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Novel Synthesis of *gem*-Dichloroaziridines from Imines via the KF/Al_2O_3-Promoted Generation of Dichlorocarbene from Chloroform

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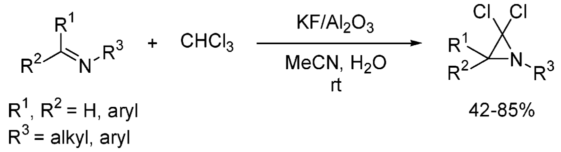

KF/Al_2O_3 was found to be an efficient base for the reaction of imines with chloroform in acetonitrile to give *gem*-dichloroaziridines **2** in moderate to high yields. The KF/Al_2O_3-promoted dichloroaziridination can be carried out with simple workup, tolerates a variety of functional groups present in the imines, and proceeds smoothly with a smaller amount of carbene source.

gem-Dichloroaziridines are valuable precursors for the preparation of pharmacologically active compounds such as indolinones,[1] analogues of natural alkaloids such as isoquinolinones[2] and isoquinolines,[3] and nitrogen-containing building blocks such as amidines[4] and aziridinones.[5] As a result, several methods for synthesis of *gem*-dichloroaziridines have been reported.[6] The preparation has been accomplished by the addition of dichlorocarbene, generated from chloroform,[6a,c,e,f] hexachloroacetone,[6b] or ethyl trichloroacetate[6d] with the appropriate bases, to imines. Among these, dichlorocarbene, which is generated from chloroform under phase-transfer-catalyzed conditions, is most frequently used for the synthesis of *gem*-dichloroaziridines because the yields are acceptable, the reaction conditions are mild, and the presence of water is not a critical factor.[6e] However, it presents problems with regard to the use of a large excess of the carbene source and the complexity of the procedures. Consequently, a general, efficient, and simple method for dichloroaziridination of imines is strongly desired.

On the other hand, the use of solid-supported reagents has become popular due to their characteristic properties such as enhanced reactivity and selectivity, a straightforward workup procedure, and milder reaction conditions.[7] For example, KF/Al_2O_3 is known to be a useful and interesting solid-supported reagent for base-induced organic reactions.[8] We recently reported on the convenient *N*-formylation of secondary amines using KF/Al_2O_3 and chloroform in acetonitrile.[9] As a result, the KF/Al_2O_3-promoted generation method of dichlorocarbene has proved to be a powerful tool for the synthesis of *N*-formamide derivatives from imines. However, since the KF/Al_2O_3-promoted methods, one of which requires both phase-transfer catalysts and KF/Al_2O_3,[10b] were regarded as being less effective than the phase-transfer-catalyzed method in addition reactions of dichlorocarbene to cyclohexene,[10] it has not been widely applied to other transformations, except in our previous report. Herein, we report on a general and convenient KF/Al_2O_3-promoted synthesis of *gem*-dichloroaziridines **2** from imines **1** and chloroform under mild reaction conditions.

Detailed studies of the reaction of *N*-benzylideneaniline (**1a**) with chloroform leading to 2,2-dichloro-1,3-diphenylaziridine (**2a**) showed that this addition reaction is influenced to a considerable extent, by bases and solvents, as shown in Scheme 1 and Table 1 (method A). The reaction of **1a** with chloroform in the presence of KF or Al_2O_3 (neutral) did not proceed at all (entries 1 and 2), while the use of commercially available KF/Al_2O_3 led to the production of the desired *gem*-dichloroaziridine **2a** in high yield. For example, when **1a** (0.5 mmol) was treated with chloroform (1.5 mmol) in the presence of KF/Al_2O_3 (2 g) in acetonitrile, **2a** was obtained in 95% yield (entry 3). As a result of an investigation of a suitable solvent for the aziridination, acetonitrile was found to

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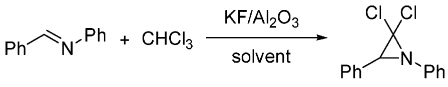
SCHEME 1. KF/Al$_2$O$_3$-Promoted Synthesis of 2a from 1a[a]



1a **2a**

[a] Method A: without addition of H$_2$O. Method B: with addition of H$_2$O.

TABLE 1. Synthesis of 2a from 1a under the Conditions of Method A[a]

entry	CHCl$_3$ (mmol)	base (g)	solvent	yield of **2a**[b] (%)	recovery of **1a**[b] (%)
1	1.5	KF (0.8)	MeCN	0	100
2	1.5	Al$_2$O$_3$ (neutral) (1.2)	MeCN	0	74
3	1.5	KF/Al$_2$O$_3$ (2)	MeCN	95 (77)[c]	0
4	1.5	KF/Al$_2$O$_3$ (2)	DMF	81	16
5	1.5	KF/Al$_2$O$_3$ (2)	CHCl$_3$	32	62
6	1.5	KF/Al$_2$O$_3$ (2)	hexane	17	74
7	1.5	KF/Al$_2$O$_3$ (2)	DME	14	80
8	1.5	KF/Al$_2$O$_3$ (2)	none	22	66
9	0.75	KF/Al$_2$O$_3$ (2)	MeCN	84	11
10	1.5	KF/Al$_2$O$_3$ (1)	MeCN	76	13

[a] Method A: the imine is treated with chloroform in the indicated solvent (3 mL) in the presence of KF/Al$_2$O$_3$ without added water. All reactions were performed at room temperature for 1.5 h on a 0.5 mmol scale. [b] NMR yields. [c] An isolated yield.

TABLE 2. Synthesis of 2a from 1a under the Conditions of Method B[a]

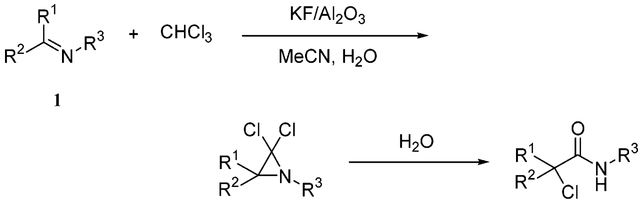
entry	CHCl$_3$ [b] (mmol)	H$_2$O (mmol)	time (h)	yield of **2a**[c] (%)	recovery of **1a**[c] (%)
1	1.5	none	1.5	61	28
2	1.5	1.5	1.5	88	1
3	1.5	5.0	1.5	55	40
4	0.75	1.5	1.5	90	8
5	0.75	1.5	15.0	98 (85)[d]	1

[a] Method B: the imine is treated with chloroform (dried and distilled) in acetonitrile (dried and distilled) in the presence of KF/Al$_2$O$_3$ and water. All reactions were performed in acetonitrile (3 mL) in the presence of KF/Al$_2$O$_3$ (1 g) at room temperature on a 0.5 mmol scale. [b] Dried and distilled. [c] NMR yields. [d] An isolated yield.

be acceptable (entries 3−8). A decrease in the amount of chloroform or KF/Al$_2$O$_3$ to 0.75 mmol or 1 g, respectively, reduced the efficiency of the reaction (entries 9 and 10).

It is well-known that the efficiency of KF/Al$_2$O$_3$ as a base is strongly affected by the amount of water present in the KF/Al$_2$O$_3$.[11] The reaction conditions were optimized by the addition of water to an acetonitrile solution of **1a** in the presence of KF/Al$_2$O$_3$ (1 g) (Scheme 1, Table 2 method B). As a consequence, the addition of water (1.5 mmol) to KF/Al$_2$O$_3$ (1 g) brought about the almost complete consumption of **1a** (entry 1 vs 2). However, the addition of a larger amount of water (5.0 mmol) decreased the rate of conversion (entry 3). Unlike the case of method A, the use of KF/Al$_2$O$_3$ (1 g) under the conditions of method B led the near completion of the reaction (Table 1 entry 10 vs Table 2 entry 2). Moreover, the yield of **2a** could be further improved by prolonging the reaction time even when the amount of chloroform was reduced from 1.5 to 0.75 mmol (entries 4 and 5). Thus, the addition of water permitted the amount of KF/Al$_2$O$_3$ and chloroform used to be decreased. In particular, it should be noted that, although conventional methods for generation of dichlorocarbene require excessive amounts of the carbene source (more than 4 equiv), the amount of chloroform needed could be reduced considerably when the present KF/Al$_2$O$_3$-promoted method was used. In addition, the solid-promoted reaction is very useful in terms of simple and nonaqueous workup, i.e., filtration of the inorganic reagent and evaporation of the solvent.

SCHEME 2. KF/Al$_2$O$_3$-Promoted Dichloroaziridination of Various Imines



1 **2** **3**

TABLE 3. KF/Al$_2$O$_3$-Promoted Synthesis of 2 (or 3) from 1[a]

entry	1	R^1	R^2	R^3	yield (%) 2	yield (%) 3
1	**1a**	H	Ph	Ph	**2a**, 85	
2	**1b**	H	Ph	1-naphthyl	**2b**, 79	
3	**1c**	Ph	Ph	benzyl	**2c**, 69	
4	**1d**	H	4-CO$_2$MeC$_6$H$_4$	Ph	**2d**, 42	
5	**1e**	H	4-CNC$_6$H$_4$	Ph	**2e**, 49	
6	**1f**	H	4-styrylphenyl	Ph	**2f**, 66	
7	**1g**	H	Ph	benzyl	(**2g**, 56[b])	**3g**, 47
8	**1h**	H	Ph	*n*-octyl	(**2h**, 29[b])	**3h**, 29

[a] Reaction conditions are described in the Supporting Information. [b] NMR yields.

Several imines **1** were examined for the KF/Al$_2$O$_3$-promoted synthesis of dichloroaziridines **2** under the conditions of method B (Scheme 2). As shown in Table 3, a variety of imines reacted smoothly with chloroform in acetonitrile in the presence of KF/Al$_2$O$_3$ and water to afford the corresponding dichloroaziridines **2** in moderate to high yields (entries 1−8). The reaction of *N*-benzylideneaniline and *N*-benzylidenenaphthylamine with chloroform under the conditions of method B gave dichloroaziridines (**2a** and **2b**) in high yields (entries 1 and 2). Treatment of a ketimine such as **1c** with chloroform under the same conditions provided **2c** in good yield (entry 3). The reaction was shown to tolerate ester, cyano, and styryl functional groups (entries 4−6). The dichloroaziridination of **1g** and **1h**, derived from unsubstituted benzaldehyde and primary aliphatic amines, was also accomplished (entries 7 and 8). In these cases, *N*-alkyl-α-chlorophenylacetamides (**3g** and **3h**) were isolated as the ring-opening products of their dichloroaziridines (**2g** and **2h**). Accordingly, this method offers an efficient route for converting various aldimines and ketimines to the corresponding dichloroaziridines.

Although the mechanistic details still remain ambiguous, the KF/Al$_2$O$_3$-promoted reaction might proceed through addition of in situ generated dichlorocarbene to imines on KF/Al$_2$O$_3$.

In summary, KF/Al$_2$O$_3$ was found to be a useful solid-supported base for the generation of dichlorocarbene from

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chloroform in the synthesis of *gem*-dichloroaziridines. The present KF/Al_2O_3-promoted dichloroaziridination, which uses reasonable amounts of chloroform, may be characterized by wide generality, simple procedures, good yields, and mild reaction conditions.

Experimental Section

Typical Procedure of Method B: 2,2-Dichloro-1,3-diphenylaziridine (2a). To a suspension of KF/Al_2O_3 (1 g) and **1a** (90.6 mg, 0.5 mmol) in distilled acetonitrile (3.0 mL) was added water (27.0 μL, 1.5 mmol), and distilled chloroform (60.0 μL, 0.75 mmol) was then added slowly under an Ar atmosphere. The reaction mixture was stirred for 15 h at room temperature. The KF/Al_2O_3 was removed by filtration and washed with ether. The combined filtrate was evaporated and purified by recrystallization from hexane to give **2a** (112.2 mg, 85%).

Supporting Information Available: Experimental procedures, reaction conditions for dichloroaziridination of **1** in Table 3, and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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