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Synthesis of functionalized nitrogen heterocycles from β- and γ-amino acids by radical decarboxylation

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Abstract—The radical decarboxylation of β- and γ-amino acids on treatment with $PhI(OAc)_2$–I_2 is a mild and efficient methodology to synthesize halogenated or oxygenated nitrogen heterocycles. The reaction was applied to the synthesis of bioactive products, such as opioid analogues, iminosugars and new antifungic agents.

The presence of functionalized piperidine and pyrrolidine rings in the structure of many natural products[1] and synthetic drugs[2] has elicited a growing interest in these nitrogen heterocycles.

Among the compounds containing them (Fig. 1), there are simple structures such as that of coniine **1**,[1a] the active principle in the hemlock poison, or the potent antipsychotic haloperidol **2**,[2a] to complex alkaloids from the *Amarillydaceae* family.[1j] Furthermore, these heterocycles are also of interest in synthetic organic chemistry as ligands and chiral auxiliaries, such as compound **3**.[3] As a result, many synthetic methodologies to obtain these heterocycles have been developed.[4]

We report now on a mild, efficient preparation of functionalized nitrogen heterocycles from β- and γ-amino acids, using a radical decarboxylation as the key step.[5] The starting amino acids are readily prepared from commercial products. For instance, the β-amino acid **4** (Scheme 1) was prepared in two steps from dimethyl itaconate,[6a] in excellent yields. The models **5** and **6** were synthesized by acylation of commercial pyrrolidine or piperidine derivatives,[6b,c] and compound **7** was obtained in three steps from isonipecotic acid.[6d]

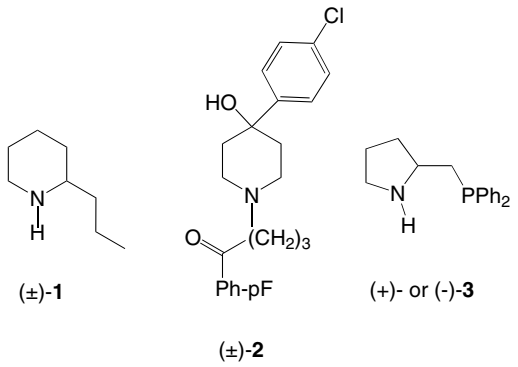

Figure 1. Piperidine and pyrrolidine rings in natural products, synthetic drugs and ligands.

The aryl acid **8** was formed from commercial 4-cyano 4-phenylpiperidine·HCl.[6e,f] Many other α-aryl acids can be synthesized by palladium-catalyzed arylation of ester enolates, followed by saponification.[7] They can also be synthesized in two steps from commercial aryl acetic esters and nitrogen mustards.[8]

When the β- or γ-amino acids **4**–**8** were treated with (diacetoxyiodo)benzene (DIB) and iodine, a radical decarboxylation took place and the iodinated or oxygenated products **9**–**13** were obtained (Scheme 1).[9]

The decarboxylation of substrate **4** afforded the iodo derivative **9** in good yield. Remarkably, due to the mild

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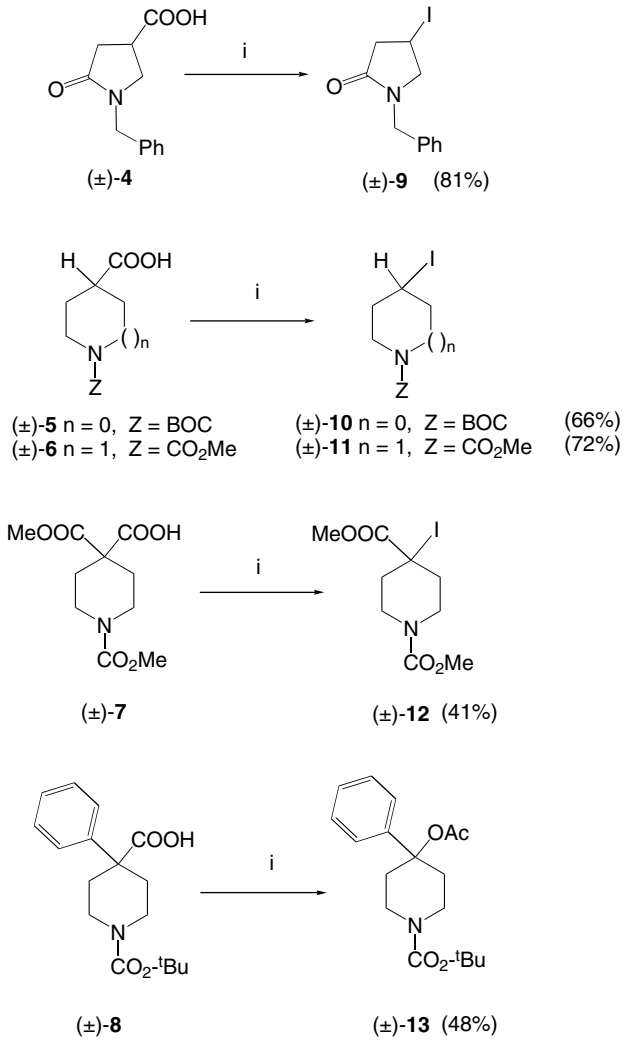


Scheme 1. Reagents and conditions: (i) $PhI(OAc)_2$ (2 equiv), I_2 (1 equiv), CCl_4, *hv* (irradiation with two 80 W tungsten lamps), reflux. Yields are given for products purified by chromatography on silica gel.

reaction conditions, no elimination was observed. The amino acid analogues **5** and **6** were treated under similar conditions, affording the desired iodo derivatives **10** and **11**.

Similarly, the malonate derivative **7** yielded the α-iodo ester **12**, although in moderate yield. However, the preparation of this quaternary iodo compound is difficult by other methodologies, since an elimination reaction usually takes place to give the α,β-unsaturated ester.[10]

To our surprise, when the radical decarboxylation was carried out with the phenyl derivative **8**, the main product was the acetate **13**, and no iodo derivatives were isolated. This result could be explained by initial formation of a tertiary benzylic iodide followed by nucleophilic substitution by acetate ions from the reagent.

The formation of the oxygenated derivative **13** seemed promising, since similar structures can be found in drugs with a potent action on the nervous system,[11] such as the widely used antipsychotic **2** and several new opiate analogues. These oxygenated derivatives are usually synthesized by addition of Grignard reagents to ketones,[11c,f,g] conditions not compatible with aryl substituents such as Br, I, *O*-acyl, etc. Our methodology could offer an alternative route towards new members of this class of compounds.

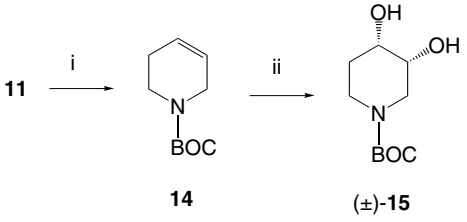
Following our current interest in biologically active products, we decided to apply the decarboxylation reaction to the synthesis of iminosugars. Many iminosugars are potent glycosidase inhibitors, and possess antiviral, antitumoural and hypoglucaemic activities.[12] In order to modulate their activity or improve their bioavailability, the development of new derivatives is of great interest.

The decarboxylation product **11** can be transformed into different iminosugars in a few steps.[13] For example, by treatment of **11** with DBU the alkene **14** (Scheme 2) was obtained in good yields. The product **14** underwent dihydroxylation affording the iminosugar (±)-**15** in satisfactory yields.

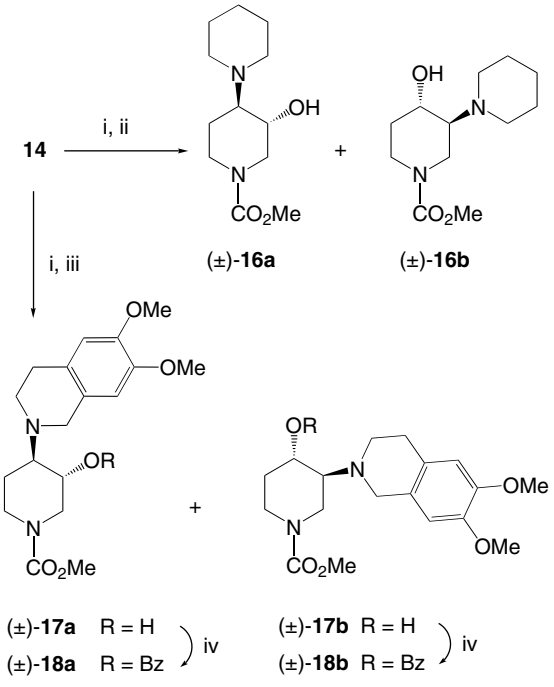
The decarboxylation of γ-amino acids was also applied to the development of new antifungic agents. Thus, the decarboxylation–elimination product **14** (Scheme 3) was epoxidated and then treated with piperidine, affording the alcohols (±)-[**16a** and **16b**].[14,15a] Similarly, by epoxidation and treatment with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, the alcohols (±)-[**17a** and **17b**] were isolated as a mixture; however, their benzoate esters (±)-[**18a** and **18b**] were easily separated.[14,15b]

Products (±)-[**18a** and **18b**] showed potent activity against opportunistic fungi of the genus *Saccharomyces*. $IC_{50} = (14 \pm 7) \times 10^{-3}$ μmol/mL for compound (±)-**18a**, $IC_{50} = (10 \pm 4) \times 10^{-3}$ μmol/mL for compound (±)-**18b**). In contrast, the activity of their analogues (±)-[**16a** and **16b**] was considerably smaller ($IC_{50} = (105 \pm 9) \times 10^{-3}$ μmol/mL for compound (±)-**16a**, $IC_{50} = (108 \pm 9) \times 10^{-3}$ μmol/mL for compound (±)-**16b**). We are currently synthesizing other derivatives in order to study their activity against different strains of pathogenic fungi. The complete biological results will be published elsewhere.

In summary, the decarboxylation of β- and γ-amino acids is a mild and efficient methodology to synthesize halogenated or oxygenated piperidines and pyrrolidines. These functionalized nitrogen heterocycles are useful intermediates in the synthesis of a variety of com-



Scheme 2. Reagents and conditions: (i) DBU, CH_2Cl_2, 84%; (ii) OsO_4, NMO, acetone–H_2O, 57%.



Scheme 3. Synthesis of antifungic agents. Reagents and conditions: (i) MCPBA, CH_2Cl_2, 98%; (ii) piperidine, EtOH, Et_3N, reflux, 53%, (16a/b 3:2); (iii) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, EtOH, Et_3N, reflux, then (iv) BzCl, CH_2Cl_2, Et_3N, DMAP (cat.), 61%, (18a/b, 2:1).

pounds, such as 4-arylpyperidines and iminosugars. The discovery of potent antifungic agents, which are synthesized from a halogenated piperidine, is also reported.

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9. Compounds **9**–**13** were characterized by ^{1}H and ^{13}C NMR, MS, HRMS, IR and elemental analysis. 2D-COSY and HSQC experiments were also carried out. Selected NMR and analysis data are given. Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, dd, $J = 7.0$, 7.5 Hz), 7.29 (1H, dd, $J = 7.1$, 7.3 Hz), 7.26 (2H, d, $J = 7.2$ Hz), 4.52 (1H, d, $J = 14.8$ Hz), 4.45 (1H, d, $J = 14.8$ Hz), 4.39 (1H, dddd, $J = 5.0$, 5.0, 6.8, 6.8 Hz), 3.74 (1H, dd, $J = 6.5$, 11.4 Hz), 3.56 (1H, dd, $J = 4.4$, 11.5 Hz), 3.06 (1H, dd, $J = 7.6$, 17.7 Hz), 2.88 (1H, dd, $J = 5.1$, 17.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.8 (C), 135.6 (C), 128.8 ($2\times$CH), 128.2 ($2\times$CH), 127.8 (CH), 58.0 (CH_2), 46.4 (CH_2), 44.7 (CH_2), 9.7 (CH). Anal. Calcd for $C_{11}H_{12}NIO$: C, 43.88; H, 4.02; N, 4.65. Found: C, 44.16; H, 4.19; N, 4.89. Compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, m), 3.81 (1H, m), 3.74 (1H, m), 3.57 (1H, m), 3.42 (1H, m), 2.25 (1H, m), 2.21 (1H, m), 1.46 (9H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C). Mixture of two rotamers: δ 79.7 (C), 57.3/57.0 (CH_2), 45.0/44.7 (CH_2), 38.3/37.5 (CH_2), 28.4 ($3\times CH_3$), 19.8 (CH). The signal for the CO group was not observed. However, in the IR spectrum its absorption band appears at 1688.3 cm^{-1}. Anal. Calcd for $C_9H_{16}INO_2$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.56; H, 5.23; N, 4.60. Compound **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (1H, dddd, $J = 5.8$, 5.9, 5.9, 5.9 Hz), 3.64 (3H, s), 3.57 (2H, m), 3.31 (2H, ddd, $J = 5.5$, 5.5, 11.6 Hz), 1.98 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ 155.7 (C), 52.6 (CH_3), 43.7 ($2\times CH_2$), 37.0 ($2\times CH_2$), 27.1 (CH). Anal. Calcd for $C_7H_{12}INO_2$: C, 31.25; H, 4.50; N, 5.21. Found: C, 31.41; H, 4.38; N, 5.25. Compound **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (3H, s), 3.70 (2H, m), 3.68 (3H, s), 3.32 (2H, ddd, $J = 3.1$, 8.8, 13.4 Hz), 2.27 (2H, m), 1.84 (2H, ddd, $J = 3.9$, 8.8, 13.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ 172.2 (C), 155.7 (C), 53.2 (CH_3), 52.8 (CH_3), 42.5 ($2\times CH_2$), 42.0 (C), 38.2 ($2\times CH_2$). Anal. Calcd for $C_9H_{14}INO_4$: C, 33.05; H, 4.31; N, 4.28. Found: C, 33.39; H, 4.44; N, 3.92. Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (5H, m), 4.12 (2H, m), 3.11 (2H, m), 2.48 (2H, d, $J = 12.3$ Hz), 2.06 (3H, s), 1.93 (2H, ddd, $J = 4.8$, 13.3, 13.6 Hz), 1.47 (9H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ 169.4 (C), 154.8 (C), 143.8 (C), 128.4 ($2\times$CH), 127.4 (CH), 124.4 ($2\times$CH), 80.3 (C), 79.6 (C), 40.1 ($2\times CH_2$), 35.3 ($2\times CH_2$), 28.4 ($3\times CH_3$), 21.9 (CH_3). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 4.39; N, 7.89. Found: C, 67.58; H, 7.96; N, 4.53.
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14. (a) The proposed structures are supported by the ^{1}H NMR, DEPT, COSY and HSQC experiments, as well as the IR and mass spectra. ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) and HRMS data for compounds (±)-[**16a** and **16b**, **18a** and **18b**]: Compound (±)-**16a**: δ_H 4.43 (1H, d, $J = 9.7$ Hz), 4.25 (1H, d, $J = 12.6$ Hz), 3.69 (3H, s), 3.45 (1H, ddd, $J = 5.1$, 10.0, 10.1 Hz), 2.74 (2H, m), 2.69 (1H, ddd, $J = 2.5$, 12.8, 13.2 Hz), 2.58 (1H, dd, $J = 10.5$, 12.4 Hz), 2.47 (2H, m), 2.40 (1H, m), 1.77 (1H, m), 1.66 (4H, m), 1.46 (2H, m), 1.44 (1H, m); HRMS calcd for $C_{12}H_{22}N_2O_3$ 242.1630, Obs. 242.1667. Compound (±)-**16b**: δ_H 4.25 (1H, d, $J = 11.8$ Hz), 4.13 (1H, d, $J = 13.7$ Hz), 3.69 (3H, s), 3.57 (1H, ddd, $J = 4.6$, 10.3, 10.3 Hz), 2.82 (2H, ddd, $J = 3.5$, 7.2, 11.1 Hz), 2.71 (1H, ddd, $J = 2.8$, 13.3, 13.3 Hz), 2.65 (1H, dd, $J = 11.7$, 12.5 Hz), 2.47 (2H, ddd, $J = 3.4$, 6.9, 10.7 Hz), 2.28 (1H, ddd, $J = 4.1$, 10.7, 10.8 Hz), 2.05 (1H, dddd, $J = 2.6$, 2.6, 4.9, 12.8 Hz), 1.65 (4H, m), 1.47 (3H, m); HRMS calcd for $C_{12}H_{22}N_2O_3$ 242.1630, Obs. 242.1655. Compound (±)-**18a**: δ_H 7.98 (2H, d, $J = 7.3$ Hz), 7.53 (1H, dd, $J = 7.4$, 7.5 Hz), 7.41 (2H, dd, $J = 7.6$, 7.7 Hz), 6.53 (1H, s), 6.50 (1H, s), 5.32 (1H, m), 4.24 (1H, m), 3.90 (1H, m), 3.9–3.7 (2H, m), 3.80 (6H, s), 3.70 (3H, s), 3.22 (1H, dd, $J = 8.1$, 13.2 Hz), 3.16 (1H, ddd, $J = 3.3$, 10.2, 13.4 Hz), 3.05 (1H, m), 3.00 (1H, m), 2.90 (1H, m), 2.81 (1H, m), 2.71 (1H, m), 2.08 (1H, m), 1.83 (1H, m). HRMS calcd for $C_{25}H_{30}N_2O_6$ 454.2104, Obs. 454.2103. Compound (±)-**18b**: δ_H 8.00 (2H, d, $J = 7.1$ Hz), 7.52 (1H, dd, $J = 7.4$, 7.5 Hz), 7.40 (2H, dd, $J = 7.7$, 7.8 Hz), 6.53 (1H, s), 6.50 (1H, s), 5.44 (1H, ddd, $J = 4.3$, 8.7, 8.8 Hz), 4.11 (1H, ddd, $J = 3.0$, 4.2, 13.7 Hz),

3.93 (1H, m), 3.90 (1H, d, $J = 14$ Hz), 3.83 (1H, d, $J = 14$ Hz), 3.82 (3H, s), 3.80 (3H, s), 3.73 (3H, s), 3.27 (1H, dd, $J = 9.1$, 13.7 Hz), 3.18 (1H, ddd, $J = 3.3$, 10.2, 13.5 Hz), 3.06 (1H, ddd, $J = 5.4$, 5.7, 11.4 Hz), 2.88 (2H, m), 2.74 (1H, ddd, $J = 5.6$, 5.7, 16.7 Hz), 2.67 (1H, ddd, $J = 5.2$, 5.3, 15.8 Hz), 2.23 (1H, m), 1.73 (1H, m); HRMS calcd for $C_{25}H_{30}N_2O_6$ 454.2104, Obs. 454.2040.

15. (a) For compounds related to **16a** and **16b**, see: Efange, S. M. N.; Khare, A. B.; Foulon, C.; Akella, S. K.; Parsons, S. M. *J. Med. Chem.* **1994**, *37*, 2574–2582, and references cited therein; (b) For compounds related to **18a** and **18b**, see: Kubota, H.; Kakefuda, A.; Watanabe, T.; Taguchi, Y.; Ishii, N.; Masuda, N.; Sakamoto, S.; Tsukamoto, S.-I. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2155–2158.