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Molecular iodine mediated oxidative cleavage of the C–N bond of aryl and heteroaryl (dimethylamino)methyl groups into aldehydes†

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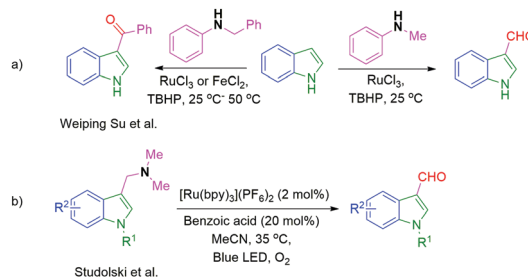
The oxidative cleavage of the C–N bond of aryl and heteroaryl (dimethylamino)methyl groups is achieved by employing molecular iodine as a mild oxidizing agent under ambient conditions in the presence of a mild base. The important reaction of C3 formylation of free NH and substituted indoles containing various substituents is accomplished from the corresponding Mannich bases. This methodology can also be extended for the synthesis of aryl and other heteroaryl aldehydes and ketones. Furthermore, the usefulness of the method is successfully demonstrated on a gram scale.

Carbonyl functionalization of indole compounds is an important process to synthesize naturally occurring bioactive molecules containing an indole motif.¹ Many methods have been developed to introduce carbonyl groups to indoles bearing different substituents. Vilsmeier–Haack,² Rieche's,³ Duff's⁴ and Reimer–Tiemann⁵ reactions are well known classical methods which are used to carry out such transformations. Due to their harsh reaction conditions, low selectivity, and poor functional group compatibility, chemists have further developed mild, effective, and regioselective carbonylation of indoles. Subjecting tertiary amines to oxidants, such as Pb(OAc)₄,^{6a} KMnO₄,^{6b–d} MnO₂,^{6e} chromic acid,^{6f} HgO·I₂,^{6g} Hg(OAc)₂,^{6h} K₂FeO₄,⁶ⁱ and Ru(bpy)₃Cl₂ with K₂S₂O₈ under visible-right irradiation,^{6j} or bromination reagents, such as cyanogen bromide,^{6k} or *N*-bromosuccinimide,^{6l} gives the corresponding aldehydes or ketones. One of the best among the rest to do C3 formylation of indoles is by oxidizing the different C3 substituted groups like methanamines,⁷ and methylene alcohols,⁸ into the corresponding carbonyl compounds. Su *et al.* established an excellent method to prepare indole-3-carboxaldehyde using *N*-methylaniline as a carbonyl source (Scheme 1a).^{9a} Emulating his work, many groups have developed strategies using *n*-Bu₄NI,^{9b} KI,^{9c} CuCl₂,^{9d,e} I₂,^{9f,g} Rose Bengal^{9h} or ceric ammonium nitrate (CAN)⁹ⁱ as catalysts for C3

formylation of indoles. Recently, Stodulski and co-workers synthesized a series of indole-3-carboxaldehyde derivatives by visible-light-mediated oxygenation of 3-(dimethylaminomethyl)-indoles bearing various substituents (Scheme 1b).¹⁰

The direct oxidation of tertiary amines to form the corresponding carbonyl compounds is less explored as compared to the alcohols.¹¹ Iodine being a mild oxidizing and environmentally benign reagent¹² is explored to convert tertiary amines to their respective lactams.^{13a–c} Having excellent affinity towards nitrogen, iodine serves as a reliable route to form imines^{13d} either in the presence of a mild base or a co-oxidant, which are then transformed to amides. Alternatives to molecular iodine, like PIDA^{14a} and TBAI,^{14b} have been studied to do α -oxygenation of tertiary amines. We envisioned that substituted gramine prepared by Mannich reaction of substituted indoles can be converted to indole-3-carboxaldehyde *via* iodine mediated oxidative cleavage of the C–N bond. In this process it was visualized that first imine formation would take place by loss of the benzylic hydrogen followed by hydrolysis to yield aldehyde.

To begin with, we treated parent gramine **1** with one equiv. of molecular iodine in chloroform, followed by workup with aq. Na₂S₂O₃ which gave 12% of aldehyde **2a** along with most of the unreacted gramine (Table 1, entry 1). We reasoned that the iodide ion liberated in the reaction may not act as a better



Scheme 1 Inter-molecular (a) and intramolecular (b) representation of synthesis of 3-formyl or keto indoles.

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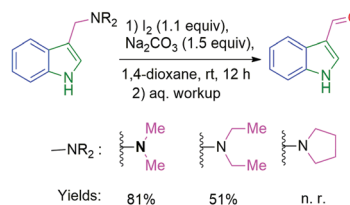
Table 1 Optimization of the reaction conditions^a

Sr. no.	Reagent	Oxidant	Base	Solvent	Yield ^b (%)
1	I ₂ (1 equiv.)	—	—	CHCl ₃	12
2	I ₂ (1 equiv.)	—	Na ₂ CO ₃ (1 equiv.)	CHCl ₃	35
3 ^a	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	CHCl ₃	65
4	I ₂ (1.1 equiv.)	—	NaHCO ₃ (1.5 equiv.)	CHCl ₃	45
5	I ₂ (1.1 equiv.)	—	Cs ₂ CO ₃ (1.5 equiv.)	CHCl ₃	49
6	I ₂ (1.1 equiv.)	—	NaOH (1 equiv.)	Ethanol	N.R.
7	NIS (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	CHCl ₃	25
8	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	DCE	53
9	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	Ethanol	45
10	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	THF	69
11	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	1,4-Dioxane	81
12	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	Acetonitrile	46
13	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	THF:H ₂ O	46
14	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	ACN:H ₂ O	37
15	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	CHCl ₃ :H ₂ O	29
16	I ₂ (1.1 equiv.)	—	Na ₂ CO ₃ (1.5 equiv.)	1,4-Dioxane:H ₂ O	62
17	I ₂ (1.1 equiv.)	TBHP	—	THF	N.R.

^a Reaction was carried out on 1 mmol of starting substrate. ^b Isolated yields.

conjugate base to abstract the methylene proton. Hence, we thought of performing the reaction under basic conditions. The reaction of **1** with one equiv. of iodine and one equiv. of Na₂CO₃ as a base increased the yield to 35% (entry 2). Increase in iodine and base loading to 1.1 equiv. and 1.5 equiv. respectively, furnished **2a** in 65% (entry 3). Alternatives for Na₂CO₃ were examined using NaHCO₃ and Cs₂CO₃, but no substantial change was seen in the yields (entries 4 and 5). Reaction with a stoichiometric amount of NaOH failed to give the product (entry 6). On the other hand, the use of NIS failed as an alternative for iodine in deamination of **1** (entry 7). Furthermore, other solvents were studied as a means to increase in the productivity. Thus, we tried 1,2-dichloroethane as an alternative for chloroform (entry 8), but chloroform remained the best. Polar solvents like ethanol, tetrahydrofuran, 1,4-dioxane and acetonitrile were tried (entries 9–12), from which 1,4-dioxane served our purpose, giving **2a** in 81% yield. To reduce the aqueous workup step in the reaction and to achieve spontaneous oxidative cleavage we studied aqueous–organic solvent mixtures. Screening was carried out in THF:H₂O, ACN:H₂O, CHCl₃:H₂O and 1,4-dioxane:H₂O solvent mixtures to observe any increase in yield (entries 13–16). But unfortunately, none of the solvent combinations achieved this goal. The use of a co-oxidant like aq. TBHP in ethanol was examined, which did not result in any product formation (entry 17).

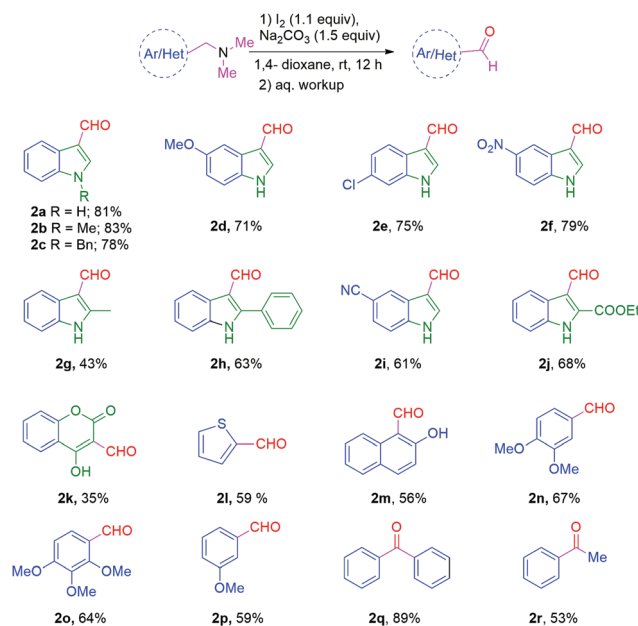
Mannich bases using diethylamine and pyrrolidine were prepared to study the generality of the reaction. It was found that dimethylamine furnished the highest yield among all others (Scheme 2).



Scheme 2 Screening of sec-amine groups of Mannich base.

Using the optimum conditions (entry 11), we prepared *N*-methyl **2b** and *N*-benzyl **2c** indole-3-carboxaldehydes (Scheme 3). Aldehydes bearing substituents like 5-OMe **2d**, 6-Cl **2e**, 5-NO₂ **2f**, 2-methyl **2g**, 2-phenyl **2h**, 5-CN **2i** and 2-COOEt **2j**, were obtained from their respective gramines in excellent to good yields. Heterocyclic amines, 3-((dimethylamino)methyl)-4-hydroxy-2H-chromen-2-one and *N,N*-dimethyl-1-(thiophen-2-yl) methanamine were also converted to 4-hydroxy-2-oxo-2H-chromene-3-carbaldehyde **2k** and thiophene-2-carboxaldehyde **2l**, respectively, in moderate yields. Furthermore, to exploit the feasibility of the reaction methodology, aryl compounds were also subjected to this oxidative cleavage reaction. Mannich adducts 1-((dimethylamino)methyl)naphthalen-2-ol, *N,N*-dimethyl veratrylamine, 2,3,4-trimethoxy-*N,N*-dimethylbenzenemethanamine and 1-(3-methoxyphenyl)-*N,N*-dimethylmethanamine were transformed into their aldehydes **2m**, **2n**, **2o** and **2p**, respectively, in good yields. Ketones like benzophenone **2q** and acetophenone **2r** were also synthesized from *N,N*-dimethyl-1,1-diphenylmethanamine and *N,N*-dimethyl-1-phenylethanamine respectively.

To make the procedure a one pot method, a three component reaction was carried out between indole, formaldehyde, and dimethylamine; however it gave **2a** in only 53% yield. The use of an excess of iodine and base did not improve



Scheme 3 Oxidative cleavage of the C–N bond of (dimethylamino)-methyl derivatives to aldehydes.

the reaction yield substantially for the one pot procedure (Scheme 4).

Gram scale synthesis for the conversion of gramine to indole-3-carboxaldehyde provided **2a** in 71% yield (Scheme 5).

The plausible mechanistic pathway for the product is depicted in (Scheme 6). We speculated that iodine might be acting as a mild Lewis acid that coordinates with the nitrogen of the dimethylamine. The base then might deprotonate the coordinated amine to generate the iminium salt, which then hydrolyses during the work up to deliver the aldehyde group. To confirm the mechanism, we carried out the reaction in an NMR tube in CDCl_3 as the solvent. As speculated, coordination of iodine shifted the methylene protons downfield initially. After a while, the signal due to the methylene protons disappeared and a salt was seen precipitated out in CDCl_3 due to its insolubility in the solvent. After removal of CDCl_3 , DMSO-d_6 was added and the NMR was recorded, in which the iminium salt proton was seen clearly. We also tried the reaction in the presence of one equiv. of dioxane to check whether the

solvent has any role in the reaction. However, no change in the spectrum was observed to suggest its participation. Also no bis-indole formation was seen ruling out the possibility of the formation of (1*H*-indol-3-yl)methanol and subsequent oxidation.

Conclusions

A cheap, environmentally benign methodology was developed to carry out oxidative cleavage of the C–N bond of the (dimethylamino) methyl group of indoles and aryl compounds. *N*-Deprotected indoles were also successively α -oxygenated to give their carboxaldehydes in good yields. This methodology proved applicable to other heterocyclic compounds. The one pot conversion of the aryl and heteroaryl systems to their corresponding aldehyde derivatives was also feasible in moderate yield.

Author contributions

SGT was involved in overall supervision while KSM was involved in project planning, execution, carrying out experiments and manuscript writing.

Conflicts of interest

There are no conflicts to declare.

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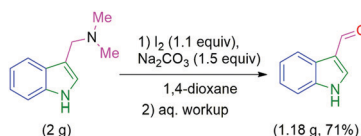
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Notes and references

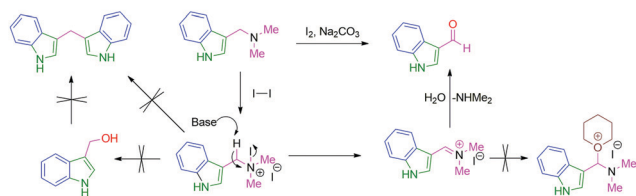
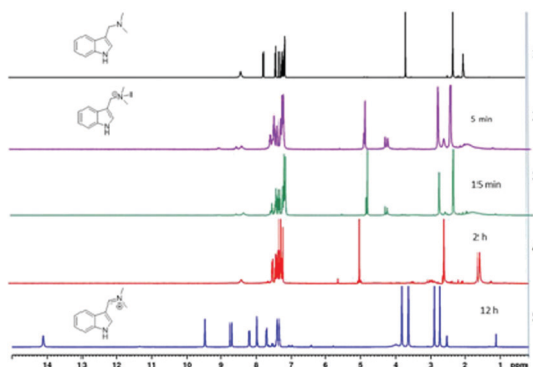
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Scheme 4 Three component synthesis of indole-3-carboxaldehyde.



Scheme 5 Gram scale synthesis of indole-3-carboxaldehyde.



Scheme 6 Plausible reaction mechanism.

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