SHORT PAPER

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Hypervalent iodine in synthesis 92. A facile synthesis of 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles by cyclocondensation of alkynyl(phenyl)iodonium salts and imidazolidine-2-thione†

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A simple method for the synthesis of 3-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles is achieved by cyclocondensation of alkynyl(phenyl)iodonium salts with imidazolidine-2-thione.

Keywords: hypervalent iodine, 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles

3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles are known to possess valuable pharmacological, anti-inflammatory and anorectic activities, and some also show a positive inotropic effect on the heart.[1,2] These heterocyclic compounds also possess fungicidal,[3] mutagenic,[4,5] antitumor[6] and radioprotective[7] activities. Generally, synthesis of these compounds involves utilisation of lachrymatory starting materials and hazardous reagents, and requires extended reaction times and drastic conditions.[1, 3, 6-17] Recently, several new methods[18-20] have been reported which involve hypervalent iodine oxidation of acetophenones by [hydroxy(tosyloxy)iodo]benzene, followed by cyclocondensation with imidazolidine-2-thione in CH_3CN under reflux or without solvent with the application of microwave irradiation to give 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles. Although they offer several superior and general alternatives to existing synthesis, the lengthy sequences and the demanding reaction conditions still remain to be optimised.

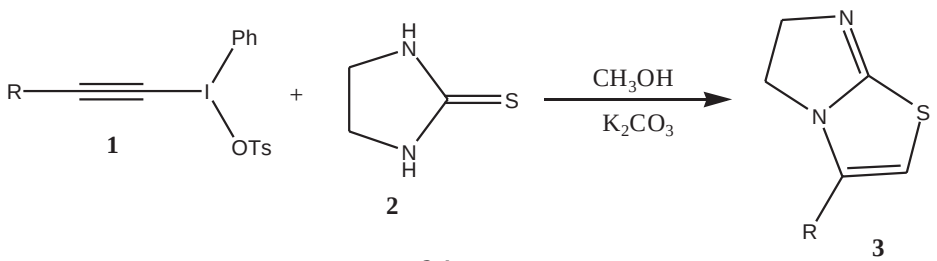
Alkynyl(phenyl)iodonium salts have recently generated a considerable interest for the synthesis of a variety of five-membered heterocycles.[21] Previously, we have reported the synthesis of 2-mercaptothiazoles and selenazoles by the cyclocondensation of alkynyl(phenyl)iodonium salts with ammonium dithiocarbamate and selenoamides respectively.[22,23] As a continuation of our research on the reaction between alkynyl(phenyl)iodonium salts and 1, 3-binucleophilic reagents to develop novel methodologies for the synthesis of some five-membered heterocyclic compounds, we examined the reaction of alkynyl-(phenyl)iodonium salts with imidazolidine-2-thione, which would provide a new route for the synthesis of bridgehead heterocyclic compounds, namely, 3-substituted 5,6-dihydroimdazo[2,1-*b*]thiazoles.

We found that the cyclocondensation of alkynyl (phenyl)iodonium salts with imidazolidine-2-thione occurred easily in CH_3OH under reflux in the presence of K_2CO_3. In fact, simple stirring of a mixture of the alkynyl (phenyl)iodonium salts **1** with imidazolidine-2-thione **2** in CH_3OH under reflux for about one hour in the presence of K_2CO_3 gave, after workup, the 3-substituted 5, 6-dihydroimidazo[2,1-*b*]thiazoles **3** in moderate to good yields (Scheme 1). The results are summarised in Table 1. The products were characterised by m.p. ^1H NMR, IR spectral data and microanalyses. They are identical to the data reported in the literature.

The reaction was found to be general and applicable to both alkyl- and aryl-ethynyl(phenyl)iodonium salts. Several arylethynyl(phenyl)iodonium salts containing various substituents, such as fluoro, chloro, bromo and n-butyl groups were successfully reacted (see Table 1).

The regiochemistry of the reaction can be confirmed by comparison with the already known 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles[19] in their physical and spectral data. As expected, the products prepared by these two methods were identical. Therefore, **3** are shown to be 3-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles, not the 2-substituted isomers.

A plausible mechanism for the formation of **3** is analogous to the earlier reported[24] synthesis of thiazoles from alkynyl(phenyl)iodonium salts and thioamides involving the intramolecular cyclisation of the intermediate alkylidenecarbene, which is shown in Scheme 2. It involves the attack of the iodonium ion of alkynyl(phenyl)iodonium



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Synthesis of 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles by cyclocondensation of alkynyl(phenyl) iodonium salts and imidazolidine-2-thione

Entry	Alkynyl(phenyl) iodonium salts	R in product **3**	Yield[a]/%
3a	Ph–C≡C–IPhOTs	Ph	67
3b	*p*-FC_6H_4–C≡C–IPhOTs	*p*-FC_6H_4	78
3c	*p*-ClC_6H_4–C≡C–IPhOTs	*p*-ClC_6H_4	71
3d	*p*-BrC_6H_4–C≡C–IPhOTs	*p*-BrC_6H_4	75
3e	*t*-Bu–C≡C–IPhOTs	t-Bu-	69
3f	*p*-BuC_6H_4–C≡C–IPhOTs	*p*-BuC_6H_4	70

[a]Isolated yield based on alkynyl(phenyl)iodonium salt **1**.

salts **1** on the sulfur of imidazolidine-2-thione **2** to form the primary addition products **4**, followed by a polyhetero-Claisen rearrangement,[25] 1,1-elimination of iodobenzene to generate the carbene **7**, and insertion of the carbene into mercapto to give 3-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles **3**.

In conclusion, the present study provides a new facile method of synthesis of 3-substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles which has some advantages over existing ones such as avoiding the use of the lachrymatory and toxic α-halogenoketones, mild reaction conditions, ready availability of alkynyl(phenyl)iodonium salts and short reaction time. Furthermore, the range of application of alkynyl-(phenyl)iodonium salts in organic chemistry has been extended.

Experimental

Melting points were determined on an X_4-Data microscopic melting point apparatus. Microanalyses were obtained using Carlo-Erba 1106. ^{1}H NMR spectra were obtained at 400 MHz in DMSO-d_6 using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 683 spectrometer.

General procedure for the synthesis of 3-substituted 5,6-dihydroimdazo[2,1-b]thiazoles **3**: To a solution of 1.2 mmol imidazolidine-2-thione in 15 ml CH_3OH was added 0.6 mmol K_2CO_3. While stirring, 1 mmol alkynyl(phenyl)iodonium salt was added and the mixture was refluxed for 1h. The resulting mixture was concentrated to 5 ml, filtered over Celite and chromatographed on a silical gel plate using EtOAc/CH_3OH (4:1) as eluent to afford pure product.

3a: M.p. 111–112 °C. ^{1}H NMR δ 3.87 (t, *J* 9.2 Hz, 2H), 4.09 (t, *J* 9.2 Hz, 2H), 6.13 (s, 1H), 7.39–7.51 (m, 5H). ν_{max}/cm^{-1} (KBr) 3080, 1670, 1305, 830 (Found: C, 65.21; H, 4.91; N, 13.92. $C_{11}H_{10}N_2S$ requires C, 65.35; H, 4.95; N, 13.86).

3b: M.p. 91–93°C. ^{1}H NMR δ 3.85 (t, *J* 9.2 Hz, 2H), 4.08 (t, *J* 9.2 Hz, 2H), 6.13 (s, 1H), 7.26–7.31 (m, 2H), 7.59–7.63 (m, 2H), ν_{max}/cm^{-1} (KBr) 3100, 1675, 1315, 830 (Found: C, 59.90; H, 4.08; N, 12.78. $C_{11}H_9FN_2S$ requires C, 59.98; H, 4.12; N, 12.72).

3c: M.p. 112 °C. ^{1}H NMR δ 3.91 (t, *J* 9.2 Hz, 2H), 4.12 (t, *J* 9.2 Hz, 2H), 6.26 (s, 1H), 7.49–7.63 (m, 4H). ν_{max}/cm^{-1} (KBr) 3090, 1673, 1310, 828 (Found: C, 55.78; H, 3.80; N, 11.88. $C_{11}H_9ClN_2S$ requires C, 55.81; H, 3.81; N, 11.84).

3d: M.p. 144–145 °C. ^{1}H NMR δ 3.86 (t, *J* 9.2 Hz, 2H), 4.08 (t, *J* 9.2 Hz, 2H), 6.23 (s, 1H), 7.47–7.53 (m, 2H), 7.63–7.65 (m, 2H). ν_{max}/cm^{-1} (KBr) 3085, 1670, 1310, 828 (Found: C, 46.91; H, 3.18; N, 9.99. $C_{11}H_9BrN_2S$ requires C, 46.98; H, 3.20; N, 9.96).

3e: M.p. 96–97 °C. ^{1}H NMR δ 1.18 (s, 9H), 3.93 (t, *J* 8.4 Hz, 2H), 4.02 (t, *J* 8.4 Hz, 2H), 5.52 (s, 1H). ν_{max}/cm^{-1} (KBr) 3065, 1670, 1305, 820 (Found: C, 59.21; H, 7.72; N, 15.41. $C_9H_{14}N_2S$ requires C, 59.30; H, 7.74; N, 15.37).

3f: M.p. 117–119 °C. ^{1}H NMR δ 0.90 (t, *J* 7.2 Hz, 3H), 1.29–1.34 (m, 2H), 1.52–1.58 (m, 2H), 2.60 (t, *J* 8.0 Hz, 2H), 3.87 (t, *J* 9.2 Hz, 2H), 4.08 (t, *J* 9.2 Hz, 2H), 6.08 (s, 1H), 7.26 (d, *J* 8.0 Hz, 2H), 7.46 (d, *J* 8.0 Hz, 2H). ν_{max}/cm^{-1} (KBr) 3070, 1668, 1305, 825 (Found: C, 69.66; H, 6.98; N, 10.89. $C_{15}H_{18}N_2S$ requires C, 69.73; H, 7.02; N, 10.84).

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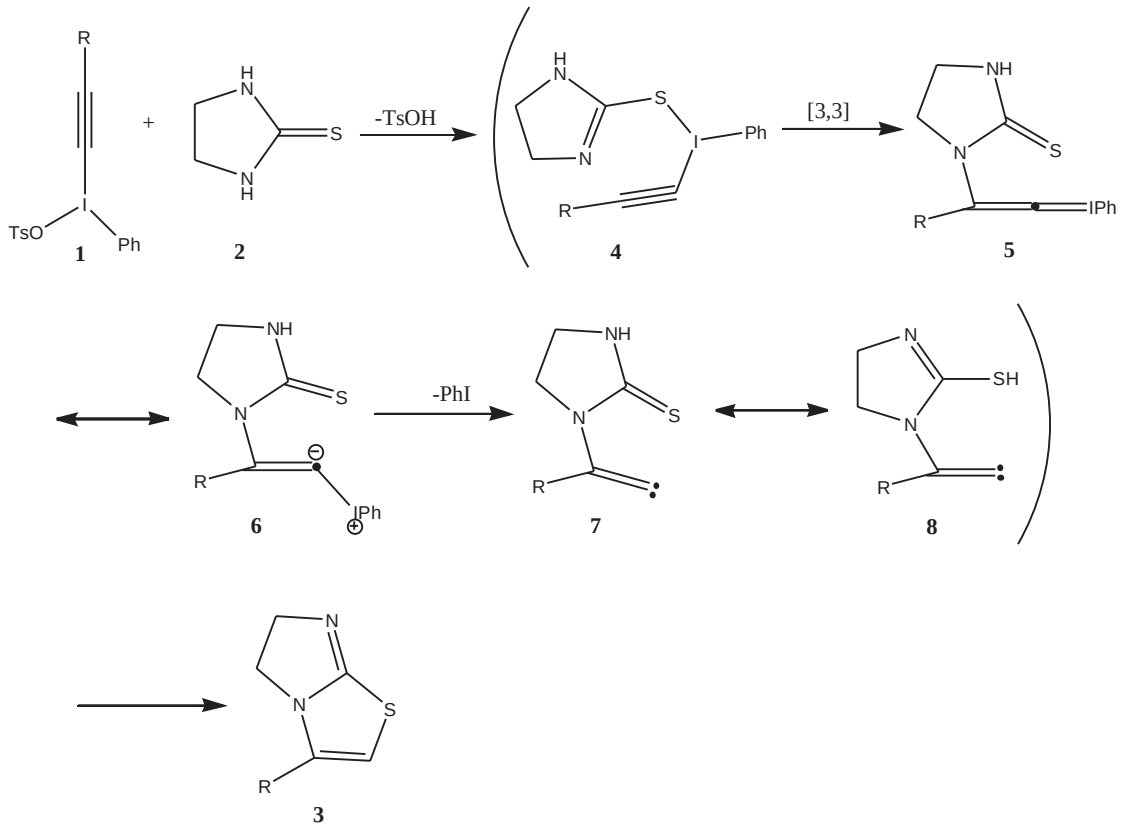

Scheme 2

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