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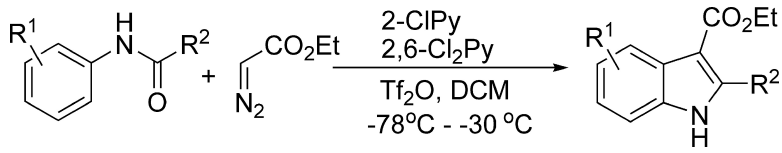

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Synthesis of Indoles via Domino Reaction of *N*-Aryl Amides and Ethyl Diazoacetate

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Indoles are probably the most ubiquitous heterocycles in nature and have been referred to as "privileged structures" in drug discovery because of their capacity of binding to many receptors with high affinity.[1] Accordingly, many powerful methodologies for the synthesis of these heterocycles have been developed,[2] the majority of which involve Fischer-type indole synthesis,[3] heteroannulations and cyclization of 2-alkynylanilines,[4] reductive cyclization,[5] and metal-catalyzed coupling/condensation cascades.[6] Still, general and efficient methods for the synthesis of indoles from simple and readily available precursors are of great value. We herein report a single-step approach to indoles via a domino reaction of *N*-aryl amides and ethyl diazoacetate (EDA).

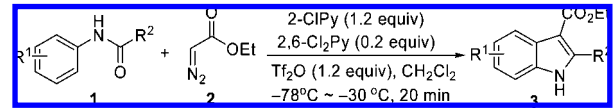
Recently, Charette and Movassaghi reported pioneering works on the electrophilic activation of amides with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine or 2-chloropyridine (2-ClPy) and a suitable nucleophile, which led to the synthesis of carboxylic acid derivatives,[7a] chiral piperidines,[7b] amines,[7c] pyridines,[7d,e] and pyrimidines.[7f] Inspired by these works and our recent findings around domino reactions,[8] we assumed that the addition of EDA to the highly activated amides would lead to the formation of indoles since diazo carbon bears a partial negative charge and thus has considerable nucleophilicity.[9]

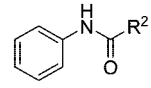
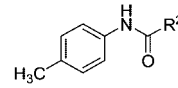
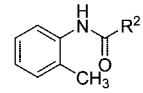
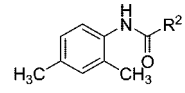
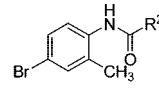
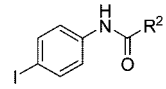
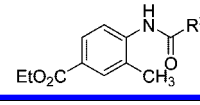
The reaction of benzamide **1a** (1 equiv), EDA (1.5 equiv), and Tf_2O (1.2 equiv) were used to screen the reaction conditions (Supporting Information, SI-Table 1). The combination of 2-ClPy (1.2 equiv) and 2,6-dichloropyridine (2,6-Cl_2Py, 0.2 equiv) proved to be the most effective base additives, which allow a direct conversion of **1a** to indole **3aa** (SI-Table 1, entry 8). It is noteworthy that 2,6-Cl_2Py (0.2 equiv) is crucial to the domino process. Thus upon optimal conditions, the reaction of EDA with the activated amide **1a** at −30 °C for 20 min afforded **3aa** in 52% yield.

We next examined the scope of the reaction with a variety of differently substituted *N*-aryl amides. As shown in Table 1, all *N*-aryl amides proceeded to furnish the corresponding substituted indoles in moderate to good yields (46−82%). Importantly, benzamides gave the corresponding 2-phenylindoles (entries 1−4, 10, 14, and 15), which are important structures owing to their biological activity and commonly prepared by multistep synthesis or by metal-catalyzed 2-arylation of indoles.[10] Moreover, *N*-*m*-tolylacetamide **1h** gave the less hindered 2,6-dimethyl-1*H*-indole **3ha** as major product and its isomer 2,4-dimethyl-1*H*-indole **3hb** as minor product while *N*-(naphthalen-1-yl)benzamide **1i** afforded 1*H*-benzo[*de*]quinoline **4** in 71% yield and no 1*H*-benzo[*g*]indole was observed (Scheme 1), so the reaction exhibited high regioselectivity. The structure of compound **3db** was unambiguously confirmed by X-ray analysis (see Supporting Information).

A demonstration of the intensive synthetic utility was shown in Scheme 2. Indole **3bd** was converted to pyrrolo[1,2-*a*]indole **5** in high yield when treated with NaH in THF. This two-step strategy for access to pyrrolo[1,2-*a*]indole from *N*-aryl amides is concise and highly efficient compared with the published methods.[11]

Table 1. Indole Synthesis via Domino Reaction of *N*-Arylamides and EDA[a]



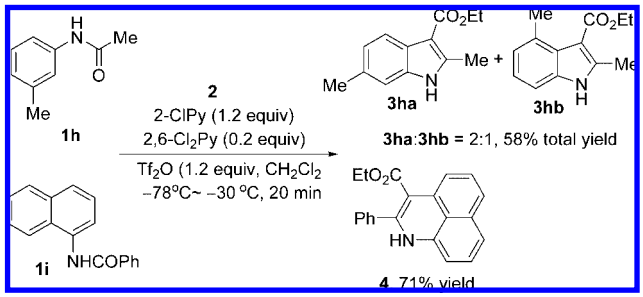
entry	amide	product	yield (%)[b]
1		**3aa** (R^2 = Ph)	52
2		**3ab** (R^2 = Tol)	49
3		**3ac** (R^2 = 4-$MeOC_6H_4$)	46
4		**3ad** (R^2 = 2-ClC_6H_4)	50
5		**3ae** (R^2 = CH_3)	58
6		**3af** (R^2 = ^{t}Bu)	82
7		**3ag** (R^2 = $CH_2CH(CH_3)_2$)	81
8		**3ah** (R^2 = $(CH_2)_4CH_3$)	70
9		**3ai** (R^2 = $^c C_6H_{11}$)	56
10		**3ba** (R^2 = Ph)	68
11		**3bb** (R^2 = CH_3)	53
12		**3bc** (R^2 = $^c C_6H_{11}$)	65
13		**3bd** (R^2 = $(CH_2)_3Cl$)	61
14		**3ca** (R^2 = Ph)	57
15		**3da** (R^2 = Ph)	61
16		**3db** (R^2 = $CH_2CH(CH_3)_2$)	84
17		**3dc** (R^2 = $^c C_6H_{11}$)	59
18		**3dd** (R^2 = $(CH_2)_3Cl$)	55
19		**3ea** (R^2 = Et)	62
20		**3fa** (R^2 = $^c C_6H_{11}$)	53
21		**3ga** (R^2 = $CH_2CH(CH_3)_2$)	59

[a] All reactions were performed on 1 mmol of amide. [b] Isolated yield refers to amide.

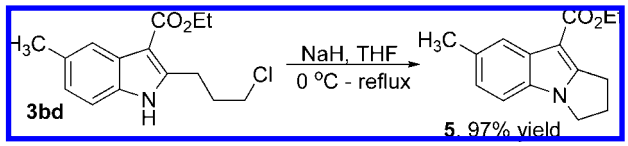
The mechanism of the domino reaction is depicted in Scheme 3. The activation of amide **1** and addition of 2-ClPy is envisioned to give a highly electrophilic 2-chloropyridinium adduct **A**,[7] which then converts to a more active electrophile **B** by a reversible exchange of 2-chloropyridinium with 2,6-Cl_2Py. **B** is then attacked by diazo anion to form a diazonium intermediate **C** followed by

10.1021/ja805706r CCC: $40.75

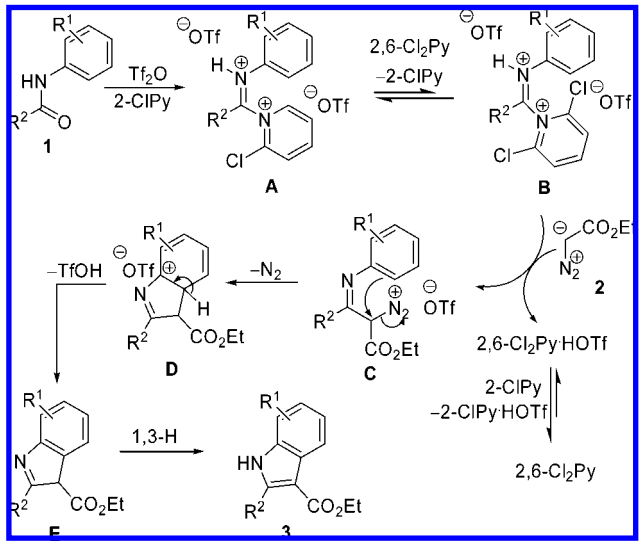
Scheme 1



Scheme 2



Scheme 3



expulsion of 2,6-Cl_2Py·TfOH. **C** undergoes an intramolecular electrophilic substitution accompanied by expulsion of N_2 and TfOH to provide **E**, which subsequently isomerizes to indole **3**. In the presence of stoichiometric 2-ClPy, the resulting 2,6-Cl_2Py·TfOH is transformed to 2,6-Cl_2Py and enters to catalysis cycle.

In summary, we have developed a general, concise, and single-step synthesis of functionalized indoles from readily available *N*-arylamides and ethyl diazoacetate. The domino approach may prove to be the most useful for the synthesis of biologically active and naturally occurring indole derivatives. Efforts are actually directed toward the extension of this methodology to natural products and drug synthesis.

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Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information files for compounds **3db**. This material is available free of charge via the Internet at http://pubs.acs.org.

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