Synthesis of Thiazoles from the Reaction of Phenyliodonium Ylids of Cyclic β-Dicarbonyl Compounds with Thioureas

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Dedicated to the memory of Professor Nicholas Alexandrou

Phenyliodonium ylids of cyclic β-dicarbonyl compounds react with substituted thioureas to form the corresponding thiouronium ylids. The latter, when they have one free amino group, are converted upon heating to fused thiazoles. The reaction can be considered as a modification of the Hantzsch synthesis.

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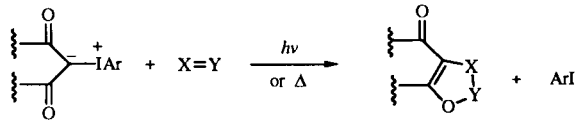
Aryliodonium ylids belong to the major class of zwitterionic iodonium compounds, the chemistry of which up to 1992 has been reviewed [1]. The term aryliodonium ylids refers to 1,2-dipoles with the formal negative charge on carbon **1**. The presence of electron-withdrawing groups is usually necessary for the stabilization of these compounds, although the most stable and important are those bearing two carbonyl groups, **2**.

1 **2**

Ylids **2** exhibit a diversity in their chemical reactivity [1]. From the synthetic point of view an interesting reaction is that with dipolophiles leading to a variety of heterocyclic products **3**, according to the general scheme.



2 **3**

The reaction takes place either thermally or photolytically, depending on the nature of the ylid and the dipolophile X = Y. Cyclization products are formed mainly with aryliodonium ylids of cyclic β-dicarbonyl compounds, whereas ylids of acyclic β-dicarbonyl compounds give rise to either cyclization compounds [2] or substitution on the ylidic C compounds [3].

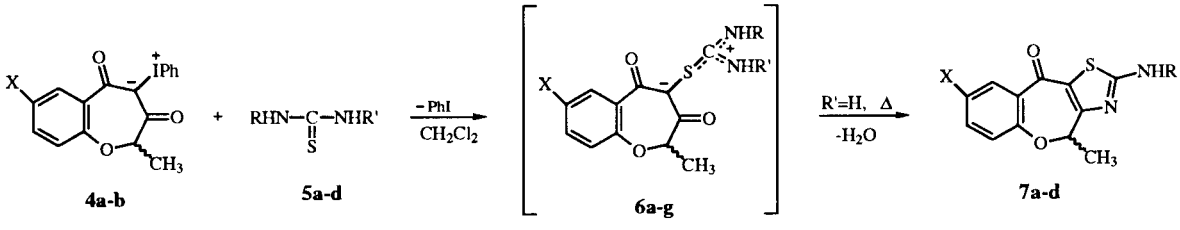
Recently we reported [4] the synthesis and cyclization reactions of phenyliodonium ylids of benz[*b*]oxepine-3,5(2*H*,4*H*)-diones **4**. Ylids **4** react under catalytic conditions with alkynes and nitriles affording fused furans and oxazoles, respectively, with remarkable regioselectivity. We wish now to report on the reaction of ylids **4** with thioureas and the formation of fused thiazole derivatives.

Results and Discussion.

The reaction takes place with equimolecular quantities of phenyliodonium ylids **4** and thioureas **5** in dichloromethane at room temperature (Scheme 1). After 24 hours the resulting solid was filtered off and ^{1}H nmr spectroscopy showed that it contained a mixture of the thiouronium ylid **6a-d** and the corresponding thiazole **7a-d**. It is most difficult to isolate the intermediate thiouronium ylid, since the condensation reaction already starts at room temperature. On the other hand, mixtures of **6a-d** and **7a-d** were converted to thiazoles **7a-d** upon reflux in dichloromethane solution.

Thiazoles **7a-d** were also conveniently obtained from the reaction of the corresponding phenyliodonium ylids **4a-b** with thioureas **5a-b** after 4 hours refluxing in dichloromethane suspension.

Scheme 1



4a-b **5a-d** **6a-g** **7a-d**

4a, X = H
4b, X = Cl

5a, R = R' = H
5b, R = CH_3, R' = H
5c, R,R' = $-CH_2CH_2-$
5d, R = R' = Ph

6a, X = H, R = R' = H
6b, X = Cl, R = R' = H
6c, X = H, R = CH_3, R' = H
6d, X = Cl, R = CH_3, R' = H
6e, X = H, R, R' = $-CH_2CH_2-$
6f, X = Cl, R, R' = $-CH_2CH_2-$
6g, X = H, R = R' = Ph

7a, X = H, R = H
7b, X = Cl, R = H
7c, X = H, R = CH_3
7d, X = Cl, R = CH_3

Table 1

Physical and Analytical Data of 4-Thiouronium-benz[*b*]oxepine-3,5(2*H*,4*H*)-diones **6e-g** and 2-Thiouronium-4,4-dimethyl-3,5-cyclohexanediones **10a-c**

Compound	Yield (%)	Mp (°C)	Mol formula (Mol weight)	Analysis (%) Calcd/Found C	H	N	IR (cm^{-1}) (Nujol)
6e	82	162-163	$C_{14}H_{14}N_2O_3S$ (290.34)	57.91 / 57.79	4.86 / 4.71	9.65 / 9.74	3280, 1590, 1580
6f	84	180-181	$C_{14}H_{13}ClN_2O_3S$ (324.79)	51.77 / 51.91	4.03 / 4.00	8.62 / 8.71	3240, 1610
6g	38	177-179	$C_{24}H_{20}N_2O_3S$ (416.45)	69.22 / 69.34	4.84 / 4.68	6.75 / 6.43	1640, 1580
10a	97	135-137	$C_9H_{14}N_2O_2S$ (214.29)	50.44 / 49.99	6.58 / 6.50	13.07 / 12.87	3300, 1640, 1570, 1500
10b	65	175-180	$C_{10}H_{16}N_2O_2S$ (228.31)	52.61 / 52.69	7.06 / 7.16	12.27 / 12.31	3305, 1640, 1565
10c	45	162-163	$C_{11}H_{18}N_2O_2S$ (242.34)	54.52 / 54.64	7.49 / 7.71	11.56 / 11.64	3350, 3280, 3200, 1640

Table 2

^{1}H NMR [δ in ppm] and MS [EI 70 eV, m/z] Data for Compounds **6e-g** and **10a-c**

Compound

6e ^{1}H nmr: 8.07 (d, J = 9 Hz, 1H arom), 7.30-7.05 (m, 3H arom), 4.57 (q, J = 9 Hz, 1H methinic), 3.74 (s, 4H), 1.45 (d, J = 9 Hz, 3H) [a]; ms: 272 (M^+-H_2O, 100), 258 (52), 230 (63)

6f ^{1}H nmr: 7.89 (s, 1H), 7.64-7.54 (m, 2H), 4.50 (q, J = 9 Hz, 1H), 3.99 (s, 4H), 3.78 (s, 2H, NH), 1.61 (d, J = 9 Hz, 3H) [b]; ms: 324 (M^+, traces), 308, 306 (M^+-H_2O, 33, 100), 294, 292 (11, 47)

6g ^{1}H nmr: 8.20 (d, J = 9 Hz, 1H), 7.54-6.89 (m, 13H), 4.63 (q, J = 9 Hz, 1H), 1.51 (d, J = 9 Hz, 3H) [b]; ms: 398 (M^+-H_2O, 76), 382 (58), 121 (47), 77 (100)

10a ^{1}H nmr: 2.63 (s, 4H), 1.13 (s, 6H) [b]; ms: 215 (M^++1, 42), 196 (M^+-H_2O, 100), 155 (35) , 144 (37)

10b ^{1}H nmr: 3.07 (s, 3H), 2.61 (s, 4H), 1.11 (s, 6H) [b]; ms: 210 (M^+-H_2O, 100), 182 (25), 154 (91)

10c ^{1}H nmr: 3.41 (q, J = 9 Hz, 2H), 2.61 (s, 4H), 1.25 (t, J = 9 Hz, 3H), 1.13 (s, 6H) [b]; ms: 242 (M^+, 48), 224 (M^+-H_2O, 100), 209 (40), 168 (42)

[a] Recorded in deuteriochloroform. [b] Recorded in deuteriochloroform-trifluoroacetic acid.

Table 3

Physical and Analytical Data of 2-Amino-10-methyl-10*H*-benz[*b*]oxepino[5,6-*d*]thiazol-4-ones **7a-d** and 2-Amino-6,6-dimethylcyclohexano[*d*]thiazol-4-ones **11a-c**

Compound	Yield (%)	Mp (°C)	Mol formula (Mol weight)	Analysis (%) Calcd/Found C	H	N	IR (cm^{-1}) (Nujol)
7a	52	150-151	$C_{12}H_{10}N_2O_2S$ (246.29)	58.52 / 58.20	4.09 / 4.00	11.37 / 11.18	3230, 3100, 1650, 1550
7b	38	145-147	$C_{12}H_9ClN_2O_2S$ (280.73)	51.34 / 51.36	3.23 / 3.38	9.98 / 9.84	3270, 3100, 1590, 1540
7c	37	135-140	$C_{13}H_{12}N_2O_2S$ (260.32)	59.98 / 59.89	4.65 / 4.78	10.76 / 10.79	3260, 1650, 1590, 1560
7d	59	135-140	$C_{13}H_{11}ClN_2O_2S$ (294.76)	52.97 / 52.68	3.76 / 4.01	9.50 / 9.63	3260, 1660, 1590, 1550
11a	75	155-157	$C_9H_{12}N_2OS$ (196.27)	55.07 / 54.98	6.16 / 6.08	14.27 / 13.98	3210, 1640, 1510
11b	50	220-225	$C_{10}H_{14}N_2OS$ (210.30)	57.11 / 57.21	6.71 / 6.80	13.32 / 13.41	3210, 3100, 1625, 1520
11c	31	185-187	$C_{11}H_{16}N_2OS$ (224.33)	58.90 / 58.99	7.19 / 7.24	12.49 / 12.61	3200, 3100, 1630, 1520

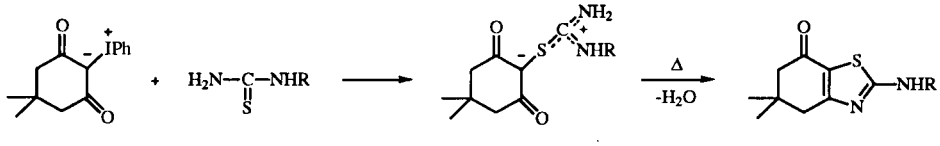
In the case of the reaction of ylids **4a-b** with symmetrically disubstituted thioureas **5c-d** thiouronium ylids **6e-g** were isolated in high yield, since no further cyclization reaction was possible. The new thiouronium ylids have analytical and spectroscopic data consistent with their structure (Tables 1 and 2).

Table 4

^{1}H NMR [δ in ppm] and ms [EI 70 eV, m/z] Data for Compounds **7a-d** and **11a-c**

Compound	
7a	^{1}H nmr: 8.03 (d, J = 8 Hz, 1H), 7.54-7.15 (m, 3H), 5.39 (q, J = 9 Hz, 1H), 1.65 (d, J = 9 Hz, 3H); ms: 246 (M^+, 10), 190 (26), 121 (100)
7b	^{1}H nmr: 7.98 (d, J = 2 Hz, 1H), 7.57 (dd, J = 2, 10 Hz, 1H), 7.13 (d, J = 10 Hz, 1H), 5.43 (q, J = 9 Hz, 1H), 2.14 (s, 2H, NH_2), 1.68 (q, J = 9 Hz, 3H); ms: 280 (M^+, 100), 265 (29), 155 (31), 126 (71)
7c	^{1}H nmr: 8.05 (d, J = 8 Hz, 1H), 7.45-7.05 (m, 3H), 6.20 (s br, 1H, NH), 5.35 (q, J = 9 Hz, 1H), 2.95 (s, 3H, N-Me), 1.61 (d, J = 9 Hz, 3H); ms: 260 (M^+, 100), 245 (19), 149 (24), 121 (71)
7d	^{1}H nmr: 8.00 (d, J = 2 Hz, 1H), 7.37 (dd, J = 2, 10 Hz, 1H), 7.02 (d, J = 10 Hz, 1H), 6.11 (s br, 1H, NH), 5.18 (q, J = 9 Hz, 1H), 3.03 (s, 3H, N-Me), 1.60 (q, J = 9 Hz, 3H); ms: 294 (M^+, 100), 279 (16), 140 (45)
11a	^{1}H nmr: 2.62 (s, 2H), 2.28 (s, 2H), 1.13 (s, 6H); ms: 196 (M^+, 54), 168 (12), 140 (93), 70 (100)
11b	^{1}H nmr: 2.99 (s, 3H, N-Me), 2.65 (s, 2H), 2.38 (s, 2H), 1.10 (s, 6H); ms: 211 (M^++1, 99), 183 (19), 168 (17), 154 (100), 126 (30), 70 (75)
11c	^{1}H nmr: 3.33 (q, J = 9 Hz, 2H), 2.64 (s, 2H), 2.37 (s, 2H), 2.14 (s, 1H, NH), 1.35 (t, J = 9 Hz, 3H), 1.11 (s, 6H); ms: 225 (M^++1, 46), 224 (M^+, 38), 208 (55), 105 (100)

Scheme 2



8 **9a-c** **10a-c** **11a-c**

9a, R = H **10a**, R = H **11a**, R = H
9b, R = CH_3 **10b**, R = CH_3 **11b**, R = CH_3
9c, R = CH_3CH_2 **10c**, R = CH_3CH_2 **11c**, R = CH_3CH_2

In the case of thiazoles **7a-d** only one regioisomer, resulting from the condensation of the amino group of the thiourea with the aliphatic carbonyl group, was isolated. Structure elucidation was based on comparison of the ^{1}H nmr chemical shift of the quadruplet of the methinic proton with that of the parent ketone, as it happened with the corresponding furan and oxazole derivatives [4]. Analytical and spectroscopic data of the new thiazoles are in agreement (Tables 3 and 4) with the proposed structure.

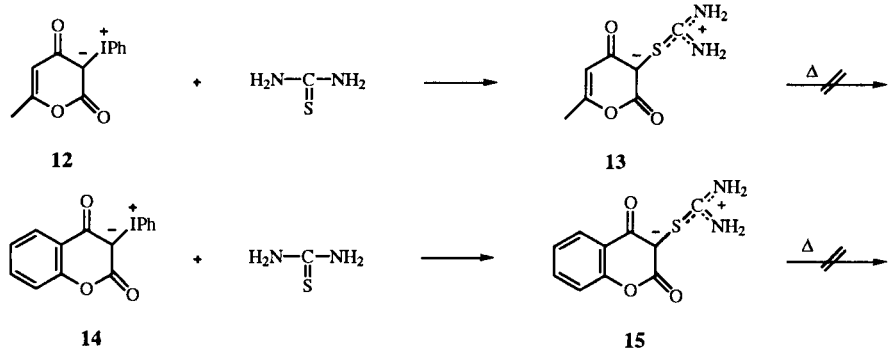
In order to investigate the scope of the reaction we tried it again under the same conditions, using a typical aryliodonium ylid, phenyliodonium dimedonate **8**. In this case both thiouronium ylids and thiazoles were isolated. Indeed at room temperature the corresponding thiouronium ylids **10a-c** were obtained in high yield, whereas in refluxing dichloromethane thiazoles **11a-c** were isolated (Scheme 2).

Both thiouronium ylids **10a-c** and thiazoles **11a-c** have analytical (Tables 1 and 3) and spectroscopic (Tables 2 and 4) data consistent with their structure.

It must be noted that thiazoles and selenazoles were obtained from the reaction of the corresponding thioureas and selenoureas with some acyclic β-dicarbonyl compounds and [(hydroxy)(tosyloxy)iodo]benzene [5,6].

Other phenyliodonium ylids, with a cyclic β-dicarbonyl moiety bearing an esteric group, such as the ylids of 4-hydroxy-6-methyl-2-pyrone **12** and 4-hydroxycoumarin **14**, gave readily the corresponding thiouronium ylids **13** and **15** upon reaction with thiourea (Scheme 3). All attempts to convert **13** and **15** into thiazoles (reflux in chloroform or ethanol) failed and the starting materials were recovered unreacted.

Scheme 3



12 **13**

14 **15**

In conclusion, we have shown that fused thiazoles can be obtained from the reaction of phenyliodonium ylids of cyclic β-dicarbonyl compounds with thioureas. The reaction proceeds through thiouronium dipoles and can be considered as a modification of Hantzsch synthesis of thiazoles.

The investigation of the reactivity of aryliodonium ylids with other types of thiocarbonyl compounds will be continued.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir-spectra were determined on a Perkin-Elmer 1370 spectrometer. The ^{1}H-nmr spectra were recorded on a Bruker AW 80 MHz spectrometer using tetramethylsilane as an internal standard. The ms spectra were recorded on a VG TS-250 instrument.

Ylids **4a,b** were prepared as it was previously described [4]. Ylids **12** and **14** were prepared by the method of Shank [7].

General Procedure for the Preparation of Thiouronium Ylids **6e-g**, **10a-c** and **13**, **14**.

The appropriate thiourea (1 mmole) was added to a stirring suspension of the corresponding phenyliodonium ylid (1 mmole) in dichloromethane (15 ml). After 24 hours at room temperature the resulting solid was filtered and washed several times with small amounts of dichloromethane to afford the thiouronium ylids **6e-g**, **10a-c** and **13**, **14**. Analytical and spectroscopic data for ylids **6e-g** and **10a-c** are reported on Tables 1 and 2.

Thiouronium Ylid of 4-Hydroxy-6-methyl-2-pyrone (**13**).

This compound was isolated in 47% yield, mp 190°; ir (nujol): ν_{max} 3330, 3280, 1650, 1580 cm^{-1} ; ^{1}H nmr (deuteriochloroform): δ 6.06 (s, 1H), 2.24 (s, 3H); ms: m/z 200 (M^+, 21), 158 (25), 116 (31), 43 (100).

Anal. Calcd. for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99. Found: C, 41.88; H, 4.17; N, 14.01.

Thiouronium Ylid of 4-Hydroxycoumarin (**15**).

This compound was isolated in 38% yield, mp 207°; ir (nujol): ν_{max} 3290, 3180, 1640, 1590 cm^{-1}; ^{1}H nmr (deuteriochloroform-trifluoroacetic acid): δ 8.10 (d, J = 9 Hz, 1H), 7.87-7.56 (m, 2H), 7.30 (d, J = 9 Hz, 1H); ms: m/z 236 (M^+, 17), 218 (M^+-H_2O, 52), 187 (47), 162 (78), 121 (100).

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41; N, 11.86. Found: C, 50.70; H, 3.41; N, 11.68.

General Procedure for the Preparation of 2-Amino-10-methyl-10*H*-benzo[*b*]oxepino[5,6-*d*]thiazol-4-ones **7a-d** and 2-Amino-6,6-dimethylcyclohexano[*d*]thiazole-4-ones **11a-c**.

The proper thiourea (1 mmole) and the corresponding iodonium ylid (1 mmole) were refluxed in dichloromethane (20 ml) for 4 hours. Any insoluble material was removed by filtration and the corresponding thiazole derivative was obtained by addition of hexane to the dichloromethane solution. It was purified either by recrystallization from dichloromethane-hexane or by column chromatography (silica gel, dichloromethane-hexane, 1:1) followed by recrystallization from the same solvent. The addition of catalytic amount of cupric acetylacetate ($Cu(acac)_2$) reduced the reaction time without affecting the yield of the reaction.

Thiazoles **11a-c** can also be prepared by refluxing solutions of the corresponding thiouronium ylids in acetonitrile or ethanol for 4 hours. This is the best way to prepare the methyl thiazole derivative **11b**.

Analytical and spectroscopic data for thiazoles **7a-d** and **11a-c** are reported on Tables 3 and 4.

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