Tetrahedron Letters,Vol.24,No.12,pp 1221-1224,1983 0040-4039/83/121221-04$03.00/0
Printed in Great Britain

SYNTHESIS OF METHYL SUBSTITUTED BENZANTHRACENES AND BENZANTHRACENE DERIVATIVES

Louis A. Levy* and Sashi Kumar V.P.

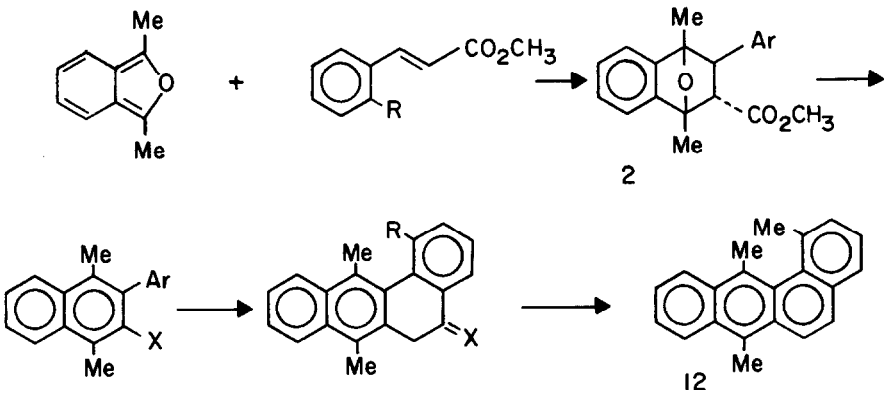
Laboratory of Environmental Chemistry, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709

Summary: Diels-Alder reaction of 1,3-dimethylisobenzofuran with cinnamic esters allows for the synthesis of a variety of 7,12 dimethylbenzanthracene derivatives. The sterically congested 1,7,12 trimethylbenzanthracene was prepared.

The synthesis of alkyl sustituted derivatives of benzanthracene, itself a weak carcinogen, has been of continuing interest in the study of metabolism of polynuclear aromatic hydrocarbons and their role in the mechanism of carcinogensis[1]. Introduction of methyl substituents at the 7 and/or 12 positions of benzanthracene greatly enhance its carcinogenic activity, while methyl substituents at other positions result in less activation or suppression of activity[2]. The availability of many of these compounds is quite limited or virtually nonexistant due to the complexity or inapplicability of existing synthetic methods[3]. We have been interested in methods which would allow for the synthesis of specifically labeled compounds and for the preparation of structures which would possess a chiral element. The latter requirement could be met by introduction of substitutents at positions 1 and 12, which because of the resulting steric congestion in the bay region would lead to atropisomers.[4]

Our success with the use of ortho-quinodimethanes for the synthesis of benzanthracenes[5] suggested the use of o-quinodimethanes alkylated at the exocyclic methylene positions as a ready route to 7,12 disubstituted benzanthracenes. 1,3-dimethylisobenzofuran, a known derivative of this type of o-quinodimethane appeared to be a good candidate for use in this approach[6]. Generation of 1,3-dimethylisobenzofuran by application

of Warrener's method using 1,4,-dimethyl-1,4 epoxynaphthalene and 3,6-di-(2-pyridyl)-1,2,4,5-tetrazine in the presence of methyl cinnamate proceeded in good yield (73%) to afford the 1,4 epoxynaphthalene 2a[8]. Brief treatment with p-toluenesulfonic acid in benzene gave the fully aromatic naphthalene, 3a, (90%). Extension of the side chain by one carbon unit was carried out in a conventional manner by reduction of the ester ($LiAlH_4$, 95%) to the benzyl alcohol 4a, conversion of the alcohol to the chloride 5a (HCl, 100%), introduction of the nitrile group (NaCN, DMF, 90%) and hydrolysis to the acid 7a (H_2SO_4, 65%). Cyclization of the acid occurs smoothly in hydrogen flouride to yield the benzanthracene derivative 8. This compound is known to exist as a mixture of keto-enol tautomers rather than the expected phenol; a manifestation of the steric inter action of the C-12 methyl and C-1 hydrogen[9].



3, x = $COOCH_3$
4, x = CH_2OH
5, x = CH_2Cl
6, x = CH_2CN
7, x = CH_2COOH
a, Ar = C_6H_5
b, Ar = o-MeC_6H_4

8, x = O, R = H
9, x = O, R = Me
10, x = H, OH; R = Me
11, x = H, H; R = Me

In a similar manner, starting with o-methyl-methylcinnamate and proceeding through the same sequence, with comparable yields, the synthesis of the trimethyl series of compounds was effected. The steric effect of the additional methyl group is noticeable in

the pmr spectra of the intermediate compounds 4b-7b. Hindered rotation of the o-methylphenyl substituent results in non-equivalence of the adjacent methylene group and its appearance as an AB pattern in their pmr spectra. Cyclization of the acid by HF proceeded cleanly to ketone 9 which slowly isomerized to the enol form. This process was readily seen by monitoring the pmr spectrum of the isolated ketone (9) and observing the appearance of three additional methyl signals at 2.24, 2.52 and 2.75δ as well as a signal at 5.52δ for the enolic hydrogen. This somewhat unstable compound was immediately reduced ($NaBH_4$) to the alcohol 10[10]. The fully aromatic hydrocarbon, 12, was prepared by dehydration (pts, benzene 95%) of 10. The 4,5 dihydrobenzanthracene derivative 11 was obtained by hydrogenolysis of the benzylic alcohol 10 using Gribble's [11] procedure of reduction with $NaBH_4$ in trifluoroacetic acid.

REFERENCES AND NOTES

1. T. Watube, T. Ishizuka, M. Isobe and N. Ozawa, Science, 215, 403 (1982).
2. S.K. Yang, M.W. Chau and P.P. Fu, In "Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects", Alf Bjorseth and Anthony J. Dennis, ed., Battelle Press; Columbus, Ohio, 1980; p 645.
3. M.S. Newman, J.M. Khanna and K.C. Lilge, Org. Prep. and Proc. Int., 11, 271 (1979); G.M. Mushik, J.E. Tomaszewski, R.I. Sato and W.B. Manning, J. Org. Chem., 44, 2150 (1979); J.E. Tomaszewski, W.B. Manning and G.M. Muschik, Tetrahedron Letters 1977, 971.
4. M.S. Newman, W.C. Sugar and M.V. George, J. Am. Chem. Soc. 82, 2376 (1960); D.W. Jones, J.M. Sowden, A.C. Hazell and R.G. Hazell, Acta Crystallogr., B34, 3021 (1978).
5. L.A. Levy and L. Pruitt, J. Chem. Soc. Chem. Comm. 1980, 227.
6. L.F.Fieser and M.J. Haddadin, Can. J. Chem., 43 1599 (1965).
7. G.M. Priestly and R.N. Warrener, Tetrahedron Letters, 1972, 4295.
8. Melting points and 'H NMR($CDCl_3$,Me_4Si) data. 2a, 116-118°; 1.36(s,3H), 2.1(s,3H), 3.26 (m,2H), 3.43(s,3H),6.8-7.75(m,8H). 2b, 1.37(s,3H), 2.08(s,3H), 2.32(s,3H), 3.28(d, J=4.5Hz,1H), 3.49(s,3H), 3.70(d,J=4.5Hz,11Hz), 7.16-7.6,(m, 8H). 3a, 53-55°;2.41 (s,3H), 2.65(s,3H), 3.43(s,3H), 7.2-8.15(m,9H). 3b, 79-80°; 2.04(s,3H), 2.31(s,3H), 2.63(s,3H), 3.39(s,3H), 7.2-8.25(m,8H). 4a, 83-84°; 2.32(s,3H), 2.79(s,3H), 4.53(s,2H), 7.2-8.25 (m,9H). 4b, 82-83°; 1.94(s,3H), 2.25(s,3H), 2.76(s,3H), 2.76(s,3H), 4.44(q, J=12.6Hz,

2H), 7.0-8.2 (m,8H). 5a, 82-85°; 2.29(s,3H), 2.74(s,3H), 4.47(s,2H), 7.2-8.2(m,9H). 5b, 81-83°; 1.98 s,3H),2.27(s,3H), 2.79(s,3H), 4.45(q, J=11.1Hz 2H), 7.25-8.35(m,8H). 6a, 118-121°; 2.34 (s,3H), 2.74(s,3H),3.49(s,2H), 7.2-8.2(m,9H). 6b, 151-152°; 1.99 (s,3H) 2.30(s,3H). 2.76 (s,3H), 3.47(q, J=14Hz,2H), 7.2-8.3(m,8H). 7b, 190°(decomp.); 1.92(s,3H), 2.62(s,3H), 3.57(q, J=15Hz,2H), 7.2-8.35(m,8H). 9, 2.29(s,3H), 2.51(S,3H), 2.61(s,3H), 3.91(m,2H), 7.1-8.3(m,7H), on standing additional singlet signals at 2.24, 2.52, 2.75 and 5.52 appear. 10, 143-145°; 2.18(s,3H), 2.53(s,3H), 2.66(s,3H), 2.59 (m,1H), 3.38, 3.47 (dd, J=4.2 and 13.5Hz,1H), 4.65(m,1H), 7.23-8.1(m,7H). 11, 152-153°, 2.19(s,3H), 2.55(s,3H), 2.55(s,3H) 2.66(s,3H), 2.5-2.7(m,2H), 7.18-8.2(m,7H). 12, 105-106°; 2.47(s,3H), 2.84(s,3H), 3.01(s,3H), 7.2-8.4(m,9H).

Mass spectra consistent with the assigned structures (M^+ and appropriate fragmentation) were obtained for these compounds.

9. M.S. Newman and D.R. Olson, J. Am. Chem. Soc., 96, 6207, (1974).

10. The stereochemistry of the reduction of compound 9 and the stereochemical properties of compounds 10-12 will be discussed in a forthcoming communication. An analysis of the similarly substituted 9,10-dihydrophenanthrene system has been carried out. H. Joshua, R. Gans and K. Mislow, J. Am. Chem. Soc. 90, 4884 (1968).

11. G.W. Gribble, R.M. Leese and B.E. Evans, Synthesis 1977, 172.

(Received in USA 9 December 1982)