VIP Synthetic Methods

DOI: 10.1002/anie.200901986

Expedient Synthesis of N-Fused Indoles: A C–F Activation and C–H Insertion Approach**

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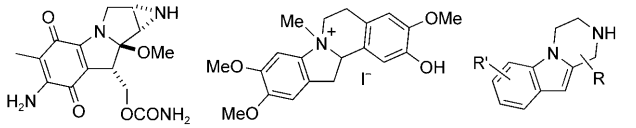
Indoles are versatile components of many natural and synthetic biologically active compounds, and a vast number of pharmaceuticals containing the indole skeleton are being used for therapeutic purposes.[1] N-fused indoles are indole derivatives that have great biological and pharmaceutical importance. For example, mitomycin C[2] and cryptaustoline[3] possess the N-fused indole structure (Scheme 1). These and

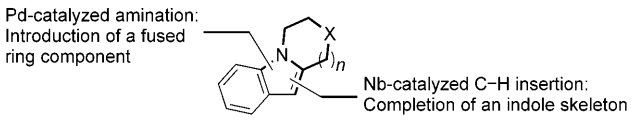


Scheme 1. Biologically active N-fused indoles.

related indole alkaloids exhibit antitumor[4] and tubulin polymerization inhibitory[5] activities. Pyrazino[1,2-*a*]indoles behave as 5-HT_{2c} receptor agonists[6] and are related to the treatment of hyperglycemia and other diseases by controlling appetite.

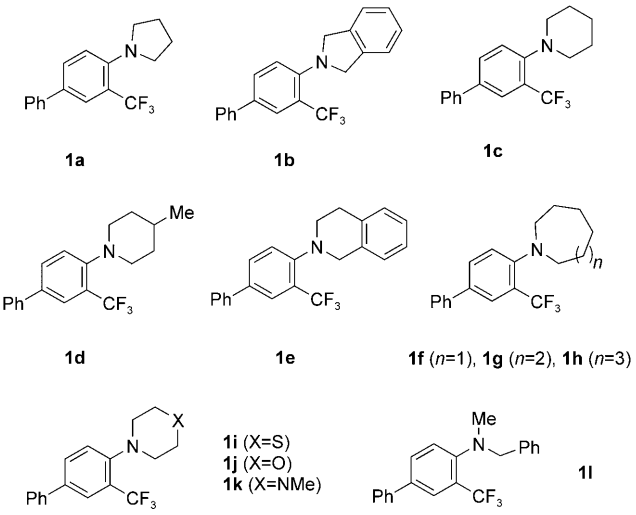
Despite the importance of N-fused indole derivatives, the synthesis of this class of compounds has not yet been fully developed: alkyl chain elongation and ring closure on an existing indole platform have been reported by many research groups (for example, by intramolecular alkylation,[7a] radical cyclization,[7b–e] and other methods[7f]). Transannulation reactions[8] also afford N-fused indoles. In recent years, many transition-metal-catalyzed reactions have been reported.[9] However, the ring-closure strategy still poses many problems and most importantly, a multistep synthesis of the substrates is required regardless of the synthetic strategy selected.

Herein we describe an expedient synthesis of N-fused indoles by means of a direct, catalytic C–H carbenoid insertion approach. Our strategy consists of two steps: 1) a cyclic amine is introduced into *o*-(trifluoromethyl)bromobenzene as a fused ring component by a palladium-catalyzed amination reaction, and 2) a niobium-catalyzed C(sp^3)–H insertion reaction completes the indole core skeleton (Scheme 2). The well-established amination reaction, originally explored by Buchwald and co-workers,[10] will ensure the flexibility of the fused-ring substructure. Insertion reactions of a niobium fluorocarbenoid center, which is generated from a CF_3 group attached to an aromatic nucleus, into a C(sp^2)–H bond were developed recently by our group.[11–13]



Scheme 2. Our strategy.

Scheme 3 shows precursors which were prepared in good yields mainly by the Buchwald amination reaction (see the Supporting Information for details).[10] Notably, CF_3 groups, which would generate the key carbenoid centers, were not affected by the C–N coupling conditions.



Scheme 3. List of insertion precursors **1**.

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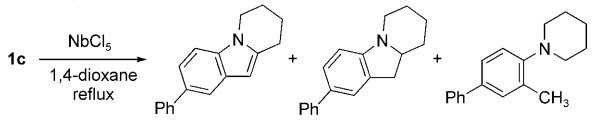
[**] This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (Japan). This work was also supported by the Saneyoshi Scholarship Foundation and the Asahi Glass Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901986.

With the insertion precursors **1** in hand, the key C–H insertion reaction was examined (Table 1). Initially, **1c** was treated with lithium aluminum hydride in the presence of

Table 1: Optimization of the reaction conditions.

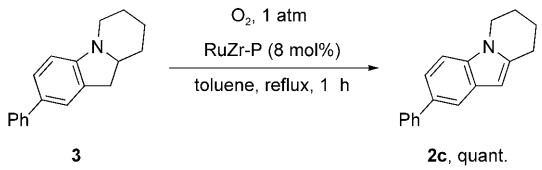


Entry	$NbCl_5$	Reducing agent[a]	*t* [h]	Yield [%] 2c	3	1c
1	1.5 equiv	$LiAlH_4$ (10)	49	20	20	52
2	30 mol%	$NaAlH_4$ (4)	23	27	46	–[b]
3	1.0 equiv	$LiAl(OtBu)H_3$ (10)	72	–	–	[c]
4	1.0 equiv	Red-Al (19)[d]	24	–	–	[c]

[a] The amount of reducing agent (equiv) is indicated in parenthesis. [b] **4** was obtained in 15% yield. [c] **1c** was recovered as the sole product (yields were not determined). [d] Red-Al = sodium bis(methoxyethoxy)-aluminum hydride.

1.5 equivalents of niobium(V) chloride.[10a] To our delight, piperidinoindole **2c** and piperidinoindoline **3** were obtained in 20% yield each, with **1c** recovered in 52% yield (Table 1, entry 1). The conversion rate improved dramatically when sodium aluminum hydride was used, giving **2c** and **3** in yields of 27% and 46%, respectively (Table 1, entry 2; 30 mol% niobium(V) chloride).[14,15] In contrast, alkoxy-substituted aluminum hydride reagents were unreactive, resulting in the recovery of starting material **1c** (Table 1, entries 3 and 4) even when an equimolar amount of niobium(V) chloride was used.[16]

Dehydrogenation of isolated **3** proceeded smoothly in the presence of a ruthenium catalyst (Scheme 4). Indoline **3** afforded indole **2c** in quantitative yield when treated with

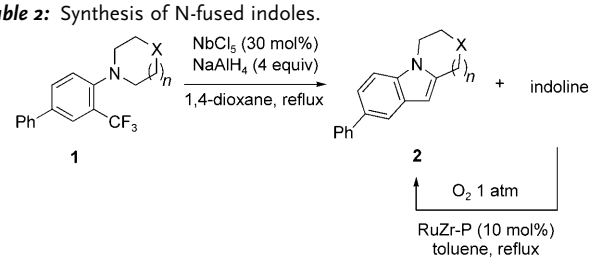


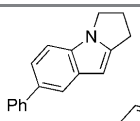
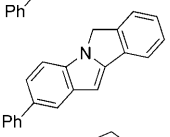
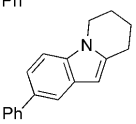
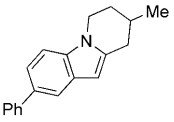
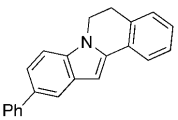
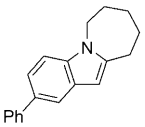
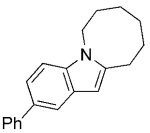
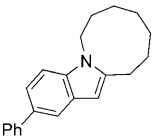
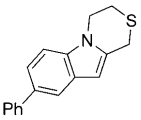
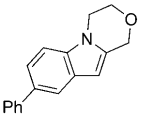
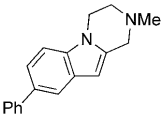
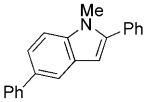
Scheme 4. Ruthenium-catalyzed dehydrogenation of indoline **3**.

8 mol% ruthenium zirconium phosphate[17] under dioxygen at atmospheric pressure. 2,6-Dichloro-3,5-dicyano-*p*-benzoquinone (DDQ) was found to be less efficient for this aromatization, giving 75% yield of **2c** upon heating for 11 h in toluene (1 equiv, RT to 50 °C; not shown).

Precursors **1a–l** were subjected to niobium-catalyzed C–H insertion conditions and the isolated indolines were then dehydrogenated with the ruthenium catalyst. Table 2 shows the overall yields of indoles **2a–l** from the consecutive reactions. The C–H insertion step was found to proceed smoothly with a range of cyclic amino groups: indoles with five- to nine-membered fused-ring substructures were syn-

Table 2: Synthesis of N-fused indoles.

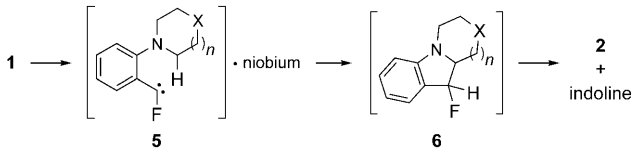


Entry	Precursor	Product	*t* [h][a]	Yield [%][b]
1	**1a**		6	65, **2a**
2	**1b**		5	78, **2b**
3	**1c**		23	70, **2c**
4	**1d**		13	64, **2d**
5	**1e**		6.5	68, **2e**
6	**1f**		19	71, **2f**
7	**1g**		4	87, **2g**
8	**1h**		6	85, **2h**
9	**1i**		15	52, **2i**
10	**1j**		25	59, **2j**
11	**1k**		13	57, **2k**
12	**1l**		19	56,[c] **2l**

[a] Reaction time of the C–H insertion step. [b] Overall yield of two contiguous reactions. [c] 1-Benzyl-5-phenylindole was obtained in 11% yield.

thesized in good to high yields (Table 2, entries 1–8). Oxygen, sulfur, and nitrogen atoms in the cyclic amino groups did not interfere with the insertion, and the corresponding heteroatom-containing N-fused indoles were obtained in good yields (Table 2, entries 9–11). Acyclic **1l** also underwent insertion, with the reaction proceeding mainly at an electronically favored benzylic site (Table 2, entry 12). This result clearly contrasts with the result of the $[Rh_2(S\text{-dosp})_4]$-catalyzed insertion (dosp = *N*-(*p*-dodecylphenylsulfonyl)prolinato),[18] in which the sterically less hindered methyl site is preferred.

Mechanistically, the C–H insertion reaction can be rationalized similarly to our previous C(sp^2)–H insertion reactions (Scheme 5):[10c] fluorine-substituted carbenoid intermediate **5** is generated in the reaction medium and then the



Scheme 5. Proposed reaction pathway.

carbenoid center undergoes insertion into a C–H σ bond adjacent to a nitrogen atom. Dehydrofluorination of the resulting fluoroindoline **6** (not detected) gives indole **2**.[19] Hydrodefluorination of **6**, however, gives indolines (for example, **3**).[20] Further studies to gain a full understanding of the niobium-catalyzed C–H insertion reaction are ongoing.

In summary, we have developed a new route to biologically and pharmaceutically important N-fused indole derivatives. Indoles with a nine-membered ring substructure (maximum ring size) and with a heteroatom-containing ring substructure could be synthesized in good yields. The combined use of a palladium-catalyzed amination reaction and a newly developed niobium-catalyzed C(sp^3)–H insertion reaction has resulted in a facile, short-step synthesis.

Experimental Section

Niobium(V) chloride (27 mg, 0.10 mmol, 30 mol%) and sodium aluminum hydride (65 mg, 1.2 mmol) were added to a solution of **1c** (103 mg, 0.338 mmol) in dioxane (3.3 mL). The reaction mixture was refluxed for 23 h and then quenched with water at 0 °C. Purification by column chromatography (SiO_2, hexane/dichloromethane 3:1) gave indole **2c** (23 mg, 0.091 mmol) and indoline **3** (39 mg, 0.16 mmol) in 27 and 46% yield, respectively. Commercially available ruthenium zirconium phosphate (40 mg, 10 mol% Ru, Kanto Co.) was added to a solution of isolated **3** in toluene (1.5 mL). Dioxygen (1 atm) was introduced into the flask and the reaction mixture was heated at reflux for 24 h. The reaction mixture was filtered through a small pad of silica gel and purified by column chromatography (SiO_2, hexane/dichloromethane 3:1) to give indole **2c** (36 mg, 0.14 mmol, 43% based on **1c**) .

Received: April 14, 2009
Published online: July 3, 2009

Keywords: carbenoids · fused-ring systems · indoles · insertion · niobium

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[17] This catalyst is available from Kanto Chemical Co., Inc. (Tokyo, Japan): ruthenium is supported on zirconium phosphate.

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[19] Thin-layer chromatographic analysis of the reaction mixture suggests that the indole is generated in the reaction medium. However, partial autooxidation of the indoline to the indole during work-up was also observed.

[20] When a reaction of **1c** was quenched with D_2O, **3** with 0.59 deuterium atoms at a benzylic position was obtained. This result suggests that the benzylic anion is reductively formed from the presumed intermediate **6** and that protonation of the anionic intermediate gives **3**.

