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Note

Syntheses of substituted-pyrrolo-[2,3-*d*] imidazoles and substituted-pyrrolo[3,2-*d*]imidazoles

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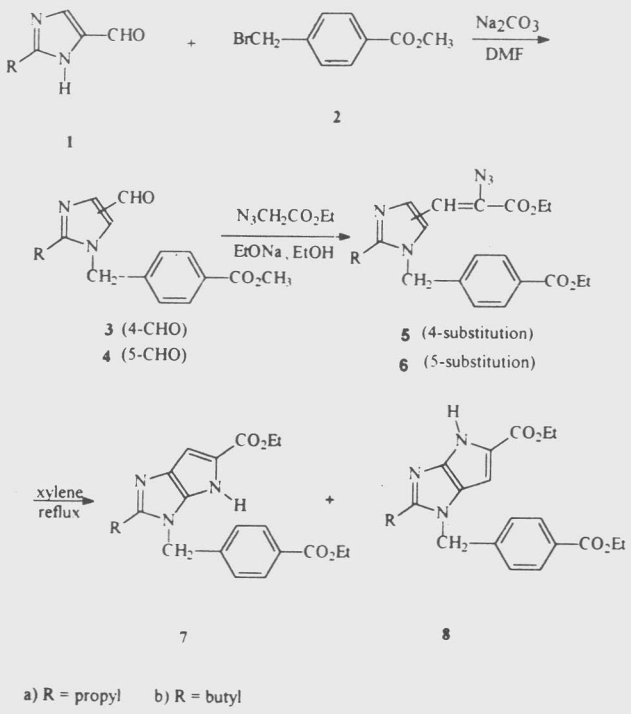
Starting from the readily available 2-alkyl-4-formylimidazole substituted-pyrrolo[2,3-*d*]imidazoles and substituted-pyrrolo[3,2-*d*]imidazoles have been prepared.

In view of antihypertensive activity of 2-alkyl-*N*-benzyl fused imidazoles[1], it was of our interest to prepare the title compounds as possible effective drugs against hypertension. The syntheses of the desired compounds was accomplished according to Scheme 1.



Scheme I

Alkylation[2] of 2-alkyl-4-formylimidazoles **1**[3] with 4- carbomethoxylbenzyl bromide **2** gave a 70:30 mixture of 2-alkyl-1- (4-carbomethoxybenzyl)-4-formylimidazole **3** and 2-alkyl-1-(4- carbomethoxybenzyl)-5-formylimidazole **4** respectively. These compounds were separated by column chromatography on silica gel. The structures of isomers were established by ^{1}H-NMR. Benzylic protons of compound **4** were more deshielded than that of compound **3**, which appeared at 5.63 and 5.17 ppm respectively. In addition NMR spectral data of compound **4** was similar to previously reported one[4].

Condensation of compounds **3** and **4** with ethyl azidoacetate under the condition reported previously[5] afforded ethyl α- azido-β-[2-alkyl-1-(4-carbethoxybenzyl) imidzol-4- yl]acrylate **5** and α-azido-β-[2-alkyl-1-(4-carbethoxybenzyl) imidazol-5-yl]acrylate **6**.

The NMR spectra of compounds **5** and **6** were in agreement with the suggested structures. The β-vinylic proton appeared at 6.60-7.10 ppm. This value is similar to the one reported previously[6].

Cyclization of compounds **5** and **6** to the desired compounds **7** and **8** was accomplished through heating the former in xylene. The structures of compounds **7** and **8** were confirmed by spectroscopic methods (IR, NMR and MS) and chemical analysis. The physical constant of compounds **7** and **8** are summarized in Table I.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR were obtained in KBr using a Perkin-Elmer Model 267 spectrograph (^{v}max in cm^{-1}), ^{1}H-NMR spectra in $CDCl_3$ on a Bruker AC-80 spectrometer using TMS as an internal standard (chemical shifts in δ, ppm) and mass spectra on a Finnigan MAT TSQ 70 spectrometer at 70 eV. Column chromatography was carried out using silica gel (230-400 mesh). Elemental analyses were carried out by the research centre of petrochemical company.

2-Butyl-1-(4-carbomethoxybenzyl) - 4 -formylimidazole 3b. A stirring suspension of compound **1b** (7g, 46 mmoles), anhyd. sodium carbonate (4.88 g,

Table I—Physical constants of compounds **7a, 7b, 8a** and **8b**.

Compd.	m.p.* (°C)	Yield (%)	Mol. formula	% Found (Calcd) C	H	N
7a	160	27	$C_{21}H_{25}N_3O_4$	65.76(65.80)	6.48(6.53)	10.71(10.97)
7b	159-61	28	$C_{22}H_{27}N_3O_4$	66.72(66.50)	6.61(6.80)	10.43(10.58)
8a	155	21	$C_{21}H_{25}N_3O_4$	65.91(65.80)	6.43(6.53)	10.86(10.97)
8b	105-8	22	$C_{22}H_{27}N_3O_4$	66.25(66.50)	6.71(6.80)	10.47(10.58)

* All compounds were crystallized from carbon tetrachloride

46 mmoles), and compound **2** (11 g, 48 mmoles) in DMF (100 mL) was heated at 100° for 24 hr. After cooling the mixture was filtered. The filtrate was evaporated at reduced pressure. The oily residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 7.4 g of oily compound **3b**, yield 54%; IR: 1720 (C=O ester), 1680 cm^{-1}(C=O aldehyde); NMR ($CDCl_3$): 9.44 (s, 1H, CHO), 8.00 (d, 2H, *J*=8.5 Hz, Ar), 7.53 (s, 1H, H-5 imidazole), 7.14 (d, 2H, *J*=8.5 Hz, Ar), 5.17 (s, 2H, CH_2 benzylic), 3.92 (s, 3H, CO_2CH_3), 2.64 (t, 2H, *J*=7.7 Hz, CH_2), 1.46 (m, 4H, CH_2), 0.87 (s, 3H, *J*=7.3, CH_3); MS: m/z (%) 301 (M^++1, 21), 258 (62), 243 (8), 167 (16), 149 (100), 121 (41).

2-Butyl-1-(4-carbomethoxybenzyl) - 5 -formylimidazole 4b. It was prepared similar to **3b** in 27% yield. Ethyl acetate-pet. ether (1:1) was used as eluent in chromatography. IR: 1720 (C=O ester), 1675 cm^{-1}(C=O aldehyde);NMR ($CDCl_3$): 9.67 (s, 1H, CHO), 7.98 (d, 2H, *J*=8.4 Hz, Ar), 7.81 (s, 1H, H_4 imidazole), 7.06 (d, 2H, *J*=8.3 Hz, Ar), 5.63 (s, 2H, CH_2 benzylic), 3.90 (s, 3H, CO_2CH_3), 2.63 (t, 2H, *J*=7.7 Hz, CH_2), 1.46 (m, 4H, CH_2), 0.87 (t, 3H, *J*=7.3 Hz, CH_3); MS: m/z (%) 301 (M^++1, 100), 271 (11), 258 (24), 229 (24), 149, (24), 121 (29).

α-Azido-β-[2-butyl-1-(4- carbethoxybenzyl)imidazol-4-yl]acrylate 5b. To a stirring solution of sodium (0.8 g, 34.68 mmoles) in abs. ethanol (25 mL) at 20° was added dropwise a solution of **3b** (2.6 g, 8.67 mmoles) and ethyl azidoacetate (4.4 g, 34.68 mmoles) in dry THF (50 mL) and abs. ethanol (80 mL). After 2 hr at -10°, the mixture was added to a saturated solution of ammonium chloride. The mixture was extracted with ether. The organic layer was evaporated at reduced pressure and the residue was purified with column chromatography, eluting with chloroform to give 1.45 g of an oily compound, yield 40%; IR: 2119 (azide), 1712 cm^{-1} (C=O); NMR ($CDCl_3$): 7.98 (d, 2H, *J*= 8.0 Hz, Ar), 7.65 (s, 1H H-5, imidazole), 7.10 (d, 2H,*J*=8.0 Hz, Ar), 7.06 (s, 1H, CH=C), 5.15 (s, 2H, CH_2 benzylic), 4.33 (q, 4H, CO_2CH_2), 2.50 (t, 2H, *J*=8.0 Hz, CH_2), 1.38 (m, 10H, CH_2, CH_3), 0.87 (t, 3H, CH_3); MS: m/z (%) 425(M^+, 1), 399 (14), 355 (5), 313 (28), 236 (9), 192 (57), 163 (100), 135 (43), 107 (88).

α-Azido-β-[2-butyl-1-(4- carbethoxybenzyl)imidazol-5-yl]acrylate 6b. It was prepared similar to **5b** in 66% yield; IR: 2126 (azide), 1719 cm^{-1} (C=O); NMR ($CDCl_3$): 8.00 (d, 2H, *J*=8.0 Hz, Ar), 7.90 (s, 1H, H_4 imidazole), 7.00 (d 2H, *J*=8.0 Hz, Ar), 6.50 (s, 1H, CH=C), 5.19 (s, 2H,CH_2 benzylic), 4.32 (m, 4H, CO_2CH_2),2.65 (t, 2H, *J*=8.0 Hz, CH_2), 1.46 (m, 10H,CH_2,CH_3), 0.88 (t, 3H, CH_3); MS: m/z (%) 426 (M^++1, 26), 399 (100), 359 (65), 315 (4), 149 (6), 102 (5).

Ethyl 2-butyl-1-(4-carbethoxybenzyl)-pyrrolo[3,2-d]imidazole-5- carboxylate 7b. A solution of **5b** (6 g, 14 mmoles) in xylene (100 mL) was refluxed for 2 hr. The solvent was evaporated and the residue was purified by column chromatography eluting with chloroform-pet. ether (1:1) to give 1.53 g of **7b**, m.p. 160° (carbon tetrachloride), yield 28%; IR: 1718 cm^{-1} (C=O); NMR ($CDCl_3$): 9.20 (bs, 1H, NH), 8.00(d, 2H, *J*=8.2 Hz, Ar), 7.20 (d, 2H, *J*=8.2 Hz, Ar), 6.92 (s, 1H, H-C_4), 5.28 (s, 2H, CH_2 benzylic), 4.35 (m, 4H, CO_2CH_2), 2.70 (t, 2H, CH_2), 1.38 (m, 10H, CH_2, CH_3), 0.89 (t, 3H, CH_3); MS: m/z (%) 397 (M^+, 4), 192 (100), 135 (28), 107 (50).

Ethyl 2-propyl-1-(4-carbethoxybenzyl)-pyrrolo[3,2-d]imidazole-5- carboxylate 7a. It was prepared from **5a** by the procedure described for **7b**. IR: 1718 cm^{-1}(C=O); NMR ($CDCl_3$): 8.90 (bs, 1H, NH), 8.03 (d, 2H, *J*=8.3 Hz, Ar), 7.02 (d, 2H, *J*=8.3 Hz, Ar), 6.92 (s, 1H, H-C_4), 5.27 (s, 2H, CH_2 benzylic), 4.28 (m, 4H, CO_2CH_2), 2.70 (t, 2H, CH_2), 1.80 (m,

2H, CH_2), 1.38 (m, 6H, CH_3); 0.99 (t, 3H, CH_3); MS: m/z (%) 383 (M^+, 13), 192 (54), 163 (100), 101 (63).

Ethyl 2-butyl-1-(4-carbethoxybenzyl)-pyrrolo[2,3-d]imidazole-5- carboxylate 8b. It was prepared similar to **7b** in 22% yield; m.p. 105-8°; IR: 1728 cm^{-1}(C=O); NMR($CDCl_3$): 9.70 (bs, 1H, NH), 8.00 (d, 2H, *J*=8.4 Hz, Ar), 7.20 (d, 2H, *J*=8.4Hz, Ar), 6.40 (s, 1H, H-C_6), 5.22 (s, 2H, CH_2 benzylic), 4.32 (q, 4H, CO_2CH_2), 2.83 (t, 2H, CH_2), 1.38 (m, 10H, CH_2, CH_3), 0.91 (t, 3H, CH_3); MS: m/z (%) 397 (M^+, 1), 192 (100), 163 (74), 107 (50), 90 (38).

Ethyl 2-propyl-1-(4-carbethoxybenzyl)-pyrrolo[2,3-d]imidazole-5- carboxylate 8a. It was prepared from **6a** by the procedure described for **8b**. IR: 1728 cm^{-1}(C=O); NMR ($CDCl_3$): 9.50 (bs, 1H, NH), 8.00 (d, 2H, *J*=8.3 Hz, Ar), 7.19 (d, 2H, *J*=8.3 Hz, Ar) 6.4 (s, 1H, H-C_6), 5.22 (s, 2H, CH_2 benzylic), 4.32 (q, 4H, CO_2CH_2), 2.80 (t, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.38 (m, 6H, CH_3), 0.99 (t, 3H, CH_3); MS: m/z (%) 383 (M^+, 27), 309 (12), 192 (59), 163 (100), 107 (68).

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