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Iodine-catalyzed thioallylation of indoles using Bunte salts prepared from Baylis–Hillman bromides†

Prince Kumar Gupta, Arvind Kumar Yadav, Anup Kumar Sharma and Krishna Nand Singh *

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Metal-free iodine-catalyzed regioselective thioallylation of indoles has been accomplished at room temperature using Bunte salts prepared from Baylis–Hillman bromides. The resulting multi-functional C3 thioallylated indoles exhibit ample structural diversity and good functional group tolerance.

Introduction

Indoles constitute a vital core of many natural products and biologically active compounds capable of binding to many receptors with high affinity.[1] Indole thioethers are particularly important due to their therapeutic value in treating obesity, cancer and allergies.[2,3] For instance, MCF-7 (**I**) is used as a cell growth inhibitor,[4] 5-chloro-3-(phenylthio)-1*H*-indole-2-carboxamide (**II**) as a HIV inhibitor,[5] and 3-((4-fluorophenyl)thio)-2-methyl-6-(methylsulfonyl)-1*H*-indole as a COX-2 inhibitor (**III**) (Fig. 1).

Therefore, the synthesis and functionalization of indoles has always been a focal point of research in organic synthesis.[6] Indoles readily undergo electrophilic substitution to form carbon–carbon and carbon–heteroatom bonds;[7] however, the selective functionalization of indoles is somewhat difficult. In particular, the C3 functionalization of indoles in an efficient way is exigent as it provides easy access to pharmaceutically active molecules.[8] In this perspective, the sulfenylation of indoles is immensely important because of the broad spectrum biological activities of the resulting products.[9] The C3 sulfenylation of indoles has been accomplished by the use of many sulfenylating reagents such as sulfonyl hydrazides,[10a] sulfenyl halides,[10b] *N*-thioimides,[10c] sulfonium salts,[10d,e] thiols,[10f,g] disulfides,[10h] quinone mono-*O*,*S*-acetals,[10i] and sulfinic acid.[10j,k] However, most of these reagents are expensive, foul-smelling, and unstable towards air or moisture. Moreover, the sulfenylation reactions of indoles frequently require an excess of the reagents/additives with harsh conditions and suffer from poor substrate scope with undesired by-product formation. The idea of the present work stemmed from the work of Zhang and Luo's group, who recently developed a catalytic synthesis of 3-thioindoles using a Bunte salt as the sulphur source under metal-free conditions.[11] Bunte salts ($RSSO_3Na$) are stable crystalline solids with no foul odour, are easy to handle, can be conveniently prepared by the reaction of inexpensive sodium thiosulfate with alkyl/aryl halides, and are valuable synthetic intermediates.[12] In view of the above, it was envisioned that Bunte salts of Baylis-Hillman bromides could be prepared, followed by their reaction with indoles to accomplish diverse thioallylated products with multi-reactive sites.

The Baylis–Hillman (BH) reaction has undergone intensive research to access various functionalized organic molecules employing BH-alcohols, BH-bromides, BH-acetates, aza-BH adducts *etc*.[13] Baylis–Hillman (BH) bromides are widely used as functionalized α,β-unsaturated olefin derivatives and are amenable to many alterations due to the presence of multi-reactive functionalities.

In view of the above and as part of our ongoing research on C–S bond formation,[14] we report herein a facile molecular iodine-catalyzed synthesis of thioallylated indoles (**3**) by the reaction of indoles (**1**) with Bunte salts (**2**) derived from Baylis–Hillman bromides in DMSO at room temperature (Scheme 1).

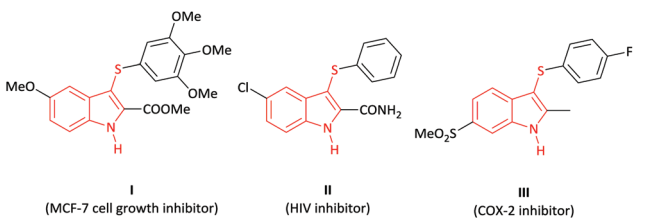

Fig. 1 Some biologically active thiolated indoles.

Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India. E-mail: knsinghbhu@yahoo.co.in, knsingh@bhu.ac.in

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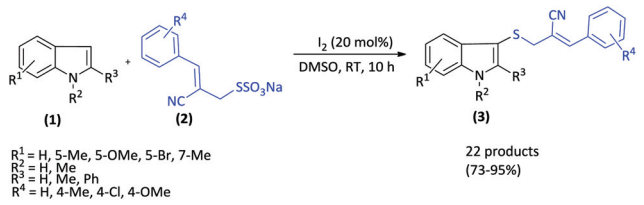


Scheme 1 C3-thioallylation of indoles.

Results and discussion

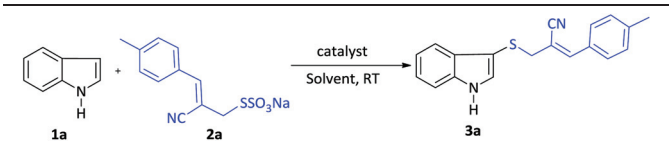
The study was commenced by using a mixture of indole **1a** (1.0 mmol), Bunte salt **2a** (1.0 mmol) obtained from BH-bromide, and molecular iodine (20 mol%) in methanol while stirring in open air at room temperature for 10 h, which led to the formation of the desired product (*E*)-2-(((1*H*-indol-3-yl) thio)methyl)-3-(*p*-tolyl)acrylonitrile (**3a**) as a single regioisomer in 30% yield (Table 1, entry 1). Intrigued by this observation, the model reaction was thoroughly investigated using different catalysts and solvents (Table 1).

Using I_2 (20 mol%) in solvents such as DMF, CH_3CN, THF and 1,4-dioxane brought about a substantial increase in the product yield (entries 2–5); but to our utmost pleasure, the use of DMSO made a phenomenal improvement in the yield (entry 6). Nevertheless, the use of solvents like DCE, DCM, toluene and *p*-xylene remained poor (entries 7–10). Then the effect of catalyst loading was explored. Increasing the catalyst concentration (30 mol%) could not enhance the product yield further (entry 11); however, a decrease in the catalyst loading from 20 mol% to 10 mol% diminished the product yield appreciably (entry 12). Markedly, the reaction in the absence of I_2 remained ineffective (entry 13). Some other iodine based catalysts *viz.*, TBAI, KI, NH_4I and NIS were also tried in DMSO (entries 14–17) but they could not surpass the efficacy of molecular iodine.

After having established the optimized conditions (entry 6), the scope of the reaction was then scrutinized using different indoles (**1**) and the Bunte salts (**2**). The outcome is shown in Table 2.

A diverse array of both reacting partners participated nicely under the optimized conditions to afford the desired products **3a–3v** in reasonably high yields. Although indoles having substituents such as Me, OMe, and Br worked exceedingly well in the reaction to afford the corresponding products, C2-substituted indoles such as 2-methylindole and 2-phenylindole remained especially impressive. When 5-cyanoindole, 5-nitroindole, 7-azaindole and C3-substituted indoles such as 3-methylindole were employed under the stipulated conditions, no conversion to the expected product occurred. 1,3,5-

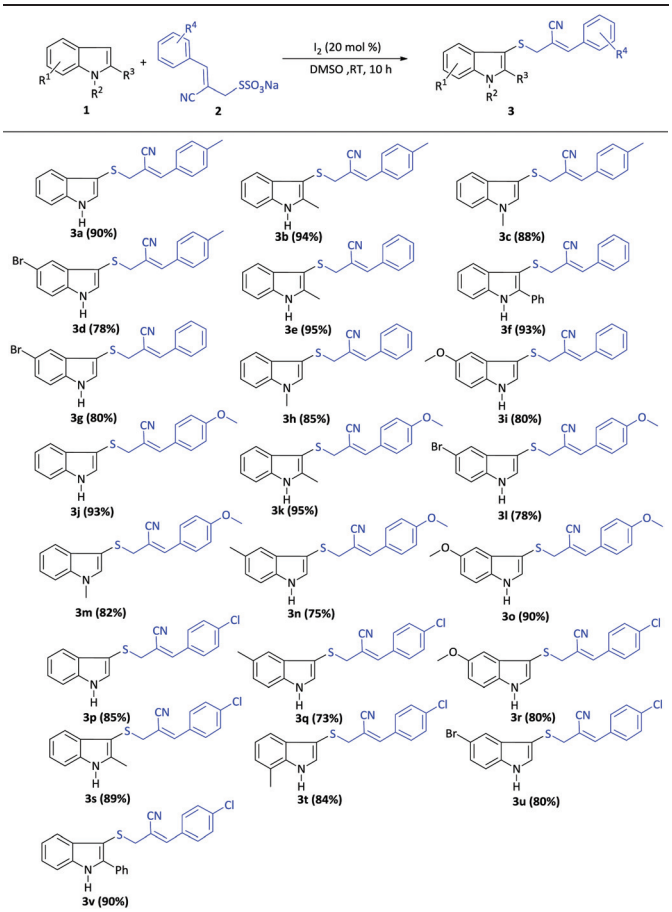
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Solvent	Yield[b] (%)
1	I_2 (20.0)	CH_3OH	30
2	I_2 (20.0)	DMF	50
3	I_2 (20.0)	CH_3CN	60
4	I_2 (20.0)	THF	62
5	I_2 (20.0)	1,4-Dioxane	70
6[c]	**I_2 (20.0)**	**DMSO**	**90**
7	I_2 (20.0)	DCE	32
8	I_2 (20.0)	DCM	29
9	I_2 (20.0)	Toluene	30
10	I_2 (20.0)	*p*-Xylene	28
11	I_2 (30.0)	DMSO	90
12	I_2 (10.0)	DMSO	80
13	—	DMSO	0
14	TBAI (20.0)	DMSO	30
15	KI (20.0)	DMSO	20
16	NH_4I (20.0)	DMSO	35
17	NIS (20.0)	DMSO	25

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (20 mol%), solvent (1.5 mL), room temperature (in open air), 10 h. [b] Isolated yield after column chromatography. [c] The bold entry 6 represents the optimized reaction conditions.

Table 2 Scope and versatility of the reaction[a,b]



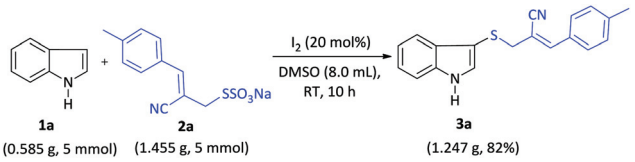
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), I_2 (20 mol%), DMSO (1.5 mL), room temperature (in an open air), 10 h. [b] Isolated yield after column chromatography.

Trimethoxybenzene and other heterocyclic compounds like imidazole, benzothiazole, and isoquinoline were also tried but did not work under the established conditions. The Bunte salts **2** prepared from the corresponding BH-bromides having substituents such as Me, OMe, Cl on the aryl part and CN on the alkene component participated well to afford the corresponding products. It was observed that the presence of an electron donating group on the aromatic ring of the Bunte salts **2** afforded a somewhat higher yield in comparison with those bearing an electron-withdrawing group. Interestingly, the reaction proceeds with complete *Z*-stereochemistry of the product **3** which was assigned on the basis of the ^{1}H chemical shifts of the vinylic/allylic protons and NOESY spectrum (see the ESI†).

To demonstrate the synthetic utility of the method, a gram scale reaction using **1a** (0.585 g, 5 mmol) and **2a** (1.455 g, 5 mmol) was carefully carried out under the optimized conditions (Scheme 2), which led to the formation of the product **3a** with a slightly diminished yield (1.247 g, 82%).

All the products are new and have been fully characterized based on their NMR (^{1}H & ^{13}C), NOESY and HRMS data. The PMR spectrum of the D_2O exchanged product **3a** (ESI†) excludes the possibility of NH substitution in the indole. Furthermore, the structure of the representative product **3v** was conclusively confirmed by single crystal X-ray analysis (Fig. 2).

To get an insight into the reaction mechanism, some control experiments were carried out (Scheme 3). Bunte salt **2a** alone (without **1a**) under the standard conditions gave rise to a dimeric intermediate **A** (Scheme 3, eqn (1)), which was confirmed by NMR and HRMS. The isolated intermediate **A**, when discretely allowed to react with **1a** under the standard conditions, afforded the desired product **3a** (85%, eqn (2)),



Scheme 2 Gram scale synthesis of the product **3a**.

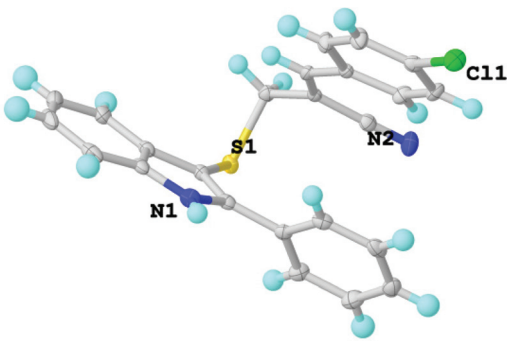
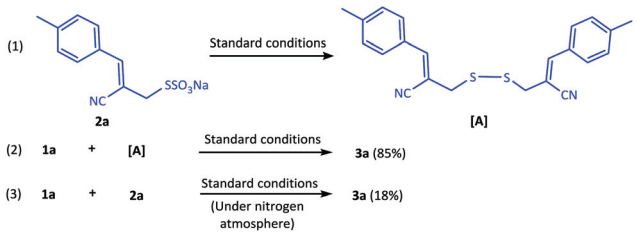
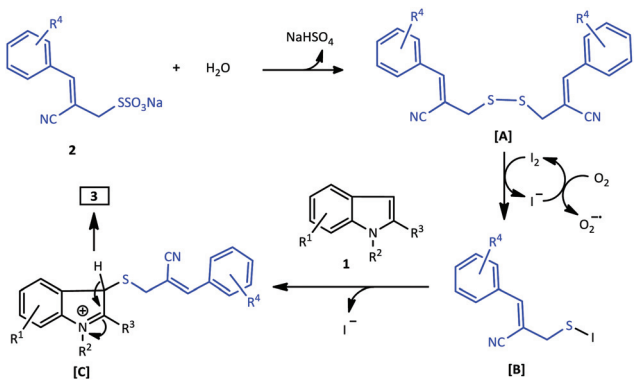


Fig. 2 ORTEP diagram of the product **3v** (CCDC: 2056356†).



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism.

suggesting the intermediacy of **A**. However, when the standard reaction proceeded under an inert atmosphere, the product **3a** was obtained only in 18% yield (Scheme 3, eqn (3)).

Based on product isolation and the existing literature,[11] a plausible mechanism is outlined in Scheme 4. The Bunte salt **2** is presumed to react with H_2O to form the corresponding disulfide intermediate **A**, which on subsequent reaction with molecular iodine forms the electrophilic sulfenyl iodide (R–S–I) **B**. The intermediate **B** then undergoes the regioselective Friedel–Crafts reaction with indole **1** to form the intermediate **C**, which on aromatization finally affords the thioallylated indole **3**. Oxidation of iodide by oxygen to molecular iodine (I_2) with *in situ* superoxide ion generation completes the catalytic cycle.[15]

Conclusions

In conclusion, a simple and regioselective C3-thioallylation of indoles has been accomplished using easy to prepare Bunte salts of Baylis–Hillman bromides at room temperature. The methodology is endowed with a wide range of substrate scope and functional group tolerance.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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