# Aziridination of Imines Mediated by Copper Catalysts

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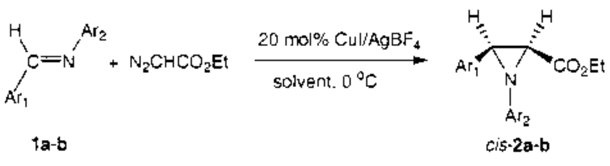
Aziridines are attractive organic molecules due to their great synthetic utilities.[1] A variety of methods has been developed for the synthesis of aziridines[2] including a ring closure reaction of 1,2-amino alcohols or their derivatives,[3] ring opening of epoxides with metal azides,[4] addition of $\alpha$-haloester enolates to imines,[5] a transfer of a nitrene group to an olefin,[6] and the reactions between diazo esters and imines mediated either by carbene transfer catalysts[7] or Lewis acid catalysts.[8]

We report herein the synthesis of aziridines from imines and ethyl diazoacetate using Cu(I) or Cu(II) catalysts under various reaction conditions. Jacobsen[7a] and Jørgensen[7b] reported the aziridination reactions using Cu(I) and Cu(II) catalysts and found the yields and diastereoselectivities were depending on the solvents used and the substituents at the nitrogen of imines. Especially a bulky or an electron-withdrawing substituent at the nitrogen atom decreased the yields for aziridines. So, we studied the solvent and substituent effects on the aziridination reaction from imines and ethyl diazoacetate using simple copper(I) iodide. Unfortunately, the reaction gave no aziridines. When $AgBF_4$ was added to remove the iodide for the vacant sites, the reaction gave the *cis*-aziridines as major products (Scheme 1). In 1,2-dichloroethane, the reaction gave the higher yields than in ether or dichloromethane solvent (Table 1, entries 3 and 6). In dichloromethane, diethyl maleate was also obtained as a side product which was formed from copper carbene complex. In case of the imine with electron-withdrawing substituent at carbon atom, the yield was improved (Table 1, entry 6).




**Scheme 1**

**Table 1**. Aziridine forming reaction using copper(I) catalyst in the presence of $AgBF_4$[a]

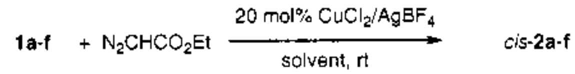
| Entry | Imine | $Ar_1$ | $Ar_2$ | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | phenyl | phenyl | ether | 26 |
| 2 | **1a** | phenyl | phenyl | $CH_2Cl_2$ | 8 |
| 3 | **1a** | phenyl | phenyl | $ClCH_2CH_2Cl$ | 51 |
| 4 | **1b** | *p*-nitrophenyl | phenyl | ether | 26 |
| 5 | **1b** | *p*-nitrophenyl | phenyl | $CH_2Cl_2$ | 11 |
| 6 | **1b** | *p*-nitrophenyl | phenyl | $ClCH_2CH_2Cl$ | 82 |

[a]0.5 equiv. of EDA was used to reduce the formation of dimers. [b]Isolated yield based on ethyl diazoacetate.

When Cu(II) catalyst was used, the aziridination reactions gave the similar results as Cu(I) catalyst (Scheme 2). *cis*-Aziridine was obtained as a major product but Cu(II) catalyst gave the higher yields than Cu(I). The imines with electron-withdrawing substituent at carbon gave the higher yields than the imine with the electron-donating substituent at carbon (Table 2, entry 3 *vs* 5). However, the imine with electron-withdrawing substituent at nitrogen gave the lower yield (Table 2, entry 8). Though the imine has the electron-withdrawing group at nitrogen, the imine with electron-withdrawing substituent at carbon gave the *cis*-aziridine in moderate yield (Table 2, entry 9).

While $CuCl_2$ is not soluble in ether or dichloromethane, it is moderately soluble in acetone solvent. So, we performed the aziridine forming reaction using $CuCl_2$ in acetone without $AgBF_4$ (Scheme 3). Surprisingly, the reaction gave the aziridines in moderate to high yields. When 20 mol% of $CuCl_2$ was used, the highest yields were obtained.[9]

The same substituent effect was observed as in the reactions using $CuI/AgBF_4$ or $CuCl_2/AgBF_4$ catalysts. *cis*-Aziridine was obtained as a major product (*cis*/*trans* = 2-4) and the diastereoselectivity was increased at lower temperature (Table 3, entry 1 *vs* 2). It is also important to notice that

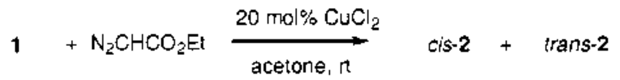



**Scheme 2**

**Table 2**. Aziridine forming reaction using copper(II) catalyst in the presence of $AgBF_4$[a]

| Entry | Imine | $Ar_1$ | $Ar_2$ | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | phenyl | phenyl | ether | 42 |
| 2 | **1a** | phenyl | phenyl | $CH_2Cl_2$ | 22 |
| 3 | **1b** | *p*-nitrophenyl | phenyl | ether | 48 |
| 4 | **1b** | *p*-nitrophenyl | phenyl | $CH_2Cl_2$ | 47 |
| 5 | **1c** | *p*-methoxyphenyl | phenyl | ether | 17 |
| 6 | **1d** | phenyl | *p*-methoxyphenyl | ether | 47 |
| 7 | **1d** | phenyl | *p*-methoxyphenyl | $CH_2Cl_2$ | 17 |
| 8 | **1e** | phenyl | *p*-nitrophenyl | $CH_2Cl_2$ | 8 |
| 9 | **1f** | *p*-nitrophenyl | *p*-nitrophenyl | $CH_2Cl_2$ | 48 |
| 10[c] | **1a** | phenyl | phenyl | ether | 22 |

[a]0.5 equiv. of EDA was used to reduce the formation of dimers. [b]Isolated yield based on ethyl diazoacetate. [c]$Cu(OTf)_2$ was used as catalyst.



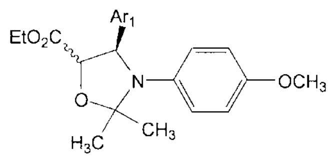

**Scheme 3**

**Table 3**. Aziridine forming reaction using $CuCl_2$ in acetone solvent

| Entry | Imine | $Ar_1$ | $Ar_2$ | *cis*/*trans*[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | phenyl | phenyl | 2.1 | 60 |
| 2[c] | **1a** | phenyl | phenyl | 3.5 | 58 |
| 3 | **1b** | *p*-nitrophenyl | phenyl | 1.8 | 83 |
| 4 | **1g** | *p*-cyanophenyl | phenyl | 1.8 | 90 |
| 5 | **1h** | *p*-nitrophenyl | *p*-methoxyphenyl | 2.8 | 70 |
| 6 | **1i** | *m*-hydroxyphenyl | phenyl | 4.2 | 72 |
| 7 | **1e** | phenyl | *p*-nitrophenyl | 2.8 | 24 |

[a]Ratios were determined by $^1$H NMR analysis. [b]Isolated yield based on ethyl diazoacetate. [c]Reaction was performed at 0 °C.

under the present reaction conditions the products formed from dimerization of EDA, *i.e.*, diethyl maleate and fumarate, were not observed. This observation implies that the reaction mechanism catalyzed by $CuCl_2$ in acetone might be different compared with that of $CuI/AgBF_4$ or $CuCl_2/AgBF_4$ catalyzed aziridination reaction. Cu(II) catalyst in acetone might act as Lewis acid which activated the imine in this aziridine forming reaction.[8] In case of the imines with the electron-donating group such as *p*-methoxyphenyl at nitrogen, the reactions also gave the 1,3-oxazolidines **3** which are the coupled products formed from imine, EDA, and acetone.[10]




**3**

$Ar_1$ = phenyl, *p*-chlorophenyl

In summary, we have demonstrated that the aziridination can be effected by Cu(I) and Cu(II) salts from imines and diazo compound in various solvents. The imines with electron-withdrawing substituent at carbon gave the higher yields and the imines with electron-withdrawing substituent at nitrogen gave the lower yields. While the reactions proceed to give the predominantly *cis*-aziridines *via* copper carbene complexes when $CuI/AgBF_4$ or $CuCl_2/AgBF_4$ catalyst is used. $CuCl_2$ catalyst in acetone might act as a Lewis acid to give the *cis*- and *trans*-aziridines.

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9. Under a nitrogen atmosphere, to a stirred solution of $CuCl_2$ (0.16 mmol, 0.1 equiv) in acetone (5 mL) was added imine (1.6 mmol, 1 equiv) and ethyl diazoacetate (0.8 mmol, 0.5 equiv) at room temperature. After stirring for 2 h, the reaction mixture was filtered through the short silica gel column. Evaporation of solvent, followed by flash chromatography (EtOAc : Hex, 1 : 5) allowed separation of the diastereomeric products.
**cis-3-(p-Nitrophenyl)-1-phenylaziridine-2-carboxylic acid ethyl ester (cis-2b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.06 (t, $J$ = 7.0 Hz, 3H), 3.29 (d, $J$ = 6.8 Hz, 1H), 3.66 (d, $J$ = 6.8 Hz, 1H), 4.01 (dq, $J$ = 10.8, 7.1 Hz, 1H), 4.07 (dq, $J$ = 10.8, 7.1 Hz, 1H), 7.00-7.10 (m, 3H), 7.20 (d, $J$ = 8.4 Hz, 2H), 7.25-7.35 (m, 2H), 8.22 (d, $J$ = 8.8 Hz, 2H); MS *m/z* 312 ($M^+$), 226, 179, 151, 105, 76; HRMS calculated for $C_{17}H_{16}N_2O_4$ 312.111, found 312.110.
10. **cis-3-(p-Methoxyphenyl)-2,2-dimethyl-4-phenyloxazolidine-5-carboxylic acid ethyl ester (3d):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.81 (t, $J$ = 7.2 Hz, 3H), 1.30 (s, 3H), 1.90 (s, 3H), 3.69 (s, 3H), 3.47-3.59 (m, 1H), 3.73-3.83 (m, 1H), 4.89 (d, $J$ = 7.5 Hz, 1H), 5.16 (d, $J$ = 8.1 Hz, 1H), 6.72 ( d, $J$ = 9.0 Hz, 2H), 6.91 (d, $J$ = 9.3 Hz, 2H), 7.18-7.21 (m, 3H), 7.33 (d, $J$ = 6.3 Hz, 2H); IR (KBr) 2970, 2927, 2830, 1750, 1511, 1452, 1382 $cm^{-1}$.