A New Synthesis of 1,4-Thiazin-3-ones by a Novel Rearrangement of 1,4-Oxathiins

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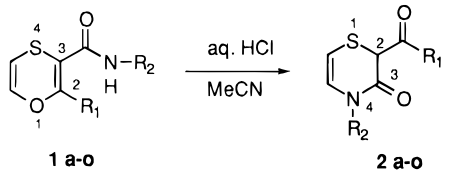
Much of the research in heterocyclic chemistry is concerned with the development of new methods for ring syntheses. There has been an increasing interest over the past several years in the chemistry of 1,4-thiazin-3-one derivatives. This is primarily due to their remarkable spectrum of biological activity. Examples of their biological activity are phospholipase A_2, lipoxygenase and cyclooxygenase inhibitors,[1] protective agents against endotoxin shock,[2] and cardiotonics.[3] However, very few convenient syntheses of 1,4-thiazin-3-ones are currently available.[4] In this study we report a facile, general synthesis of these compounds through an acid-catalyzed rearrangement of 1,4-oxathiins **1**.



1 a-o **2 a-o**

a : R_1 = CH_3, R_2 =phenyl
b : R_1 = CH_3, R_2 = 2-methylphenyl
c : R_1 = CH_3, R_2 = 4-methylphenyl
d : R_1 = CH_3, R_2 = 2-chlorophenyl
e : R_1 = CH_3, R_2 = 4-chlorophenyl
f : R_1 = CH_3, R_2 = 2-methoxyphenyl
g : R_1 = CH_3, R_2 = 4-methoxyphenyl
h : R_1 = CH_3, R_2 = 2-nitrophenyl
i : R_1 = CH_3, R_2 = 2,6-dimethylphenyl
j : R_1 = CH_3, R_2 = 2,4-dimethoxyphenyl
k : R_1 = CH_3, R_2 = 2,4-dimethylphenyl
l : R_1 = CH_3, R_2 = 4-ethylphenyl
m: R_1 = C_6H_5, R_2 =phenyl
n : R_1 = CH_3, R_2 = methyl
o : R_1 = CH_3, R_2 = ethyl

Results and Discussion

The starting 1,4-oxathiin carboxamides **1** were prepared through previously reported methods.[5] Treatment of the 1,4-oxathiin **1a** with concentrated hydrochloric acid (HCl) in acetonitrile (MeCN) at 80 °C for 10 min afforded 2-acetyl-4-phenyl-2*H*-1,4-thiazin-3(4*H*)-one (**2a**) in 70% yield accompanied by a trace of acetoacetanilide (4%). With this initial data in hand we decided to investigate conditions under which this rearrangement proceeds. Thus, a number of solvents were examined with varying concentrations of HCl. For instance, reaction of **1a** with concentrated HCl in MeCN at 80 °C gave the 1,4-thiazin-3-one **2a** in 70% yield, whereas with 10% HCl the yield was somewhat lower (47%). Additionally, product **2a** slowly decomposed to a complex mixture of products and acetoacetanilide. Thus, it is conceivable that very short reaction times and solvent are critical factors in obtaining high yields of the products. Table 1 shows product yield as a function of solvent, acid concentration, reaction temperature, and time. From Table 1 it is clear that MeCN is the solvent of choice, possibly due to the greater solubility of aqueous HCl. Table 2 provides a listing of the various compounds that were prepared, the yields, and melting points.

Table 1. Conversion of 2-Methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (1a) to 2-Acetyl-4-phenyl-2*H*-1,4-thiazin-3(4*H*)-one (2a) with Aqueous Acids

solvent	aqueous acid (%)	temp (°C)	reactn time	yield (%)[a]
benzene	HCl (10)	80	20 h	22
toluene	HCl (10)	110	19 h	4
dixoane	HCl (10)	80	2 h	21
THF	HCl (10)	80	10 h	8
MeCN	HCl (10)	80	1.5 h	47
MeCN	HCl (35)	80	10 min	70
EtOH	HCl (10)	80	30 min	62
MeCN	H_2SO_4 (50)	80	26 min	60

[a] Isolated yield.

Table 2. Conversion of 1,4-Oxathiin 1 to 1,4-Thiazin-3-ones 2 in the Presence of Concentrated HCl in MeCN

compd	R_1	R_2	mp (°C)	yield (%)[a]
2a	CH_3	phenyl	98−99	70
2b	CH_3	2-methylphenyl	oil	77
2c	CH_3	4-methylphenyl	115−117	59
2d	CH_3	2-chlorophenyl	oil	84
2e	CH_3	4-chlorophenyl	oil	55
2f	CH_3	2-methoxyphenyl	oil	100
2g	CH_3	4-methoxyphenyl	96−97	73
2h	CH_3	2-nitrophenyl	oil	69
2i	CH_3	2,6-dimethylphenyl	oil	55
2j	CH_3	2,4-dimethoxyphenyl	oil	53
2k	CH_3	2,4-dimethylphenyl	oil	84
2l	CH_3	4-ethylphenyl	oil	51
2m	C_6H_5	phenyl	127−130	67
2n	CH_3	methyl	oil	69
2o	CH_3	ethyl	oil	18

[a] Isolated yield.

The mechanism for the rearrangement can be explained as follows. Protonation of the amide carbonyl in **3** followed by addition of water[6] resulted in hemiacetal **4** which can undergo a ring-opening to provide **5**. Protonation of the newly formed carbonyl in **6** can result in trapping of the carbenium ion by either the lone pair on nitrogen (path a) or the oxygen of the enol form of the amide (path b).[7] Through path a, the formed animal **7** undergoes dehydration to the 1,4-thiazin-3-one. Since neither **9** or **10** was the observed product, path b can be

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(1) Naka, T.; Hisano, M. JP 02,275,869; *Chem. Abstr.* **1991**, *114*, 185525p.

(2) Yamazaki, H.; Harada, H.; Matsuzaki, K.; Watanabe, T.; Saito, H. *Chem. Pharm. Bull.* **1992**, *40*, 1025.

(3) Takase, M.; Yoshioka, K.; Yamazaki, H. PTC Int. Appl. WO 91 18,893; *Chem. Abstr.* **1992**, *116*, 106323m.

(4) (a) deStevens, G.; Halamandaris, A.; Dorfman, L. *J. Am. Chem. Soc.* **1958**, *80*, 5198. (b) Hojo, M.; Masuda, R.; Kosaka, S.; Nagase, K. *Synthesis* **1979**, 272. (c) Bobek, M. *J. Heterocycl. Chem.* **1982**, *19*, 131.

(5) (a) Hahn, H. G.; Nam, K. D.; Chang, K. H. *J. Korean Chem. Soc.* **1995**, *39*, 127. (b) A new 2,*N*-diphenyl-1,4-oxathiin-3-carboxamide (**1m**) was prepared from the ethyl benzoylacetate using a method[5a] similar to that for the preparation of 2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (**1a**). For **1m**: mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (d, 1H, J = 5.2), 6.49 (d, 1H, J = 5.2), 6.95 (br s, 1H), 7.00−7.51 (m, 10H).

(6) (a) Lee, W. S.; Hahn, H. G.; Nam, K. D. *J. Org. Chem.* **1986**, *51*, 2789. (b) Corbeil, M. A.; Curcumelli-Rodostamo, M.; Fanning, R. J.; Graham, B. A.; Kulka, M.; Pierce, J. B. *Can. J. Chem.* **1973**, *51*, 2650.

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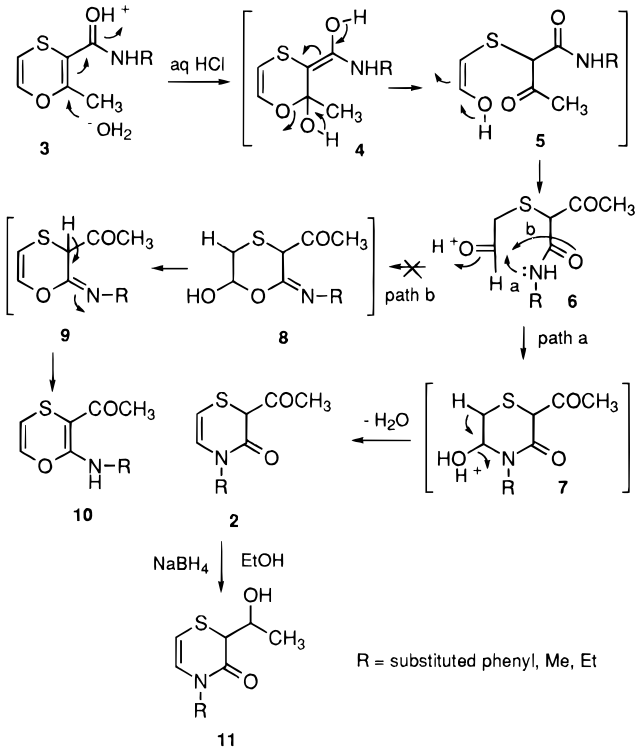
Scheme 1



ruled out. All of these thiazin-3-ones were characterized by their elemental analyses and spectral data (see the Experimental Section for details). As a final confirmation of structure, we subjected **2** to reduction by sodium borohydride. A diastereomeric mixture of products was obtained in an ~3:1 ratio and had spectral features consistent with structure **11**.

An interesting phenomenon was observed for 1,4-thiazin-3-ones **2b** and **2k**, which have ortho substituents in the aromatic nucleus (example R = Me). The products in these cases were obtained as an ~5:4 mixture of two isomers, presumably rotamers, as determined by proton NMR spectroscopy. This is possibly due to the presence of an ortho substituent in the aromatic ring which inhibits free *N*-aryl bond rotation resulting in atropisomers as in the case of substituted biphenyls. However, we have not attempted separation of these isomers.

Experimental Section

Melting points were obtained with an Electrothermal melting point apparatus. All chromatographic isolations were accomplished on silica gel GF 254 (70-230 mesh). All reagents were of commercial quality. *J* values are in hertz.

Preparation of 1,4-Thiazin-3-ones 2. General Procedure. To a solution of 2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (**1a**) (852 mg, 3.6 mmol) in MeCN (20 mL) was added concentrated HCl (10 mL). The solution was placed in an 80 °C oil bath with stirring for 10 min. The reaction mixture was diluted with methylene chloride, washed with a saturated sodium bicarbonate solution and water, and then dried (Na_2SO_4). The solvent was evaporated and the resulting residue was purified by flash chromatography using *n*-hexane/ethyl acetate (7/3) to give 2-acetyl-4-phenyl-2*H*-1,4-thiazin-3(4*H*)-one (**2a**) (596 mg, 70%) as a colorless solid.

2-Acetyl-4-phenyl-2*H*-1,4-thiazin-3(4*H*)-one (2a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.14 (d, 1H, J = 1.7),[8] 5.56 (dd, 1H, J = 1.7, 7.2), 6.44 (d, 1H, J = 7.2), 7.30−7.47 (m, 5H); ^{13}C NMR (78.5 MHz, $CDCl_3$) δ 26.9, 51.4, 96.9, 127.3, 128.6, 129.9, 130.7, 141.2, 161.1, 199.6; IR 1705 (acetyl C=O), 1660 (amide C=O); MS 233 (M^+, 44), 191 ($M^+ - O{=}C{=}CH_2^+$, 100); HRMS for $C_{12}H_{11}NO_2S$ calcd 233.0511, found 233.05213. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.8; H, 4.75; N, 6.00. Found: C, 61.99; H, 4.71; N, 6.00.

2-Acetyl-4-(2-methylphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2b), a mixture of A isomer and B isomer (10:8): isomer A, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.40 (s, 3H), 4.13 (d, 1H, J = 1.8), 5.55 (dd, 1H, J = 1.8, 7.2), 6.28 (d, 1H, J = 7.2), 7.26−7.31 (m, 4H); isomer B, ^{1}H NMR δ 2.36 (s, 3H), 2.41 (s, 3H), 4.21 (d, 1H, J = 1.8), 5.57 (dd, 1H, J = 1.8, 7.2), 6.30 (d, 1H, J = 7.2), 7.26−7.31 (m, 4H); IR 1713 (acetyl C=O), 1670 (amide C=O); MS 247.3 (M^+), 205 ($M^+ - COCH_2^+$); HRMS for $C_{13}H_{13}NO_2S$ calcd 247.0667, found 247.0669.

2-Acetyl-4-(4-methylphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.40 (s, 3H), 4.14 (d, 1H, J = 1.7), 5.53 (dd, 1H, J = 1.7, 7.1), 6.40 (d, 1H, J = 7.1), 7.22−7.27 (m, 4H); IR 1716 (acetyl C=O), 1674 (amide C=O); HRMS for $C_{13}H_{13}NO_2S$ calcd 247.0667, found 247.0667.

2-Acetyl-4-(2-chlorophenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.18 (s, 1H), 5.59 (d, 1H, J = 7.0), 6.25 (d, 1H, J = 7.0), 7.26−7.50 (m, 4H); IR 1715 (acetyl C=O), 1662 (amide C=O); MS 267 (M^+, 26), 225 ($M^+ - COCH_2^+$, 100).

2-Acetyl-4-(4-chlorophenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.13 (d, 1H, J = 1.3), 5.57 (dd, 1H, J = 1.3, 7.3), 6.38 (d, 1H, J = 7.3), 7.26−7.41 (m, 4H); IR 1668 (acetyl C=O), 1662 (amide C=O); MS 267 (M^+, 39), 225 ($M^+ - COCH_2^+$, 100); HRMS for $C_{12}H_{10}NO_2SCl$ calcd 267.0121, found 267.0121.

2-Acetyl-4-(2-methoxyphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.78 (s, 3H), 4.19 (s, 1H), 5.47 (br s, 1H), 6.20 (d, 1H, J = 7.1), 6.92−7.38 (m, 4H); IR 1712 (acetyl C=O), 1666 (amide C=O); MS 263 (M^+, 26), 221 ($M^+ - COCH_2^+$, 100); HRMS for $C_{13}H_{13}NO_3S$ calcd 263.0616, found 263.0617.

2-Acetyl-4-(4-methoxyphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.82 (s, 3H), 4.13 (d, 1H, J = 1.8), 5.52 (dd, 1H, J = 1.8, 7.3), 6.39 (d, 1H, J = 7.1), 6.93−7.23 (m, 4H); IR 1718 (acetyl C=O), 1674 (amide C=O); MS 263 (M^+, 11), 221 ($M^+ - COCH_2^+$, 100), 134 (51), 108 ($C_6H_5OCH_3$); HRMS for $C_{13}H_{13}NO_3S$ calcd 263.0616, found 263.0611.

2-Acetyl-4-(2-nitrophenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.23 (s, 1H), 5.68 (d, 1H, J = 7.0), 6.35 (d, 1H, J = 7.0), 7.10−8.68 (m, 4H); IR 1717 (acetyl C=O), 1672 (amide C=O); MS 278 (M^+, 36), 236 ($M^+ - COCH_2^+$, 100); HRMS for $C_{12}H_{10}N_2O_4S$ calcd 278.0361, found 278.0361.

2-Acetyl-4-(2,6-dimethylphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 and 2.36 (2s, 6H), 2.41 (s, 3H), 4.21 (d, 1H, J = 2.0), 5.63 (dd, 1H, J = 2.0, 7.1), 6.18 (d, 1H, J = 7.1), 7.08−7.17 (m, 3H); IR 1668 (acetyl C=O), 1662 (amide C=O); MS 261 (M^+, 43), 219 ($M^+ - COCH_2^+$, 100); HRMS for $C_{14}H_{15}NO_2S$ calcd 261.0824, found 261.0823.

2-Acetyl-4-(2,4-dimethoxyphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.81 and 3.82 (2s, 6H), 4.28 (br s, 1H), 5.52 (br s, 1H), 6.25 (d, 1H, J = 7.2), 6.50−7.30 (m, 3H); IR 1714 (acetyl C=O), 1676 (amide C=O); MS 293 (M^+, 59), 251 ($M^+ - COCH_2^+$, 96), 138 ($C_6H_4(OCH_3)_2$, 100); HRMS for $C_{14}H_{15}NO_4S$ calcd 293.0722, found 293.0724.

2-Acetyl-4-(2,4-dimethylphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2k), a mixture of A isomer and B isomer (10:8): isomer A, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 and 2.32 (2s, 6H), 2.39 (s, 3H), 4.13 (d, 1H, J = 1.7), 5.55 (dd, 1H, J = 1.7, 6.8), 6.27 (d, 1H, J = 7.2), 7.02−7.26 (m, 3H); isomer B, ^{1}H NMR δ 2.16 and 2.33 (2s, 6H), 2.40 (s, 3H), 4.20 (d, 1H, J = 1.8), 5.52 (dd, 1H, J = 1.8, 6.8), 6.29 (d, 1H, J = 6.8), 7.02−7.26 (m, 3H); HRMS for $C_{14}H_{15}NO_2S$ calcd 261.0824, found 261.0823.

2-Acetyl-4-(4-ethylphenyl)-2*H*-1,4-thiazin-3(4*H*)-one (2l): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.6), 2.40 (s, 3H),

(7) Challis, B. C.; Challis, J. A. *The Chemistry of Amids*; Zabicky, J., Ed.; Interscience Publishers: London, 1970; pp 731−857 and references cited therein.

(8) This coupling was due to long range coupling (^4J) between a methine proton on C-2 and a vinyl proton on C-6. A lone pair of electrons on sulfur can serve as a p donor to the neighboring protons and thereby make ^4J more positive.

5.53 (dd, 1H, J = 1.5, 7.2), 6.42 (d, 1H, J = 7.2), 7.20−7.27 (m, 3H); IR 1720 (acetyl C═O), 1676 (amide C═O); MS 261 (M^+, 41), 219 ($M^+ - COCH_2^+$, 100); HRMS for $C_{14}H_{15}NO_2S$ calcd 261.0824, found 261.0824.

2-Benzoyl-4-phenyl-2*H*-1,4-thiazin-3(4*H*)-one (2m): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, 1H, J = 2.04), 5.52 (dd, 1H, J = 2.0, 7.1), 6.51 (d, 1H, J = 7.1), 7.35−7.94 (m, 10H); IR 1675 (acetyl C═O), 1665 (amide C═O), 1295; MS 295 (M^+, 25), 105 ($CO^+C_6H_5$, 100); HRMS for $C_{17}H_{13}NO_2S$ calcd 295.0667, found 295.0667.

2-Acetyl-4-methyl-2*H*-1,4-thiazin-3(4*H*)-one (2n): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.23 (s, 3H), 4.04 (d, 1H, J = 1.8), 5.46 (dd, 1H, J = 1.8, J = 7.2), 6.27 (d, 1H, J = 7.2); IR 1662 (acetyl C═O), 1718 (amide C═O); MS 171 (M^+, 28), 129 ($M^+ - O{=}C{=}CH_2^+$, 100); HRMS for $C_7H_9NO_2S$ calcd 171.0354, found 171.0354.

2-Acetyl-4-ethyl-2*H*-1,4-thiazin-3(4*H*)-one (2o): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.7), 2.35 (s, 3H), 3.62−3.75 (m, 2H), 4.03 (d, 1H, J = 1.8), 5.50 (dd, 1H, J = 1.8, J = 7.1), 6.31 (d, 1H, J = 7.1); IR 1656 (acetyl C═O), 1719 (amide C═O); MS 185 (M^+, 35), 143 ($M^+ - O{=}C{=}CH_2^+$, 100); HRMS for $C_8H_{11}NO_2S$ calcd 185.0511, found 185.0499.

Preparation of 2-(2′-Hydroxyethyl)-*N*-phenyl-1,4-thiazin-3(4*H*)-one (11). To a solution of **2a** (153 mg, 0.66 mmol) in ethanol (10 mL) cooled to 0 °C in an ice bath was added sodium borohydride (13 mg, 0.33 mmol) portionwise over 5 min. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into ice water (50 mL) and extracted with methylene chloride. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a diastereomeric mixture of the alcohol **11** (154 mg, 100%) as a colorless solid. A mixture of A isomer and B isomer (3:1): mp 97−98 °C; IR 3450 (O−H), 1660 (C═O). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found C, 61.26; H, 5.57; N, 6.06.

Isomer A: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, 3H, J = 6.4), 3.06 (br s, 1H), 3.51 (dd, 1H, J = 1.4, J = 6.0),[9] 4.34−4.42 (m, 1H), 5.72 (dd, 1H, J = 1.4, J = 7.2), 6.43 (d, 1H, J = 7.2), 7.23−7.46 (m, 5H).

Isomer B: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, 3H, J = 6.4), 3.06 (br s, 1H), 3.42 (d, 1H, J = 8.8), 4.20−4.30 (m, 1H), 5.78 (d, 1H, J = 7.2), 6.43 (d, 1H, J = 7.2), 7.23−7.46 (m, 5H).

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(9) This coupling was caused by ^4J between a methine proton on C-2 and a vinyl proton on C-6.