Tetrahedron Letters, Vol.22, No.43, pp 4283 - 4286, 1981
Printed in Great Britain

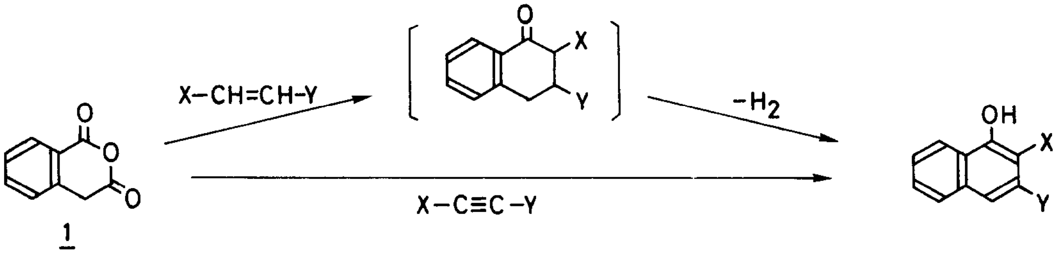
0040-4039/81/434283-04$02.00/0

CYCLOADDITION OF HOMOPHTHALIC ANHYDRIDE: A NEW AND SIMPLE ROUTE TO LINEARLY CONDENSED PHENOLIC COMPOUNDS

Y. Tamura,* A. Wada, M. Sasho, and Y. Kita
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka, Japan

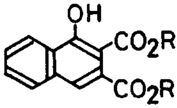
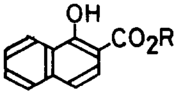
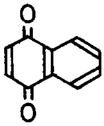
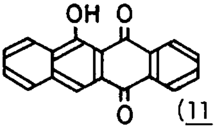
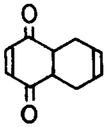
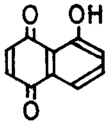
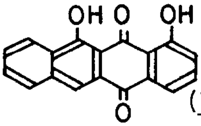
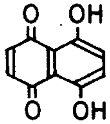
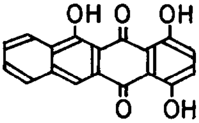
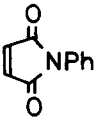
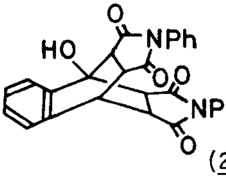
Summary: Diels-Alder reaction of homophthalic anhydride (1) with some dienophiles gave a considerable yield of linearly condensed phenolic compounds, directly.

Although homophthalic anhydride (1) is known to react readily with polar double bonds such as C=O[1)] and C=N bonds[2)] and has been used as a useful synthon for the synthesis of some natural products,[3)] none of the reactions of 1 with C=C and C≡C bonds has been reported. We have now found that the anhydride (1) can react with these bonds, where 1 acts as a diene in the Diels-Alder reaction. The present paper describes a simple and direct route to a linear polynuclear phenolic system, a structural feature present in many antibiotics and other natural products.[4)]



When a solution of 1 and alkyl acetylenedicarboxylate (2 or 3) in toluene was heated at 150° for 1 day, the naphthol (4 or 5) was obtained in a considerable yield. The regiochemical outcome of this cycloaddition was determined by the reaction of 1 with methyl propiolate (6). The reaction gave one adduct, 1-hydroxy-2-naphthoic acid methyl ester (7), which was identified with an authentic sample obtained by methylation of 1-hydroxy-2-naphthoic acid. Having established the methodology for effecting the Dields-Alder reaction at 1- and 4-positions of 1, some further examples were examined. As a mode for anthracycline and/or tetracycline type structures, 1 was treated with some naphthoquinones (10, 12, 13, and 15) in dichlorobenzene to give a considerable yield of tetracyclic compounds (11, 14, and 16), directly. The results are summarized in the Table.

Table Diels-Alder Reactions of 1 with Some Dienophiles

Dienophile	Reaction Conditions	Product[a)]	Yield[b)] (%)	M.p. (°C) Found[c)] (Solvent)	M.p. (°C) Reported
RO_2C-C≡C-CO_2R (2); R=Me	in toluene at[d)] 150° for 24 h	 (4); R=Me	65	102-103.5 (C_6H_6-n-hexane)	102-108[5)]
(3); R=Et	"	(5); R=Et	63	54-54.5 (n-hexane)	e[6)]
HC≡C-CO_2R (6); R=Me	"	 (7); R=Me	9	74.5-76 (MeOH)	76-77[5)]
(8); R=Et	"	(9); R=Et	19	40.5-41 (n-hexane)	48-49[7)]
 (10)	in dichloro-benzene at 200° for 7 h	 (11)	44	262-264 ($CHCl_3$)	268-270[8)]
 (12)	in dichloro-benzene at 200° for 15 h	(11)	27	262-264 ($CHCl_3$)	268-270[8)]
 (13)	in dichloro-benzene at 200° for 7 h	 (14)	49	275-278 ($CHCl_3$)	276[9)]
 (15)	"	 (16)	38	290-292 ($CHCl_3$)	294[10)]
 (20)	in dichloro-benzene at 200° for 20 h	 (21)[f,g)]	48	232-234 ($CHCl_3$-n-hexane)	—

---

a) All spectroscopic data (N.M.R., IR., U.V., and mass spectra) are in good agreement with the proposed structures.

b) Isolated yields were based on 1.

c) The melting points are not corrected.

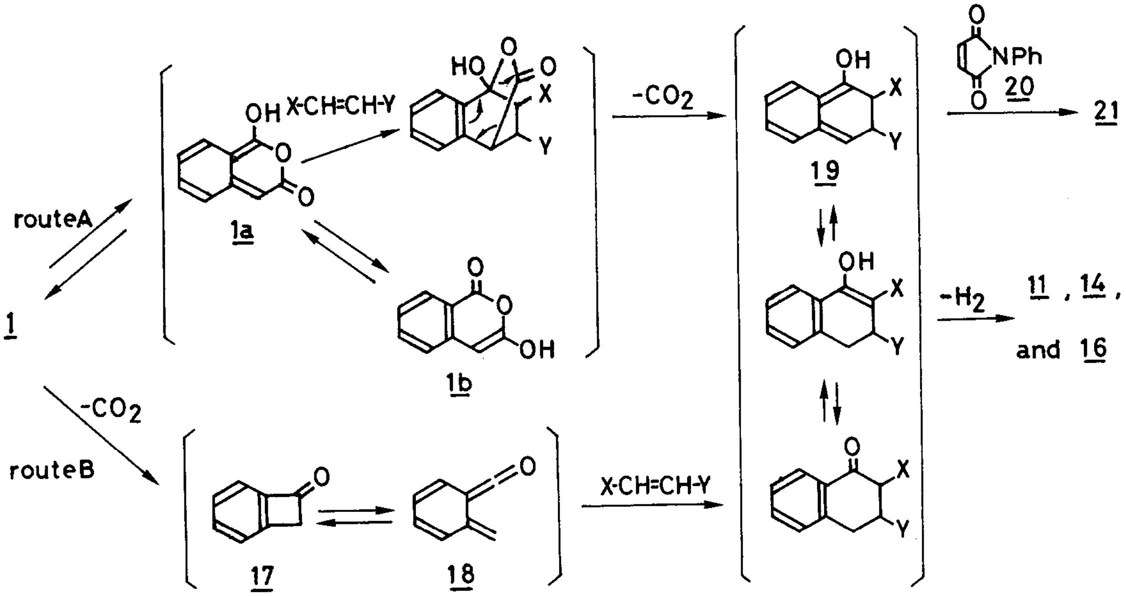
d) The reaction was carried out in a sealed tube.

e) The boiling point was reported; b.p. 163-164°C/0.05 mmHg.

f) Although a single isomer was formed, the stereochemistry could not be confirmed yet.

g) Satisfactory elemental and spectral data were obtained; [ν_{max} ($CHCl_3$); 1770, 1715, 1705, and 1640 cm^{-1}; δ ($CDCl_3$); 7.9-6.8 (14H, m, Ar-H), 4.37 (1H, t, J 9 Hz, CH), 3.8-3.3 (3H, m, 2×CH and OH), 3.15 (1H, d, J 9 Hz, CH), and 3.09 (1H, d, J 9 Hz, CH); *m/e* 464 (M^+)].

There are two possible routes for the formation of the linearly condensed adduct from 1, i.e. Diels-Alder reaction of the dienol isomer (1a) rather than another possible tautomer (1b) with dienophile followed by spontaneous extrusion of CO_2 (route A) or Diels-Alder reaction of *ortho*-xylylene intermediate (18)11) generated from benzocyclobutenone (17)12) with dienophile (route B) as shown in the Scheme. Although definite evidence could not be obtained, the following results strongly support route A for the formation of the adduct; i) prolong heating of 1 in dichlorobenzene did not give 17 or its derivative at all and 1 was recovered unchanged and ii) 1:2-adduct (21) was obtained by the thermal reaction of 1 with N-Phenylmaleinimide (20) probably through the enol intermediate (19).



REFERENCES AND NOTES

1) M.A. Haimova, N.M. Mollov, S.C. Ivanova, A.I. Dimitrova, and V.I. Ognyanov, *Tetrahedron*, 33, 331 (1977) and references cited therein.

2) M.A. Haimova, V.I. Ognyanov, and N.M. Mollov, *Synthesis*, 1980, 845.

3) M. Cushman, J. Gentry, and F.W. Dekow, *J. Org. Chem.*, 42, 1111 (1977); M. Cushman and F.W. Dekow, *Tetrahedron*, 34, 1435 (1978); *idem*, *J. Org. Chem.*, 44, 407 (1979); S.O. de Silva, I. Ahmad, and V. Snieckus, *Can. J. Chem.*, 57, 1598

(1979); M. Cushman, T.C. Choong, J.T. Valko, and M.P. Koleck, J., *J. Org. Chem.*, 45, 5067 (1980); K. Iwasa, Y.P. Gupta, and M. Cushman, *Tetrahedron Lett.*, 22, 2333 (1981).

4) The aglycone portion of numerous naturally occurring quinones consists of linear polynuclear phenolic systems: R.H. Thompson, "Naturally Occurring Quinones", Academic Press, New York, N.Y., 1971.

5) N.J. Broom and P.G. Sammes, *J. Chem. Soc. Perkin I*, 1981, 465.

6) Z. Horii, T. Katagi, Y. Tamura, and T. Tanaka, *Chem. Pharm. Bull.*, 10, 887 (1962).

7) F.M. Hauser and S.A. Pogang, *J. Het. Chem.*, 15, 1535 (1978).

8) D.H. Barton, J.H. Bateson, S.C. Datta, and P.D. Magnus, *J. Chem. Soc. Perkin I*, 1976, 503.

9) H. Brockmann, R. Zunker, and H. Brockmann. Jr., *Ann.*, 696, 145 (1966).

10) H. Brockmann and W. Müller, *Chem. Ber.*, 92, 1164 (1959).

11) *ortho*-Xylylenes have been involved in the construction of the ring skelton of some anthracyclinones: B.J. Arnold, P.G. Sammes, and T.W. Wallace, *J. Chem. Soc. Chem. Commun.*, 1972, 30; T. Kametani, M. Takeshita, H. Nemoto, and K. Fukumoto, *Chem. Pharm. Bull.*, 26, 556 (1978); J.R. Wiseman, N.I. French, R.K. Hallmark, and K.G. Chiong, *Tetrahedron Lett.*, 1978, 3765; R.K. Boeckman, Jr., M.H. Delton, T.M. Dolak, T. Watanabe, and F. Farina, *Tetrahedron Lett.*, 1979, 3983; T. Laduanty, L. Lapage, and Y. Lapage, *Can. J. Chem.*, 58, 1161 (1980); R.L. Funk and K.P.C. Volhardt, *Chem. Soc. Reviews*, 9, 41 (1980) and references cited therein.

12) Flash thermolysis of 1 at high temperature (over 500°) in a stream of nitrogen is known to give the benzocyclobutenone (17) together with fulveneallene: R.L. Spangler and J.H. Kim, *Tetrahedron Lett.*, 1972, 1249. Similar thermal decomposition of 3-isochromanones into benzocyclobutenes has also been reported by the same group: R.J. Spangler, B.G. Beckmann, and J.H. Kim, *J. Org. Chem.*, 42, 2989 (1977); R.J. Spangler and B.G. Beckmann, *Tetrahedron Lett.*, 1976, 2517.

(Received in Japan 11 July 1981)