An Exception of Eschweiler-Clarke Methylation : Cyclocondensation of α-Amino Amides with Formaldehyde and Formic Acid

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An exception of Eschweiler-Clarke methylation was found for α-amino amides. The α-amino amides on treatment with formaldehyde and formic acid produce cyclocondensation products, imidazolidin-4-ones, but *N*-methylation process becomes important when three substituents of the α-amino amides are very bulky. On the other hand, *N*-methylation is the only product for Eschweiler-Clarke methylation of the α-amino amides with *N*,*N*-disubstituted amide.

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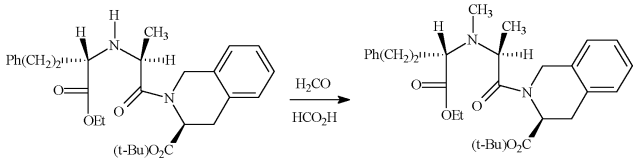
Introduction.

N-Methylation is an important procedure in organic synthesis and has some application. For example, *N*-methylation of amino acids increases pharmacokinetically useful parameters such as membrane permeability, proteolytic stability, and conformational rigidity [1]. Eschweiler-Clarke methylation [2] is a well-known *N*-methylation method to smoothly undergo methylation of aliphatic amines by warming in formic acid solution with formaldehyde, resulting in corresponding tertiary amines. In 1986, Klutchko *et al*. converted the α-amino amide **1** to its *N*-methyl analogue **2** by Eschweiler-Clarke methylation [3] (Scheme I). However, when an α-amino amide **3a**, whose structure is similar to that of **1**, was subjected to Eschweiler-Clarke methylation conditions, we didn't isolate the *N*-methylation product **4a** but obtained a cyclocondensation product **5a**, imidazolidin-4-one, which was reported to have potential in reversibly inhibiting amino acid decarboxylases [4] (Scheme II). Even though the imidazolidin-4-ones have been made by treatment of α-amino amides with paraformaldehyde in the presence of catalytic *p*-toluenesulfonic acid [5], the exception for the Eschweiler-Clarke methylation of α-amino amides has not been reported and not all the Eschweiler-Clarke methylation of α-amino amides produces corresponding cyclocondensation products. Therefore, it is necessary to describe the novel exception of Eschweiler-Clarke methylation in this article.

Scheme I

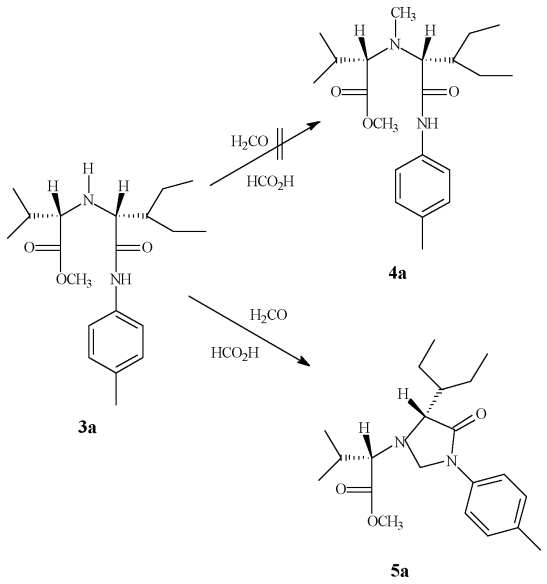


1 **2**

Results and Discussion.

Reaction of α-Amino Amides with Formaldehyde and Formic Acid.

Scheme II



Application of the conventional Eschweiler-Clarke procedure [2b] to **3a** with a ratio of aliphatic amine **3a**: formaldehyde:formic acid = 1:2.5:5 gave low conversion of the starting material **3a** because some formaldehyde evaporated and collected in the condenser as its trimer. After the ratio of aliphatic amine **3a**:formaldehyde:formic acid was increased to 1:20:40, not only was conversion of the starting material **3a** complete but also no by-product was found. In addition to that, according to NMR spectra, configuration of chiral centers of the α-amino amides is retained after the Eschweiler-Clarke methylation process. However, the product of the reaction is not the expected *N*-methylation product **4a** but the cyclocondensation product **5a**. To investigate more about the exception of Eschweiler-Clarke methylation, other α-amino amides **3b** ~ **3f** were subjected to the modified Eschweiler-Clarke methylation conditions and the results are shown in Table I.

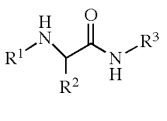
Structure of **3b** is very close to that of **3a**, but reaction of **3b** with formaldehyde and formic acid produces both

N-methylation product **4b** and cyclocondensation product **5b** in a ratio of 1:1. On the other hand, when the α-amino amide **3c** with two bulky t-butyl substituents was treated with formaldehyde and formic acid, only a cyclocondensation product **5c** was obtained. Other α-amino amides **3d** ~ **3f** with less bulky substituents produced cyclocondensation products **5d** ~ **5f** respectively, when treated with formaldehyde and formic acid.

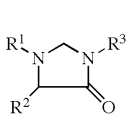
Due to production of carbon dioxide, mechanism of Eschweiler-Clarke methylation was proposed to involve decarboxylation of a formic ester of hemiaminal [2b,6]. Therefore, Eschweiler-Clarke methylation of α-amino amides may involve competition between decarboxylation (route 1) of the formic ester of hemiaminal **6** and cyclocondensation (route 2 and 3) of the hemiaminal analogues (Scheme III). It was reported that cyclocondensation of hemiaminal of α-amino amides was carried out without any catalyst or in the presence of acids or bases [5,7]. It is reasonable to assume that cyclocondensation of hemiaminal of α-amino amides may be promoted by hydronium ion, formic acid, and formate leaving group when they are subjected to Eschweiler- Clarke methylation conditions. According to the results in Table I, cyclocondensation is preferred. However, when R^1, R^2, and R^3 are all very bulky, the rates for both decarboxylation and cyclocondensation become comparable. For example, both structure and substituents of **3a** are very close to those of **3b**, but **3a** gives the cyclocondensation product **5a** only while **3b** leads to both *N*-methylation product **4b** and cyclocondensation product **5b** in a ratio of 1:1. This is because cyclohexyl substituent on **3b** is bulkier than *p*-tolyl substituent on **3a**, in addition to two other bulky substituents. On the other hand, the tertiary amide **1** cannot follow route 2 and 3 at all because the amide nitrogen cannot participate in aminal formation, and *N*-methylation product **2** is the only product.

Table 1

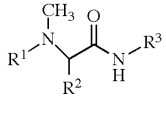
α-Amino Amides Subjected to Eschweiler-Clarke Methylation Conditions



3a ~ 3f



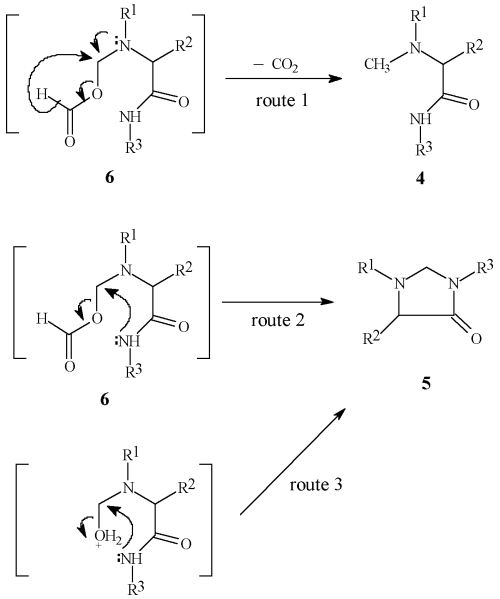
5a ~ 5f



4b

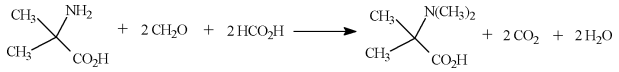
reactant	R^1	R^2	R^3	product (yield)
3a	$(CH_3)_2CH$, MeO_2C, CH—	$(CH_3CH_2)_2CH$—	*p*-tolyl	**5a** (90%)
3b	$(CH_3)_2CH$, MeO_2C, CH—	$(CH_3CH_2)_2CH$—	cyclohexyl	**5b** (38%) **4b** (38%)
3c	*t*-butyl	H	*t*-butyl	**5c** (80%)
3d	*t*-butyl	H	*p*-tolyl	**5c** (87%)
3e	*n*-butyl	H	*p*-tolyl	**5c** (83%)
3f	*n*-butyl	H	*n*-butyl	**5c** (94%)

Scheme III



6 **4** **5**

Scheme IV

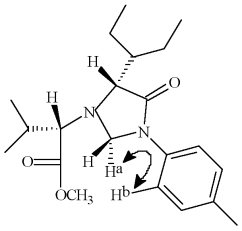


Eschweiler-Clarke methylation of some α-amino acids has been done previously [2b]. For example, α-aminoisobutyric acid on treatment with formaldehyde and formic acid gave its *N*,*N*-dimethyl derivative in 80% yield, and no cyclocondensation product was found [2b], indicating that nucleophilicity of carboxylic acid functionality is much less than that of amide (Scheme IV).

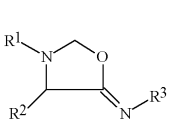
Structure Determination of Imidazolidin-4-ones.

There are two possible structures for the cyclocondensation product of Eschweiler-Clarke methylation of **3a**; one is imidazolidin-4-one **5a** and the other is 1,3-oxazolidin-5-imine **7**. According to the NOESY spectrum of the product, H^a of the methylene group correlates with H^b of *N*-tolyl group, indicating that the product is imidazolidin-4-one **5a**, instead of 1,3-oxazolidin-5-imine **7**. In addition to that, the 1,3-oxazolidin-5-imine **7** was reported to be labile in water [4a,8], which is present as the solvent of the reagents used in the Eschweiler-Clarke methylation procedure, indicating that 1,3-oxazolidin-5-imine **7** is not a product of the reaction.

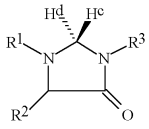
Bulky substituents of the imidazolidin-4-ones (**5a** ~ **5f**) make the 5-membered ring less flexible, and chemical shift difference of methylene protons (H^c & H^d) of the imi-



Correlation in NOESY of **5a**



7



5a ~ **5f**

dazolidin-4-ones is an indicator for the flexibility of the ring. For example, **5a** and **5b** have 3 bulky substituents on the 5-membered ring, and that results in large chemical shift difference (0.46 ppm) between H^c and H^d, indicating inflexibility of the ring. Two of three substituents are bulky for **5c** and **5d**, and that causes chemical shift difference (0.02 ppm for **5c**, 0.01 ppm for **5d**) between H^c and H^d much smaller, indicating that the ring is more flexible. Three substituents of **5e** and **5f** are not bulky, and that causes no chemical shift difference between H^c and H^d, indicating that the ring is much more flexible.

Conclusion.

Eschweiler-Clarke methylation of the α-amino acids produces *N*-methylation products. In contrast to that, Eschweiler-Clarke methylation of the α-amino amides gives cyclocondensation products, imidazolidin-4-one, except for the α-amino amides with *N*,*N*-disubstituted amide. However, for the Eschweiler-Clarke methylation of the α-amino amides with three very bulky substituents, the rates for both cyclocondensation and *N*-methylation become comparable, and both cyclocondensation and *N*-methylation products are obtained.

EXPERIMENTAL

All the reagents were obtained from commercial suppliers and used as received. The α-amino amides (**3a** ~ **3f**) were prepared according to literature procedures [9].

General Method for Eschweiler-Clarke Methylation of α-Amino Amides.

A mixture of an α-amino amide (10 mmol), formaldehyde (37% in water) (14.8 mL, 200 mmol), and formic acid (90% in water) (16.7 mL, 400 mmol) in a ratio of 1:20:40 was heated at 120 °C under reflux and nitrogen atmosphere for 10 h. The reaction mixture was neutralized with $NaHCO_3$, followed by extraction with diethyl ether. The diethyl ether solution was dried over anhydrous $MgSO_4$, and evaporated in vacuum to give crude products, which were purified by column chromatography on silica gel with an eluent of hexane/ethyl acetate.

Methyl 3-methyl-(2*S*)-2-[3-(4-methylphenyl)-4-oxo-(5*R*)-5-(pentan-3-yl)imidazolidin-1-yl]butanoate (**5a**).

This compound was obtained as yellow oil; $[\alpha]^{20}_D$ = -3.02° (c = 0.13 g/mL, ethyl acetate); ^{1}H nmr ($CDCl_3$): δ 0.85~0.98 (9H, m, CH_3), 1.11 (3H, d, J=4.8 Hz, CH_3), 1.45 (4H, m, CH_2), 1.56 (1H, m, CH), 2.06 (1H, m, CH), 2.31 (3H, s, CH_3), 3.01 (1H, d, J=10.7 Hz, CH), 3.67 (4H, m, CH&CH_3), 4.62 (1H, d of d, J=5.5, 1.7 Hz, CH), 5.08 (1H, d, J=5.5 Hz, CH), 7.11 (2H, d, J=8.5 Hz, CH), 7.44 (2H, d of d, J=8.5, 1.7 Hz, CH); ^{13}C nmr ($CDCl_3$): δ 12.12, 12.24, 19.58, 19.77, 20.79, 22.44, 23.16, 28.19, 44.78, 51.29, 64.28, 65.93, 70.06, 119.45, 129.43, 134.61, 134.89, 171.78, 172.59; ir (thin film): 1732, 1703 (C=O) cm^{-1}; ms (EI): m/z 360 (10, M^+), 289 (100), 228 (30), 175 (25), 154 (45), 120 (90); hrms (EI): m/z calcd for $C_{21}H_{32}N_2O_3$ 360.2407, found 360.2410.

Methyl 3-Methyl-(2S)-2-[3-cyclohexyl-4-oxo-(5R)-5-(pentan-3-yl)imidazolidin-1-yl]butanoate (**5b**).

This compound was obtained as yellow oil; ^{1}H nmr ($CDCl_3$): δ 0.6~0.8 (12H, m, CH_3), 1.06~1.16 (4H, m, CH_2), 1.19~1.30 (4H, m, CH_2), 1.59~1.75 (4H, m, CH_2), 1.76~1.90 (2H, m, CH_2), 1.90~1.97 (2H, m, CH), 2.90 (1H, d, J=8.0 Hz, CH), 3.67 (5H, m, CH&CH_3), 4.18 (1H, d of d, J=5.6, 2.3 Hz, CH), 4.64 (1H, d, J=5.6 Hz, CH); ^{13}C nmr ($CDCl_3$): δ 12.09, 12.15, 19.88, 19.92, 22.96, 23.33, 24.56, 24.59, 24.62, 28.92, 30.22, 31.33, 44.50, 46.85, 51.09, 59.81, 70.25, 70.32, 171.73, 172.58; ir (thin film): 1731, 1712 (C=O) cm^{-1}; hrms (FAB): m/z calcd for $C_{20}H_{37}N_2O_3$ 353.2804, found 353.2811.

Methyl (2*S*)-2-{[(1*R*)-1-cyclohexylcarbamoyl-2-ethylbutyl]-methylamino}-3-methylbutanoate (**4b**).

This compound was obtained as yellow oil; ^{1}H nmr ($CDCl_3$): δ 0.6~0.8 (12H, m, CH_3), 1.06~1.16 (4H, m, CH_2), 1.19~1.30 (4H, m, CH_2), 1.59~1.75 (4H, m, CH_2), 1.76~1.90 (2H, m, CH_2), 1.90~1.97 (2H, m, CH), 2.27 (3H, s, CH_3), 2.82 (1H, d, J=7.9 Hz, CH), 2.89 (1H, d, J=6.1 Hz, CH), 3.67 (4H, m, CH&CH_3), 6.05 (1H, d, J=8.3 Hz, NH); ^{13}C nmr ($CDCl_3$): δ 11.07, 11.42, 19.35, 19.68, 21.59, 22.02, 25.28, 25.31, 25.35, 27.52, 32.77, 32.86, 33.07, 44.89, 47.48, 50.69, 65.40, 69.77, 171.87, 172.72; ir (thin film): 1737, 1682 (C=O) cm^{-1}; hrms (FAB): m/z calcd for $C_{20}H_{39}N_2O_3$ 355.2960, found 355.2953.

1,3-Di-*tert*-butylimidazolidin-4-one (**5c**).

This compound was obtained as yellow oil; ^{1}H nmr ($CDCl_3$): δ 1.14 (9H, s, CH_3), 1.35 (9H, s, CH_3), 3.27 (1H, d, J=1.5 Hz, CH), 3.29 (1H, d, J=1.5 Hz, CH), 4.22 (1H, d, J=1.5 Hz, CH), 4.24 (1H, d, J=1.5 Hz, CH); ^{13}C nmr ($CDCl_3$): δ 27.68, 28.66, 51.05, 52.32, 53.90, 62.57, 171.10; ir (thin film): 1729 (C=O) cm^{-1}; hrms (FAB): m/z calcd for $C_{11}H_{23}N_2O$ 199.1810, found 199.1810.

1-*tert*-Butyl-3-(4-methylphenyl)imidazolidin-4-one (**5d**).

This compound was obtained as brown oil; ^{1}H nmr ($CDCl_3$): δ 1.15 (9H, s, CH_3), 2.32 (3H, s, CH_3), 3.53 (1H, d, J=1.4 Hz, CH), 3.54 (1H, d, J=1.4 Hz, CH), 4.61 (1H, d, J=1.4 Hz, CH), 4.62 (1H, d, J=1.4 Hz, CH), 7.18 (2H, d, J=8.3 Hz, CH), 7.43 (2H, d, J=8.3 Hz, CH); ^{13}C nmr ($CDCl_3$): δ 20.86, 25.39, 50.73, 52.42, 65.23, 119.43, 129.50, 134.63, 134.99, 170.02; ir (thin film): 1700 (C=O) cm^{-1}; ms (EI): m/z 232 (10, M^+), 217 (80), 119 (50), 99 (40), 91 (50), 70 (100); hrms (EI): m/z calcd for $C_{14}H_{20}N_2O$ 232.1570, found 232.1572.

1-Butyl-3-(4-methylphenyl)imidazolidin-4-one (**5e**).

This compound was obtained as yellow oil; ^{1}H nmr ($CDCl_3$): δ 0.92 (3H, t, J=7.2 Hz, CH_3), 1.35~1.51 (4H, m, CH_2), 2.30 (3H, s,

CH_3), 2.62 (2H, t, J=7.2 Hz, CH_2), 3.42 (2H, s, CH_2), 4.51 (2H, s, CH_2), 7.14 (2H, d, J=8.3 Hz, CH), 7.38 (2H, d, J=8.3 Hz, CH); ^{13}C nmr ($CDCl_3$): δ 13.78, 20.17, 20.74, 29.88, 54.57, 57.10, 70.87, 119.34, 129.40, 134.49, 134.75, 169.86; ir (thin film): 1712 (C=O) cm^{-1}; ms (EI): m/z 232 (15, M^+), 119 (40), 98 (100), 57 (90); hrms (EI): m/z calcd for $C_{14}H_{20}N_2O$ 232.1570, found 232.1571.

1,3-Dibutylimidazolidin-4-one (**5f**).

This compound was obtained as yellow oil; ^1H nmr ($CDCl_3$): δ 0.92 (6H, t, J=7.2 Hz, CH_3), 1.35~1.51 (8H, m, CH_2), 2.55 (2H, t, J=7.2 Hz, CH_2), 3.27 (4H, m, CH_2), 4.09 (2H, s, CH_2); ^{13}C nmr ($CDCl_3$): δ 13.63, 13.85, 20.01, 20.72, 29.60, 30.08, 40.80, 54.82, 56.15, 70.04, 170.88; IR (thin film) 1737 (C=O) cm^{-1}; ms (EI): m/z 198 (20, M^+), 155 (100), 98 (40), 86 (50), 57 (60); hrms (EI): m/z calcd for $C_{11}H_{22}N_2O$ 198.1732, found 198.1727.

Acknowledgment.

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