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SYNTHESIS OF SUBSTITUTED BENZOFURAN3(2H)ONE ENAMINES

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Abstract: The first examples of substituted 3-(1-pyrrolidinyl)benzofurans and 3-(1-morpholinyl)benzofuran were successfully synthesized from the reactions of secondary heterocyclic amines and substituted benzofuran3(2H)ones.

INTRODUCTION

Enamines have been synthetically important intermediates since 1954[1] and their chemistry has been extensively reviewed[2]. Several medium sized heterocycles such as 1,3-thiazepins[3], dihydrothiepins[4] and 1-benzoxepin[5] can be successfully prepared via ring enlargement with two carbon atoms starting from enamines[6]. We were interested in exploring the reactivity of enamine derivatives of substituted benzofuran3(2H)ones (2 and 3) which may similarly undergo [2+2] cycloadditions with activated acetylenes for the synthesis of substituted 1-benzoxepins. We now report the syntheses of enamines of some substituted benzofuran3(2H)ones.

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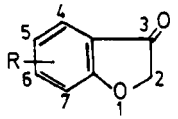

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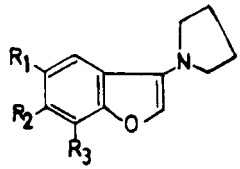
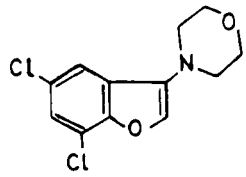


2

a) $R_1, R_3 = H$ $R_2 = OMe$
b) $R_1, R_3 = Cl$ $R_2 = H$
c) $R_1 = CH_3$ $R_2, R_3 = H$



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The syntheses of such systems require the corresponding benzofuran3(2H)ones (1) as starting materials. Benzofuran3(2H)ones comprise an important class of natural products[7] with a wide spectrum of biological activity[8]. Thus, they have been the focus of attention up to date.

RESULTS AND DISCUSSION

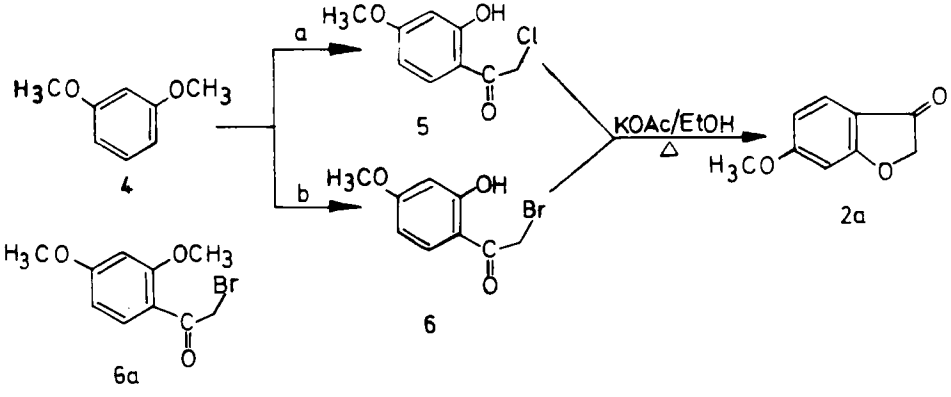
In this study, the effects of benzene substituents and secondary cyclic amines on enamine formation were examined[9].

Benzofuran3(2H)ones polymerize by self condensation, are hard to store for long periods, and that when both hydrogen atoms of the 2-methylene group are replaced, there is a marked increase in stability; in fact, no naturally occuring benzofuran3(2H)one has hydrogen at position 2[10]. Many different syntheses for benzofuran3(2H)ones have been reported[11], but they were in low yields.

In our study, 5,7-dichlorobenzofuran3(2H)one (2b) was prepared by an unambigous literature method, starting with 2,4-dichlorophenol[11a]. An increase in

product yield from 45% to 70% was observed when the compound was purified by fractional elution using methanol[12, 13].

6-Methoxybenzofuran3(2H)one (2a) was prepared as described by Blom and Tambor[11c]. The synthesis includes acylation of dimethoxyresorcinol and structure 6a was reported as the product of this step while we have obtained compound 6. When the same reaction procedure was repeated by using α-chloroacetyl chloride instead of α-bromoacetyl bromide, compound 5 was obtained. The compounds 5 and 6 were characterized from ^{1}H-NMR and elemental analysis data which suggested that one of the methoxy groups on benzene ring in compound 4 was hydrolysed.



a) $ClCH_2COCl, AlCl_3$ b) $BrCH_2COBr, AlCl_3$

The attempts to cyclize 5 and 6 to the corresponding benzofuran3(2H)one (2b) without using potassium acetate were unsuccessful.

During the course of our investigation, the enamines were prepared by mixing 5:1 ratio of secondary amine and a substituted benzofuran3(2H)one over 4A

molecular sieves under inert atmosphere. This procedure is similar to a literature method where secondary amines were reacted with aldehydes[14]. Further experimental studies that employ CaH_2 for the destruction of water rather than its immobilization with molecular sieves are undertaken[15].

Different results were obtained in enamine syntheses. Compound 3 was the only morpholinyl derivative which could be obtained. This may be attributed to both the structure and steric hindrance of the carbonyl group, and the basicity and steric hindrance of secondary amines. The electron withdrawing effect of the two chlorine groups in 5,7-dichlorobenzofuranone enhances the electrophilicity of the carbonyl carbon to promote the enamine formation. On the other hand, the electrophilicities of carbonyl carbons in 6-methoxybenzofuranone and 5-methyl benzofuranone are reduced by the electron-donating substituents, methoxy and methyl groups, respectively. In addition, longer reaction time was necessary when the electron-donating effect of the substituent is higher. 5-Methyl-3-(1-pyrrolidinyl)benzofuran was prepared in 3 days at room temperature, and 4 days were necessary for the synthesis of 6-methoxy-3-(1-pyrrolidinyl)benzofuran, whereas the reaction between 5,7-dichlorobenzofuranone and pyrrolidine took place only in 45 minutes. The results are given in Table 1.

Besides the effect of the carbonyl group, the structures of the secondary amines used, can be discussed. The free electron pair on pyrrolidine nitrogen has a stronger nucleophilic effect than the electron pair of morpholine nitrogen. The steric hindrance of the amine is also important. Morpholine is a larger molecule

Table 1: Yields, mps and elemental analysis data of 2a-c and 3.

Comp	R_1	R_2	R_3	Time	mp(°C)	Yield (%)
2a	H	OCH_3	H	3 days (room temp.)	oil	55
2b	Cl	H	Cl	45 min (room temp.)	78-80	77
2c	CH_3	H	H	4 days (room temp.)	oil	60
3	Cl	H	Cl	5 hr (reflux)	53-55	70

than pyrrolidine that it is less reactive. The reaction between 5,7-dichloro-benzofuran3(2H)one and pyrrolidine was realized at room temperature in 45 minutes but morpholine enamine was obtained under reflux conditions in 5 hours. When the IR and NMR spectra of the enamines were compared, the olefinic proton in enamines replaced the CH_2 peak at position 2- of benzofuranones. The characteristic peak of hydrogens at C-2 for 3-substituted benzofurans is at δ: 7.42 ppm, whereas for 3-(1-pyrrolidinyl)benzofuran is at δ: 6.89 ppm. The enamine character of 3-(1-pyrrolidinyl)benzofuran can be understood from the chemical shift of the olefinic proton in NMR spectrum. Pyrrolidine group donates electrons to the ring, increasing the electron density and the olefinic peak shifts to higher field. In our study, the two chlorine groups reduced the electron density and the

Table 2 : 1H-NMR and IR data of 2a-c and 3.

Comp	^{1}H-NMR (δ) (ppm)	IR (C=C) (ν, cm^{-1})
2a	7.3 (s, 3H, PhH), 6.6 (s, 1H, H-2), 3.8 (s, 1H, OCH_3), 3.0 (t, 4H, NCH_2), 1.75 (t, 4H, NCH_2CH_2).	1720
2b	7.3-7.9 (m, 2H, PhH), 7.1 (s,1H, H-2),3.2 (m, 4H, NCH_2) 2.0 (m, 4H, NCH_2CH_2).	1740
2c	7-7.8 (m, 3H, PhH), 6.9 (s, 1H, H-2), 3.2 (m, 4H, NCH_2), 2.3 (s, 3H, CH_3), 1.9 (m, 4H, NCH_2CH_2).	1720
3	7.3-7.8 (m, 2H, PhH), 7.2 (s, 1H, H-2), 3.8(m, 4H,NCH_2) 2.9 (m, 4H, NCH_2CH_2).	1620

olefinic peak shifted to lower field (δ: 7.10 ppm), where the aromatic protons appear. The olefinic peak of 5,7-dichloro-3-(1-morpholinyl) benzofuran was at δ:7.20 ppm which shows that pyrrolidine group strengthens the enamine character more effectively than morpholine. Methoxy group in 6-methoxy-3-(1-pyrrolidinyl)benzofuran increased the electron density, thus, the olefinic proton appeared at δ: 6.65 ppm. Methyl group is a weaker electron donor than methoxy group and the olefinic proton of 5-methyl-3(1-pyrrolidinyl)benzofuran appears close to its normal value (δ: 6.90 ppm).

In IR spectra of enamines, the carbonyl bands of benzofuranones at around 1700 cm^{-1},(For 5,7-dichlorobenzofuran3(2H)one ν:1740cm^{-1}; for 6-methoxybenzofuran

3(2H)one ν: 1680 cm^{-1} ; for 5-methylbenzofuran3(2H)one ν:1730 cm^{-1}) were replaced by C=C double bond bands at around 1600 cm^{-1}. The NMR and IR data of the compounds synthesized, are given in Table 2.

EXPERIMENTAL

All operations were carried out under a nitrogen atmosphere. All glassware were oven dried and cooled to room temperature under nitrogen flux before use. Solvents were purified by the known methods, prior to use. ^{1}H-NMR spectra were recorded on a Varian EM 360 L at 60 MHz with deuteriochloroform and carbontetrachloride as the solvents and TMS as the internal standard. Peak multiplicities were abbreviated as follows: singlet, s; triplet, t; multiplet, m. Chemical shifts (δ) were expressed in ppm downfield from TMS. IR spectra were obtained on a Hitachi 270-30 spectrometer as potassium bromide pellet and absorbtion maxima were reported in wavenumbers (cm^{-1}). All the enamines are fairly unstable species and they decompose partly during crystallization. Therefore we have purified them by fractional elution[12,13]. GCMS spectra were recorded on 5890 Series 2 Gas Chromotography, 5971 Series Mass Selective Detector Combine System and gave a parent peak and other fragmentations in agreement with the proposed structures. All melting points were recorded in sealed capilleries and were uncorrected.

For the synthesis of substituted benzofuran3(2H)ones, see ref[11a,b,c,d]. The second step for the synthesis of 6-methoxybenzofuran3(2H)one, the acylation of

dimethoxyresorcinol using α-bromoacetyl bromide, is given below:

1-(ω-Bromoacetyl)-2-hydroxy-4-methoxybenzene (6)

This compound was synthesized by the literature method[11c] in 36% yield, mp. 100-101°, IR: 3300, 3100-2950, 1680, 1600-1450 cm^{-1}. ^{1}H-NMR: δ 12.2 (s, 1H, OH), 6.5-7.5 (m, 3H, PhH), 4.5 (s, 2H, CH_2Br), 3.9 (s, 3H, OCH_3).

1-(ω-Chloroacetyl)-2-hydroxy-4-methoxybenzene (5)

This compound was synthesized by the same method[11c] in 55% yield by using α-chloroacetyl chloride instead of α-bromoacetyl bromide, mp. 107-108°, IR: 3300, 3100-3000, 1680, 1600-1450 cm^{-1}. 1H-NMR: δ 12.1(s, 1H, OH), 6.5-8.2 (m, 3H, PhH), 4.8(s, 2H, CH_2Cl), 3.9 (s, 3H, OCH_3).

Typical procedure for 2a-c: 5,7-Dichloro-3-(1-pyrrolidinyl)benzofuran (2b)

A mixture of 5,7-dichloro3(2H)benzofuranone (0.5 g,0.004 mol) and pyrrolidine (1.5 g, 0.02 mol), molecular sieves(4A) was stirred for 45 minutes under nitrogen atmosphere at room temperature. The mixture was filtered and solvent was removed under reduced pressure. The solid was purified by fractional elution at -15° using methanol to give 0.49 g (77%) of 2b.

5,7-Dichloro-3-(1-morpholinyl)benzofuran (3)

This compound was prepared as above by using 0.21 g (0.003 mol) 5,7-dichlorobenzofuran3(2H)one. The only difference was that the reaction mixture was refluxed for 5 hours under nitrogen atmosphere to give a solid. It was then purified by using fractional elution at -15° using methanol.

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REFERENCES

1. Stork, G. , Brizzolara, A. , Landesman, H. , Szmuszkovicz, J. and Terrel, R. , J. Am. Chem. Soc. , 1963, 85, 207.
2. Cook, A. G. , " Enamines: Synthesis, Structure and Reactions", Marcel Dekker, London, 1969; Dyke, S. F. , "The Chemistry of Enamines", Cambridge Chemistry Texts, Cambridge, 1973.
3. Reinhoudt, D. N. , Recl. Trav. Chim. Pays-Bas, 1973, 92, 20.
4. Reinhoudt, D. N. and Kouwenhoven, C. G. , Recl. Trav. Chim. Pays-Bas, 1973, 92, 865.
5. a) Reinhoudt, D. N. and Kouwenhoven, C. G. , Recl. J. Royal Netherlands Chem. Soc. , 1974, 93/5, 129. b) Reinhoudt, D. N. and Kouwenhoven, C. G. , Tetrahedron Lett. , 1972, No: 51, 5203.
6. Reinhoudt, D. N. and Leliveld, C. G. , Tetrahedron Lett. , 1972, No: 31, 3119.
7. a) Padwa, A. , Dehm, D. , Oine, T. , Lee, G. A. , J. Am. Chem. Soc. , 1975, 97, 1837. b) Fukagawa, T. , Fujiwara, Y. , Taniguchi, H. , J. Org. Chem. , 1982, 47, 2491. c) Hillery, P. S. , Cohen, L. A. , J. Org. Chem. ,1983, 48, 3465. d) Coppola, G. M. , J. Heterocycl. Chem. , 1981, 18, 845.
8. a) Rathore, H. G. S. , Reddy, V. M. , J. Indian Chem. Soc. , 1984, 61, 556. b) Weston, A. W. , Brownwell, W. B. , J. Am. Chem. Soc. , 1952, 74, 653. c) Tegeler, J. J. , Diamond, C. J. , Wilker, J. C. , Kruse, H. , Spauldung, T. C. , Helsley, G. C. , J. Pharm. Sci. , 1985, 74, 44.
9. Tunoğlu, N. , PhD Thesis, Hacettepe University, Ankara, 1990.
10. Mustafa, A. , " Benzofurans", Copyright by John Wiley and Sons, 1974, pp. 210-246.
11. a) Stefanye, D. and Howard, W. L. , J. Org. Chem. , 1955, 20, 813. b) Friez, K. and Finck, G. , Ber. , 1958, 41, 4271. c) Blom, A. and Tambor, J. , Ber. , 1905, 38, 3589. d) Carbon, J. A. and Fosdick, L. S. , J. Am. Chem. Soc. , 1956, 78, 1504.
12. Trompen, W. P. and Geevers, J. , Recl. Trav. Chim. Pays-Bas, 1976, 95, 106.
13. Buehler, C. A. and Pearson, D. E. , "Survey of Organic Syntheses", Wiley - Interscience, New York, Vol.2, pp. 913.
14. Singaram, B. , Goralski, C. T. and Fisher, G. B. , J. Org. Chem. , 1991, 56, 5691.
15. Fisher, G. B. , Lee, L. and Kettke, F. W. , Synth. Commun. , 1994, 24(11), 1541.

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