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One-Pot Two-Step Multicomponent Process of Indole and Other Nitrogenous Heterocycles or Amines toward α-Oxo-acetamidines

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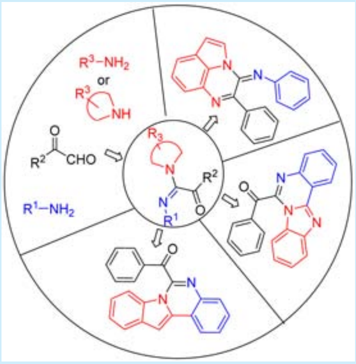
S *Supporting Information*

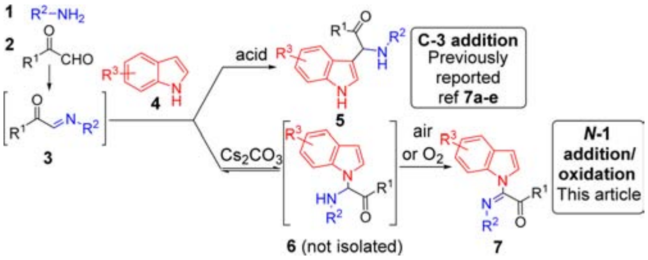
ABSTRACT: A cesium carbonate promoted three-component reaction of N−H containing heterocycles, primary or secondary amines, arylglyoxaldehydes, and anilines is reported. The key step involves a tandem sequence of *N*-1 addition of a heterocycle or an amine to preformed α-iminoketones, followed by an air- or oxygen-mediated oxidation to form α-oxo-acetamidines. The scope of the reaction is enticingly broad, and this novel methodology is applied toward the synthesis of various polycyclic heterocycles.



Nitrogenous heterocycles are present in the majority of small molecule Food and Drug Administration (FDA) approved drugs, with nearly 60% comprised of at least one nitrogen-containing heterocycle. Indoles in particular are a ubiquitous chemotype and are incorporated in 17 FDA-approved drugs.[1] Indeed, the indole architecture not only is frequently utilized in analgesics but also is present in a diverse set of natural products (e.g., alkaloids), essential amino acids (e.g., tryptophan), and the neurotransmitter serotonin.[1,2] Due to its biological significance, indole is often considered a privileged motif in medicinal chemistry and as part of tryptophan is the most prevalent "hot spot" in mediating protein−protein interactions.[3] As such, this has led to increasing numbers of new chemical methodologies designed to enhance the occurrence of the indole scaffold in corporate compound collections for biological interrogation.[4]

Over the past 20 years multicomponent reactions (MCRs),[5,6] which generate products from 3 or more starting materials in one pot, have been heavily exploited to expeditiously garner new heterocyclic ring systems in processes that are high in atom-economy, affording molecules with inherent high iterative efficiency potential for exploitation in the drug discovery arena.[7] In regard to indole-based MCRs, the well established electrophilic substitution at the C-3 position of indole with preformed Schiff bases **3**, derived from amines **1** and aryl glyoxaldehydes **2**, has been widely exploited to access compounds of generic structure **5** (Scheme 1)[8] whereas *N*-1 indole reactivity remains largely unexplored beyond simple alkyl halide alkylations. Given our interest in the development of novel MCRs and new molecular diversity via subsequent product manipulation[9] and initially inspired by the extensively studied indole C-3 Friedel−Craft alkylation of preformed Schiff bases between anilines **1** and aryl glyoxaldehydes **2**, we envisioned a one-pot MCR where the *N*-1 indole position could feasibly interact with α-imino-ketones to access compounds of generic structure **6**. Herein, we describe formation of chemotype **7** in expected (*E*)-stereoselective fashion and more importantly expand on this concept to other heterocycles and amines in general, Scheme 2, ultimately using post-MCR modifications to afford a suite of novel polycyclic scaffolds. To the best of our knowledge, this is the first report of general base promoted oxidative C_{sp^2}−N bond formation between the N-H of azoles (e.g., indoles, benzimidazoles, and pyrazoles) or amines with α-iminoketones.[10]

Scheme 1. Exploring the *N*-1 Reactivity of Indole



Extensive optimization studies were conducted to evaluate the effect of solvents, bases, additives, stoichiometry, and temperatures (Tables S1−S5, Supporting Information (SI)) on

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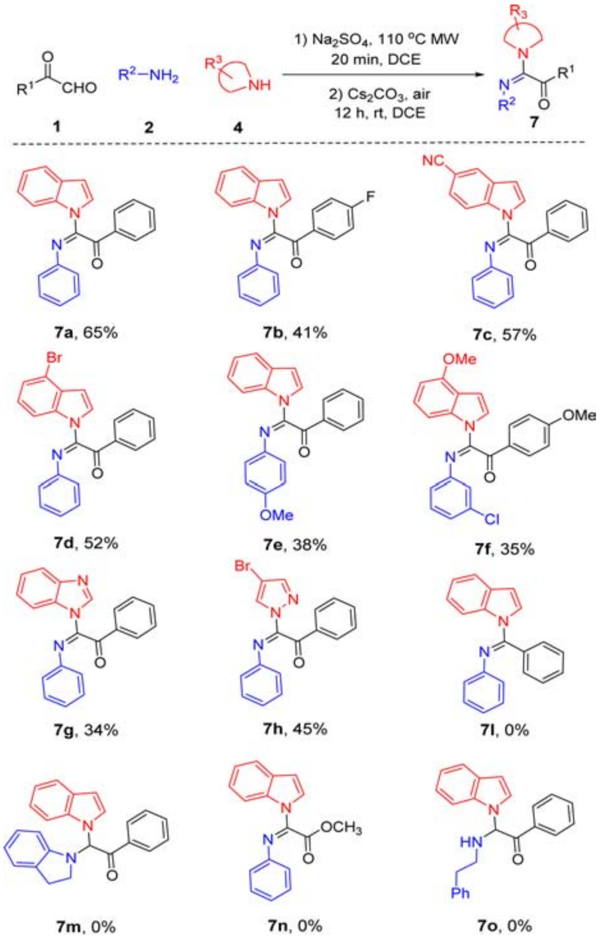
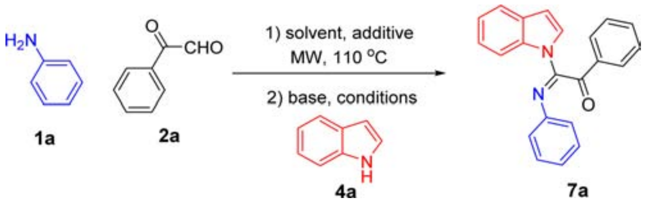
Scheme 2. Multicomponent Reaction between Arylglyoxaldehyes, Anilines, and *NH*-Containing Heterocycles



the model reaction, and select results are shown in Table 1. Polar aprotic solvents were found to be optimal, dichloroethane proving most advantageous with acetonitrile being a reasonable alternative (entries 1 and 2, Table 1). Cs_2CO_3 proved to be the most effective base for the transformation, and notably, Na_2CO_3 and K_2CO_3 (entries 4 and 5, Table 1) were significantly inferior, possibly exemplifying the well-documented "cesium-effect".[11] Final oxidation of the intermediate MCR product **6**, Scheme 1, required reaction exposure to air, and predictably similar yields of **7a** were observed under an atmosphere of oxygen (entries 8 and 9), both in the presence of Na_2SO_4 to promote more effective Schiff base formation through sequestration of water. The latter proved the most optimal water scavenger (Table S3, SI). As expected, final product formation of **7a** was not observed during reaction under an inert atmosphere and only starting material was recovered suggesting a reversible process (entry 10, Table 1). Moreover, intermediate **6** (Scheme 1) was never isolated during these studies due to its rapid oxidation to **7**.

Table 1. Optimization of Reaction Conditions



entry	solvent	base	additive	yield 7a[a] [%]
1	DCE	Cs_2CO_3	air	66
2	MeCN	Cs_2CO_3	air	63
3	MeOH	Cs_2CO_3	air	0
4	DCE	K_2CO_3	air	37
5	DCE	Na_2CO_3	air	3
6	DCE	TEA	air	0
7	DCE	DBU	air	57
8	DCE	Cs_2CO_3	Na_2SO_4, air	75
9	DCE	Cs_2CO_3	Na_2SO_4, O_2	73[b]
10	DCE	Cs_2CO_3	Na_2SO_4, N_2	0

[a] Optimization reactions were performed on a 0.25 mmol scale at rt for 12 h. Reported % yields are "Area under the Curve" yields of desired product (A%) as judged by LC/MS at UV 254 nm. [b] Under an oxygen atmosphere (1 atm, balloon), the reaction was carried out at rt for 3 h.

Exploration of the reaction scope showed versatility and some robustness among indole substituents, Scheme 2. For example, electron-withdrawing groups were well tolerated (57% **7c**, 52% **7d**) and moderate decreases in yield were observed with electron-donating groups (**7f**). Remarkably, the reaction proceeded in similar fashion with other heterocyclic rings and amines, **4**, allowing the establishment of the broader generic reaction depicted in Scheme 2. Thus, both benzimidazoles and pyrazoles afforded a final product in reasonable yield under conditions originally optimized for an indole (**7g** and **7h**, Scheme 2). Introducing electron-donating (38%, **7e**) and -withdrawing groups (35%, **7f**) on the aromatic ring of the aniline afforded product in modest yields, in similar fashion to modulation of electron density on the aromatic ring of the arylglyoxaldehyde (41%, **7b** and 35%, **7f**). Use of indoline (**7m**), where final oxidation is prohibited, or phenethylamine as aniline replacements and either benzaldehyde or methyl glyoxylate as an arylglyoxaldehyde replacement, delivered no identifiable stable products (**7l**, **7n**, **7o**, Scheme 2). These observations suggest that the C═N bond is promoted through the stabilizing effect of adjacent aromaticity via enhanced conjugation. The structure of **7d** was confirmed via X-ray crystallography (Figure 1).[12]

Gratifyingly, the formation of α-oxo-acetamidines **9** (Scheme 3) was also observed during initial stoichiometry studies on this reaction when using excess aniline **1a** (>1.3 equiv) (Table S4, Supporting Information), leading to the realization that anilines and other amines were also effective nucleophiles in sequestering the α-imino-ketone **3**. Six examples with generic

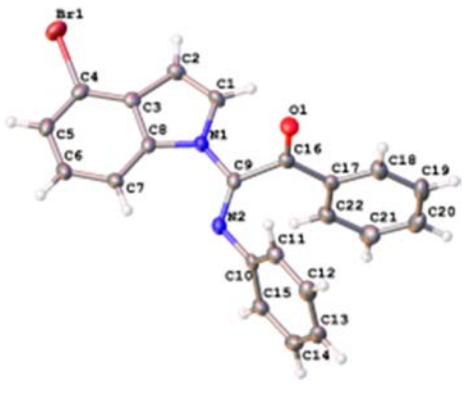
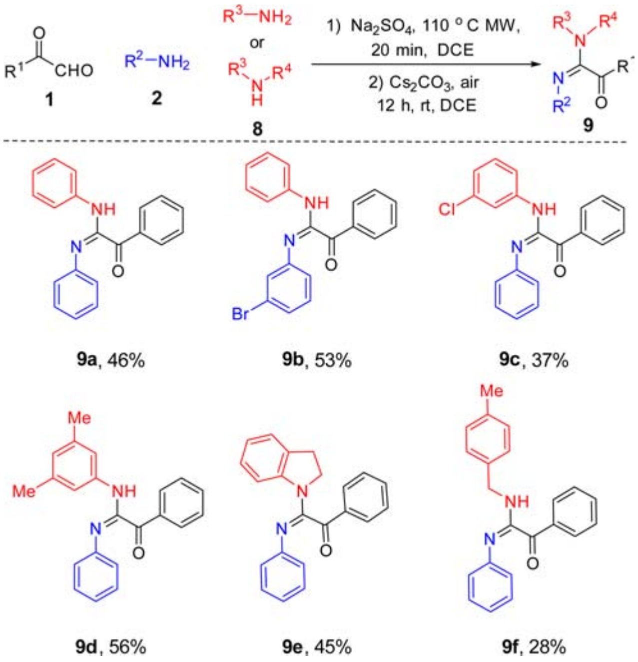


Figure 1. X-ray ORTEP diagram at 50% of probability of **7d**.[12]

Scheme 3. Replacement of Heterocycles for Amines in the MCR



structure **9** were thus prepared, spanning the anilines (**9a–d**), indoline (**9e**), and aliphatic amines (**9f**) (Scheme 3). X-ray crystallography confirmed the structure of **9e** (Figure 2),[12] and remarkably a literature search of product **9** showed this product to have only two-reported syntheses,[13] with neither using mild or metal-free conditions.

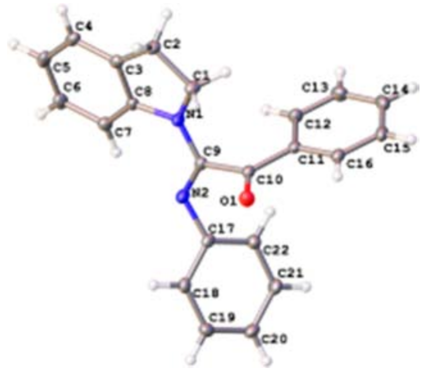
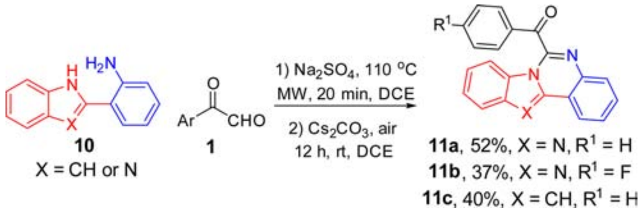


Figure 2. X-ray ORTEP diagram at 50% of probability of **9e**.[12]

At this stage, with a highly generic and fundamentally simple transformation in place, studies focused on methods to deliver additional rigidification of these products. Thus, we employed reagents containing the indole or benzimidazole motif coupled to the aniline motif in the same molecule (**10**), a strategy previously coined the "bifunctional approach" toward rigidification of MCR products.[14] This approach led to the synthesis of benzimidazole[1,2-*c*]quinazolines and indole[1,2-*c*]-quinazolines (**11a–c**, Scheme 4) in good yields (37–52%) and one pot. Interestingly, these scaffolds have been reported to possess antimicrobial activity.[15] Additionally, the use of an *N*-Boc protected 7-amino-indole **13** enabled a facile three-step one-pot synthesis of the stable, novel pyrrolo-quinoxaline imine **15** in moderate yield (32%) (Scheme 5).

Scheme 4. Synthesis of Tetracyclic Chemotypes Using a Bifunctional Approach



Scheme 5. Synthesis of Tricyclic Scaffolds Using an MCR–Deprotection–Cyclization Approach

In summary, a diverse suite of one-pot multicomponent transformations have been developed, unveiling the underexplored *N*-1 reactivity of common heterocycles and primary and secondary amines to access *α*-oxo-acetamidines with generic structures **7** and **9**. This new reaction was subsequently utilized to prepare benzimidazole[1,2-*c*]quinazolines (**11a–b**), indole-[1,2-*c*]quinazolines (**11c**), and the fused pyrrolo-quinoxaline (**15**), delivered in less than three steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00634.

> Complete tables of optimization of reaction conditions; general procedures for the synthesis of **7**, **9**, **11**, **13**, and **15**; and ^{1}H and ^{13}C NMR spectra (PDF)
> X-ray CIF file for compound **7d** (CIF)
> X-ray CIF file for compound **9e** (CIF)

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Notes

The authors declare no competing financial interest.

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