CHEMISTRY LETTERS, pp. 1107-1108, 1989.

An Improved Method for the Preparation of Symmetrically Substituted Porphyrins via 2-Methoxymethyl-3,4-disubstituted Pyrrole Derivatives

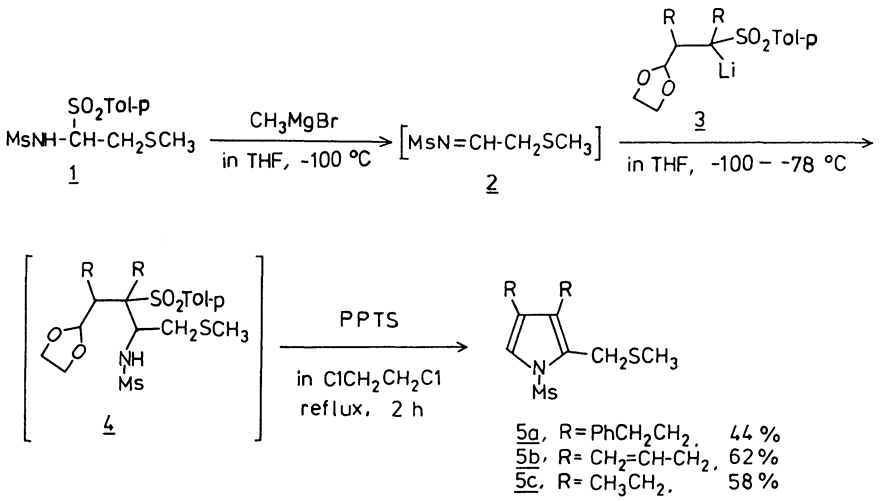
Hideki KINOSHITA,* Shingo TANAKA, and Katsuhiko INOMATA
Department of Chemistry, Faculty of Science, Kanazawa University, Kanazawa 920

2-Methoxymethylpyrrole derivatives readily available from 2-methylthiomethylpyrroles were found to be readily cyclized to porphyrinogens with formic acid, and subsequent oxidation with O_2 affords the corresponding porphyrins in excellent yields.

A number of methods for the preparation of pyrroles have been exploited so far[1] because they are fundamental constituents of very important substances such as heme, chlorophyll, and vitamin B_{12}, and some of them have pharmacological activities themselves.

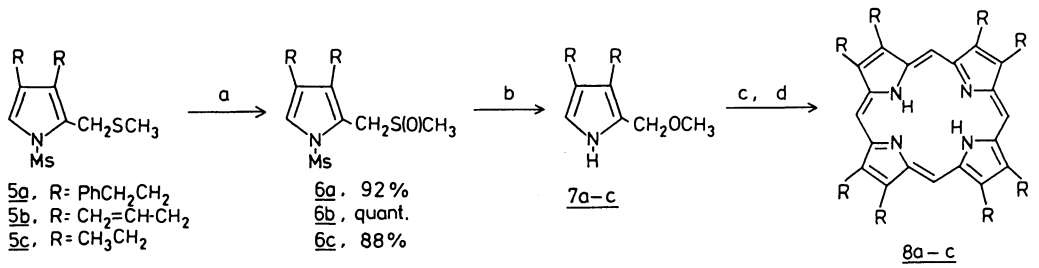
In the previous papers,[2] we have reported convenient synthetic methods for pyrroles employing 3-substituted-propanal ethylene acetal derivatives. Herein we wish to report that 2-methylthiomethylpyrrole derivatives (5) derived from the 3-(p-toluenesulfonyl)propanal ethylene acetal derivatives (3) and N-(2-methylthio-1-p-toluenesulfonylethyl)methanesulfonamide (1)[3] are readily transformed into the corresponding 2-methoxymethylpyrroles (7), which were found to be excellent precursors of porphyrins (8).

The addition of the carbanion (3) to the methanimine (2), produced in situ from 1 and methylmagnesium bromide in the similar manner described in the previous paper,[2a] afforded the adduct (4). Treatment of the crude 4 with a catalytic amount of pyridinium p-toluenesulfonate (PPTS) in dichloroethane gave 2-methylthiomethylpyrrole derivatives (5) in moderate yields as shown in the following scheme.



Recently, Eschenmoser[4] and Ono[5] have reported the preparation of porphyrins from 2-hydroxymethyl-3,4-disubstituted pyrroles, however, the yields of the resulting porphyrins were rather low.[5] This reminded us the elimination of hydroxymethyl group on α-position of pyrroles as formaldehyde by an acid catalyst. Therefore, an attempt to convert 5 to 2-methoxymethyl-3,4-disubstituted pyrroles (7) was examined to prevent the loss of α-substituent of the pyrroles during the cyclization. The sulfide (5c) was first oxidized to the corresponding sulfoxide (6c) with sodium metaperiodate followed by treatment with 2M-methanolic KOH to give the desired product (7c) in a quantitative yield. This reaction seems to proceed via an N-demesylation followed by elimination of methanesulfenic acid to form an azafluvene derivative, and an attack of MeOH to afford 7c. Treatment of 7c with an acidic MeOH for 2 h at room temperature gave the corresoponding porphyrinogen [NMR ($CDCl_3$) δ=1.10 (t, 24H, J=7.62 Hz), 2.40 (q, 16H, J=7.62 Hz), 3.71 (s, 8H), 6.69 (s, 4H); m/z 540 (M^+)] in a quantitative yield. Oxidation of the porphyrinogen under oxygen in dichrolomethane for 3 h at room temperature and the subsequent purification on a silica gel column (CH_2Cl_2) gave the desired 2,3,7,8,12,13,17,18-octaethyl-12H,23H-porphine (8c) in a 96% yield (mp 328 °C).[5]

In the same way, 8a (mp 293 °C, from benzene) and 8b (mp 270 °C, from cyclohexene) were prepared from the corresponding 6a and 6b without isolation of 2-methoxymethylpyrroles (7a,b) and the porphyrinogens in 77% and 93% yields, respectively.



(a) $NaIO_4$ (2 equiv.) in aq. MeOH, r. t. (b) 2M-KOH in MeOH, reflux, 10 min (c) HCO_2H/MeOH (2/1) r. t. (d) O_2, in CH_2Cl_2

Consequently, 2-methoxymethyl-3,4-disubstituted pyrrole derivatives proved to be very useful intermediates for porphyrin synthesis.

References

1) A. Gossauer, "Die Chemie der Pyrrole," Springer-Verlag, Berlin (1974); R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles," Academic Press, New York (1977).
2) a) H. Kinoshita, K. Inomata, M. Hayashi, T. Kondoh, and H. Kotale, Chem. Lett., 1986, 1033; b) K. Inomata, H. Suhara, H. Kinoshita, and H. Kotake, ibid., 1988, 813.
3) The reagent 1 was prepared from methanesulfonamide (1 equiv.), methylthioacetaldehyde dimethyl acetal (1 equiv.), and p-toluenesulfenic acid (1.5 equiv.) by stirring at room temperature for 4 d in the presence of p-toluenesulfonic acid (0.2 equiv.) in dichloromethane. (71% yield, mp 121-122 °C from EtOH).
4) G. Ksander, G. Bold, R. Lattmann, C. Lehmann, T. Früh, Y. B. Xiang, K. Inomata, H. P. Buser, J. Schreiber, E. Zass, and A. Eschenmoser, Helv. Chim. Acta, 70, 1115 (1987); M. Ono, R. Lattmann, K. Inomata, C. Lehmann, T. Früh, and A. Eschenmoser, Croatica Chem. Acta, 58, 627 (1985).
5) N. Ono and K. Maruyama, Chem. Lett., 1988, 1511.

(Received February 27, 1989)