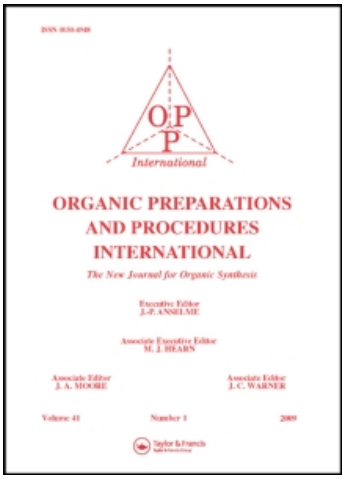

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[2+2] CYCLOADDITIONS OF BENZOFURAN-3(2H)-ONE ENAMINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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[2+2] CYCLOADDITIONS OF BENZOFURAN-3(2H)-ONE ENAMINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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(05/01/00)

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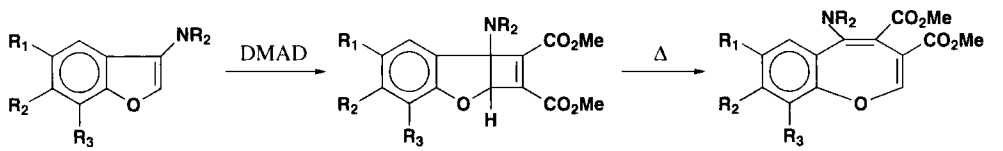
[2+2]Cycloaddition reactions have been used for the ring expansion by two-carbon atoms.[1] The reactions of enamines derived from cyclic ketones with activated acetylenes via cycloadditions involve the formation of fused cyclobutene adducts which may then undergo thermal isomerization to yield two carbons-enlarged rearrangement products.[2] Different cyclic products can be obtained by modifying the structure of the cyclic enamine and of the acetylene. We were interested in the synthesis of enamines derived from substituted benzofuran-3(2H)-ones[3] which might react similarly with electron-deficient acetylenes to yield [2+2]cycloadducts and then isomerize to substituted 1-benzoxepins. Even though, seven-membered heterocycles with 8π electrons have been synthesized, 1-benzoxepins belong to a class of little known heterocycles which have proved difficult to prepare. Herein we describe the [2+2]cycloaddition reaction of enamines of substituted benzofuran-3(2H)-one with dimethyl acetylenedicarboxylate (DMAD) in benzene and methanol.

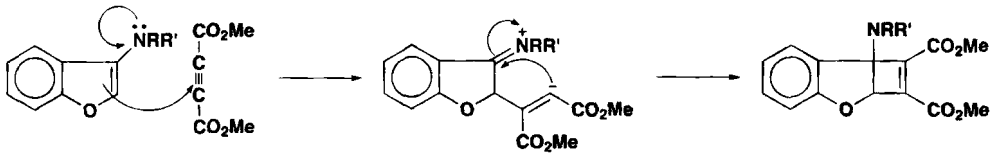


1 2 3

a) NR_2 = pyrrolidine, R_1 = H, R_2 = OCH_3, R_3 = H
b) NR_2 = pyrrolidine, R_1 = CH_3, R_2 = H, R_3 = H
c) NR_2 = pyrrolidine, R_1 = Cl, R_2 = H, R_3 = Cl
d) NR_2 = morpholine, R_1 = Cl, R_2 = H, R_3 = Cl

In previous sudies,[1b,2-4] it had been reported that the majority of the fused cyclobutene adducts synthesized are unstable and spontaneously undergo thermal rearrangement to yield the corresponding two carbons-enlarged cyclic products. Besides the structure of the enamines and the type of the acetylenes, the polarity of the solvent influences the course of the reaction. Whereas fused cyclobutene adducts are formed in a non polar solvent such as benzene, the expected products of the [2+2]cycloaddition reaction are usually pyrrolizine derivatives in polar solvents such as methanol.[4]

In this study, the cycloaddition of pyrrolidine and morpholine enamines of substituted benzofuran-3(2H)-ones (**1a-d**) with equimolar amounts of DMAD at 0° resulted in the formation of the corresponding fused cyclobutene adducts (**2a-d**) both in benzene and in methanol solutions.[5] The cyclobutene derivatives (**2a-d**) were then thermally isomerized to yield 1-benzoxepins (**3a-d**) by reflux in dioxane. Even though the solvent polarity did not alter the course of the reaction, methanol seemed to be a better solvent than benzene to stabilize the 1,4-dipolar intermediate; thus, for all the enamines used, the [2+2]cycloaddition reaction reached completion more rapidly in methanol.



The ability of the pyrrolidine group to supply electrons is greater than that of morpholine so that pyrrolidine moiety increased the electron density of the β-carbon atom of the enamine more effectively thus leading to a more facile nucleophilic attack on the triple bond of the electron-deficient acetylene. Thus, the cycloaddition reaction of 5,7-dichloro-3-(N-morpholinyl)benzofuran (**1d**) with DMAD required a longer time than the reaction of 5,7-dichloro-3-(N-pyrrolidinyl)benzofuran (**1c**) under the same reaction conditions (see Table).

The "olefinic" proton in benzofuran-3(2H)-one enamines (**1a-d**) appeared together with the aromatic protons in the NMR spectrum. Besides the other spectral data, the formation of the stable fused cyclobutene derivatives (**2a-d**) was easily confirmed by the appearance of a characteristic bridgehead proton around δ 4.5 in the NMR spectra. This characteristic peak disappeared and a new olefinic proton peak appeared near the aromatic protons in the NMR spectra of the 1-benzoxepins (**3a-d**).

TABLE. Yields, mps and Reaction Times of Compounds **2-3**

Cmpd	Time (solvent)	Temp (°C)	mp. (°C)	Yield (%)
2a	24 h (in methanol); 48 h (in benzene)	RT	60	40
2b	24 h (in methanol); 48 h (in benzene)	RT	75	35
2c	48 h (in methanol); 144 h (in benzene)	RT	oil	48
2d	72 h (in methanol); 192 h (in benzene)	RT	oil	55

TABLE. Continued...

Cmpd	Time (solvent)	Temp (°C)	mp. (°C)	Yield (%)
3a	2 h (in dioxane)	Reflux	55	90
3b	2 h (in dioxane)	Reflux	40	85
3c	2 h (in dioxane)	Reflux	oil	67
3d	2 h (in dioxane)	Reflux	oil	75

EXPERIMENTAL SECTION

All reactions were performed under nitrogen atmosphere. All solvents were carefully purified and dried by standard methods. IR spectra were obtained on a Hitachi 270-30 spectrometer as potassium bromide pellet; absorption maxima are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on either Varian EM 360L 60 MHz NMR spectrometer or a Bruker 80 AC NMR spectrometer; $CDCl_3$ was the solvent and tetramethylsilane (TMS) was used as the internal standard. Chemical shifts are reported in ppm (δ) downfield from the signal of TMS. GCMS spectra were recorded on 5890 Series 2 Gas Chromatography, 5971 Series Mass Selective Detector Combine System and gave a parent peak and other fragmentations in agreement with the proposed structures. Melting points were determined with an Electrothermal melting point apparatus.

6-Methoxy-3-(N-pyrrolidinyl)benzofuran(**1a**),5-methyl-3-(N-pyrrolidinyl)benzofuran (**1b**), 5,7-dichloro-3-(N-pyrrolidinyl)benzofuran(**1c**) and 5,7-dichloro-3-(N-morpholinyl) benzofuran (**1d**) were prepared as described previously.[3]

General Procedure for the Reaction of Enamines (1a-d) with DMAD.- A solution of DMAD (1.0 mL, 8.14 mmol) in 30 mL benzene was added over a period of 1h to a solution of **1a-d** (7.39 mmol) in 30 mL of benzene at 0°. The reaction mixture was stirred for the given time interval (as in the Table) at room temperature and the reaction times were determined using TLC. Then the solvent and excess DMAD were removed under reduced pressure.

All reactions were repeated in methanol as the solvent.

Dimethyl 5-Methoxy-7b-(N-pyrrolidinyl)cyclobuta[b]benzofuran-1,2-dicarboxylate (2a).- The crude product was purified by fractional elution on silica gel and methanol as solvent at –15°.[6] MS (70 ev): 359 (M^+); IR (KBr): 3050, 1750, 1650, 1050 cm^{-1}; ^1H NMR: δ 7.8-7.5 (m, 3H, ArH), 4.7 (s, 1H, H-2a), 4.0 (s, 3H, $COOCH_3$), 3.9 (s, 3H, $COOCH_3$), 3.6 (s, 3H, Ar-OCH_3), 3.2 (m, 4H, NCH_2), 2.1 (m, 4H, $NCH_2\mathbf{CH_2}$).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89. Found: C, 63.50; H, 5.89

Dimethyl 6-Methyl-7b-(N-pyrrolidinyl)cyclobuta[b]benzofuran-1,2-dicarboxylate (2b).- The crude product was purified by fractional elution on silica gel and methanol as solvent at –15°. MS (70 ev): 343 (M^+); IR (KBr): 3100, 1700, 1600, 1050 cm^{-1}; ^1H NMR: δ 7.6-7.0 (m, 3H, ArH), 4.2 (s, 1H, H-2a), 3.8 (s, 3H, $COOCH_3$), 3.4 (s, 3H, $COOCH_3$), 3.1 (m, 4H, NCH_2), 2.3 (s, 3H, Ar-CH_3), 1.8 (m, 4H, $NCH_2\mathbf{CH_2}$).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16. Found: C, 66.36; H, 6.21

Dimethyl 4,6-Dichloro-7b-(N-pyrrolidinyl)cyclobuta[b]benzofuran-1,2-dicarboxylate (2c).- Column chromatography of the residue [silica gel, hexane-ethyl acetate (2:1)] afforded pure **2c**. MS (70 ev): 398 (M^+); IR (KBr): 3100, 1730, 1620, 1080 cm^{-1}; ^1H NMR: δ 7.6-7.2 (m, 2H, ArH), 4.5 (s, 1H, H-2a), 3.5 (s, 3H, $COOCH_3$), 3.6 (s, 3H, $COOCH_3$), 3.3 (m, 4H, NCH_2), 2.0 (m, 4H, NCH_2 **CH_2**).

Anal. Calcd for $C_{18}H_{17}Cl_2NO_5$: C, 54.29; H, 4.30. Found: C, 54.24; H, 4.40

Dimethyl 4,6-Dichloro-7b-(N-morpholinyl)cyclobuta[b]benzofuran-1,2-dicarboxylate (2d).- Column chromatography of the residue [silica gel, hexane-ethyl acetate (1:1)] afforded pure **2d**. MS (70 ev): 414 (M^+); IR (KBr): 3100, 1740, 1650, 1080 cm^{-1}; ^1H NMR: δ 7.5-6.8 (m, 2H, ArH), 4.6 (s, 1H, H-2a), 3.8 (s, 3H, $COOCH_3$), 3.7 (s, 3H, $COOCH_3$), 3.6 (m, 4H, NCH_2), 2.8 (m, 4H, NCH_2 **CH_2**O).

Anal. Calcd for $C_{18}H_{17}Cl_2NO_6$: C, 52.19; H, 4.13. Found: C, 52.29; H, 4.08

General Procedure for the Thermal Rearrangement of Cyclobutene Adducts (2a-d).- A solution of 0.5 g of compound **2a-d** in 50 mL dioxane was refluxed for 2h and the solvent was removed under reduced pressure.

Dimethyl 8-Methoxy-5-(N-pyrrolidinyl)-1-benzoxepin-3,4-dicarboxylate (3a).- The partly crystalline residue was recrystallized from petroleum ether to give pure **3a**. MS (70 ev): 359 (M^+); IR (KBr): 3080, 1750, 1650, 1050 cm^{-1}; ^1H NMR: δ 7.2 (s, 3H, ArH), 6.5 (m, 1H, H-2), 3.9 (s, 3H, $COOCH_3$), 3.7 (s, 3H, $COOCH_3$), 3.5 (s, 3H, Ar-OCH_3), 3.3 (m, 4H, NCH_2), 1.9 (m, 4H, NCH_2 **CH_2**).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89. Found: C, 63.45; H, 5.94

Dimethyl 7-Methyl-5-(N-pyrrolidinyl)-1-benzoxepin-3,4-dicarboxylate (3b).- The crude product was purified by fractional elution on silica gel and methanol as solvent at –15°. MS (70 ev): 343 (M^+); IR (KBr): 3050, 1720, 1620, 1050 cm^{-1}; ^1H NMR: δ 7.5-6.9 (m, 3H, ArH), 6.8 (m, 1H, H-2), 4.2 (s, 3H, $COOCH_3$), 3.7 (s, 3H, $COOCH_3$), 3.2 (m, 4H, NCH_2), 2.2 (s, 3H, Ar-CH_3), 1.8 (m, 4H, NCH_2 **CH_2**).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16. Found: C, 66.48; H, 6.11

Dimethyl 7,9-Dichloro-5-(N-pyrrolidinyl)-1-benzoxepin-3,4-dicarboxylate (3c).- Column chromatography [silica gel, hexane-ethyl acetate (3:1)] of the crude product gave pure **3c**. MS (70 ev): 398 (M^+); IR (KBr): 3100, 1750, 1650, 1050 cm^{-1}; ^1H NMR: δ 7.3-7.1 (m, 3H, ArH+H-2), 4.7 (s, 3H, $COOCH_3$), 4.5 (s, 3H, $COOCH_3$), 4.3 (m, 4H, NCH_2), 3.7 (m, 4H, NCH_2 **CH_2**).

Anal. Calcd for $C_{18}H_{17}Cl_2NO_5$: C, 54.29; H, 4.30. Found: C, 54.09; H, 4.40

Dimethyl 7,9-Dichloro-5-(N-morpholinyl)-1-benzoxepin-3,4-dicarboxylate(3d).- Column chromatography [silica gel, hexane-ethyl acetate (3:1)] of the crude product gave pure **3d**. MS (70 ev): 414 (M^+); IR (KBr): 3070, 1780, 1630, 1020 cm^{-1}; ^1H NMR: δ 7.3-7.1 (m, 3H, ArH+H-2), 3.7 (s, 3H, $COOCH_3$), 3.5 (s, 3H, $COOCH_3$), 3.3 (m, 4H, NCH_2), 2.7 (m, 4H, NCH_2 **CH_2**O).

Anal. Calcd for $C_{18}H_{17}Cl_2NO_6$: C, 52.18; H, 4.14. Found: C, 52.01; H, 4.24

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SELECTIVE CATALYTIC OXIDATION OF ALCOHOLS USING HYDROGEN PEROXIDE

Submitted by (06/13/00)

J. H. Wynne, C. T. Lloyd, D. R. Witsil, G. W. Mushrush and W. M. Stalick*

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The incorporation of a variety of aldehydes in the synthesis of many biologically active molecules is well documented.[1] There are many examples in the current literature, which employ copper or chromium salts that are either low yielding, non-atom economical, require complex starting materials, or involve multi-step syntheses.[2] Larock states that most general aldehyde forming oxidation reactions require stoichiometric quantities of an inorganic oxidant and proceed under non-neutral or extreme thermal conditions and therefore limit the substrates that can be subjected to oxidative processes.[3] Although much attention has been given to the use of catalytic organometallic ruthenium species in the oxidation process, most are ineffective on aliphatic alcohols, frequently leading to over-oxidation to the carboxylic acids.[4] Drago made use of an oxotriruthenium complex oxidation catalyst,