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HYPERVALENT IODINE IN THE SYNTHESIS OF BRIDGEHEAD HETEROCYCLES[1]: A NEW SYNTHESIS OF 3,5-DIARYLTHIAZOLO[2,3-c]-S-TRIAZOLES

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Abstract: The synthesis of 3,5-diarylthiazolo[2,3-c]-s-triazoles (**3a-f**) has been accomplished by using a new method involving oxidation of arenecarbaldehyde-4-arylthiazol-2-ylhydrazones (**2a-f**) with iodobenzene diacetate (**IBD**) in dichloromethane by intramolecular cyclization in high yields.

Hypervalent iodine reagents have acquired considerable interest because of their versatile use in organic synthesis[2]. Our recent investigations dealing with the hypervalent iodine mediated syntheses have shown that iodobenzene diacetate (IBD) in methanolic KOH and [hydroxy(tosyloxy)iodo]benzene (HTIB) are

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extremely important reagents particularly for the synthesis of a large variety of heterocyclic[3] and bridgehead heterocyclic compounds[1,3]. This approach has distinct advantages over the literature methods as the methodology involves simple experimentation and avoids the use of highly toxic reagents. Encouraged by these observations we now report a new and facile synthesis of 3,5-diarylthiazolo[2,3-c]-s-triazoles (**3a-f**) using IBD.

Part of the reason for developing such synthesis is that many thiazolotriazoles are known to possess diverse biological activities[4] such as potential antibacterial[5,6] and as fungicide against A. niger, C. albicans[7] and for the control of piricularia oryzae in the prevention of rice blast[8]. 1,2,4-Triazoles are shown to have antineoplastic activity[9].

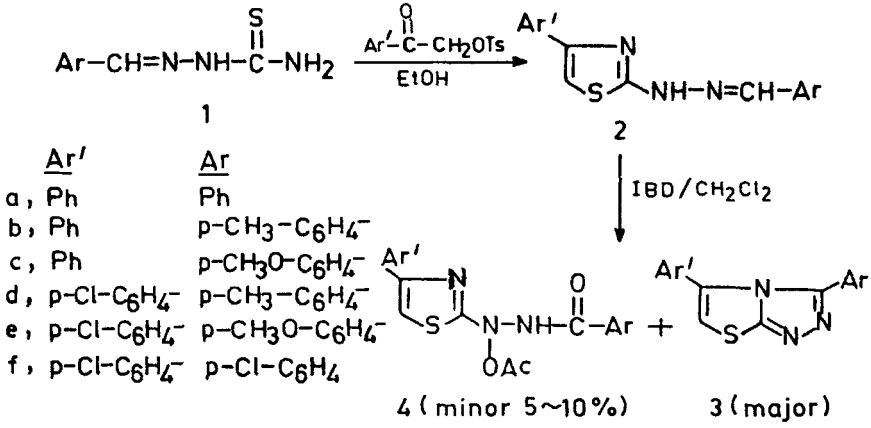
Reaction of benzaldehyde-4-phenylthiazol-2-ylhydrazone (**2a**) [prepared from the reaction of thiasemicarbazone of benzaldehyde **1a** with a-tosyloxyacetophenone] and IBD in refluxing CH_2Cl_2 resulted in the formation of mainly 3,5-diphenylthiazolo[2,3-c]-s-triazole (**3a**), identified on the basis of its m.p. 164-165°C (lit.[10], m.p. 165°C), IR and NMR data. The minor product formed in the reaction was found to be 1-acetoxy-1-(5-phenylthiazol-2-yl)-2- benzoyl hydrazine (**4a**) in 5% yield as calculated from the ^1H NMR of the crude product of

the above reaction mixture. Similarly other thiazolylhydrazones (**2b-f**) also afforded a mixture of **3b-f** and **4b-f** respectively as major and minor products (**Scheme I**).

The characterization of the major products was made through the comparison of their m.p.s. and spectral properties (IR $ NMR) with those reported in literature (**Table I**) . No attempts were made to isolate the minor products **4a-f**, which were formed in 5-10% yields as calculated from the ^{1}H NMR data (a characteristic singlet at about δ 2.4).

However when the reaction was carried out in acetic acid as solvent it did not proceed to completion. There remained largely the starting compound and about 30% of the cyclised product **3a-f** along with the traces of the acetoxy product **4a-f.** Oxidation of **2a-f** using IBD-H_2SO_4/ACOH led to the formation of desired cyclic products **3a-f** without any side product. But yields of the products **3a-f** were found to be in the range of 30-40% because of the recovery of unreacted hydrazone in all the cases.

The mechanistic pathways we propose for the formation of **3** and **4** from **2** are analogous to the oxidation of arenecarbaldehyde hydrazones with lead tetraacetate[11] as outlined in **Scheme II.** The first step involves the electrophilic attack of IBD at the



Scheme I

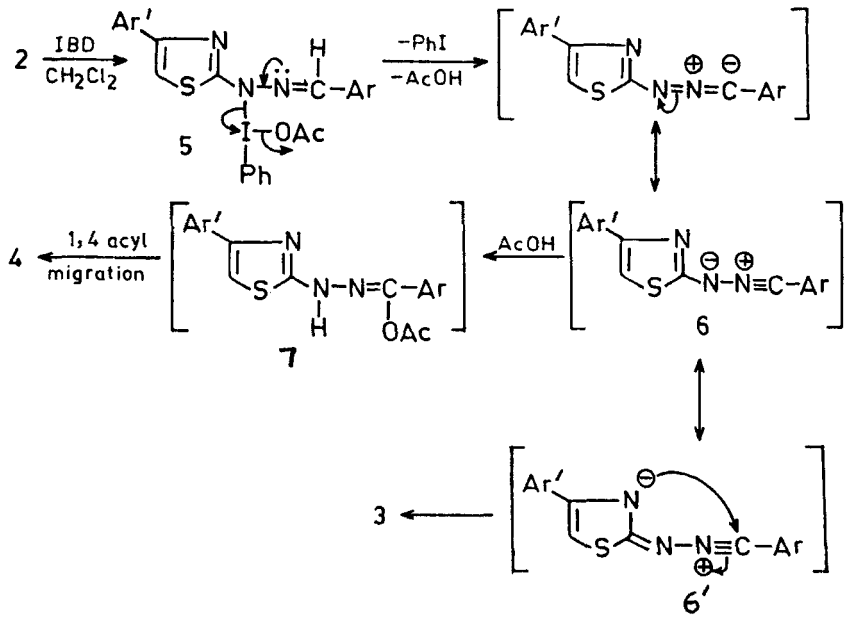
Table I. Analytical data for 3

Compound	Yield[a] (%)	m.p./°C	Lit. m.p.[7,10,12]/°C
3a	80	164-165	165
3b	78	140	138
3c	82	139-141	141
3d	75	207-208	210
3e	74	187-188	190
3f[b]	78	160-161	—

[a] Based on the isolated products w.r.t. quantity of 1 used

[b] ν_{max}/cm^{-1} (Nujol) 1650 (C=C & C=N), 1610, 1575 (C-N); δ_H (TFA) 7.05 (1H, S, C_6-H), 6.9-7.85 (8H, m, ArH)

[#] The IR and NMR data of other compounds are in good agreement with the reported literature.



Scheme II

'N' atom of hydrazone **2** to yield N-iodine (III) adduct (**5**). Subsequently **5** generates a nitrilimine intermediate (**6**) along with the expulsion of a molecule of iodobenzene and acetic acid. The nitrilimine **6** *via* resonating structure **6'** can lead to the intramolecular cyclization thereby yielding **3**. The formation of minor product **4** probably involves two steps (i) nucleophilic attack of acetic acid (generated *in situ*) on **6** to give hydrazonyl acetate **7** and (ii) 1,4-acyl migration of **7** to produce **4**. Since no appreciable increase in the yields of azoacetate **4** was observed using acetic acid as solvent in this reaction, it

implies that an intramolecular cyclization process leading to **3** is preferred over the intermolecular nucleophilic attack of acetic acid (external or internal nucleophile).

The formation of **3** apparently proceeds with ring closure involving the nitrogen atom of thiazolyl moiety. Ring closure via sulfur atom is also conceivable though unlikely, since the product of such a process would have a mesoionic structure.

Finally the present method provides a general, facile and superior method for the synthesis of **3**. The method is particularly advantageous over the reported procedures[4,7,10,12] involving the use of PPA & $POCl_3$ as the reaction conditions are milder and the yields of the products are better.

Experimental:

M.p.s. were determined in open capillaries and are uncorrected. IR spectra were recorded on a Beckman spectrophotometer (IR-20) using nujol mulls. ^1H NMR spectra were recorded in $CDCl_3$ or $CDCl_3$-CF_3COOH or CF_3COOH at 90 MHz on a Perkin-Elmer R-32 machine with $SiMe_4$ as internal standard.

α-Tosyloxyacetophenones were prepared from different substituted acetophenones by treatment with HTIB in acetonitrile

according to the procedure of Koser et al[13] for α-tosyloxylation of ketones.

All arenecarbaldehyde-4-arylthiazol-2-ylhydrazones (**2**) were synthesized by condensation of thiosemicarbazone of arenealdehyde with α-tosyloxyacetophenone in ethanol[14].

Preparation of 3,5 diaryl 1,2,4 thiazolo [2,3-c]-s-triazoles (3a-f)

General procedures: To a solution of arenecarbaldehyde-4-arylthiazol-2-ylhydrazone (**2a-f**, 3.58 mmol) in dichloromethane (30 ml), was added iodobenzene diacetate (3.94 mmol) in portions. The contents were refluxed for 4-5 h and the completion of the reaction was monitored by TLC. The resulting dark brown solution was cooled, washed with $NaHCO_3$ solution followed by water and dried (Na_2SO_4). The solvent was removed and the crude product was purified by column chromatography over neutral alumina using pet.ether-ethyl acetate mixture followed by crystallization with ethanol to afford (**3a-f**).

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