Letter

# Ring-opening of Indoles: An Unconventional Route for the Transformation of Indoles to 1H-Pyrazoles using Lewis Acid

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# Ring-opening of Indoles: An Unconventional Route for the Transformation of Indoles to 1*H*-Pyrazoles using Lewis Acid

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KEYWORDS: Cyclization • indole • Lewis acid • 1*H*-pyrazole • ring-opening.

ABSTRACT: An unusual transformation of indoles to pyrazoles via an aromatic ring-opening strategy has been developed. The salient feature of this strategy involves the C2-N1 bond opening and concomitant cyclization reaction of the C2=C3 bond of the indole moiety with the tosylhydrazone which proceeds under transition-metal and ligand free conditions. This ring-opening functionalization of indoles provides a wide scope of differently substituted pyrazoles.

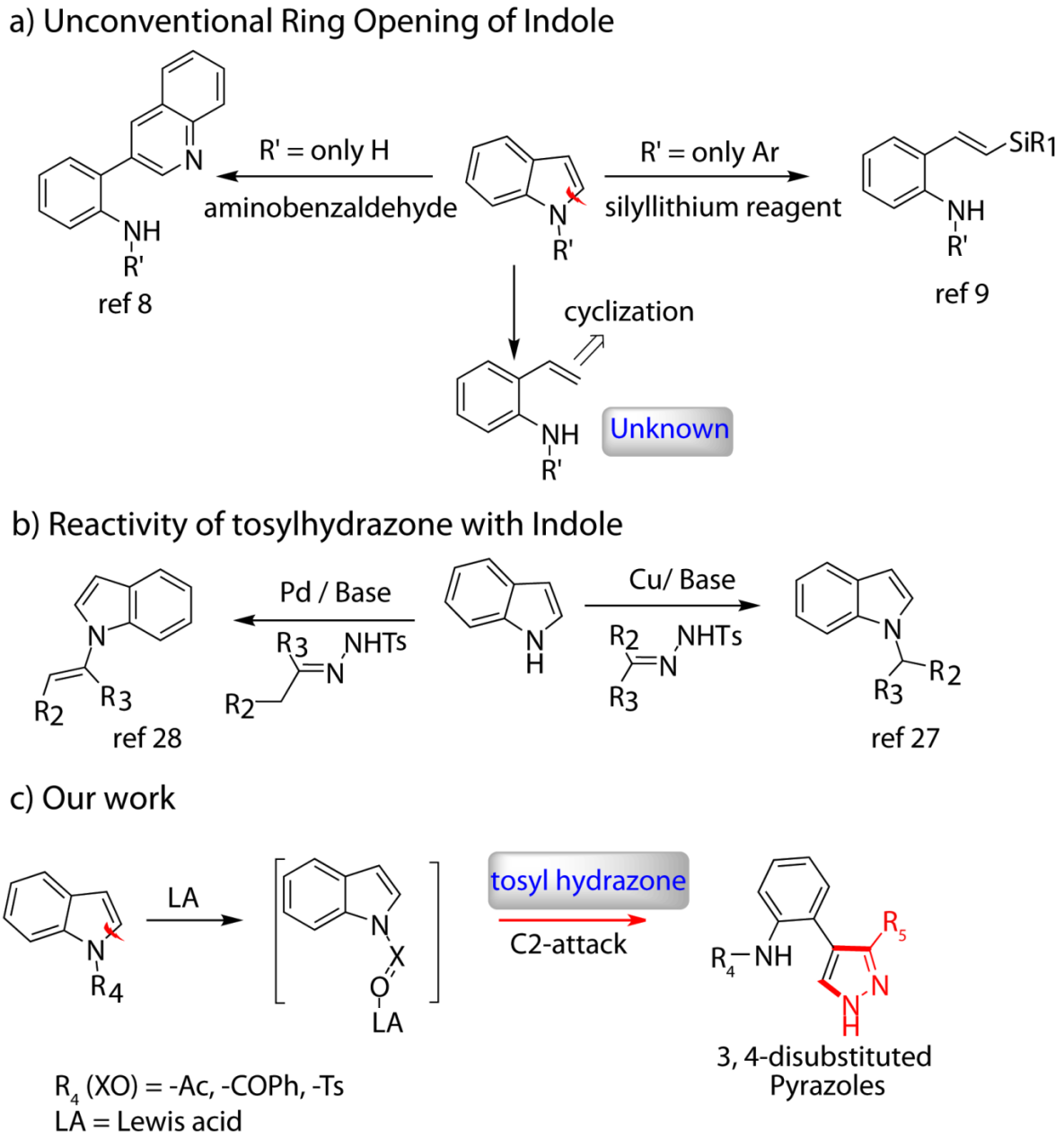
The indole scaffold represents one of the most important structural subunits present in various pharmaceutically active and naturally occurring products. Conventional ways of indole functionalization follow nucleophilic and electrophilic reactions in which the indole scaffold

retains its aromaticity.[1-3] Transition-metal catalyzed C-H functionalization of both the benzene and pyrrole rings of indole has also been widely studied and considered as one of the fascinating strategies for arene functionalization in modern chemistry.[4-7] Ring-opening functionalization of indole is uncommon and more challenging. The aromaticity of indole restricts such ring-opening functionalization strategy. Recently, unconventional opening of C2-N1 bond of indoles was described (Scheme 1a).[8-11] On the other hand, the usage of C2=C3 bond as electrophile for the in-situ cyclization reaction followed by ring-opening of indole is unknown.

In our previous report, we described the regioselective synthesis of 1*H*-pyrazoles through the coupling reaction between the ambiphilic tosylhydrazones and alkenes or alkynes.[12] Other references also describe that the aryl hydrazones are an important structural unit for the transformation of alkene or alkyne to pyrazoles.[13-24] We and other research groups demonstrated that tosylhydrazone have tremendous application in synthetic organic chemistry, especially in cyclization reactions. However, its reactivity towards indole has not been greatly explored.[12, 25-26] Recent studies described that the reaction of tosylhydrazone with indole favors N-alkylation or N-vinylation of indole, rather than cyclization reactions with C2=C3 bond (Scheme 1b).[27-29] We hypothesized that C2-N1 bond opening could be one of the driving forces for C2=C3 bond activation.

It is well documented that the carbonyl and sulfonyl groups form stable adducts with Lewis acids.[30] Hence, we judiciously introduced the carbonyl or sulfonyl containing directing groups like acyl, benzoyl and tosyl at the N1-position of indoles assuming that the complexation between Lewis acids and these directing groups would induce the C2-N1 bond opening (Scheme 1c).[10, 29, 31-40] Therefore, the decrease in electron density of the C2=C3 bond would lead to a cyclization reaction with tosylhydrazones leading to the formation of pyrazoles. They are known

**Scheme 1.** C2-N1 bond opening and the reactivity of indole towards hydrazone




to display a wide spectrum of biological activities including, anti-microbial, anti-fungal, anti-tubercular, anti-inflammatory, anti-convulsant, anti-cancer, anti-viral, neuroprotective.[41-42] The

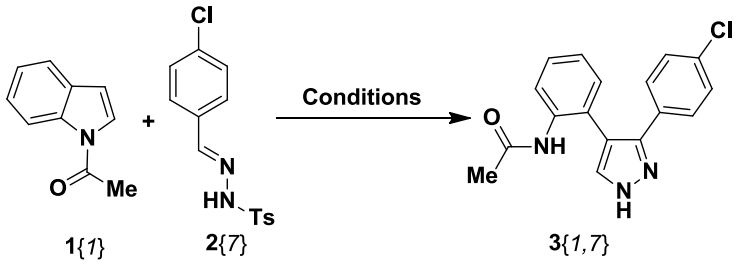
pyrazole is a versatile synthetic intermediate and potent medicinal scaffold.[43-44] The synthesis of pyrazoles still continues to attract considerable attention because of its applications in pharmaceutical and agrochemical industries. We reveal herein transition-metal and ligand free ring-opening functionalization and regioselective transformation of indole to 1*H*-pyrazoles. The product, 1*H*-pyrazole was obtained with moderate to excellent yield. The inhibitory activities of these synthesized compounds were performed against purified human immunosuppressive enzyme indoleamine 2,3-dioxygenase 1 (IDO1).

Our initial investigations commenced with the aim of enhancing the electrophilicity of C2=C3 bond of the indole moiety, so that the C2-N1 bond opening would become more facile leading to the annulation reaction with tosylhydrazone. For this purpose, we decided to study the reaction under mild acidic conditions using 1-acyl-1*H*-indole (**1**{*1*}) and tosylhydrazone (**2**{*7*}) as model substrates. To our delight, tosylhydrazone (**2**{*7*}) in the presence of $BF_3.OEt_2$ (catalytic amount) provided the regioisomeric 1*H*-pyrazole (**3**{*1,7*} under ambient temperature (Table 1, entry1). As expected, the model reaction in the absence of $BF_3.OEt_2$ failed to provide the desired product even at higher temperature (Table 1, entry 2). This model reaction was also performed at higher temperatures and with different equivalents of $BF_3.OEt_2$. Reaction at 50 °C with 0.3 equivalents of $BF_3.OEt_2$ provided the target product in higher yield (Table 1, entry 4). Other Lewis and Bronsted acids such as $AlCl_3$, $FeCl_3$, $Zn(OTf)_2$, $I_2$, AcOH, TsOH, TfOH and TFA were found to be ineffective (Table 1). Solvent screening was also carried out, but dichloroethane (DCE) remained the best solvent for successful formation of pyrazole from indole (Table 1). This ring-opening reaction was unsuccessful under the basic reaction conditions.

These optimized reaction conditions for the unusual indole ring-opening and cyclization reaction encouraged us to explore the scope and limitations of the synthesis of pyrazoles from

the corresponding indoles (Figure 1). We hypothesized that the transformation of an indole into a pyrazole strongly depends on the C2-N1 bond opening proficiency of the indoles. The electronic effects of the substituents could play an important role for the formation of desired pyrazoles. Reaction between 1-acyl-1*H*-indole and electron-neutral phenyl tosylhydrazone provided the targeted pyrazole with moderate yield (55%, Table 2, **3**{*1,1*}).

**Table 1.** Optimization of the reaction conditions for the synthesis of 1*H*-pyrazole (**3**{*1,7*})[a]




1{*1*} 2{*7*} 3{*1,7*}

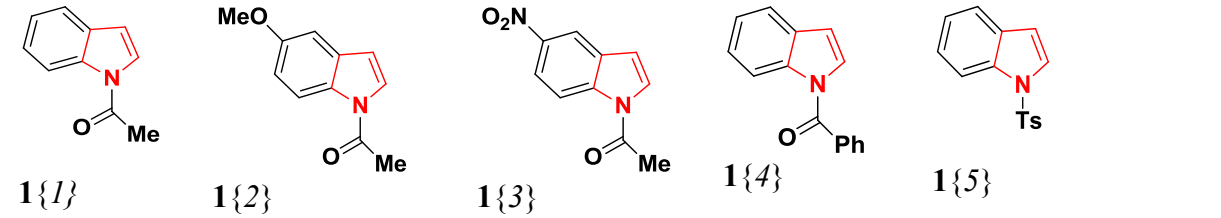
| Entry | Acid / Base (equiv.) | Solvent | Time (h) | Temperature (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1[c] | $BF_3.OEt_2$ (0.3) | DCE | 14 | RT | 55 |
| 2[d] | - | DCE | 48 | RT → 50 | - |
| 3[c] | $BF_3.OEt_2$ (0.1) | DCE | 8 | 50 | 40 |
| 4[c] | $BF_3.OEt_2$ (0.3) | DCE | 8 | 50 | 92 |
| 5[c] | $BF_3.OEt_2$ (0.5) | DCE | 8 | 50 | 72 |
| 6[c] | $BF_3.OEt_2$ (0.3) | DCE | 8 | 80 | 88 |
| 7[d] | $AlCl_3$ (0.3) | DCE | 14 | 50 | - |
| 8[d] | $FeCl_3$ (0.3) | DCE | 14 | 50 | trace |
| 9[d] | $Zn(OTf)_2$ (0.3) | DCE | 14 | 50 | - |
| 10[d] | Iodine (0.3) | DCE | 14 | 50 | - |
| 11[d] | AcOH (0.3) | DCE | 14 | 50 | - |
| 12[d] | TsOH (0.3) | DCE | 14 | 50 | - |

| | | | | | |
|---|---|---|---|---|---|
| 13[d] | TfOH (0.3) | DCE | 14 | 50 | - |
| 14[d] | TFA (0.3) | DCE | 14 | 50 | - |
| 15[c] | $BF_3.OEt_2$ (0.3) | $CHCl_3$ | 14 | 50 | 55 |
| 16[c] | $BF_3.OEt_2$ (0.3) | $CH_2Cl_2$ | 14 | 50 | 60 |
| 17[d] | $BF_3.OEt_2$ (0.3) | DMF | 14 | 80 | - |
| 18[d] | $BF_3.OEt_2$ (0.3) | DMSO | 14 | 80 | - |
| 19[d] | $BF_3.OEt_2$ (0.3) | toluene | 14 | 70 | - |
| 20[d] | $BF_3.OEt_2$ (0.3) | $CH_3CN$ | 14 | 70 | - |
| 21[d] | $BF_3.OEt_2$ (0.3) | $CH_3OH$ | 14 | 50 | - |
| 22[c] | $Et_3N$ (0.3) | DCE | 14 | 50 | N.D |
| 23[c] | $Cs_2CO_3$ (0.3) | DCE | 14 | 50 | N.D |

[a]All the reactions were performed using 0.1 mmol (1 equiv) of **1**{*1*} and 0.11 mmol (1.1 equiv) of **2**{*7*} under acidic conditions. [b]Isolated yield of product (1*H*-pyrazole). [c]5-60% starting material **1**{*1*} and **2**{*7*} was recovered. [d]100% Starting materials **1**{*1*} and **2**{*7*} were recovered.

Alternation in the electronic environments on both indole and hydrazone moieties affected the reaction yield under the optimized reaction conditions. The aryl-tosylhydrazones bearing electron-rich substituents such as –Me and –OMe produced the corresponding pyrazoles in lower yields (**3**{*1,2*}, **3**{*1,3*}). While, the presence of an electron-deficient aryl-tosylhydrazone allowed the formation of corresponding pyrazoles (**3**{*1,4-8*}, **3**{*2,7*}, **3**{*3,7*}) in higher yields. It is important to mention that the synthesis of pyrazoles containing the nitro-, cyano- and halogen groups are highly significant as these functional groups could be deployed in transition-metal catalyzed cross-coupling reactions. The use of tosylhydrazones with such reactive groups was well tolerated in the presence of $BF_3.OEt_2$ thus providing the opportunity for further

1*H*-indoles **1**:




Tosylhydrazones **2**:

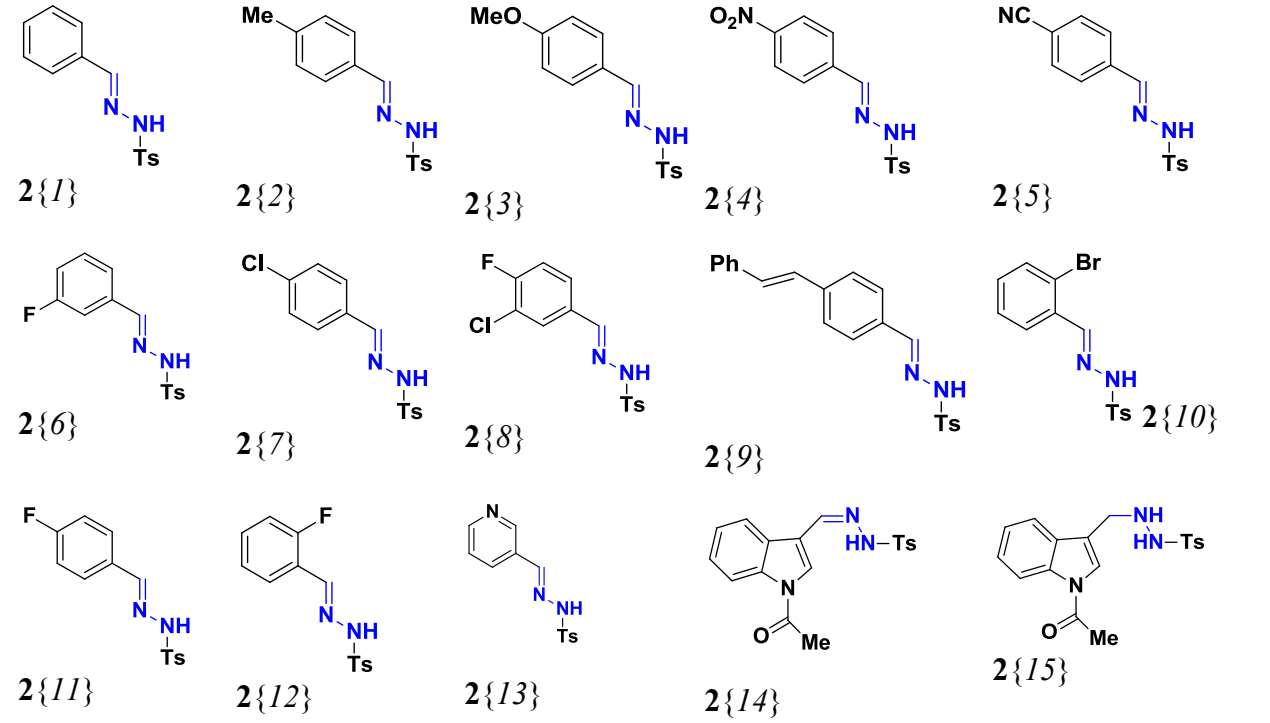
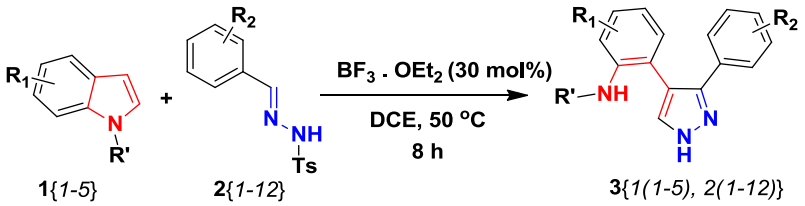



**Figure 1.** Substrates used in the synthesis of pyrazole derivatives

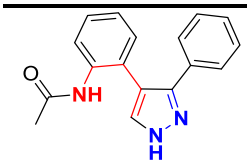
functionalization of these pyrazoles. Interestingly, tosylhydrazone with alkene as substituent shows high selectivity for the synthesis of regioselective pyrazole **3**{*1,9*} with only a moderate yield. Reactions with substituted indoles also displayed quite interesting results. The presence of electron-withdrawing group (–$NO_2$) in the benzene ring of the indole produced the corresponding pyrazole in higher yield. However, the desired pyrazole was obtained in lower yields when an

electron-donating group (-OMe) was present in the benzene ring of the indole. The reaction of methyl substituted (at C2 or C3 position) indoles was unsuccessful. A combination of both

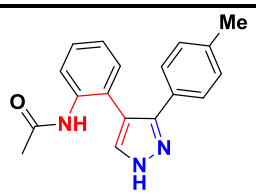
**Table 2.** Substrate scope for the synthesis of 1*H*-pyrazoles[a].



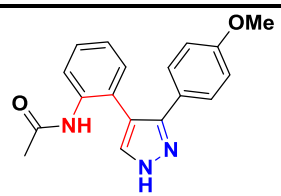

1{*1-5*} 2{*1-12*} 3{*1(1-5), 2(1-12)*}



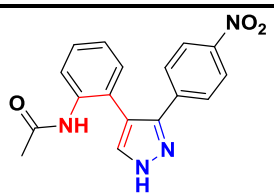
**3**{*1,1*}; 55%



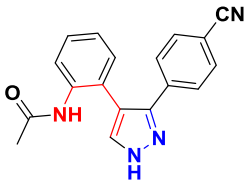
**3**{*1,2*}; 52%



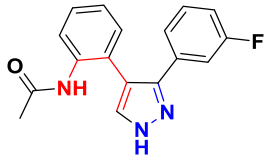
**3**{*1,3*}; 48%



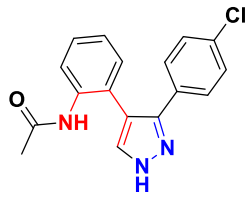
**3**{*1,4*}; 90%



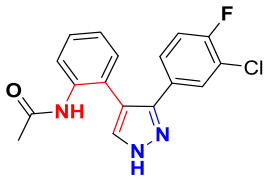
**3**{*1,5*}; 85%



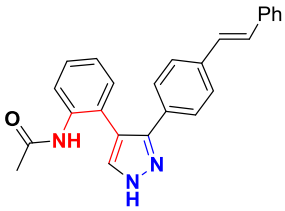
**3**{*1,6*}; 88%



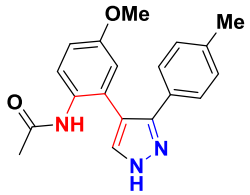
**3**{*1,7*}; 92%



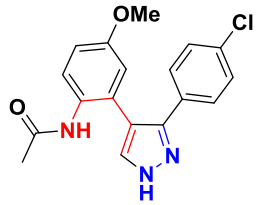
**3**{*1,8*}; 86%



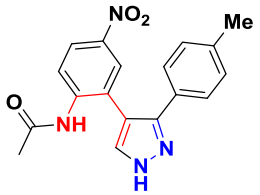
**3**{*1,9*}; 60%



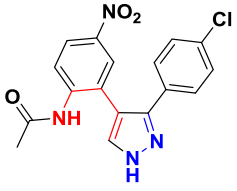
**3**{*2,2*}; 42%



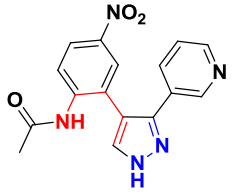
**3**{*2,7*}; 65%



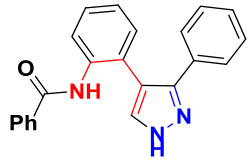
**3**{*3,2*}; 65%



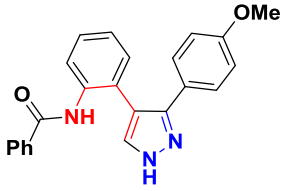
**3**{*3,7*}; 94%



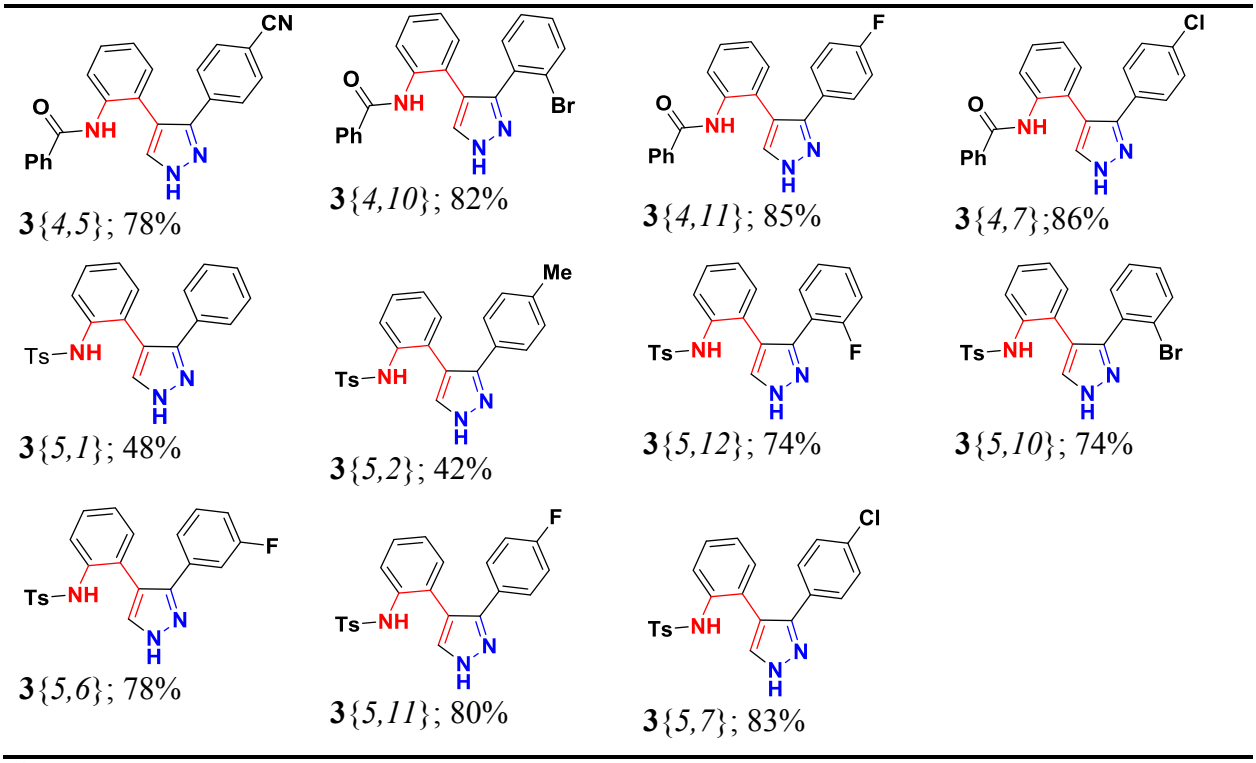
**3**{*3,13*}; 45%



**3**{*4,1*}; 52%



**3**{*4,3*}; 42%




[a]All the reactions were performed using 0.2 mmol of **1**{*1-5*} (1 equiv) and 0.22 mmol of **2**{*1-12*} (1.1 equiv) in the presence of 0.06 mmol of $BF_3.OEt_2$ (0.3 equiv) in 2 mL of DCE at 50 °C.

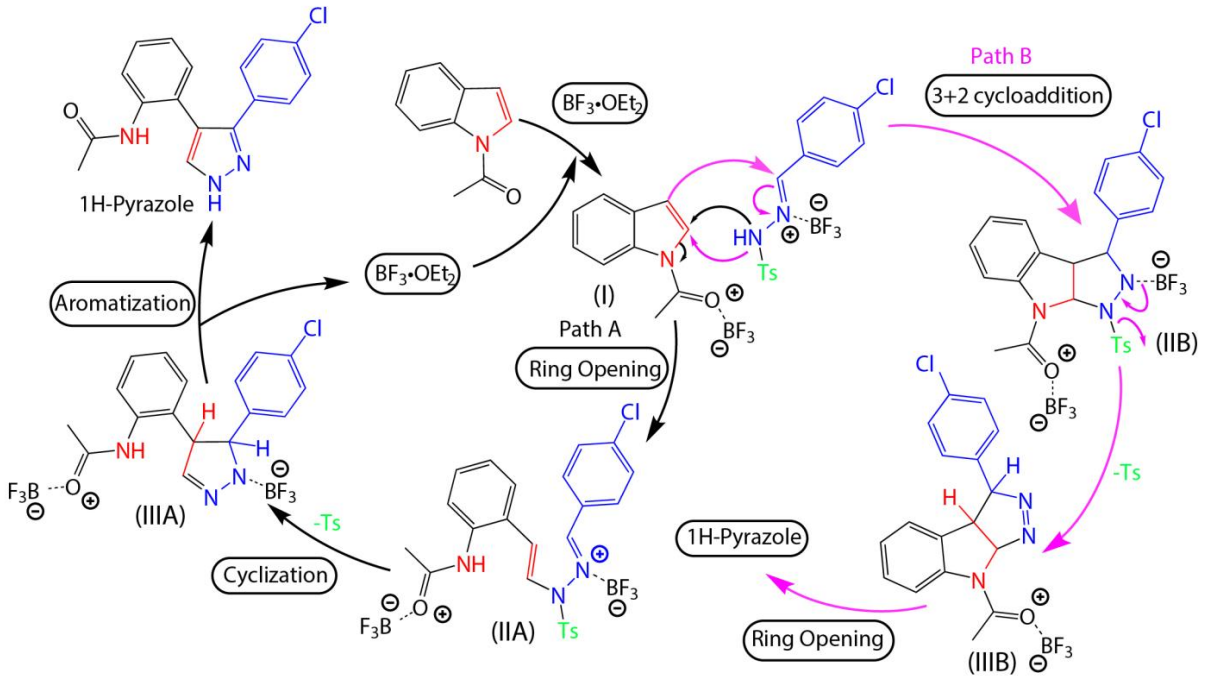
electron deficient indole and tosylhydrazone provided the targeted pyrazoles with maximum yield (**3**{*3,7*}). The reaction with tosylhydrazones bearing pyridine ring produced the target pyrazole with only moderate yield. Unfortunately, the reaction of C2/C3-methyl substituted N-acyl indole failed to provide the targeted pyrazole.

This uncommon reactivity of 1-acyl-indole with aryl-tosylhydrazone prompted us to extend our heterocycles compound library using various N1-substituted indoles. The N1-benzoyl and N1-tosyl indoles successfully participated in this ring-opening and concomitant cyclization reaction. The reaction between N1-benzoyl and N1-tosyl indoles with both electron-rich and electron-deficient aryl-tosylhydrazone showed similar reactivity trends (Table 2) as that with the acyl group, but the yields of the desired pyrazoles were reduced to some extent. The XRD analysis of the compound **3**{*4,5*} confirmed the structure of the desired pyrazole (Figure S1 and

Table S1). Unfortunately, N1-methyl and N1-benzyl containing indole or unsubstituted (N1-H) indole failed to provide the corresponding pyrazole under these optimized reaction conditions (most of the starting materials were recovered). The reaction between 1-acyl-1*H*-indole and the acetophenone tosylhydrazone under the similar experimental conditions failed to provide the target product.

Based on the reported literatures and our results, we propose the following atypical mechanistic pathways for the synthesis of 1*H*-pyrazoles from indoles (Scheme 2). The complexation of Lewis acid ($BF_3.OEt_2$) with the oxygen of N-acyl / N-benzoyl / N-tosyl indoles sequestrated the nitrogen lone-pair and allowing the activation of C2=C3 bond.[10, 45] The

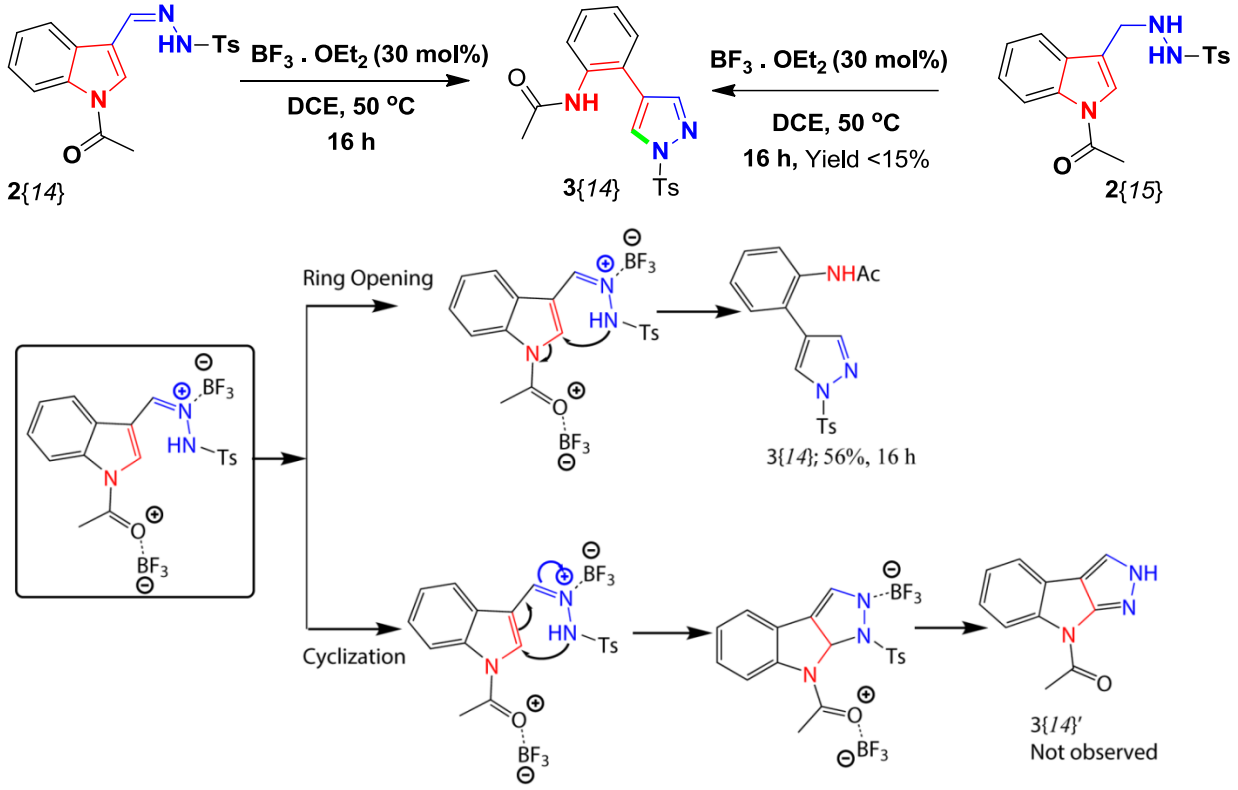
**Scheme 2.** Plausible coupling reaction of activated indoles with tosylhydrazones.



formation of activated N-acyl indole (**I**) in the presence of $BF_3.OEt_2$ was supported by the $^{13}C$ NMR and 2D-NMR (HSQC) experiments (Figure S2 and S3). The unsuccessful ring-opening reaction of alkyl or aryl substituted indoles also support this hypothesis. The nucleophilic attack of the NH of Lewis acid-tosylhydrazone complex at the C2 of activated indole would lead to the formation of intermediate **IIA** followed by the cleavage of C2-N1 bond (Path A).46 Isolation of pyrazole **3**{*14*} from compound **2**{*14*} supported both the nucleophilic attack at the C2-centre and C2-N1 bond cleavage (Scheme 3). However, we failed to isolate any intermediates, indicating stronger reactivity of the reactants/intermediates under the optimized experimental reaction conditions. The intramolecular cyclization of intermediate **IIA** would lead to the formation of intermediate **IIIA** which could produce the desired pyrazoles through aromatization.

The other probable pathway (Path B) describe the 3+2 cycloaddition reaction between the tosylhydrazone, (complexed with $BF_3.OEt_2$) and activated indole (intermediate I). Then the aromatization through cleavage of indole ring of intermediate **IIIB** would lead to the desired pyrazole. However, the intramolecular cyclization of compound **2**{*14*} failed to produce the desired pyrazole **3**{*14*}′ indicating the preference for Path A over Path B mechanistic pathway The cyclization reaction strongly depends on the electrophilic nature of imine bond of hydrazone. The withdrawal of electron density from the C=N bond of the hydrazones should be facile for the electron deficient aryl group. Hence, the cyclization reactions for hydrazones with electron withdrawing groups are more effective in comparison with the electron rich hydrazones. We also performed the intramolecular cyclization of compound **2**{*15*}, which is the reduced product of compound **2**{*14*}. However, the compound **2**{*15*} also produced the pyrazole **3**{*14*}, which could be due to the oxidized aromatization.

**Scheme 3.** Plausible mode of reaction of compound **2**{*14*} for the synthesis of 1*H*-pyrazole

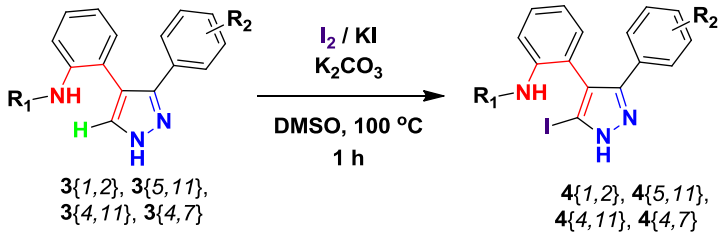



The mechanistic studies suggested that the ring opening reaction is directed by the complex formation ability of the N-acyl (or tosyl or benzoyl) indole with the Lewis acid. The formation of complex of the Lewis acid ($BF_3.OEt_2$) with the –C=O (or sulphonyl) group of the protected indole results in the cleavage of C2-N1 bond of the indole ring. The absence of such carbonyl or sulphonyl group in N1-methyl, N1-benzyl or unsubstituted (N1-H) indole failed to undergo through the ring opening and concomitant cyclization reaction with tosylhydrazone. Interestingly, these observations also demonstrate the importance of carbonyl or sulphonyl group at N1 position of the indole. We hypothesize that the formation of intermediate **IIIA** requires the

presence of H-atom at the imine carbon for the final aromatization reaction. For this reason, the hydrazone of acetophenone failed to produce the target product.

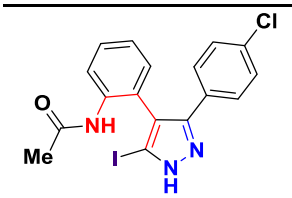
To demonstrate further the synthetic utility of these pyrazoles, we performed iodination reactions. The newly generated amide or sulphonamide group can act as powerful directing groups for the functionalization of the C5-position of pyrazoles (Table 3). To our delight, the selective C-H iodination of the pyrazole over the two other aromatic rings was performed with excellent yield (**4**{*1,2*}, **4**{*4,11*}, **4**{*4,7*} and **4**{*5,11*}; 40 – 98%). The carbon- iodine bond has tremendous synthetic applications in modern chemistry.[47-48] The presence of sulphonamide and benzamide with the aryl ring of pyrazoles shows better result in comparison with the acetamide group for this iodination reaction, which indicates the importance of these directing groups. The directing group of compound **3**{*4,11*} was deprotected under basic condition using ethanolic solution at high temperature (Scheme 4). The free amine group of compound **4**{*4,11*} can be utilized for further functionalization.[49]

**Table 3.** Synthetic applications of this novel class of pyrazoles.

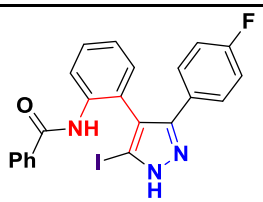



3{*1,2*}, 3{*5,11*}, 3{*4,11*}, 3{*4,7*}

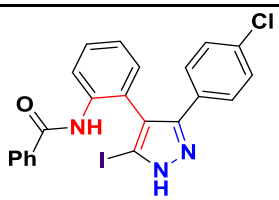
4{*1,2*}, 4{*5,11*}, 4{*4,11*}, 4{*4,7*}



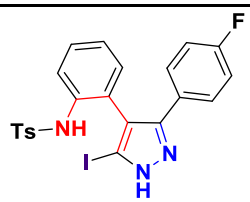

**4**{*1,2*}; 40%




**4**{*4,11*}; 75%




**4**{*4,7*}; 77%



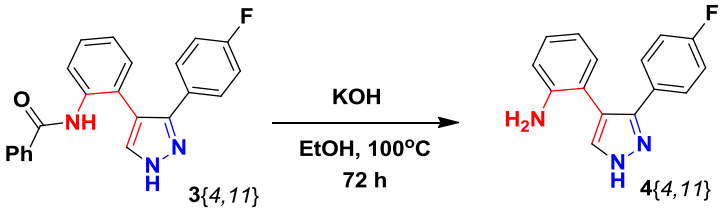

**4**{*5,11*}; 98%

[a]All the reactions were performed using 1 equiv of **3**{*1,2*} or **3**{*5,11*} or **3**{*4,11*} or **3**{*4,7*}, 1 equiv. of iodine, 2 equiv. of KI and 2 equiv. of $K_2CO_3$ in the presence of 0.3 equiv. of $BF_3.OEt_2$

in 1 mL of DMSO at 100 °C.

Synthesis of substituted pyrazoles using such quick and easy to perform mild reaction conditions is a part of our on-going heterocyclic drug discovery program for cancer immunotherapy. Immunotherapeutic approach is being considered as one of the most promising approaches in the battle against cancer.[50-51] In this regard, we explored the IDO1 inhibitory activity of these compounds (HPLC purified). The $IC_{50}$ values were measured against purified human IDO1 enzyme using standard spectrophotometric method (Table 4 and S2). Compounds, **3**{*2,2*} ($IC_{50}$ = 40.33 μM) and **3**{*5,1*} ($IC_{50}$ = 25.0 μM) showed moderate IDO1 inhibitory activity, which could be due to the presence of substituted aryl containing pyrazole and sulfonamide moieties.[52-53] Nonetheless, the inhibitory activity study suggests that this pyrazole scaffold can be used as the lead compound and its modifications may lead to the development of potent IDO1 inhibitors with favorable biochemical and biophysical properties.

**Scheme 4.** Removal of the directing group




In summary, we described an unusual ring-opening and cyclization reaction of a stable aromatic heterocyclic compound. This transition-metal and ligand free synthesis of pyrazoles from the corresponding indoles through the C2-N1 bond cleavage is unknown. Complexation of the Lewis acid with indoles and tosylhydrazones could be the driving force for this reaction. This method could be a useful alternative to the existing methods for regioselective synthesis of

pyrazoles. The inhibitory activities of these synthesized pyrazoles were tested against immune suppressive enzyme, IDO1. The preliminary results suggest that the pyrazole moiety can be used as synthetically amenable lead for future development of IDO1 inhibitors.

**Table 4.** Inhibitory activity of the 1*H*-pyrazoles against purified human IDO1 enzyme.

| Compound | IDO1 $IC_{50}$ (μM)[a] | Compound | IDO1 $IC_{50}$ (μM)[a] |
|---|---|---|---|
| **3**{*1,4*} | 84.50 ± 3.6 | **3**{*5,1*} | 25.0 ± 3.5 |
| **3**{*2,2*} | 40.33 ± 0.3 | **3**{*5,2*} | 115.5 ± 5.8 |
| **3**{*4,3*} | 74.17 ± 2.3 | **3**{*5,6*} | 96.8 ± 5.8 |

[a]$IC_{50}$ values are the mean of three independent assays.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Spectroscopic data for all compounds; crystallographic information for compounds **3**{*4,5*} (PDF)

X-ray data for compounds **3**{*4,5*} (CIF).

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## Author Contributions

The manuscript was written through contributions of all authors.

## Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

IDO1, indoleamine 2,3-dioxygenase; DCE, dichloroethane.

## REFERENCES

(1) Kang, Q.; Zhao, Z.-A.; You, S.-L. Highly Enantioselective Friedel− Crafts Reaction of Indoles with Imines by a Chiral Phosphoric Acid. *J. Am. Chem. Soc.* **2007,** *129* (6), 1484-1485.

(2) Yang, Y.; Zhang, Y.; Wang, J. Lewis Acid Catalyzed Direct Cyanation of Indoles and Pyrroles with N-Cyano-N-Phenyl-P-Toluenesulfonamide (Ncts). *Org. lett.* **2011,** *13* (20), 5608-5611.

(3) Qi, L.-W.; Mao, J.-H.; Zhang, J.; Tan, B. Organocatalytic Asymmetric Arylation of Indoles Enabled by Azo Groups. *Nat. Chem.* **2018,** *10*, 58-64.

(4) Stuart, D. R.; Villemure, E.; Fagnou, K. Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling. *J. Am. Chem. Soc.* **2007,** *129* (40), 12072-12073.

(5) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. Cu(Ii)-Catalyzed Direct and Site-Selective Arylation of Indoles under Mild Conditions. *J. Am. Chem. Soc.* **2008,** *130* (26), 8172-8174.

(6) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. Regioselective Oxidative Arylation of Indoles Bearing N-Alkyl Protecting Groups: Dual C−H Functionalization Via a Concerted Metalation−Deprotonation Mechanism. *J. Am. Chem. Soc.* **2010,** *132* (41), 14676-14681.

(7) Roche, S. P.; Youte Tendoung, J.-J.; Tréguier, B. Advances in Dearomatization Strategies of Indoles. *Tetrahedron* **2015,** *71* (22), 3549-3591.

(8) Vecchione, M. K.; Sun, A. X.; Seidel, D. Divergent Reactions of Indoles with Aminobenzaldehydes: Indole Ring-Opening Vs. Annulation and Facile Synthesis of Neocryptolepine. *Chem. Sci.* **2011,** *2* (11), 2178-2181.

(9) Xu, P.; Wurthwein, E. U.; Daniliuc, C. G.; Studer, A. Transition-Metal-Free Ring-Opening Silylation of Indoles and Benzofurans with (Diphenyl-Tert-Butylsilyl) Lithium. *Angew. Chem. Int. Ed.* **2017,** *56* (44), 13872-13875.

(10) Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. Intermolecular Dearomative C2-Arylation of N-Ac Indoles Activated by Fecl3. *Chem. Comm.* **2016,** *52* (30), 5328-5331.

(11) Noland, W.; Kuryla, W. The Synthesis of Triindole, and the Mixed Indole and Indole: Pyrrole Trimers. *J. Org. Chem.* **1960,** *25* (3), 486-487.

(12) Panda, S.; Maity, P.; Manna, D. Transition Metal, Azide, and Oxidant-Free Homo- and Heterocoupling of Ambiphilic Tosylhydrazones to the Regioselective Triazoles and Pyrazoles. *Org. Lett.* **2017,** *19* (7), 1534-1537.

(13) Panda, N.; Jena, A. K. Fe-Catalyzed One-Pot Synthesis of 1,3-Di- and 1,3,5-Trisubstituted Pyrazoles from Hydrazones and Vicinal Diols. *J. Org. Chem.* **2012,** *77* (20), 9401-9406.

(14) Fan, X.-W.; Lei, T.; Zhou, C.; Meng, Q.-Y.; Chen, B.; Tung, C.-H.; Wu, L.-Z. Radical Addition of Hydrazones by A-Bromo Ketones to Prepare 1,3,5-Trisubstituted Pyrazoles Via Visible Light Catalysis. *J. Org. Chem.* **2016,** *81* (16), 7127-7133.

(15) Deng, X.; Mani, N. S. Reaction of N-Monosubstituted Hydrazones with Nitroolefins: A Novel Regioselective Pyrazole Synthesis. *Org. Lett.* **2006,** *8* (16), 3505-3508.

(16) Deng, X.; Mani, N. S. Base-Mediated Reaction of Hydrazones and Nitroolefins with a Reversed Regioselectivity: A Novel Synthesis of 1,3,4-Trisubstituted Pyrazoles. *Org. Lett.* **2008,** *10* (6), 1307-1310.

(17) Lee, S.; Park, S. B. An Efficient One-Step Synthesis of Heterobiaryl Pyrazolo[3,4-B]Pyridines Via Indole Ring Opening. *Org. Lett.* **2009,** *11* (22), 5214-5217.

(18) Kong, Y.; Tang, M.; Wang, Y. Regioselective Synthesis of 1,3,5-Trisubstituted Pyrazoles from N-Alkylated Tosylhydrazones and Terminal Alkynes. *Org. Lett.* **2014,** *16* (2), 576-579.

(19) Zhang, Q.; Meng, L.-G.; Wang, K.; Wang, L. Nbu3p-Catalyzed Desulfonylative [3 + 2] Cycloadditions of Allylic Carbonates with Arylazosulfones to Pyrazole Derivatives. *Org. Lett.* **2015,** *17* (4), 872-875.

(20) Senadi, G. C.; Hu, W.-P.; Lu, T.-Y.; Garkhedkar, A. M.; Vandavasi, J. K.; Wang, J.-J. I2–Tbhp-Catalyzed Oxidative Cross-Coupling of N-Sulfonyl Hydrazones and Isocyanides to 5-Aminopyrazoles. *Org. Lett.* **2015,** *17* (6), 1521-1524.

(21) Ma, C.; Li, Y.; Wen, P.; Yan, R.; Ren, Z.; Huang, G. Copper(I)-Catalyzed Synthesis of Pyrazoles from Phenylhydrazones and Dialkyl Ethylenedicarboxylates in the Presence of Bases. *Synlett* **2011,** *2011* (09), 1321-1323.

(22) Sha, Q.; Wei, Y. An Efficient One-Pot Synthesis of 3,5-Diaryl-4-Bromopyrazoles by 1,3-Dipolar Cycloaddition of in Situ Generated Diazo Compounds and 1-Bromoalk-1-Ynes. *Synthesis* **2013,** *45* (03), 413-420.

(23) Tang, M.; Wang, Y.; Wang, H.; Kong, Y. Aluminum Chloride Mediated Reactions of N-Alkylated Tosyl-Hydrazones and Terminal Alkynes: A Regioselective Approach to 1,3,5-Trisubstituted Pyrazoles. *Synthesis* **2016,** *48* (18), 3065-3076.

(24) Qi, L. W.; Mao, J. H.; Zhang, J.; Tan, B. Organocatalytic Asymmetric Arylation of Indoles Enabled by Azo Groups. *Nat. Chem.* **2018,** *10* (1), 58-64.

(25) Pérez-Aguilar, M. C.; Valdés, C. Regioselective One-Step Synthesis of Pyrazoles from Alkynes and N-Tosylhydrazones: [3+2] Dipolar Cycloaddition/[1,5] Sigmatropic Rearrangement Cascade. *Angew. Chem. Int. Ed.* **2013,** *52* (28), 7219-7223.

(26) Zheng, Y.; Zhang, X.; Yao, R.; Wen, Y.; Huang, J.; Xu, X. 1,3-Dipolar Cycloaddition of Alkyne-Tethered N-Tosylhydrazones: Synthesis of Fused Polycyclic Pyrazoles. *J. Org. Chem.* **2016,** *81* (22), 11072-11080.

(27) Ling, L.; Cao, J.; Hu, J. F.; Zhang, H. Copper-Catalyzed N-Alkylation of Indoles by N-Tosylhydrazones. *Rsc Adv.* **2017,** *7* (45), 27974-27980.

(28) Zeng, X. B.; Cheng, G. L.; Shen, J. H.; Cui, X. L. Palladium-Catalyzed Oxidative Crosscoupling of N-Tosylhydrazones with Indoles: Synthesis of N-Vinylindoles. *Org. Lett.* **2013,** *15* (12), 3022-3025.

(29) Cusmano, G.; Macaluso, G.; Vivona, N.; Ruccia, M. Synthesis of 2h-Pyrazolo[3,4-C]Quinoline Derivatives by One Pot Rearrangement of Phenylhydrazones of 3-Acylindoles. *Heterocycles* **1986,** *24* (11), 3181-3186.

(30) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. Microwave-Assisted Tandem Cross Metathesis Intramolecular Aza-Michael Reaction: An Easy Entry to Cyclic B-Amino Carbonyl Derivatives. *J. Am. Chem. Soc.* **2007,** *129* (21), 6700-6701.

(31) Tajima, N.; Hayashi, T.; Nakatsuka, S.-i. Structures of Dimers and Trimers of 1-Trimethylacetylindole Produced in Presence of Aluminum Chloride. *Tett. Lett.* **2000,** *41* (7), 1059-1062.

(32) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. Fecl3-Mediated Friedel–Crafts Hydroarylation with Electrophilic N-Acetyl Indoles for the Synthesis of Benzofuroindolines. *Angew. Chem. Int. Ed.* **2012,** *51* (50), 12546-12550.

(33) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. Regioselective Hydroarylation Reactions of C3 Electrophilic N-Acetylindoles Activated by Fecl3: An Entry to 3-(Hetero) Arylindolines. *Chem. Eur. J.* **2014,** *20* (24), 7492-7500.

(34) Beaud, R.; Nandi, R. K.; Perez-Luna, A.; Guillot, R.; Gori, D.; Kouklovsky, C.; Ghermani, N.-E.; Gandon, V.; Vincent, G. Revealing the Electrophilicity of N-Ac Indoles with Fecl3: A Mechanistic Study. *Chem. Comm.* **2017,** *53* (43), 5834-5837.

(35) Morimoto, N.; Morioku, K.; Suzuki, H.; Takeuchi, Y.; Nishina, Y. Lewis Acid and Fluoroalcohol Mediated Nucleophilic Addition to the C2 Position of Indoles. *Org. Lett.* **2016,** *18* (9), 2020-2023.

(36) Attar, K.; Camara, H.; Benchidmi, M.; Essassi, E. M.; Garrigues, B. Synthèse De Nouveaux Dérivés Du 1-Hydroxyindole Et Du Pyrazole. *Comptes. Rendus. Chimie.* **2002,** *5* (6), 551-557.

(37) Colotta, V.; Catarzi, D.; Varano, F.; Capelli, F.; Lenzi, O.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Ciampi, O.; Pugliese, A. M.; Pedata, F.; Schiesaro, A.; Morizzo, E.; Moro, S. New 2-Arylpyrazolo[3,4-C]Quinoline Derivatives as Potent and Selective Human A3 Adenosine Receptor Antagonists. Synthesis, Pharmacological Evaluation, and Ligand−Receptor Modeling Studies. *J. Med. Chem.* **2007,** *50* (17), 4061-4074.

(38) Danielson, M. E.; Hays, D. S.; Kshirsagar, T. A.; Haraldson, C. A.; Lundquist, G. D.; Wurst, J. R.; Lindstrom, K. J.; Mackey, S. S.; Willie, D. J.; Heppner, P. D.; Leir, C. M.; Benson, K. E. Deprotonation and Regioselective Addition of 2h-Pyrazolo[3,4-C]Quinolines to Electrophiles. *J. Org. Chem.* **2007,** *72* (12), 4570-4573.

(39) Lenzi, O.; Colotta, V.; Catarzi, D.; Varano, F.; Squarcialupi, L.; Filacchioni, G.; Varani, K.; Vincenzi, F.; Borea, P. A.; Ben, D. D.; Lambertucci, C.; Cristalli, G. Synthesis, Structure–Affinity Relationships, and Molecular Modeling Studies of Novel Pyrazolo[3,4-C]Quinoline Derivatives as Adenosine Receptor Antagonists. *Bioorg. Med. Chem.* **2011,** *19* (12), 3757-3768.

(40) Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C. Tricyclic Heteroaromatic Systems. Pyrazolo[3,4-C]Quinolin-4-Ones and Pyrazolo[3,4-C]Quinoline-1,4-Diones: Synthesis and Benzodiazepine Receptor Activity. *Archiv. der. Pharmazie.* **1997,** *330* (12), 383-386.

(41) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Pyrazole Ligands: Structure−Affinity/Activity Relationships and Estrogen Receptor-A-Selective Agonists. *J. Med. Chem.* **2000,** *43* (26), 4934-4947.

(42) Kiyonaka, S.; Kato, K.; Nishida, M.; Mio, K.; Numaga, T.; Sawaguchi, Y.; Yoshida, T.; Wakamori, M.; Mori, E.; Numata, T. Selective and Direct Inhibition of Trpc3 Channels Underlies Biological Activities of a Pyrazole Compound. *Proc. Natl. Acad. Sci.* **2009,** *106* (13), 5400-5405.

(43) Chinchilla, R.; Nájera, C.; Yus, M. Metalated Heterocycles and Their Applications in Synthetic Organic Chemistry. *Chem. rev.* **2004,** *104* (5), 2667-2722.

(44) Kuwata, S.; Ikariya, T. Metal–Ligand Bifunctional Reactivity and Catalysis of Protic N-Heterocyclic Carbene and Pyrazole Complexes Featuring B-Nh Units. *Chem. Comm.* **2014,** *50* (92), 14290-14300.

(45) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. Regioselective Hydroarylation Reactions of C3 Electrophilic N-Acetylindoles Activated by Fecl3: An Entry to 3-(Hetero)Arylindolines. *Chem. Eur. J.* **2014,** *20* (24), 7492-7500.

(46) Wang, W.-L.; Feng, Y.-L.; Gao, W.-Q.; Luo, X.; Deng, W.-P. A Highly Efficient Bf3[Middle Dot]Et2o-Catalysed Intramolecular [3+2] Cycloaddition for the Synthesis of 3,4-Dihydrobenzopyrano[3,4-C]Pyrazoles. *RSC Adv.* **2013,** *3* (6), 1687-1690.

(47) Newman, S. G.; Lautens, M. Palladium-Catalyzed Carboiodination of Alkenes: Carbon−Carbon Bond Formation with Retention of Reactive Functionality. *J. Am. Chem. Soc.* **2011,** *133* (6), 1778-1780.

(48) Li, Y.-X.; Wang, H.-X.; Ali, S.; Xia, X.-F.; Liang, Y.-M. Iodine-Mediated Regioselective C2-Amination of Indoles and a Concise Total Synthesis of (±)-Folicanthine. *Chem. Comm.* **2012,** *48* (17), 2343-2345.

(49) Wang, S.; Qiu, D.; Mo, F.; Zhang, Y.; Wang, J. Metal-Free Aromatic Carbon–Phosphorus Bond Formation Via a Sandmeyer-Type Reaction. *J. Org. Chem.* **2016,** *81* (23), 11603-11611.

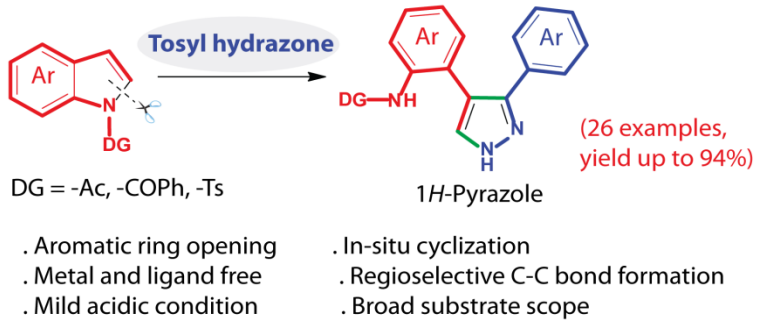
(50) Zou, W. P. Immunosuppressive Networks in the Tumour Environment and Their Therapeutic Relevance. *Nat. Rev.Cancer* **2005,** *5* (4), 263-274.

(51) Munn, D. H.; Mellor, A. L. Indoleamine 2,3-Dioxygenase and Tumor-Induced Tolerance. *J. Clin. Investig.* **2007,** *117* (5), 1147-1154.

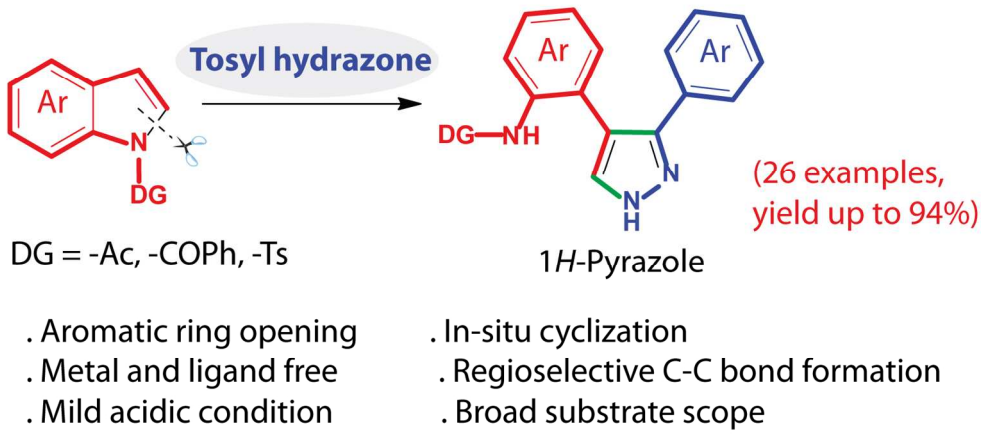
(52) Panda, S.; Roy, A.; Deka, S. J.; Trivedi, V.; Manna, D. Fused Heterocyclic Compounds as Potent Indoleamine-2,3-Dioxygenase 1 Inhibitors. *Acs Med. Chem. Lett.* **2016,** *7* (12), 1167-1172.

(53) Paul, S.; Roy, A.; Deka, S. J.; Panda, S.; Trivedi, V.; Manna, D. Nitrobenzofurazan Derivatives of N '-Hydroxyamidines as Potent Inhibitors of Indoleamine-2,3-Dioxygenase 1. *Eur. J. Med. Chem.* **2016,** *121*, 364-375.

**TOC**




**Ring-opening**: Lewis acid catalyzed ring-opening of the indoles afforded regeoselective pyrazole in the presence of tosylhydrazones. *In-situ* cyclization after the cleavage of C2-N1 bond of the indoles proceeds in the absence of any transition-metal and ligand.




Ring-opening: Lewis acid catalyzed ring-opening of the indoles afforded regeoselective pyrazole in the presence of tosylhydrazones. In-situ cyclization after the cleavage of C2-N1 bond of the indoles proceeds in the absence of any transition-metal and ligand.

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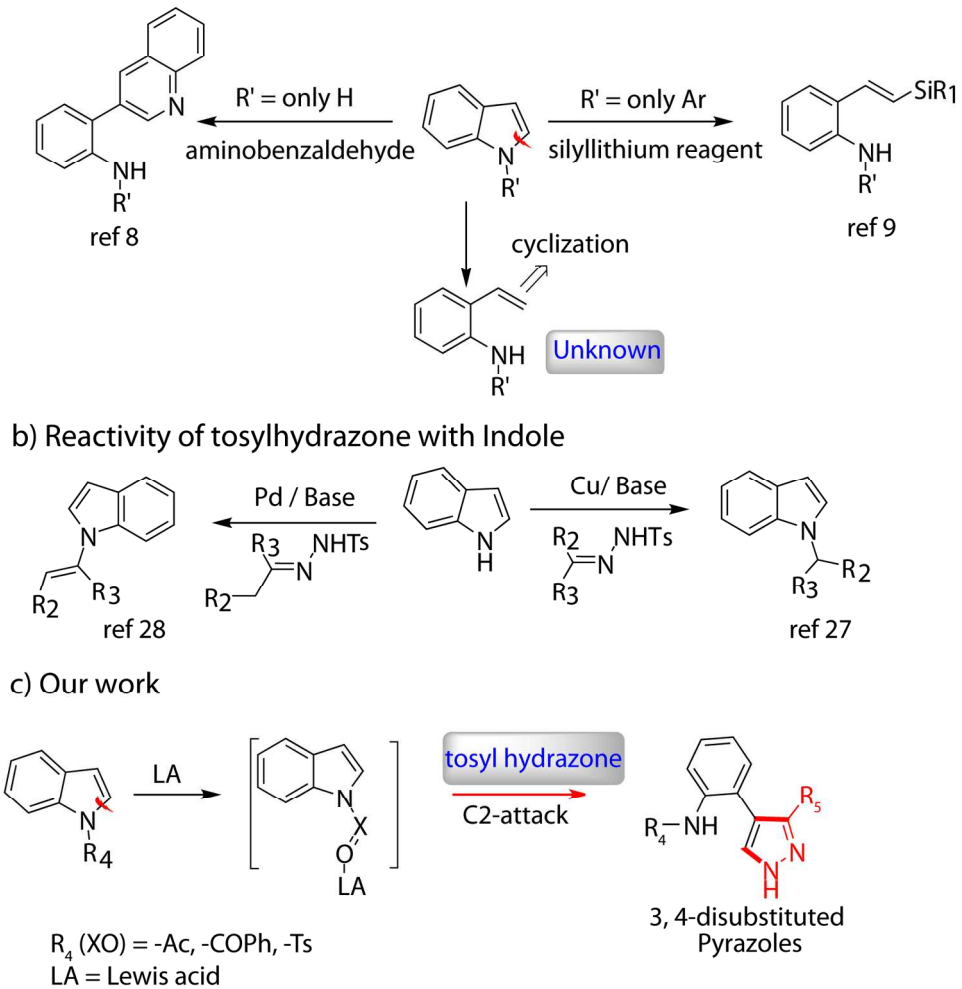


C2-N1 bond opening and the reactivity of indole towards hydrazone.

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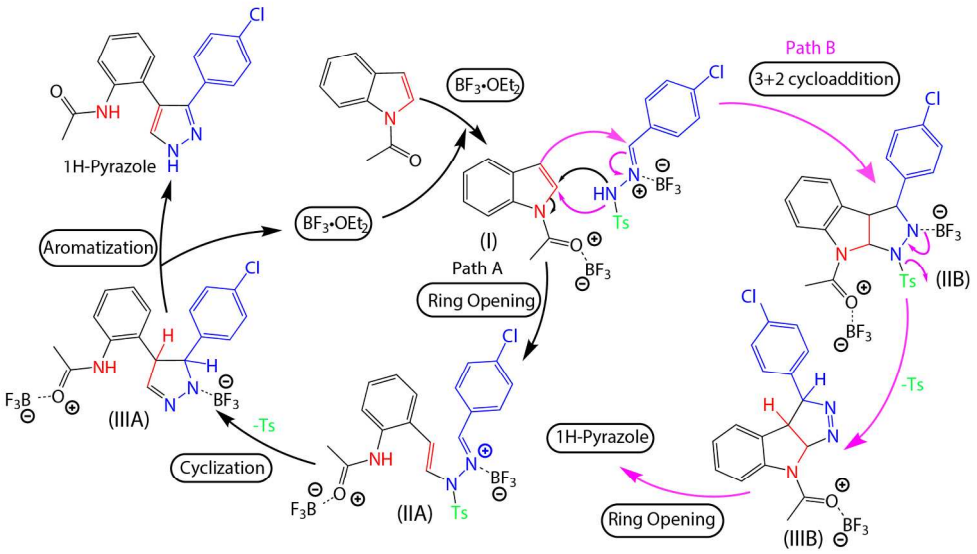


Plausible coupling reaction of activated indoles with tosylhydrazones.

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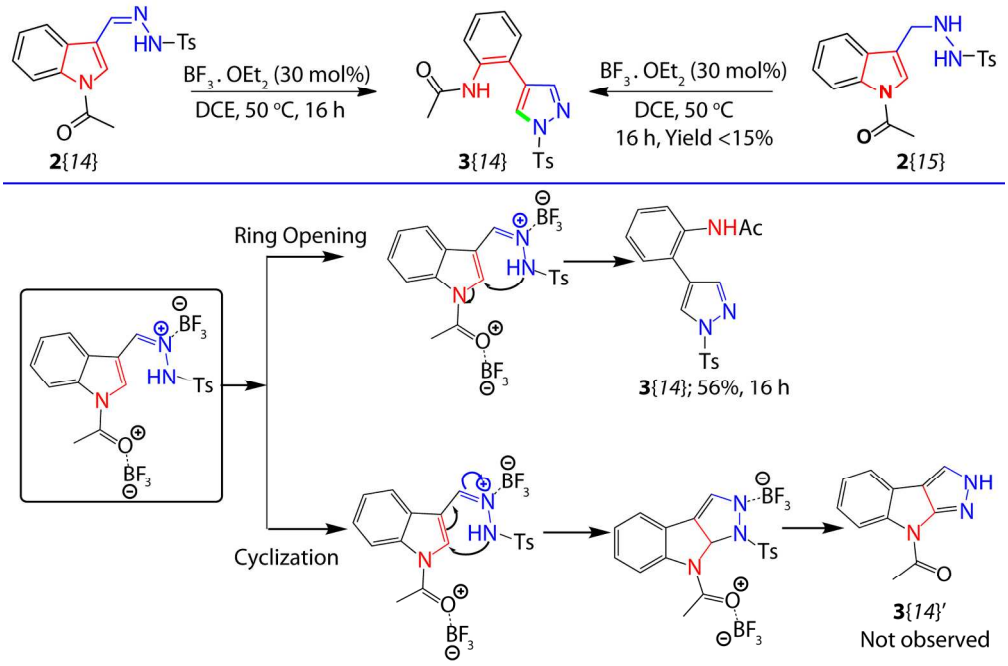


Plausible mode of reaction of compound 2{14} for the synthesis of 1H-pyrazole.

183x125mm (300 x 300 DPI)