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DOI: 10.1039/C7CC06267B

COMMUNICATION

Weak Interactions Controlled C-H Mono-Nitration of Indolines

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Under mild condition an unprecedented C-H mononitration of indolines either at -C_5 or -C_7 positions is reported here. The role of multiple weak interactions such as steric factors, electronic effects, cation-π interaction, solvent polarity, etc. was established for the 100% regioselective electrophilic aromatic (ArSE) nitration using $Cu(NO_3)_2$ or $AgNO_3$.

Nitroarenes are important synthetic precursors in various industries like agrochemical, pesticides, pharmacology, dyes, polymers, etc. and preparations of those molecules are the most extensively studied chemical reactions.[1] High synthetic utility of the nitroaryl moieties is due to their abundance and easy synthetic transformation to other functional groups like amino, diazo, etc.[1-2] Few of the nitro substituted indoles have potent activity towards *tuberculosis*.[3]

Regioselective nitration reactions of pharmaceutically important indolines are desirable but challenging due to unavailability of suitable methods.[4] The aromatic electrophilic nitration reactions (ArSE) are generally performed under harsh conditions[5] using the reagents like conc. HNO_3-H_2SO_4,[6] nitronium tetrafluoroborate,[7] conc. HNO_3-mixed anhydrides,[8] *N*-nitropyridinium salts, $NaNO_3$-TFA,[9] etc.[10] Therefore, ArSE reactions may cause non-selective nitration of starting materials[4a] or over oxidation on the products. Also, under highly acidic condition some functional groups like -CN, -CHO might get affected to make isolation procedure tedious.[11] However, selective ArSE C-H nitrations are done *via* transition metal-templated strategies.[12] For example, commonly used transition metals in the C-H nitrations[13] are Fe,[14] Pd,[15] Rh, Ru,[16] etc. Zhang and co-workers have developed first *meta*-selective Ru- catalysed C-H nitration *via ortho*-metalation template strategy (Fig. 1b).[16] Also, using organometallic reagents,[17] the *ipso*-nitration are reported for the systems like aryl boronic acids, carboxylic acids,[18] aryl halides, aryl triflates, etc.[19] A reported example by Maiti and co-workers is shown in Fig. 1c for the *ipso*-nitration on aryl boronic acids.[17b]

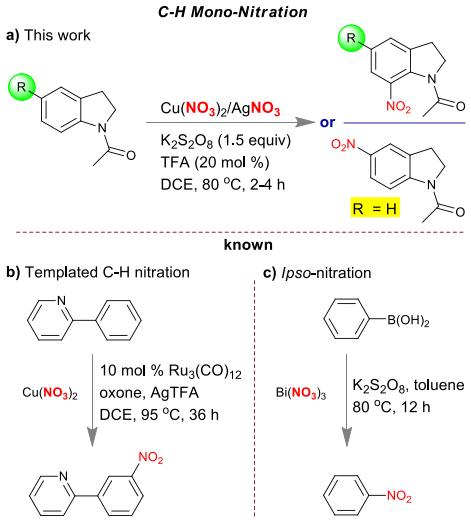

Fig. 1 The C-H mono-nitration. a) Our mono-nitration approach on the non-prefunctionalized system under mild condition with 100% selectivity. b) Zhang's Ru- templated *meta*-selective C-H nitration *via ortho*-metalation template strategy.[16] c) Maiti's *ipso*-nitration on aryl boronic acids.[17b]

Reactivity of chemical systems is known to be altered by environment.[20] The soft force[21] of several low-energy and low-level multiple cooperative non-covalent or weak interactions[22] like hydrophobic effect,[23] anion-π,[24] cation-π,[25] etc. are considerably being explored in chemical systems.[26] By exploiting the weak interactions, the -C_7 or -C_5 selective ArSE C-H mono-nitration of indolines (Fig. 1a) is demonstrated here with an easy, convenient and mild[27] approach. The mechanism of the highly selective mono-nitration reaction is explained by the use of non-covalent interactions and that can be correlated to the concept of supramolecular catalysis.[28]

After screening several conditions using the unsubstituted *N*-acetyl indoline (**1a**) as the model substrate, the standard condition of this nitration reaction was optimised (Table 1, entry 11, 13). The best yield (up to 82%) of 5-nitro-1-acetyl

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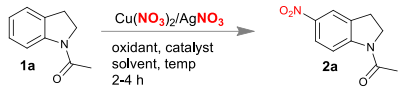
Electronic Supplementary Information (ESI) available: [details of synthesis, characterization and spectra]. See DOI: 10.1039/x0xx00000x

indoline (**2a**) was obtained using $Cu(NO_3)_2.3H_2O$ (1.1 equiv) or $AgNO_3$ (1.5 equiv) as $-NO_2$ (nitro) source, potassium persulfate ($K_2S_2O_8$, 1.5 equiv) as oxidant and trifluoroacetic acid (TFA, 20 mol %), in 1,2-dichloroethane (DCE) at 80 ºC. Among the solvents examined, acetonitrile, DMSO, DMF, 1,4-dioxane, ethyl acetate, dichloromethane (entries 1-6) etc. were completely ineffective for the transformation. In TFE, 68% (entry 7) of **2a** was isolated after 2.5 h, however, no product could be detected in toluene (entry 8). Following, we have also screened several nitrating agents and no products could be isolated with KNO_3 (entry 16) and $NaNO_3$ (entry 17). The **2a** was obtained in 23% and 54%, using $Bi(NO_3)_3$ (entry 18) and $Fe(NO_3)_3$ (entry 23), respectively. Moreover, using $Ni(NO_3)_2$ and $Zn(NO_3)_2$ the yield of **2a** was obtained in 42% (entry 24) and 39% (entry 25), respectively. Oxidants oxone or phenyliodine diacetate (PIDA) (entry 19-21) were proved to be less efficient compared to $K_2S_2O_8$. However, under oxygen atmosphere 48% of **2a** was isolated after 24 h (entry 22). A representational example is shown in entry 9 (Table 1) that varying temperatures than 80 ºC did not have any positive impact in the improvement of yields.

Table 1. Optimization Method



entry	$-NO_2$ source (equiv)	oxidant (equiv)	Solvent, ºC	**2a** (%)
1[a]	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	ACN, 90	--[b]
2	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	DMSO, 110	--
3	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	Dioxane, 90	--
4	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	DMF, 90	--
5	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	EtOAc, 90	--
6	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	DCM, 50	--
7	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	TFE, 80	68
8	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	Toluene, 80	--
9	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	DCE, 90	58
10	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (1.5)	DCE, 80	73
11[c]	$Cu(NO_3)_2$ (1.1)	$K_2S_2O_8$ (1.5)	DCE, 80	82
12	$AgNO_3$ (1.0)	$K_2S_2O_8$ (3.0)	DCE, 80	45
13[c]	$AgNO_3$ (1.5)	$K_2S_2O_8$ (1.5)	DCE, 80	80
14[d]	$AgNO_3$ (0.2), KNO_3 (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	18
15[d]	$AgNO_3$ (0.2), $NaNO_3$ (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	<10
16	KNO_3 (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	--
17	$NaNO_3$ (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	--
18[d]	$Bi(NO_3)_3.5H_2O$	$K_2S_2O_8$ (3.0)	DCE, 80	23
19[d]	$Cu(NO_3)_2$ (1.2)	Oxone(3.0)	DCE, 80	42
20[d]	$AgNO_3$ (1.5)	Oxone(3.0)	DCE, 80	30
21	$Cu(NO_3)_2$ (1.2)	PIDA (2.0)	DCE, 80	28
22[e]	$Cu(NO_3)_2$ (1.1)	O_2	DCE, 80	48
23[f]	$Fe(NO_3)_3.9H_2O$	$K_2S_2O_8$ (1.5)	DCE, 80	54
24[f]	$Ni(NO_3)_2.6H_2O$ (1.2)	$K_2S_2O_8$ (1.5)	DCE, 80	42
25[f]	$Zn(NO_3)_2.6H_2O$ (1.2)	$K_2S_2O_8$ (1.5)	DCE, 80	39

[a]$Cu(NO_3)_2$ used as $Cu(NO_3)_2.3H_2O$, [b]No reaction, [c]TFA 20 mol %. [d]Continued for 16 h instead of 2 h. [e]24 h. [f]8 h.

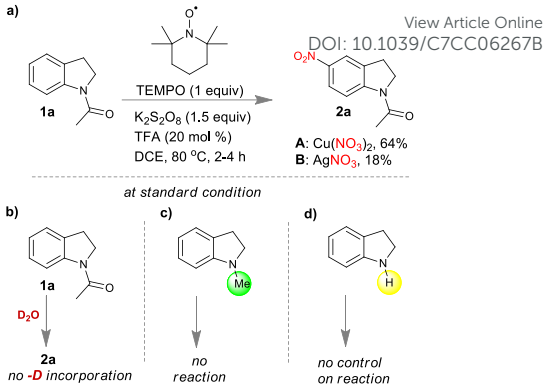


Fig. 2 Control Experiments.

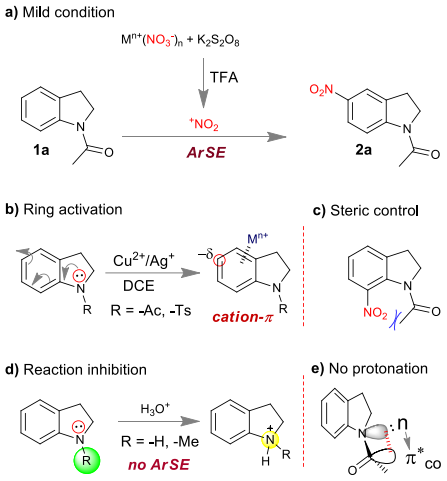


Fig. 3 The non-covalent interactions in the nitration reaction.

To understand the mechanism of the reaction several control experiments were performed. Using 1.0 equiv of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), **2a** was isolated in 64% yield (Fig. 2a) and that ruled out the possibility of the nitration reaction *via* radical pathway. Under standard condition D_2O was added in the reaction mixture (Fig. 2b) to confirm that any metal templated C-H activation mechanism was not operating. The 1-methyl indoline and 1-H indoline failed to give any nitrated products (Fig. 2c,d) and thus the presence of carbonyl group was proved to be essential.

The mechanism of selective mono-nitration of indoline derivatives was proposed to be an aromatic electrophilic substitution reaction (ArSE). The nitronium ion ($^+NO_2$) was generated from $Cu(NO_3)_2/AgNO_3$ in non-polar solvent DCE in the presence of TFA (catalyst) and $K_2S_2O_8$ (oxidant). For ArSE, the C_5- or C_7- positions of the indolines were expected to be sufficiently electron rich due to +R effect by nitrogen (Fig. 3b). Therefore to avoid protonation under protic-environment and simultaneous activation of the aromatic rings, *N*-centre of indolines were protected with π-acceptors like $-SO_2$ (tosyl, mesyl) or -C=O (acetyl, pivaloyl, benzoyl) group (Fig. 3e). So, 1-methyl indoline and 1-H indoline failed to give any product and led to a very complex reaction mixture might be due to

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protonation (Fig. 2c,d). Amongst the metal ions and solvents examined (Table 1), the Cu^{2+}/Ag^{+} ions in non-polar solvent DCE led to the best results. The influence of cation-π interaction for activation at C_5- or C_7- by Cu^{2+} or Ag^{+} ions (Fig. 2b) was anticipated in the nitration reaction. Due to soft acid - soft base nature (HSAB approach),[29] Cu^{2+}/Ag^{+} - aryl ring interaction was preferred over K^{+}/Na^{+} (hard acid) - aryl ring (soft base) *via* cation-π activation. Obtaining 23% of the C_5-H nitrated product in presence of $Bi(NO_3)_3.5H_2O$ was also an indication for inferior activation of aromatic ring by a relatively harder acid (Bi^{3+}) than Cu^{2+}/Ag^{+}. In high polar solvents (ACN, DMF, DMSO, etc.) no products could be detected might be due to the absence of weak cation-π interaction. The formation of C_5-H nitration was observed over C_7-H nitration possibly because of the steric effect of *N*-acetyl group (Fig. 3c). Therefore, C_5-substituted indolines led to C_7-H nitration preferentially (*vide infra*). In one pot the di-nitration reaction was unsuccessful even in presence of excess nitrate salts (3.0 equiv) and TFA (1.0 equiv).

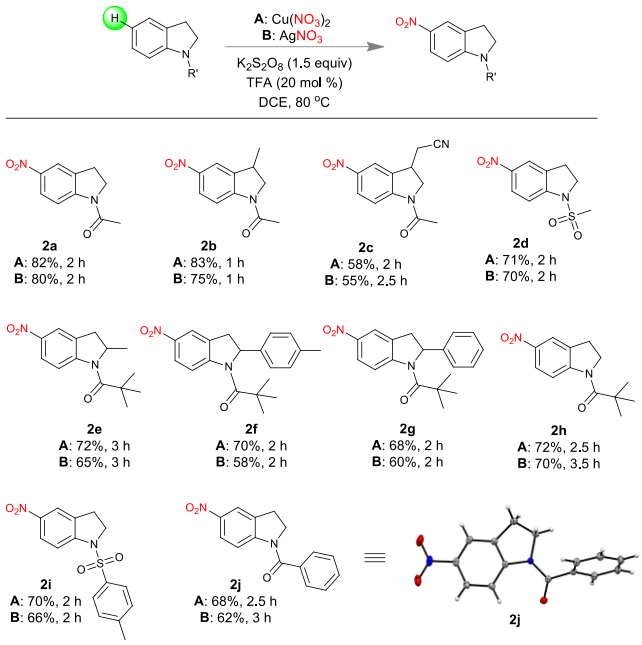

Fig. 4 Scope of C_5-Nitration of Indolines.

The substrates scope of the C-H mono-nitration protocol was explored (Fig. 4). Compounds with substitution in the pyrrolidine ring of indolines underwent smooth reaction to give C_5-nitrated products in good yields (Fig. 4). C_2-Aryl substituted indolines (**2f, 2g**) also resulted in the desired products in 58% to 70% yield. C_5-H nitrated products with other *N*-protected indolines like *N*-pivaloyl (**2e, 2f, 2g, 2h**), *N*-mesyl (**2d**) *N*-tosyl (**2i**) and *N*-benzoyl (**2j**) were also obtained in 58 to 72% as single regioisomer within 3 h.

C_7-H nitrated products were obtained as the sole regioisomeric products on C_5-substituted indolines (Fig. 5). Interestingly, C_5-nitro indoline led to C_5,C_7-dinitro (**2k**) derivative in 60% yield at slightly longer time (4 h). The aryl groups at the C_5- position remain unaffected during the nitration reaction (**2p**, **2q**, **2r**, **2s**). Halogenated indolines also worked efficiently (**2l**). Furthermore, *N*-methylacetanilide did not results in any products even after 24 h.

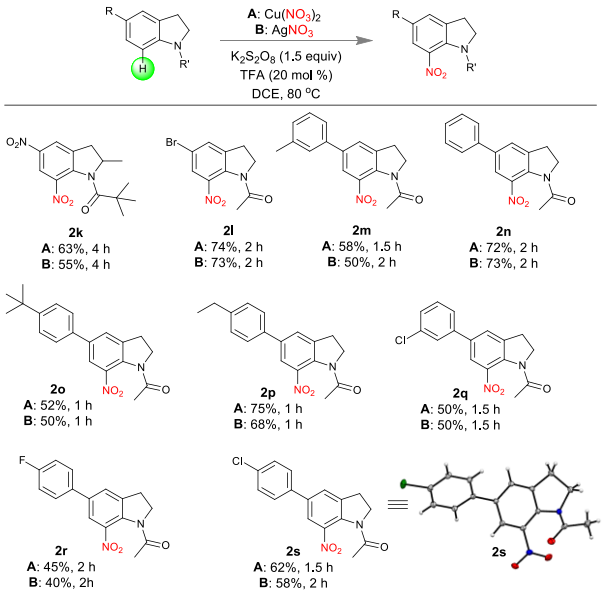

Fig. 5 Scope of C7-Nitration of Indolines.

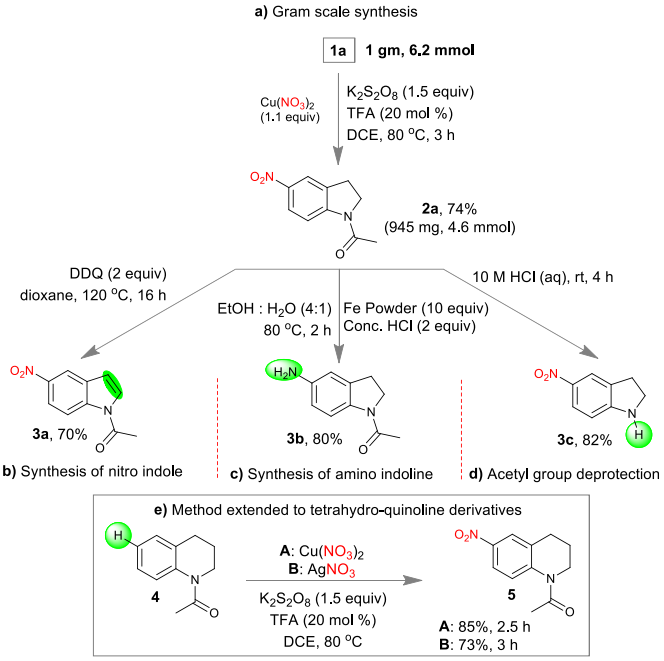

Fig. 6 Synthetic Utility. a) Gram scale synthesis of **2a**. b) Oxidation of nitroindoline to nitroindole. c) Reduction of nitro-indoline to amino-indoline. d) Acetyl group deprotection. e) Nitration of tetrahdroquinoline derivatives.

Towards synthetic utility, the compound **1a** was converted to **2a** in gram scale (ca. 1 gm) with 74% yield (Fig. 6a). The 5-nitroindoline **2a** was oxidised with DDQ and converted to 5-nitroindole (**3a**) in 70% yield (Fig. 6b). The nitro group of **2a** was reduced to the corresponding amine with Fe (powder)-HCl to obtain **3b** in 80% yield (Fig. 6c). Deprotection of the acetyl group with 10 M HCl led to 5-nitroindoline **3c** (82% yield) (Fig. 6d). This methodology was also effective for the nitration of

tetrahydroquinoline derivative (**4**, Fig. 6e) to 6-nitro-*N*-acyl-tetrahydroquinoline (**5**) with 85% and 73% yields from the methods A and B, respectively.

In summary, the class of reactions and their suggested mechanism prescribe a systematic pathway towards programmable functional molecules using non-covalent interactions. Strategically it is shown that by choosing appropriate reaction condition difficult transformation can also be done easily. Herein, we have demonstrated a method for regioselective C_5-H or C_7-H mono-nitration of indolines. In general, these results may also add a new aspect towards development of supramolecular catalysis in organic chemistry. The synthetic utility of the nitro-indolines towards synthesis of various synthetic precursors are also documented. We foresee that this mild and selective efficient nitration methodology can offer direct access to the heterocyclic compounds and might have a major impact on synthesis of functionalized materials, complex molecules and pharmaceuticals.

Acknowledgement

"*We thank DST (New Delhi, India) for support and A.B. thank CSIR (India) for fellowship*

Conflicts of interest

"There are no conflicts to declare"

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DOI: 10.1039/C7CC06267B

Weak Interactions Controlled C-H Mono-Nitration of Indolines

By utilising simultaneous cooperative multiple weak interactions (soft force), mild and selective C_5-H or C_7-H mono-nitration of indoline is demonstrated.