Notes

Aqueous Organometallic Chemistry: Phase-Transfer-Catalyzed Alkylation of Fischer Carbene Complexes†

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Summary: Fischer carbene complexes can be conveniently alkylated, often with high diastereoselectivity, by reactive halides under biphasic conditions.

Introduction

Fischer carbene complexes of group VI transition metals have emerged as a versatile class of organometallic intermediates useful in organic synthesis[1] as testified by a large number of natural products that have been synthesized *via* Fischer carbene complexes. Several important applications include carbocyclic[2] and heterocyclic[3] annulation by thermal reactions, as well as photochemical CO insertions leading to β-lactams[4] and cyclobutanones.[5]

Since the most common route to these complexes involves reaction of organolithium or organomagnesium reagents with metal hexacarbonyl, sensitive functionalities are incompatible with such a procedure. Therefore, alkylation of the acidic α-carbon is often a method of choice[6] to prepare functionalized Fischer carbene complexes. Alkylations are usually carried out in tetrahydrofuran using *n*-butyllithium as a base. However, certain limitations are encountered with this protocol. For instance, reactions are unsatisfactory if alkoxycarbene complexes are not alkylated using primary triflates.[7] This disadvantage has been redressed partly by the use of aminocarbene complexes[8] or by replacement of a *cis*-CO ligand with a phosphine.[7] While dialkylation may be achieved with reactive substrates,[9] alkylation of a secondary carbon center is often difficult.

A possible source of such difficulty could lie in the magnitude of nucleophilicity of the metal carbene anion. This is reminiscent of the task of alkylating aliphatic nitro compounds at the α-carbon. The pK_a of the α-methyl group of alkoxycarbene complexes has been estimated by Casey[6] to be 8.0 in THF. Later, the pK_a of (methylmethoxycarbene)chromium complex was determined[10] in water–piperidine solvent mixture as 12.3, a value comparable to the pK_a of diethyl malonate or ethyl acetoacetate.[11] Water is known to modify the reactivity of various types of substances and the course of several reactions including organometallic ones.[12a] It was of interest, therefore, to explore whether alkylation of alkoxycarbene complexes could be achieved efficiently in the presence of water.[12b]

In this paper, we describe a facile alkylation procedure for alkoxycarbene complexes in a biphasic medium mediated by a phase-transfer catalyst. In particular, this procedure even allows efficient dialkylation with reactive electrophiles, and secondary centers can be alkylated in high yield. High diastereoselectivity has also been observed in certain reactions.

Results and Discussion

When (methyl(benzyloxy)carbene)chromium complex **3** in dichloromethane was treated with excess methyl iodide in the presence of 50% aqueous NaOH and 10 mol % of tetrabutylammonium bromide at room temperature, the dialkylated product was obtained after overnight stirring in 64% yield as the sole product. The reaction was less efficient with ethyl iodide but proceeded satisfactorily with allyl and benzyl halides. The results are summarized in Table 1 and Schemes 1 and 2.

With methylcarbene complexes **1**–**6**, in all cases, the dialkylation product was observed as the only product.

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(12) (a) Gyldenfeltd, F. V.; Marton, D.; Tagliavini, G. *Oganometallics* **1994**, *13*, 906 and ref 1–10 therein. (b) For a recent example of O-alkylation of Fischer carbene complexes using tetraalkylammonium salts, see: Hoye, T. R.; Chen, K.; Vyvyan, J. R. *Organometallics* **1993**, *12*, 2806.

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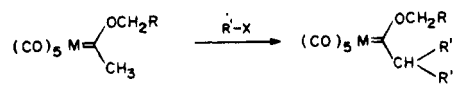
Table 1

entry	substrate	electrophile[a]	time (h)	product	yield (%)[b]
1	**1**	$(CH_3)_2C{=}CHCH_2Br$	4	**7a**	73
2	**2**	CH_3I	overnight	**8a**	64
3	**2**	$CH_2{=}CHCH_2Br$	3.5	**8b**	70[c]
4	**2**	$CH_2{=}CHCH2Cl$	3.5	**8b**	51
5	**2**	$C_6H_5CH_2Br$	3	**8c**	56
6	**2**	C_2H_5I	overnight		*d*
7	**3**	CH_3I	overnight	**9a**	64
8	**3**	$CH_2{=}CHCH_2Br$	3	**9b**	80
9	**3**	$CH_2{=}CHCH_2Br$	5	**9b**	48[e]
10	**4**	CH_3I	overnight	**10a**	58
11	**4**	$(CH_3)_2C{=}CHCH_2Br$	4	**10b**	70
12	**5**	$CH_2{=}CHCH_2Br$	3	**11a**	63
13	**5**	$C_6H_5CH{=}CHCH_2Cl$	1.5	**11b**	56
14	**5**	$C_6H_5CH_2Br$	3	**11c**	62
15	**6**	CH_3I	overnight	**12a**	61
16	**6**	$CH_2{=}CHCH_2Br$	3.5	**12b**	78
17	**13**	$C_6H_5CH_2Br$	4.5	**15**	67
18	**14**	$C_6H_5CH{=}CHCH_2Cl$	2	**16**	69

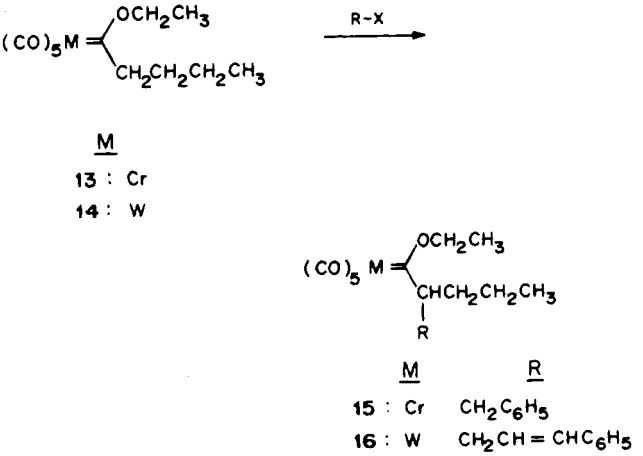
[a] 2–5 equiv used in all cases. [b] Isolated yield after chromatography. [c] When 1 equiv of allyl bromide was used, 40% dialkylated and 10% monoalkylated products were obtained. [d] Poor yield (<15%) accompanied by extensive decomposition. [e] Reaction in benzene with K_2CO_3/18-crown-6.

Scheme 1



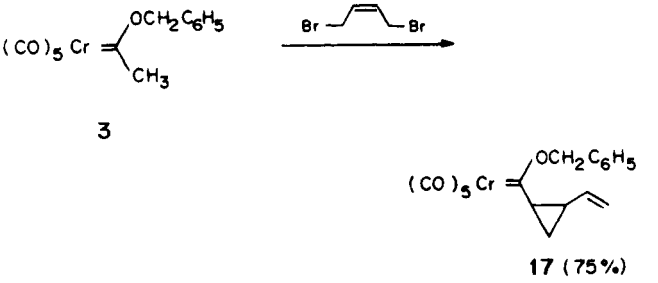
	M	R	M	R	R'
1	Cr	H	7a	H	$CH_2CH=C(CH_3)_2$
2	Cr	CH_3	8a	CH_3	CH_3
3	Cr	C_6H_5	8b	CH_3	$CH_2CH=CH_2$
4	W	H	8c	CH_3	$CH_2C_6H_5$
5	W	CH_3	9a	C_6H_5	CH_3
6	W	C_6H_5	9b	C_6H_5	$CH_2CH=CH_2$
			10a	H	CH_3
			10b	H	$CH_2CH=C(CH_3)_2$
			11a	CH_3	$CH_2CH=CH_2$
			11b	CH_3	$CH_2CH=CHC_6H_5$
			11c	CH_3	$CH_2C_6H_5$
			12a	C_6H_5	CH_3
			12b	C_6H_5	$CH_2CH=CH_2$

Scheme 2

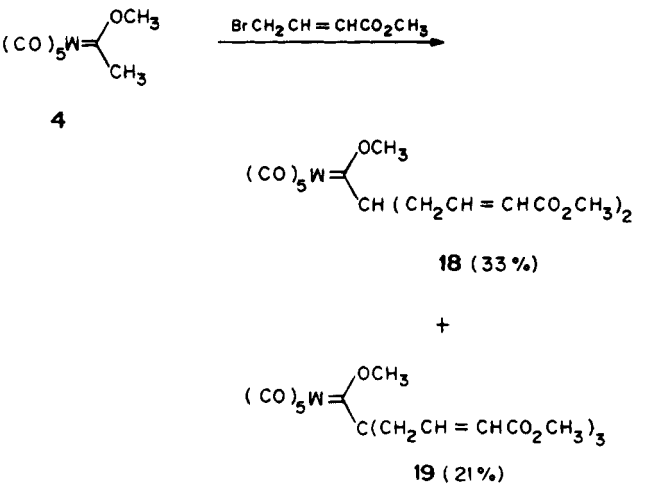


When 1 equiv of allyl bromide was used with complex **2**, the dialkylated product was obtained predominantly (40%) along with some monoalkylated product (10%), while 25% of the starting material was recovered unchanged. This indicated that the secondary carbanion underwent alkylation faster than the primary one. Indeed, the alkylations of secondary carbanionic centers were achieved in high yield, as seen from the last entries of Table 1.

Scheme 3



Scheme 4



In order to effect cyclization, *cis*-1,4-dibromo-2-butene was chosen as an electrophile. As depicted in Scheme 3, a vinylcyclopropane, rather than a cyclopentene, was readily obtained as a single diastereomer (^1H and ^{13}C NMR spectra) in high yield. The first nucleophilic substitution was followed by an intramolecular S_N2' displacement. The stereochemistry of the product was tentatively deduced[13] from the coupling constants of vicinal protons (3.6 Hz) as *trans*.

When methyl 3-bromocrotonate was used as the electrophile, di- and trialkylated products were obtained (Scheme 4). No cyclic product corresponding to alkylation followed by an intramolecular Michael addition was obtained.

Diastereoselectivity in such alkylations was studied with the cyclic carbene complex **20** reported by Casey.[14] Although the reaction shown in Scheme 5 was carried out at room temperature, only one diastereomer of the product **21** was obtained in 71% yield. The coupling constant (1.5 Hz) of the methine proton adjacent to the carbene carbon indicated the *trans*-relationship between vicinal substituents.

An interesting spiro-compound **22**, also a single diastereomer, was isolated when the substrate **20** was

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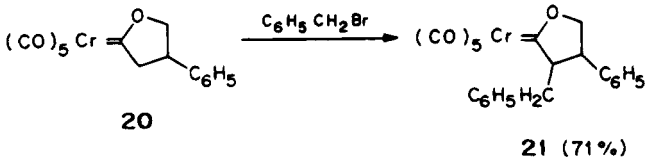
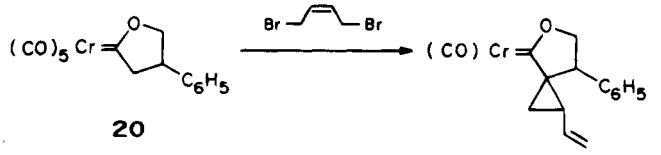
Scheme 5



20 21 (71%)

Scheme 6



20 22 (69%)

alkylated with *cis*-1,4-dibromo-2-butene (Scheme 6). A fast second alkylation leading to the cyclopropane could explain the high diastereoselectivity.

Thus, the biphasic reaction condition was found to be eminently suitable for functionalizing simpler Fischer carbene complexes by facile C−C bond formation. The origin of such facility of alkylation is, however, less clear. It was observed that the alkylation of the carbene complex **3** with allyl bromide proceeded in benzene with K_2CO_3 as base and 18-crown-6 as the PTC, to give the diallylated product **9b** in 48% yield (accompanied by some decomposition). Although this yield was lower than that obtained (80%) with aqueous NaOH/dichloromethane, the fact that the reaction at all takes place in nonaqueous medium raises an interesting question about the exact role of water.

Recently it has been shown that "naked" enolates are reactive enough to generate acylmetalates which, in turn, can be converted to carbene complexes.[15] Thus, one may need to consider the role of ion-pairing in such reactions. The carbanion generated from a carbene complex by BuLi is likely to form an ion pair between lithium and oxygen (of CO) of considerable tightness. On the other hand, in the present procedure, the tetrabutylammonium counterion may not form an efficient ion pair and thus the carbanionic reactivity would be localized on the α-carbon of the carbene complex. The same should be true if 18-crown-6 is used to capture potassium ions. The aminocarbene complexes, with pK_a of around 20.0 (see ref 16), cannot be alkylated at carbon under these biphasic conditions.[17]

Summary

In summary, we have described a mild and facile C-alkylation procedure for Fischer carbene complexes that can provide diversely functionalized products. In view of the fact that these are important synthetic intermediates and are ester (or amide) equivalents, this practical protocol is likely to find extensive application in the future. However, simple primary halides are not strong enough electrophiles to be useful with this procedure.

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(17) It is possible to *N*-alkylate aminocarbene complexes under PTC conditions, an account of which will be reported in due course.

Experimental Section

All reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Infrared spectra were recorded on a Perkin-Elmer 599B spectrometer in chloroform. ^1H and ^{13}C NMR spectra were taken either on a Bruker WH-90 or on a Bruker AC 200 spectrometer in $CDCl_3$. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal reference. Elemental analyses of solid compounds were carried out on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL. The liquid samples did not give satisfactory elemental analyses. Melting points in the Celsius scale were determined in open capillary tubes on a Thermonik Campbell melting point apparatus and are uncorrected.

Pentacarbonyl(methylmethoxycarbene)chromium(0),[18] pentacarbonyl(methylethoxycarbene)chromium(0),[19] pentacarbonyl(methyl(benzyloxy)carbene)chromium(0),[20] pentacarbonyl(*n*-butylethoxycarbene)chromium(0),[19] pentacarbonyl(methylmethoxycarbene)tungsten(0),[18] pentacarbonyl(methylethoxycarbene)tungsten(0),[19] pentacarbonyl(*n*-butylethoxycarbene)tungsten(0),[19] and pentacarbonyl(4-phenyl-2-oxacyclopentylidene)chromium(0)[14b] were prepared according to literature procedures.[21] All other reagents were obtained from Aldrich (Milwaukee, WI) and Loba Chemie (Bombay, India) and used without further purification.

General Procedure for the Alkylation of Carbene Complexes. Method A. The carbene complex (*n* mmol) and tetrabutylammonium bromide (0.1*n* mmol) in dichloromethane (15*n* mL) was treated with 50% aqueous NaOH and the halide (2−5*n* mmol). The mixture was stirred at room temperature under argon until the starting material was consumed (TLC). The reaction mixture was diluted with water, extracted with dichloromethane, dried, and concentrated under reduced pressure. The pure product was isolated by flash chromatography.

Method B. The carbene complex (*n* mmol), potassium carbonate, and 18-crown-6 (0.05*n* mmol) was treated with the halide (2−5*n* mmol). The pure product was isolated as described in method A.

Complex 7a: Orange oil. IR: 2050 (m), 1975 (sh), 1930 (s) cm^{-1}.

Complex 8a: Yellow solid (mp 39 °C). IR: 2060 (m), 1990 (sh), 1945 (s) cm^{-1}. Anal. Calcd for $C_{11}H_{12}CrO_6$: C, 45.20; H, 4.10. Found: C, 45.70; H, 4.40.

Complex 8b: Orange oil. IR: 2055 (m), 1985 (sh), 1945 (s) cm^{-1}.

Complex 8c: Orange oil. IR: 2055 (m), 1990 (sh), 1945 (s) cm^{-1}.

Complex 9a: Yellow solid (mp 52 °C). IR: 2080 (m), 2000 (sh), 1960 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{14}CrO_6$: C, 54.24; H, 3.9. Found: C, 54.84; H, 4.49.

Complex 9b: Orange oil. IR: 2060 (m), 1990 (sh), 1950 (s) cm^{-1}.

Complex 10a: Yellow solid (mp 66 °C). IR: 2060 (m), 1980 (sh), 1930 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{10}WO_6$: C, 29.27; H, 2.44. Found: C, 29.62; H, 2.47.

Complex 10b: Orange oil. IR: 2060 (m), 1980 (sh), 1920 (s) cm^{-1}.

Complex 11a: Orange oil. IR: 2080 (m), 1995 (sh), 1955 (s) cm^{-1}.

Complex 11b: Orange oil. IR: 2080 (m), 1995 (sh), 1950 (s) cm^{-1}.

Complex 11c: Orange oil. IR: 2085 (m), 2000 (sh), 1950 (s) cm^{-1}.

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(21) The substrates **1**−**6** were prepared according to the procedure described in ref 12b.

Complex 12a: Yellow solid (mp 60 °C). IR: 2090 (m), 2000 (sh), 1950 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{14}WO_6$: C, 39.50; H, 2.88. Found: C, 39.73; H, 2.87.

Complex 12b: Red oil. IR: 2080 (m), 2000 (sh), 1955 (s) cm^{-1}.

Complex 15: Orange oil. IR: 2080 (m), 1995 (sh), 1950 (s) cm^{-1}.

Complex 16: Orange oil. IR: 2075 (m), 1985 (sh), 1940 (s) cm^{-1}.

Complex 17: Yellow solid (mp 65 °C). IR: 2060 (m), 1995 (sh), 1945 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{14}CrO_6$: C, 57.14; H, 3.70. Found: C, 56.93; H, 3.94.

Complex 18: Red oil. IR: 2070 (m), 1980 (sh), 1920 (s), 1723 (s), 1657 (m) cm^{-1}.

Complex 19: Red oil. IR: 2069 (m), 1985 (sh), 1939 (s), 1731 (s), 1651 (m) cm^{-1}.

Complex 21: Yellow solid (mp 58 °C). IR: 2060 (m), 1985 (sh), 1940 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{16}CrO_6$: C, 61.68; H, 3.74. Found: C, 61.27; H, 4.16.

Complex 22: Red oil. IR: 2065 (m), 1985 (sh), 1940 (s) cm^{-1}.

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Supplementary Material Available: Tables of ^1H and ^{13}C NMR spectral data and figures showing spectra of all new compounds (54 pages). Ordering information is given on any current masthead page.

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