidize Fischer-type alkoxy and amino carbene complexes, but there are sometimes problems in terms of low yields (e.g., using DMSO,[5] oxone,[5] ceric ammonium nitrate (CAN),[5,6] PhIO,[5] air[7]) or the formation of byproducts (e.g., using pyridine N-oxide (PNO),[8] silica and air,[9] wet silica and air,[10] CAN[5,9]).

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(1) For recent reviews, see: (a) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 1385–1391. (b) De Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964–4002. (c) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591–3637. (d) Barluenga, J.; Fananas, F. J. *Tetrahedron* **2000**, *56*, 4597–4628. (e) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257–1280. (f) Barluenga, J.; Florez, J.; Fananas, F. J. *J. Organomet. Chem.* **2001**, *624*, 5–17.
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Tetracarbonyl chelate hydrazinocarbene complexes such as **1a** are very stable toward air (several months are needed for a complete oxidation of **1a** into the hydrazide **2a**[3], Scheme 1), whereas the treatment of **1a** with CAN affords

Scheme 1. First Attempts to Oxidize **1a**
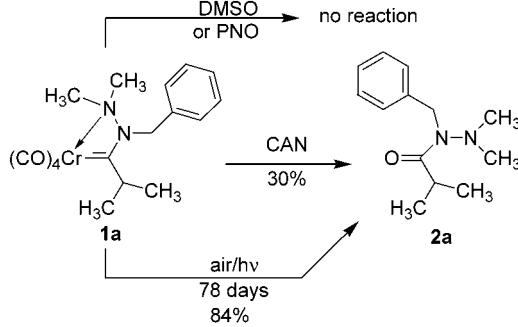
2a in only 30% yield, and DMSO or PNO give no reaction at all.

Hydrazides are also known to be very sensitive to many oxidants, such as Pb(OAc)₄, SeO₂, DDQ, MnO₂, NaNO₂,[11a] and CAN,[11b,c] and this could explain the low yield obtained with CAN. Another potential drawback is that hydrazides are neutral bidentate chelating ligands for transition metal cations[12] and may coordinate the Cr(III) arising from the oxidation of the complexes or the Ce(III) formed from CAN, thus making it difficult to isolate the hydrazides. A similar problem has been reported in the case of the oxidation of aminocarbene complexes[13] with CAN. We therefore sought alternative and efficient oxidation methods for both tetracarbonyl and pentacarbonyl hydrazinocarbene complexes.

We now report three complementary oxidation methodologies using three different reagents. The first protocol is reported in Table 1 and uses NaOCl or KOCl as the oxidizing agents, slowly generated in situ from Ca(OCl)₂ (which is not very soluble in the reaction medium), and NaHCO₃ or a phosphate buffer (Table 1).[14,15]

The reactions described in Table 1 are very fast (10 min or less) in the presence of a catalytic amount of a quaternary ammonium salt (Bu₄NHSO₄); otherwise, they are very slow. The pH of the reactions performed with NaHCO₃ (condition A) was 8−9; it was around 7 with the phosphate buffer (condition B). The use of a phosphate buffer was expressly investigated in order to oxidize pH-sensitive hydrazinocar-

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(14) This methodology ensures a low concentration of oxidant (NaOCl or KOCl) in the reaction medium.

Table 1. Oxidation of Tetracarbonyl Hydrazinocarbene Complexes **1b−e** into Hydrazides **2b−e**

entry	R¹	R²	conditions[a]	hydrazide	yield (%)
1	CH₂Ph	CH₂Ph	A	**2b**	92
2[b]	CH₃	CH₂Ph	A	**2c**	96
3[b]	H	CH₃	B	**2d**	90
4	H	HO-cyclohexyl	B	**2e**	28
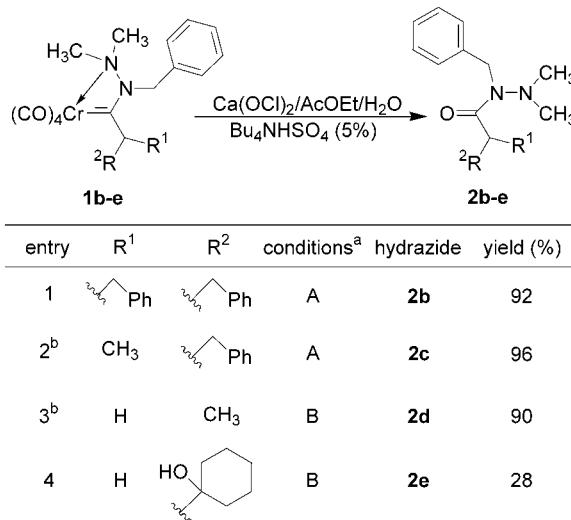
[a] Reaction conditions: room temperature, water/AcOEt = 1/1. A: 3 equiv of Ca(OCl)₂, 10 equiv of NaHCO₃. B: 2 equiv of Ca(OCl)₂, 10 equiv of K₂HPO₄, 10 equiv of KH₂PO₄. [b] For the synthesis of complexes see ref 3; for complexes **1** and **4** see Supporting Information.

bene complexes such as those arising from aldol[16] (Table 1, entry 4) or Michael addition reactions (Table 2, entry 3), which could epimerize in basic medium.[17] Under reaction conditions, the Cr(III) gives insoluble salts and does not interfere with hydrazide extraction. This method was also successfully used to oxidize hydrazino and amino pentacarbonylcarbene complexes **3**, **5**, and **7** (Scheme 2).

The yields reported in Table 1 and Scheme 2 were generally very high, with the exceptions of entry 4 (Table

Table 2. Oxidation of Tetracarbonyl Hydrazinocarbene Complexes Using in Situ Generated Iodine

entry	R¹	R²	conditions[a]	hydrazide	yield (%)
1[b]	CH₃	CH₂Ph	A	**2c**	96
2	H	HO-cyclohexyl	B	**2e**	84
3[b]	H	oxocyclohexyl	A	**2f**	96
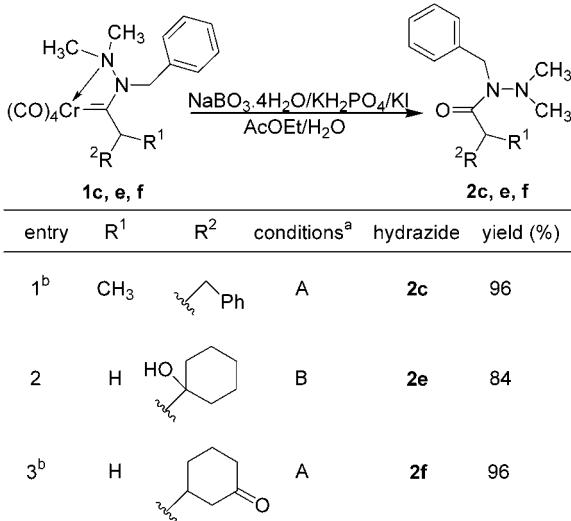
[a] Reaction conditions: water/AcOEt = 1/1, 10 equiv of KH₂PO₄. A: 6.7 equiv of NaBO₃·4H₂O, 10 mol % of KI. B: 5 equiv of NaBO₃·4H₂O, 3 mol % of KI. [b] For the synthesis of starting complexes see ref 3.

Scheme 2. Oxidation of Pentacarbonyl Carbene Complexes **3**, **5**, and **7**[a]
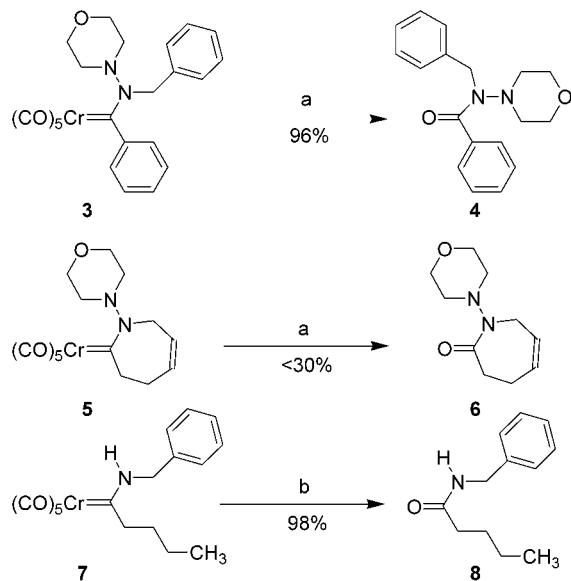
[a] Reaction conditions: 10 equiv of NaHCO$_3$, water/AcOEt = 1/1; (a) 4 equiv of Ca(OCl)$_2$; (b) 3 equiv of Ca(OCl)$_2$.

1) and complex **5** (Scheme 2) because the hydrazides **1e** and **6** were unstable in the oxidative condition. We were particularly interested in solving these two problems because complex **1e** (entry 4) and compound **5** are representative of two classes of carbenes respectively arising from the aldol addition and metathesis reactions[4] studied in our laboratories. We therefore turned our attention toward alternative oxidizing reagents and set up a new method that uses the iodine generated in situ by the oxidation of KI with sodium perborate at pH 7 by the addition of 10 equiv of KH$_2$PO$_4$[18] in the biphasic water/AcOEt system (Table 2).

In this way, it is possible to modulate oxidation by varying the amount of KI. This method is very mild because of the neutral condition and the small amount of free I$_2$[19] and makes possible the oxidation of the complex **1e** in high yield (entry 2, Table 2). Using this complex, only 5 min were enough to complete the reaction with 3 mol % of KI[20] and 5 equiv of

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(15) **General Procedure. Oxidation of Complexes by Ca(OCl)$_2$.** A solution of the carbene complex (1 equiv) in ethyl acetate (10 mL for 3.7 mmol of complex) was added to an aqueous solution of NaHCO$_3$ (10 equiv; pH 8−9, Scheme 2 and Table 1, condition A) or K$_2$HPO$_4$/KH$_2$PO$_4$ (10 equiv each; pH 7, Table 1, condition B) and tetrabutylammonium bisulphate (TBAB; 5 mol %) in water (10 mL for 0.37 mmol of complex). Ca(OCl)$_2$ (2 equiv at pH 7, condition B, 3 equiv at pH 8−9, condition A, 4 equiv with complexes **3** and **5**, Scheme 2) was added by stirring. After a few minutes the reaction was quenched with a Na$_2$SO$_3$ saturated aqueous solution and extracted with diethyl ether (3 × 20 mL). The organic layer was collected, filtered on Celite, and dried over Na$_2$SO$_4$, and the solvent was removed in vacuo to give the hydrazide as the only product and in high yield (exceptions are Table 1, entry 4 and Scheme 2, complex **5**).

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(17) We have achieved high diastereoselective Michael additions, e.g., the addition of **1d** to chalcone and cyclohexenone gave a de ≥ 92%. Results to be published.

(18) For the experimental procedure see Supporting Information.

perborate. Entries 1 and 3 needed 2 h of stirring, 10 mol % of KI, and 6.7 equiv of perborate. However, pentacarbonyl complexes **3** and **5** are not oxidized by this method. These negative results could be in line with our hypothesis of the reaction mechanism, outlined in Scheme 3. In the first step,

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Scheme 3. Hypothesis of the Oxidation Mechanism
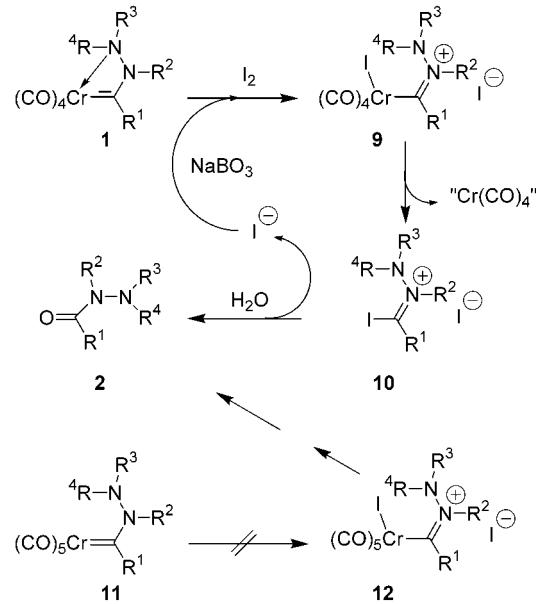
iodine attacks the metal of complex **1** displacing the nitrogen atom; this is not possible in the case of the pentacarbonyl-carbene complexes **11** because, in the expected intermediate **12**, the metal would be seven-coordinated and carbonyl chromium complexes, contrary to molybdenum and tungsten complexes, have no tendency to show such coordination[21] (except for very electron-rich complexes).[19b,21a] The oxidation of the pentacarbonylcarbene complexes **11** cannot take place in these conditions. On the contrary, the addition of iodine to tetracarbonylcarbene complexes **1** leads to the easy opening of the four-membered ring to give the intermediate **9**. Reductive elimination of the chromium tetracarbonyl unit affords **10**, which are hydrolyzed to give the final hydrazides **2**. Iodine is regenerated by the oxidation of iodide with sodium perborate.

Compounds similar to iodide **10** have been isolated as the products of oxidation of diaminocarbene complexes of

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(19) Only a few examples of the oxidation of group VI metal carbene complexes by iodine have been reported. These complexes have in common the fact that they are very electron-rich as diaminocarbenes, metal acylates, and anions. (a) Lappert, Michael F.; Pye, Peter L. *J. Chem. Soc., Dalton Trans.* **1977**, 1283−1291. (b) Soderberg, Bjorn C.; Bowden, Brian A. *Organometallics* **1992**, *11*, 2220−2223. (c) Liu, Shiuh-Tzung; Ku, Rong-Zhi; Liu, Chung-Yuan; Kang, Fu-Mei. *J. Organomet. Chem.* **1997**, *543*, 249−250. (d) Fuchibe, Kohei; Iwasawa, Nobuharu. *Tetrahedron* **2000**, *56*, 4907−4915.

(20) With 10 mol % of KI, the yield was lower and many byproducts were formed.

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Scheme 4. Oxidation of Tetracarbonyl Hydrazinocarbene Complexes: Third Method[a]
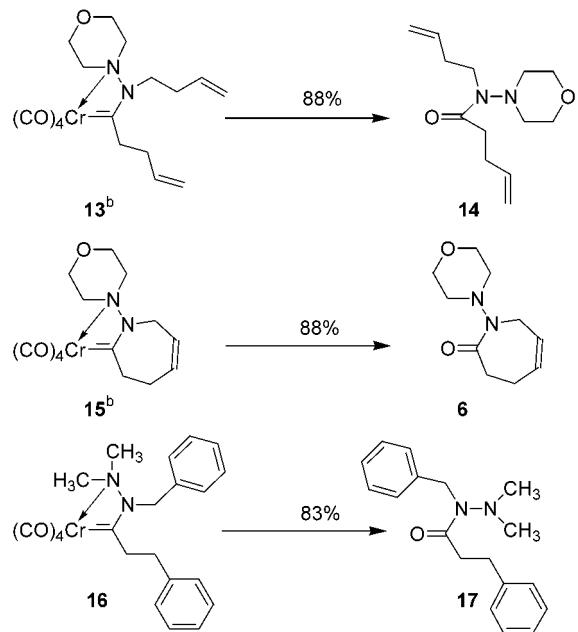
[a] Reaction conditions: water/AcOEt = 1/1, 10 equiv of NaHCO₃, 1.1 equiv of iodine. [b] For the synthesis of the starting complexes see ref 4.

chromium[19c] and molybdenum[19a] with iodine. On the basis of the above considerations, it seems that the oxidation of the pentacarbonyl complexes **11** requires their initial conversion into the reactive tetracarbonyl complexes **1** by heating in dichloromethane at reflux[3]. However, we have observed that complexes **13** and **15**[4] (Scheme 4), and generally the tetracarbonyl complexes with the morpholine residue, need

1.1 equiv of iodine as oxidant in a biphasic water/AcOEt system and sodium bicarbonate.[18] In this way, the reaction is very fast and completed in about 5 min. On the contrary, with the catalytic amount of iodide described in Table 2, the oxidation is too slow. In brief, we studied the oxidative detachment of the metal on penta- and tetracarbonylhydrazinocarbene complexes and have developed three new complementary methods of oxidation that cover a wide range of hydrazinocarbene complexes. In particular, tetracarbonylcarbene can be oxidized with NaOCl or KOCl, and with I₂ (generated in situ by KI or added as such), and pentacarbonyl derivatives are oxidized by NaOCl.

The examples selected in this article are representative of new classes of hydrazinocarbene complexes obtained in our laboratory by means of aldol addition (Table 2, entry 2), Michael addition (Table 2, entry 3), and metathesis reactions (complex **15**). Their transformation into the corresponding organic isolobal hydrazides allows this chemistry to be exploited for organic synthesis. In addition, we demonstrate that the method using Ca(OCl)₂ can be useful with different Fischer-type carbene complexes such as aminocarbenes (Scheme 2, complex **7**).

Supporting Information Available: Experimental details and characterization data for the products and the complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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