A FACILE SYNTHESIS OF 4-ARYL-2H-1,4-BENZOTHIAZIN-3(4H)-ONES: REACTION OF N,N-DIARYLACETAMIDES WITH THIONYL CHLORIDE

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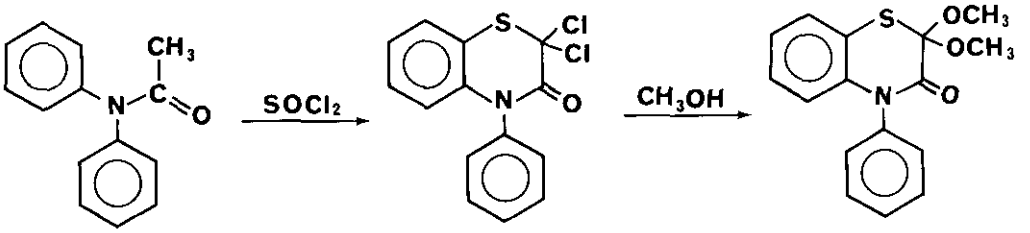
Abstract—The reaction of N,N-diarylacetamides with thionyl chloride yielded 4-aryl-2,2-dichloro-2H-1,4-benzothiazin-3(4H)-ones, which reacted with methanol to give 2,2-dimethoxy derivatives in good yield.

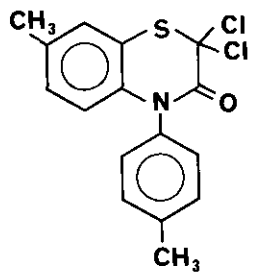
2H-1,4-Benzothiazin-3(4H)-ones are prepared by the condensation of 2-aminobenzenethiols with 2-haloacetic acids,[1] glycidyl esters,[2] or α,β-unsaturated acids,[3] or by the reductive cyclization of 2-nitrobenzenethioglycolic acids.[4] Here we wish to report a new synthetic method for 2H-1,4-benzothiazin-3(4H)-ones from N,N-diarylacetamide derivatives.

A solution of N,N-diphenylacetamide 1 (2.11 g, 10 mmol) in 20 ml of thionyl chloride was stirred at 50 °C, and the reaction was checked by ^{1}H NMR spectroscopy. After stirring for 25 h, just a trace of the acetamide remained, and the excess of thionyl chloride was removed under reduced pressure, and the residue was dissolved in benzene, and the insoluble material was removed by filtration. Evaporation of the solvent gave 2.45 g of 2a as a yellow solid.[5] Treatment of 2a with methanol for 24 h at ambient temperature, column chromatograph on silica gel (benzene), followed by recrystallization from carbon tetrachloride afforded pure

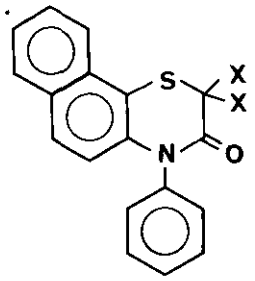


1 2a 2b

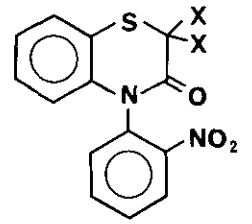
2,2-dimethoxy-4-phenyl-2H-1,4-benzothiazin-3(4H)-one 2b as light yellow needles, mp 142-144.5 °C, in 62% yield. The molecular ion peak was observed at m/z 301.0783 (calcd for $C_{16}H_{15}NO_3S$ 301.0773). The infrared spectrum (KBr) showed strong bands at 1690 cm^{-1} (amide carbonyl) and 1100 cm^{-1} (ether). In the ^{13}C NMR spectrum ($CDCl_3$) of 2b, the signals for methoxy carbon (52.0), carbonyl carbon (162.2), quatenary carbon (103.2), and ten aromatic carbons were observed.[6] The 200 MHz ^1H NMR spectrum ($CDCl_3$) showed a sharp singlet (6H) for the methoxy group at δ 3.45 and a characteristic multiplet (1H) for H_5 at δ 6.52. Comparison of the chemical shifts of the aromatic protons of 2H-1,4-benzothiazin-3(4H)-one with those of 2b showed an upfield shift of 0.5-0.6 ppm for H_5 of 2b. The upfield shift of the H_5 protons of 4-aryl-1,4-benzothiazinones is the characteristic feature of the ^1H NMR spectra. The upfield shift may be attributed to the anisotropic effect of the benzene ring attached to the nitrogen atom. The molecular structure of 2b was determined by X-ray crystallography,[7] and the stereochemistry accounts for the upfield shift of H_5 in the ^1H NMR spectrum. Treatment of N,N-bis(4-methoxyphenyl)acetamide 3 with thionyl chloride for 20 h at 55 °C gave the dichloro derivative 4a, which was recrystallized from benzene to yield needles, mp 142 °C, in 60% yield: ^1H NMR ($CDCl_3$, δ) 6.44 (d, J=8.4 Hz). The reaction of N-(2-naphthyl)-N-phenylacetamide 5 with thionyl chloride for 22 h at 60 °C gave 2,2-dichloro-2H-naphtho[1,2-b]-1,4-thiazin-3(4H) one 6a as needles (from benzene), mp 156-158 °C, in 46% yield. The ^1H NMR spectrum showed a half part of AB quartet at δ 6.73 (J=9.1 Hz) for H_5, and was consistent with the naphthothiazine structure. Treatment of the dichloride 6a with methanol resulted in the quantitative formation of the dimethoxy derivative 6b, mp 157-177 °C: ^1H NMR ($CDCl_3$, δ) 6.74 (d, J=9.1 Hz); IR (KBr, cm^{-1}) 1700, 1345, 1110, 750. N-(2-Nitrophenyl)-N-phenylacetamide 7 is less reactive than 1, 3 and 5. After refluxing for 96 h, the excess of thionyl chloride was removed in vacuo. Recrystallization of the residue from benzene yielded a 49% of the dichloride 8a, mp 166-168 °C. The ^1H NMR spectrum of 8a shows the presence of a characteristic aromatic proton at δ 6.52, and indicates that the cyclization occurs on the unsubstituted benzene ring. Treatment of 8a with methanol yielded the dimethoxy derivative 8b, mp 103-105 °C, in quantitative yield. In the ^1H NMR spectrum of 8b, the methoxy protons appear as two sharp singlets (δ 3.35 and 3.50). This may be due to the restricted rotation around the C-N bond.



4a



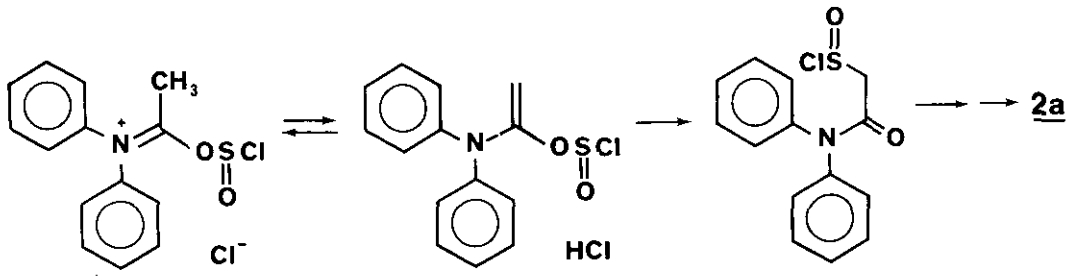
6a,b



8a,b

6,8	X
a	Cl
b	OCH_3

The reaction of diphenylamine derivatives with thionyl chloride has been investigated to give chlorinated diphenylamines and/or phenothiazines,[8,9] and the reaction of 1 with thionyl chloride at reflux temperature gave a quantitative yield of 1,3,7,9-tetrachlorophenothiazine.[9] Under our experimental conditions, however, we could not detect the tetrachloride. The ^{1}H NMR spectrum of 1 in thionyl chloride at 50 °C showed the methyl signal at δ 2.38, and the chemical shift suggested the formation of the O-complex (A).[10] The methyl signal gradually decreased as the characteristic aromatic signal of 2a gradually increased in intensity, and there was no evidence for the presence of any intermediate. The mechanism for the formation of the benzothiazinone may be explained as follows. The O-complex is in equilibrium with the vinyl chlorosulfite (B), which reacts with thionyl chloride to give the chlorosulfinyl compound (C). And the dichlorobenzothiazinone structure forms by the Pummerer-type deoxygenation-chlorination and electrophilic aromatic substitution. An example of the thionation onto the alpha-position to the amide carbonyl group with thionyl chloride has been reported,[11] and a vinyl chlorosulfite was proposed as an intermediate. Detailed mechanistic studies and application of this cyclization are now under investigation.



(A) (B) (C)

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2. C. C. J. Culvenor, W. Davies, and N. S. Heath, J. Chem. Soc., 1949, 278.
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5. IR (KBr, cm^{-1}) 1680, 1320, 880, 750, 710. ^1H NMR ($CDCl_3$, δ) 6.53 (m, 1H), 7.1-7.6 (m, 8H). The yield of the crude product was 70%. We could not obtain an analytically pure sample of 2a by recrystallization from common solvents.
6. Chemical shifts of aromatic carbons of 3a are as follows: 119.7 (d), 120.4 (s), 123.5 (d), 126.9 (d), 128.2 (d), 128.6 (d), 128.6 (d), 129.7 (d), 139.5 (s), 140.4 (s).
7. Crystal data of 2b: monoclinic (from CCl_4), space group $P2_1/C$, a=8.89, b=14.33, c=11.66 A, β=91.0°, and Z=4. The structure was solved by direct method (MULTAN) and refined by a block-diagonal least squared method to R=0.0738.
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9. M. Fujimoto, Bull. Chem. Soc. Jpn., 1959, 32, 296.
10. In the ^1H NMR spectra, the chemical shifts of the methyl protons of 1 in trifluoroacetic acid and in carbon tetrachloride are δ 2.40 and δ 1.90, respectively.
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