# Autoxidation of Intermediary Mesoionic 1,3-Oxazolium-5-olates Generated from Cyclic *N*-Acyl α-Amino Acids

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**Mesoionic 1,3-oxazolium-5-olates (munchnones) react fairly rapidly with oxygen to give the autoxidation products when the C-4 substituent is aromatic. The autoxidation occurred in the munchnones generated from *N*-acyl tetrahydroisoquinoline-1-carboxylic acids or tetrahydro-β-carboline-1-carboxylic acids. The mechanism was elucidated by $^{18}O$ labeling experiments and involved a series of well-precedented autoxidative processes including oxygenation, cyclization of the resulting peroxy anion, and oxidative cleavage.**

**Key words** autoxidation; 1,3-oxazolium-5-olate; munchnone; mesoionic compound; $^{18}O$-label

The 1,3-oxazolium-5-olates **2**, commonly known as munchnones, are the most extensively studied class of mesoionic compounds.[1] In general, the munchnones are readily prepared by cyclodehydration of *N*-alkyl-*N*-acyl α-amino acids **1** with reagents such as acetic anhydride, trifluoroacetic anhydride, or dicyclohexylcarbodiimide (DCC), and are utilized *in situ* because they are too unstable to be isolated. [2] Only munchnones with aryl substituents in both the 2- and 4-positions or with an acyl group in the 4-position have been isolated so far.[2,3] In contrast with the detailed studies on their reactivity as 1,3-dipoles in cycloaddition reactions,[4] other reactions of **2** have not been fully explored.

During the course of our studies on the reactivities of munchnones,[5] we found the autoxidation reaction of intermediary munchnones **5** generated from *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**4**) and DCC.[6] Huisgen and his coworkers have reported the course of the autoxidation of *N*-methyl-2,4-diphenylmunchnone (**2a**) obtained from *N*-benzoyl-*N*-methylphenylglycine (**1a**).[2] This is the only autoxidation of munchnones hitherto reported, to our knowledge. Therefore, we decided to investigate the scope and limitations of this reaction of other munchnones derived from "cyclic" α-amino acids, namely, tetrahydroisoquinoline-1- and 3-carboxylic acids, tetrahydro-β-carboline-1-carboxylic acid, 2,3-dihydroindole-1-carboxylic acid, and proline. In addition, an $^{18}O$ labeling experiment was conducted in order to elucidate the course of autoxidation of munchnones. Our results are not consistent with the mechanism of formation of the autoxidation product (**3a**) reported by Huisgen's group (*vide infra*).[2]

## Results and Discussion

Various munchnones were readily generated by cyclodehydration of the corresponding *N*-acyl α-amino acids with DCC. The derivatives employed in this study along with the autoxidation products are summarized in Chart 1.

The *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**4a—d**) required for this study have been prepared by the catalytic hydrogenation of ethyl isoquinoline-1-carboxylate followed by *N*-acylation and subsequent hydrolysis of the resulting ethyl *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylates.[7,8]

When a solution of *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**4a**) and DCC in $CH_2Cl_2$ was stirred at room temperature for 18 h, the yellow color of the solution gradually faded, and finally *N*-pivaloyl-1-isoquinolone (**6a**) was formed in 95% yield. No attempt was made to isolate the intermediate munchnones, since Huisgen *et al.* have shown the oxazolium-5-olate system to be extremely unstable.[2] The $O_2$ present in the solvent was enough for completion of the reaction. The imide structure of **6a** was deduced from spectroscopic data, and acid hydrolysis of **6a** gave **17**, which was identical with an authentic sample prepared by the literature method (Chart 2).[9]

The effect of 2-substituents on the autoxidation was studied by utilizing a series of munchnones (**5a—d**) obtained from several *N*-acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**4a—d**). As shown in Table 1, munchnones **5a—d**, in which the 2-substituent was phenyl, methyl, or *tert*-butyl, were easily transformed to the 1-isoquinolones **6a—d** in high yields and no by-product could be detected. It appears that all the munchnones (**5a—d**), regardless of substitution pattern on C-2, form 1-isoquinolone derivatives.

Next, we examined the effect of 4-substituents on the autoxidation by the use of other munchnones (**2b, c**, **8a—c**, **11a, b**, **14**, and **16**) indicated in Chart 1, and the results are summarized in Table 1. The nature of the 4-substituents does influence the reaction. The autoxidation occurred in the munchnones **8a—c** and **2b**, in which the 4-substituents were aromatics (Table 1). On the other hand, munchnones **11a, b**, **14**, **16**, and **2c**, in which the 4-substituents were alkyls, afforded autoxidation products in low yields or not at all. For example, the munchnone **11a** derived from *N*-pivaloylproline (**10a**) reacted very slowly with oxygen and the yield of the product **12a** was poor (9%) in spite of the long reaction time (9 d). In the reaction, the starting material (**10a**) was recovered in 38% yield, after acid hydrolysis of the reaction mixture. These results have been attributed to the electronic effects of the aromatic substitution at the C4 position in the munchnones.

**Mechanistic Consideration** The reaction pathway was examined by the measurement of $CO_2$ formed during the reaction and by conducting the reaction under an $^{18}O_2$ atmosphere. The product (***6a**) contained two $^{18}O$'s (Chart

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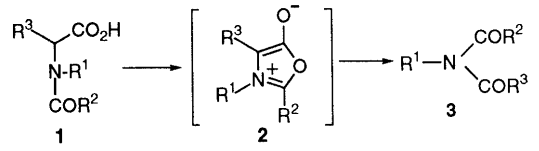
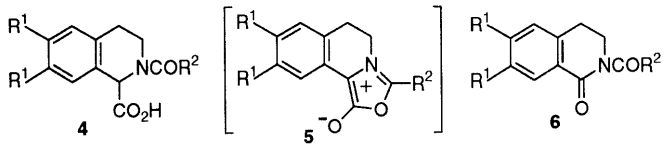
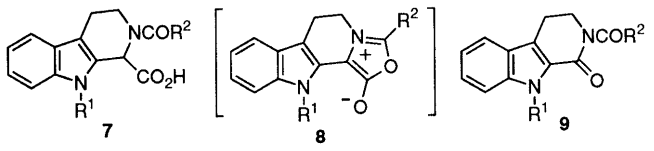


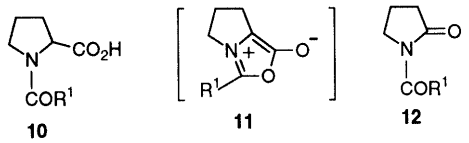
**1a**, **2a**, **3a**: $R^1$=Me, $R^2$=$R^3$=Ph
**1b**, **2b**,**3b**: $R^1$=Me, $R^2$=Bu$^t$, $R^3$=Ph
**1c**, **2c**: $R^1$=Me, $R^2$=Ph, $R^3$=PhCH$_2$



**4a**, **5a**, **6a**: $R^1$=MeO, $R^2$=Bu$^t$
**4b**, **5b**, **6b**: $R^1$=H, $R^2$=Bu$^t$
**4c**, **5c**, **6c**: $R^1$=H, $R^2$=Ph
**4d**, **5d**, **6d**: $R^1$=H, $R^2$=Me



**7a**, **8a**, **9a**: $R^1$=H, $R^2$=Bu$^t$
**7b**, **8b**, **9b**: $R^1$=Me, $R^2$=Bu$^t$
**7c**, **8c**, **9c**: $R^1$=H, $R^2$=Ph



**10a**, **11a**, **12a**: $R^1$=Bu$^t$
**10b**, **11b**, **12b**: $R^1$=Ph

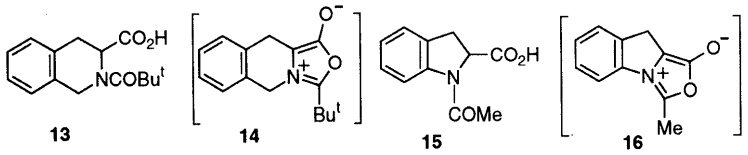


Chart 1

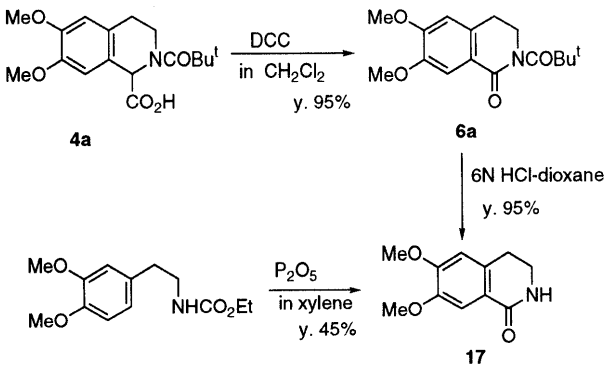


Chart 2

3). The $^{13}$C-NMR spectrum indicated that $^{18}$O had been incorporated on both carbonyl groups of the imides, based on the $^{18}$O-isotope effects on the chemical shifts of both carbonyl carbons (Table 2). The observed $^{18}$O-isotope effects are comparable to those reported in the literature for some simple amides and ketones.[10] Both carbonyl

Table 1. Autoxidation of Munchnones Generated from *N*-Acyl α-Amino Acids

| Compd. | $R^1$ | $R^2$ | $R^3$ | Product (yield, %) |
|---|---|---|---|---|
| **1a** | Me | Ph | Ph | **3a** (18)[a] |
| **1b** | Me | Bu$^t$ | Ph | **3b** (78) |
| **1c** | Me | Bu$^t$ | PhCH$_2$ | —[b] |
| **4a** | MeO | Bu$^t$ | — | **6a** (95) |
| **4b** | H | Bu$^t$ | — | **6b** (99) |
| **4c** | H | Ph | — | **6c** (80) |
| **4d** | H | Me | — | **6d** (84) |
| **7a** | H | Bu$^t$ | — | **9a** (93) |
| **7b** | Me | Bu$^t$ | — | **9b** (83) |
| **7c** | H | Ph | — | **9c** (99) |
| **10a** | Bu$^t$ | — | — | **12a** (9)[c] |
| **10b** | Ph | — | — | **12b** (6)[c] |
| **13** | — | — | — | —[b] |
| **15** | — | — | — | —[b] |

*a*) Literature data.[2] *b*) The autoxidation product was not isolated. *c*) The reaction time was 9 d.

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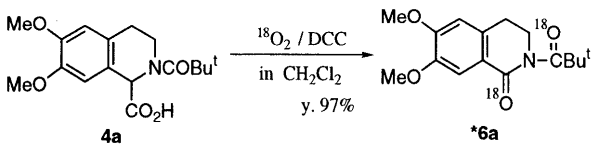


Chart 3

Table 2. $^{18}O$ Effect on the Chemical Shifts of **6a** and ***6a** in $^{13}C$ NMR Spectra

| | 6a | *6a | Difference (Hz) |
|---|---|---|---|
| $CH_3$ | 27.91 | 27.91 | 0 |
| C-4 | 28.53 | 28.53 | 0 |
| $Me_3C$ | 43.66 | 43.66 | 0 |
| C-3 | 46.31 | 46.31 | 0 |
| $CH_3O$ | 56.10 | 56.10 | 0 |
| $CH_3O$ | 56.16 | 56.16 | 0 |
| C-5 (or C-8) | 109.38 | 109.38 | 0 |
| C-8 (or C-5) | 110.80 | 110.80 | 0 |
| C-4a | 121.00 | 121.00 | 0 |
| C-8a | 134.44 | 134.44 | 0 |
| C-6 | 148.34 | 148.33 | 0.68 |
| C-7 | 153.27 | 153.26 | 0.68 |
| C-1 | 165.82 | 165.76 | 4.07 |
| $^t$BuC=O | 189.15 | 189.07 | 5.42 |

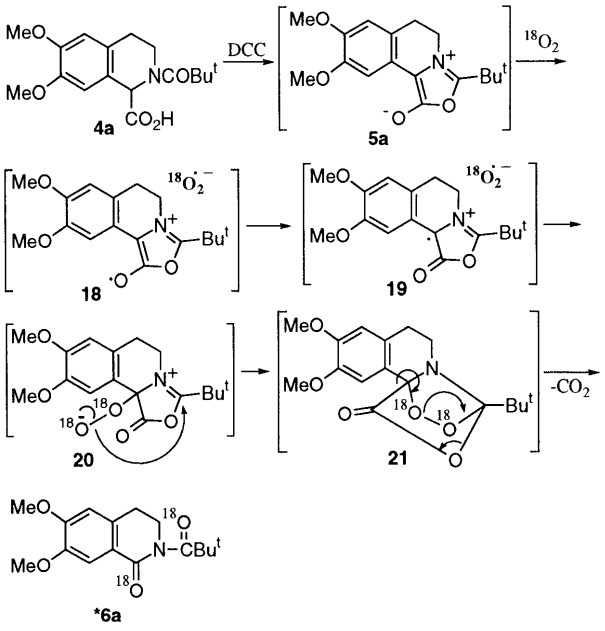


Chart 4

groups of the imides in compound ***6a*** contained more than 95% $^{18}O$ as evaluated by mass spectrometry.

A plausible mechanism for this reaction is suggested in Chart 4. The reaction apparently involves autoxidation of munchnone (**5a**) and fragmentation of **21** to **6a** and $CO_2$.

The munchnone **5a** undergoes a single electron-transfer reaction with $O_2$, yielding the radical **18** and superoxide radical anion. The radical **18** isomerizes to the incipient carbon free radical **19**, which might combine with superoxide radical anion to give the hydroperoxide anion **20**. This anion **20** could then cyclize to give **21**. The loss of carbon dioxide from the cycloadduct **21** should result in the formation of ***6a***. Direct formation of **20** by a concerted interaction between the ground state (singlet) munchnone **5a** and ground state (triplet) $O_2$ is unlikely on the basis of the usual spin conservation rules.[11] For the same reason, formation of **21** by a 1,3-dipolar cycloaddition reaction[4] between $O_2$ and the munchnone **5a** may also be unlikely. It may be pointed out here that Huisgen and co-workers have proposed two possible courses of autoxidation of 3-methyl-2,4-diphenyloxazolium-5-olate (**2a**).[2] However, the mechanisms reported by Huisgen's group can not explain our observation that the autoxidation product contained two $^{18}O$'s.

The results indicate that the autoxidation of munchnones is spontaneous in that it is initiated by direct reaction of triplet oxygen with munchnones. The ease with which initiation occurs is related to the nature of the C-4 substituents of the ring. We can only speculate as to the exact nature of the initiation process, involving an overall triplet–singlet change, at the moment. One highly attractive mechanism seems to be initial single electron transfer from the munchnone to triplet oxygen to produce the corresponding radical ions or a charge-transfer complex, respectively, in a reversible step. Furthermore, the efficiency of autoxidation reaction depends on the stability of the radical **19**.

In summary, the efficiency of the autoxidation of munchnones is a function of the substitution pattern on the C4 position of the ring. The results of these $^{18}O$-labeling studies confirmed the course of the autoxidation of munchnones. The mechanism of product formation involves a series of well-precedented autoxidative processes including oxygenation, cyclization of the resulting peroxy anion, and oxidative cleavage. We conclude that munchnones react fairly rapidly with oxygen to give autoxidation products if the C-4 substituent is aromatic, but not if it is alkyl in nature.

## Experimental

**General Methods** All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. $^1H$-NMR spectra were measured on either a JEOL JNM-PMX60SI or a JEOL JNM-FX270 spectrometer with tetramethylsilane ($Me_4Si$) as an internal reference and $CDCl_3$ as the solvent unless otherwise noted. $^{13}C$-NMR spectra were obtained on a JEOL JNM-FX270 spectrometer (at 67.8 MHz). Both $^1H$- and $^{13}C$-NMR spectral data are reported in parts per million ($\delta$) relative to $Me_4Si$. Infrared (IR) spectra were recorded on a JASCO IR810 spectrometer. Low- and high-resolution mass (MS) spectra were obtained with a JEOL JMS-DX300 spectrometer with a direct inlet system at 70 eV. Combustion analyses were carried out in the microanalytical laboratory of this university.

**Materials** The following compounds were prepared by reported procedures: Ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: mp 185—186 °C (oxalate) [mp[12] 188—189 °C (oxalate)]. *N*-Pivaloylproline (**10a**): mp 131—132 °C (mp[13] 128.3—129.6 °C). *N*-Benzoylproline (**10b**): mp 155—157 °C (mp[13] 153.9—154.3 °C). *N*-Acetyl-2,3-dihydroindole-2-carboxylic acid (**15**): mp 187—189 °C (mp[14] 186—189 °C).

**Benzyl *N*-Methyl-*N*-pivaloylphenylglycinate (22)** A solution of benzyl phenylglycinate[15] (1.95 g, 8.1 mmol) and paraformaldehyde (269 mg, 8.1 mmol) in formic acid (15 ml) was stirred at 95 °C for 4 h. The solvent was then evaporated under reduced pressure. The residue was diluted with $CH_2Cl_2$ (20 ml) and 10% $Na_2CO_3$ (20 ml). To this vigorously stirred solution was added a solution of pivaloyl chloride (1.1 ml, 8.1 mmol) in $CH_2Cl_2$ (5 ml) with cooling. The reaction mixture was stirred for 12 h at room temperature and then extracted with $CH_2Cl_2$ (2 × 60 ml). The combined extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was chromato-

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graphed on a column of silica gel with EtOAc–hexane (1 : 5) as the eluent to give **22** (330 mg, 36%) as a colorless oil: bp 205 °C (2 mmHg) (bath temperature). $^1$H-NMR (60 MHz) $\delta$: 1.33 (s, 9H), 2.87 (s, 3H), 5.27 (s, 2H), 6.33 (s, 1H), 7.33 (s, 5H). IR (neat) cm$^{-1}$: 1745, 1675, 1635. CI-MS *m/z*: 340 ($M^+ + 1$, 100). *Anal.* Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.03; H, 7.28; N, 3.96.

***N*-Methyl-*N*-pivaloylphenylglycine (1b)** A mixture of **22** (330 mg, 1 mmol) and 10% Pd–C (30 mg) in EtOAc (5 ml) was stirred under a hydrogen atmosphere at room temperature for 0.5 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give **1b** as colorless crystals (238 mg, 98%). An analytical sample was obtained by recrystallization from $Et_2O$–hexane, mp 119—121 °C. $^1$H-NMR (60 MHz) $\delta$: 1.33 (s, 9H), 2.87 (s, 3H), 6.20 (s, 1H), 7.27 (s, 5H), 10.68 (s, 1H). IR (Nujol) cm$^{-1}$: 3400 (br), 1730. MS *m/z*: 249 ($M^+$, 0.4), 57 (100). *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.31; H, 7.69; N, 5.45.

**Methyl *N*-Benzoyl-*N*-methylphenylalaninate (23)** Methyl *N*-benzyloxycarbonyl-*N*-methylphenylalaninate[16] (4.15 g, 12.7 mmol) was hydrogenated in a similar fashion to **1b**. The obtained methyl *N*-methylphenylalaninate was directly benzoylated by means of the Schotten–Bauman reaction using benzoyl chloride to give **23** (3.42 g, 91% in two steps) as a colorless oil: High-resolution MS: Calcd for $C_{18}H_{19}NO_3$: 297.1365. Found: 297.1370. $^1$H-NMR (270 MHz) $\delta$: 2.77 + 3.07 (s, 3H), 3.14—3.23 + 3.46—3.59 (m, 2H), 3.80 (s, 3H), 4.54—4.57 + 5.38—5.44 (m, 1H), 6.75—7.45 (m, 10H). IR (neat) cm$^{-1}$: 1740, 1640. MS *m/z*: 297 ($M^+$, 0.9), 105 (100).

***N*-Benzoyl-*N*-methylphenylalanine (1c)** A solution of **23** (1.5 g, 5 mmol) and 2 N NaOH (3.8 ml) in dioxane (6 ml) was stirred at 65 °C for 2 h. The reaction mixture was diluted with $Et_2O$ (60 ml) and $H_2O$ (50 ml). The aqueous layer was acidified with concentrated HCl and extracted with EtOAc (60 ml × 2). The combined extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized from EtOAc and hexane to give **1c** (1.37 g, 96%). mp 137—138 °C ($Et_2O$). $^1$H-NMR (270 MHz) $\delta$: 2.79 + 3.09 (s, 3H), 3.18—3.37 + 3.46—3.54 (m, 2H), 4.52—4.65 + 5.10—5.25 (m, 1H), 6.78 + 6.97 (br s, 1H), 7.15—7.40 (m, 10H). IR (Nujol) cm$^{-1}$: 3000 (br), 1750. MS *m/z*: 283 ($M^+$, 6.8), 105 (100). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.96; H, 6.12; N, 4.88.

The following compounds were prepared in high yields by Schotten–Baumann reaction of the appropriate α-amino acids or esters and acyl chlorides.

2-Benzoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic Acid (**7c**): mp 161—164 °C (acetone). $^1$H-NMR (270 MHz, DMSO-$d_6$) $\delta$: 2.70—2.90 (m, 2H), 3.50—3.59 (m, 1H), 3.88—3.95 (m, 1H), 5.97 (s, 1H), 6.97—7.13 (m, 2H), 7.40—7.54 (m, 7H), 11.04 (s, 1H). IR (Nujol) cm$^{-1}$: 3420, 3260, 1725, 1620. MS *m/z*: 320 ($M^+$, 0.3), 276 (100). *Anal.* Calcd for $C_{19}H_{16}N_2O_3 \cdot 1/2H_2O$: C, 69.29; H, 5.05; N, 8.51. Found: C, 69.34; H, 5.35; N, 8.55.

Ethyl 6,7-Dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: mp 100—101 °C (hexane). $^1$H-NMR (60 MHz) $\delta$: 1.27 (t, 3H, $J$ = 7.0 Hz), 1.33 (s, 9H), 2.70—2.98 (m, 2H), 3.67—4.13 (m, 2H), 3.83 (s, 6H), 4.15 (q, 2H, $J$ = 7.0 Hz), 5.67 (s, 1H), 6.75 (s, 1H), 7.03 (s, 1H). IR (Nujol) cm$^{-1}$: 1740, 1630. MS *m/z*: 349 ($M^+$, 0.7), 264 (100). *Anal.* Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.29; H, 7.73; N, 3.85.

Ethyl 2-Pivaloyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**24**): mp 165—167 °C (EtOAc/hexane). $^1$H-NMR (60 MHz) $\delta$: 1.27 (t, 3H, $J$ = 7.0 Hz), 1.40 (s, 9H), 2.70—3.03 (m, 2H), 3.33—3.92 (m, 1H), 4.20 (q, 2H, $J$ = 7.0 Hz), 4.33—4.83 (m, 1H), 6.07 (s, 1H), 6.97—7.63 (m, 4H), 8.37—8.70 (br, 1H). IR (Nujol) cm$^{-1}$: 3300, 1745, 1610. MS *m/z*: 328 ($M^+$, 2.9), 243 (100). *Anal.* Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.52; H, 7.42; N, 8.43.

Ethyl 2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate: Yield 84% (after column chromatography) (EtOAc/hexane 1/1): High-resolution MS: Calcd for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1687. $^1$H-NMR (60 MHz) $\delta$: 1.13 (t, 3H, $J$ = 7.0 Hz), 1.35 (s, 9H), 3.17 (d, 2H, $J$ = 5.0 Hz), 4.07 (q, 2H, $J$ = 7.0 Hz), 4.55 (d, 1H, $J$ = 16.0 Hz), 4.97 (d, 1H, $J$ = 16.0 Hz), 5.20 (d, 1H, $J$ = 5.0 Hz), 7.13 (s, 4H). IR (neat) cm$^{-1}$: 1735, 1635. MS *m/z*: 289 ($M^+$, 1.3), 204 (100).

**Ethyl 1,2,3,4-Tetrahydroisoquinoline-1-carboxylate (25)** A mixture of ethyl isoquinoline-1-carboxylate[17] (2 g, 10 mmol) and $PtO_2 \cdot 2H_2O$ (200 mg) in EtOH (18 ml) was stirred under a hydrogen atmosphere at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give **25**. The obtained ester (**25**) was utilized in the Schotten–Baumann reaction without further purification.

Ethyl 2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: Yield 84%: bp 186—188 °C (4 mmHg). $^1$H-NMR (60 MHz) $\delta$: 1.23 (t, 3H, $J$ = 7.0 Hz), 1.33 (s, 9H), 2.77—3.08 (m, 2H), 3.83—4.13 (m, 2H), 4.10 (q, 2H, $J$ = 7.0 Hz), 5.77 (s, 1H), 7.01—7.70 (m, 4H). IR (neat) cm$^{-1}$: 1740, 1635. MS *m/z*: 289 ($M^+$, 0.1), 57 (100). *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.62; H, 7.97; N, 4.61.

Ethyl 2-Benzoyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: Yield 95%: bp 206—208 °C (3 mmHg). $^1$H-NMR (60 MHz) $\delta$: 1.25 (t, 3H, $J$ = 7.0 Hz), 2.67—3.07 (m, 2H), 3.53—3.88 (m, 2H), 4.13 (q, 2H, $J$ = 7.0 Hz), 5.87 (s, 1H), 6.95—7.60 (m, 9H). IR (neat) cm$^{-1}$: 1740, 1640. MS *m/z*: 309 ($M^+$, 0.2), 105 (100). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.77; H, 6.23; N, 4.37.

Ethyl 2-Acetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: Yield 92%: bp 200 °C (2 mmHg) (bath temperature). $^1$H-NMR (60 MHz) $\delta$: 1.22 (t, 3H, $J$ = 7.0 Hz), 2.18 (s, 3H), 2.67—3.13 (m, 2H), 3.60—3.88 (m, 2H), 4.13 (q, 2H, $J$ = 7.0 Hz), 5.82 (s, 1H), 7.03—7.63 (m, 4H). IR (neat) cm$^{-1}$: 1740, 1650. MS *m/z*: 247 ($M^+$, 0.7), 132 (100). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.98; H, 6.93; N, 5.55.

**Ethyl 9-Methyl-2-pivaloyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate** Prepared by *N*-methylation[18] of **24**. Yield 63% (after column chromatography) (EtOAc/hexane 1/4). High-resolution MS: Calcd for $C_{20}H_{26}N_2O_3$: 342.1943. Found: 342.1942. $^1$H-NMR (270 MHz) $\delta$: 1.28 (t, 3H, $J$ = 7.2 Hz), 1.38 (s, 9H), 2.75—3.04 (m, 2H), 3.65—3.82 (m, 1H), 3.83 (s, 3H), 4.10—4.32 (m, 2H), 4.46—4.58 (m, 1H), 6.31 (s, 1H), 7.11 (t, 1H, $J$ = 8.1 Hz), 7.24 (t, 1H, $J$ = 8.1 Hz), 7.33 (d, 1H, $J$ = 8.4 Hz), 7.50 (d, 1H, $J$ = 7.9 Hz). IR (neat) cm$^{-1}$: 1740, 1645. MS *m/z*: 342 ($M^+$, 9.3), 257 (100).

The following carboxylic acids were prepared in high yields by the hydrolysis of the appropriate esters in a similar fashion to **1c**.

6,7-Dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**4a**): mp 146—147 °C ($Et_2O$/hexane). $^1$H-NMR (60 MHz) $\delta$: 1.33 (s, 9H), 2.67—2.97 (m, 2H), 3.67—4.20 (m, 2H), 3.80 (s, 6H), 5.67 (s, 1H), 6.57 (s, 1H), 6.97 (s, 1H), 9.87 (s, 1H). IR (Nujol) cm$^{-1}$: 2950 (br), 1735. MS *m/z*: 321 ($M^+$, 0.4), 236 (100). *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.42; H, 7.21; N, 4.16.

2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**4b**): mp 103—105 °C ($Et_2O$/hexane). $^1$H-NMR (60 MHz) $\delta$: 1.33 (s, 9H), 2.77—3.07 (m, 2H), 3.77—4.12 (m, 2H), 5.77 (s, 1H), 7.03—7.60 (m, 4H), 10.60 (s, 1H). IR (Nujol) cm$^{-1}$: 2950 (br), 1730. MS *m/z*: 261 ($M^+$, 0.2), 57 (100). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.12; H, 7.20; N, 5.21.

2-Benzoyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**4c**): mp 224—227 °C ($Et_2O$/hexane). $^1$H-NMR (60 MHz) $\delta$: 2.71—3.05 (m, 2H), 3.55—3.93 (m, 2H), 6.00 (s, 1H), 7.07—7.77 (m, 9H), 9.63 (br s, 1H). IR (Nujol) cm$^{-1}$: 3450 (br), 1720. MS *m/z*: 281 ($M^+$, 0.9), 236 (100). *Anal.* Calcd for $C_{17}H_{15}NO_3 \cdot H_2O$: C, 68.21; H, 5.72; N, 4.67. Found: C, 67.97; H, 5.77; N, 4.44.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**4d**): mp 179—181 °C (EtOAc). $^1$H-NMR (270 MHz) $\delta$: 2.18 (s, 3H), 2.83—2.95 (m, 1H), 3.01—3.10 (m, 1H), 3.66—3.75 (m, 1H), 3.89—3.95 (m, 1H), 5.82 (s, 1H), 7.15—7.26 (m, 3H), 7.51—7.56 (m, 1H). IR (Nujol) cm$^{-1}$: 3400 (br), 1730. MS *m/z*: 219 ($M^+$, 0.4), 132 (100). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.58; H, 6.07; N, 6.12.

2-Pivaloyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic Acid (**7a**): mp 181 °C (dec.) (acetone). $^1$H-NMR (270 MHz) $\delta$: 1.39 (s, 9H), 2.78—2.99 (m, 2H), 3.35—3.64 (m, 1H), 4.45—4.79 (m, 1H), 6.04 (s, 1H), 7.02—7.54 (m, 4H), 8.65 (s, 1H). IR (Nujol) cm$^{-1}$: 3400 (br), 1720. MS *m/z*: 300 ($M^+$, 5.0), 215 (100). *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.75; H, 6.79; N, 9.14.

9-Methyl-2-pivaloyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic Acid (**7b**): mp 181—182 °C (acetone). $^1$H-NMR (270 MHz) $\delta$: 1.39 (s, 9H), 2.86—3.06 (m, 2H), 3.59—3.71 (m, 1H), 3.73 (s, 3H), 3.95—4.35 (br, 1H), 4.46—4.53 (m, 1H), 6.18 (s, 1H), 7.11—7.51 (m, 4H). IR (Nujol) cm$^{-1}$: 3000 (br), 1740. MS *m/z*: 314 ($M^+$, 6.8), 185 (100). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.47; H, 7.13; N, 8.61.

2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (**13**): mp 167—169 °C (EtOAc/hexane). $^1$H-NMR (270 MHz) $\delta$: 1.34 (s, 9H), 3.18—3.22 (m, 2H), 4.58 (d, 1H, $J$ = 15.8 Hz), 4.98 (d, 1H, $J$ = 15.8 Hz), 5.08—5.13 (m, 1H), 7.13—7.24 (m, 4H). IR (Nujol) cm$^{-1}$: 3000 (br), 1730. MS *m/z*: 261 ($M^+$, 20.9), 176 (100). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.68; H, 7.35; N, 5.27.

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**General Procedure for the Autoxidation Reaction** A stirred solution of an *N*-acyl-α-amino acid (1.5 mmol) in dry $CH_2Cl_2$ (5 ml) was treated with DCC (1.57 mmol) under ice cooling, and the mixture was stirred at room temperature for 18 h. Acetic acid (0.3 ml) was added, and stirring was continued for 0.5 h. The mixture was diluted with $CH_2Cl_2$, filtered, washed with 3% $Na_2CO_3$, and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel to give the autoxidation product.

*N*-Methyl-*N*-pivaloylbenzamide (**3b**): Yield 78% (after column chromatography) (EtOAc/hexane 1/1): bp 155 °C (2 mmHg) (bath temperature). $^1$H-NMR (270 MHz) $\delta$: 1.32 (s, 9H), 3.16 (s, 3H), 7.42—7.59 (m, 3H), 7.66—7.72 (m, 2H). $^{13}$C-NMR (67.8 MHz) $\delta$: 28.46 (q), 35.20 (q), 42.85 (s), 128.72 (d), 128.90 (d), 132.38 (s), 134.66 (s), 174.96 (s), 186.21 (s). IR (Neat) cm$^{-1}$: 1680. MS *m/z*: 219 ($M^+$, 5.7), 105 (100). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.28; H, 7.61; N, 6.30.

6,7-Dimethoxy-1-oxo-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**6a**): Yield 95% (after column chromatography) (EtOAc): mp 113—114 °C ($Et_2O$–hexane). $^1$H-NMR (270 MHz) $\delta$: 1.38 (s, 9H), 2.97 (t, 2H, $J$=6.2 Hz), 3.83 (t, 2H, $J$=6.2 Hz), 3.93 (s, 3H), 3.95 (s, 3H), 6.70 (s, 1H), 7.63 (s, 1H). $^{13}$C-NMR (67.8 MHz) $\delta$: 27.89 (q), 28.51 (t), 43.66 (s), 46.30 (t), 56.08 (q), 56.15 (q), 109.37 (d), 110.77 (d), 120.98 (s), 134.43 (s), 148.31 (s), 153.24 (s), 165.78 (s), 189.10 (s); IR (neat) cm$^{-1}$: 1695, 1655. MS *m/z*: 291 ($M^+$, 32.7), 207 (100). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.81; H, 7.52; N, 4.75.

1-Oxo-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**6b**): Yield 99% (after column chromatography) (EtOAc): bp 160 °C (2 mmHg)(bath temperature). $^1$H-NMR (270 MHz) $\delta$: 1.38 (s, 9H), 3.04 (t, 2H, $J$=6.2 Hz), 3.84 (t, 2H, $J$=6.2 Hz), 7.25 (d, 1H, $J$=8.1 Hz), 7.37 (t, 1H, $J$=8.1 Hz), 7.50 (t, 1H, $J$=8.1 Hz), 8.17 (d, 1H, $J$=8.1 Hz). $^{13}$C-NMR (67.8 MHz) $\delta$: 27.85 (q), 28.74 (t), 43.74 (s), 45.93 (t), 127.26 (d), 127.49 (d), 128.62 (s), 129.22 (d), 133.16 (d), 140.04 (s), 165.78 (s), 189.18 (s). IR (neat) cm$^{-1}$: 1690. MS *m/z*: 231 ($M^+$, 8.6), 147 (100). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.70; H, 7.33; N, 5.90.

2-Benzoyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (**6c**): Yield 80% (after column chromatography) (EtOAc): bp 210 °C (2 mmHg) (bath temperature). $^1$H-NMR (270 MHz) $\delta$: 3.15 (t, 2H, $J$=6.2 Hz), 4.10 (t, 2H, $J$=6.2 Hz), 7.26—7.55 (m, 6H), 7.60—7.66 (m, 2H), 8.07 (d, 1H, $J$=7.3 Hz). $^{13}$C-NMR (67.8 MHz) $\delta$: 28.43 (q), 44.27 (q), 127.36 (d), 127.68 (d), 128.09 (d), 128.10 (s), 128.18 (d), 129.63 (d), 131.61 (d), 133.60 (d), 136.24 (s), 1140.17 (s), 165.57 (s), 174.42 (s). IR (neat) cm$^{-1}$: 1695, 1680. MS *m/z*: 251 ($M^+$, 8.6), 105 (100). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.42; H, 5.28; N, 5.49.

2-Acetyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (**6d**): Yield 84% (after column chromatography) (EtOAc): mp 97—98 °C ($Et_2O$–hexane). $^1$H-NMR (270 MHz) $\delta$: 2.66 (s, 3H), 2.99 (t, 2H, $J$=6.2 Hz), 4.11 (t, 2H, $J$=6.2 Hz), 7.25 (d, 1H, $J$=7.3 Hz), 7.40 (t, 1H, $J$=7.3 Hz), 7.51 (t, 1H, $J$=7.3 Hz), 8.15 (d, 1H, $J$=7.3 Hz). $^{13}$C-NMR (67.8 MHz) $\delta$: 27.62 (q), 28.14 (t), 41.73 (t), 127.37 (d), 129.04 (s), 129.53 (d), 133.39 (d), 140.27 (s), 165.74 (s), 173.71 (s). IR (neat) cm$^{-1}$: 1695. MS *m/z*: 189 ($M^+$, 71.8%), 118 (100%). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.67; H, 5.97; N, 7.30.

1-Oxo-2-pivaloyl-1,2,3,4-tetrahydro-β-carboline (**9a**): Yield 93% (after column chromatography) ($CH_2Cl_2$/EtOAc 10/1): mp 172—173 °C ($Et_2O$–hexane). $^1$H-NMR (270 MHz) $\delta$: 1.43 (s, 9H), 3.08 (t, 2H, $J$=6.4 Hz), 4.08 (t, 2H, $J$=6.4 Hz), 7.16 (t, 1H, $J$=8.1 Hz), 7.34 (t, 1H, $J$=8.1 Hz), 7.46 (d, 1H, $J$=8.4 Hz), 7.62 (d, 1H, $J$=7.9 Hz). $^{13}$C-NMR (67.8 MHz) $\delta$: 21.42 (t), 27.93 (q), 43.75 (s), 48.83 (t), 112.71 (d),120.69 (d), 120.80 (s), 123.16 (s), 124.85 (d), 126.26 (s), 126.54 (d), 138.38 (s), 162.55 (s), 188.40 (s). IR (Nujol) cm$^{-1}$: 1650, 1690, 3270. MS *m/z*: 270 ($M^+$, 85.3), 186 (100). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.90; H, 6.75; N, 10.45.

9-Methyl-1-oxo-2-pivaloyl-1,2,3,4-tetrahydro-β-carboline (**9b**): Yield 83% (after column chromatography) ($CH_2Cl_2$/EtOAc 10/1): mp 115—117 °C ($Et_2O$–hexane). $^1$H-NMR (270 MHz) $\delta$: 1.39 (s, 9H), 3.04 (t, 2H, $J$=6.4 Hz), 3.99 (t, 2H, $J$=6.4 Hz), 4.09 (s, 3H), 7.12—7.20 (m, 1H), 7.33—7.37 (m, 2H), 7.60 (d, 1H, $J$=7.9 Hz). $^{13}$C-NMR (67.8 MHz) d: 21.58 (t), 28.00 (q), 31.56 (q), 43.77 (s), 48.32 (t), 110.36 (d), 120.47 (d), 120.80 (d), 123.16 (s), 123.62 (s), 125.77 (s), 125.99 (d), 140.07 (s), 162.84 (s), 188.88 (s). IR (Nujol) cm$^{-1}$: 1670. MS *m/z*: 284 ($M^+$, 57.7), 199 (100). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.88; H, 7.14; N, 9.71.

2-Benzoyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (**9c**): Yield 99% (after column chromatography) ($CH_2Cl_2$/EtOAc 10/1): mp 271—273 °C (AcOEt). $^1$H-NMR (270 MHz, DMSO-$d_6$) $\delta$: 3.21 (t, 2H, $J$=6.4 Hz), 4.23 (t, 2H, $J$=6.4 Hz), 7.14 (t, 1H, $J$=7.4 Hz), 7.33 (t, 1H, $J$=8.1 Hz), 7.39—7.54 (m, 4H), 7.59 (d, 2H, $J$=6.9 Hz), 7.72 (d, 1H, $J$=7.9 Hz), 11.80 (s, 1H). $^{13}$C-NMR (67.8 MHz, DMSO-$d_6$) $\delta$: 20.52 (t), 46.45 (t), 112.75 (d), 120.05 (d), 120.91 (d), 123.20 (s), 124.37 (s), 125.67 (s), 125.84 (d), 127.89 (d), 127.98 (d), 131.10 (d), 136.49 (s), 138.56 (s), 161.03 (s), 173.13 (s). IR (Nujol) cm$^{-1}$: 1675, 3270. MS *m/z*: 290 ($M^+$, 85.3), 1105 (100). *Anal.* Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.23; H, 4.97; N, 9.41.

1-Pivaloyl-2-pyrrolidinone (**12a**): Yield 9% (after column chromatography) ($CH_2Cl_2$/EtOAc 10/1): bp 83—84 °C (0.2 mmHg) [bp[19] 85—87 °C (0.2 mmHg)].

1-Benzoyl-2-pyrrolidinone (**12b**): Yield 6% (after column chromatography) ($CH_2Cl_2$/EtOAc 10/1): mp 88—90 °C (acetone) (mp[19] 89—90 °C).

**6,7-Dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (17)** A solution of **6a** (100 mg) in dioxane (1 ml) and 6 N HCl (3 ml) was refluxed for 0.5 h. The mixture was then diluted with $CH_2Cl_2$ (50 ml), washed with 10% $Na_2CO_3$ (30 ml) and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was recrystallized from $CH_2Cl_2$–hexane to give **17** (67.2 mg, 95%). mp 172—173 °C (mp[8] 169—171 °C).

**Detection of $CO_2$ during the Autoxidation Reaction of 4a** The detection of $CO_2$ in the reaction was done with a Kitagawa precision gas detector tube (Koumyo Rikagaku). In another reaction, Ar gas was bubbled through the reaction solution and the gas released was absorbed in 1% $Ba(OH)_2$ aqueous solution. The solution became cloudy and $BaCO_3$ was precipitated.

**Oxidation of 4a with $^{18}O_2$** A mixture of **4a** (321 mg, 1 mmol) and DCC (216.7 mg, 1.05 mmol) was evacuated for a few minutes (to 2 mmHg) and Ar gas was introduced. The same procedure was repeated three times and finally $^{18}O_2$ (97 atom% $^{18}$O, MSD Isotope) was added to the mixture. Immediately thereafter, deoxygenated $CH_2Cl_2$ (5 ml) was introduced. The reaction mixture was stirred under an $^{18}O_2$ atmosphere at room temperature for 18 h. Work-up as described in the general procedure for autoxidation gave 286 mg (97%) of colorless crystals with melting point and $^1$H-NMR properties identical with those of **6a**. The $^{13}$C-NMR data are presented in Table 2.

## References and Notes


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