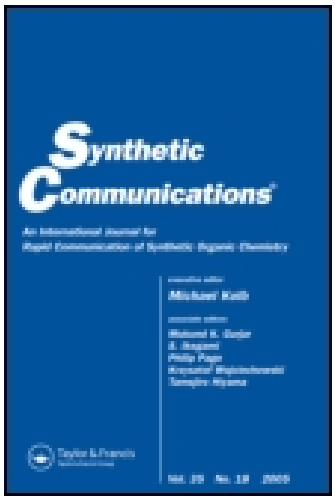

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Nucleophilic Ring Enlargement of 2-Substituted-3-isothiazolones to 1,3-Thiazin-4-ones

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ABSTRACT

1,3-Thiazin-4-ones **9** and **10** have been prepared from the corresponding isothiazolones **7** and **8** by a clean and smooth reaction with tertiary amines at room temperature. This rearrangement is attributed to the abstraction of a methine proton from the 2-position isothiazolone substituent, followed by ring enlargement through cleavage of the S-N bond.

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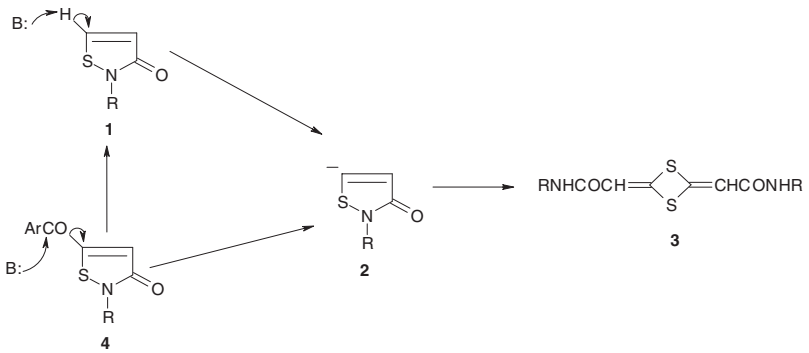
Key Words: 3-Isothiazolones; 1,3-Thiazin-4-ones; Nucleophilic ring expansion; Two phase reactions.

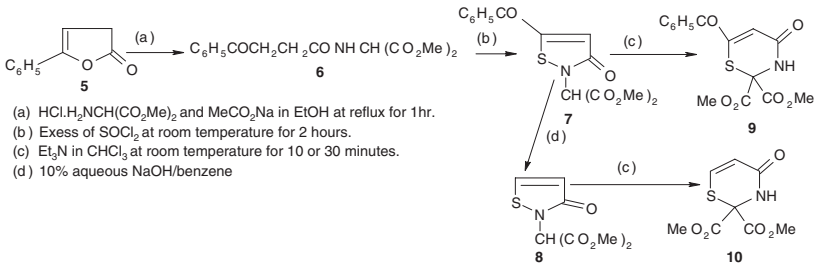
The 1,3-thiazin-4-one ring is found in a wide range of biologically active molecules. Most intensive investigation has focused on the modification of substituents in the thiazinone ring and on the synthesis of thiazinones fused with heterocycles. A large number of articles and patents deal with biochemical properties of these compounds, such as analgesics,[1,2] antimicrobial agents,[3,4] psychostimulants,[5] and others.

N-Substituted-3-isothiazolones bearing a free 5-position, of the general formula **1**, have been found[6] to be dimerized readily by bases to 2,4-bismethylene-1,3-dithietanes **3** (Sch. 1). Dithietanes of the general formula **3** have been also obtained from *N*-substituted-5-aroyl-3-isothiazolones **4**. For instance, the reaction of the *N*-benzyl-5-benzoylisothiazolone **4** (Ar = -C_6H_5, R = -$CH_2C_6H_5$) with bases (e.g., EtONa/EtOH, NaOH/H_2O) has been found[7] to yield the corresponding dithietane **3** (R = -$CH_2C_6H_5$). The dimerization was shown to proceed through the attack of the formed 5-anion **2** on the S-N bond of a second isothiazolone molecule **1**.

In the case of isothiazolone **4**, the 5-anion **2** would result from a nucleophilic displacement of the 5-benzoyl group. In a previous communication,[8] the partial or the complete transformation of the isothiazolone **4** to the corresponding dithietane **3**, by treatment with aqueous sodium hydroxide, has been examined. The reaction of a benzene solution of the same compound with a 10% aqueous solution of sodium hydroxide (a two phase aqueous-organic system) resulted



Scheme 1.



Scheme 2.

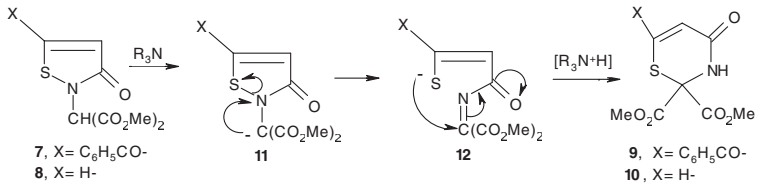
easily and quantitatively to the corresponding isothiazolone **1** (R = $-CH_2C_6H_5$).

Now we have prepared an isothiazolone namely 2-dimethylmalonate-5-benzoyl-3-isothiazolone (**7**) from the reaction of ketoamide **6**. The synthesis sequence (Sch. 2) is an application of the general procedure[7] for the preparation of isothiazolones of the general type **4** (Sch. 1).

When the isothiazolone **7** in a benzene solution was treated with a 10% aqueous sodium hydroxide at room temperature, a nucleophilic displacement reaction of 5-benzoyl group was occurred and isothiazolone **8** was obtained quantitavely according to the general method.[8] The same isothiazolone in a chloroform solution when treated with triethylamine at room temperature or 1,8-*bis*(dimethylamino)naphthalene in refluxing xylene, an isomeric compound was isolated in 88% yield. Structure **9** was assigned to this new compound on the basis of its ^{1}H NMR spectrum; besides the aromatic and aliphatic protons' signals, one low-field one-proton's signal was found to be coupled to an exchangeable N-H proton. In deuteriochloroform solution, a doublet at 6.60 ppm, $J = 1{,}2$ Hz, was assigned to the C 5 vinylic proton. The coupling between the C 5-H and the N-H protons would be typical case of long range coupling, as encountered in unsaturated systems incorporating a planar W-path.

Since the possibility of a nucleophilic displacement of the 5-benzoyl group in **7** should be excluded, as anticipated, the ring enlargement of **7** into **9** can only be explained by the abstraction of a methine proton from the dimethylmalonate group to form the anion **11** (Sch. 3).

Under the conditions used for the transformation of the isothiazolone **7** to the thiazinone **9**, the debenzoylated isothiazolone **8** gave also quantitatively the corresponding thiazinone **10**, though it has the easily abstracted 5-position ring's proton (Sch. 1). In this case obviously the dimethylmalonate anion **11** is formed faster, and is more stabilized, from the 5-anion of the isothiazolone ring.



Scheme 3.

The anion **11** can then be assumed to give compounds **9** and **10** through the acylimine intermediate **12**, an elimination-addition process (E1cb mechanism). This mechanism however is favored by the labile S-N bond[9] of the isothiazolone ring system.

In conclusion the nucleophilic displacement of the 5-benzoyl group of isothiazolone **7** to the corresponding isothiazolone **8** was finally found to proceed with a simple two phase reaction, though these isothiazolones have the acidic dimethylmalonate methine proton. These isothiazolones were converted into the corresponding 1,3-thiazin-4-ones easily in high yields. We are currently investigating the application of the reactions sequences (Sch. 2) to the preparation of 1,3-thiazin-4-ones and from there to fused 1,3-thiazin-ring systems with probable interest as potential prodrugs.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard). The IR spectra were obtained with a Nicolet Magna 560 spectrometer; as nujol mulls and were calibrated against the polystyrene 1601 cm^{-1} band, and given in reciprocal centimetres. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

N-Dimethylmalonate-3-benzoylpropionamide (6)

A mixture of butenolide **5**,[10] 13.48 g (84.17 mmol), 15.45 g (84.15 mmol) of aminodimethylmalonate hydrochloride, 7.61 g (92.60 mmol) of anhydrous sodium acetate in 6 mL of water and 50 mL of ethanol

refluxed on a steam bath for 1 h. The hot mixture was filtered from the salts and the filtrate after cooling gave a crystalline solid 19.5 g (75.4%). M.p. 137–139°. After further recrystallization from ethanol it gave an analytically pure sample of ketoamide **6**, m.p. 140–142°. Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.57; H, 5.48; N, 4.42. IR (Nujol mull, cm^{-1}): 3311, 1739, 1691, 1650, 1597, 1582. ^{1}H NMR (60 MHz, $CDCl_3$); δ 2.78 and 3.36 (two t, $J = 6$ Hz, 4H, -CH_2CH_2-), 3.81 (s, 6H, two -CH_3), 5.23 (d, $J = 7$ Hz, 1H, CH), 6.96 (br d, $J = 7$ Hz, 1H, -NH-), 7.38–8.16 (m, 5H, aromatic protons).

2-Dimethylmalonate-5-benzoyl-3-isothiazolone (7)

Following the general method[7] a solution of the ketoamide **6**, 20 g (65.08 mmol) in 200 mL of thionyl chloride, was stirred at room temperature for 2 h. The dark green solution was concentrated under vacuum at room temperature and the solid residue was recrystallized from methanol to give 16 g (73.3%) of a yellow crystalline product, m.p. 96–99°. A further recrystallization from methanol gave an analytically pure sample of compound **7**. M.p. 101–102°. Anal. Calcd. for $C_{15}H_{13}NO_6S$: C, 53.73; H, 3.90; N, 4.17; S, 9.56. Found: C, 53.58; H, 3.91; N, 4.20; S, 9.37. IR (Nujol mull, cm^{-1}): 1763, 1748, 1742, 1666, 1650, and 1594. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.90 (s, 6H, two -CH_3), 6.13 (s, 1H, CH), 6.75 (s,1H, vinylic proton), and 7.50–8.11 (m, 5H, aromatic protons).

2-Dimethylmalonate-3-isothiazolone (8)

To a solution of the benzoylisothiazolone **7,** 1 g (2.98 mmol) in benzene (20 mL), a 10% aqueous sodium hydroxide solution (20 mL) was added and the mixture was stirred vigorously at room temperature for 10 min. The water layer was then separated, acidified with a 10% hydrochloric acid solution and saturated with NaCl, the precipitated benzoic acid was filtered, and the filtrate was extracted some times with chloroform. The chloroform extracts washed with a 0.1% sodium bicarbonate solution some times and then with a 5% hydrochloric acid solution and finally with water. The organic layer was dried (magnesium sulfate) and concentrated under vacuum to give compound **8** as a retinous mass 0.52 g (75%), as evidenced from ^{1}H NMR spectrum. IR (as retinous mass, cm^{-1}): 1754, 1647, and 1512. ^{1}H NMR (60 MHz, $CDCl_3$); δ 3.91 (s, 6H, two -CH_3), 6.10 (s, 1H, CH), 6.31 and 8.48 (two d, $J = 6.5$ Hz, 2H, vinylic protons).

2,2-Dimethoxycarbonyl-6-benzoyl-1,3-thiazin-4-one (9)

To a solution of the benzoylisothiazolone **7**, 1 g (2.98 mmol) in 20 mL of chloroform, 2 mL of triethylamine were added and the solution was left at room temperature for 10 min. The solution washed with a 10% hydrochloric acid solution and concentrated under vacuum to give a quantitative yield of a solid residue, which was shown (^{1}H NMR spectrum) to be a pure sample of the corresponding thiazinone **9**. A recrystallization from benzene/petroleum ether gave an analytical sample 0.88 g (88%). M.p. 119–121°. Anal. Calcd. for $C_{15}H_{13}NO_6S$: C, 53.73; H, 3.90; N, 4.17; S, 9.56. Found: C, 53.74; H, 3.90; N, 4.18; S, 9.76. IR (Nujol mull, cm^{-1}): 3164, 1760, 1746, 1669, 1650, and 1594. ^{1}H NMR (60 MHz, $CDCl_3$); δ 3.95 (s, 6H, two -CH_3), 6.60 (d, $J = 1{,}2$ Hz,1H, vinylic proton), 7.18 (br s, 1H, -NH-), 7.50–8.00 (m, 5H, aromatic protons).

2,2-Dimethoxycarbonyl-1,3-thiazin-4-one (10)

A solution of 0.48 g (2.07 mmol) of the isothiazolone **8**, in 20 mL chloroform and 1 mL of triethylamine was left at room temperature for 30 min. The solution washed with a 10% hydrochloric acid solution and concentrated under vacuum to give an almost quantitative yield of a solid residue which was shown (^{1}H NMR spectrum) to be a pure sample of the corresponding thiazinone **10**. A recrystallization from benzene gave an analytical sample 0.40 g (83.3%). M.p. 96–97°. Anal. Calcd. for $C_8H_9NO_5S$: C, 41.55; H, 3.92; N, 6.06; S, 13.87. Found: C, 41.55; H, 4.03; N, 6.12; S, 13.63. IR (Nujol mull, cm^{-1}): 3425, 1751, and 1677. ^{1}H NMR (60 MHz, $CDCl_3$); δ 3.93 (s, 6H, two -CH_3), 6.15, and 7.10 (two d, $J = 10.5$ Hz, 2H, vinylic protons), 6.91 (br s, 1H, -NH-).

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