Hypervalent Iodine in the Synthesis of Bridgehead Heterocycles: Novel and Facile Syntheses of 3-Substituted-5,6-Dihydroimidazo[2,1-*b*]thiazoles and 3-Phenylthiazolo[3,2-*a*]benzimidazole from Acetophenones using [hydroxy(tosyloxy)iodo]benzene

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The synthesis of 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles **3a–f** has been achieved by using a novel and facile method involving hypervalent iodine oxidation of acetophenones **1a–f** with [hydroxy(tosyloxy)iodo]benzene, followed by the treatment of the resultant α-tosyloxyacetophenones **2a–f** (generated *in situ*) with ethylenethiourea. The same approach starting from **1a** and 2-mercaptobenzimidazole also supplied 3-phenylthiazolo[3,2-*a*]benzimidazole **7** *via* the intermediate 2-phenacylmercaptobenzimidazole.

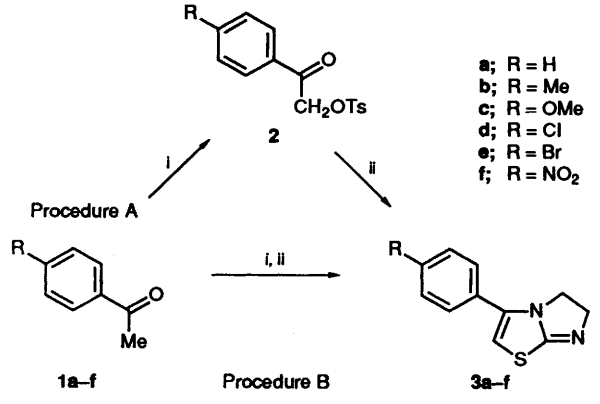
Our recent investigations[1,2] dealing with hypervalent iodine mediated syntheses have shown that [hydroxy(tosyloxy)iodo]-benzene (HTIB)[3] is an extremely important reagent providing new and useful syntheses of various heterocyclic compounds. The new approach has distinct advantages over the literature methods especially for 2-aroylcoumaran-3-ones[2] as this novel synthesis involves simple experimentation, and avoids the highly lachrymatory and not readily available α-halogeno-ketones which were used in earlier methods. Encouraged by these observations, we now report upon new and facile syntheses of series of bridgehead heterocyclic compounds, namely: 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles **3a–f** and 3-phenylthiazolo[3,2-*a*]benzimidazole **7**.

Part of our reason for undertaking this study was that compounds similar to **3** and **7** are known to possess important biological properties.[4,8]

Results and Discussion

The synthetic scheme used in the present study for **3** and **7** is based upon the assumption that α-halogenoketones and α-tosyloxyketones behave in an analogous manner. Thus, it was anticipated that α-tosyloxyacetophenones **2**, accessible from hypervalent iodide oxidation of acetophenones **3** with HTIB, on reaction with ethylenethiourea (2-mercaptoimidazoline, **4**) might provide a new synthesis of **3**. To check the feasibility of this idea, **1a** was converted to **2a** by treatment with HTIB in acetonitrile according to the procedure of Koser *et al.*[5] for α-tosyloxylation of ketones. Treatment of **2a** (colourless crystalline solid) with **4** by refluxing in acetonitrile for 13 h afforded the desired product **3a** as the toluene-*p*-sulfonate **3a**·TsOH in 60% overall yield with respect to **1a**. When ethanol was used as solvent instead of acetonitrile, the reaction was completed in 3–4 h. Basification of **3a**·TsOH with sodium carbonate or sodium hydroxide gave free base **3a**. Although the above procedure (Procedure A, Scheme 1) offered a novel and facile technique for synthesising **3a** and could be applied to other substituted derivatives *e.g.* **3b–f**, we realised that it could be simplified further by avoiding the step of isolation of intermediate **2a**. Accordingly, we attempted the above transformation using a direct procedure and indeed obtained **3a** from **1a** in 62% yield (Procedure B, Scheme 1).

The new synthesis was found to be general as various *para*-substituted acetophenones **1b–f** underwent smooth conversion to the corresponding products **3b–f** in good yields (Table 1). We



Scheme 1 *Reagents:* i, PhI(OH)OTs–MeCN; ii, Ethylenethiourea–MeCN or EtOH, dil. NaOH or Na_2CO_3

Table 1 3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles **3a–f** and their toluene-*p*-sulfonates **3a–f**·TsOH prepared according to procedure B of Scheme 1

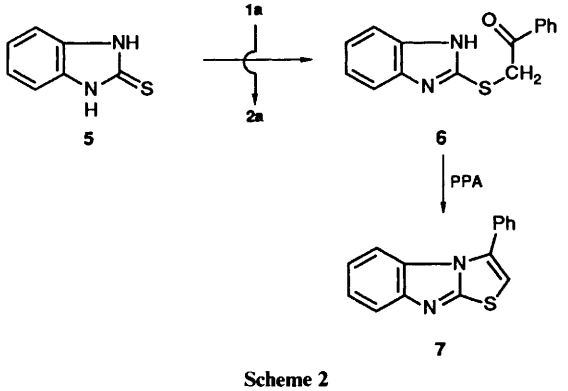
	Free base **3**[b]		**3**·TsOH[c]	
Compounds **3**, **3**·TsOH (R)	Yield (%)	M.p. (°C) (lit. m.p.)	Yield (%)	M.p. (°C)
a (H)	62	112–113 (110–111)[7]	66	167–169
b (Me)	75	gummy	82	205–208
c (OMe)	78	85–88	83	198–200
d (Cl)	60	113–114 (113–114)[7]	62	203–205
e (Br)	63	145–147 (145–146)[7]	73	202–203
f (NO_2)	66	216–218 (216–218)[7]	70	229

[a] Based on isolated products **3** and **3**·TsOH with respect to the quantity of acetophenone **1** used. [b] Spectral properties (^{1}H, NMR, IR) of all compounds agreed with the required/reported data. [c] δ_H($CDCl_3$–[$^2H_6$]DMSO) **3b**·TsOH: 2.21 (3 H, s, CH_3), 2.24 (3 H, s, $O_3SC_6H_4CH_3$), 4.00 (4 H, m, NCH_2CH_2N=), 5.88 (1 H, s, SC*H*=) and 6.90–7.73 (8 H, s, CH_3, aromatic protons). **3d**·TsOH: 2.23 (3 H, s, CH_3), 4.02 (4 H, br s, NCH_2CH_2N=), 6.19 (1 H, s, SC*H*=) and 6.90–7.67 (8 H, m, aromatic protons), **3e**·TsOH: 2.20 (3 H, s, CH_3), 3.87 (4 H, m, NCH_2CH_2N=), 5.96 (1 H, s, SC*H*=) and 6.90–7.75 (8 H, m, aromatic protons).

also found that it was not necessary to isolate the toluene-*p*-sulfonates of **3**; and basification was carried out during the reaction work up. Further it was observed that the reaction of **4** with α-tosyloxyacetophenones **2a–c** (generated *in situ*) which contain electron donating substituents, required longer reaction times (12–15 h) than those possessing electron withdrawing groups **2d–f** (4–6 h). This problem was overcome by performing the reactions in ethanol solvent rather than acetonitrile (see Experimental section).

It is evident from the data (Table 1) that procedure B, offering a one pot and convenient synthesis of **3a–f** from **1a–f** should be the method of choice over procedure A and all literature procedures.[6–9] It must be noted that the well known route to **3** makes use of α-halogenoketones. In view of the difficulties encountered in using and preparing α-halogenoketones Pujari *et al.*[8,9] modified the technique by replacing the halogenoketones by halogens[8] [or *N*-bromosuccinimide[9] (NBS)] and ketones but the technique suffers from the drawback that the procedure is cumbersome, more time consuming (about 25 h refluxing) and the product yields are low to moderate.

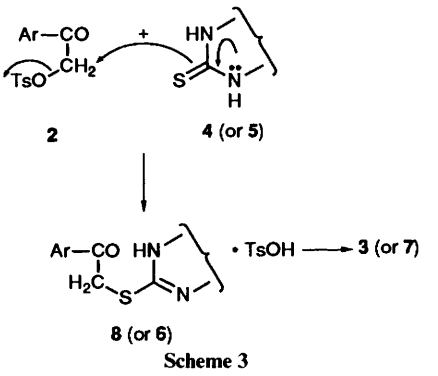
The most striking and useful feature of the newly developed I^{III} mediated approach is that there exists the possibility of furnishing a general synthetic replacement of several existing procedures involving halogenoketones for various classes of organic compounds in general, and bridgehead heterocyclic compounds in particular. To test the validity of this view we carried out the analogous reactions between α-tosyloxyacetophenone **2a** (generated *in situ* from **1a**) and 2-mercaptobenzimidazole **5** to synthesise **7**. This reaction resulted in the formation of expected 2-phenacylmercaptobenzimidazole **6** which on treatment with polyphosphoric acid using known conditions[12] afforded the final product **7**. However, our attempts to prepare **7** by a direct one pot approach (analogous to procedure B of Scheme 1) were not successful (Scheme 2).



5 6 7

Scheme 2

The mechanistic pathways for the new transformations obviously are analogous to the literature procedures[6–9] involving α-halogenoketones and thus transformation **1**→**3** proceeds *via* three main steps: (1) **1**→**2**, (2) **2**→2-phenacylmercaptoimidazolines **8** and (3) **8**→**3**. Step 1 occurs according to the pathways suggested by Koser *et al.*[5] The second step is simply the nucleophilic attack of sulfur (from **4**) onto the α-carbon atom of α-tosyloxyacetophenones to give **8** along with the expulsion of a molecule of toluene-*p*-sulfonic acid. Finally step 3, **8**→**3**, is well established. In order to confirm the occurrence of step 2, we actually isolated an intermediate of type **8** in one case (*p*-nitro derivative **8f**) by using acetone as solvent for this conversion. The conversion **1a**→**6**→**7** also occurs in a similar manner (Scheme 3).



2 4 (or 5) 8 (or 6)

Scheme 3

Experimental

M.p.s were taken in open capillaries and are uncorrected. IR spectra were recorded on a Beckman Spectrophotometer (IR-20) using Nujol mulls. ^{1}H NMR spectra were recorded in [$^2H_6$]DMSO–$CDCl_3$ or $CDCl_3$ at 90 MHz on a Perkin-Elmer R-32 machine, with $SiMe_4$ as internal standard. *J* values are given in Hz.

All acetophenones and ethylenethiourea were commercially available. HTIB was prepared by the method of Neiland and Karele[10] and Koser *et al.*[11]

Synthesis of 3-*Aryl*-5,6-*dihydroimidazo*[2,1-b]*thiazoles* **3a–f**. —*Procedure A:* via *Isolation of* α-*tosyloxyacetophenones* **2**. Step 1: α-Tosyloxyacetophenone **2a**. HTIB (2 g, 5.1 mmol) was added to a solution of acetophenone **1a** (0.6 g, 5 mmol) in acetonitrile (40 cm^3) and refluxed for 2 h. The solvent was removed by distillation and the residue was crystallised out by the addition of a little ethanol (1–2 cm^3). Filtration and washing with cold ethanol gave compound **2a** (0.55 g, 76%), m.p. 92–93 °C (lit.,[5] m.p. 91–92 °C).

Step 2: 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium tosylate **3a**•TsOH. α-Tosyloxyacetophenone **2a** (0.725 g, 2.5 mmol) and ethylenethiourea **4** (0.255 g, 2.5 mmol) were refluxed in acetonitrile (20 cm^3) for 14 h or in ethanol (50 cm^3) for 4 h. The solvent was distilled off and a little acetone (5 cm^3) was added with stirring. Filtration and washing with cold acetone afforded compound **3a**•TsOH, m.p. 167–169 °C.

Step 3:* 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole **3a**. The salt **3a**•TsOH obtained from the preceding step was dissolved in hot water and basified with dil. sodium hydroxide solution or saturated aqueous sodium carbonate. The salt was filtered off, washed with water and dried to give the title compound **3a** (79%), overall yield 60%, m.p. 112–113 °C (from benzene–light petroleum) (lit.,[7] m.p. 110–111 °C).

Procedure B: Without isolating α-*tosyloxyacetophenones* **2a–f**. Step 1: 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium tosylate **3**•TsOH from acetophenone. HTIB (2 g, 5.1 mmol) was added to a solution of acetophenone (0.6 g, 5 mmol) in acetonitrile (40 cm^3) and refluxed for *ca.* 2 h.† To the resulting solution, was added ethylenethiourea (0.51 g, 5 mmol) and the mixture was refluxed for 14 h. Most of the solvent was distilled off and the salt was crystallized out by adding acetone (5 cm^3) and stirring. The salt was filtered off, washed with cold acetone and dried to give **2a** (1.2 g, 66%), m.p. 167–169 °C which was used as such without further purification for the basification in the next step.

Step 2:* 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole **3**.

* It is not necessary to isolate **3**•TsOH as it can be basified during the work up of step 1.

† Alternatively, removal of the solvent by distillation, followed by addition of ethylenethiourea, ethanol (50 cm^3) and then refluxing the residual solution yielded product during 3–4 h. The use of ethanol rather than acetonitrile in other cases **3b–f** gave better results. The time required for the completion of reaction was reduced to 2–4 h. So it is recommended that **3b–f** are prepared using ethanol.

Basification followed, as described in procedure A. Yield 93%; m.p. 112–113 °C, overall yield 62%.

Following the same procedure **1b–f** were converted to **3b–f**. The characterization data of **3a–f** and their toluene-*p*-sulfonates (**3a–f**·TsOH, crude) are given in Table 1.

Preparation of 2-(4-*Nitrophenacyl*)*mercaptoimidazoline* **8f** *Using Acetone as Solvent.*—A solution of *p*-nitro-α-tosyloxyacetophenone **2f** (m.p. 139 °C) (0.42 g, 2.5 mmol) and ethylenethiourea (0.125 g, 2.5 mmol) in acetone was refluxed for 1 h and the resulting solution was cooled in a refrigerator. This solution after filtration and washing with cold acetone gave the salt (0.36 g, 68%) as colourless crystalline solid.

A small amount of salt was dissolved in hot water and filtered. The filtrate was basified with dil. sodium hydroxide solution and filtered to yield **8f** (67%) as a yellow solid, overall yield 46%, m.p. 162–164 °C (lit.,[7] m.p. 165–168 °C).

Preparation of 3-*Phenylthiazolo*[3,2-a]*benzimidazole* **7**.—*Step* 1. 2-*Phenacylmercaptobenzimidazole* **6**. Acetophenone (0.6 g, 5 mmol) was treated with HTIB (2 g, 5.1 mmol) according to procedure B for about 2 h. To the resulting solution was added 2-mercaptobenzimidazole (0.75 g, 5 mmol) and the mixture was refluxed for 6–7 h. Acetonitrile was distilled off and the salt was isolated by adding a little ethanol (1–2 cm^3) and stirring. This solution was filtered, washed with cold ethanol and dried, and treatment with saturated sodium hydrogen carbonate solution followed by filtration and washing gave the free base **6**, m.p. 172–173 °C (lit.,[12] m.p. 172 °C).

Step 2. 3-*Phenylthiazolo*[3,2-a]*benzimidazole* **7**. Compound **7** was prepared by cyclisation of **6** using polyphosphoric acid according to the conditions described in ref. 12, m.p. 139–140 °C (lit.,[12] m.p. 140 °C).

Acknowledgements

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