Tetrahedron Letters,Vol.24,No.45,pp 4939-4942,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain 

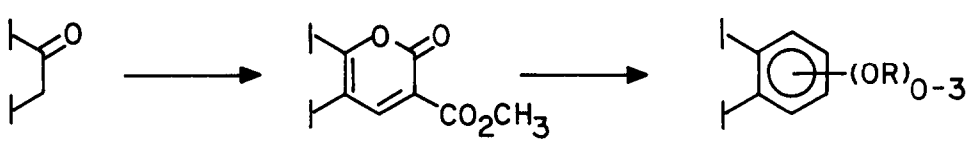
# INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF 3-CARBOMETHOXY-2-PYRONES. CONTROLLED INTRODUCTION OF OXYGENATED AROMATICS: BENZENE, PHENOL, CATECHOL, RESORCINOL, PYROGALLOL ANNULATION.

Dale L. Boger*[1a] and Michael D. Mullican[1b]

Department of Medicinal Chemistry, University of Kansas
Lawrence, Kansas 66045

**Summary:** Implementation of one of four inverse electron demand Diels-Alder reactions of 3-carbomethoxy-2-pyrones with N-vinyl-2-pyrrolidinone, vinylene carbonate, 1,1-dimethoxyethylene or 1,1,2-trimethoxyethylene followed by choice of two standard reaction sequences: (1) removal of the carbomethoxy group (NaOH; copper powder, quinoline, Δ) or (2) its conversion to an acetate [NaOH; $(CO)_2Cl_2$; $(CH_3)_2CuLi$; m-CPBA] allows the preparation of a full range of oxygen substituted aromatics from a single intermediate and represent methods of benzene, 1-, 2- or 3-phenol, symmetrical or unsymmetrical catechol, resorcinol and pyrogallol annulation.

We have described an investigation of the Diels-Alder reaction of 3-carbomethoxy-2-pyrones with 1,1-dimethoxyethylene for salicylate[2a] preparation and reported the implementation of this work in a regiospecific, total synthesis of juncusol[2b] and preparation of racemic 6,7-benzomorphans.[2c] Herein we describe a select survey of the inverse electron demand Diels-Alder reactions of 3-carbomethoxy-2-pyrones, including this salicylate preparation, designed to allow the utilization of a single intermediate for the introduction of a full range of oxygen substituted aromatics, equation 1. The results suggest considerable synthetic potential for these and related inverse electron demand Diels-Alder reactions.[3d]



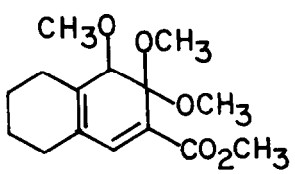

eqn. 1

The aryl introduction, illustrated with the 3-carbomethoxy-2-pyrone **1** prepared directly from cyclohexanone,[2a] relies on the cycloaddition reaction of **1** with one of four electron-rich dienophiles[4]: N-vinyl-2-pyrrolidinone[4a] (**2a**), vinylene carbonate[4b] (**2b**), 1,1-dimethoxyethylene[4c] (**2c**), and 1,1,2-trimethoxyethylene[4d] (**2d**), scheme I. In each instance, cycloaddition was found to occur under relatively mild conditions and was followed by thermal elimination of carbon dioxide. In the Diels-Alder

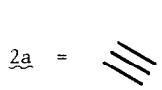
reactions of **2a-c** with **1** aromatization occurs competitively with cycloaddition and **3a-c** are the isolated products. Exclusive formation of **3b** can be attributed to loss of the more acidic proton with elimination of carbon dioxide. In contrast, the principle product of the Diels-Alder reaction of **1** with **2d** is **i** containing trace amounts of **3d**. Aromatization of **i**, which is stable to chromatography on silica gel, required acid treatment (cat. $CH_3SO_3H$, benzene, 25°C, 5 h) of the **i/3d** mixture. Choice of two standard reaction sequences: (1) removal of the carbomethoxy group (NaOH; copper powder, quinoline,[5] Δ) or (2) its conversion to an acetate (NaOH; $(CO)_2Cl_2$[6]; $(CH_3)_2CuLi$[7]; m-CPBA[8]) completes the preparation of a full range of oxygenated aromatics from a single precursor. The ability to prepare the selectively protected symmetrical and unsymmetrical o-catechols **4f** and **4g** [5], the differentially protected resorcinol **4d** and the selectively protected pyrogallol **4h** is of considerable interest. Such differentiation in di- and tri-oxygenated aromatics is otherwise difficult.

The dienophiles **2a-2d** serve as functional equivalents of **ii-v** in their Diels-Alder reactions with 3-carbomethoxy-2-pyrones. The use of **2b** versus **2c** serves the purpose of controlling, or reversing, the regiospecificity of the addition of the identical equivalents **iii** versus **iv**.

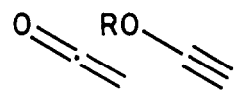
The ease with which 3-carbomethoxy-2-pyrones may be prepared,[2] the facility with which they participate in inverse electron demand Diels-Alder reactions, and the additional capability of this approach to accommodate the preparation of selectively protected di- and tri-oxygenated aromatics indicate that this methodology should prove to be of value in the preparation of natural or synthetic materials in which the concurrent or systematic variation of an aryl oxygenation substitution pattern is required.



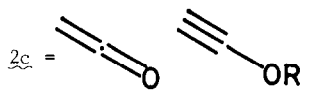

i



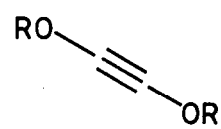
2a = ii




= 2b iii



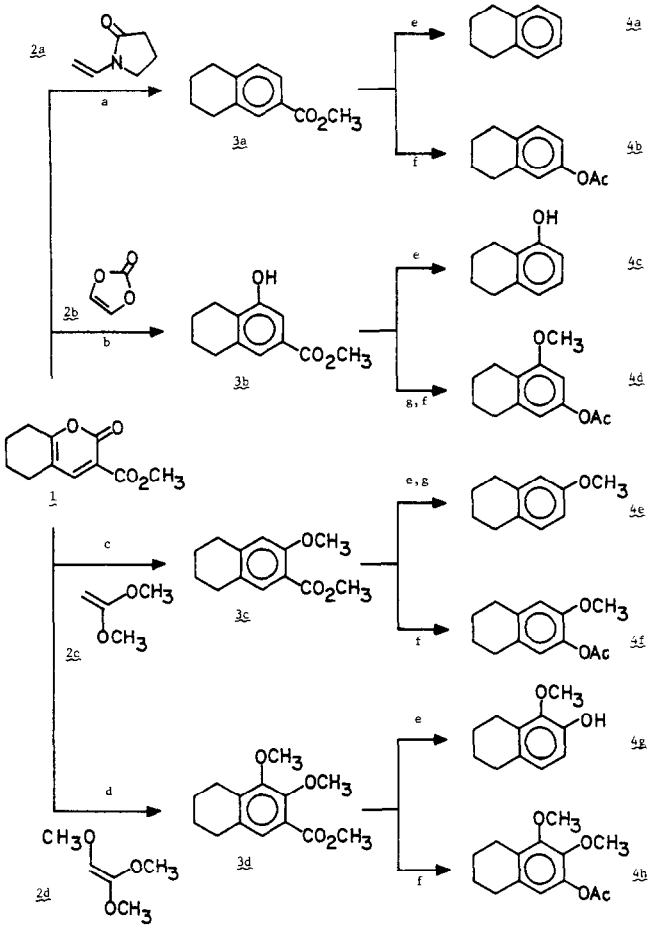

2c = iv




= 2d v

**Acknowledgment.** This work was supported by the Chicago Community Trust Co./Searle Scholars Program, National Institutes of Health (DA 03153-01), the University of Kansas General Research Allocation 3244-X0-0038 and a Biomedical Research Grant (RR 5606). We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for funds used in the purchase of equipment.

Scheme I



(a) 3 Equiv **2a**, mesitylene, 160°C, 42 h, 98%. (b) 5-10 Equiv **2b**, mesitylene, 180°C, 40 h, 79-83%. (c) 5 Equiv **2c**, toluene, 110°C, 15 h, 86%. (d) 5 Equiv **2d**, neat, 150°C, 78 h; 0.1 equiv $CH_3SO_3H$, benzene, 25°C, 5 h, 57%. (e) 2.0 Equiv aq. NaOH, THF, 25-60°C, 12-25 h; 10 equiv copper, quinoline,[5] 210-260°C, 1-7 h; **4a** (68%), **4c** (88%), **4e** (92%), **4g** (90%). (f) 2.0 Equiv aq. NaOH, THF, 25-60°C, 12-25 h; Excess $(CO)_2Cl_2$[6]; THF or $C_6H_6$, 25°C, 0.5-2 h; 3-4 equiv $(CH_3)_2CuLi$,[7] THF, -78°C, 0.25 to 1.0 h; 1.3 - 3.0 equiv m-CPBA, $CH_2Cl_2/CHCl_3$,[8] 25-60°C, 24-84 h; **4b** (59%), **4d** (40%), **4f** (40%), **4h** (56%). (g) 2-2.4 Equiv $CH_3I$, 1.6-2.0 equiv NaH, THF, 25°C, 4.5-20 h; **4d** (75%), **4e** (92%).[9]

**References and Notes**


1. (a) Chicago Community Trust Co./Searle Scholar Recipient, 1981-85; Recipient of a Career Development Award, 1983-1988, from the National Cancer Institute of the National Institutes of Health (Grant No. CA 00898). (b) National Institutes of Health Predoctoral Trainee, 1980-83; (Grant No. GM 07775).
2. (a) Boger, D. L.; Mullican, M. D. Tetrahedron Lett. **1982,** 23, 4551; (b) Boger, D. L.; Mullican, M. D. Ibid. **1982,** 23, 4555; (c) Boger, D. L.; Patel, M.; Mullican, M. D. Ibid. **1982,** 23, 4559. For additional work on the inverse electron demand Diels-Alder reactions of 3-carbomethoxy-2-pyrones, see: (d) Bryson, T. A.; Donelson, D. M. J. Org. Chem. **1977,** 42, 2930; (e) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. J. Am. Chem. Soc. **1983,** 105, 1988 and references cited therein. For reviews on the Diels-Alder reactions of α-pyrones, see: (f) Shusherina, N. P. Russian Chemical Reviews **1974,** 43, 851; Matsumoto, K.; Uchida, T. Heterocycles **1981,** 16, 1367; Sauer, J. Angew. Chem. Int. Ed. Eng. **1966,** 5, 211.
3. (a) Sauer, J.; Sustmann, R. "Topics in Current Chemistry", in preparation; (b) Sauer, J. Angew. Chem. Int. Ed. Eng. **1966,** 5, 211; Idem Ibid. **1967,** 6, 16; Sauer, J.; Sustmann, R. Ibid. **1980,** 19, 779.
4. (a) N-Vinyl-2-pyrrolidinone (**2a**) is available from Aldrich Chemical Company. (b) Vinylene carbonate (**2b**) is available from Aldrich Chemical Company. (c) 1,1-Dimethoxyethylene (**2c**) is available from Wiley Organics. (d) 1,1,2-Trimethoxyethylene (**2d**) was prepared as described: Bakker, C. G.; Scheeren, J. W.; Nivard, R. J. F. Recl. Trav. Chim. Pays-Bas **1981,** 100, 13; Spinning band distillation used to separate **2d** from methyl methoxyacetate and 1,1,1,2-tetramethoxyethane was found to be unnecessary and material which was 30% **2d** worked satisfactorily.
5. Trost, B. M.; Kinson, P. L. J. Org. Chem. **1972,** 37, 1273; For a review on copper powder, quinoline decarboxylation, see: Leake, P. H. Chem. Rev. **1956,** 56, 27. We found that this copper promoted decarboxylation may selectively demethylate aryl methyl ethers ortho to a carboxylate prior or concurrent with decarboxylation.
6. For **4b** and **4d,** catalytic dimethylformamide in THF was used for acid chloride formation, see: Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. Synthesis **1976,** 767. For **4f** and **4h,** the potassium salt of the carboxylic acid in benzene was used for the acid chloride formation, see: Miyano, M. J. Am. Chem. Soc. **1965,** 87, 3958.
7. Posner, G. H.; Whitten, C. E.; McFarland, P. E. J. Am. Chem. Soc. **1972,** 94, 5106.
8. Godfrey, I. M.; Sargent, M. V.; Elix, J. A. J. Chem. Soc. Perkin I **1974,** 1353. For **4d,** Potassium carbonate was added to the reaction mixture.
9. All compounds described herein exhibited the reported or expected $^1$H-NMR, IR, and mass spectral characteristics. All new compounds gave satisfactory elemental analysis (±0.40%) or high resolution mass spectral information. All yields are based on purified product isolated by column, medium pressure or radial chromatography ($SiO_2$).


(Received in USA 9 August 1983)