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SHORT COMMUNICATIONS

A New Method of Synthesis of Methyl *N*-Boc-2,3-dehydropyrrolidine- and piperidine-2-carboxylates

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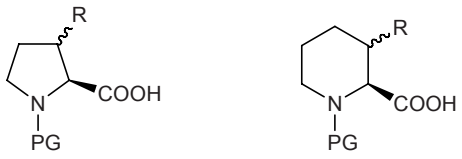
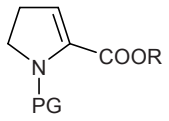
Modification of α-amino acids at the β-position provides a convenient synthetic approach to various unnatural amino acids. Conformationally rigid amino acid units play an important role in studies on potential biologically active compounds containing a peptide fragment [1–3]. Such cyclic α-amino acids are various derivatives of 3-substituted proline (**I**) and pipecolic acid (**II**), which can be obtained from unsaturated compounds **III** and **IV**, respectively, via introduction of appropriate substituents into the 3-position of five- [4–6] or six-membered ring [7–12].

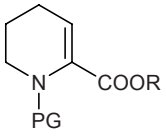


I

II



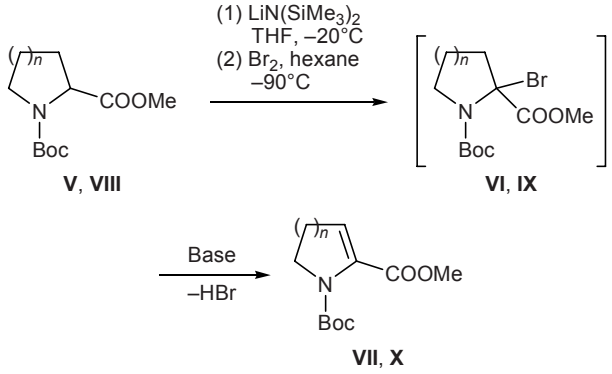
III



IV

Syntheses of cyclic enamines **III** and **IV** from the corresponding saturated precursors containing such departing groups as $PhSO_2$ [1], AcO [11, 12], F [13], and OH [14] in the 3-position were reported. Electrochemical oxidation of saturated amino acids was described in [6, 15, 16]. It should be emphasized that cyclic amino acid esters like **III** and **IV** are not only important intermediates in the synthesis of peptidomimetics but also inhibitors of biosynthesis of ethylene [6]; furthermore, they can be used as starting compounds for the synthesis of alkaloids, e.g., 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines [10–12]. Therefore, development of new direct procedures for the preparation of 2,3-dehydro derivatives of proline and pipecolic acid is an important synthetic problem.

In the present communication we describe a new convenient procedure for the synthesis of 2,3-dehydro derivatives **VII** and **X** via bromination of Boc-protected amino acid esters **V** and **VIII** at the α-position, followed by dehydrohalogenation of intermediate bromides **VI** and **IX**. An advantage of the proposed procedure is that bromine atom as departing group is introduced into heterocyclic system already containing protecting groups which make it convenient for further transformations. α-Lithiated precursors derived from **V** and **VIII** smoothly reacted with molecular bromine. Here, the key feature is addition of bromine to the lithium derivative below –90°C; as a result, unstable intermediate capable of undergoing subsequent dehydrohalogenation is formed. Higher temperature favors formation of by-products, while lowering the tempera-



V, **VIII** **VI**, **IX**

VII, **X**

V–**VII**, $n = 1$; **VIII**–**X**, $n = 2$.

ture and shortening the time of lithiation lead to incomplete conversion. The entire reaction sequence is performed without isolation and purification of intermediate compounds.

1-*tert*-Butyl 2-methyl 4,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (VII) [13]**.** A solution of 687 g (3 mol) of 1-*tert*-butyl 2-methyl pyrrolidine-1,2-dicarboxylate in 3 l of tetrahydrofuran was cooled to –40°C, 3 l of a 1.06 M solution of lithium hexamethyldisilylazide in THF was added over a period of 2.5 h, the mixture was kept for 1 h at –20°C and cooled to –90°C, and 170.3 ml (3.3 mol) of bromine was added under vigorous stirring (the time of the addition depended on the efficiency of cooling and ranged from 0.5 to 1 h). The mixture was stirred allowing it to warm up to room temperature, a solution of 630 g (3 mol) of citric acid monohydrate in 3 l of water was added, the mixture was stirred for 10 min, and the organic phase was separated, washed with 2 l of water, and dried over 1 kg of potassium carbonate for 1 h. The drying agent was filtered off, the filtrate was evaporated, and the residue was recrystallized from 3 l of diethyl ether–hexane (1:2); the product was washed on a filter with 0.5 l of diethyl ether–hexane (1:2). Yield 633 g (93%), mp 88–90°C. ^{1}H NMR spectrum, δ, ppm: 5.84 t (1H, J = 2.93 Hz), 3.8 t (2H, J = 8.9 Hz), 3.7 s (3H), 2.59 d.d (2H, ^1J = 8.9, ^2J = 2.93 Hz), 1.37 s (9H). ^{13}C NMR spectrum, δ_C, ppm: 162.1, 152.2, 135.8, 119.9, 80.2, 51.7, 48.1, 27.7. Found, %: C 58.35; H 7.62; N 6.12. $C_{11}H_{17}NO_4$. Calculated, %: C 58.14; H 7.54; N 6.16.

1-*tert*-Butyl 2-methyl 1,4,5,6-tetrahydropyridine-1,2-dicarboxylate (X) [1] was synthesized in a similar way from 729 g (3 mol) of 1-*tert*-butyl 2-methyl piperidine-1,2-dicarboxylate. The metalation step was carried out at –30°C (2 h). Yield 585 g (81%), mp 73–75°C; published data [1]: oily substance. ^{1}H NMR spectrum, δ, ppm: 5.92 t (1H, J = 3.91 Hz), 3.67 s (3H), 3.46–3.42 m (2H), 2.2–2.1 m (2H), 1.7–1.5 m (2H), 1.35 s (9H). ^{13}C NMR spectrum, δ_C, ppm: 164.8, 152.4, 132.1, 122.1, 80.5, 51.6, 42.7, 27.6, 22.4. Found, %: C 59.6; H 7.82; N 6.01. $C_{12}H_{19}NO_4$. Calculated, %: C 59.74; H 7.94; N 5.81.

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in DMSO-d_6 on a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Initial protected amino acids were synthesized from commercially available amino acids, following the procedure described in [17] for proline.

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