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 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.

The synthesis begins with a 1,3-dipolar addition of acetonitrile oxide (generated in situ by the nitroalkane dehydration method) to 1,5-cyclooctadiene. The alkene is used in large excess to ensure production of the mono-adduct. After the sym-diphenylurea and excess 1,5-cyclooctadiene were removed, isoxazoline 2 was obtained in 74% yield after distillation, based on the amount of nitroethane employed. Dehydrogenation of 2 using activated γ-MnO₂ in benzene with azeotropic removal of water 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, CHCl₃, 0°C; 96%) followed by periodate cleavage to the dialdehyde 4 (1.05 equiv. H₂IO₆, H₂O, pH 7.1, 85°C, 20 min.; 96%) which was used in the next step without further purification. Wittig
olefination of $\mathbf{4}$ using carbethoxymethylene triphenylphosphorane (2.2 equiv., THF, 25°C, 12 h) produced the bis-unsaturated ester $\mathbf{5}$ in 97% yield after purification by column chromatography ($\text{SiO}_2$, ethyl acetate). Hydrogenolysis of the isoxazole ring$^7$ (5% Pd-C, 1:1 ethanol/triethylamine, 4 atm $H_2$, 30 h) was accompanied by hydrogenation of the unsaturated ester side-chains, giving enaminone $\mathbf{6}$ in nearly quantitative yield. The synthesis was completed by reductive condensation of diethyl 2-oximinomalonate ($\mathbf{7}$) with $\mathbf{6}$ (1.4 equiv. $\mathbf{7}$, excess Zn dust, acetic acid, reflux, 2 h) to give pyrrole $\mathbf{8}$ in 80% yield after column chromatographic purification ($\text{SiO}_2$, ether). Thus, preparation of $\mathbf{8}$ was achieved in 63% overall yield from isoxazoline $\mathbf{5}$, the latter being available in multi-gram quantities.

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REFERENCES AND NOTES


4. Partial spectroscopic and physical data for the intermediates are as follows: $\mathbf{5}$, bp 74-79°C (0.1 mm), $^1$H NMR $\delta$ 5.5 (m, 2H), 4.3 (m, 1H), 1.9 (s, 3H); $\mathbf{6}$, bp 77°C (0.1 mm), $^1$H NMR $\delta$ 5.4 (m, 2H), 2.9 (m, 2H), 2.5 (m, 6H), 2.1 (s, 3H), IR 1650, 1625 cm$^{-1}$; epoxide of $\mathbf{7}$, mp 76-77°C, $^1$H NMR $\delta$ 9.7 (s, 2H), 2.9 (t, 4H), 2.7 (s, 4H), 2.2 (m, 3H), IR 1725, 1630 cm$^{-1}$; $\mathbf{8}$, $^1$H NMR $\delta$ 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$^{-1}$; $\mathbf{9}$, $^1$H NMR $\delta$ 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$^{-1}$; $\mathbf{10}$, $^1$H NMR $\delta$ 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.


7. Hydrogenolysis of this trisubstituted isoxazole proved to be exceedingly slow using the more conventional Pd and Pt$\text{O}_2$ 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 $\mathbf{7}$) adds in a regioselective manner to the enaminone $\mathbf{6}$, a β-diketone equivalent.

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