Tetrahedron Letters,Vol.24,No.29,pp 2945-2948,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

2-AZAISOBENZOFURANS AS INTERMEDIATES IN A CONVENIENT ANNELATION OF AROMATIC TERTIARY AMIDES

Peter Beak*and Chin-Wen Chen

Department of Chemistry, University of Illinois
Champaign-Urbana, Illinois 61801 USA

Abstract. The conversion of *N*,*N*-diisopropylbenzamide and dienophiles to *N*,*N*-diisopropylamino-2-carboxy-4-hydroxyl-3,4-dihydronapthalenes via ortho lithiation, formylation, diazotization, ring closure, cycloaddition, and ring opening is reported and postulated to involve the intermediacy of a novel 2-azaisobenzofuran.

The ortho lithiation and electrophilic substitution of aromatic tertiary amides is an efficient methodology for the synthesis of a wide variety of polysubstituted aromatics and heteroaromatics.[1] In approaches developed primarily by Snieckus and coworkers, annelation of the aromatic ring to carbocyclic and heterocyclic derivatives is achieved by introduction of an ortho substituent which bears a nucleophilic site that is used to complete the cycle by addition to the amide.[2] We wish to report a sequence which begins with ortho lithiation and involves annelation of the ring by incorporation of a dienophile into an isobenzofuran. Synthetically, this approach allows fusion of four differently substituted atoms onto the aromatic ring with stereochemical control at two sites. Mechanistically, it appears to involve the previously unreported 2-azaisobenzofuran system.

The sequence begins with the formation of the 2-diazo derivative **2** in 70% yield via ortho lithiation of *N*,*N*-diisopropylbenzamide (**1**) followed by formylation, addition of hydrazine, and oxidation. Reaction of **2** in the presence of a catalytic amount of $Cu(acac)_2$ and 1.5 equivalents of a dienophile gives the substituted products **3**-**7** as shown in Scheme I and Table I.[3]

Scheme I

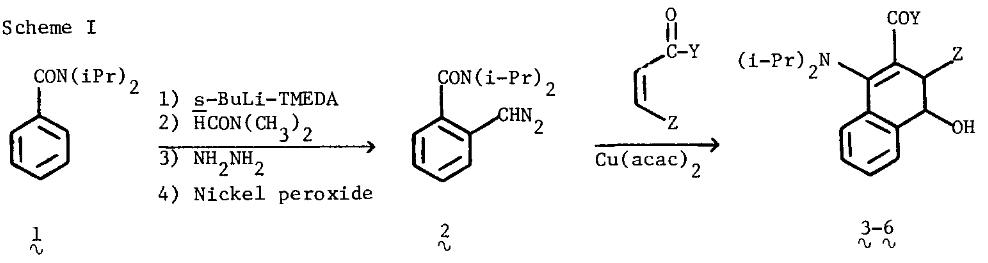
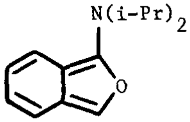
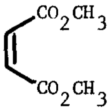
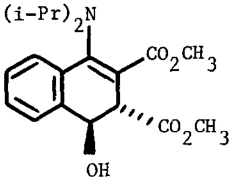
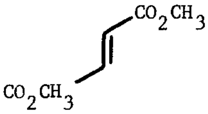
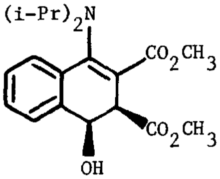
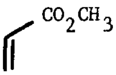
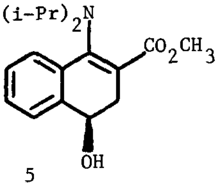
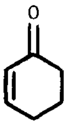
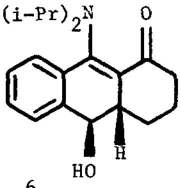
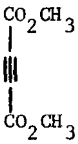
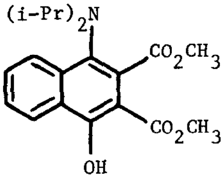
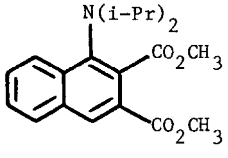


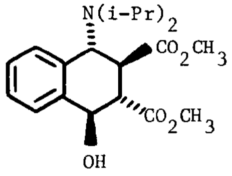
Table I - Products from the Reaction of 11 with Dienophiles

Diene	Dienophile	Product	Yield
 11		 3	75%
11		 4	43%
11		 5	52%
11		 6	33%
11		 7	28%

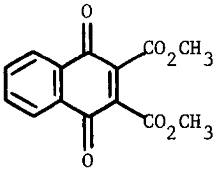
The stereochemistry of 6 is assigned on the basis of a coupling constant of 13 Hz for the benzylic proton, which indicates that endo addition is favored. The stereochemical assignments made to 3 and 4 are based on that assumption. Conversions of 3 to 8, 9 or 10 can be carried out by treatment with $NaHCO_3$, Zn/HOAc/CH_3OH or Collins oxidation - silver (II) oxide, respectively, in the yields indicated.



8 (86%)



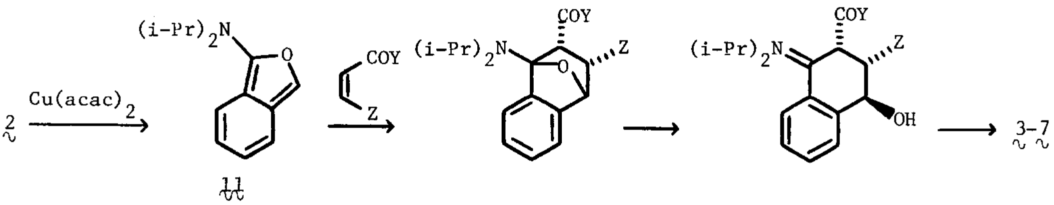
9 (52%)



10 (5%)

The mechanism of formation of 3-7 can be rationalized by the formation of 2-N,N-diisopropylazaisobenzofuran 11 as shown in Scheme II. Circumstantial evidence for the formation of 11 and its concerted cycloaddition to the dienophiles is the stereospecificity of the reactions with dimethyl maleate and dimethyl fumarate. In addition, there is close analogy with the work of Hamaguchi and Ibata, who generate 1-methoxyisobenzofurans as intermediates by a similar approach from methyl-o-diazomethylbenzoate.[4,5] The postulation of 11 appears to be the first of a 2-azaisobenzofuran.[6] The role of the nitrogen in the ring opening is indicated in Scheme II.

Scheme II



In summary, the present approach to annelation of tertiary aromatic amides allows addition of a formyl carbon and a dienophile to complete a six-membered ring. Although the yields are not high, the regio- and stereochemistry is predictable and a novel 1-azaisobenzofuran appears to be involved. The extension of this approach to other systems is under further investigation.

Acknowledgement. We are grateful to the National Institutes of Health for support.

References and Notes

1. Beak, P.; Snieckus, V. Accounts of Chem. Res. (1982), **15**, 306.

2. Snieckus, V. Heterocycles (1980), **14**, 1649. For recent examples see Iwao, M.; Real, J. N.; Snieckus, V. J. Am. Chem. Soc. (1982), **104**, 5531; Harvey, R. G.; Cortez, C.; Jacobs, S. A. J. Org. Chem. (1982), **47**, 2120.

3. **3** - Yellow oil. NMR δ ($CDCl_3$): 7.37-7.27 (m, 4 H), 5.0 (b, s, 1 HO, 4.07 (d, J = 4.7 Hz, 1 H), 3.77 (s, 3 H), 3.65-3.61 (m, 2 H), 2.18 (b, s, 1 H, O-H), 1.10-1.09 (m, 12 H). High Resolution Mass Spectrum: Calc.: 361.1889. Obs.: 361.1886.

   4 - Yellow solid: mp 107-108°C. NMR δ ($CDCl_3$): 7.69-7.27 (m, 4 H), 5.10-5.06 (d,d J = 5.6 and 10.7 Hz, 1 H), 3.94 (d, J = 5.6 Hz, 1 H), 3.86 (d, J = 10 Hz, 10 H), 3.80 (s, 3 H), 3.57 (m, 2 H), 3.52 (s, 3, H), 1.64-1.03 (m, 12 H). Mass Spectrum: M^+ = 361. Anal. Calc. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.42; N, 3.91. IR (KBr): 3555, 1719 cm^{-1}.

   5 - Yellow solid: mp = 85-86°C. NMR δ ($CDCl_3$): 7.75-7.26 (m, 4 H), 4.74 (b, s, 1 H), 3.78 (s, 3 H), 3.56-3.52 (m, 2 H), 2.81 (d, 2 H, J = 5.8 Hz), 1.11-1.07 (m, 12 H). Mass Spectrum: M^+ = 303. Anal. Calc. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.12; H, 8.42; N, 4.39. IR (KBr): 3470, 1760 cm^{-1}.

   6 - Red oil. NMR δ ($CDCl_3$): 7.86-7.27 (m, 4 H), 4.53 (d, J = 13.1 Hz, 1 H), 3.46-3.39 (m, 2 H), 2.76-1.41 (m, 7 H), 1.16 (d, 6 H, J = 6.3 Hz), 0.96 (d, 6 H, J = 6.3 Hz). High resolution Mass Spectrum Calc. for $C_{20}H_{27}NO_2$ 313.2042. Obs: 313.2026. IR (Neat): 3360, 1680, 1660 cm^{-1}.

   7 - Colorless oil. NMR δ ($CDCl_3$) = 12.14 (s, 1 H), 8.45-7.64 (m, 4 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 3.85-3.70 (m, 2 H), 1.12-0.94 (m, 12 H). Mass Spectrum: M = 359. Anal. Calc. for $C_{20}H_{25}NO_2$: C, 66.83; H, 7.01; N, 4.00. Found: C, 66.70; H, 7.04; N, 3.72.

4. Hamaguchi, M.; Ibata, T. Chemistry Letters (1976), 287, for recent work on 1-alkoxyisobenzofurans see Makhlouf, M. A.; Rickborn, B. J. Org. Chem. (1982), **46**, 2734.

5. See Taylor, K. G. Tetrahedron (1982), **38**, 2751.

6. Friedrickson, W. Adv. Heterocyclic Chem. (1980), **26**, 135.

(Received in USA 4 April 1983)