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Title: Synergistic Cooperative Effect of Sodium borohydride-Iodine Towards Cascade C-N and C-S/Se Bond Formation: One-pot Regioselective Synthesis of 3-Sulfenyl/selenyl Indoles and Mechanistic Insight

Authors: ADITYA LAVEKAR, DANISH EQUBAL, SAIMA Malik, and Arun Sinha

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Synergistic Cooperative Effect of Sodium borohydride-Iodine Towards Cascade C-N and C-S/Se Bond Formation: One-pot Regioselective Synthesis of 3-Sulfenyl/selenyl Indoles and Mechanistic Insight

Aditya G. Lavekar,[a,b] Danish Equbal,[a] Saima[a] and Arun K Sinha[a,b]

[a.] Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow-226031, Uttar Pradesh India; E-mail: aksinha08@rediffmail.com; ak.sinha@cdri.res.in

[b] Academy of Scientific and Innovative Research (AcSIR), New Delhi, India

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Abstract. In this work, a new strategy to synthesize 3-sulfenyl/selenyl indole is reported wherein LC-MS reveals a novel insight into synergistic cooperative effect of $NaBH_4$-I_2 which allows cascade C-N and C-S/C-Se bond formations via reduction-nucleophilic cyclization-chalcogenylation, three steps in one-pot, towards regioselective synthesis of diverse 3-chalcogenyl indoles including 5-bromo-3-[(3,4,5-trimetoxyphenyl)thio]-1H-indole, a known lead anticancer compound, directly from 2-amino-phenacylchlorides and thiophenols or disulfides/diselenides in aqueous dioxane under transition-metal-free condition.

Keywords: cascade C-N and C-S/C-Se bond,cooperative catalysis, heterocycles, LC-MS based reaction mechanism, reduction-cyclization-chalcogenylation

The indole nucleus[1] is one of the most widespread heterocycle compounds in the realm of pharmaceuticals, agrochemicals and organic materials. The excellent binding ability of indole to interact with different biological targets makes them "privileged structures" in drug design and development. Among numerous indole nuclei, 3-chalcogenyl-indoles (3-sulfenyl and 3-selenyl indoles) are one of such attracting candidates possessing several potential therapeutic uses[2] as antitumor, antibacterial, antiviral activities (Figure 1).

Due to the special pharmacological properties, much effort has been devised towards development of efficient route to access indole-based sulfides and their derivatives. In general, two synthetic routes[3,4] have been known in the literature for synthesis of chalcogenylated indoles (Scheme 1) in which the first route involves direct chalcogenylation of an existing indole ring[3] with sulfenylating agents whereas other route involves cascade electrophilic cyclization and coupling reactions of various designer aniline derivatives[4] (such as 2-alkynyl aniline or 2-vinyl aniline) followed by subsequent chalcogenylation. Despite the fact that there are a wide range of sulphur sources (such as arylsulfenyl/sulfonyl halides,[3d,e] and arylsulfonium salts[3i] which contribute immensely in the first route during direct chalcogenylation of pre-existing indoles with C-S bond formation (Scheme 1, Route - 1), however, many commercially available indole derivatives are either expensive or possessing limited scope in structural diversity besides some of sulphur sources requires some additional step to prepare or are sensitive to moisture. Against this milieu, the second cascade route offers advantage in a way to design a mild, efficient and diversified method for the simultaneously constructing the substituted indole nucleus and subsequent chalcogenylation with C-N and C-S bond formation in one manoeuvre (Scheme 1, Route - 2). For example, Larock[4a,b] *et al*

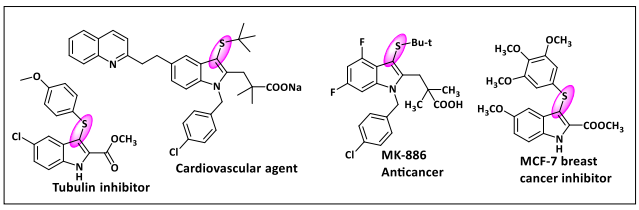
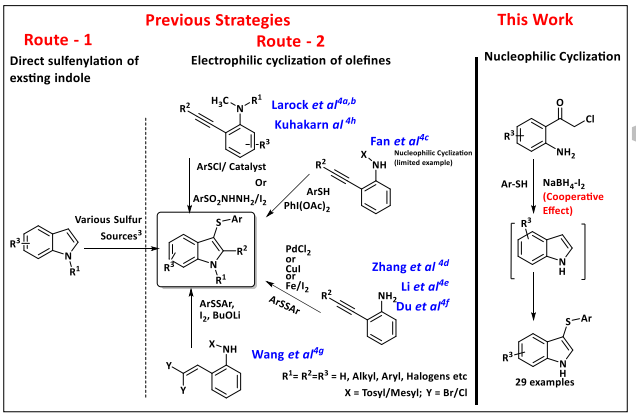


Figure 1: Some examples of bioactive 3-sulfenylated indole.



Scheme 1: Distinct synthetic approaches to 3-sulfenyl-indoles.

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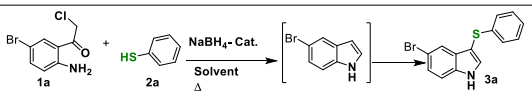
reported a novel synthetic route to 3-chalcogenyl-indoles by palladium/ copper catalyzed coupling of N,N-dialkyl-o-iodoanilines and terminal alkynes followed by electrophilic cyclization with arylsulfenyl(selenyl) chlorides in the presence of $(n\text{-}Bu)_4NI$.

Similarly, Zhang[4d] *et al* provides another route for synthesis of 3-sulfenylindoles by palladium-catalyzed annulation of 2-(1-alkynyl)benzenamines with disulfides as a sulphur source (Scheme 1). At times, the high cost and the toxicity of transition metals limits the utility of many synthetic routes. Most importantly, Li[4e] and Du[4f] *et al* disclosed copper[4e] or iodine/iron-mediated[4f] electrophilic annulation of 2-alkynyl-aniline[4f] derivatives with disulfides or diselenides provides corresponding 3-sulfenyl/selenenyl indoles in moderate to excellent yields. Among various sulfenylation agents (such as arylsulfenyl chlorides or diaryldisulfide etc), sulfonyl hydrazide[3f] being shelf-stable reagent, has received considerable attention as a sulphur source. In this context, Kuhakarn[4h] *et al* described the synthesis of N-alkyl-3-sulfanylindoles from 2-alkynyl-N,N-dialkylanilines and sulfonyl hydrazides in the presence of iodine and tert-butylhydroperoxide (TBHP). While the second route provides indole thioethers with N-protected indole and/or substituent at 2nd position of indole core *via* electrophilic cyclization of 2-alkynyl aniline derivatives[4a-4f] (Scheme 1), 2-vinyl aniline derivative[4g] also surfaced as one of the precursors which provides regioselective synthesis of 3-chalcogenyl indoles with free NH group via tandem electrophilic reactions of 2-(gem-dibromo(chloro)vinyl)-N-methyl sulfonyl anilines and disulfides/diselenides in the presence of t-BuOLi and I_2 in DMSO as solvent. Very recently, Fan[4c] *et al* developed an oxidative nucleophilic cyclization of 2-alkynylanilines with thiophenols towards the construction of 3-chalcogenyl-indoles in the presence of $PhI(OAc)_2$ (Scheme1). Further, there is still scope for development of new methodology and selection of green catalyst for the titled compounds.

New reactions provide new ways to think about bond construction/breaking thereby achieving step economic synthesis while selection of inexpensive starting material, non-toxic solvent and non-metal based catalyst, is highly desirable. In this context, there has been rapidly expanding interest in the field of cooperative catalysis which allows the construction of several bonds in one pot due to synergistic-cooperative[5] effect of both the catalysts otherwise the desired products are not obtainable by the use of one catalyst alone. As a part of our on-going interest in green chemistry with emphasis on the use of cooperative catalysis[3c,5f] and revisiting of some classical named reactions[6] (Heck, [6a,b] Suzuki-Aldol, [6c] Knoevenagel-Perkin-Heck reactions[6d] in one pot) towards concise synthesis of bioactive molecules**,** we herein report first multiple C-N and C-S/C-Se bond formation under transition metal free conditions via cascade route for *in situ* generation of indole with free -NH group by Sugasawa[7] annulation followed by selective chalcogenylation at 3-position of indole in the same pot by comprising synergistic co-operative effect of $NaBH_4$-I_2 which finally produces highly effective and diversity oriented regioselective synthesis of bioactive 3-sulfenyl/selenyl indoles utilizing 2-amino-phenacylchlorides[8] and thiophenol[3c] as cheaper and versatile precursors in aq.-dioxane. Moreover, LC-MS provides powerful insights into the mechanistic aspects of the above cascade reduction-cyclisation-sulfenylation reaction in one pot.

At the beginning of our investigation, a model reaction of 4- bromo-2-amino phenacylchloride[7b] (**1a**, 1 mmol) and thiophenol (**2a**, mmol) with $NaBH_4$ (2 mmol) in aqueous dioxane (4ml, 1:9), at reflux temperature was performed to optimize the reaction conditions and the results are summarized in Table 1 (entries 1-14). Unfortunately, the desired product (**3a**)

Table 1: Optimization of reaction conditions[a] for 3-sulfenyl indoles via Sugasawa annulation-chalcogenylation.



Sr No.	Reductant $NaBH_4$	Catalyst	Solvent	Yield of 3a (%)[b]	Sr No.	Reductant $NaBH_4$	Catalyst	Solvent	Yield of 3a (%)[b]
1	2 equiv	-	aq.Dioxane	nd	8	2 equiv	NBS (2 equiv)	aq.Dioxane	nd
2	3 equiv	-	aq.Dioxane	nd	9	2 equiv	PIDA (2 equiv)	aq.Dioxane	nd
3	2 equiv	NaOH (1 equiv)	aq.Dioxane	nd	10	2 equiv	$FeCl_3$ (2 equiv)	aq.Dioxane	nd
4	2 equiv	I_2 (1 equiv)	aq.Dioxane	41	11	2 equiv	I_2 (2 equiv)	EtOH	10
5	2 equiv	I_2 (1.5 equiv)	aq.Dioxane	59	12	2 equiv	I_2 (2 equiv)	THF	nd
6	2 equiv	I_2 (2 equiv)	aq.Dioxane	72	13	-	I_2 (2 equiv)	aq.Dioxane	nd
7	2 equiv	I_2 (3 equiv)	aq.Dioxane	71	14	2 equiv	I_2 (2 equiv)	aq.Dioxane	72[c]

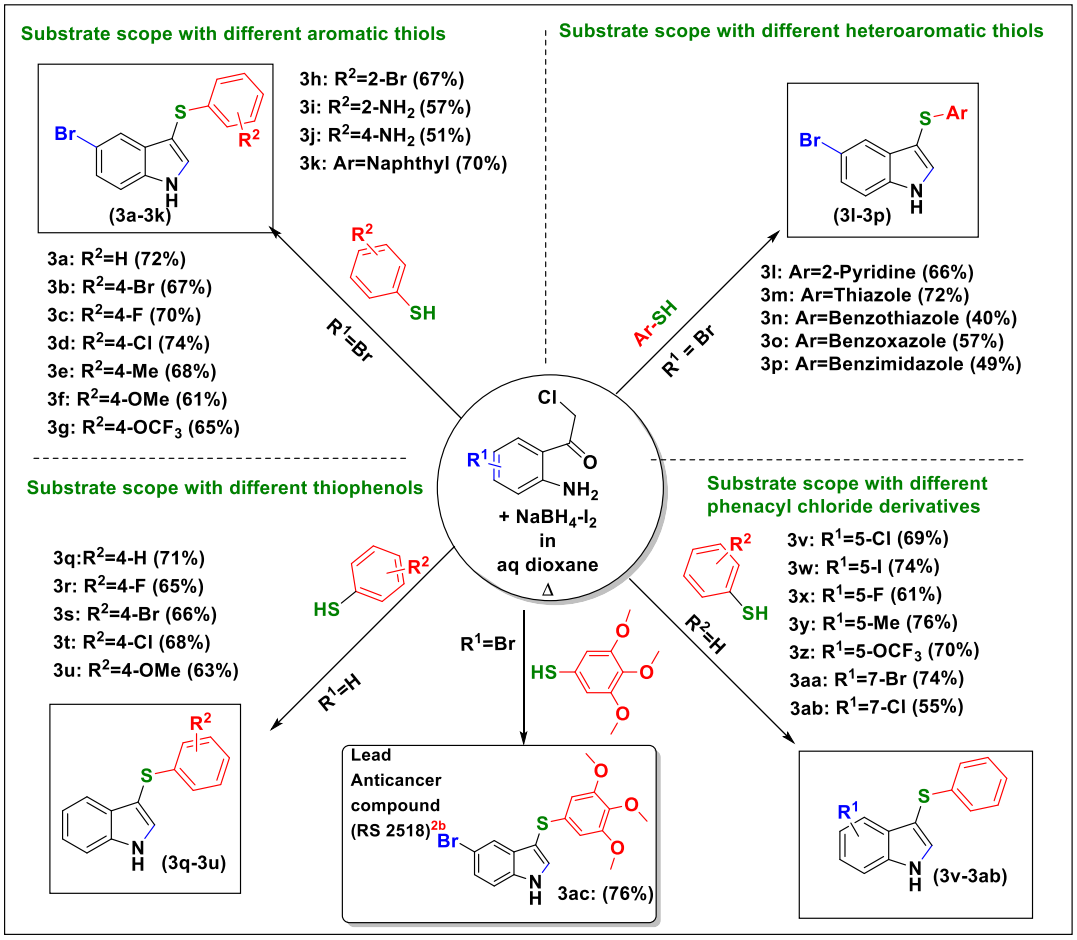
[a] Reaction conditions: 1a (0.25 mmol), 2a (0.275 mmol) and solvent 4 ml (1:9); [b] isolated yield; [c] = 2a (0.75 mmol); refluxing time 3.5 hr (entries 6-14); nd = Not detected

was not formed even after refluxing the reaction mixture of **1a** and **2a** for 12 h or more (Table 1**, e**ntry 1) and TLC observation revealed the formation of only intermediate indole[7a] *via* Sugasawa annulation without subsequent sulfenylation with thiophenol as it was initially presumed that in-situ generated NaOH from $NaBH_4$ would allow the sulfenylation in alkaline medium. [3l] Further an increase in amount of $NaBH_4$ (upt o 3 equiv.) and addition of external NaOH[3l] (1 equiv.) as co-catalyst could not allow the formation of product **3a** (entries 2-3). Hence, our attention moved towards exploration of iodine[3l,q] as a compatible cooperative catalyst with $NaBH_4$ for subsequent sulfenylation of indole in the same pot**.** To our satisfaction, 1 equiv. of iodine provides the desired product **3a** in 41% yield (entry 4) along with some amount of unreacted intermediate indole. Further increase in amount of iodine upto 3 equiv. (entries 5-7) wherein 2 equiv. of iodine (entry 6) successfully provided the optimum yield of desired product **3a** up to 71% yield in shorter reaction time of 3.5 h without any trace of unreacted intermediate indole. Replacing the iodine with other oxidants[3] (such as NBS, [3m] PIDA[3n] and $FeCl_3$[3o] (entries 8-10) and aq-dioxane

by another solvents (entries 11-12) were found ineffective for the above cascade transformation. In controlled experiments for which the above cascade reaction was conducted with iodine alone (without $NaBH_4$), the formation of **3a** was not observed (entry 13), which clearly indicated the role of a $NaBH_4$–I_2 combination as an activator for the cascade Sugasawa annulation-sulfenylation reaction. Further, 3 equiv. of thiophenol (**2a**) was used for the above cascade reaction, however, no further improvement in the yield of product **3a** was noticed as well as ^{1}HNMR of the product showed no trace of 2,3 bis-sulfenylated indole[3b] thus it confirmed that our protocol is a highly regioselective as only 3 position of indole is occupied during sulfenylation.

With the optimized conditions in hand (Table 1, entry 6), the substrate scope was studied by changing the thiols (aromatic/heteroaromatic) and 2-amino phenacylchloride derivatives and the desired 3-sulfenylated indoles (Table 2, **3a-3ac**) were obtained in moderate to good yield without any much influence of electron-donating or electron-withdrawing groups present either on aromatic ring of thiol or 2- amino phenacylchloride derivative. Gratifyingly, 2/4-aminothiophenols i.e. thiophenol (-SH) having additional acidic proton (- NH_2) also reacts

Table 2: Substrate scope of 3-sulfenyl-indoles [a]



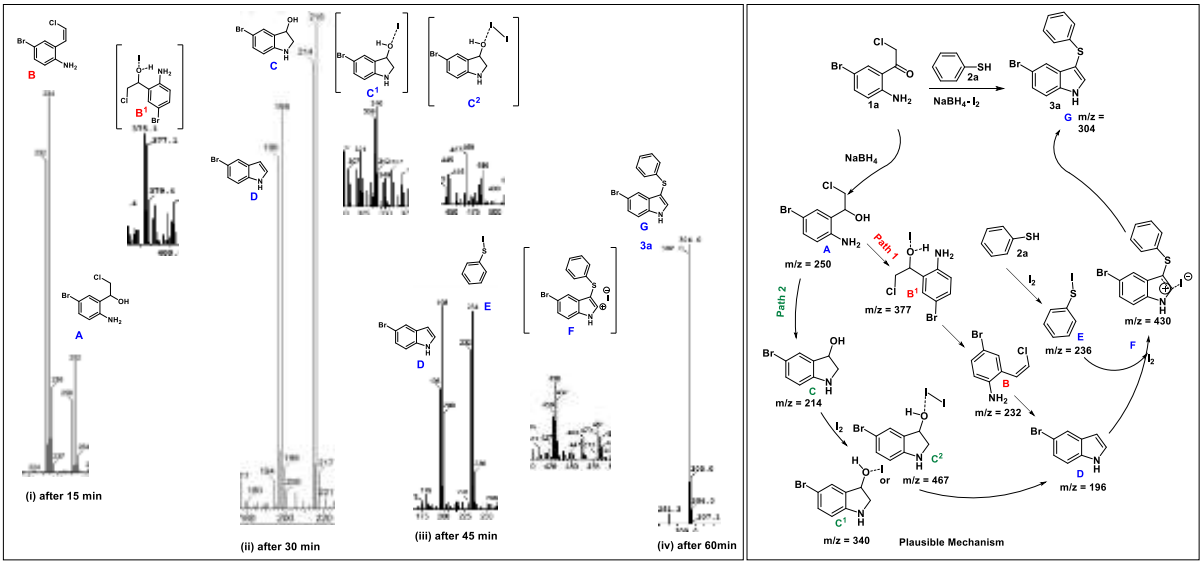
[a] **Reaction conditions: 2-amino phenacylchloride derivative (0.25 mmol), thiophenol (0.275 mmol) and aq.dioxane 4 ml (1:9), $NaBH_4$ (0.50 mmol), I_2 (0. 50 mmol), reflux 3.5 h**

successfully with 2-amino phenacylchloride derivative yielding products 3i-3j (Table 2) under mild reaction condition. [9] Unfortunately, dodecanethiol, an aliphatic thiol, did not provide the corresponding desired product. Thus, this chemoselectivity[3p] can be a significant addition to the growing arsenal for substrate-selective sulfenylation (aromatic versus aliphatic) in the total synthesis of bioactive complex molecule bearing indole core. [9] While implementing the study into the substrate scope (Table 2, entries **3a-3ab**), we further got interested to react 3,4,5-trimethoxythiophenol with 4-bromo-2-amino phenacylchloride (**1a**) which successfully provided a lead antitumor compound RS 2518[2c] i.e. 5-bromo-3-[(3,4,5-trimetoxyphenyl)thio]-1H-indole (Table 2, entry **3ac**) in one pot under metal-free condition, thus overall demonstrating the generality, greenness and robustness of our cooperative catalytic protocol.

To properly address the synergism between $NaBH_4$ and I_2 towards the formation of the product **3a**, LC-MS spectroscopy was used to visualize *in situ* generation of the intermediates (A-F) (Scheme 2) as well as to monitor the progress of the reaction to provide deeper insight into the mechanism of the reaction pathway for both steps. Towards this goal, aliquots were taken after an time intervals of 15,30,

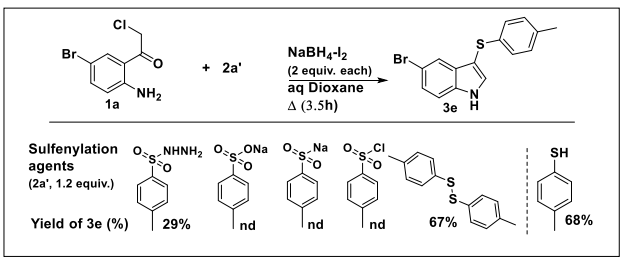
45 and 60 min (see S.I. for details) from reaction mixture of **1a** and **2a** and the outcome was rationalized by assuming reduction of **1a** into intermediate "A" (m/z=250) which gets converted into indole "D" by two plausible paths (i) dehydration of "A" into "B" (m/z = 234) via "B^1" (m/z = 377) as detected after 15 min (ii) cyclization of "A" into 3-hydroxyindoline "C" (m/z=214) after 30 min of reaction**.** Interestingly, the cooperative role of iodine appears crucial in Sugasawa annulation as evident from LC-MS[10] wherein the intermediate indole "D" (m/z 196) formed via "C^1" (m/z=467) or "C^2" (m/z=340) involving iodine mediated dehydration of alcohol "C" (see S.I.). Next, iodination of **2a** into reactive species i.e. phenylsulfenyl iodide "E" (m/z=235) detected after 45 min of reaction which enters in the second stage of reaction i.e. sulfenylation at the third position of indole with formation of an ionic intermediate- "F" (m/z=430) which finally confirmed the formation of desired product **3a** marked as "G" (m/z =304) after 60 min of reaction (see S.I.). Based on this analysis a plausible mechanism is shown in scheme 2.

With remarkable success towards synthesis of sulfenylating agent. (Table 2, 29 examples of 3-sulfenylated indoles),



Scheme 2: Plausible mechanism and LC-MS collage of reaction intermediates for cascade Sugasawa anuulation-sulfenylation

now our attention turned towards further widening the scope and compatibility of commercially available other sulfenylating agents[3d-k] (such as sulfonylhydrazide, sulfonylchlorides, sulfinate and disulfide derivatives) in optimized reaction condition (Scheme 3). Among them, sulfonylhydrazide provided **3e** in poor yield (29%) whereas *p*-tolyl disulfide appears as an effective sulphur source which successfully reacts with **1a** to provide the desired product **3e** in 67%yield (Scheme 3) which is comparable in respect to yield of **3e** as obtained using thiophenol (68%, Table 2) as a sulfenylating agent. It

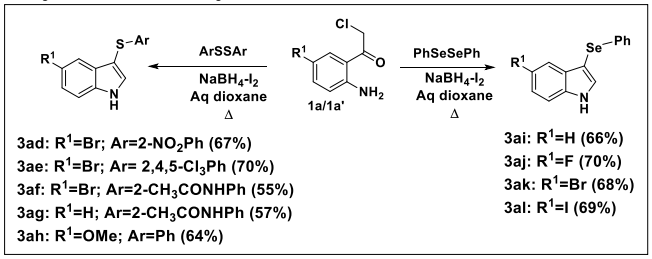


Scheme 3: Comparative study of different sulfenylating agents towards 3-sulfenylindole (**3e**)

is to mention that diaryldisulfide being odourless and inexpensive, also appear as alternative sulfenyalting agents towards formation of 3e. Further, few more diaryldisulfides (Table 3, **3ad-3ah**) were investigated with 2-amino phenacylchloride derivatives wherein half equivalent of disulfides in comparison to thiol was found sufficient to form the desired C-3 sulfenylated indoles **3ad-3ah** (Table 3) via multiple C-N and C-S bond formation in one pot.

Further venturing into the robustness of our

Table 3: Substrate scope of 3 sulfenyl/selenyl indoles with diaryldisulfides/diaryldiselenide[a]



3ad: R^1=Br; Ar=2-NO_2Ph (67%)
3ae: R^1=Br; Ar= 2,4,5-Cl_3Ph (70%)
3af: R^1=Br; Ar=2-$CH_3CONHPh$ (55%)
3ag: R^1=H; Ar=2-$CH_3CONHPh$ (57%)
3ah: R^1=OMe; Ar=Ph (64%)

3ai: R^1=H (66%)
3aj: R^1=F (70%)
3ak: R^1=Br (68%)
3al: R^1=I (69%)

[a] Reaction conditions: 1a' (0.25 mmol), ArSSAr/ArSeSeAr (0.14 mmol), $NaBH_4$ (2 equiv)-I_2(2 equiv) and solvent 4 ml; refluxing time 3.5 h

developed protocol, we investigated the reaction towards 3-selenyl indoles as many of organoselenium compounds[11] are known for a large number of biological activities. Hence, 2- amino phenacylchloride derivative (1a') was reacted with commercial diaryldiselenide (Table 3) in the same cooperative catalytic system which furnished desired 3- selenyl indoles (Table 3, **3ai-3al**) via C-N and C-Se bond formation in same pot under metal free condition

In conclusion, we have disclosed an efficient $NaBH_4$-I_2 catalyzed one-pot two-step reaction of 2-amino-phenacylchlorides and thiophenols or diaryldisulfides/diaryldiselenide in which the intermediate indole is formed by *in situ* nucleophilic Sugasawa-annulation that becomes the starting material for second step i.e. C(sp2)–H chalcogenylation thereby furnishing structurally diverse 3-sulfenyl/selenyl indoles. The main advantage of our protocol is cascade C-N and C-S/C-Se bond formation under influence of cooperative catalyst ($NaBH_4$-I_2) besides being milder reaction condition, ample substrate scope with high regioselectivity and high atom economy. Additional investigations aimed at the exploring the biological activities of the titled structurally diverse heterocyclic compounds are underway in our laboratory.

Experimental Section

2-Aminophenacyl chloride derivative (0.25 mmol) was taken in aq. dioxane (4 ml) in a RBF and then a $NaBH_4$ (0.5 mmol) and iodine (0.50 mmol) and thiophenol (0.275mol) or diaryl disulfide/diaryl diselenide (0.14 mmol) were added and reaction mixture was refluxed for duration of 3.5 h. After completion of the reaction, crude reaction mixture was allowed to come to rt then conc. on rotatory evaporator. Water was added to crude product and then extracted with ethyl acetate (5 ml, 3 times) and combined organic layer was washed with saturated $Na_2S_2O_3$ solution to remove any traces of iodine followed by brine, dried over anhydrous Na_2SO_4 and conc. under vacuum. Colum purification of crude product was performed on silica gel (60/120 mesh) using ethyl acetate in hexane as eluent to afford the different 3-sulfenyl/selenyl indoles (3a-3al).

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[8] Aminophenacyl chlorides are stable and versatile reagents[7b] which are not only exploited for Sugasawa annulation[7a] but also used during many organic transformations including natural product synthesis.[7c]

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[10]It is worth mentioning that reaction intermediates (i.e. reduction-cyclization-dehydration steps)[7a] of well reported Sugasawa annulation is identified for the first time by LC-MS wherein synergism of Iodine found crucial for the both Sugasawa annulation as well as chalcogenylation to provide product **3a.**

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UPDATE

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Aditya G. Lavekar,[a,b] Danish Equbal,[a] Saima[a] and Arun K Sinha[a,b]*