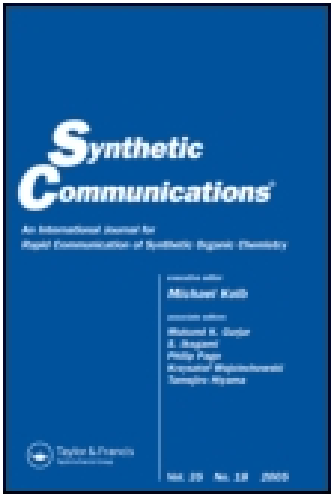

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of 4-(2-Furyl)-2-substituted Thiazoles Utilising [Hydroxy(tosyloxy)iodo]benzene

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Published online: 20 Aug 2006.

To cite this article: Shiv P. Singh , Rajesh Naithani , Ranjana Aggarwal & Om Prakash (1998) A Convenient Synthesis of 4-(2-Furyl)-2-substituted Thiazoles Utilising [Hydroxy(tosyloxy)iodo]benzene, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:13, 2371-2378, DOI: 10.1080/00397919808004289

To link to this article: http://dx.doi.org/10.1080/00397919808004289

SYNTHETIC COMMUNICATIONS, 28(13), 2371-2378 (1998)

A CONVENIENT SYNTHESIS OF 4-(2-FURYL)-2-SUBSTITUTED THIAZOLES UTILISING [HYDROXY(TOSYLOXY)IODO]BENZENE

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Abstract A facile synthesis of 4-(2-furyl)-2-substituted thiazoles by hypervalent iodine oxidation of 2-acetylfuran (1) using [hydroxy(tosyloxy)iodo]benzene, followed by treatment of the reaction mixture with appropriate thioureas/thioamides is described.

One of the most common syntheses of thiazoles involves the condensation of α-halogenoketones with thioureas/ thioamides (Hantzsch thiazole synthesis). However, the versatility of this reaction is somewhat limited by the difficulty in preparation, purification, toxicity and lachrymatory property of the intermediate α-halogenoketones[1]. Furthermore, direct halogenation of ketones with a reactive moiety often leads to the formation of side products.

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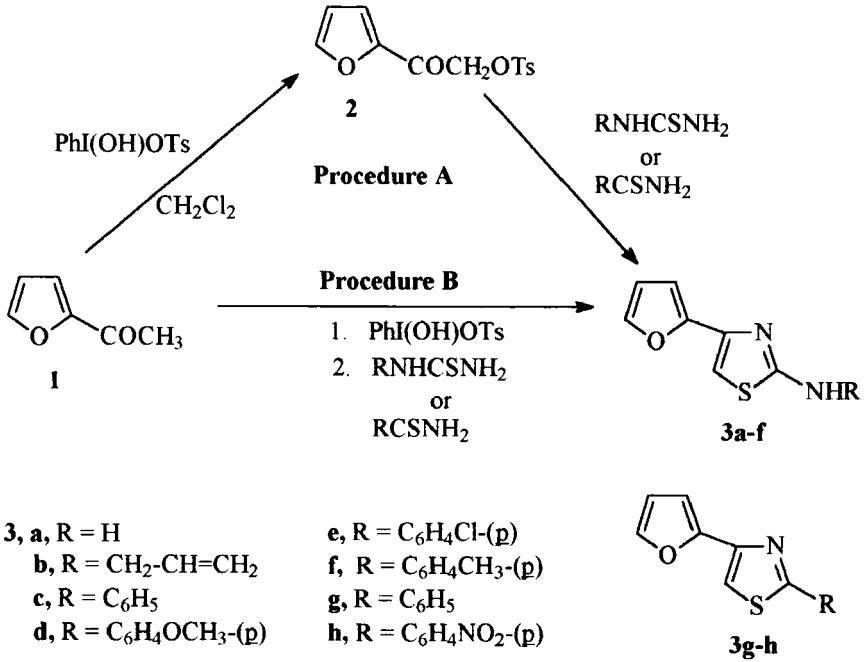
Because of our continued interest in the synthesis of potential phototoxic molecules bearing close resemblance with α-terthienyl[2-4], we planned to undertake the synthesis of several 4-(2-furyl)-2-substituted thiazoles (**3**). Synthesis of a few **3** was earlier reported by Knott[5] utilizing the conventional Hantzsch thiazole synthesis. The intermediate 2-halo-acetylfurans (chloro or bromo) were obtained by a hazardous procedure involving the treatment of 2-furoylchloride (highly lachrymatory) with diazomethane (highly toxic) followed by the decomposition of the intermediate with dry HCl or HBr. Subsequently, Antonino ***et al.***[6] attempted direct bromination of 2-acetylfuran in CCl_4. The product was obtained in poor yield, apparently due to a number of side reactions on the highly reactive furan ring including the bromination of position-5.

We report in this communication a facile synthesis of the title compounds (**3**) through a very simple and eco-friendly methodology, consisting of one or two steps, starting from 2-acetylfuran (**1**). Stirring of **1** with [hydroxy(tosyloxy)iodo]benzene (HTIB) in CH_2Cl_2 at room temperature, provided 2-tosyloxyacetylfuran (**2**) as a crystalline, stable solid in 70% yield. Synthesis of **2** has earlier been reported by converting **1** into its trimethyl silyl enol ether followed by its treatment with HTIB[7]. Our procedure thus has a distinct advantage over the existing method.

Synthesis of **3** can then readily be achieved by two alternate procedures (A or B) as outlined in the Scheme 1.



Scheme 1

Procedure A consists of conversion of **1** into **2** followed by its condensation with thioureas/thioamides, whereas procedure B involves direct transformation of **1** to **3** without the need for the isolation of **2**. Apparently, there is *in situ* formation of **2** which underwent smooth transformation with thiourea/thioamides affording **3** in excellent yields.

Finally, the present work is significant because of two reasons :

1. Synthesis of several **3** which may have phototoxic property can be achieved from **1** in one pot.

2. A facile synthesis of **2** which may have diverse synthetic applications is available.

Experimental

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 IR spectrophotometer and ^{1}H NMR spectra on a Bruker 300 MHz instrument. Mass spectra were recorded on Kratos MS-50 mass spectrometer.

4-(2-Furyl)-2-substituted thiazoles (3a-h): General Procedure

Procedure A: (via isolation of α-tosyloxyketone)

α-Tosyloxyacetylfuran (2): Step 1

To a stirred solution of 2-acetylfuran (**1**, 1.1 g, 0.01 mol) in dichloromethane (100 ml) was added [hydroxy(tosyloxy)iodo]benzene (3.9 g, 0.01 mol) and the reaction mixture was stirred at room temperature for 24hr. Excess dichloromethane was distilled off under reduced pressure and the residual mass was crystallised from ethanol. The product was further washed with cold ethanol and dried, yield 1.95 g (70%), m.p. 65°C, Lit.m.p. 66°C.

4-(2-Furyl)-2-substituted thiazoles : Step 2

To a solution of (tosyloxy)methyl 2-furyl ketone (**2**, 0.002 mol) in ethanol was added equimolar amount of appropriate thiourea/thioamide and the reaction mixture was refluxed for 4 hr. On cooling, a crystalline product was separated out which was filtered, washed with saturated sodium bicarbonate solution, then with water and recrystallised from aq. ethanol.

Procedure B : One pot synthesis of 3 starting from 2-acetylfuran

To a solution of 2-acetylfuran (**1**, 1.1 g, 0.01 mol) in dichloromethane was added HTIB (3.9 g, 0.01 mol) and the reaction mixture was allowed to stir for 24 hr. at room temperature. Excess of dichloromethane was distilled off under reduced pressure and to the reaction mixture was added equimolar amount of appropriate thiourea/thiomide and ethanol (20 ml). The resulting mixture was refluxed for three to four hours. On cooling the product was separated out as a crystalline solid which was filtered washed with saturated sodium bicarbonate solution, then with water and recrystallised from aqueous ethanol.

4-(2-Furyl)-2-aminothiazole (**3a**), yield 67%, m.p. 115°C, Lit.m.p. 117°C.

4-(2-Furyl)-2-aminoallythiazole (**3b**), yield 72%, m.p. 104°C, ^{1}H NMR ($CDCl_3$): δ 3.87(d, 2H, CH_2-CH=CH_2), 5.14-5.19 (m, 2H, CH_2-CH=CH_2), 5.81-5.92 (s, 1H, CH_2-CH=CH_2), 6.40-6.41 (m, 1H, Furyl-4H), 6.42 (m,

1H, NH-H), 6.60-6.61 (d, 1H, Furyl-3H), 6.65 (s, 1H, Thiazol-5H), 7.37 (m, 1H, Furyl-5H); Mass spectra : M^+, m/z 206

Elemental analysis	Calculated	C 58.25	H 4.80	N 13.50
	Found	C 58.00	H 4.90	N 13.65

4-(2-Furyl)-2-aminophenylthiazole (**3c**), yield 73%, m.p. 106°C, Lit.m.p. 107°C.

4-(2-Furyl)-2-amino-4-p-methoxyphenylthiazole (**3d**), yield 68%, m.p. 108°C, ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 3H, OCH_3), 6.35-6.37 (m, 1H, Furyl-4H), 6.61-6.62 (d, 1H, Furyl-3H), 6.65 (s, 1H, Thiazol-5H), 6.80-7.29 (m, 4H, aromatic-H), 7.30 (s, 1H, Furyl-5H), 7.90-9.30 (s, 1H, NH-H); Mass spectra : M, m/z 272;

Elemental analysis	Calculated	C 61.76	H 4.40	N 7.30
	Found	C 61.38	H 3.95	N 7.15

4-(2-Furyl)-2-amino-4-p-chlorophenylthiazole (**3e**), yield 69%, m.p. 114°C, ^{1}H NMR ($CDCl_3$): δ 6.32 (m, 1H, Furyl-4H), 6.42-6.43 (d, 1H, Furyl-3H), 6.56 (s, 1H, Thiazol-5H), 7.24-7.27 (s, 4H, aromatic-H), 7.30 (m, 1H, Furyl-5H), 8.15 (s, 1H, NH-H)

Elemental analysis	Calculated	C 56.52	H 3.26	N 10.14
	Found	C 56.20	H 3.60	N 10.50

4-(2-Furyl)-2-amino-4-p-methylphenylthiazole (**3f**), yield 64%, m.p. 106°C, ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 6.41-6.42 (m, 1H, Furyl-4H), 6.65-6.66 (d, 1H, Furyl-3H), 6.73 (s, 1H, Thiazol-5H), 7.10-7.20 (m, 4H, aromatic-H), 7.37-7.38 (m, 1H, Furyl-5H), 7.91 (s, 1H, NH-H); Mass spectra : M^+, m/z 272;

Elemental analysis	Calculated	C 69.70	H 4.40	N 11.60
	Found	C 69.23	H 4.14	N 12.01

4-(2-Furyl)-2-phenylthiazole (**3g**), yield 71%, m.p. 66°C, Lit. m.p. 68°C.

4-(2-Furyl)-2-amino-p-nitrophenylthiazole (**3h**), yield 78%, m.p. 118°C, ^{1}H NMR ($CDCl_3$): 6.68 (m, 1H, Furyl-4H), 6.95 (s, 1H, Furyl-3H), 7.80 (s, 1H, Thiazol-5H), 8.03 (s, 1H, Furyl-5H), 8.05-8.29 (m, 4H, aromatic-H);

Elemental analysis	Calculated	C 57.35	H 2.90	N 10.28
	Found	C 57.80	H 3.23	N 10.05

Acknowledgements

We are grateful to Director, Regional Sophisticated Instrumentation Centre, Chandigarh for providing results of elemental analyses, IR and NMR data. We are indebted to Mass Spectrometry Facility supported by the Biomedical Research Technology Programme of the National Centre for Research Resources, University of California, San Francisco for providing us the high resolution mass spectra. We are also indebted to Ranbaxy Research Laboratories Ltd., New Delhi for providing financial assistance.

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(Received in the UK 10 November 1997)