Tetrahedron Letters,Vol.25,No.3,pp 309-312,1984
Printed in Great Britain

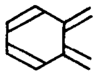
0040-4039/84 $3.00 + .00

STRONG BASE INDUCED CYCLOADDITION OF 3-CARBOXY-1-METHYLINDOLE-2-ACETIC ANHYDRIDE AND 2-CARBOXYBENZO[b]FURAN-3-ACETIC ANHYDRIDE: SYNTHESIS OF POLYCYCLIC peri-HYDROXYLATED INDOLE AND BENZOFURAN COMPOUNDS

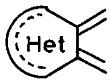
Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho, and Y. Kita
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka, 565 Japan

Summary: Generation of indole- and benzofuran-2,3-orthoquinodimethane-like intermediates is described. The cycloaddition reaction of these intermediates to dienophiles provided an efficient one-pot synthesis of polycyclic peri-hydroxylated indole and benzofuran compounds.

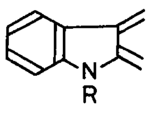
Since the utilization of so-called *o*-quinodimethane intermediates (1) is well established for the annulation of polycyclic aromatics involving alkaloids, steroids, and terpenes,1) the application to heteroaromatic systems is quite attractive for the synthesis of polycyclic heteroaromatic compounds such as indole, pyridine, and benzofuran possessing important pharmacological properties. Many methods have been devised for the generation of 1, but few routes are applicable to the heteroaromatic *o*-quinodimethanes (2).2) In the case of indole-2,3-orthoquinodimethanes (3), a [1,5]-sigmatropic shift of 2-alkyl-3-vinylindole3) or 3-alkyl-2-vinylindole4) and a 1,4-elimination from the fluoride-ion induced benzylsilane fragmentation5) have been explored recently. The generation of benzofuran-2,3-orthoquinodimethanes has not appeared in the literature, and furanic homologs (4) of 1 have been generated only by a flash vacuum thermolysis of the corresponding tetrahydrobenzofurans.6) We have recently reported the strong base induced Diels-Alder type reaction of homophthalic anhydrides via the *o*-quinodimethane-like intermediates (5) and its application to an efficient synthesis of polycyclic peri-hydroxyaromatic compounds such as anthracyclinones.7) We now found that this method is applicable to the indole- and benzofuran-2,3-orthoquinodimethane analogs (6 and 7) from 3-



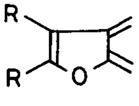
1



2

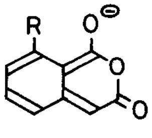


3



R=H, alkyl

4



R=H, OMe

5

carboxy-1-methylindole-2-acetic anhydride (8) and 2-carboxybenzo[b]furan-3-acetic anhydride (9),[8)] which affords otherwise hardly accessible polycyclic peri-hydroxylated indole and benzofuran compounds in a single step.

The starting anhydrides (8 and 9), prepared by the reported methods,[9,10)] were deprotonated by the treatment with NaH in THF under mild conditions and reacted with 1.1 equivalents of dienophiles to give the corresponding adducts (10-15): The cycloaddition occurred regioselectively in a fashion that the nucleophilic end of the indole- and benzofuran-2,3-orthoquinodimethane-like intermediates (6 and 7) reacts at the electrophilic site of the dienophiles as observed in the reaction with ethyl propiolate or haloquinone (Run 2, 3, 5, or 6). The reaction routes, conditions, products, and yields are shown in Scheme 1 and Table I. The structures of the products were characterized by IR, ^{1}H-NMR, and mass spectral data, which are summarized in Table II.

Scheme 1

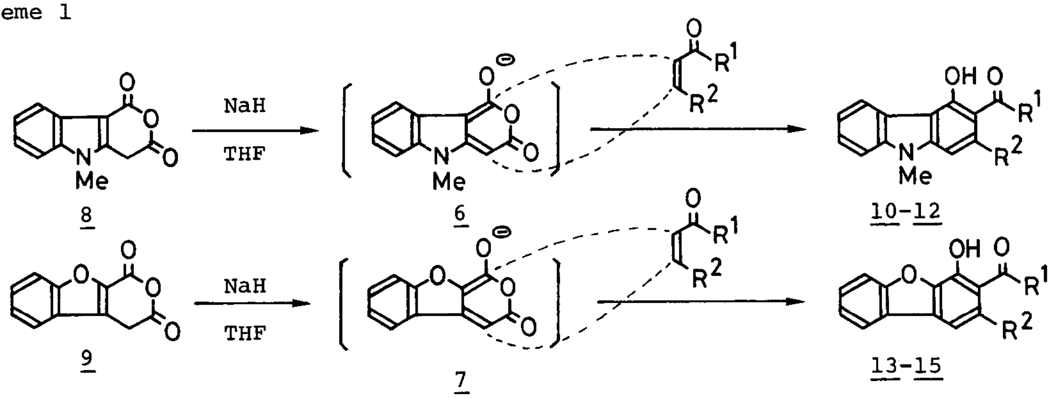
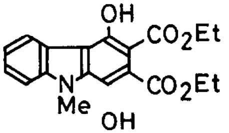
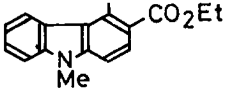
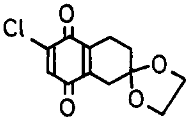
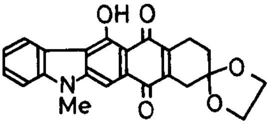
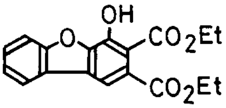
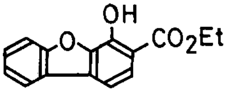
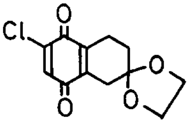
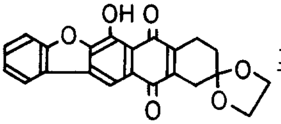


Table I Products from the Reaction of 8 or 9 with Dienophiles

Run	Anhydride	Dienophile	Reaction Conditions	Product[a)]		Yield (%)
1	8	$EtO_2CC{\equiv}CCO_2Et$	r.t., 3 h		10	45
2		$HC{\equiv}CCO_2Et$	reflux, 4.5 h		11	21
3			reflux, 5 h		12	27

4	9	$EtO_2CC{\equiv}CCO_2Et$	r.t., 3 h		13	76
5		$HC{\equiv}CCO_2Et$	reflux, 5 h		14	17
6			r.t., 0.5 h		15	31

a) The microanalyses of all products were in satisfactory agreement with the calculated values.

Table II Physical and Spectral Data for Indole and Benzofuran Compounds (10-15)

Compd.	M.p. (°C) (Solv. for Recryst.)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	^1H-NMR (in $CDCl_3$): δ
10	130.5 (ligroin)	3500-3100 1740,1675	11.87(1H,s,OH), 8.45-8.3(1H,m, ArH), 7.45-7.15(3H,m,ArH), 6.92 (1H,s,ArH), 4.38(2H,q,J=8Hz,CH_2), 4.35(2H,q,J=8Hz,CH_2), 3.80(3H,s, NCH_3), 1.40(6H,t,J=8Hz,2×CH_3)
11	132-133 (ligroin)	3500-3100 1660	11.81(1H,s,OH), 8.37(1H,dd,J=7 and 2Hz,ArH), 7.86(1H,d,J=9Hz,ArH), 7.45-7.25(3H,m,ArH), 6.79(1H,d,J= 9Hz,ArH), 4.40(2H,q,J=7Hz,CH_2), 3.79(3H,s,NCH_3), 1.43(3H,t,J=7Hz, CH_3)
12	273-275 (benzene-n·hexane)	3500-3100 1650,1630,1620 1600	13.47(1H,s,OH), 8.5-8.35(1H,m,ArH), 7.70(1H,s,ArH), 7.55-7.3(3H,m,ArH), 4.05(4H,s,OCH_2CH_2O), 3.92(3H,s, NMe), 3.6-2.75(4H,m,CH_2), 2.0-1.8 (2H,m,CH_2)
13	132 (ligroin)	3450-3100 1725,1675	11.11(1H,s,OH), 8.0-7.85(1H,m,ArH), 7.75-7.3(3H,m,ArH), 7.55(1H,s,ArH), 4.41(2H,q,J=7Hz,CH_2), 4.35(2H,q, J=7Hz,CH_2), 1.40(6H,t,J=7Hz,2×CH_3)
14	128 (ligroin)	3400-3050 1675	11.31(1H,s,OH),8.0-7.3(4H,m,ArH), 7.81(1H,d,J=9Hz,ArH), 7.38(1H,d,J= 9Hz,ArH), 4.44(2H,q,J=7Hz,CH_2), 1.45(3H,t,J=7Hz,CH_3)
15	233-235 (benzene)	3400-3050 1640,1615	12.73(1H,s,OH), 8.18(1H,s,ArH), 8.05-7.9(1H,m,ArH), 7.75-7.3(3H,m, ArH), 4.04(4H,s,OCH_2CH_2O), 3.0-2.75(4H,m,CH_2CH_2), 2.0-1.75(2H,m, CH_2)

Although none of these strong base induced reactions of the anhydrides (8 and 9) has been optimized, the present method is quite useful for the construction of polycyclic peri-hydroxylated indole and benzofuran compounds, since the reaction occurred regioselectively in one step under remarkably mild conditions. Further applications to other heteroaromatic systems are being explored currently.

Acknowledgement: We thank Miss Yuko Nakajima for technical assistance.

References and Notes

1) For a general review of o-quinodimethanes in synthesis, see: T. Kametani and K. Fukumoto, Heterocycles, 3, 29 (1975); W. Oppolzer, Synthesis, 1978, 793; J. J. McCullough, Account. Chem. Res., 13, 270 (1980); R. L. Funk and K. P. C. Vollhardt, Chem. Soc. Reviews, 9, 41 (1980) and references cited therein.
2) For a review, see: C. Kaneko and T. Naito, Heterocycles, 19, 2183 (1982).
3) J. Bergman and R. Carlsson, Tetrahedron Lett., 1977, 4663.
4) S. Kano, E. Sugino, S. Shibuya, and S. Hibino, J. Org. Chem., 46, 2979 (1981).
5) Magnus has recently reported the intramolecular indole-2,3-quinodimethane cyclization that gives fused pentacyclic compounds, which has been applied to an efficient and elegant synthesis of (±)-aspidospermidine, see: S. Djuric, T. Sarkar, and P. Magnus, J. Am. Chem. Soc., 102, 6885 (1980); T. Gallagher and P. Magnus, Tetrahedron, 37, 3889 (1981); J. Am. Chem. Soc., 104, 1140 (1982); ibid., 105, 2086 (1983); C. Exon, T. Gallagher, and P. Magnus, J. Chem. Soc. Chem. Commun., 1982, 613; J. Am. Chem. Soc., 105, 4739 (1983); T. Gallagher, P. Magnus, and J. C. Huffman, ibid., 105, 4750 (1983); E. R. Marinelli, Tetrahedron Lett., 23, 2745 (1982).
6) J. Jullien, J. M. Pechine, F. Perez, and J. J. Piade, Tetrahedron Lett., 1979, 3079; ibid., 21, 611 (1980).
7) Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, and Y. Kita, J. Org. Chem., 47, 4376 (1982); Y. Tamura, M. Sasho, K. Nakagawa. T. Tsugoshi, and Y. Kita, ibid., in press.
8) We are trying to obtain the pyridineacetic anhydrides from the pyridineacetic acids, but it is now quite difficult because of the insolubility in organic solvents and high reactivity of pyridine nitrogen toward the condensed reagents such as acetic anhydride, acetyl chloride, and oxalyl chloride.
9) G. A. Bahadur, A. S. Bailey, N. W. Middleton, and J. M. Peach, J. Chem. Soc. Perkin I, 1980, 1688.
10) J. N. Chatterjea and R. P. Sahai, J. Ind. Chem. Soc., 57, 633 (1980).

(Received in Japan 27 September 1983)