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3-(CARBAZOL-2-YL)- AND 3-(CARBAZOL-3-YL)-dl-ALANINES

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ABSTRACT:

A facile transformation of 2- and 3-methylcarbazoles into 3-(carbazol-2-yl)- and 3-(carbazol-3-yl)-dl-alanines compounds is described.

Phenylalanine, tryptophan, and their derivatives are potential antisickling agents[1], and efforts have been made to improve their potency with the goal of developing clinically useful antisickling agents.[2] In general, tryptophan related compounds are at least two times more potent than phenylalanine.[1] Computer-aided modeling has predicted that this enhanced potency is mostly due to the change of the monocyclic benzene ring into the more hydrophobic bicyclic indole ring.[2-4] Similarly 3-(2-naphthyl)alanine was also found to be more potent than phenylalanine.[1] These results have prompted us to develop some tricyclic ring-derived amino acids, e.g.: carbazolylalanines, as potential antisickling agents. In addition, functionally substituted carbazoles are also sought for the synthesis of anticancer drugs.[5-7] A literature search revealed that carbazolylalanines are not available and needed to be synthesized. The present article describes a general method for the synthesis of 3-(carbazol-2-yl)- and 3-(carbazol-3-yl)-dl-alanines.

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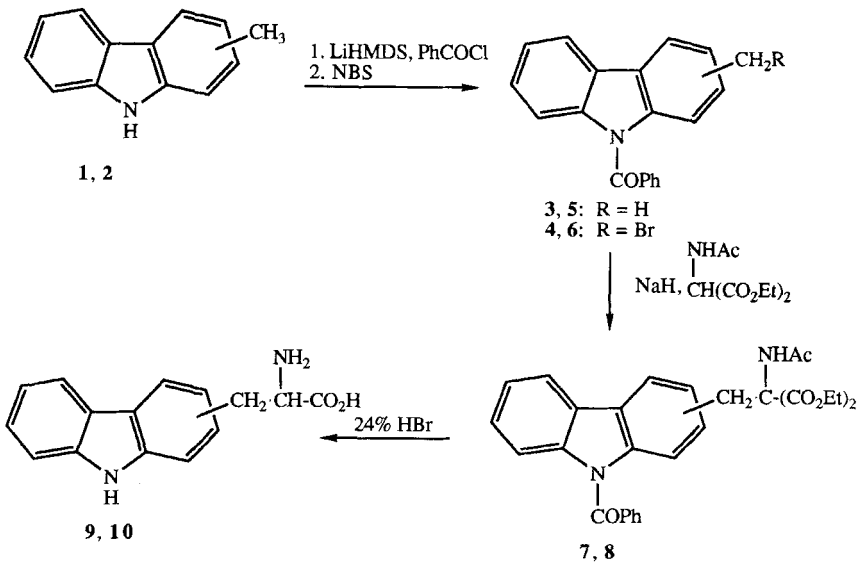
Reaction of 2-methylcarbazole (**1**) with lithium hexamethyldisilazide (LiHMDS) in THF, followed by treatment with benzoyl chloride gave 9-benzoyl-2-methylcarbazole (**3**) in 94% yield after crystallization. Compound **3**, on treatment with *N*-bromosuccinimide in boiling carbon tetrachloride in the presence of a catalytic amount of dibenzoyl peroxide for 20 h, gave the bromomethylcarbazole **5** in 82% yield.

Alkylation of the sodium salt generated from diethyl acetamidomalonate with the bromomethylcarbazole **5** in THF gave product **7** in good yield. Initially, hydrolysis and decarboxylation reactions of **7** by boiling with 48% aqueous hydrobromic acid,[8] resulted in the formation of a complex mixture of products. However, when the reaction was repeated in boiling 24% hydrobromic acid for 12 h, followed by evaporation of the solvents, it gave a 1:1 mixture of the desired product, 3-(carbazol-2-yl)-dl-alanine (**9**) and benzoic acid, from which the benzoic acid was removed by washing with diethyl ether.

This reaction sequence also worked well with 3-methylcarbazole (**2**) to give 3-(carbazol-3-yl)-dl-alanine (**10**), via the intermediates **4**, **6**, and **8**, in comparable yields. The ^{1}H NMR spectra of both amino acids **9** and **10**, in DMSO-d_6, showed two multiplets for the aliphatic protons, integrating as 1H and 2H for the α-CH and β-CH_2 protons, respectively. Compared to similar bromination reactions of *N*-benzoylindoles with *N*-benzoylcarbazoles,[9,10] the latter takes more time for completion of the reaction, and also forms a significant amount (about 10-12%) of dibromomethyl compounds, as observed by the ^{1}H NMR analysis of the reaction mixture at frequent intervals.



1, 3, 5, 7, 9: substitution at 2-position; **2, 4, 6, 8, 10:** substitution at 3-position

In conclusion, we believe the procedure described here could also be adopted for the synthesis of a variety of substituted carbazolylalanines. Efforts are underway to synthesize and evaluate a series of such compounds for their antisickling activities.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. IR spectra were obtained on a Midac 101280-1 spectrophotometer and MS (CI, EI and FAB) spectra were recorded on a Finnegan MAT-90 double focussing spectrometer.

Preparation of *N*-benzoylmethylcarbazoles 3 and 4. To a cooled solution of methylcarbazole **1** or **2**[10] (8 g, 44.1 mmol) in THF (100 mL) at -78 °C under a nitrogen atmosphere, a solution of LiHMDS in THF (1 *M*, 44.5 mL, 44.5 mmol) was added dropwise during 10 min. The reaction mixture was allowed to warm to room temperature and kept at that temperature for 2 h. It was cooled again to -78 °C and benzoyl chloride (6.27 g, 44.6 mmol) was added during 30 min. The resulting mixture was stirred at -78 °C for 1 h, and at room temperature for 12 h. Solvent was evaporated under reduced pressure and the residue was poured into ice cold 10% HCl (200 mL) and extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with water (2 x 100 mL), brine (2 x 100 mL), and dried (Na_2SO_4). Solvent was evaporated and the crude product was crystallized from ethyl acetate-hexanes.

9-Benzoyl-2-methylcarbazole (3): yield: 11.8 g (94%); mp 127-128 °C.

$C_{20}H_{15}NO$ (285.3)	calc.	C, 84.18	H, 5.29
	found	C, 83.90	H, 5.23

IR (KBr) ν 1674, 1493, 1452, 1358, 1331 cm^{-1}.

^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 7.12-7.33 (m, 3H), 7.43 (s, 1H), 7.48 (t, 2H, J = 7.5 Hz), 7.58-7.69 (m, 4H), 7.82 (d, 1H, J = 7.6 Hz), 7.90 (d, 1H, J = 7.9 Hz).

MS (CI, CH_4) m/z 286 (M+1, 100), 285 (27).

9-Benzoyl-3-methylcarbazole (4): yield: 12.3 g (97%); mp 118-119 °C (Lit.[11] 116 °C).

***Preparation of* bromomethylcarbazoles 5 and 6.** A mixture of benzoylmethylcarbazole **3** or **4** (10 g, 35 mmol), finely powdered *N*-bromosuccinimide (6.3 g, 35 mmol), and benzoyl peroxide (30 mg) in dry carbon

tetrachloride (200 mL) was heated under reflux for 20 h. After filtering the succinimide formed, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel) using chloroform as the eluent.

9-Benzoyl-2-bromomethylcarbazole (5): yield: 10.53 (82%); mp 156-157 °C.

$C_{20}H_{14}BrNO$ (364.2)	calc.	C, 65.95	H, 3.87
	found	C, 65.94	H, 3.81

IR (KBr) ν 1674, 1493, 1452, 1358, 1331, 1224, 1070 cm^{-1}.

^1H NMR ($CDCl_3$) δ 4.65 (s, 2H), 7.31-7.36 (m, 3H), 7.44-7.54 (m, 4H), 7.63-7.71 (m, 3H), 7.95-8.00 (m, 2H).

MS (CI, CH_4) m/z 367 (10), 366 (47), 365 (M+1, 21), 364 (48), 285 (21), 284 (100).

9-Benzoyl-3-bromomethylcarbazole (6): yield: 10.85 g (85%); mp 147-148 °C.

$C_{20}H_{14}BrNO$ (364.2)	calc.	C, 65.95	H, 3.87
	found	C, 65.85	H, 3.92

IR (KBr) ν 1670, 1460, 1371, 1326, 1199, 1055 cm^{-1}.

^1H NMR ($CDCl_3$) δ 4.67 (s, 2H), 7.32-7.36 (m, 4H), 7.47-7.55 (m, 3H), 7.64-7.72 (m, 3H), 7.98-8.03 (m, 2H).

MS (CI, CH_4) m/z 366 (26), 365 (M+1, 14), 364 (29), 285 (21), 284 (100).

Preparation of products 7 and 8. To a well-stirred cold (0 °C) suspension of NaH (0.40 g, 16.6 mmol) in dry THF (100 mL) under nitrogen, diethyl acetamidomalonate (2.97 g, 13.7 mmol) was added in small portions. After the addition was completed, the mixture was stirred at room temperature for 1 h and

cooled again to 0 °C. To this, a solution of the appropriate bromomethylcarbazole **5** or **6** (5.0 g, 13.7 mmol) in THF (75 mL) was added dropwise during 20 min and the mixture was allowed to warm to room temperature in 1 h. The reaction mixture was heated at 50-60 °C for 6 h and the solvents were evaporated under reduced pressure. The residue was poured into ice-cold saturated NH_4Cl solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate extracts were washed with brine (2 x 75 mL), dried (Na_2SO_4) and the solvents evaporated. The residue was purified by flash column chromatography (silica gel), using ethyl acetate-hexanes (1:1) as the eluent.

Product 7: yield: 5.8 g (84%); mp 183-184 °C.

IR (KBr): ν 3288, 1755, 1732, 1666, 1516, 1188, 1122 cm^{-1}.

^1H NMR ($CDCl_3$) δ 1.30 (t, 6H, J = 7.2 Hz), 2.04 (s, 3H), 3.80 (s, 2H), 4.28 (q, 4H, J = 7.2 Hz), 6.59 (s, 1H, NH), 6.96 (d, 1H, J = 9 Hz), 7.29-7.70 (m, 10H), 7.89 (d, 1H, J = 7.4 Hz).

MS (CI, CH_4) m/z 501 (M + 1, 100).

HRMS (EI) calc. for $C_{29}H_{28}N_2O_6$: 500.1947, found: 500.1944.

Product 8: yield: 5.6 g (82%); mp 172-173 °C.

IR (KBr): ν 3288, 1755, 1732, 1666, 1516, 1462, 1188, 1122 cm^{-1}.

^1H NMR ($CDCl_3$) δ 1.31 (t, 6H, J = 6.9 Hz), 2.07 (s, 3H), 3.76 (s, 2H), 4.29 (q, 4H, J = 6.9 Hz), 6.56 (s, 1H, NH), 7.00 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 8.3 Hz), 7.20 (t, 1H, J = 9 Hz), 7.30 (t, 1H, J = 9 Hz), 7.53 (t, 2H, J = 9 Hz), 7.64-7.93 (m, 6H).

MS (CI, CH_4) m/z 501 (M + 1, 100).

HRMS (FAB) calc. for $C_{29}H_{28}N_2O_6$: 500.1947, found: 500.1947.

Preparation of amino acids 9 and 10. A mixture of compound **7** (1 g, 2 mmol) and 24% aqueous HBr (20 mL) was heated under reflux for 12 h.

Solvents were evaporated to dryness under vacuo and the residue was washed with ether (30 mL). Recrystallization of the crude product from 95% ethanol gave an analytical sample.

3-(Carbazol-2-yl)-dl-alanine (9): yield: 0.49 g (96%); mp 314-316 °C (dec.).

IR (KBr): ν 3400, 3047, 2926, 1640, 1645, 1510,1495, 1464, 1448, 1406, 1334, 1244 cm^{-1}.

^1H NMR (DMSO-d_6-D_2O) δ 3.22-3.45 (m, 2H), 4.07-4.17 (m, 1H), 7.08 (d, 1H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.4 Hz), 7.34 (d, 1H, 8 Hz), 7.38 (s, 1 H), 7.46 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 8.2 Hz), 11.29 (s, 1H, NH).

MS (CI, CH_4) m/z 255 (M + 1, 100), 238 (84).

HRMS (EI) calc. for $C_{15}H_{14}N_2O_2$: 254.1133, found: 254.1132.

3-(Carbazol-3-yl)-dl-alanine (10): yield: 0.5 g (98%); mp 261-263 °C (dec.).

IR (KBr): ν 3410, 3020, 2879, 1641, 1558, 1461, 1377, 1188 cm^{-1}.

^1H NMR (DMSO-d_6-D_2O) δ 3.18-3.42 (m, 2H), 4.16-4.24 (m, 1H), 7.16-8.01 (m, 7H), 11.31 (s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ 37.13, 54.96, 112.24, 119.71, 121.22, 122.23, 123.31, 123.76, 125.65, 126.79, 128.17, 140.20, 141.19, 170.58.

MS (CI, CH_4) m/z 255 (M + 1, 61), 238 (100).

HRMS (FAB) calc. for $C_{15}H_{14}N_2O_2$: 254.1133, found: 254.1130.

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