Heteroatom Chemistry
Volume 6, Number 4, 1995

Novel Synthesis of 2,6-Benzothiazonine Derivatives

Sung Hoon Kim and Kyongtae Kim*

Department of Chemistry, Seoul National University, Seoul 151-742, Korea

Received 15 November 1994; revised 21 December 1994

ABSTRACT

The reaction of 1-alkylamino-1-alkylthio-3-phenyl-3-thioxopropenes with phthaloyl chloride in toluene at 60°C, followed by treatment with triethylamine, afforded 6-alkyl-3-phenyl-2,6-benzothiazonine-1,5,7-triones in good to excellent yields.

INTRODUCTION

Synthesis of nine-membered benzothiazonines has been of interest owing not only to a new method of synthesis of compounds containing a medium-sized ring but also to the potential biological activities of such compounds depending on their structures. Several methods for the synthesis of benzothiazonines have appeared in the literature. For example, the thermolysis of 2-vinylthiacylohexane N-(p-toluenesulfonyl)imide in xylene at 140°C gave a 1,2-thiazonine derivative in 54% yield [1]. This is the only example of the preparation of a 1,2-thiazonine. The reaction of 6-bromohexyl isothiocyanate with aromatic amines in ethanol at reflux gave 2-(N-arylimino)-1,3-thiazonines in good yields [2]. An example of a method to give a 1,5-thiazonine derivative involves the Beckmann rearrangement of thiacyclooctan-5-one oxime p-toluenesulfonate [3]. The reaction of sodium 2-aminobenzenethiolate with an alkyl 5-aryl-5-chloropentanoate, followed by hydrolysis gave a 5-(2-aminophenylthio)-5-arylpentanoic acid, which was cyclized to give a 3-aryl-1,7-benzothiazonine [4]. This method provides a cyclic compound containing a sulfur and a nitrogen atom originated from 2-aminobezenethiol.

A useful method for the preparation of a 6,1-benzothiazonine is the reaction of N-(4-methylthiobutyl)amine with N-chlorosuccinimide in CH_2Cl_2, below 0°C, followed by reaction with sodium methoxide. In addition to 6,1-benzothiazonines, the general method can be utilized for the synthesis of heterocycles with various ring sizes containing a sulfur and a nitrogen atom [5].

The reaction of 2-aryl-3-oxo-1,4-thiazines with methyl iodide, followed by treatment with base, was reported to give 2,5-benzothiazonine derivatives [6], but the experimental procedures were not described in detail.

Some of these benzothiazonine derivatives are reported to be potentially useful for pharmacological applications, such as for anthelmintic [2] and antihypertensive activities [3], central nervous system depressants, tranquilizers, blood platelet aggregation inhibitors, intestinal contraction inhibitors, and coronary vasodilators [6].

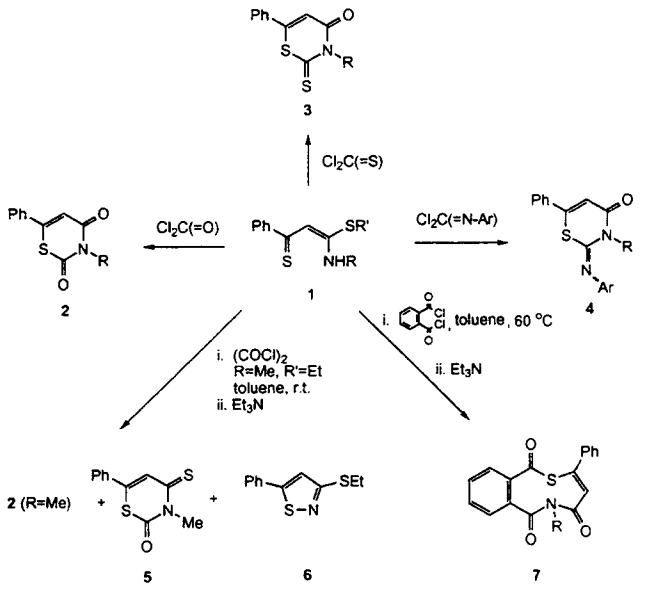
Recently, we reported a facile method for the synthesis of thiophenacylketene S,N-acetals (**1**) [7,8], which reacted with phosgene, thiophosgene, and N-arylimidoyl dichloride to give 2,3-dihydro-2,4-dioxo- (**2**), 2,3-dihydro-4-oxo-2-thioxo- (**3**), and 3-alkyl-2-(N-arylimino)-2, 3-dihydro -4-oxo-6-phenyl-4H-1,3-thiazines (**4**), respectively, in good to excellent yields [9].

As a part of a study for exploring additional synthetic utility of compounds **1**, **1a** (R = Me, R' = Et) was reacted with oxalyl chloride in toluene, at room temperature, followed by addition of triethylamine (TEA). From the reaction mixture, there were obtained **2** (R = Me), 2,3-dihydro-3-methyl-2-oxo-6-phenyl-4-thioxo-4H-1,3-thiazine (**5**), and 3-ethylthio-5-phenylisothiazole (**6**) in 41, 3, and 3% yields, respectively. It is noteworthy that decar-

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

*To whom correspondence should be addressed.

1042-7163/95/$5.00 + .25



SCHEME 1

bonylation of oxalyl chloride occurred during the reaction. The result is in contrast with the formation of 4-aryl-5-methylthio-N-substituted pyrroline-2,3-diones from the reactions of analogous compounds, phenacylketene S,N-acetals, with oxalyl chloride [10]. On the other hand, the reaction of **1** with phthaloyl chloride in toluene at 60°C, followed by treatment with triethylamine, gave 2,6-benzothiazonine derivatives (**7**), which were, to the best of our knowledge, the first examples of 2,6-benzothiazonines.

EXPERIMENTAL

All solvents were dried by standard methods. Phthaloyl chloride and TEA were purchased from Aldrich. 1-Alkylamino-1-alkylthio-3-phenyl-3-thioxopropenes (**1**) were synthesized by literature methods [7,8]. Column chromatography was performed on silica gel (Merck, 230–400 mesh). ^{1}H NMR spectra were measured on a Varian gemini-300 300 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin–Elmer 1310 infrared spectrometer. Mass spectra (MS) (70 eV, electron impact) were obtained using HP 5890A (GC) with HP 5970 (MSD). Microanalyses were performed by Perkin–Elmer 240Ds and Carlo Erbra 1106 instruments. Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected.

Synthesis of 6-Alkyl-3-phenyl-2,6-benzothiazonine-1,5,7-triones (**7**)

General Procedure. To a solution of **1** (R′ = Et for **1a**, R′ = Me for **1b–1k**) in toluene (6 mL) was added phthaloyl chloride using a microsyringe. Upon addition of phthaloyl chloride, a sticky solid was formed in the solution. To the mixture was added TEA using a microsyringe, and the mixture was stirred for 3 hours at which time no spot corresponding to **1** was observed on TLC (Kiesel gel PF_{254}). Water (10 mL) was added to the reaction mixture, and the mixture was extracted with diethyl ether (10 mL). The organic layer was washed with water (2 × 10 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by chromatography of the residue using CH_2Cl_2 as eluent gave phthaloyl chloride and **7**, which was recrystallized from EtOH.

6-Methyl-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7a**

Typical procedure is as follows: The reaction of 1-ethylthio-1-methylamino-3-phenyl-3-thioxopropene (**1a**) (45 mg, 0.19 mmol) with phthaloyl chloride (39 mg, 0.19 mmol) in the presence of TEA (38 mg, 0.39 mmol) gave a mixture, which was chromatographed to give unreacted phthaloyl chloride (10 mg, 0.05 mmol) and **7a** (40 mg, 0.12 mmol, 65%) as a white solid; mp 183–184°C. ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H, CH_3), 6.70 (s, 1H, =CH), 7.42–7.49 (m, 3H, ArH), 7.59–7.62 (m, 2H, ArH), 7.74–7.79 (m, 2H, ArH), 7.86–7.88 (m, 1H, ArH), 8.02–8.05 (m, 1H, ArH). IR (KBr) 1788, 1651, 1606, 1356, 1275, 1263, 1076, 866, and 729 cm^{-1}. Anal calcd for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33; S, 9.91. Found: C, 66.74; H, 4.13; N, 4.28; S, 9.85.

6-Ethyl-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7b**

Ivory solid; yield 80%; mp (dec) 141.5–142.0°C. ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, J = 7.2 Hz, CH_3), 3.35 (q, 2H, J = 7.2 Hz, CH_2), 6.68 (s, 1H, =CH), 7.42–7.48 (m, 3H, ArH), 7.57–7.58 (m, 2H, ArH), 7.77–7.90 (m, 3H, ArH), 8.02–8.05 (m, 1H, ArH). IR (KBr) 1786, 1651, 1606, 1468, 1375, 1259, 1082, 864, and 731 cm^{-1}. Anal calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15; S, 9.50. Found: C, 67.94; H, 4.66; N, 4.26; S, 9.41.

6-Cyclohexyl-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7c**

White solid; yield 25%; mp (dec) 188–189°C. ^{1}H NMR ($CDCl_3$) δ 0.76–2.56 (m, 10H, cyclohexyl), 2.65–2.88 (m, 1H, NCH), 6.59 (s, 1H, =CH), 7.40–7.47 (m, 3H, ArH), 7.57–7.60 (m, 2H, ArH), 7.75–7.90 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH). IR (KBr) 1778, 1647, 1466, 1446, 1344, 1097, 874, and 781 cm^{-1}. Anal calcd for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.44; H, 5.37; N, 3.51; S, 8.11.

6-Benzyl-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7d**

White solid; yield 86%; mp 123–124°C. ^{1}H NMR ($CDCl_3$) δ 4.50 (d, 1H, J_{gem} = 15.9 Hz, NCH_a), 4.75 (d, 1H, J_{gem} = 15.9 Hz, NCH_b), 6.80 (s, 1H, =CH), 6.81 (d, 2H, J = 7.2 Hz, ArH), 7.12–7.17 (m, 3H, ArH), 7.39–7.50 (m, 4H, ArH), 7.60–7.70 (m, 4H, ArH), 7.87–7.89 (m, 1H, ArH). IR (KBr) 1786, 1645, 1574, 1466, 1369, 1358, 1286, 1095, and 876 cm^{-1}. Anal calcd for $C_{24}H_{17}NO_3S$: C, 72.16; H, 4.29; N, 3.51; S, 8.03. Found: C, 72.35; H, 4.17; N, 3.51; S, 7.98.

6-Allyl-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7e**

Ivory solid; yield 72%; mp 190.0–190.5°C. ^{1}H NMR ($CDCl_3$) δ 3.77 (dd, 1H, J_{gem} = 15.6 and J_{vic} = 7.2 Hz, NCH_aC=), 4.17 (dd, 1H, J_{gem} = 15.6 and J_{vic} = 4.5 Hz, NCH_bC=), 4.59 (d, 1H, J = 17.1 Hz, CH_2–C=C–H_{trans}), 4.96 (d, 1H, J = 10.2 Hz, CH_2–C=C–H_{cis}), 5.69–5.81 (m, 1H, CH_{ab}–CH=C), 6.71 (s, 1H, =CH), 7.41–7.52 (m, 3H, ArH), 7.59–7.62 (m, 2H, ArH), 7.74–7.88 (m, 3H, ArH), 7.98–8.01 (m, 1H, ArH). IR (KBr) 1788, 1655, 1603, 1468, 1446, 1358, 1290, 1090, 872, 856, 775, and 723 cm^{-1}. Anal calcd for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01; S, 9.18. Found: C, 68.80; H, 4.39; N, 4.07; S, 9.12.

6-(4-Methylbenzyl)-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7f**

White solid; yield 83%; mp 164.5–165.5°C. ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 4.46 (d, 1H, J_{gem} = 15.6 Hz, NCH_a), 4.71 (d, 1H, J_{gem} = 15.6 Hz, NCH_b), 6.70 (d, 2H, J = 7.8 Hz, ArH), 6.79 (s, 1H, =CH), 6.96 (d, 2H, J = 7.8 Hz, ArH), 7.42–7.50 (m, 4H, ArH), 7.61–7.68 (m, 4H, ArH), 7.87–7.90 (m, 1H, ArH). IR (KBr) 1784, 1649, 1514, 1466, 1446, 1365, 1284, 1096, and 874 cm^{-1}. Anal calcd for $C_{25}H_{19}NO_3S$: C, 72.62; H, 4.63; N, 3.39; S, 7.75. Found: C, 72.80; H, 4.51; N, 3.35; S, 7.68.

6-(2-Chlorobenzyl)-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7g**

Ivory solid; yield 96%; mp 170–171°C. ^{1}H NMR ($CDCl_3$) δ 4.33 (d, 1H, J_{gem} = 16.8 Hz, NCH_a), 5.06 (d, 1H, J_{gem} = 16.8 Hz, NCH_b), 6.82 (s, 1H, =CH), 7.13–7.70 (m, 12H, ArH), 7.92–7.94 (m, 1H, ArH). IR (KBr) 1780, 1655, 1466, 1446, 1373, 1317, 1248, 1095, 1078, 864, 807, and 787 cm^{-1}. Anal calcd for $C_{24}H_{16}ClNO_3S$: C, 66.43; H, 3.72; N, 3.23; S, 7.39. Found: C, 66.30; H, 3.50; N, 3.25; S, 7.31.

6-(3-Chlorobenzyl)-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7h**

White solid; yield 87%; mp 151.5–152.0°C. ^{1}H NMR ($CDCl_3$) δ 4.43 (d, 1H, J_{gem} = 15.9 Hz, NCH_a), 4.74 (d, 1H, J_{gem} = 15.9 Hz, NCH_b), 6.68 (s, 1H, ArH), 6.79 (s, 1H, =CH), 6.81 (d, 1H, J = 9.6 Hz, ArH), 7.09–7.18 (m, 2H, ArH), 7.41–7.50 (m, 4H, ArH), 7.62–7.74 (m, 4H, ArH), 7.91–7.93 (m, 1H, ArH). IR (KBr) 1790, 1639, 1601, 1572, 1469, 1435, 1371, 1302, 1203, 1080, 881, and 783 cm^{-1}. Anal calcd for $C_{24}H_{16}ClNO_3S$: C, 66.43; H, 3.72; N, 3.23; S, 7.39. Found: C, 66.51; H, 3.65; N, 3.10; S, 7.42.

6-(4-Chlorobenzyl)-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7i**

White solid; yield 96%; mp 203.5–204.0°C. ^{1}H NMR ($CDCl_3$) δ 4.36 (d, 1H, J_{gem} = 15.6 Hz, NCH_a), 4.76 (d, 1H, J_{gem} = 15.6 Hz, NCH_b), 6.77 (d, 2H, J = 8.4 Hz, ArH), 6.79 (s, 1H, =CH), 7.14 (d, 2H, J = 8.4 Hz, ArH), 7.39–7.51 (m, 4H, ArH), 7.62–7.71 (m, 4H, ArH), 7.91–7.93 (m, 1H, ArH). IR (KBr) 1786, 1647, 1491, 1466, 1365, 1309, 1284, 1093, 1014, 876, 785, and 769 cm^{-1}. Anal calcd for $C_{24}H_{16}ClNO_3S$: C, 66.43; H, 3.72; N, 3.23; S, 7.39. Found: C, 66.38; H, 3.75; N, 3.19; S, 7.34.

3-Phenyl-6-phenethyl-6H-2,6-benzothiazonine-1,5,7-trione **7j**

White solid; yield 64%; mp 182–183°C. ^{1}H NMR ($CDCl_3$) δ 2.64–2.72 (m, 1H, $PhCH_a$), 2.85–2.95 (m, 1H, $PhCH_b$), 3.25–3.35 (m, 1H, NCH_a), 3.49–3.59 (m, 1H, NCH_b), 6.73 (s, 1H, =CH), 6.87–6.90 (m, 2H, ArH), 7.18–7.20 (m, 3H, ArH), 7.42–7.50 (m, 4H, ArH), 7.61–7.63 (m, 2H, ArH), 7.75–7.84 (m, 2H, ArH), 8.02–8.05 (m, 1H, ArH). IR (KBr) 1782, 1664, 1647, 1448, 1433, 1356, 1315, 1227, 1097, 1082, 872, and 783 cm^{-1}. Anal calcd for $C_{25}H_{19}NO_3S$: C, 72.62; H, 4.63; N, 3.39; S, 7.75. Found: C, 72.60; H, 4.50; N, 3.34; S, 7.69.

6-(4-Methoxybenzyl)-3-phenyl-6H-2,6-benzothiazonine-1,5,7-trione **7k**

White solid; yield 90%; mp 179–180°C. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, OCH_3), 4.48 (d, 1H, J_{gem} = 15.6 Hz, NCH_a), 4.67 (d, 1H, J_{gem} = 15.6 Hz, NCH_b), 6.67–6.79 (m, 4H, ArH), 6.80 (s, 1H, =CH), 7.42–7.47 (m, 4H, ArH), 7.61–7.68 (m, 4H, ArH), 7.89–7.90 (m, 1H, ArH). IR (KBr) 1784, 1647, 1610, 1510, 1466, 1439, 1367, 1284, 1174, 1095, 1034, and 874 cm^{-1}. Anal calcd for $C_{25}H_{19}NO_4S$: C, 69.91; H, 4.46; N, 3.26; S, 7.46. Found: C, 69.60; H, 4.19; N, 3.27; S, 7.37.

Reaction of **1a** *with Oxalyl Chloride*

To a solution of oxalyl chloride (43 mg, 0.34 mmol) in toluene (1 mL) was added dropwise a solution of **1a** (80 mg, 0.34 mmol) in toluene (6 mL), which gave brown solids immediately. Subsequent addition of TEA (68 mg, 0.67 mmol) to the mixture gave a dark solution containing TEA · HCl. The

mixture was stirred for an additional 10 minutes, followed by addition of water (7 mL), and the new mixture was extracted with ethyl ether (3 × 5 mL). The extracts were washed with water twice and then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a dark residue, which was chromatographed on a silica gel column (2 × 8 cm). Elution with a mixture of CH_2Cl_2 and *n*-hexane (v:v, 2:1) gave 3-methyl-2-oxo-6-phenyl-4-thioxo-4H-1,3-thiazine (**5**) (2 mg, 0.008 mmol, 3%): mp 116–117.5°C. ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H, CH_3), 7.32–7.51 (m, 5H, ArH), 7.63 (s, 1H, =CH). IR (KBr) 1655, 1561, 1495, 1295, and 1167 cm^{-1}. MS (relative intensity) *m/z* 235 (M^+, 96.2), 207 (23.4), 178 (81.0), 145 (31.9), 121 (100), 102 (37.9). Anal calcd for $C_{11}H_9NOS_2$: C, 56.15; H, 3.86; N, 5.95; S, 27.25. Found: C, 56.05; H, 4.03; N, 6.01; S, 27.14.

Further elution with the same solvent mixture gave 3-ethylthio-5-phenylisothiazole (**6**) (2 mg, 0.009 mmol, 3%): colorless liquid. ^1H NMR ($CDCl_3$) δ 1.45 (t, 3H, J = 7.5 Hz, CH_3), 3.26 (q, 2H, J = 7.5 Hz, CH_2), 7.15 (s, 1H, =CH), 7.42–7.63 (m, 5H, ArH). IR (KBr) 2968, 2928, 1516, 1482, 1446, 1390, 1370, 814, 760, and 688 cm^{-1}. MS (relative intensity) *m/z* 221 (M^+, 88.1), 188 (100), 145 (54.2), 121 (70.4). Anal calcd for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.01; N, 6.33; S, 28.97. Found: C, 59.53; H, 4.85; N, 6.44; S, 28.84.

Still further elution with the same solvent mixture gave 3-methyl-2,4-dioxo-6-phenyl-4H-1,3-thiazine (**2**) (30 mg, 0.14 mmol, 41%) [9].

ACKNOWLEDGMENT

The authors are grateful for financial support by the Basic Science Research Institute Program, Ministry of Education (BERI-93-315).

REFERENCES

[1] H. Sashida, T. Tsuchida, *Heterocycles, 22,* 1984, 1303.
[2] D. L. Garmaise, G. Y. Paris, G. Efthymidis, *Can. J. Chem., 49,* 1971, 971.
[3] L. D. Wise, G. C. Morrison, K. Egan, M. A. Commarato, G. Kopia, E. C. Latlime, *J. Med. Chem., 17,* 1974, 1232.
[4] J. Krapcho, C. F. Turk, U.S. Patent 3,155,649 (1964); *Chem. Abstr., 62,* 1965, 7784c.
[5] S. Sato, K. Tomita, H. Fujita, Y. Sato, *Heterocycles, 22,* 1984, 1045.
[6] Suntory, Ltd. Jpn. Kokkai Tokkyo Koho JP 60 48979 (1985); *Chem. Abstr., 103,* 1985, 37511p.
[7] S. H. Kim, K. Kim, *J. Heterocycl. Chem., 30,* 1993, 929.
[8] S. H. Kim, Y. Y. Lee, K. Kim, J. H. Kim, *Bull. Korean Chem. Soc., 15,* 1994, 273.
[9] S. H. Kim, Y. H. Rha, Y. Y. Lee, K. Kim, J. H. Kim, *J. Heterocycl. Chem., 31,* 1994, 1361.
[10] H. Junjappa, H. Ila, C. V. Asokan, *Tetrahedron, 46,* 1990, 5423.