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A Simple and Efficient Transformation of Fischer Carbene Complexes into Bromomethyl Ketones or β-Ketoesters

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Abstract

Fischer-type carbene complexes react *via* nucleophilic attack with dibromomethyllithium or haloester lithium enolates to afford bromomethyl ketones or β-ketoesters, respectively.

Keywords: Fischer carbene complexes; bromomethylketones; β-ketoesters.

Fischer-type carbene complexes have become highly useful intermediates in organic synthesis, due to the role that the metal center plays in controlling the reactivity and selectivity of reactions at the substituent of the carbene carbon, showing advantages in comparison with their organic analogues [1-5].

In this synthetic strategy the last, key step involves the cleavage of the carbon-metal double bond in the Fischer-type carbene complex. Several methodologies can be used to transform Fischer carbene complexes into different organic compounds such as esters [6-9], aldehydes [10], ketones [11, 12], ethers [13] or methyl vinyl ethers [14]. In this context, we have previously described a simple one-pot transformation of aromatic methoxycarbene complexes into aromatic ketones, using *in situ* generated chloromethyllithium [15].

In the present communication we report two easy and simple one-pot transformations of alkoxycarbene complexes, using dibromomethyllithium or α-haloester lithium enolates, into bromomethyl ketones or β-ketoesters, respectively; when enolates derived from α,α-dihaloesters are used instead of α-haloester lithium enolates, α-halo-β-ketoesters are obtained. These compounds are useful in organic synthesis [16,17].

Thus, treatment of carbene complexes **1** with dibromomethyllithium generated *in situ* at -78 °C [18] gives, after hydrolysis, the corresponding bromomethyl ketones **5** (Scheme 1 and Table 1).

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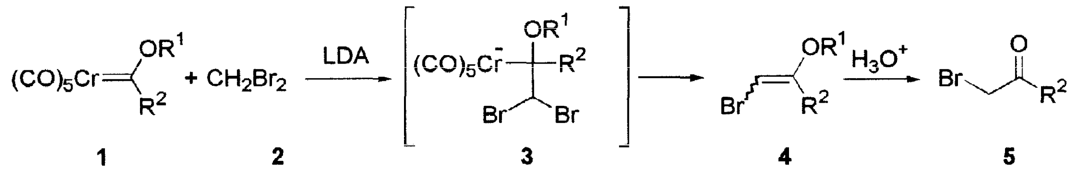


Scheme 1

In a typical reaction, LDA [prepared from MeLi (1 mL of 1.5 M solution in Et_2O; 1.5 mmol) and diisopropylamine (0.21 mL; 1.5 mmol) in THF (5 mL)] was added dropwise to a stirred solution of carbene complex **1** (1 mmol) and dibromomethane **2** (0.11 mL; 1.5 mmol) in THF (5 mL) at -78°C, over 5 min. After stirring at -78°C for 5 min, the mixture was allowed to warm to room temperature, hydrolysed with H_2SO_4 (1N; 15 mL) and extracted with Et_2O (3x10 mL). The solvents were distilled (0.1 mm Hg) and the crude mixture product was subjected to flash chromatography over silica gel to provide pure bromomethyl ketones **5**.

Table 1.

Conversion of Fischer carbene complexes **1** into bromomethyl ketones **5** with dibromomethyllithium.

Entry	R^1	R^2	Product[a]	Yield (%)[b]
1	Me	phenyl	**5a**	94
2	Me	*p*-methoxyphenyl	**5b**	89
3	Me	2-furyl	**5c**	85
4	Me	β-naphthyl	**5d**	81
5	Me	*trans*-phenylcyclopropyl	**5e**	82
6	Me	*trans*-(*p*-chlorophenyl)cyclopropyl	**5f**	79
7	Me	2-bromo-3-phenylcyclopropyl	**5g**	85
8	(-)-8-phenylmenthyl	*trans*-phenylcyclopropyl	**5h**	71
9	(-)-8-phenylmenthyl	*trans*-(*p*-chlorophenyl)cyclopropyl	**5i**	81
10	(-)-8-phenylmenthyl	2-bromo-3-phenylcyclopropyl	**5j**	76

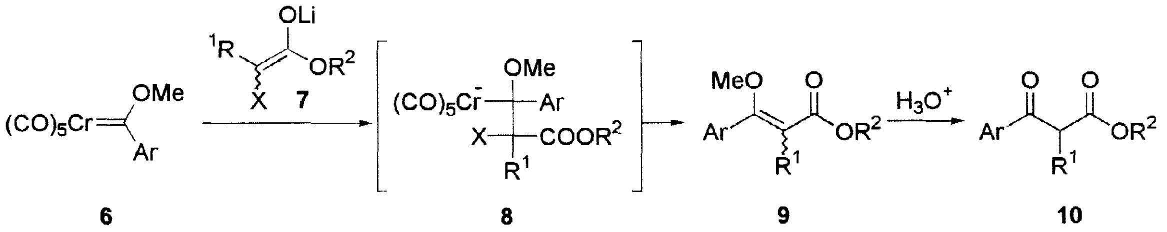
[a] All products were fully characterized by spectroscopic methods (IR, ^{1}H- and ^{13}C-NMR, and mass spectroscopy).

[b] Isolated yield based on the starting Fischer carbene complex.

The reaction may be viewed as proceeding *via* nucleophilic attack by the dibromomethyllithium upon the electron-deficient carbene carbon to produce the intermediate **3** which subsequently undergoes a spontaneous β-elimination affording the corresponding bromo enol ether **4**. Hydrolysis of **4** affords the bromomethyl ketone **5**. This mechanism is supported by the isolation, before hydrolysis, of the bromo enol ethers **4a**, **4d**, **4f** and **4h** (with a *Z*/*E* relationship of approximately 1:1) from the carbene complexes **1a**, **1d**, **1f** and **1h**.

This described method is general for aromatic, heteroaromatic and cyclopropyl carbene complexes (Table 1); however, no alkyl ketones were obtained from alkylmethoxycarbene complexes since in this case dibromomethyllithium was protonated by the acidic H_α to the carbene-carbon atom.

We have also examined the nucleophilic addition of haloester lithium enolates, generated by deprotonation of the corresponding α-monohalo- or α,α-dihalo-esters with LDA, to aromatic alkoxycarbene complexes.



Scheme 2

The reaction of aromatic alkoxycarbene complex **6** with the corresponding α-haloester or α,α-dihaloester lithium enolate **7** at -78 °C led, after quenching with silica gel and standard purification by silica gel column chromatography, to enol ethers **9** as a 1:1 mixture of *Z* and *E* isomers. Subsequent hydrolysis of enol ethers **9** with H_2SO_4 in THF afforded the corresponding pure β-ketoesters **10** (Table 2 and Scheme 2).

Table 2.

Conversion of aromatic Fischer carbene complexes **6** into enol ethers **9** and β-keto esters **10** with α-haloester or α,α-dihaloester lithium enolates.

Entry	Ar	X	R^1	R^2	Product[a]	Yield (%)[b]
1	phenyl	Cl	H	Et	**9a**	80
2	phenyl	Cl	H	Et	**10a**	80
3	phenyl	Cl	C_4H_9	Et	**9b**	77
4	phenyl	Cl	C_4H_9	Et	**10b**	75
5	phenyl	Cl	Cl	Me	**9c**	90
6	pheny	Cl	Cl	Me	**10c**	88
7	phenyl	Br	H	Me	**9d**	87
8	*p*-methoxyphenyl	Cl	H	Et	**9e**	91
9	*p*-methoxyphenyl	Cl	H	Et	**10e**	90
10	*p*-methoxyphenyl	Cl	C_4H_9	Et	**9f**	95
11	*p*-methoxyphenyl	Cl	C_4H_9	Et	**10f**	90
12	*p*-methoxyphenyl	Cl	Cl	Me	**9g**	90
13	*p*-methoxyphenyl	Br	H	Me	**9h**	87
14	*p*-methoxyphenyl	Br	H	Me	**10h**	81
15	2-furyl	Cl	Cl	Me	**9i**	78
16	2-furyl	Cl	Cl	Me	**10i**	75
17	2-furyl	Br	H	Me	**9j**	73

[a] All products were fully characterized by spectroscopic methods (IR, ^{1}H- and ^{13}C-NMR, and mass spectroscopy).

[b] Isolated yield based on the starting Fischer carbene complex.

In a typical reaction, to a solution of LDA [prepared from diisopropylamine (0.21 mL; 2 mmol) and BuLi (1.25 mL of 1.6 M solution in hexane; 2 mmol) in THF (10 mL)] was added dropwise a stirred solution of α-haloester or α,α-dihaloester (2 mmol) in THF (5mL) at -78 °C. After stirring at -78 °C for 1 h., the carbene complex **6** (1.5 mmol) dissolved in THF (15 mL) was added. The mixture was stirred at -78 °C for 1 h. and then was allowed to warm to room temperature. The reaction was quenched with silica gel (ca. 1 g), the solvents were distilled (0.1 mmHg), and the residue was subjected to flash column chromatography over silica gel to provide the enol ethers **9**.

This transformation presumably involves the successive nucleophilic attack of the lithium enolate **7** to the carbon-metal double bond and further β-elimination of the intermediate **8** yielding the corresponding enol ether **9**, which could be isolated. Acidic hydrolysis of **9** leads to ketoester **10**.

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References.

[1] Dötz KH. Angew. Chem., Int. Ed. Engl. 1984;23:587-608.

[2] Dötz KH, Fischer H, Hofmann P, Kreissel FR, Schubert U, Weiss K. Transition Metal Carbene Complexes. Deerfield Beach: Verlag Chemie, 1984.

[3] Wulff WD. Metal-Carbene cycloadditions. In: Trost BM, Fleming I. editors. Comprehensive Organic Synthesis. Oxford: Pergamon:, 1991;Vol. 5:1065-1113.

[4] Wulff WD. Transition Metal Carbene Complexes: Alkyne and Vinyl Ketene Chemistry. In: Abel AW, Stone FGA, Wilkinson G. editors. Comprehensive Organic Synthesis II. Oxford: Pergamon, 1995;Vol. 12:469-547.

[5] Hegedus LS. Transition Metal Carbene Complexes: Photochemical Reactions of Carbene Complexes. In: Abel AW, Stone FGA, Wilkinson G. editors. Comprehensive Organic Synthesis II. Oxford: Pergamon, 1995;Vol. 12:549-576.

[6] With dimethylsulfoxide: Casey CP, Burkhardt TJ, Bunnell CA, Calabrese JC. J. Am. Chem. Soc. 1977;99:2127-2133.

[7] With Ce(IV): Casey CP, Burkhardt TJ. J. Am. Chem. Soc. 1972;94:6543-6544.

[8] With pyridine *N*-oxide: Erker G, Sonsa F. Organometallics 1990;9:1949-1953.

[9] With dimethyldioxirane: Lluch A, Jordi L, Sánchez-Baeza F, Ricart S, Camps F, Moretó JM. Tetrahedron Lett. 1992;33:3021-3022.

[10] With hydrogen bromide: Fischer EO, Walz S, Kreis G, Kreissl FR. Chem. Ber. 1977;110:1651-1658.

[11] Casey CP, Burhkardt TJ. J. Am. Chem. Soc. 1972;94:6543-6544.

[12] Casey CP, Bertz SH, Burkhardt TJ. Tetrahedron Lett. 1973:1421-1424

[13] Casey CP, Neumann SM. J. Am. Chem. Soc. 1977;99:1651-1652.

[14] Fischer EO, Plabst D. Chem. Ber. 1974;107:3326-3331.

[15] Barluenga J, Bernad Jr. PL, Concellón JM. Tetrahedron Lett. 1994;35:9471- 9472.

[16] De Kimpe R, Verhé R. Synthesis and Reactivity of α-Halogenated Ketones. In: Patai S, Rappoport Z, editors. The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines. New York: John Wiley & Sons, 1988:1-225.

[17] Tietze LF, Beifuss U. The Knoevenagel Reaction. In: Trost B M, Fleming, I, editors. Comprehensive Organic Synthesis, Vol 2. Oxford: Pergamon Press, 1991:341-394.

[18] Barluenga J, Llavona L, Concellón JM, Yus M. J. Chem. Soc., Perkin Trans. 1 1991:297-300.