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NOVEL OXIDATION OF PROLINE DERIVATIVES TO PYRROLES BY HYPERVALENT IODINE#

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Abstract: Oxidative decarboxylations of proline derivatives by hypervalent iodine, as a new convenient methodology for obtaining tetrasubstituted pyrroles, are described.

Hypervalent iodine reagent have been extensively used in organic synthesis and their applications have been reviewed[1-3]. However, no attempt has been made to oxidise pyrrolidine or proline to pyrroles. A comparatively new synthetic strategy for obtaining tetrasubstituted pyrroles would be oxidative decarboxylation of substituted prolines. In principle this strategy is expected to furnish advantages over the conventional synthesis. For example, a conventional synthesis of ethyl 2-aryl-5-methylpyrrole-3,4-dicarboxylate would require ethyl 1-acyl-2-aroyl succinate as the starting material which in itself is a multistep synthesis. Compared to this strategy, tetrasubstituted prolines are easily prepared[4] and if the envisaged oxidative decarboxylation proceeds smoothly, the desired tetrasubstituted pyrroles can then be

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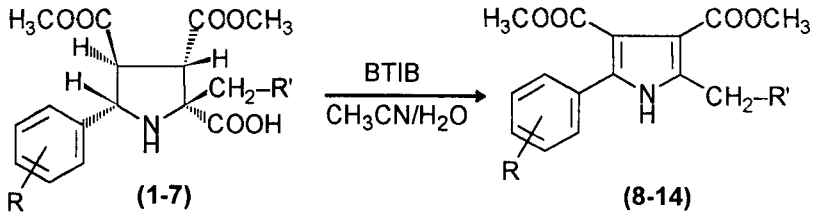
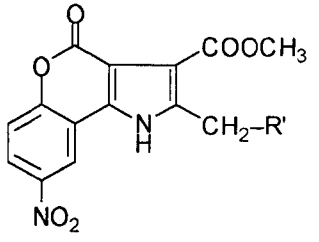


Compound No.	R	R^1
1,8	H	H
2, 9	2-OCH_3	H
3, 10	2,5-$(OCH_3)_2$	H
4, 11	3-NO_2	H
5, 12	2-OH, 5-NO_2	H
6, 13	H	OH
7, 14	2, 5-$(OCH_3)_2$	OH



(15)

prepared only in two steps. The present investigation is aimed towards this exploration and the details of this first report are presented here.

Reactions[4] of substituted benzaldehydes with alanine or serine in the presence of dimethyl fumarate in our hands gave a mixture of isomeric proline derivatives but the major isomer invariably separated out from the hot reaction mixture. The steriochemical asignment of this isomer was made on the basis of its NMR spectrum and was characterised as dimethyl 2-methyl or hydroxymethyl-cis-5(substituted phenyl)pyrrolidine-cis-3-trans-4-dicarboxylate-r-2-carboxylic acid (**1-7**). These were oxidised with [bis(trifluoroacetoxy)iodo]benzene (BTIB) to obtain substituted pyrroles (**8-14**).

The yield of substituted pyrroles ranged between 25-30% and in none of the cases the starting material was recovered unchanged. The effect of different functional group of the reactants on the general applicability of this oxidation reaction was studied. The presence of a primary hydroxyl group as in compound (**6,7**) remained unaffected but the yield of the product was comparitively less. However, the presence

of an acidic phenolic group as in compound (**5**) led to an intramolecular ring, closure reaction leading to product (**15**).

The cause of low to moderate yield was investigated in one case (**1**). It was observed that the product (**8**) was associated with dimethyl fumarate and alanine. This indicated that other pathways of this oxidation by BTIB were also operative. Although the yields of tetrasubstituted pyrroles are extremely moderate, it may be concluded that the present method of preparing tetrasubstituted pyrroles acquire importance in the light of problems associated with conventional synlhesis[5].

Experimental

All reagents and starting materials were from commercial sources and used without further purification. All melting points were recorded on hot stage apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer881 spectrophotometer. ^{1}H & ^{13}C-NMR spcctra were recorded on Bruker 400 FT, or Bruker DRX-300 FT or Avance Bruker 200 FT NMR instrument using; TMS as a standard and mass spectra on a JEOL-JMS-D-300 or JEOL SX 102/DA-6000 mass spectrometer. Chemical analysis were carried out on Carlo Erbo 1103 analyzer.

The starling pyrrolidines(**l-7**) were prepared by the reported method[4] and the spectral data for new compounds are given here.

(**3**) Yield: 68%, m.p. 210°C (dec), IR (cm^{-1}): 3478, 2914, 1730, 1647. EIMS; m/z : 381 (M^{+}). ^{1}H-NMR (400 MHz, C_5H_5N) : δ 2.93 (s, 3H, C-Me), 4.48 and 4.52 (2s, 6H, 2 x OMe), 4.58 and 4.81 (2s, 6H, 2 x CO_2Me), 4.81 (d, IH, J=11 Hz, 3-H), 5.01 (t, 1H, 4-H), 6.22 (d, 1H, J=10 Hz, 5-H), 7.26-8.62 (m, 3H, Ar-H) 9.62 (brs, 1H, NH, exchangeable with D_2O) Anal. Calcd. for $C_{18}H_{23}NO_8$; C, 56.69; H, 6.08; N, 3.67. Found; C, 56.55; H, 5.90; N, 3.8%.

(**4**) Yield : 50%, m.p. 230-2°C (dec), IR (cm^{-1}) : 3090, 1738, 1614, 1412. FABMS; m/z : 367 (M^{+} + 1). ^{1}H-NMR(400 MHz, C_5H_5N) : δ 2.10 (s, 3H, C-Me), 3.66

and 3.68 (2s, 6H, 2 x CO_2Me), 3.95 (d, 1H, J= 11.1 Hz, 3-H), 4.22 (t, IH, 4-H), 4.98 (d, 1H, J=9.6 Hz, 5-H), 7.38-8.86 (m, 4H, Ar-H). Anal. Calcd. for $C_{16}H_{18}N_2O_8$; C, 52.48; H, 4.91; N, 7.62. Found; C, 52.38; H, 4.82; N, 7.60%.

(5) Yield: 68%, m.p. 225°C (dec), 1R (cm^{-1}) : 3080, 2958, 1740, 1628. FABMS; m/z : 383 ($m^+ + 1$). ^{1}H-NMR (400 MHz, C_5H_5N) : δ 2.12 (s, 3H, C-Me), 3.68 (2s, 6H, 2 x CO_2 Me), 3.98 (d, 1H, J = 11.1 Hz, 3-H), 4.24 (t, 1H, 4-H), 5.40 (d, I H, J=9.9 Hz, 5-H), 7.10-8.88 (m, 3H, ArH). Anal Calcd. for $C_{16}H_{18}N_2O_9$; C, 50.25; H, 4.69, N, 7.33. Found; C, 50.30; H,4.76, N, 7.50%.

(6) Yield : 42%, m.p. 220°C (dec.), IR (cm^{-1}) : 3164, 2974, 1764, 1668. EIMS; m/z : 337 (M^+). ^{1}H-NMR (200 MHz, C_5H_5N) : δ 3.49 (s, 3H, CO_2Me), 3.70 (s, 3H, CO_2Me), 4. 12 (t, 1H, 4-H) 4.46 (d, 1H, J= 11Hz, 3-H) 4.58 (dd, 2H, Jgem = 11 & 18.5 Hz, CH_2OH), 4.88 (d, 1H, J=10Hz, 5-H), 7.2 - 7.7 (m, 5H, ArH). Anal. Calcd. for $C_{16}H_{19}NO_7$; C, 50.63; H, 5.60, N, 4.10, Found ;C, 50.47; H, 5.99, N, 4.08%.

(7) Yield : 50%, m.p. 247° C (dec.), IR (cm^{-1}) : 3184, 2956, 1743, 1633. EIMS : m/z : 397 (M^+). ^{1}H-NMR(200 MHz, C_5H_5N) : δ 3.56 (s, 3H, CO_2 Me), 3.59 (s. 3H, CO_2Me), 3.61 (s, 3H, OMe), 3.66 (s, 3H, OMe), 4. 12 (t, IH, 4-H), 4.44 (d, 1H, J = 11 Hz, 3-H), 4.56 (dd, 2H, Jgem = 11 & 18.6 Hz CH_2OH), 4.9 (d, 1 H, J = 11 Hz, 5-H), 7.2 - 7.5 (m, 3H, Ar-H) Anal. Calcd. for $C_{18}H_{23}NO_9$; C, 54.40; H, 5.70; N, 3.52; Found ; C, 54.32; H, 5.72; N, 3.60%.

Preparation of Dimethyl 2-methyl/hydroxymethyl-5-(substituted phenyl) pyrrole-3, 4-dicarboxylate (8-14)

General Method: A suspension of compound (**1-7**) (l mmol) in acetonitrile: water (3: 1; 10 ml) was stirred at 0-5°C for 10 min. Then BTIB (2.2 mmol) was added portionwise and the whole reaction mixture was stirred at room temperature (30°C) for 7-8 hr. The reaction mixture was then quenched with CH_2Cl_2 (20 ml), the organic

layer was washed with water (3 x 20 ml). The combined organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed over silica. Elution with CH_2Cl_2 gave dimethyl fumarate. Further elution with CH_2Cl_2 : MeOH (99: 1, v/v) gave the desired pyrrole derivatives (**8-14**). In one case, further elution with CH_2Cl_2: MeOH (96:4, v/v) gave the cyclised product (**15**). The aqueous layer on TLC was found to contain alanine as was evident from TLC and Co-TLC with authentic alanine.

(**8**) Yield : 25%; m.p. 125°C ; 1R (cm^{-1}) : 3432, 2948, 1726, 1690. FABMS ; m/z : 274 ($M^+ + 1$); ^{1}H-NMR(400 MHz, $CDCl_3$) : δ 2.52 (s, 3H, C-Me), 3.82 and 3.84 (2s, 6H, 2 x CO_2Me), 7.0-7.76 (m, 5H, Ar-H), 8.4 (brs, 1H, NH exchangeable with D_2O). Anal. Calcd. for $C_{15}H_{15}NO_4$; C, 65.08; H, 5.40; N, 4.11. Found : C, 65.10; H, 5.34; N, 4.15%.

(**9**) Yield : 22%, m.p. 154°C ;1R(cm^{-1}) : 3232, 2950, 1714, 1686. EIMS ; m/z :303 (M^+) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 2.52 (s, 3H, C-Me), 3.76 and 3.80 (2s, 6H, 2 x CO_2Me), 6.8-7.5 (m, 4H, Ar-H), 8.6 (brs, 1H, NH exchangeable with D_2O). Anal. Calcd. for $C_{16}H_{17}NO_5$;C, 63.30; H, 5.61 ; N, 4.62. Found : C, 63.38 ; H, 5.56; N, 4.60%.

(**10**) Yield : 35%, m.p. 104-6°C ;IR(cm^{-1}) : 3234, 2954, 1710, 1682. EIMS ; m/z: 333 (M^+) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 2.52 (s, 3H, C-Me), 3.76 and 3.80 (2s, 6H, 2 x OMe), 3.82 and 3.84 (2s, 6H, 2 x CO_2Me), 6.82-7.12 (m, 3H, Ar-H), 9.22 (brs, 1H, NH exchangeable with D_2O). Anal. Calcd. for $C_{17}H_{19}NO_6$; C, 61.23 ; H, 5.73 ; N, 4.20. Found : C, 61.16; H, 5.81; N, 4.01%.

(**11**) Yield : 20%, m.p. 108°C; IR (cm^{-1}) : 3442, 3024, 1708, 1682. EIMS ; m/z : 318 (M^+) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 2.50 (s, 3H, C-Me), 3.86 and 3.88 (2s, 6H, 2 x CO_2Me), 7.6 and 8.36 (m, 4H, Ar-H), 8.68 (brs, 1H, NH exchangeable with D_2O). Anal. Calcd. for $C_{15}H_{14}N_2O_6$; C, 56.60 ; H, 4.42 ; N, 8.87. Found : C, 56.82; H, 4.40; N, 8.61%.

(12) Yield : 28%, m.p. 170-4°C ; IR (cm^{-1}) : 3284, 2929, 1697, 1446. EIMS ; m/z : 334 (M^+) ; ^{1}H-NMR (400 MHz, $CDCl_3$) ; δ 2.50 (s, 3H, C-Me), 3.80 (s, 6H, 2 x CO_2Me) 7.0 and 8.0 (m, 3H, Ar-H), 9.2 (brs, 1H, NH) 11.5 (s, 1H, OH). Anal. Calcd. for $C_{15}H_{14}N_2O_7$; C, 53.59 ; H, 4.19 ; N, 8.38 ; found ; C, 53.63 ; H, 4.24 ; N, 8.20%.

(13) Yield : 22%, m.p. 160-5°C ; IR (cm^{-1}) : 3448, 2956, 1746 ; EIMS ; m/z : 289 (M^+) ; ^{1}H-NMR (200 MHz, $CDCl_3$) ; δ 3.74 & 3.76 (2s, 6H, 2 x CO_2Me), 4.81 (s, 2H, O-CH_2) 7.20-7.42 (m, 5H, Ar-H), 9.06 (brs, 1H, NH). Anal. Calcd. for $C_{15}H_{15}NO_5$; C, 62.29 ; H, 5.10 ; N, 4.84 ; found ; C, 62.20 ; H, 5.16 ; N, 4.96%.

(14) Yield : 22%, m.p. 180-5°C ; IR (cm^{-1}) : 3426, 2938, 1718 ; FABMS ; m/z : 349 ($M^+ + 1$) ; ^{1}H-NMR (200 MHz, $CDCl_3$) ; δ 3.76, 3.79, 3.81 & 3.82 (4s, 12H, 2 x (CO_2Me and O-Me)), 4.84 (s, 2H, O-CH_2) 6.78-7.03 (m, 3H, Ar-H), 9.83 (brs, 1H, NH). Anal. Calcd. for $C_{17}H_{19}NO_7$; C, 7.10 ; H, 5.44 ; N, 4.01 ; found ; C, 7.31 ; H, 5.40 ; N, 4.11%.

(15) Yield : 22%, m.p. >270°C ; IR (cm^{-1}) : 1703, 1737, EIMS ; m/z : 284 (M^+ - H_2O) ; ^{1}H-NMR (400 MHz, C_5H_5N) ; δ 2.64 (s, 3H, C-Me, 4.0 (s, 3H, CO_2Me), 7.44-8.64 (m, 3H, Ar-H). ^{13}C-NMR (400 MHz, C_5H_5N) ; 13.22, 57.67, 108.35, 112.13, 112.27, 114.45, 118.89, 118.20, 135.64, 142.55, 144.14, 155.50, 156.83, 164.87. Anal Calcd. for $C_{14}H_{10}N_2O_6$: C, 55.62 ; H, 3.33 ; N, 9.27 found ; C, 55.58 ; H, 3.42 ; N, 9.30%.

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