A FACILE ROUTE TO 3,4-SYMMETRICALLY SUBSTITUTED 2-CARBETHOXY-5-METHYLPYRROLES

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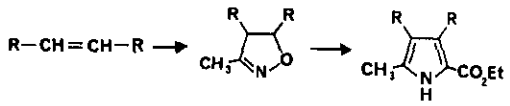
Abstract—A synthesis of 3,4-disubstituted 2-carbethoxy-5-methylpyrroles from alkenes via isoxazoles is described.

As the precursor for the synthesis of symmetrical octasubstituted porphyrins[1] we have investigated the production of pyrrole derivatives which have identical substituents in the 3 and 4 positions. We describe here a pyrrole synthesis in which the basic strategy is to utilize the symmetry of a disubstituted alkene for the generation of a pyrrole with the general structure 1.[2]



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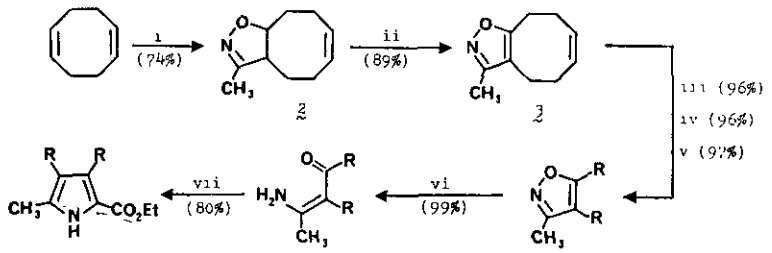
The synthesis begins with a 1,3-dipolar addition of acetonitrile oxide (generated in situ by the nitroalkane dehydration method)[3] to 1,5-cyclooctadiene. The alkene is used in large excess to ensure production of the mono-adduct. After the syn-diphenylurea and excess 1,5-cyclooctadiene



Reagents: (i) $EtNO_2$, Et_3N, Ph—NCO; (ii) MnO_2, benzene; (iii) mCPBA, $CHCl_3$; (iv) H_5IO_6, H_2O pH 7.1; (v) $Ph_3P{=}CHCO_2Et$, THF; (vi) H_2, 5% Rh—C, 1:1 EtOH—Et_3N; (vii) $(EtO_2C)_2C{=}NOH$ (7), Zn, HOAc

were removed, isoxazoline 2 was obtained in 74% yield[4] after distillation, based on the amount of nitroethane employed. Dehydrogenation of 2 using activated γ-MnO_2 in benzene with azeotropic removal of water[5] gave the unsaturated isoxazole 3 in 89% yield after distillation. The isolated double bond in 3 was cleaved by first making the epoxide (1.1 equiv. m-chloroperoxybenzoic acid, $CHCl_3$, 0°C; 96%) followed by periodate cleavage[6] to the dialdehyde 4 (1.05 equiv. H_5IO_6, H_2O, pH 7.1, 85°C, 20 min.; 96%) which was used in the next step without further purification. Wittig

olefination of 4 using carbethoxymethylenetriphenylphosphorane (2.2 equiv., THF, 25°C, 12 h) produced the bis-unsaturated ester 5 in 97% yield after purification by column chromatography (SiO_2, ethyl acetate). Hydrogenolysis of the isoxazole ring[7] (5% Rh—C, 1:1 ethanol/triethylamine, 4 atm H_2, 30 h) was accompanied by hydrogenation of the unsaturated ester side-chains, giving enaminone 6 in nearly quantitative yield. The synthesis was completed by reductive condensation of diethyl 2-oximinomalonate (7) with 6 (1.4 equiv. 7, excess Zn dust, acetic acid, reflux, 2 h) to give pyrrole 8 in 80% yield after column chromatographic purification (SiO_2, ether).[8] Thus, preparation of 8 was achieved in 63% overall yield from isoxazoline 2, the latter being available in multi-gram quantities.

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REFERENCES AND NOTES

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2. Pyrroles with this substitution pattern are readily converted to porphyrins, see: Dolphin, D. "The Porphyrins" Part A, Structure and Synthesis, Vol. I; Academic Press, New York, 1978, pp. 85-234.
3. Wakefield, B. J.; Wright, D. J. Adv. Heterocyclic Chem., Vol. 25, Academic Press, New York, 1979, pp. 147-204.
4. Partial spectroscopic and physical data for the intermediates are as follows: 2, bp 74-79°C (0.1 mm), ^{1}H NMR δ 5.5 (m, 2H), 4.3 (m, 1H), 1.9 (s, 3H); 3, bp 72 77°C (0.1 mm), ^{1}H NMR δ 5.4 (m, 2H), 2.9 (m, 2H), 2.5 (m, 6H), 2.1 (s, 3H), IR 1650, 1625 cm^{-1}; epoxide of 3, mp 76-77°C, ^{1}H NMR δ 2.1 (s, 3H), IR 1630 cm^{-1}; 4, ^{1}H NMR δ 9.7 (s, 2H), 2.9 (t, 4H), 2.7 (s, 4H), 2.2 (s, 3H), IR 1725, 1630 cm^{-1}; 5, ^{1}H NMR δ 6.8 (m, 2H), 5.7 (d, 2H), 4.1 (q, 4H), 2.7 (m, 4H), 2.4 (m, 4H), 2.2 (s, 3H), 1.2 (t, 6H), IR 1725, 1630 cm^{-1}; 6, ^{1}H NMR δ 7.8 (v. broad s, 2H), 4.1 (q, 4H), 2.3 (m, 8H), 1.9 (s, 3H), 1.6 (m, 8H), 1.2 (t, 6H), IR 3340, 1740, 1620 cm^{-1}; 8, ^{1}H NMR δ 9.25 (br, s, 1H), 4.2 (q, 2H), 4.1 (q, 4H), 2.6 (br, t, 2H), 2.3 (m, 6H), 2.2 (s, 3H), 1.6 (m, 8H), 1.3 (t, 3H), 1.2 (t, 6H), IR 3320, 1740, 1680, 1660 cm^{-1}, mass spectrum M$^+$ at m/e 409.
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6. Nagarkatti, J. P.; Ashley, K. R. Tetrahedron Lett. 1973, 4599-4600.
7. Hydrogenolysis of this trisubstituted isoxazole proved to be exceedingly slow using the more conventional Pd and PtO_2 catalysts; for other examples see ref. 3, p. 186.
8. This reaction represents a variant of the Knorr's pyrrole synthesis in which the aminomalonate (generated in situ from 7) adds in a regioselective manner to the enaminone 6, a β-diketone equivalent.

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