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Three-Component Synthesis of Polysubstituted 6-Azaindolines and Its Tricyclic Derivatives

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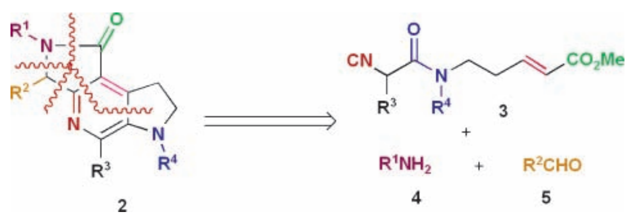
ABSTRACT



By simply heating a toluene solution of isocyanoacetamide (3), amine (4), and aldehyde (5), a clean three-component reaction occurred to provide the pyrrolidinone-fused azaindoline (2). In this multicomponent reaction, the isocyanoacetamide (3) reacted four times in a highly ordered manner creating three heterocylic rings with the concurrent formation of five chemical bonds and a minimal loss of molecular weight. Heating is the only external energy required to promote this powerful complexity-generating MCR.

The synthesis of functionalized indoles and indolines has been of interest to organic chemists for many years due to the presence of these structural units in a variety of biologically active natural products[1] and medicinally relevant compounds.[2] Numerous elegant methods have continuously been developed to reach this important bicyclic skeleton over the years.[3] Incorporation of an additional basic nitrogen atom into the indole derivatives are known to not only enlarge the SAR studies of parent compounds but also induce a different physical[4] and pharmacological profile.[5] Therefore, azaindoles and azaindolines are attractive scaffolds in medicinal chemistry[6] and various synthetic methods, including ionic,[7] radical,[8] and transition-metal-catalyzed processes,[9] photocyclization,[10] and cycloaddition,[11] have been developed. A recent zirconcene-mediated coupling of silicon-tethered diyne and nitrile developed by Xi and co-workers is noteworthy since the bicyclic ring system of 5-azaindole is constructed in a single step from the linear starting materials.[12]

In continuation of our research program aimed at the development of multicomponent synthesis of polyheterocycles,[13] we report herein a three-component synthesis of

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6-azaindoline (**1**) and its tricyclic derivative (**2**) from a readily accessible linear precursor.[14] Key to the present approach is the design and use of a densely functionalized isocyanoacetamide[15] whose functional groups, isonitrile, amide, double bond, and ester, participated in the reaction sequentially and in a highly ordered manner to provide **1** and **2** in good yield (Figure 1).

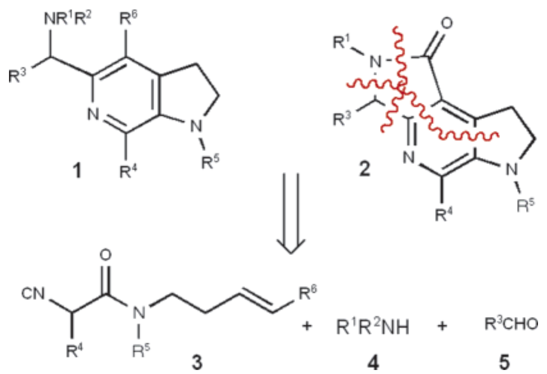
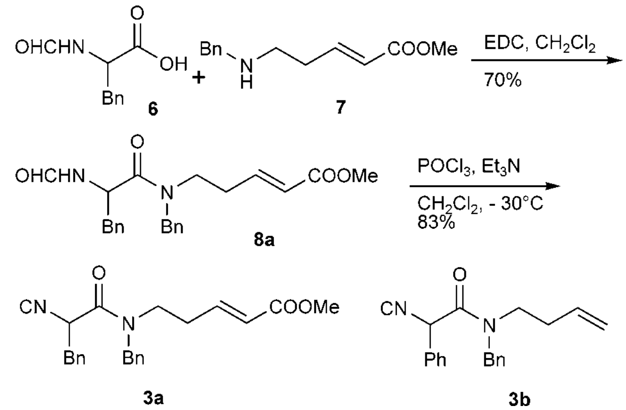


Figure 1. 6-Azaindoline and its tricyclic derivative: structure and synthesis strategy.

The previously unknown α-substituted α-isocyanoacetamide (**3a**) is synthesized as shown in Scheme 1. Coupling of *N*-formyl phenylalanine (**6**) with 5-benzylamino-2-pentenoate (**7**)[16] in the presence of EDC in dichloromethane gave the amide **8a**, which was dehydrated ($POCl_3$, Et_3N, CH_2Cl_2) to give the desired isonitrile **3a** in 58% overall yield. Compound **3b** containing an electronically neutral double bond was prepared similarly from *N*-formyl-phenylglycine and 5-benzylamino-1-pentene.

Scheme 1. Synthesis of Isocyanoacetamides **3a** and **3b**



Using isocyanoacetamide **3a**, morpholine **4a**, and heptanal **5a** as test substrates (Scheme 2), we performed a survey of reaction conditions; the results are summarized in Table 1. When the reaction was carried out in MeOH at room temperature, oxazole **9a** was isolated in 88% yield (entry 1).[17] However, when the toluene solution was heated to reflux, the desired 6-azaindoline **1a** was isolated in 61% yield (entry 2). Addition of ammonium chloride[18] and camphorsulfonic acid[19] did not improve the product yield (entries 6

Scheme 2. Three-Component Synthesis of 6-Azaindoline

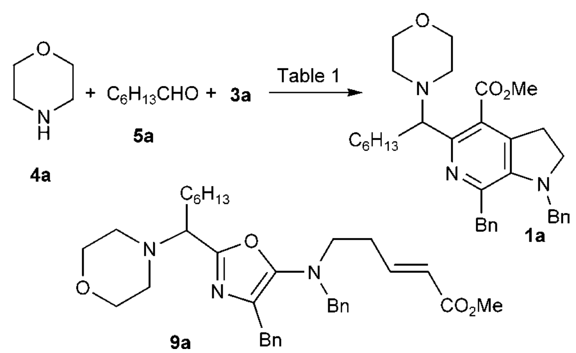


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Table 1. Three-Component Synthesis of Azaindoline **1a**, a Survey of Conditions[a]

entry	solvent	additive	yield[e] [%]
1	MeOH[b]		(88[f])
2	toluene		61
3	*o*-xylène		50
4	DMSO[c]		21
5	toluene	LiBr	21(41[f])
6	toluene	NH_4Cl	63
7	toluene	SiO_2	(63[f])
8	toluene	CSA[d]	60

[a] Concentration = 0.1 M; additive = 1.0 equiv; room temperature for 1 h followed by reflux for 15 h. [b] Room temperature, 2 h. [c] T = 110 °C. [d] Performed with 0.5 equiv of CSA. [e] Isolated yield. [f] Yield of oxazole **9a**; CSA = camphorsulfonic acid; LiBr = lithium bromide; NH_4Cl = ammonium chloride.

and 8), while the presence of lithium bromide[20] and silica gel has a detrimental effect on the reaction outcome (entries 5 and 7). The reaction performed in the polar solvent DMSO at 110 °C did produce **1a**, but with much reduced yield (entry 4).

Using a primary amine ($C_4H_9NH_2$, **4d**) as an input, a tricyclic compound **2a** was obtained in 54% yield under optimum conditions (toluene, *c* 0.1 M, room temperature for 1 h and then reflux for 15 h). The reaction appears to be general, and tricyclic compounds **2a**−**e** were obtained in good yields from all the primary amines used, including aniline (Figure 3).

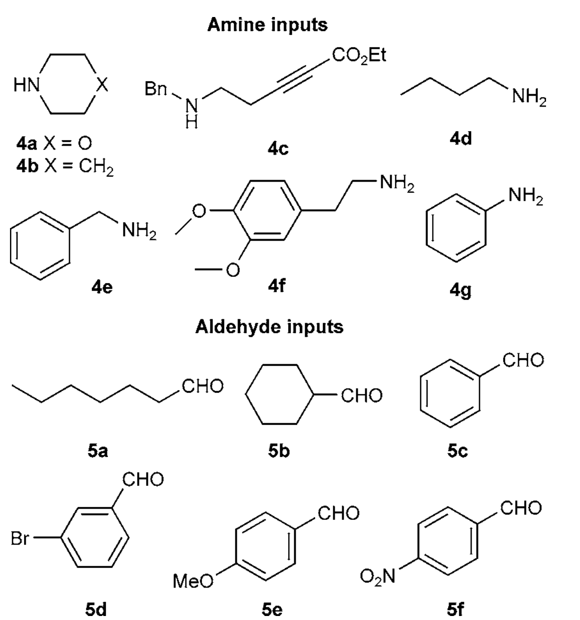

Figure 2. Amine and aldehyde inputs used for three-component reaction.

A possible reaction sequence that accounts for the formation of 6-azaindoline **1** and its pyrrolidinone-fused derivative

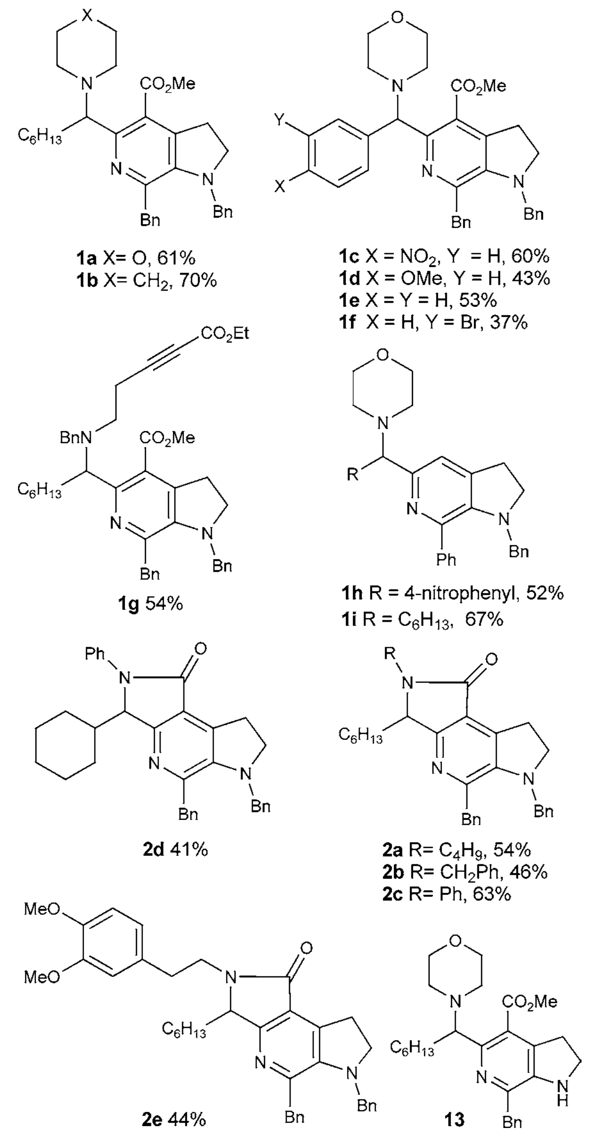

Figure 3. Three-component synthesis of 6-azaindolines and its tricyclic derivatives. In the cases of **1h** and **1i**, *o*-xylene was used as the solvent (room temperature, 1 h, then reflux, 15 h).

2 is depicted in Scheme 3. A three-component reaction between amine, aldehyde, and isocyanide is expected to provide the oxazole **9** via an ininium (**10**) and then a nitrilium (**11**) intermediate according to our previous results.[17] The isolation of oxazole **9a** supported this hypothesis. We stress that under these conditions, Michael addition between amine and the enoate moiety of isocyanoacetamide (**3a**) did not occur that could otherwise interrupt the entire reaction sequence. The condensation between amine and aldehyde is apparently a much faster process or thermodynamically more favorable over the undesired Michael addition in this circumstance. Interception of the resultant oxazole by the tethered

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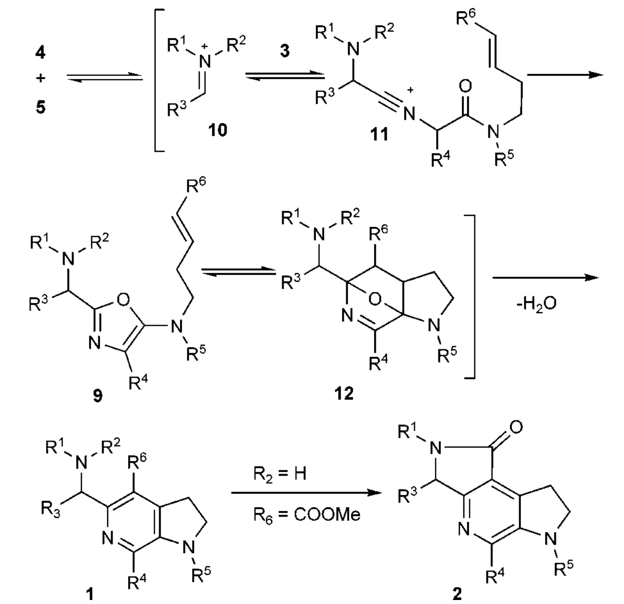
Scheme 3. Three-Component Synthesis of **1** and **2**: A Mechanistic Working Hypothesis



dienophile via an intramolecular Diels−Alder (D−A) cycloaddition[21] should then afford the oxa-bridged intermediate, which would undergo nitrogen-assisted fragmentation leading to azaindoline (**1**). When primary amine was used as an input, a further intramolecular transamidation (R_6 = COOMe) took place to afford the tricyclic compound (**2**). The intermediate **12** was not isolable, indicating that the fragmentation is an easy process in this case. This final irreversible step might provide the driving force to the overall process.

The scope of this novel multicomponent reaction is examined with various inputs, including two isocyano acetamides (Scheme 1), seven representative amines, and six aldehydes (Figure 2). As is indicated in Figure 3, this MCR was quite versatile and 6-azaindolines (**1a**−**i**) as well as its tricyclic derivatives (**2a**−**e**) having different substitution patterns were readily synthesized in good yield. Both aliphatic and aromatic aldehydes having different steric and electronic properties were tolerated, and aliphatic amines as well as anilines participated in this reaction. Importantly, the electronically neutral double bond of isonitrile **3b** acted as a dienophile efficiently leading to the formation of **1h** and **1i**, although higher temperature (xylene, reflux) was necessary to accelerate the cycloaddition process. On the other hand, when aminopentynoate (**4c**) was used as an amine input, two potential Diels−Alder reactions could occur leading to two different heterocycles. However, only azaindoline **1g** was isolated in this case.

The *N*-benzyl function of azaindoline **1** and **2** is readily removed. Thus, treatment of **1a** under standard hydrogenolysis conditions [H_2, 1 atm, $Pd(OH)_2$, EtOH) provided the N_a-unsubstituted azaindoline **13** (Figure 3) in 83% yield. The presence of the ester and amine functions in **13** provided handles for additional structural diversification.

In summary, by the proper design of the reaction partners, we have developed a novel, very convenient, and conceptually simple multicomponent synthesis of polysubstituted 6-azaindoline **1** and its tricyclic derivative **2**. Initiated by the nucleophilic addition of the isonitrile carbon to the iminium species, four functional groups of isocyanoacetamide **3a** participated in the bond-forming process at different stages, and heating is the only external energy required to promote this powerful MCR that generates five chemical bonds in a one-pot fashion. We emphasize also that only two molecules of water were lost on the way to azaindoline **1**, making it both ecologically benign and atom-economic.[22,23]

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Supporting Information Available: Experimental details and physical data for compounds **1a**−**i**, **2a**−**e**, **3a**, **3b**, **8a**, **8b**, **9a**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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