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Aqueous Titanium Trichloride Promoted Reductive Cyclization of *o*-Nitrostyrenes to Indoles: Development and Application to the Synthesis of Rizatriptan and Aspidospermidine

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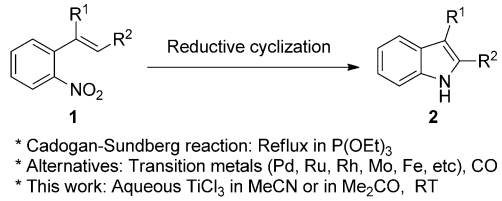
Abstract: *Treatment of o-nitrostyrenes with aqueous $TiCl_3$ solution at room temperature afforded indoles through a formal reductive C(sp^2)–H amination process. A range of functions such as halides (Cl, Br), carbonyl (ester, carbamate), cyano, hydroxy, and amino groups were tolerated. From β,β-disubstituted o-nitrostyrenes, 2,3-disubstituted indoles were formed by a domino reduction/cyclization/migration process. Mild conditions, simple experimental procedure, ready accessibility of the starting materials and good to excellent yields characterize the present transformation. The methodology was used as a key step in a concise synthesis of rizatriptan and a formal total synthesis of aspidospermidine.*

The indole ring system, one of the most important heterocycles, appears as a motif in a large number of bioactive natural products, pharmaceuticals, and agrochemicals.[1] The synthesis and functionalization of indoles have attracted chemists for over a century and remain an active research area.[2,3] Nitroarenes, due to their widespread availability and their ease of synthesis,[4] are attractive starting materials for the preparation of indoles as witnessed by the existence of a number of named transformations such as Reissert indole synthesis,[5] Leimgruber–Batcho reaction,[6] Bartoli indole synthesis,[7] and Cadogan–Sundberg reaction (Scheme 1).[8]

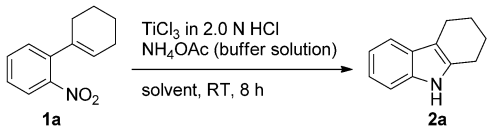
The classic Cadogan–Sundberg conditions involved heating to reflux a solution of *o*-nitrostyrenes in neat triethyl phosphite (b.p. 156 °C).[9,10] The yields of the corresponding indoles are typically moderate because of the concurrent formation of *N*-hydroxy-, and *N*-ethoxyindoles.[11] Alternative procedures for this reductive cyclization have been developed using high-pressure carbon monoxide as a stoichiometric reductant in the presence of a transition-metal catalyst.[12] Recently, Driver and co-workers reported an efficient synthesis of 3*H*-indoles by reductive cyclization of nitrostyrenes in the presence of $Mo(CO)_6$ and a catalytic amount of $Pd(OAc)_2$.[13] While *o*-nitrostyrenes have been recognized to be ideal precursors for indoles, the potential of this transformation has not been fully exploited because of the moderate synthetic efficiency and harsh conditions often associated with the established protocols. In connection with our ongoing research program, we serendipitously discovered that aqueous titanous chloride was able to promote the reductive cyclization of *o*-nitrostyrenes to indoles in good to excellent yields.[14] Literature search after our own observation revealed a single isolated example from the group of Banwell.[15] We report herein the development and applications of this novel reductive C(sp^2)–H amination process for the synthesis of indoles. The characteristic features of our reaction included mild conditions, good to excellent yields, a wide application scope, and tolerance of functional groups including the reducible ones.

Conditions were surveyed using 1-(2′-nitrophenyl)-cyclohexene (**1a**) as a test substrate (Table 1). Six equivalents of titanous chloride were initially employed since this is the theoretical amount of $TiCl_3$ needed to reduce nitroarenes to anilines. Performing the reaction in acetone in an ammonium acetate-buffered solution afforded the tetrahydrocarbazole **2a** in 58% yield. Further increasing the amount of $TiCl_3$



Scheme 1. Reductive cyclization of *o*-nitrostyrenes.

Table 1: $TiCl_3$-promoted reductive cyclization of *o*-nitrostyrenes: optimization of reaction conditions.[a]



Entry	$TiCl_3$ [equiv]	Solvent	NH_4OAc [equiv][b]	**2a** [%][c]
1	6.0	acetone	33	58
2	8.0	acetone	33	63
3	10.0	acetone	33	65
4	4.0	acetone	33	32
5	8.0	acetone	25	67
6	8.0	acetone	0	90
7[d]	8.0	MeCN	0	90
8	8.0	MeOH	0	73

[a] Reaction conditions: **1a** (0.2 mmol), $TiCl_3$ (20% solution in 2.0 N HCl), solvent (c = 0.2 M), RT, 8 h. [b] NH_4OAc (2.5 N) was used as a buffer solution. [c] Isolated yield. [d] c = 0.4 M.

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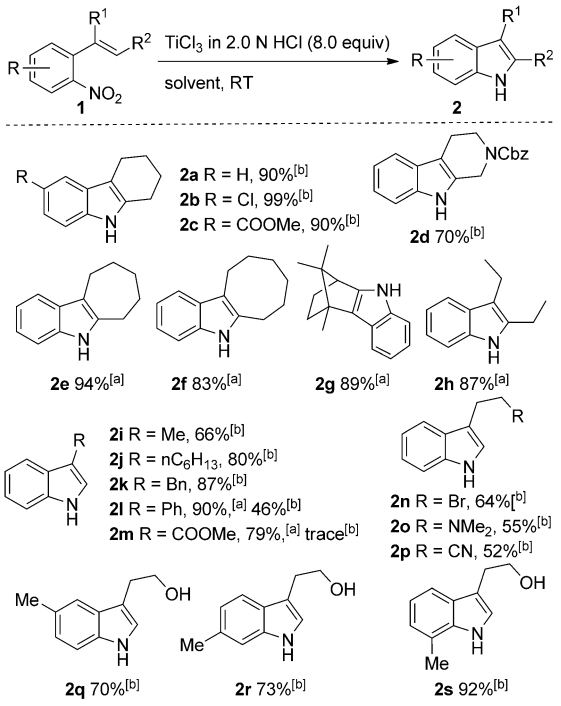
augmented slightly the yield of **2a**, whereas reducing the stoichiometry of $TiCl_3$ (4.0 equiv, entry 4) diminished significantly the efficiency of the reaction. Gratefully, compound **2a** was isolated in 90% yield when the reaction was performed without adding the ammonium acetate buffer (entry 6). A similar yield of **2a** was isolated when MeCN was used as co-solvent, although the reaction mixture was biphasic in the latter case (entry 7). The reaction proceeded less efficiently using MeOH as co-solvent (entry 8).

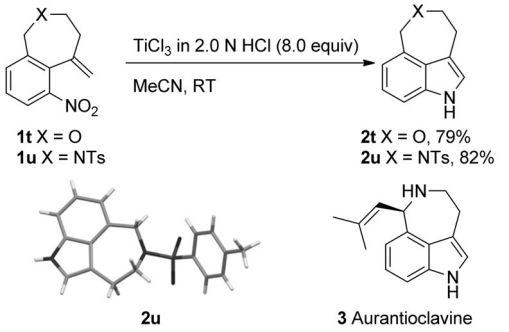
With the optimized conditions in hand, the generality of this novel reductive cyclization method was examined (Scheme 2). The presence of reducible functional groups



Scheme 2. General conditions: **1** (0.2 mmol), $TiCl_3$ (20% solution in 2.0 N HCl, 1.6 mmol), solvent ($c = 0.2$ M), RT, 8 h. [a] Acetone as co-solvent. [b] Acetonitrile as co-solvent ($c = 0.4$ M).

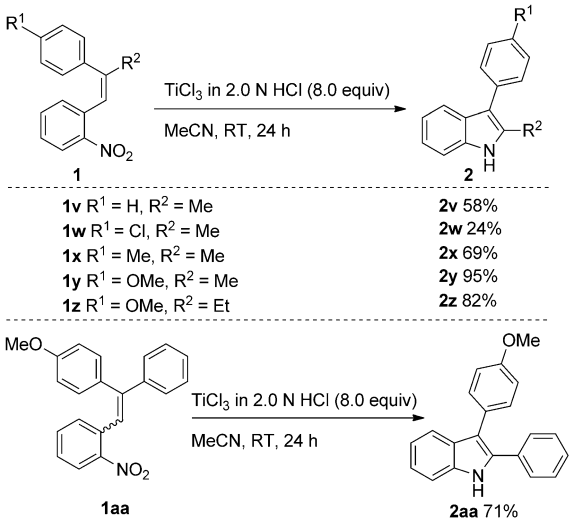
(Cl, Br, NCbz, CN, COOMe) and polar functions (OH, NMe_2) are well tolerated and indoles fused to 6- (**2a**–**2d**), 7- (**2e**), 8-membered (**2f**) rings as well as to the steric hindered bridged bicyclic motif (**2g**) are readily accessible. However, when 1-(2′-nitrophenyl)-cyclopentene was submitted to our standard conditions, only the corresponding aniline was produced. An acyclic trisubstituted olefin was converted to 2,3-disubstituted indole **2h** in 87% yield. The 3-substituted indoles were also prepared in good to excellent yields from the corresponding 1-substituted-1-(2′-nitrophenyl)-ethylenes, providing therefore an easy access to medicinally important tryptamine (**2o**) and tryptophol derivatives (**2q**–**2s**). In general, both acetonitrile and acetone are appropriate co-solvents for the synthesis of 2,3-disubstituted indoles (**2a**–**2h**). However, the former turned out to be the solvent of choice for 3-substituted ones (**2i**–**2s**). Most of the α-substituted *o*-nitrostyrenes **1i**–**1s** were synthesized by a regioselective Heck reaction according to Zhou's protocol.[16]

Treatment of **1t** and **1u** with $TiCl_3$ under standard conditions provided 3,4-bridged indoles **2t** and **2u** in yields of 79% and 82%, respectively (Scheme 3).[17] Compound **2u**, the identity of which was confirmed by X-ray crystallographic analysis,[18] is the core structural unit of aurantioclavine (**3**) and other related natural products.[19]



Scheme 3. Synthesis of 3,4-bridged indoles.

The reductive cyclization of β,β-disubstituted *o*-nitrostyrenes was next investigated as this could provide not only an entry to 2,3-disubstituted indoles, but also provide us with useful mechanistic information. Gratefully, treatment of **1v** under standard conditions afforded 2-methyl-3-phenylindole (**2v**) by a domino sequence involving reductive cyclization and migration of the phenyl group (Scheme 4). Of mechanistic importance, we observed a) the process worked better with substrates having an electron-rich aromatic ring (**2x**–**2z**) than an electron-poor one (**2w**). This result is indicative of a cationic rather than a radical rearrangement process; b) the high migratory aptitude of the electron-rich aryl group is independent of the geometry of the olefin as both *Z*-**1aa** and *E*-**1aa** were converted to indole **2aa** with similar efficiency. This result supported the notion that the reaction went through a stepwise process and that nitrene was not an intermediate of this indolization process.



Scheme 4. Domino process involving *N*-cyclization and aryl migration.

Applying the standard conditions to methyl *o*-nitrocinnamate (**1ab**), *o*-nitrocinnamyl alcohol (**1ac**) and *o*-nitrostilbene (**1ad**, Figure 1) provided only the corresponding ani-

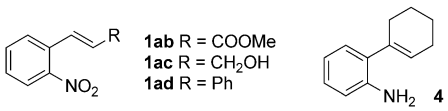
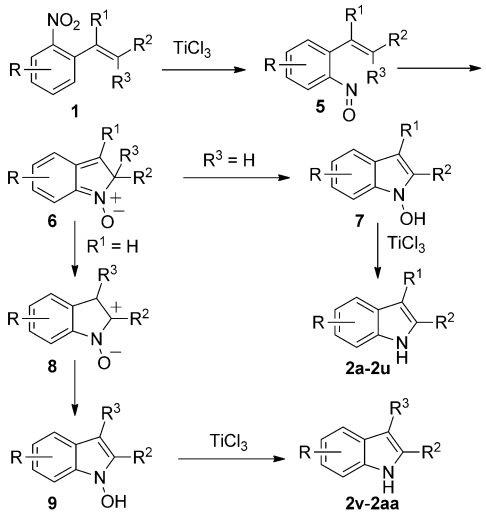


Figure 1. Substrates that failed to undergo the indolization.

lines. Therefore, the present method is not applicable to the synthesis of 2-substituted indoles. When 1-(2′-aminophenyl)-cyclohexene (**4**, Figure 1) was submitted to our standard conditions, indole **2a** was not formed indicating that aniline **4** was not an intermediate on the way to indole. This result is also in line with the conversion of **1m** to indole **2m**. Should the aniline be an intermediate, an oxindole resulting from the 5-*exo*-trig cyclization would be produced.[20]

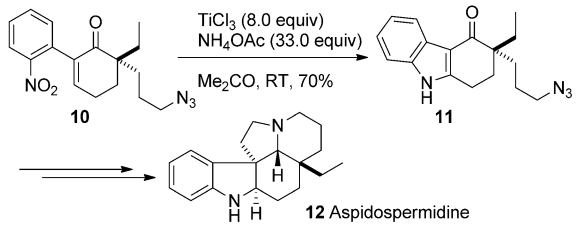
A possible reaction pathway for this reductive cyclization is presented in Scheme 5. Reduction of the nitro group to



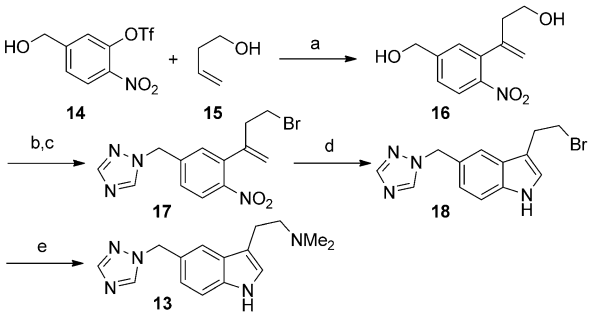
Scheme 5. Reaction pathways for the reductive cyclization of *o*-nitrostyrenes.

a nitroso[21] group followed by a 6e electrocyclization would give zwitterion **6**.[22] In the case of $R^3 = H$, a rapid re-aromatization would occur leading to *N*-hydroxy indole **7**, that would be further reduced by $TiCl_3$ to afford indoles **2a**–**2u**. In case of $R^1 = H$, the group with high migratory aptitude, irrespective of the initial olefin geometry, will shift from C2 to C3 position which, upon deprotonation, would provide *N*-hydroxy indole **9**. Reduction of the latter would then furnish the 2,3-disubstituted indoles **2v**–**2aa**.

The application of our protocol to the synthesis of natural products and drugs was pursued. Compound **10** was a key intermediate in our total synthesis of mersicarpine and leuconoxines.[23] We were pleased to find that simply stirring a solution of **10** in acetone-NH_4OAc in the presence of $TiCl_3$ at RT afforded the tetrahydrocarbazolone **11** in 70% yield



Scheme 6. Formal synthesis of aspidospermidine.



Scheme 7. Synthesis of rizatriptan. [a] $Pd_2(dba)_3$ (0.05 equiv), dppf (0.12 equiv), urotropine (2.0 equiv), THF, 80 °C, 48 h, 91%. [b] CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 83%. [c] Sodium salt of 1*H*-1,2,4-triazole, DMF, −20 °C, 2 h, 64%. [d] $TiCl_3$ (8.0 equiv), MeCN, RT, 4 h, 51%. [e] Dimethylamine (excess), MeOH, 50 °C, 48 h, 98%. dba = dibenzylidenacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, THF = tetrahydrofuran, and DMF = *N*,*N*-dimethylformaide.

(Scheme 6). Tricycle **11** has been converted to aspidospermidine **12** and other aspidosperma-type alkaloids.[24]

Rizatriptan **13**, one of the tryptamine-based triptan drugs used in the treatment of migraines and cluster headaches, was synthesized as shown in Scheme 7.[25] Regioselective Heck reaction between aryl triflate **14** and but-3-en-1-ol (**15**) according to Zhou provided terminal olefin **16** in 91% yield.[16] Bromination of diol followed by chemoselective displacement of the benzyl bromide by sodium salt of 1*H*-1,2,4-triazole provided **17**. $TiCl_3$-promoted reductive cyclization of **17** afforded indole **18** (51%) that was converted to rizatriptan (**13**) under standard conditions. We note that the classic Cadogan-Sundberg conditions won't be applicable to **17** because of the presence of an alkyl bromide function.

In summary, we developed a $TiCl_3$-promoted reductive cyclization of *o*-nitrostyrenes for the synthesis of functionalized indoles. Mild conditions, simple experimental procedure, ready accessibility of the starting materials, and good to excellent yields characterized the present transformation. We anticipate that the reaction will find applications in the synthesis of natural products and pharmaceuticals.

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Keywords: C–H amination · indoles · nitroarenes · reductive cyclization · total synthesis

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