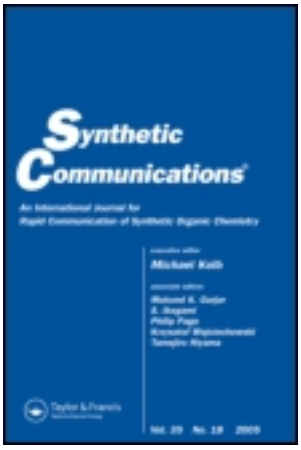

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile [hydroxy(tosyloxy)iodo]benzene Mediated Synthesis of Symmetrical Triazolo-[3,4-b]-1,3,4-Thiadiazines

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Published online: 23 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(16), 3133-3141 (1998)

A FACILE [HYDROXY(TOSYLOXY)IODO]BENZENE MEDIATED SYNTHESIS OF SYMMETRICAL TRIAZOLO-[3,4-b]-1,3,4-THIADIAZINES

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ABSTRACT : Synthesis of the title compounds has been accomplished by a one-pot procedure involving the reaction of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles and a variety of heterocyclic ketones in the presence of [hydroxy(tosyloxy)iodo]benzene.

In view of the pharmacological properties associated with the triazoles as well thiadiazine moieties[1-5], we focussed our attention to the synthesis of a few triazolothiadiazines with a five-membered heterocyclic unit which could be screened for their antimicrobial activity.

The reported procedure for synthesizing this ring system involves condensation of alpha-halogenoketones with

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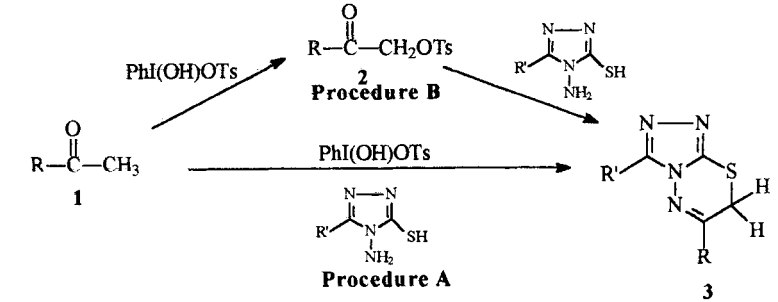
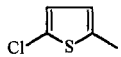
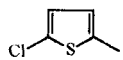
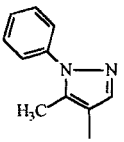
4-amino-5-mercapto-1,2,4-triazoles. Due to the hazards associated with the halogenation of ketones, the unstability and toxicity of alpha-halogeno ketones, it looked attractive to find suitable alternative to them.

We have already reported that synthesis of alpha-tosyloxy ketones can easily be achieved by treating a variety of ketones with [hydroxy(tosyloxy)iodo]benzene (HTIB)[6-9]. These compounds are stable, crystalline solids and provide a safe eco-friendly alternative route for synthesis of compounds conventionally prepared through alpha-halogeno ketones.

We report in this paper a one-pot HTIB mediated synthesis of triazolo-[3,4-b]-1,3,4-thiadiazines (**3**) using several heterocyclic ketones (**1**) and 4-amino-5-mercapto-1,2,4-triazoles in excellent yields following a simple work-up (Procedure A, Scheme 1). Intermediacy of alpha-tosyloxy ketones (**2**) in this reaction is demonstrated by the conversion of acetyl ketones into the corresponding tosyloxy derivatives which on treatment with triazoles yielded **3** as expected (Procedure B, Scheme 1). Procedure A was found to be more convenient than Procedure B. Structures of the newly synthesized compounds were confirmed by elemental analysis, ^{1}H NMR and mass spectral



3	R	R'
a		CH_3
b		H
c		CH_3
d		H

3	R	R'
e		CH_3
f		H
g		CH_3

Scheme 1

data. The compounds were evaluated for their anti-bacterial properties.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR was recorded on Bruker 300MHz FT NMR spectrometer. Elemental analysis was carried out on a

Perkin-Elmer 2400 instrument and mass spectra was recorded in Kratos MS-50 mass spectrometer.

Synthesis of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles

3-Substituted-4-amino-5-mercapto-1,2,4-triazoles were prepared according to the lietrature procedure[10].

7H-6-substituted symmetrical triazolo-[3,4-b]-1,3,4-thiadiazines (3a-g) : General Procedure

Procedure B (*via* isolation of aplha-tosyloxy ketone) : α-(tosyloxyacetyl)thiophene (2b) : Step 1

To a stirred solution of 2-acetyl thiophene (**1**, 1.26 gm, .01 m) in acetonitrile was added HTIB (3.9 gm, 0.01m) and reaction mixture was refluxed for 4-6 hr. Excess of acetonitrile was distilled off under reduced pressure and residual mass was crystallized from ethanol. The product was further washed with cold ethanol and dried, yield 70% (1.97 gm), m.p. 95° (Lit.[11] m.p. 96°).

3-Methyl-7H-6-(2-thienyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine Step 2:

To a solution of **2b** (0.560 gm, 0.002 m) in ethanol was added equimolar amount of 3-methyl-4-amino-5-mercapto-1,2,4-triazole and reaction mixture was refluxed for 4 hrs. On cooling, a crystalline product was separated out which was

filtered, washed with saturated sodium bicarbonate solution, then with water and recrystallized from aqueous ethanol, yield 90% (1.02 gm), m.p. 163-64° (decomposes).

One pot synthesis of 3 starting from acetyl compound Synthesis of 7H-6-substituted symmetrical triazolo-[3,4-b]-1,3,4-thiadiazines

To a solution of the ketones **1a-1d** and **1g** (0.01m) in acetonitrile was added HTIB (0.01m) and the reaction mixture was refluxed for 4-6 hrs. Excess of acetonitrile was distilled off. The formation of the respective alpha-tosyloxy ketones was confirmed by monitoring the TLC of the reaction mixture. This was treated with substituted 4-amino-5-mercapto-1,2,4-triazoles to yield the title compounds.

Compounds **3e** and **3f** were prepared through the *in situ* generation of 2-(tosyloxyacetyl)furan was accomplished by simply stirring 2-acetylfuran with HTIB for 24-48 hrs. To the reaction mixture, appropriately substituted 4-amino-5-mercapto-1,2,4-triazoles in dry ethanol were added. The resulting mixture was refluxed for 5-6 hrs. The solvent was distilled off under reduced pressure. On cooling, the products separated out as crystalline solids which were filtered, washed with saturated

bicarbonate solution, then with water and recrystallized from aqueous ethanol.

3-Methyl-7H-6-(2-thienyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3a**): yield 72%, m.p. 163-164° (decomposes)

Elemental Analysis :	Calculated	C, 45.76	H, 3.78	N, 23.72
	Found	C, 45.96	H, 4.10	N, 23.95

^{1}H NMR ($CDCl_3$) : δ 2.57 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 7.15-7.18 (m, 1H, thienyl-4H), 7.56-7.59 (d, 1H, thienyl-3H), 7.60 (d, 1H, thienyl-5H).

7H-6-(2-thienyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3b**): yield 66%, m.p. 154° (decomposes)

Elemental Analysis :	Calculated	C, 43.24	H, 2.70	N, 25.22
	Found	C, 43.72	H, 3.20	N, 24.98

^{1}H NMR ($CDCl_3$) : δ 4.01 (s, 2H, CH_2), 7.16-7.18 (m, 1H, thienyl-4H), 7.58-7.59 (d, 1H, thienyl-3H), 7.61-7.63 (d, 1H, thienyl-5H), 8.58 (s, H, triazol-3H); Mass spectra M, m/z 222.

3-Methyl-7H-6-(5-chloro-2-thienyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3c**): yield 72%, m.p. 216° (decomposes)

Elemental Analysis :	Calculated	C, 40.00	H, 2.59	N, 20.74
	Found	C, 39.74	H, 3.01	N, 20.19

^{1}H NMR ($CDCl_3$) : δ 2.55 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 6.98-6.99 (d, 1H, thienyl-3H), 7.32-7.33 (d, 1H, thienyl-4H).

7H-6-(5-chloro-2-thienyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3d**): yield 62%, m.p. 190° (decomposes)

Elemental Analysis :	Calculated	C, 37.50	H, 1.95	N, 21.87
	Found	C, 37.45	H, 2.20	N, 21.60

^{1}H NMR ($CDCl_3$) : δ 3.93 (s, 2H, CH_2), 6.99-7.00 (d, 1H, thienyl-3H), 7.34-7.36 (d, 1H, thienyl-4H), 8.59 (s, 1H, triazol-3H).

3-Methyl-7H-6-(2-furyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3e**): yield 61%, m.p. 182° (decomposes)

Elemental Analysis :	Calculated	C, 49.09	H, 3.63	N, 25.40
	Found	C, 48.95	H, 3.46	N, 25.21

^{1}H NMR ($CDCl_3$) : δ 2.58 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 6.64-6.65 (m, 1H, furyl-4H), 7.16-7.17 (s, 1H, furyl-3H), 7.68 (s, 1H, furyl-5H).

7H-6-(2-furyl)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3f**) : yield 60%, m.p. 182° (decomposes)

Elemental Analysis :	Calculated	C, 46.60	H, 2.91	N, 27.18
	Found	C, 46.30	H, 3.19	N, 26.91

^{1}H NMR ($CDCl_3$) : δ 3.96 (s, 2H, CH_2), 6.64-6.65 (m, 1H, furyl-4H), 7.16-7.18 (d, 1H, furyl-3H), 7.68 (s, 1H, furyl-5H), 8.59 (s, 1H, triazol-3H).

3-Methyl-7H-6-(4-phenyl-5-methylpyrazole)-s-triazolo-[3,4-b]-1,3,4-thiadiazine (**3g**): yield 66%, m.p. 212° (decomposes)

Elemental Analysis : Calculated C, 62.06 H, 4.60 N, 28.18
Found C, 61.60 H, 4.35 N, 27.62

^{1}H NMR ($CDCl_3$) : δ 2.56 (s, 3H, triazol-CH_3), 2.64 (s, 3H, pyrazol-CH_3), 3.87 (s, 2H, CH_2), 7.44-7.58 (m, 5H, aromatic-H), 7.95 (s, 1H, pyrazol-3H).

ACKNOWLEDGEMENTS

We are grateful to Director, Regional Sophisticated Instrumentation Centre, Chandigarh for providing results of elemental analysis, IR and NMR data. We are indebted to Ms. Yosman Dhar, Central Research Institute, Kasauli for anti-bacterial screening. We are also 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 the high resolution mass spectra. Thanks are due to Ranbaxy Research Laboratories, New Delhi for providing financial assistance.

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(Received in the USA 11 March 1998)