## Iron-catalyzed synthesis of glycine derivatives *via* carbon-nitrogen bond cleavage using diazoacetate<sup>†</sup>

Yoichiro Kuninobu,\* Mitsumi Nishi and Kazuhiko Takai\*

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Treatment of tertiary amines with diazoacetate in the presence of a catalytic amount of an iron salt, FeCl<sub>3</sub>, in ethanol gave glycine derivatives. In this reaction, a carbon-nitrogen single bond of the amine was cleaved.

The carbon–nitrogen bond (C–N bond) is strong in organic molecules. Therefore, transformations *via* C–N bond cleavage are usually difficult. However, such transformations would be useful and powerful methods in synthetic organic chemistry because many organic molecules contain carbon–nitrogen bonds. There have been several reports on stoichiometric carbon–nitrogen bond cleavage.<sup>1</sup> However, it is still difficult to cleave such bonds catalytically,<sup>2–4</sup> except by using substrates such as diazonium salts.<sup>5</sup>

There have been several reports on transition metal-catalyzed reactions between tertiary amines and diazoacetates.<sup>6</sup> However, in these reactions, the ethoxycarbonylmethyl group of the diazoacetates was inserted into the C–H bond of the  $\alpha$ -position of amines (Fig. 1 (a)). We report herein iron-catalyzed reactions between tertiary amines and diazoacetate.<sup>7,8</sup> In our reaction, the cleavage of a C–N single bond occurred and glycine derivatives were formed in good yields (Fig. 1 (b)).

Treatment of *N*,*N*-dimethylaniline (**1a**) with ethyl diazoacetate (**2**) in the presence of 5.0 mol% of an iron salt, FeCl<sub>3</sub>, in toluene gave glycine **3a** in 25% yield.<sup>9</sup> As a result of investigating several solvents, ethanol was found to be the most effective in promoting the reaction, and **3a** was obtained in 57% yield.<sup>10</sup> In this reaction, a methyl–nitrogen bond (not a phenyl–nitrogen bond) was cleaved selectively, and ethyl 3-*N*-methyl-*N*-phenylaminopropanoate, which is derived from C–H functionalization of the methyl group of **1a**, was not formed.<sup>10</sup> It is interesting that ethanol provided a high yield because the reaction of **2** with ethanol (insertion of a carbene into the O–H bond of ethanol) usually occurs in the presence of



**Fig. 1** The difference between previous works and our reaction of tertiary amines with a diazoacetate.

transition metal catalysts.<sup>11</sup> By increasing the amount of FeCl<sub>3</sub>, the yield of **3a** increased to 83% yield (eqn (1)). $\ddagger^{12}$ 

$$\begin{array}{c} Me \\ Ph-N \\ Me \\ 1a \\ 2 \\ (2.0 equiv) \end{array} + \begin{array}{c} V_2 \\ N_2 \\ \hline EtOH, 115 \ ^\circC, 24 \ h \\ Me \\ 3a \ 83\% \\ \end{array} + \begin{array}{c} Ph-N \\ Me \\ 3a \ 83\% \\ \end{array}$$

To investigate the scope and limitations, reactions between several amines 1 and diazoacetate 2 were carried out (Table 1). N,N-Dimethylanilines bearing an electron-donating group at the *para*-position of the aromatic ring, 1b and 1c, gave glycines 3b and 3c in 92% and 73% yields, respectively (entries 1 and 2). When N,N-dimethylaniline with a trifluoromethyl group, 1d, was treated with FeCl<sub>3</sub>, solvolysis of the trifluoromethyl group of 1d occurred, 3d was not formed. By changing the catalyst to MnBr<sub>2</sub>, the desired glycine 3d was obtained (entry 3). The yields of the glycines 3e and 3f decreased when N,N-dimethylanilines having a halogen atom at the *para*position of the aromatic ring were used (entries 4 and 6).

Table 1 Reactions between several tertiary amines 1 and ethyl diazoacetate  $(2)^a$ 

R <sup>1</sup> -I 1	$ \begin{array}{c}                                     $	Et Fe EtO	Cl <sub>3</sub> (20 r H, 115 °	mol%)  C, 24 h	R <sup>1</sup> -N	∕—CO₂Et R <sup>3</sup> 3
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>			Yield <sup>b</sup> (%)
$ \frac{1^{c}}{2} \\ 3^{d} \\ 4^{c} \\ 5^{e} \\ 6 \\ 7^{e} \\ 8^{c} \\ 9^{d,e} $	$\begin{array}{c} 4\text{-MeOC}_{6}\text{H}_{4} \\ 4\text{-MeC}_{6}\text{H}_{4} \\ 4\text{-CF}_{3}\text{C}_{6}\text{H}_{4} \\ 4\text{-BrC}_{6}\text{H}_{4} \\ 4\text{-BrC}_{6}\text{H}_{4} \\ 4\text{-ClC}_{6}\text{H}_{4} \\ 3\text{-MeC}_{6}\text{H}_{4} \\ 2\text{-MeC}_{6}\text{H}_{4} \end{array}$	Me Me Me Me Me	Me Me Me Me Me	1b 1c 1d 1e 1f 1g 1h	3b 3c 3d 3e 3f 3g 3h	92 (99) 73 (77) 34 (41) 52 (57) 72 (76) 49 (50) 69 (71) 77 (79) 50 (55)
10 <sup><i>d</i>,<i>e</i></sup>		Me	Me	1i	3i	41 (46)
$11^{f}$ $12^{d,e}$ $13^{d}$	<sup>n</sup> C <sub>12</sub> H <sub>25</sub> Ph Ph	Me Et Me	Me Et Et	1j 1k 11	3j 3k 3k 3a	33 (38) 51 (55) 22 (23) 35 (38)

<sup>&</sup>lt;sup>*a*</sup> **2** (2.0 equiv.). <sup>*b*</sup> Yield determined by <sup>1</sup>H NMR is reported in parentheses. <sup>*c*</sup> 48 h. <sup>*d*</sup> MnBr<sub>2</sub> (20 mol%) was used as a catalyst. <sup>*e*</sup> CF<sub>3</sub>CH<sub>2</sub>OH was used as a solvent. The yield was determined after the treatment of the reaction mixture with ethanol at 115 °C for 24 h. <sup>*f*</sup> 150 °C.

Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Kita-ku, Okayama 700-8530, Japan. E-mail: kuninobu@cc.okayama-u.ac.jp, ktakai@cc.okayama-u.ac.jp; Fax: +81 (0)86-251-8094; Tel: +81 (0)86-251-8095

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When 2,2,2-trifluoroethanol was used instead of ethanol, the yields were improved, and 3e and 3f were generated in 72% and 69% yields, respectively (entries 5 and 7). Although 3g was afforded in 77% yield when an aniline derivative with a methyl group at the *meta*-position, 1g, was used (entry 8), a substituent at the ortho-position of an aromatic ring decreased the yield of the glycine 3h (entry 9). The corresponding glycine **3i** was produced in 41% yield in the case of naphthylamine **1i** (entry 10). Dodecyldimethylamine 1j also gave 3j; however, the yield was low (entry 11). Another C-N bond, instead of the methyl-nitrogen bond, was also cleaved (entry 12). By the reaction of N,N-diethylaniline (1k) with ethyl diazoacetate (2) in the presence of a catalytic amount of an iron salt, FeCl<sub>3</sub>, ethyl (N-ethyl-N-phenylamino)acetate (3k) was formed in 51% yield (entry 12). In the case of an amine with methyl and ethyl groups, 11, glycines 3k and 3a were generated in 22% and 35% yields, respectively (entry 13). This result shows that the cleavage of an ethyl-nitrogen bond occurs more easily than the methyl-nitrogen bond. In Table 1, the amines 1 were recovered, and the total percentages of 3 and 1 were more than 90% except in the case of entry 11. The reaction did not proceed using N-methylindole, N,N-dimethylacetoamide, or N-methyl-2-pyrrolidone as tertiary amines. In the case of N,N-dimethylaniline and N,N-dimethylanilines with an electron-donating group, FeCl<sub>3</sub> is more effective than MnBr<sub>2</sub>. On the other hand, MnBr<sub>2</sub> showed a higher catalytic activity compared with FeCl<sub>3</sub> when N,N-diethylaniline and *N*.*N*-dimethylanilines bearing an electron-withdrawing group were employed as substrates.

Next, we investigated the reaction mechanism. Since an ethoxycarbonylmethyl group was introduced on the nitrogen atom of 3a or 3k when *N*,*N*-dimethylaniline (1a) or *N*,*N*-diethylaniline (1k) was used (eqn (1) and Table 1, entry 12), it is clear that the ethoxycarbonylmethyl group came from diazoacetate **2**, not from the methyl (or the methylene moiety of the ethyl) group of aniline derivative 1a (or 1k) and the ethoxycarbonyl moiety of **2**.

In some cases, the C–N bond cleavage of *N*-methylamines occurs *via* the formation of iminium intermediates.<sup>13</sup> However, iminium intermediates are usually formed under oxidative conditions. In our case, the reaction was not performed under oxidative conditions. Therefore, we did not consider this pathway further.

To identify a byproduct, which is formed by the cleavage of the C–N bond, the following experiment was conducted. Treatment of 1-phenylpyrrolidine (1m) with diazoacetate 2 formed ethyl ether **3l** (eqn (2)). This result shows that an alkyl chain on the nitrogen atom of amine 1 must be trapped by ethanol. In addition, this reaction did not proceed *via* the formation of an imnium intermediate, which would cause formation of an addehyde.<sup>13c,14</sup>



Another possible mechanism is that the reaction proceeds *via* the formation of an ammonium salt, which is derived from the nucleophilic addition of an amine to a diazoacetate followed by the elimination of N<sub>2</sub> and protonation.<sup>15</sup> To examine this possibility, the following experiment was carried out. Heating ammonium salt **4** in the presence or absence of FeCl<sub>3</sub>, glycine **3a** was obtained in 47% and 63% yields, respectively (eqn (3)). These results indicate that **3a** was formed *via* the formation of ammonium salt **4**, and FeCl<sub>3</sub> was not necessary in the elimination of the methyl group of **4**.

$$\begin{array}{c}
\stackrel{I \Theta}{\bigoplus} & CO_2Et \\
\stackrel{Ph-N}{\longleftarrow} & Me \\
\stackrel{I}{4} & EtOH, 115 \ ^\circC, 24 \ h \\
\stackrel{I}{4} & Gatalyst \ Yield \ (\%) \\
\stackrel{I}{5} & FeCl_3 \ 47 \\
\stackrel{I}{5} & none \ 63 \\
\end{array}$$
(3)

By the above investigations, we propose the reaction mechanism shown in Fig. 2: (1) Coordination of diazoacetate **2** to a metal center (activation of **2** by the Lewis acid);<sup>16,17</sup> (2) nucleophilic substitution of the formed metal-containing zwitterionic intermediate with amine **1** *via* the elimination of N<sub>2</sub>; (3) protonation of the formed zwitterionic intermediate to give an ammonium salt and regeneration of the metal catalyst;<sup>18</sup> (4) elimination of a methyl group from the nitrogen atom (C–N bond cleavage) to give glycine derivative **3** and trapping of one of the methyl groups by ethanol.<sup>19</sup>

A carbon–sulfur bond was also cleaved by the reaction between thioanisol (5) and ethyl diazoacetate (2) in the presence of a catalytic amount of MnBr<sub>2</sub>. As a result, ethyl 2-(phenylthio)acetate (6) was obtained in 51% yield (eqn (4)). However, the desired product was not formed when FeCl<sub>3</sub> was used as a catalyst.<sup>20</sup>

$$\begin{array}{c} Me \\ Ph-S \\ \textbf{5} \\ \textbf{5} \\ (2.0 \text{ equiv}) \end{array} + \underbrace{\sqrt{-CO_2Et}}_{\textbf{CF_3CH_2OH, 115 °C, 24 h}} \underbrace{\frac{MnBr_2 (20 \text{ mol}\%)}{CF_3CH_2OH, 115 °C, 24 h}}_{\textbf{6} 51\%} Ph-S \\ \textbf{6} 51\% \\ \textbf{6} \end{array}$$

In summary, we have succeeded in iron-catalyzed cleavage of a non-strained C–N bond by the reactions of tertiary amines with a diazoacetate. As a result, glycine derivatives were obtained in moderate to good yields. This reactivity is in sharp contrast to the previous transition metal-catalyzed reactions between tertiary amines and diazoacetates, which produce glycine derivatives *via* the insertion of the ethoxycarbonylmethyl group of the diazoacetates into a C–H bond at the  $\alpha$ -position of the amines. To cleave C–N bonds, novel



Fig. 2 Possible reaction mechanism for the formation of glycine derivatives *via* C–N bond cleavage.

transition metal complexes or salts have previously been used as catalysts. Iron is well known as one of the most abundant and cheapest metals. However, there have only been a few reports on iron-catalyzed cleavage of unactivated bonds.<sup>21</sup> From this viewpoint, this iron-catalyzed cleavage of C–N bond is interesting. We hope that this reaction will provide useful insight into transformations *via* the cleavage of C–N bonds.

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## Notes and references

<sup>‡</sup> Synthesis of **3a**. A mixture of *N*,*N*-dimethylaniline (**1a**, 30.3 mg, 0.250 mmol), ethyl diazoacetate (**2**, 57.1 mg, 0.500 mmol), iron(III) chloride FeCl<sub>3</sub> (8.1 mg, 0.050 mmol), and ethanol (0.25 mL) was heated at 115 °C for 24 h. After heating, the reaction mixture was purified by silica gel column chromatography using hexane/ethyl acetate (10 : 1) as the eluent to give glycine derivative **3a** (40.1 mg, 83% yield).

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