An Improved Method for the Synthesis of 2-Thioxo-2,3-dihydro-1,3-benzoxazoles [2(3*H*)-Benzoxazolethiones]

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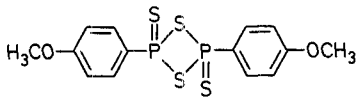
Some substituted 2(3*H*)-benzoxazolethiones were needed in substantial quantities as intermediates for the synthesis of benzoxazole derivatives of medicinal interest. However, the reported methods[1,2,3] were found to be unsatisfactory for the large-scale preparation of these compounds as they all involve the use of substituted 2-aminophenols as intermediates, some of which require tedious multistep procedures for their preparation. In addition, some of the methods also suffer from the inconvenience of using toxic and hazardous reagents like thiophosgene and carbon disulfide. Although a patent[4] has claimed the preparation of several substituted 2-aminophenols by ring cleavage of benzoxazolones, the synthesis of 2-benzoxazolethiones from the 2-aminophenols thus obtained would still be unsatisfactory from a preparative point of view. Thus, it was desirable to develop a convenient method for the direct conversion of the benzoxazolones into the required thiones. Such a method should have certain advantages like operational convenience and better yields over the conventional methods since several benzoxazolones can be conveniently prepared[5,6] in good yields starting from easily available materials like salicylic acid and its derivatives. The only reaction of this type hitherto reported[7] is the synthesis of 3-methyl-2-thioxo-2,3-dihydro-1,3-benzoxazole **(3h)** in unspecified yield by heating the 2-oxo analogue **(2h)** with phosphorus(V) sulfide at 170°C. In our hands, the reaction of a few benzoxazolones **(2a, b, c, h)** with phosphorus(V) sulfide under different conditions[7,8,9] gave the 2-thioxo analogues **(3a, b, c, h)** in relatively low yields (35–45%).

We have previously reported[10] the use of 2,4-bis[4-methoxyphenyl]-1,3,2,4-dithiadiphosphetane 2,4-bis-sulfide (**1**; Lawesson reagent) for the conversion of lactams into thiolactams in nearly quantitative yields. We now report that the interaction of reagent **1** with 2(3*H*)-benzoxazolones **(2)** under mild conditions provides a convenient method for the synthesis of the desired benzoxazolethiones **(3)**.



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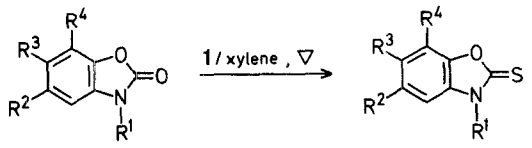

2 **3**

2,3	R^1	R^2	R^3	R^4	2,3	R^1	R^2	R^3	R^4
a	H	H	H	H	**g**	H	CH_3	H	CH_3
b	H	Cl	H	H	**h**	CH_3	H	H	H
c	H	CH_3	H	H	**i**	CH_3	CH_3	H	H
d	H	H	Cl	H	**j**	CH_3	CH_3	H	CH_3
e	H	H	Br	H	**k**	H	NO_2	H	H
f	H	Cl	Cl	H	**l**	H	H	NO_2	H

Table. 2-Thioxo-2,3-dihydro-1,3-benzoxazoles [**3**; 2(3*H*)-Benzoxazolethiones] prepared[a]

Product **3**	Yield[b] [%]	m.p. [°C]	Molecular formula[c] or Lit. m.p.	M.S. (70 eV) *m/e* (M^+)	^{1}H-N.M.R. (solvent[d]/TMS_{int}) δ [ppm]
a	80	189–191°	189–191°[3]	151	7.1–7.45 (m, 4H); 12.2 (bh, 1H)
b	88	260°	260–261°[3]	185, 187	—
c	90	224°	223–225°[11]	165	2.4 (s, 3H); 6.9–7.1 (m, 3H); 7.43 (s, 1H)
d	70	223–225°	224–225°[3]	185, 187	—
e	72	226–228°[e]	198–200°[7]	229, 231	7.1–7.8 (m, 3H)
f	80	221–223°	$C_7H_3Cl_2NOS$ (220.1)	219, 221, 223	—
g	78	228–230°[f]	202–203°[3]	179	2.34 (s, 6H); 6.85 (s, 2H)
h	74	133°	133–134°[7]	165	3.71 (s, 3H); 7.0–7.4 (m, 4H)
i	76	151–152°	C_9H_9NOS (179.2)	179	2.3 (s, 3H); 3.6 (s, 3H); 6.8–7.3 (m, 3H)
j	78	161–162°	$C_{10}H_{11}NOS$ (193.2)	193	2.4 (s, 6H); 3.66 (s, 3H); 6.72 (s, 1H); 6.85 (s, 1H)
k	70[g]	239–241°	241°[2]	196	—
l	70[g]	230°	230°[2]	196	—

[a] Compounds **2** were prepared according to Ref.[7,12–15].

[b] Yield of pure recrystallized product based on **2**.

[c] The microanalyses were in good agreement with the calculated values: C, ±0.30; H, ±0.30; N, ±0.30.

[d] Solvent $CDCl_3$ for **3e, h, i, j**; DMSO-d_6 for **3e, g**; acetone-d_6 for **3a**.

[e] An authentic sample of **3e**, prepared by condensing 5-bromo-2-aminophenol with potassium ethyl xanthate, had m.p. 226–228°C (undepressed on admixture of a sample prepared by the present method). The structure of **3e** was further confirmed by its spectral and microanalytical data.

[f] An authentic sample of **3g** prepared following the reported method[3] melted in our hands at 228–230°C (undepressed on admixture with a sample obtained in the present method). The structure of **3g** was further confirmed by its spectral and microanalytical data.

[g] For the completion of the thionation reaction, the nitrobenzoxazolones **2k** and **2l** require excess of the reagent **1** and relatively longer reaction times. Thus, a stirred mixture of **2k** (30 mmol) and reagent **1** (30 mmol) is refluxed in xylene (200 ml) for 5 h and the resultant product **3k** is isolated following the general procedure. Product **3l** is prepared in an analogous manner.

The structure of products **3** was confirmed by microanalyses, mass-, I.R.-, and ^{1}H-N.M.R.-spectral data.

The mild reaction conditions, the easy work-up, the high yields (70–90%), and the purity of the products make the present synthesis a convenient general method for the preparation of 2(3*H*)-benzoxazolethiones and their 3-alkyl derivatives.

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were performed using a Hosli microcombustion apparatus MK 101. Mass spectra were recorded on a Varian MAT CH 7A mass spectrometer. I.R. spectra were taken on a Perkin-Elmer 577 spectrophotometer and the ^{1}H-N.M.R. spectra were recorded on a Varian A-90 (EM-390) spectrometer.

2-Thioxo-2,3-dihydro-1,3-benzoxazoles [3; 2(3*H*)-Benzoxazolethiones]; General Procedure:

A stirred mixture of Lawesson reagent (**1**; 18 mmol) and the benzoxazolone **2** (30 mmol) is heated under reflux in xylene (150 ml). The progress of the reaction is monitored by T.L.C. (silica gel, hexane/ethyl acetate). After completion of the reaction (2–3 h), the mixture is cooled to room temperature and filtered through a 25 × 5 cm column filled with silica gel using hexane/ethyl acetate (9/1 v/v) as eluent. The residue, obtained on evaporation of the solvent, is recrystallized from ethanol/water to give the pure product **3**.

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