N,*N*-Dialkylation of Aminocarbene Complexes under Phase-Transfer Conditions

Li Zhao, Haruo Matsuyama, and Masahiko Iyoda*
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Hachioji, Tokyo 192-03

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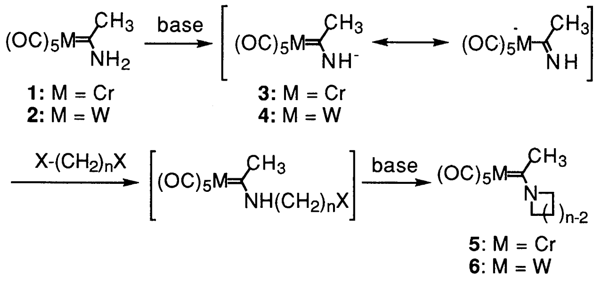
The reaction of amide anions derived from aminocarbene complexes with alkyl halides under phase-transfer conditions has been investigated. The reaction of aminocarbene complexes of chromium and tungsten with α,ω-dihaloalkanes in the presence of sodium hydroxide and tetrabutylammonium bromide in dichloromethane-water produces azetidine, pyrrolidine, hexamethyleneimine and dihydroisoindole derivatives in moderate to good yields.

Although many types of reactions of carbanions derived from alkoxy- and aminocarbene complexes have been reported,[1] only a few reactions of amide anions derived from aminocarbene complexes were known until now.[2,3]

The NH_2 groups of aminocarbene complexes (**1** and **2**) show higher acidity than that of acetamide, because amide anions (**3** and **4**) derived from **1** and **2** are stabilized by the neighboring metal carbonyl moieties.[4] Thus, the amide anions (**3** and **4**) can be generated by a rather weaker base and can be expected to react with carbon electrophiles to form nitrogen-carbon bonds.

We now report here a new methodology for the one-pot *N*,*N*-dialkylation of aminocarbene complexes under phase-transfer conditions.



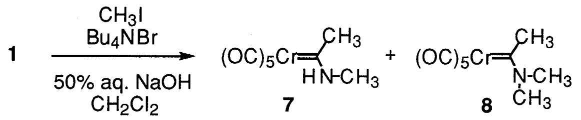
1: M = Cr
2: M = W
3: M = Cr
4: M = W
5: M = Cr
6: M = W

Our preliminary work showed that the amide anion **3** generated from **1** with butyllithium reacted with methyl iodide to produce the *N*-methylated and *N*,*N*-dimethylated aminocarbene complexes in a good yield.[5] However, the reaction of the amide anion **3** with α,ω-diiodoalkanes gave the corresponding cyclic amines only in poor yields, and a large amount of the starting materials was recovered.[5] In order to improve the reaction conditions, many basic conditions were examined. After several attempts, we found the phase-transfer conditions can be successfully applied to the alkylation of amino carbene complexes.[6]

The aminocarbene complex (1 mmol), methyl iodide (3-12 mmol), and tetrabutyl-ammonium bromide (0.1-0.2 mmol) in dichloromethane (5 ml) was treated with 50% aq. NaOH (4-8 mmol). The mixture was stirred under argon at room temperature or in an oil bath of 40-46 °C. The reaction was monitored by TLC until the starting material was consumed. After aqueous work-up, the products were isolated by column chromatography on silica gel. The results are summarized in Table 1.

Phase-transfer-catalyzed methylation proceeds at room temperature to give the monomethylated **7** as the major product (entries 1 and 2). In addition, the dimethylated product **8** can be prepared using higher temperature and increased amounts of NaOH and methyl iodide (entries 3 and 4). Thus, monomethylation and dimethylation can be carried out selectively.

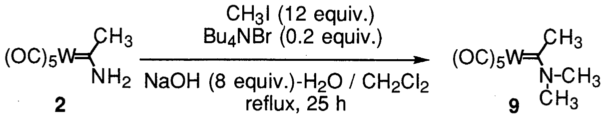
Table 1. Reactions of **1** with methyl iodide under phase-transfer conditions



Entry	NaOH (equiv.)	Bu$^n_4$NBr (equiv.)	MeI (equiv.)	Temp^a (°C)	Time (h)	Yields (%)^b **7**	**8**
1	4	0.1	3	23	7	48	0
2	4	0.2	3	23	8	49	6
3	6	0.2	6	40	15	39	20
4	8	0.2	12	46	25	0	57

^{a}Bath temperature. ^{b}Isolated yields.

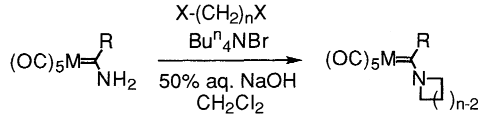
In a similar manner as above, the dimethylation of the tungsten complex **2** proceeded smoothly under phase-transfer conditions to give **9** in 64% yield.



The phase-transfer-catalyzed alkylation of aminocarbene complexes can be successfully applied to the synthesis of the azetidine derivatives as shown in Table 2. Thus, the reaction of **1** with 1,3-diiodopropane using 50% aq. NaOH (6 equiv.) and butylammonium bromide (0.2 equiv.) in refluxing CH_2Cl_2 gave **5a** in 47% yield (entry 1). In a similar manner, the reaction of the tungsten complex **2** afforded **6a**[7] in 58% yield (entry 11). The better yield in **6a** may depend on the difference in the stability of aminocarbene complexes under the reaction conditions.

The aminocarbene complexes (**10** and **11**) having a phenyl substituent react similarly with 1,3-diiodopropane to give the azetidine derivatives (**12a** and **13a**) in 49 and 51% yields, respectively. Thus, the carbene complexes (**1**, **2**, **10**, and **11**) can be converted into the azetidine derivatives (**5a**, **6a**, **12a**, and **13a**) in moderate yields under phase-transfer conditions. These results suggest that the alkylation of aminocarbene complexes under phase-transfer conditions can be applied to the synthesis of a series of carbene complexes containing nitrogen heterocycles. As shown in Table 2, the reaction of aminocarbene complexes with 1,4- and 1,5-dihaloalkanes in refluxing dichloromethane under argon for 15-24 h afforded the carbene complexes containing pyrrolidine and piperidine rings in good yields (entries 2-4, 7-9, 12-14, and 17-19). In the case of the seven-membered ring formation, the reactions of the aminocarbene complexes with 1,6-dibromohexane produced the hexamethyleneimine derivatives in 29-35% yields (entries 5, 10, 15, and 20).

Table 2. Reactions of aminocarbene complexes with α, ω-dihaloalkanes under phase-transfer conditions[a]



1: M = Cr, R = CH_3
2: M = W, R = CH_3
10: M = Cr, R = Ph
11: M = W, R = Ph

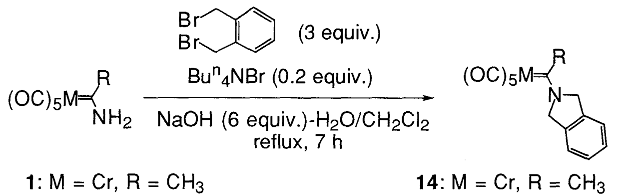
5: M = Cr **a**: n = 3
6: M = W **b**: n = 4
12: M = Cr **c**: n = 5
13: M = W **d**: n = 6

Entry	M	R	$X-(CH_2)_nX$	Product	Yield (%)[b]
1	Cr	CH_3	$I-(CH_2)_3I$	**5a**[8,9]	47
2	Cr	CH_3	$I-(CH_2)_4I$	**5b**[9,10]	65
3	Cr	CH_3	$Br-(CH_2)_4Br$	**5b**[9,10]	57
4	Cr	CH_3	$I-(CH_2)_5I$	**5c**[11]	62
5	Cr	CH_3	$Br-(CH_2)_6Br$	**5d**	29
6	Cr	Ph	$I-(CH_2)_3I$	**12a**[8,9]	49
7	Cr	Ph	$I-(CH_2)_4I$	**12b**[8,9,12]	73
8	Cr	Ph	$Br-(CH_2)_4Br$	**12b**[8,9,12]	72
9	Cr	Ph	$I-(CH_2)_5I$	**12c**[8,13]	73
10	Cr	Ph	$Br-(CH_2)_6Br$	**12d**	32
11	W	CH_3	$I-(CH_2)_3I$	**6a**	58
12	W	CH_3	$I-(CH_2)_4I$	**6b**[14]	69
13	W	CH_3	$Br-(CH_2)_4Br$	**6b**[14]	68
14	W	CH_3	$I-(CH_2)_5I$	**6c**	66
15	W	CH_3	$Br-(CH_2)_6Br$	**6d**	33
16	W	Ph	$I-(CH_2)_3I$	**13a**	51
17	W	Ph	$I-(CH_2)_4I$	**13b**	81
18	W	Ph	$Br-(CH_2)_4Br$	**13b**	76
19	W	Ph	$I-(CH_2)_5I$	**13c**	73
20	W	Ph	$Br-(CH_2)_6Br$	**13d**	35

[a] Reactions were carried out by using 1 equiv. (1 mmol) of **1**, **2**, **10** or **11**, 3 equiv. of dihaloalkane, 0.2 equiv. of Bu_4NBr and 6 equiv. of NaOH in refluxing CH_2Cl_2 for 15-24 h.
[b] Isolated yields.

The reactions shown in Table 2 proceed very smoothly, although the isolated yields are not high in some cases. The five- and six-membered ring formations occur easily as compared with the four- and seven-membered ring formations. The amino carbene complexes (**1**, **2**, **5**, **6** and **10-13**) are rather stable at room temperature but gradually decompose under the reaction conditions. Except for the reactions of aminocarbene complexes with 1,6-diiodohexane, the reactions shown in Table 2 give the *N*,*N*-dialkylated aminocarbene complexes as the sole product.

In order to apply our method to the synthesis of aminocarbene complexes containing an isoindoline moiety, the carbene complexes **14-17** were prepared. The reactions of the aminocarbene complexes with α,α'-dibromo-*o*-xylene under phase-transfer conditions proceeded smoothly to give the corresponding products in 61-63% yields. The reactivity of α,α'-dibromo-*o*-xylene was very high as compared with alkyl iodides and bromides in Table 2, and the reactions of **1**, **2**, **10** and **11** with α,α-dibromo-*o*-xylene were completed within 7 h.



1: M = Cr, R = CH_3
2: M = W, R = CH_3
10: M = Cr, R = Ph
11: M = W, R = Ph

14: M = Cr, R = CH_3
15: M = W, R = CH_3
16: M = Cr, R = Ph
17: M = W, R = Ph

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3 For organic synthesis using aminocarbene complexes, see L. H. Hegedus, *Acc. Chem. Res.*, **28**, 299 (1995).
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