ORGANIC LETTERS

2010
Vol. 12, No. 17
3736−3739

Fe(II)-Catalyzed Amination of Aromatic C−H Bonds via Ring Opening of 2*H*-Azirines: Synthesis of 2,3-Disubstituted Indoles

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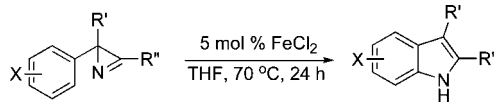
Received May 17, 2010

ABSTRACT



A general method for the synthesis of 2,3-disubstituted indoles is described. The key feature of this method is the amination of aromatic C−H bonds via $FeCl_2$-catalyzed ring opening of 2*H*-azirines. The method tolerates a variety of functional groups such as Br, F, NO_2, OMe, CF_3, OTBS, alkenes, and OPiv. The method can also be extended to synthesize azaindoles.

The widespread occurrence of the indole motif in bioactive natural products and pharmaceuticals has drawn synthetic chemists' long-lasting interest in developing general methods to prepare them.[1a,b] In fact, almost all conceivable bond disconnections for the indole nucleus have been explored.[1c,d] Yet the efficiency and the substrate scope for most of these approaches still leave much to be desired. For example, very few of them employ direct amination of aromatic C−H bonds,[2] which obviates the need for prefunctionalizing the substrate. Furthermore, simultaneous introduction of substituents at C2 and C3 of the indole nucleus remains a continual challenge for organic chemists.[3] Additionally, most of the existing methods are not particularly effective for preparing azaindoles that are of great interest to medicinal chemists.[4]

We were interested in developing a general and catalytic method for the synthesis of 2,3-disubstituted indoles based on the direct amination of aromatic C−H bonds. To implement this strategy, a suitable vinyl nitrene precursor would be needed. Vinyl azides are typically used as precursors to generate the vinyl nitrenes.[5a,b] However, their use as the vinyl nitrene precursor is often limited by their narrow substrate scope as they are generally prepared by the condensation of methyl azidoacetate and aromatic

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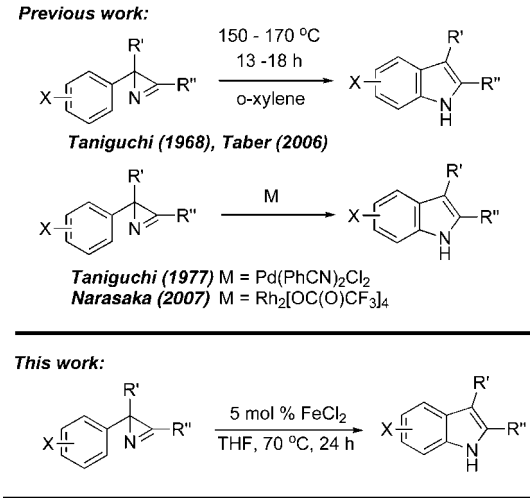
10.1021/ol101130e
Published on Web 08/03/2010

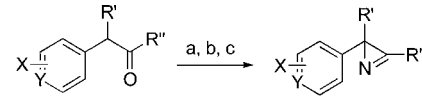
aldehydes.[5c] Thermal rearrangement of 2-aryl-2*H*-azirines via vinyl nitrene intermediates[6a] provides an efficient route to indoles, although it remains in scattered use in indole syntheses (Scheme 1).[6] This rearrangement could be catalyzed by $Pd(PhCN)_2Cl_2$[7a] or $Rh_2[OC(O)CF_3]_4$.[7b] The catalytic variant of the rearrangement has also received little attention from the chemistry community and only two reports have been published to date.[7] Although a vinyl nitrene metal complex was speculated to be involved in one of the catalyzed rearrangements, no mechanistic studies were performed.[7b] Only one example of azaindoles prepared by the thermal rearrangement has been reported,[4a] while the catalyzed process has not been applied to azaindole synthesis. Since a wide variety of 2*H*-azirines have been reported in the literature,[8] they could be potentially a much better vinyl nitrene precursor than the vinyl azides. We also sought alternative catalysts that could intercept the vinyl nitrene intermediates. Iron stands out among commonly used metals because it is far cheaper than Pd or Rh, abundant, and generally nontoxic. $FeCl_2$ has been reported to catalyze cleavage of azirines to form N−N bonds[9a,b] or open azirine rings as a stoichiometric one-electron donor.[9c] To the best of our knowledge, the rearrangement of azirines to indoles is not known to be catalyzed by $FeCl_2$. Herein we report a general method for the synthesis of 2,3-disubstituted indoles and azaindole via ring opening of 2*H*-azirines catalyzed by inexpensive $FeCl_2$, offering a solution to the unmet needs in indole synthesis mentioned above and probes toward the mechanism.

Scheme 1. Rearrangement of 2*H*-Azirines to Indoles



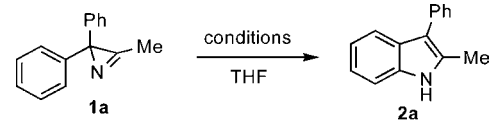
2*H*-Azirines can be readily prepared from ketones using modified Neber rearrangement processes via hydrazones in three steps developed by Padwa[7b,10] or oximes in two steps developed by Taber[6b] (Scheme 2). Azirine **1a**[6b,7] was chosen as the model substrate to study the rearrangement of 2-aryl-*2H*-azirines to indoles. Among the catalysts screened, $FeCl_2$ was found to be particularly effective to catalyze the rearrangement (Table 1). With 5 mol % $FeCl_2$ in THF at rt, the rearrangement was complete after 12 h to provide indole **2a** in 75% yield (entry 1). The rearrangement was cleaner at

Scheme 2. Synthesis of 2*H*-Azirines[a]



[a] Y = CH: (a) NH_2NMe_2, NaOAc, AcOH; (b) MeI; (c) NaH. Y = N: (a) NH_2OH·HCl, NaOAc; (b) MsCl, Et_3N; (c) DBU (one pot).

Table 1. Optimization of Catalytic Conditions



entry	catalyst (mol %)	temp (°C), time	**2a**, yield (%)
1	$FeCl_2$ (5)	rt, 12 h	75[a]
2	$FeCl_2$ (5)	70, 24 h	77[a]
3	none	70, 24 h	0
4	$FeBr_2$ (5)	rt, 12 h	69[a]
5	FeI_2 (5)	rt, 12 h	60[a]
6	$Fe(OAc)_2$ (5)	rt, 12 h	0
7	$FeCl_3$ (5)	rt, 12 h	0
8	CuCl (5)	rt, 12 h	27[b,c]
9	$CuCl_2$ (5)	rt, 12 h	trace[b,d]
10	$AlCl_3$ (100)	70, 24 h	0[d]
11	BF_3·Et_2O (100)	70, 24 h	0[d]
12	HCl/Et_2O (100)	70, 24 h	0[d]

[a] Yield after chromatography. [b] NMR yield using hexamethyl benzene as an internal standard. [c] **1a** (40%) was recovered. [d] None of **1a** was recovered.

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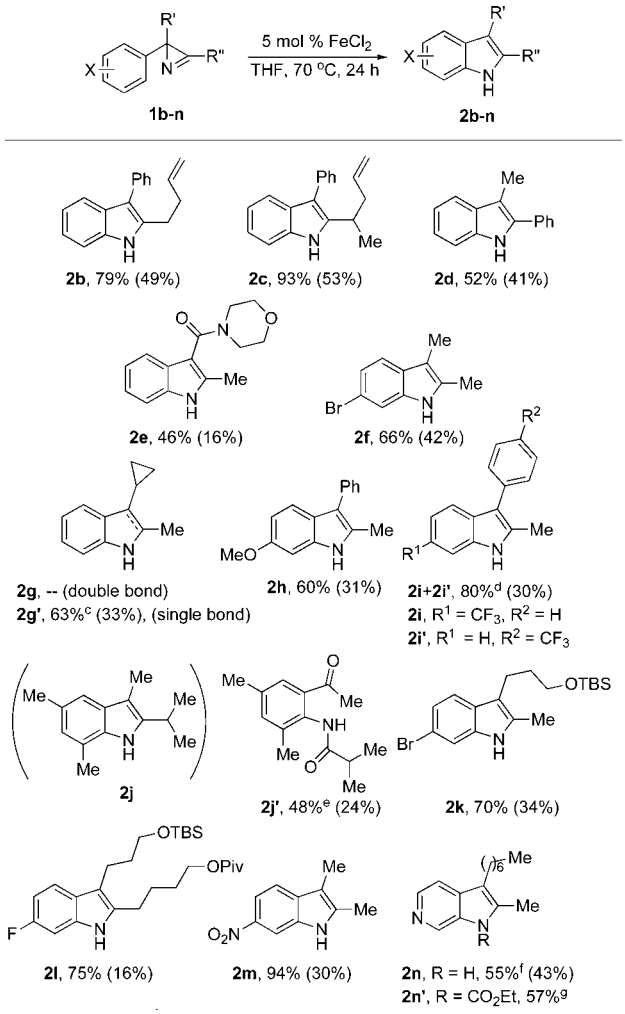
Scheme 3. Substrate Scope[a,b]



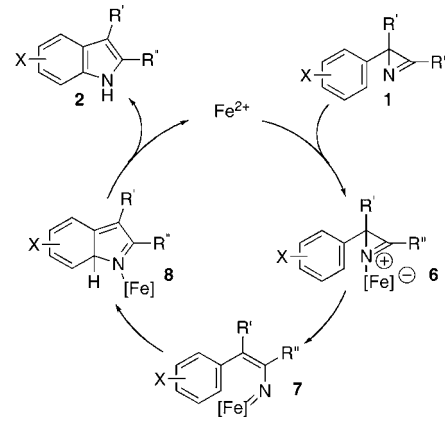
[a] Isolated yield. [b] Yields in parentheses refer to overall yields from the corresponding ketones. The synthesis of 2*H*-azirines was not optimized. [c] Two steps (a 2:1 mixture of two isomers). Indole **2g** was reduced to **2g′** by $NaBH_3(CN)$. [d] **2i**:**2i′** = 1:1.8. [e] Two steps. Indole **2j** was oxidized to **2j′** by O_2. [f] 50 mol % $FeCl_2$. [g] NaHMDS then $ClCO_2Et$.

70 °C (entry 2). In the absence of $FeCl_2$, no indole (**2a**) was formed, and azirine **1a** was completely recovered (entry 3). Other Fe(II) halide salts such as Br and I also catalyzed the reaction, although they were not as effective as $FeCl_2$ (Entries 4 and 5). $Fe(OAc)_2$ and $FeCl_3$ show no catalytic activity (entries 6 and 7). CuCl was only moderately effective for catalyzing the rearrangement, and $CuCl_2$ led to a mixture of unidentified products with a trace amount of indole **2a** (entries 8 and 9). Treatment of **1a** with common Lewis acids ($AlCl_3$ and $BF_3{\cdot}Et_2O$) or Brønsted acids (HCl) led to complete conversion to unidentified products (entries 10−12). The rearrangement was very sensitive to the solvent used. Among the solvents screened at rt (THF, DME, CH_2Cl_2, 1,2-dichloroethane, and toluene), the rearrangement occurred in only THF. At 70 °C, in addition to THF, 1,2-dichloroethane was also suitable yet less effective (see Supporting Information).

With these screening results in hand, we sought to examine the scope and the generality of the method under the optimized condition (5 mol % of $FeCl_2$, 70 °C, 24 h in THF). As shown in Scheme 3, functional groups are generally well tolerated, as a variety of groups such as amides, aryl, cyclopropyl, CF_3, halides, OTBS, and OPiv can be incorporated into the indoles. Particularly, the method tolerates substitution on the aromatic ring undergoing functionalization and substituents with a wide range of electronic properties from electron-donating (OMe) to electron-withdrawing groups (NO_2) can be accommodated. The rearrangement is also quite tolerant of the C2 and C3 substituents of 2*H*-azirine **1** as aryl and alkyl groups with various steric sizes are generally compatible. In the cases where two regioisomeric products could be obtained, cyclization onto more electron-rich aromatic rings is generally favored. Modest to excellent regioselectivities were observed depending on the substituent. It is worth noting that thermal rearrangement of **1h** provided indole **2h** with modest selectivity (3.4:1),[6b] whereas this method provided **2h** as the only product. The method also proves particularly effective for preparing electron-rich indoles. The low yields of **2g** and **2j** were due to their isolation, since they were notoriously prone to air oxidation. The method can be also extended to synthesize 6-azaindoles, but a higher catalyst loading (50 mol %) was required to obtain an acceptable yield of **2n**.[11] The method has one limitation about its substrate scope: the C2 carbon of **1a**−**n** needs to be disubstituted (R′ ≠ H), and R′ can be alkyl, cyclopropyl, aryl, or amide groups.

Scheme 4 shows our proposed catalytic cycle: initial coordination of Fe(II) to the imine nitrogen atom of 2*H*-azirine **1** would form iron azirine complex **6**; subsequent

Scheme 4. Proposed Catalytic Cycle



cleavage of the C−N bond would provide iron vinyl nitrene complex **7**; and finally, indole **2** could be formed by a five-centered 6-π electrocyclization[12] of **7** via intermediate **8**.

We think that the rearrangement likely involves an iron nitrene complex such as **7**. This hypothesis was consistent with

(11) Compound **2n** was converted to **2n′** because we were unable to purify **2n** to the degree required for publication.

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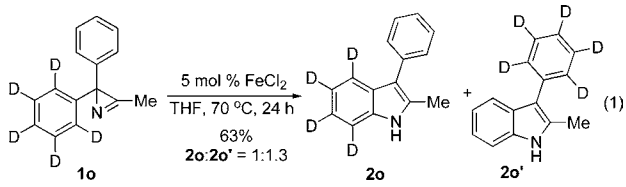
the following observations. $FeCl_2$ was unique and effective for the rearrangement, whereas other salts such as $FeCl_3$ and common Lewis and Brønsted acids were completely ineffective. Pyridines that are generally inert in electrophilic substitution reactions participated in the rearrangement. Other potential pathways such as opening of the azirine ring via a radical pathway[9c] were ruled out on the basis of the formation of indole **2g** with the cyclopropyl group intact. Submission of penta-deuterated substrate **1o** to the optimized condition revealed a kinetic isotope effect of 1.3 (eq 1). The magnitude of the kinetic isotope effect is more consistent with the 6-π electrocyclization where the C−H bond breaking event is not the rate-determining step.[2c,6b]



In conclusion, we have developed a catalytic and general method for the synthesis of 2,3-disubstituted indoles whose syntheses still lack a general solution. The method employing inexpensive and nontoxic $FeCl_2$ has a broader substrate scope than the similar processes catalyzed by $Pd(PhCN)_2Cl_2$ or $Rh_2[OC(O)CF_3]_4$.

Acknowledgment. We thank the University of Arkansas, the Arkansas Bioscience Institute, and the NIH NCRR COBRE grant (P20 RR15569) for generous support of this research. Core facilities were funded by the NIH NCRR COBRE grant (P20 RR15569) and the Arkansas Bioscience Institute.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101130E