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AN INTERRUPTED PUMMERER REACTION INDUCED BY HYPERVALENT IODINE(III) REAGENT : FACILE SYNTHESIS OF 2-ARYL-1,2-BENZISOTHIAZOL-3(2*H*)-ONES

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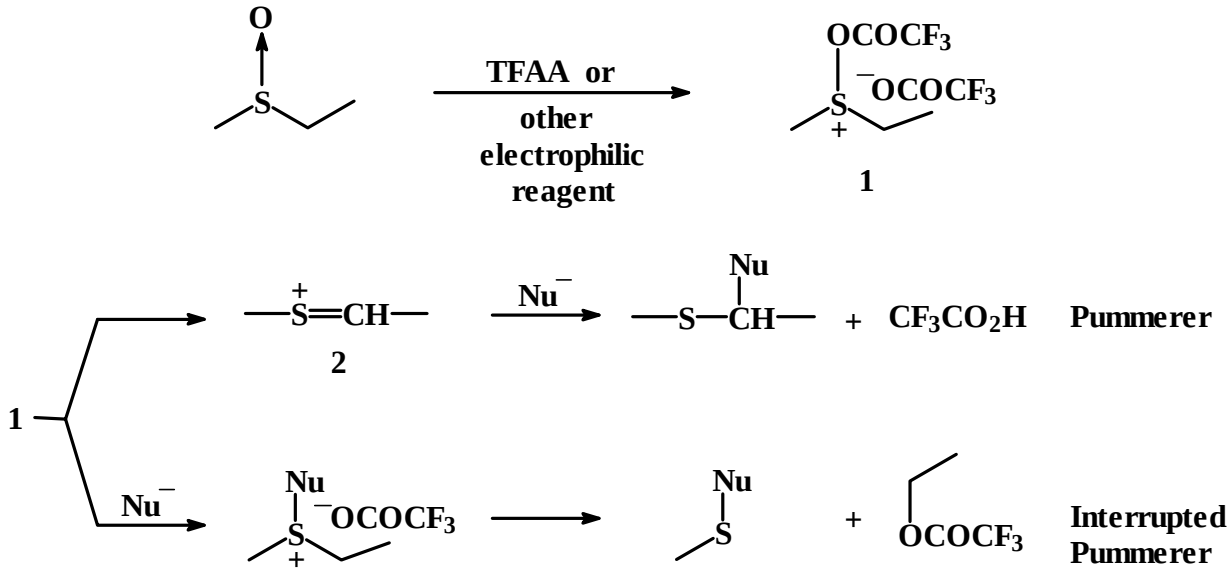
Abstract—Treatment of *N*-aryl-2-(benzylthio)benzamides with phenyliodine(III) bis(trifluoroacetate) containing trifluoroacetic acid resulted in an interrupted Pummerer-type reaction to give 2-aryl-1,2-benzisothiazol-3(2*H*)-ones rather than the normal Pummerer-type products.

The Pummerer reaction of sulfoxides normally proceeds *via* an activated sulfoxide (**1**) and then a thionium ion (**2**) which reacts with a nucleophile at carbon to afford an α-substituted sulfide.[1] In an interrupted Pummerer reaction, the tricoordinate sulfur intermediate (**1**) undergoes reaction with a nucleophile at sulfur leading to unexpected product (Scheme I).[2]



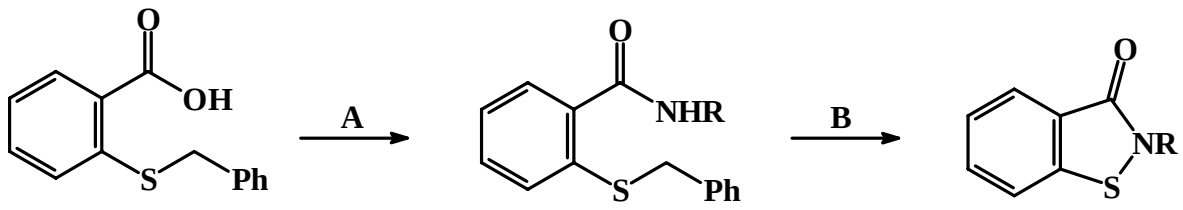
Scheme I

2-Aryl-1,2-benzisothiazol-3(2*H*)-ones have received much attention because of their antibacterial and

antifungal properties.[3-6] The methods used for their synthesis involve the reaction of 2-(chlorothio)benzoyl chloride with appropriate amines,[4] cyclization of 2-carbamoylbenzenesulfenyl halides with amines,[5] reaction of bis(2-carbamoylphenyl) disulfides with thionyl chloride,[6] catalytic cyclization of *N*-substituted 2-(methoxycarbonyl)benzenesulfenamides by a strong base,[7] and cyclization of sulfoxide substrates acting as sulfenyl halide equivalents.[8] Nevertheless, it is desirable to develop a convenient and useful procedure for the preparation of 2-aryl-1,2-benzisothiazol-3(2*H*)-ones.

Recently, hypervalent iodine reagents have been used extensively in organic synthesis due to their low toxicity, ready availability and easy handling. As a continuation of our studies concerning hypervalent iodine(III) chemistry,[9] we have reported a Pummerer-type reaction that provides a very simple and convenient procedure for the preparation of 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines by treatment of α-acyl sulfides with phenyliodine(III) bis(trifluoroacetate) (PIFA).[10] We report here an interrupted Pummerer-type reaction of sulfides using PIFA, which has been applied to prepare 2-aryl-1,2-benzisothiazole-3(2*H*)-ones *via* intramolecular N-S bond formation.

The requisite *N*-aryl-2-(benzylthio)benzamides (**4**) were readily prepared from 2-(benzylthio)benzoic acid (**3**) with NCS/Ph_3P-complex followed by treatment with appropriate arylamines .[11] Treatment of **4** with PIFA containing trifluoroacetic acid (TFA) in CH_2Cl_2 caused cyclization to give 2-aryl-1,2-benzisothiazol-3(2*H*)-ones (**5**) in moderate yields.[12] Under these conditions no sulfoxides and normal Pummerer-type products were obtained (Scheme II).



3 **4** **5**

Reagents : A) NCS / Ph_3P−complex / RNH_2
B) PIFA−TFA / CH_2Cl_2

Scheme II

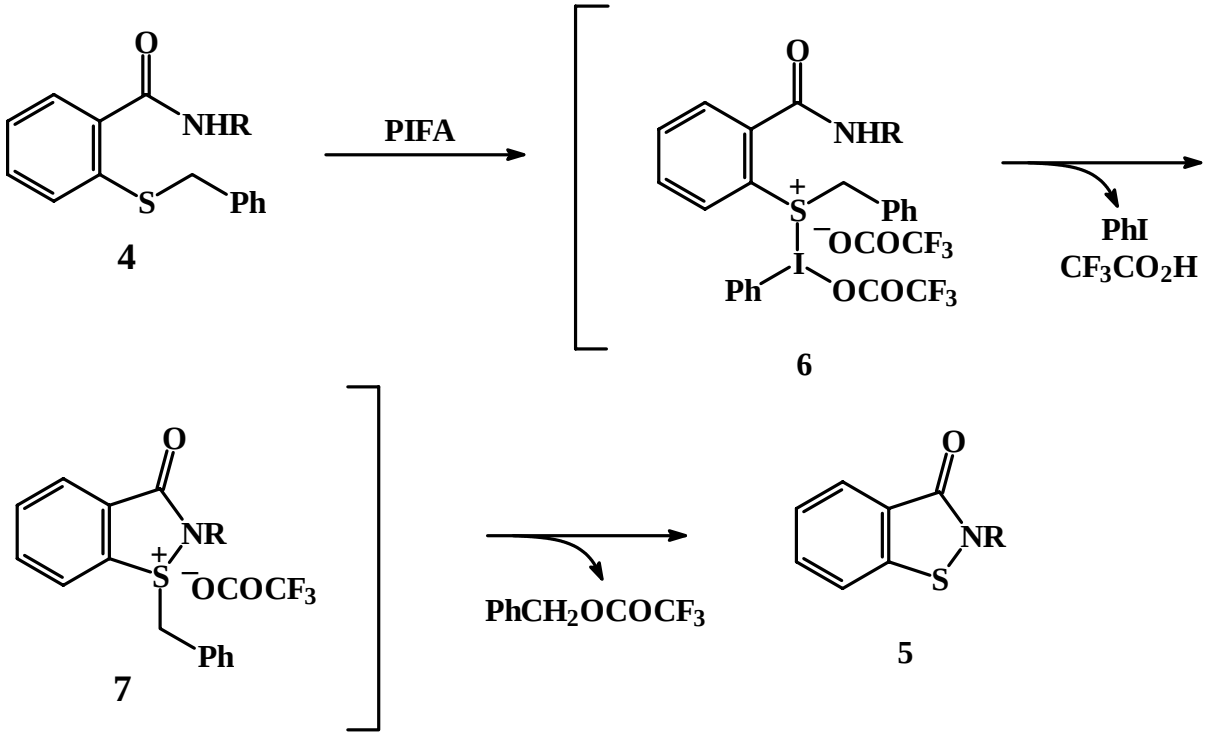
The results are given in Table 1. It was observed that electron-rich aromatic substituents on the nitrogen led to improved yields of cyclization with sulfides (**4c-e)** (Table 1, Runs 3~5). Conversely, electron-deficient substituents hindered the reactions of the *N*-(4-ethoxycarbonylphenyl) substrate (**4g**) and *N*-(4-cyanophenyl) substrate (**4h**) to give the corresponding cyclization products in only 35 and 32 % yields, respectively (Table 1, Runs 7 and 8). Moreover, the *N*-(4-nitrophenyl) substrate (**4i**) proved unreactive

(Run 9).

Table 1. Yields of 2-Aryl-1,2-benzisothiazol-3(2*H*)-ones (**5**) in the Reaction of Sulfides **4** with PIFA

Run	substrate	R	substrate	Yield / %
1	**4a**	Ph	**5a**	72
2	**4b**	CH_2Ph	**5b**	75
3	**4c**	4-$MeOC_6H_4$	**5c**	80
4	**4d**	3,5-$(MeO)_2C_6H_3$	**5d**	71
5	**4e**	3,4,5-$(MeO)_3C_6H_2$	**5e**	76
6	**4f**	4-ClC_6H_4	**5f**	64
7	**4g**	4-$EtO_2CC_6H_4$	**5g**	35
8	**4h**	4-NCC_6H_4	**5h**	32
9	**4i**	4-$O_2NC_6H_4$	**5i**	0

A machanistic sequence for 1,2-benzisothiazol-3(2*H*)-one ring formation using PIFA is shown in Scheme III. The cyclization from **4** to **5** is assumed to proceed through an interrupted Pummerer-type reaction intermediate (**7**) which would be formed by attack of PIFA on the sulfur atom of **4**, followed by simultaneous elimination of the iodobenzene and trifluoroacetic acid from the resultant sulfonium salt (**6**). Apparently, without the electron withdrawing group on the carbon alpha to the sulfide group, trifluoroacetate ion is not basic enough to generate the thionium ion.



Scheme III

In summary, our results herein demonstrate that the use of a combined reagent PIFA-TFA in CH_2Cl_2 is a convenient and useful method for the interrupted Pummerer-type reaction of sulfides to prepare 2-aryl-1,2-benzisothiazol-3(2*H*)-ones.

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12. General procedure for the preparation of **5** : A solution of *N*-aryl-2-(benzylthio)benzamides (**4**) (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of the mixture of PIFA (1.25 mmol) and TFA (2 mmol) in CH_2Cl_2 (2 mL) at 0 ˚C and the mixture was stirred at the same temperature for 1 h. Then the mixture was refluxed for 2 h to complete the reaction. The resultant mixture was quenched with water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column, eluting with hexane-chloroform to give **5**.