[4 + 2]-CYCLOADDITION TO 4-DEMETHOXYCARBAZOMYCIN

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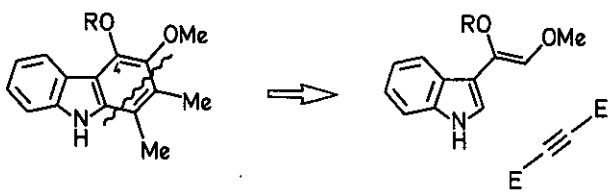
Abstract ——— The first synthesis of 4-demethoxycarbazomycin is described; the key step is the cycloaddition using a 3-vinylindole equivalent and dimethyl acetylenedicarboxylate as the dienophile.

Interest in the chemistry of carbazoles and related annelated systems is increasing continuously [1,2] as some of these compounds, both naturally occurring and synthetic [2-5], exhibit physiological activity. The [4 + 2]-cycloaddition to 2- and 3-vinylindoles has proved to be a synthetically efficient concept for the construction of selectively functionalized carbazole derivatives because cycloaddition reactions with vinyl-heterocycles give condensed heterocycles with substitution patterns which are not accessible so directly and elegantly by other routes [1,6,7].

Of the newer carbazole alkaloids, we were interested in the total syntheses of the antibiotically active carbazomycins A (1a) and B (1b) [5], which have not yet been realized, using the Diels-Alder reaction as a key step.

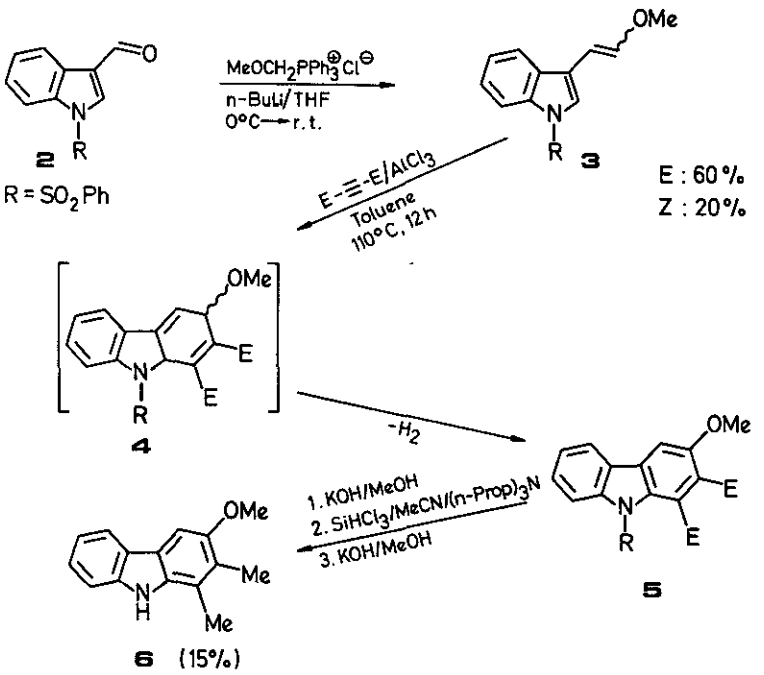


1a R = Me
1b R = H
E = COOMe

We now report on the first realization of this strategy, initially for the preparation of the title compound, 4-demethoxycarbazomycin (6).

The N-protected indole-3-carboxaldehyde 2 was converted in good yield to the (E/Z)-3-vinylindoles 3 (60 and 20% yields) [8,9] by a Wittig reaction. Finally, the reactive enophile 3 was subjected to cycloaddition with dimethyl acetylenedicarboxylate as the C_4 synthon; under the thermal conditions prevailing (dehydrogenating Diels-Alder reaction) the trisubstituted carbazole 5 was formed preferentially. As a side reaction, elimination of methanol followed the [1,3]-H shift to give the

demethoxy derivative of 5 (15% yield). The step 4 → 5 was driven to completion by dehydrogenation of the reaction mixture using chloranil (yield of 5: 28%). The method described in Ref. [11] appeared to be suitable for conversion of the ester functions in 5 to methyl groups and was also achieved for phthalic acid. Firstly, the diester 5 was hydrolyzed with simultaneous cleavage of the protecting group and the free dicarboxylic acid obtained was separated by column chromatography on silica gel (petroleum ether/ethyl acetate). Finally, both carboxylic acid functions were reduced using trichlorosilane [11] to give the product 6 [5] directly (yield of dicarboxylic acid to 6 step: 15%).



The compounds 3, 5, and 6 were isolated by MPLC (petroleum ether/ethyl acetate). The constitutions of these compounds and that of the dicarboxylic acid derived from 5 were elucidated by mass and 400 MHz ^{1}H-NMR spectrometric methods [12].

Studies on the application of this cycloaddition strategy to the syntheses of 3-demethoxycarbazomycin and carbazomycin A (1a) in which the corresponding methoxy substituted 3-vinylindoles are to be used as educts are in progress.

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REFERENCES AND NOTES

1. L. Pfeuffer and U. Pindur, Chimia, 1986, 40, 124.

2. J. A. Joule, Adv. Heterocycl. Chem., 1984, 35, 83; and refs. therein.

3. G. W. Gribble and M. G. Saulnier, Heterocycles, 1985, 23, 1277; and refs. therein.

4. D. P. Chakraborty, Progress in the Chemistry of Organic Natural Products, 1977, 34, 300; D. P. Chakraborty, Planta Med., 1980, 39, 97; M. Suffness and G. A. Cordell, The Alkaloids, 1985, 25, 86; and refs. therein; H.-P. Husson, The Alkaloids, 1985, 26, 17.

5. K. Sakano and S. Nakamura, J. Antibiotics, 1980, 33, 961; M. Kaneda, K. Sakano, S. Nakamura, Y. Kushy and Y. Iitaka, Heterocycles, 1981, 15, 993.

6. U. Pindur and L. Pfeuffer, Chem.-Ztg., 1986, 110, 95; and refs. therein.

7. E. Akgün and U. Pindur, Chimia, 1985, 39, 264.

8. For a related synthesis leading to methoxy substituted vinylindoles, see: S. Kano, E. Sugino, S. Shibuya and S. Hibino, J. Org. Chem., 1981, 46, 3856.

9. S. Kano, E. Sugino and S. Hibino, J. Chem. Soc., Chem. Commun., 1980, 1241.

10. J. D. Lambert and Q. N. Porter, Aust. J. Chem., 1981, 34, 1483.

11. R. A. Benkeser, K. M. Foley, J. M. Gaul and G. S. Li. J. Am. Chem. Soc., 1970, 92, 3232.

12. More experimental details and reactions of 3 with other dienophiles will be reported in a later full paper. Product 3 (E): m p 196-197°C; MS: m/z = 313 (20 %). Product 3 (Z): m p 175-176°C; MS: m/z = 313 (10 %). Product 5: m p 199-200°C; MS: m/z = 493 (15 %). Product 6: m p 129-131°C [5]. MS: m/z = 225 (30 %). IR (KBr): 3340 cm^{-1} (NH). ^1H NMR ($CDCl_3$): 2.36 (s, 2-CH_3), 2.48 (s, 1-CH_3), 7.18 - 7.53 (m, H-6, H-7, H-8), 7.46 (s, H-4), 8.00 (br. s, NH), 8.08 (dd, H-5).

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