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Unprecedented $SnCl_2$-Mediated Cyclization of Nitro Arenes via N–N Bond Formation†

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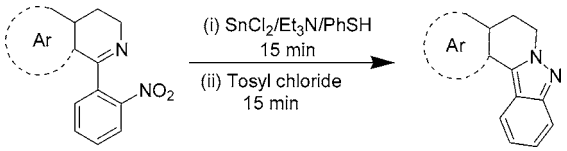
ABSTRACT



A mild, efficient, one-pot protocol for the cyclization of nitro-aryl substrates using $SnCl_2$ has been described. The mechanistic course of the reaction suggests the involvement of a hydroxylamine intermediate leading to an intramolecular cyclization via N–N bond formation. The versatility of the methodology has been demonstrated by using two nitro-aryl substrates derived from dihydroisoquinolines and dihydro-β-carbolines. The intramolecular cyclization led to the formation of indazoles in high yields and purities.

Substituted heterocyclic compounds can offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Among the various heterocyclic frameworks, benzoannelated nitrogen heterocycles are widely used as biologically active compounds.[1] One of the widely acclaimed methods for the synthesis of benzoannelated nitrogen heterocycles is via intramolecular cyclization of *ortho*-nitro arene precursors. It generally involves reduction of the nitro-aryl group followed by interaction of the reduced intermediate with the functionality in an ortho-position leading to heterocyclic compounds. The ring closure in these precursors can be accomplished by two possible methods: first, by the generation of an amino group from a nitro group via reduction, which then participates in the cyclization, and second, by direct involvement of intermediates generated in situ from the nitro functionality during its reduction that leads to the cyclization. Out of these two methods, the latter has been utilized for the synthesis of N-rich heterocycles via an intramolecular N−N bond formation. Reductive cyclizations by direct involvement of aryl nitro compounds for N−N bond formation are generally performed in the presence of tervalent phosphorus reagents.[2] It involves deoxygenation of the nitro compounds by nucleophilic attack of tervalent phosphorus reagents and subsequent cyclization to give heterocyclic frameworks. Although a non-nitrene pathway was thought to be the probable intermediate during the course of cyclization,[3] subsequent studies in this area hinted at the possibility of an arylnitrene pathway as well.[4] The reactions are commonly carried out in an excess of triethyl phosphite, as both the reductant and the reaction solvent at high temperatures.[2b] However, this methodology suffers from the drawback that the sensitive functional groups on heterocycles may undergo alkylation leading to the formation of side products and a decrease in yields.[2b] Additionally, intramolecular cyclizations via N−N bond formation using methods other than tervalent phosphorus reagents are rather scarce.[5] During the course of our studies on dihydroisoquinolines, we observed in-

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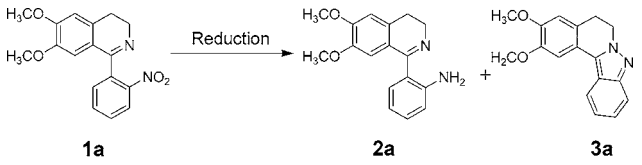
tramolecular cyclization of nitro compounds without involving the use of tervalent phosphorus reagents. In this communication, we report an unprecedented $SnCl_2$-mediated cyclization via N−N bond formation in nitro arenes.

In our effort directed toward the reduction of the nitro group of 1-(2-nitrophenyl)-3,4-dihydroisoquinoline (**1a**) using $SnCl_2 \cdot 2H_2O$, we observed formation of an unusual side product with a molecular weight of 280 Da in 3% isolated yield along with the corresponding amine **2a** in 85% isolated yield (Scheme 1). Subjecting the byproduct to NMR and

Scheme 1



Reaction conditions	2a[a] (%)	3a[a] (%)	Recovered 1a
$SnCl_2.2H_2O$, MeOH	85	3	0
Pd/C, MeOH	95	0	0
$(EtO)_3P$	0	0	100[b]

[a] Isolated yield. [b]Recovered crude yield.

X-ray analysis revealed that an intramolecular cyclization via N−N bond formation had occurred resulting in a novel heterosystem 2,3-dimethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline **3a**. The ORTEP structure of the byproduct **3a** has been depicted in Figure 1. Interestingly, the catalytic reduc-

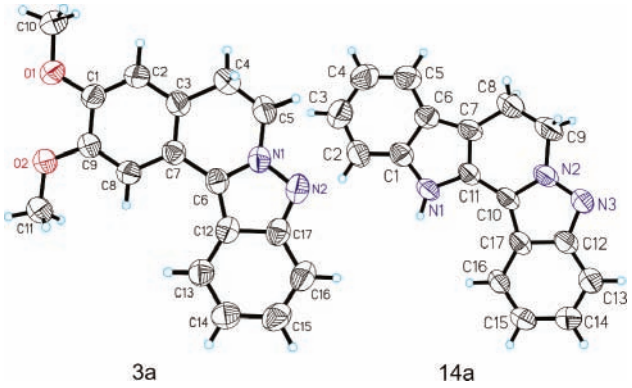
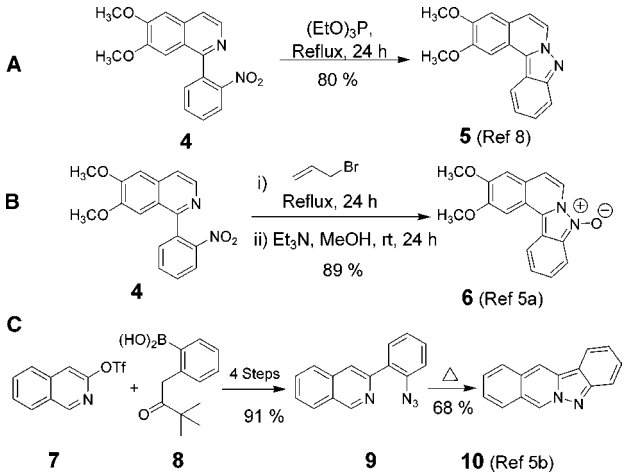


Figure 1. ORTEP plot of the molecular structure of compound **3a** and **14a** in the crystal (at 50% probability level).[6]

tion using Pd−C of the nitro substrate **1a** furnished amine **2a** (Scheme 1) as the only product without any detectable cyclization (**3a**) as evident by HPLC. Similarly, treatment of **1a** with $(EtO)_3P$ also failed to yield the cyclized product **3a** and led to the recovery of unconsumed starting material (Scheme 1). This is the first example of a $SnCl_2$-mediated synthesis of 2*H*-indazole under mild conditions. It is quite different from the transition-metal complexed-catalyzed N−N bond formation via reductive carbonylation of *N*-(2-nitrobenzylidene)amine performed under drastic conditions (i.e., at 100 °C under 20 kg cm^{-2} of CO pressure).[7] A careful survey of the literature revealed three other methods[5a,b,8] for the intramolecular formation of a N−N bond leading to indazole derivatives, but all of them involved harsh and stringent reaction conditions (Scheme 2). Other syntheses

Scheme 2



of indazole derivatives employ the thermal decomposition of *N*-(2-azidobenzylidene)amines[9a] and oxidative cyclization of acylhydrazones.[9b]

The indazole is one of the crucial heterocyclic skeletons which is a part of various biologically active molecules, e.g., the marketed antiinflammatory drugs Bendazac[10] and Benzydamine.[11]

Armed with these observations, we set out to study the course of cyclization that led to the formation of **3a** from

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(6) **Crystal data for 3a:** $C_{17}H_{16}N_2O_2$, $M = 280.32$, monoclinic, $P2_1/c$, $a = 11.438(1)$, $b = 7.421(1)$, $c = 16.332(1)$ Å, $\beta = 98.35(1)°$, $V = 1371.6(2)$ Å^3, $T = 293(2)$ K, $Z = 4$, $D_c = 1.357$ g cm^{-3}, $\mu = 0.09$ mm^{-1}, λ(Mo Kα) = 0.71073 Å, transparent block, crystal size = 0.325 × 0.250 × 0.250 mm, R1 = 0.0478 for 1681 $F_o > 4\sigma(F_o)$ and 0.0740 for all 2411 data, 193 parameters. CCDC No. 299440. **Crystal data for 14a:** $C_{17}H_{13}N_3$, $M = 259.30$, monoclinic, $P2_1/n$, $a = 12.167(1)$, $b = 17.406(3)$, $c = 12.419(1)$ Å, $\beta = 93.74(1)°$, $V = 2624.5(5)$ Å^3, $T = 293(2)$ K, $Z = 8$, $D_c = 1.313$ g cm^{-3}, $\mu = 0.08$ mm^{-1}, λ(Mo Kα) = 0.71073 Å, yellow block, crystal size = 0.175 × 0.375 × 0.225 mm, R1 = 0.0761 for 1929 $F_o > 4\sigma(F_o)$ and 0.2041 for all 4604 data, 361 parameters. CCDC No. 299441. (For X-ray queries: maulik_prakas@yahoo.com.)

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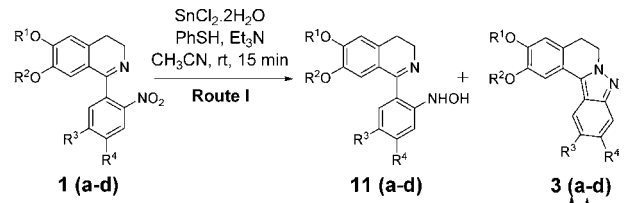
substrate **1a** under relatively mild conditions followed by the development of a method for the quantitative synthesis of dihydroindazoloisoquinolines **3**. We envisaged that both the products **2a** and **3a** were the outcome of a single intermediate with the amine **2a** having synthetic preference over that of the cyclized product **3a** when exposed to $SnCl_2 \cdot 2H_2O$ conditions. Reduction of the nitro group is generally well-known to proceed through nitroso and hydroxylamine intermediates.[12] Although, Pd-catalyzed reduction (Pd/C) also proceeds via the same intermediate, it is possible that conversion of amines may be occurring on the catalyst's surface without the concomitant release of intermediates at any stage,[12] thus furnishing amine **2a** without the cyclized product **3a**. To comprehend the mechanistic course for the formation of dihydroindazoloisoquinoline **3a**, the reduction of the nitro group was abated at the hydroxylamine stage with the view to examine its ability to undergo N−N cyclization. Examples of cyclization involving the intramolecular capture of an intermediate hydroxylamine are well-documented in the literature.[13] However, the role of hydroxylamine as an intermediate in the formation of a N−N bond has not yet been reported.

For our studies, reduction of the nitro group to hydroxylamine was achieved by treating substrate **1a** with $SnCl_2 \cdot 2H_2O$ in the presence of PhSH and Et_3N (route I, Scheme 3) as per literature procedure.[14] The progress of the reduction

Scheme 3



Route	11a#	3a#
I	71	29
II	-	100
III	0	100

1, 11, 3	R^1	R^2	R^3	R^4	Yield$ (%)
a	CH_3	CH_3	H	H	89
b	CH_3	CH_3	H	Cl	88
c	CH_3	CH_3	CH_3	H	90
d	—CH_2—		OCH_3	OCH_3	91

Conversion was monitored by HPLC (%). $Isolated yield of **3** from **1**.

was monitored by HPLC, and within 15 min, we were pleased to observe the complete disappearance of **1a** and the formation of **3a** (29%) along with the intermediate **11a** (71%). It appears that the basic condition probably played a dual role by hindering the complete reduction of the nitro group to amine **2a** and by promoting the cyclization to furnish product **3a**, thus kinetically favoring formation of **3a** over **2a**. A closer look on the course of the cyclization via hydroxylamine **11a** to the cyclized product **3a** revealed that the cyclization may have occurred by the loss of a water molecule, which in turn may have formed by the combination of a proton obtained from the protonated base and the hydroxyl anion departing from the hydroxylamine in **11a**. This gets support from the fact that the formation of cyclized product **3a** did occur, albeit in low yield (29%), because the hydroxyl group is known to be a poor leaving group. Hence, we decided to improve the leaving group tendency of the hydroxyl group by derivatizing it with a tosyl group.[15] Accordingly, we treated **11a** with tosyl chloride, and after 15 min, we observed complete conversion to indazole **3a** (route II, Scheme 3). Next, the one-pot conversion of **1a** to **3a** was achieved by sequentially treating **1a** with $SnCl_2 \cdot 2H_2O$, PhSH, and Et_3N for 15 min and then with tosyl chloride for 15 min (route III, Scheme 3). The crude product so obtained was purified by successively treating with water, hexane, and methanol to yield the final product with >99% purity.[16] However, we further established the purity of **3a** by determining its melting point and HRMS, which matched with the material obtained after passing through silica gel column chromatography. A plausible mechanism for the intramolecular cyclization of arylhydroxylamine **11a** to dihydroindazoloisoquinoline **3a** could be via an electron-deficient nitrene intermediate, as depicted in Scheme 4. Recently, Lebel et al. demonstrated nitrene formation starting from tosyloxy carbamates in the presence of potassium carbonate as base.[17] The scope and limitation of the strategy was established by synthesizing three more congeners based on **3** (route III, Scheme 3) by varying the phenethylamines and *o*-nitro benzoic acids. The dihydroisoquinoline derivatives **1a**−**d** were synthesized by literature procedure using

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(16) **General experimental procedure:** Triethylamine (0.45 g, 3.20 mmol) was added dropwise to a stirred solution of $SnCl_2 \cdot 2H_2O$ (0.22 g, 0.96 mmol) and PhSH (0.32 g, 2.90 mmol) in acetonitrile (5 mL) at room temperature to generate yellow precipitate over a period of 5 min. Then, **1a** (0.180 g, 0.64 mmol) was transferred to the suspension and stirred at room temperature for 5 more min. After complete consumption of the nitro substrate on TLC, TsCl (0.15 g, 0.83 mmol) was added to this solution and monitoring of the reaction was done on TLC and HPLC. After completion of the reaction, the solvent was evaporated and the resulting residue was triturated with water (10 mL). The solid material was filtered and washed extensively with water. It was dried in a desiccator in vacuo and then again triturated with hexane. The solid was again filtered and washed extensively with hexane and then dried in vacuo. The solid obtained was then dissolved in methanol, and the insoluble material separated was removed by filtration. The filtrate was finally evaporated, and the residue was crystallized from EtOAc−hexane to give 2,3-dimethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline [**3a**]: white solid; yield = 0.16 g (89%); mp 180−182 °C; t_R = 16.9 min; R_f = 0.63 (2:3 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, 1H, J = 8.4 Hz, ArH), 7.73 (d, 1H, J = 8.7 Hz, ArH), 7.48 (s, 1H, ArH), 7.32 (t, 1H, J = 7.2 Hz, ArH), 7.16 (t, 1H, J = 7.5 Hz, ArH), 6.85 (s, 1H, ArH), 4.62 (t, 2H, J = 6.9 Hz, CH_2), 4.02 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 3.21 (t, 2H, J = 6.9 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.1, 148.8, 131.1, 126.4, 125.3, 122.3, 121.1, 120.5, 118.2, 117.9, 111.9, 107.7, 56.6, 56.5, 48.3, 29.1; IR (KBr) ν_{max} 1603, 1696, 1217; MS (FAB) 281 for $[M + 1]^+$; MS (HR EI) *m/z* calcd for $[M]^+$ 280.12118, found 280.12300.

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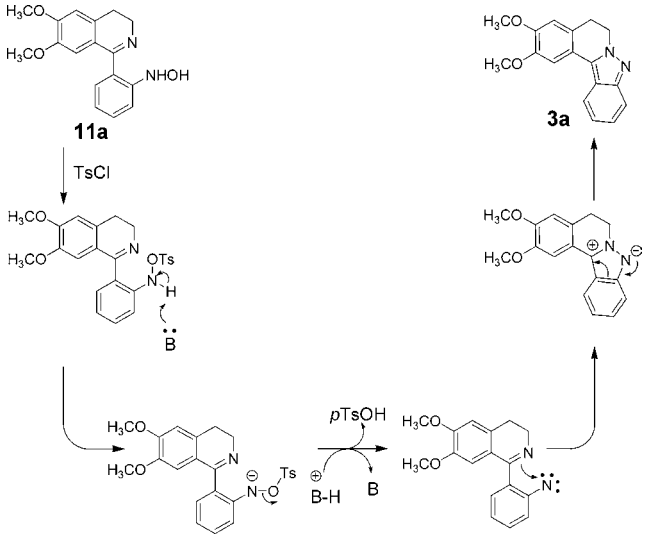
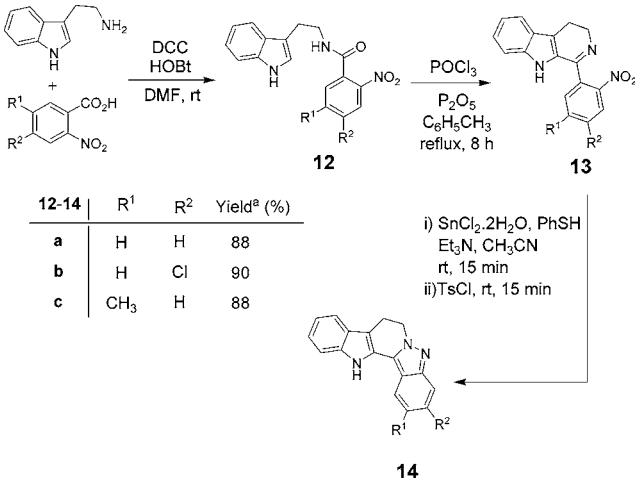
Scheme 4



Scheme 5



12-14	R^1	R^2	Yield[a] (%)
a	H	H	88
b	H	Cl	90
c	CH_3	H	88

[a] Isolated yield of **14**.

the conventional Bishler−Napieralski reaction.[18] The cyclized products dihydroindazoloisoquinolines **3b**−**d** were obtained in >85% isolated yields, and substitutions on either phenethylamines or *o*-nitro benzoic acids had no effect on the outcome of the reaction. The compounds were characterized using NMR and HRMS. We next examined the versatility of our strategy by replacing phenethylamines with tryptamines. The synthetic strategy for synthesizing indole-based N−N cyclized products triazaindeno[1,2-*a*]fluorenes **14a**−**c** from tryptamine has been depicted in Scheme 5. A literature survey revealed **14** to be novel chemotypes whose synthesis has not yet been reported. Our synthesis commenced with the conversion of amide **12** derived by coupling tryptamine with *o*-nitro benzoic acid derivatives to dihydro-β-carboline **13** by a modified Bishler−Napieralski reaction reported for indoles.[19] Our protocol involved the use of 5 equiv of $POCl_3$ in the presence of 7 equiv of P_2O_5 in acetonitrile as solvent under reflux which furnished **13** in moderate to good yields. The dihydro-β-carboline **13** was finally subjected to one-pot intramolecular cyclization by successively treating with $SnCl_2 \cdot 2H_2O$/PhSH/Et_3N in CH_3CN for 15 min and then with TsCl for 15 min at room temperature to give N−N cyclized product **14**. The scope and limitation of our strategy was established by synthesizing three congeners based on **14** (Scheme 5), and in each case, the product was obtained in >88% isolated yields. The compounds were characterized using NMR, ESMS, and HPLC, and one of the derivatives was characterized by X-ray crystallography. The ORTEP structure of **14a** has been depicted in Figure 1.

We have thus successfully developed a mild, efficient, and one-pot protocol for the intramolecular cyclization of nitro arene substrates. The mechanistic course of the reaction suggests involvement of a hydroxylamine intermediate for cyclization via N−N bond formation. The versatility of the methodology has been demonstrated by using two nitro arene substrates derived from dihydroisoquinolines and dihydro-β-carbolines. The methodology may find application in practicable heterocyclic syntheses using a suitable molecular framework, and the results will be published shortly.

Acknowledgment. We thank one of the referees for his valuable suggestion concerning the mechanistic aspect of the reaction described in this paper. D.S. is thankful to CSIR, New Delhi, India, for providing fellowship.

Supporting Information Available: Experimental details, spectroscopic characterization, and X-ray crystallographic data of **3a** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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