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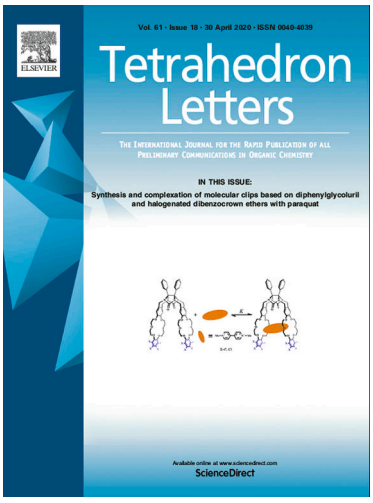

$FeCl_3$ catalyzed intermolecular reaction between enol ethers and anilines: Access to 2,3-substituted indoles through aryl group migration

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PII: S0040-4039(20)31082-0
DOI: https://doi.org/10.1016/j.tetlet.2020.152583
Reference: TETL 152583

To appear in: *Tetrahedron Letters*

Received Date: 10 September 2020
Revised Date: 15 October 2020
Accepted Date: 19 October 2020

Please cite this article as: Jena, T.K., Khan, F.A., $FeCl_3$ catalyzed intermolecular reaction between enol ethers and anilines: Access to 2,3-substituted indoles through aryl group migration, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152583

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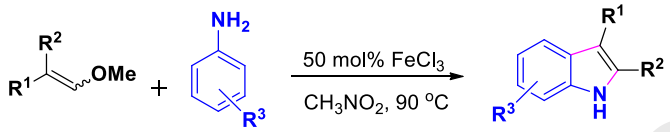
Tapan Kumar Jena and Faiz Ahmed Khan*



R^1 = Ar-(H, Me, Alkyl, OMe, F, Cl)
R^2 = Me, Ph
R^3 = OMe, H, Me, Alkyl, Br, F

22 Examples

- C-C, C-N bond formation
- Aryl group migration
- Broad substrate scope
- Inexpensive catalyst

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$FeCl_3$ catalyzed intermolecular reaction between enol ethers and anilines: Access to 2,3-substituted indoles through aryl group migration

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Methyl enol ethers
Indoles
C-C, C-N bond
Aryl group migration

ABSTRACT

An intermolecular $FeCl_3$ catalyzed reaction between anilines and enol ethers is described. A variety of enol ethers and aromatic amines undergo a C-C bond formation followed by cyclization via C-N bond formation to afford the 2,3-disubstituted indoles, involving an unexpected aryl group migration. In this methodology, anilines act as bis-nucleophiles, wherein the initial attack occurs at the α-position of enol ether from the *ortho* position of aniline followed by the subsequent reaction of the amine moiety of aniline at the β-position, leading to the indole framework. This method is simple, obviates the use of expensive/hazardous transition-metal catalysts, and offers a wide range of substrate scope.

Introduction:-

Indole nucleus is a ubiquitous structural motif present in numerous natural products and pharmaceutically related compounds, and its syntheses attract much interest. In the field of natural products, compounds in clinical trials and marketed drugs are filled with molecules containing indole moiety in their structures as exemplified in Figure 1.[1] As a result, many methods have been utilized to synthesize the indole derivatives, as evidenced in the literature.[2] Among them, C2- and C3-disubstituted indoles are of great interest due to the virtue of leading to discovery of interesting biological functions.[3] The broad applicability of this heterocycle system continues to hold a fascination for a chemist to develop an efficient methodology.

In past decades several methods have been described from a variety of substrates to synthesize indole derivatives, which includes Fischer indole synthesis,[4a-4c] Rh (I) catalyzed reaction of N-propargylanilines,[4d] oxidative coupling of alkynes with acetanilides,[4e] transition metal-catalyzed intermolecular C-H functionalization,[4f-4j] and among them few are shown in Scheme 1. Similarly, other metal-catalyzed intramolecular reactions were also well explored. In this context, palladium-catalyzed reactions which involve, oxidative cyclization of N-arylenamines,[5,6] microwave-assisted reaction via intramolecular arene-olefin coupling,[7] amination of aromatic C-H bonds with oxime acetates,[8] being used in the reactions. While other advanced syntheses of these moieties were also reported, however, intermolecular synthesis of indole attracts much interest. An alternative method for Fischer indole synthesis was demonstrated by Buchwald group from arylhydrazones and halo arenes.[9] Pd-catalyzed indolization of haloanilines with alkynes also used for the syntheses of disubstituted indole derivatives.[10] Ring-opening strategy of 2H-azirines also involved for the construction of 2,3-disubstituted indoles.[11] Synthesis of 3-substituted indoles via a 1,2-aryl shift was also explored in the literature.[12] An acid-catalyzed two-step synthesis of azaindole derivatives was demonstrated by Hoelder and co-worker from chloroamino-N-heterocycles and Ethoxyvinylborolane through Suzuki-Miyaura coupling reaction.[13] Although many routes are available for the construction of indole derivatives, but for the synthesis of 2-methyl-3-aryl or 2,3-diaryl indoles from methyl enol ethers via aryl group migration has remained unexplored. In continuation of our earlier work on enol ether, where it was used as a nucleophile,[14] as well as an electrophile,[15] herein, we report an acid-catalyzed novel method for the synthesis of 2-methyl-3-aryl substituted indoles from methyl enol ethers and anilines through aryl group migration.

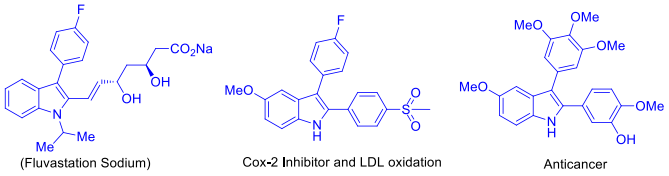

Figure 1. Biologically active 2,3-disubstituted indole scaffold.

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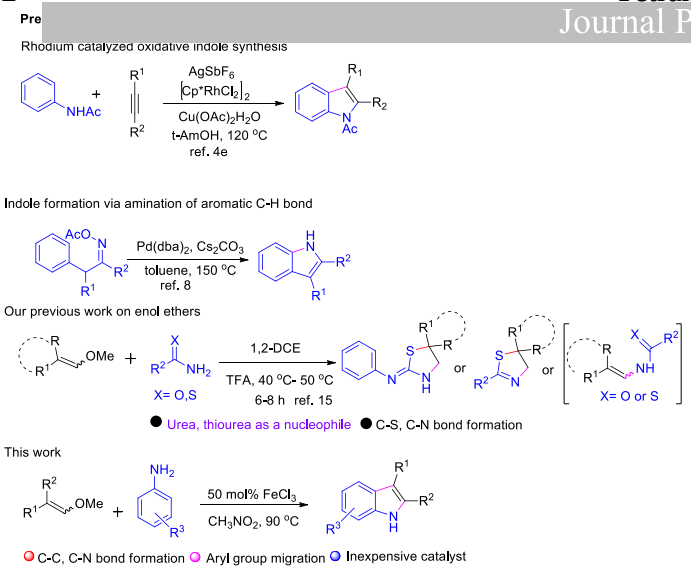
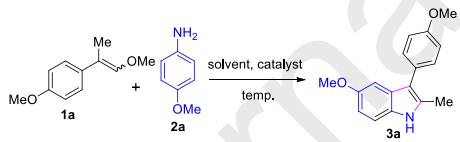


Scheme 1. Previous reports

Results and Discussion

Previously, we have synthesized thiazolines using thiourea as a nucleophile with methyl enol ethers via C-N and C-S bond formation. In continuation of this, we became interested to know the reactivity of methyl enol ethers using aniline as nucleophilic source. Our initial attempts furnished an unexpected product which was identified as 2-methyl-3-aryl indole, formed via aryl group migration. Further, to improve the yield, several optimizations were carried out using different solvents, temperatures, and catalysts (Table 1) and compound **1a** (1-methoxy- 4-(1 methoxyprop-1-en -2-yl)benzene and 4-methoxy aniline (**2a**) were chosen as a model substrate.

Table 1. Optimization for reaction conditions[a]



Entry	Catalyst (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	*p*TSA (0.5)	DCM	AT	24	ND
2	TfOH (0.5)	DCM	AT	24	ND
3	TFA (1.0)	DCM	AT	24	ND
4	MsOH (0.5)	DCM	AT	12	ND
5	$FeCl_3$ (0.2)	CH_3CN	AT	12	ND
6	$FeCl_3$ (0.2)	CH_3CN	reflux	12	ND
8	**$FeCl_3$ (0.5)**	**CH_3NO_2**	**90**	**8**	**83**
9	$Bi(OTf)_3$ (0.5)	CH_3NO_2	90	18	57
10	$BF_3.OEt_2$ (0.5)	CH_3NO_2	90	13	37
11	*p*TSA (0.5)	CH_3NO_2	90	24	ND
12	TFA (0.5)	CH_3NO_2	90	24	ND
13	MsOH (0.5)	CH_3NO_2	90	24	ND
14	TfOH (0.5)	CH_3NO_2	90	24	Trace[c]
15	$FeCl_3$ (0.3)	CH_3NO_2	50	14	57
16	$FeCl_3$ (0.4)	CH_3NO_2	70	11	64

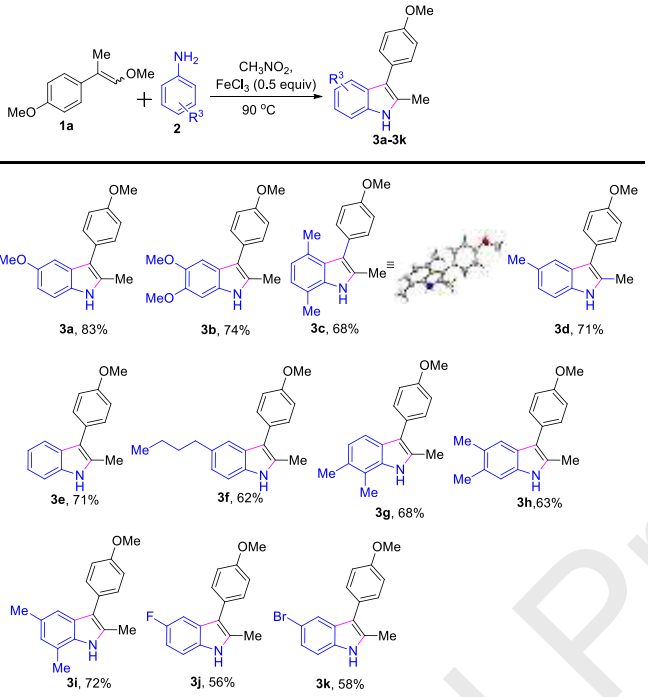
[a]Reaction conditions: **1a** (0.393 mmol), **2a** (0.589 mmol), catalyst (quantity noted), solvent (4 mL) under N_2 atm. [b]Isolated yield after column chromatography. AT = Ambient temperature. ND = Not detected. [c]TLC observation with authentic compound.

Initially, different acids such as *p*TSA, TfOH, TFA, MsOH, in DCM (dichloromethane) at ambient temperature were tried and found to be inactive for the product formation (Table 1, entries 1-4). Lewis acid such as $FeCl_3$ in the presence of solvent CH_3CN (acetonitrile) also remains inactive even up-to reflux temperature (Table 1, entries 5 and 6). Gratifyingly, $FeCl_3$ (20 mol%) in nitromethane (CH_3NO_2) found to be effective in delivering an interesting new product with aryl group migration from enol ether to form **3a** in 52% yield (entry 7, Table 1). When the reaction was performed by using $FeCl_3$ (50 mol%) in CH_3NO_2 at 90 °C, the yield has improved to 83% (entry 8, Table 1). Lewis acids like $Bi(OTf)_3$ and $BF_3.OEt_2$ also catalyze the reactions (entries 9 and 10, Table 1), although they were not as effective as $FeCl_3$. The screening of solvents indicates that only CH_3NO_2 is promoting the product formation, and in other solvents such as CH_2Cl_2 (DCM), CH_3CN unreacted starting materials were observed. Bronsted acids like *p*TSA, TFA, MsOH didn't furnish the product, while TfOH gave traces (entries 11-14, Table 1). Optimizations conducted using 30 mol% and 40 mol% of $FeCl_3$ at 50 °C and 70 °C respectively (entries 15-16), furnished moderate yields. After screening different acids, anhydrous $FeCl_3$ was found to exhibit the highest reactivity. The evaluation of the substrate scope was then carried out in CH_3NO_2 at 90 °C, using 0.5 equivalent of $FeCl_3$ as the catalyst (Table 1 entry 8).

Having optimized condition in our hand, we examined different substituted anilines as shown in Scheme 2. Electron-donating, as well as electron-withdrawing groups on anilines, are well tolerated in this method (**3a-3k**, Scheme 2). First, compounds with donating (–OMe) substituents on aryl group of

anili

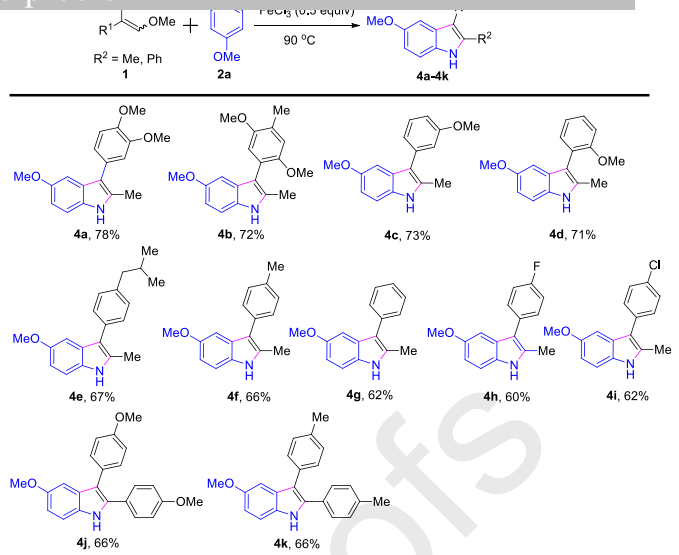
optimized reaction condition and gave the products **3a**-**3b** in good yields. Similarly, simple aniline as well as alkyl substituted anilines also delivered the indole derivatives as expected (**3c**-**3i**) in good yields. Moderate electron-withdrawing substituents like –F, -Br group on anilines reacted smoothly with **1a** and gave the products **3j** and **3k** in moderate yields. However, no product formation achieved when *p*-niroaniline was reacted with compound **1a** under the optimized condition. One of the synthesized compound **3c** was also confirmed with single crystal X-ray analysis.



[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol), catalyst (0.5 equiv), solvent (4 mL) under N_2 atm. for 4-18 h. [b]Isolated yield after column chromatography.

Scheme 2. Substrate scope of aromatic amines.

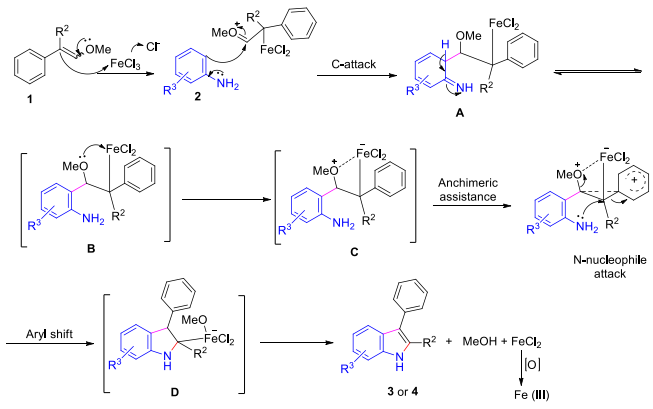
Further to extend the scope of the reactions, different substituted enol ethers were reacted with compound **2a**. As shown in Scheme 3, electron-donating and electron-withdrawing substituted enol ethers reacted well under the optimized reaction condition, and afforded the expected product in moderate to good yields. First, acetophenone derived enol ethers with methoxy substituent underwent the reactions and gave the indole derivatives in good yields (**4a**-**4d**, Scheme 3). Alkyl substituted enol ether reacted moderately and yielded the indole derivatives (**4e** and **4f**) in 67% and 66% respectively. Simple acetophenone derived enol ether (**1h**) also furnished the indole derivative (**4g**) in moderate yield. Compound **1** with substituents like –F, -Cl, were successfully transformed into the expected indole products (**4h** and **4i**) in 60% and 62% yields, respectively. Unfortunately, indole formation was not observed with 3-nitroacetophenone derived enol ether. Benzophenone derived enol ethers also furnished the product in good yields (**4j**, **4k**).



[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.6 mmol), catalyst (0.5 equiv), solvent (4 mL) under N_2 atm. for 4-18 h. [b]Isolated yield after column chromatography.

Scheme 3. Substrate scope of enol ether.

Based on the products obtained from the scope of enol ethers and anilines, a plausible mechanism can be rationalized as follows in Scheme 4. Initially, in the presence of Fe-catalyst could facilitate the attack of C-nucleophile from the *ortho* position of aniline to the α-position of enol ether to form the intermediate **A**. The intermediate **A** where the imine nitrogen is present would undergo tautomerization to furnish the intermediate **B**. Further, formation of intermediate **C** would take place via attack of oxygen lone pair of OMe group to the "Fe" metal. In the next step, intermediate **C** may trigger anchimeric assistance followed by N-nucleophile attack, resulting in aryl migration, to give the intermediate **D**. In the last step, MeOH elimination would take place to deliver the indole derivatives **3** or **4**.



Scheme 4. Plausible reaction mechanism

Conclusion.

In conclusion, we have described a catalytic and an efficient method for the synthesis of 2,3-disubstituted indoles via two

proposed a plausible reaction mechanism where anilines acts as bisnucleophiles. Aryl group migration from enol ether was observed in this protocol. Electron-donating, as well as moderately electron-withdrawing groups, were well tolerated in this methodology.

Acknowledgments

We gratefully acknowledge Department of Science and Technology, Science and Engineering Research Board (EMR/2017/003484), India for financial support. TKJ thanks MHRD, India for the award of the research fellowship.

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Supplementary Material

Click here to remove instruction text...

- $FeCl_3$ catalyzed C-C, C-N bond formation between methyl enol ethers and anilines.
- 2,3-disubstituted indole formation via aryl group migration.
- Anilines act as bis-nucleophiles.