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Synthesis of Oxindolyl Pyrazolines and 3-Amino Oxindole Building Blocks *via* a Nitrile Imine [3 + 2] Cycloaddition Strategy

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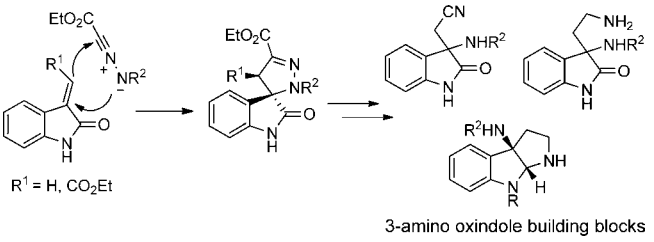
ABSTRACT



The [3 + 2] dipolar cycloaddition reaction of nitrile imines with 3-alkylidene oxindoles is described. The pyrazoline spiroadducts were obtained in high yields and with excellent regio- and diastereoselectivities. These spirocyclic intermediates have been elaborated to synthetically versatile 3-amino oxindole building blocks such as β-amino nitrile, 1,3-diamine, and pyrrolo[2,3-*b*]indoline derivatives.

Substituted oxindole-based scaffolds represent a large family of compounds that have been the subject of synthetic interest owing to their medicinal promise and overall versatility as natural product building blocks.[1] Our laboratory has been involved in the synthesis of oxindole-based spirocyclic molecules generated *via* a [3 + 2] cycloaddition reaction using nitrile oxide dipoles.[2,3] Herein, we present results from our ongoing method development program highlighting the first reported cycloaddition of nitrile imines with 3-alkylidene-oxindole dienophiles. We were interested in exploring the isosteric equivalency of nitrile oxides to nitrile imines as an opportunity to establish efficient synthesis of novel pyrazolines and studying their synthetic applications. The prevalence of the pyrazoline scaffold in bioactive molecules has also sparked interest.[4] Our objective was to demonstrate the efficient synthesis of novel oxindole-based spirocyclic derivatives with subsequent elaboration to 3,3-amino-disubstituted oxindole and pyrrolo[2,3-*b*]indoline-based scaffolds.

Having established a convenient, practical, and scalable cycloaddition toward 3-hydroxy-disubstituted oxindoles using nitrile oxides,[2] we next explored the application of nitrile imines as the dipole component of the cycloaddition reaction.[5] We envisioned a conceptually distinct synthesis

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of the 3-amino-oxindole moiety wherein a nucleophilic nitrogen equivalent is employed. Although the 3-amino-oxindole substructure is found in natural products and non-natural small molecules of therapeutic interest, a limited number of methods exist for their synthesis. Moreover, reported methods for the 3-amination of oxindoles employ an electrophilic vs a nucleophilic nitrogen source (Figure 1).[6]

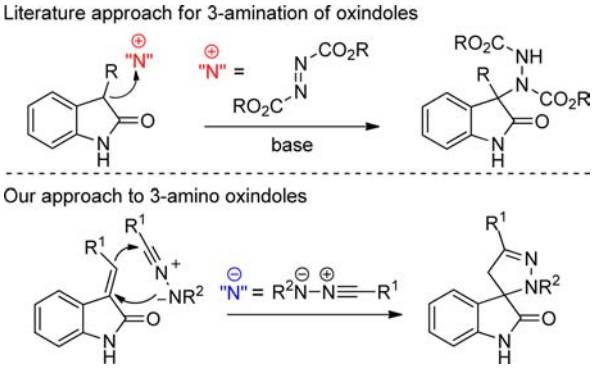
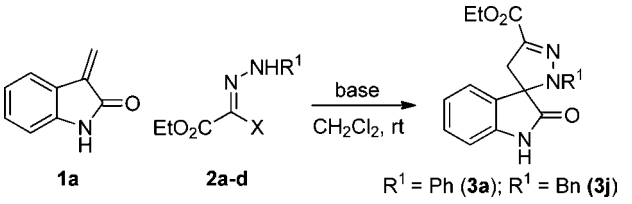


Figure 1. Approaches to 3-amino oxindoles.

Preliminary investigations revealed that the nature of the nitrile imine precursor had a profound effect on the reaction outcome (Table 1). When the chloro substrate **2a** was employed with Et_3N as the base, modest yields of the desired product were obtained albeit in a regioselective manner. The use of biphasic conditions using $NaHCO_3$ or K_2CO_3 failed to induce reactivity due to the inability of these bases to generate the nitrile imine. This result indicated that the dehydrohalogenation of hydrazonoyl chlorides is less facile than hydroxyiminoyl chlorides (precursors to nitrile oxides). In order to facilitate the generation of the nitrile imine, we evaluated the corresponding bromo substrate **2b** and were pleased to observe that the pyrazoline products were obtained in high yield.[7] The *N*-benzyl nitrile imine also displayed a similar reactivity profile (Table 1, entries 5 and 6). As shown in Table 1, only 2 equiv of the nitrile imine are needed to achieve an efficient cycloaddition.

The nitrile-imine cycloadditions were found to be very general as depicted in Table 2. A variety of electronically distinct 3-methylene-oxindoles underwent efficient cycloaddition to afford spiro-pyrazolines in excellent yields and regioselectivities. Substitutions at all possible positions of the oxindole were well tolerated. An experiment performed on a 1 g scale to prepare pyrazoline **3a** resulted in an 87% yield. The ability to use *N*-Bn nitrile imine (Table 2 entry 10) will allow the generation of orthogonally protected diamines.

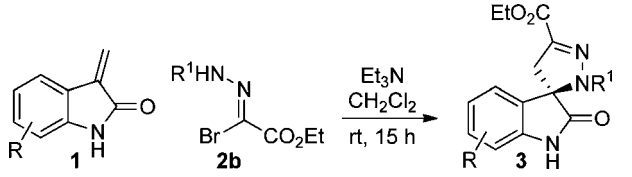
Table 1. Nitrile Imine Cycloaddition: Reaction Optimization



entry	dipole equiv	X	R^1	base	yield[a] (%)
1	2	Cl	Ph (**2a**)	Et_3N	58
2	2	Cl	Ph (**2a**)	$NaHCO_3$	no reaction
3	2,3	Br	Ph (**2b**)	Et_3N	93,94
4	2,3	Br	Ph (**2b**)	$NaHCO_3$	81,86
5	2	Cl	Bn (**2c**)	Et_3N	23
6	2	Br	Bn (**2d**)	Et_3N	85

[a] Isolated yields.

Table 2. [3 + 2] Dipolar Cycloadditions of Nitrile Imines to 3-Methylene Oxindoles: Reaction Scope



entry	R	R^1	product	yield[a] (%)	rr[b]
1	H	Ph	**3a**	93	>20:1
2	4-Br	Ph	**3b**	89	>20:1
3	5-F	Ph	**3c**	82	>20:1
4	5-OMe	Ph	**3d**	85	>20:1
5	5-OCF_3	Ph	**3e**	86	>20:1
6	6-Br	Ph	**3f**	90	>20:1
7	6-Cl	Ph	**3g**	89	>20:1
8	7-F	Ph	**3h**	94	>20:1
9	4,6-di-Br	Ph	**3i**	81	>20:1
10	H	Bn	**3j**	86	>20:1

[a] Isolated yields. [b] Regioisomer ratios (rr) were measured using ^1H NMR.

Extending this reaction to substituted alkenyl oxindoles will provide access to more densely functionalized pyrazolines and also afford insight into the regio- and stereoselectivity of the cycloaddition reaction.[8] As shown in Table 3, it was found that a variety of substituted 3-alkenyl

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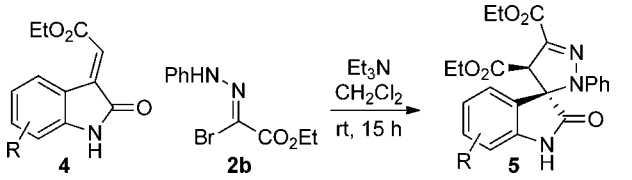
oxindoles (**4**) underwent smooth cycloaddition with nitrile imine precursor **2b**. The regioselectivity of the reaction was maintained, and the resulting adducts were obtained as single diastereomers. The identity of the stereoisomer obtained was confirmed by X-ray diffraction analysis of derivative **5g** (Table 3).

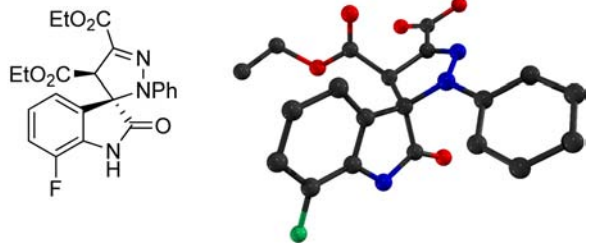
Table 3. [3 + 2] Cycloadditions of Nitrile Imines to 3-Alkylidene Oxindoles: Reaction Scope



entry	R	product	yield[a] (%)	rr[b]
1	H	**5a**	91	>20:1
2	5-Br	**5b**	83	>20:1
3	5-F	**5c**	86	>20:1
4	5-Cl	**5d**	84	>20:1
5	6-Br	**5e**	90	>20:1
6	6-Cl	**5f**	81	>20:1
7	7-F	**5g**	84	>20:1
8	7-Cl	**5h**	88	>20:1

[a] Isolated yields. [b] Regioisomer ratios (rr) were measured using ^{1}H NMR.

Crystal structure of derivative **5g**



Having established convenient methods for the synthesis of novel oxindolyl pyrazolines, we sought to functionalize these spirocycles to generate molecular building blocks. Although pyrazolines have similar bonding attributes to isoxazolines, the use of pyrazolines as synthetic intermediates is rare, primarily owing to the significantly stronger N−N bond (compared to the N−O bond in isoxazolines).[9] We planned to demonstrate that access to pyrazolines could also be leveraged for the generation of useful oxindole building blocks.

As shown in Scheme 1, pyrazolines **3a**−**c** can be cleaved to afford substituted aminonitriles after ester hydrolysis and subsequent thermal elimination of carbon dioxide.

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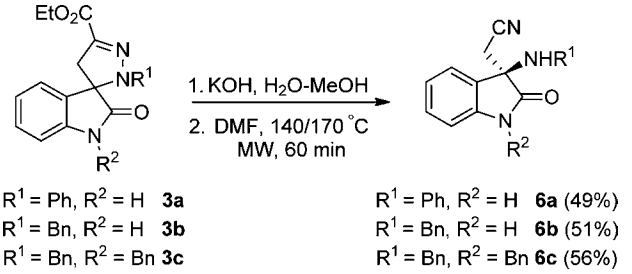
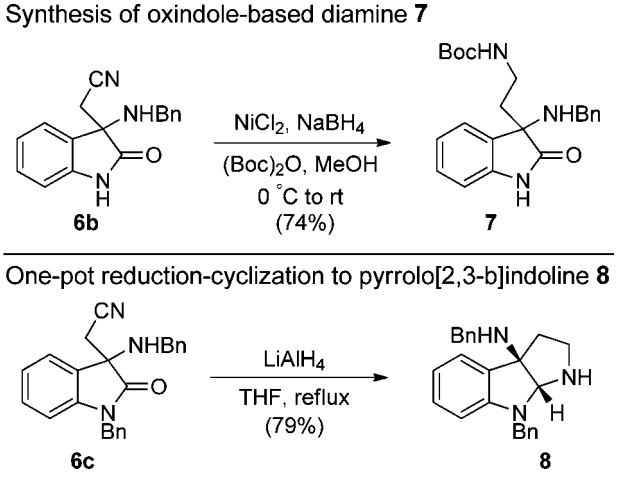
Compared to our previous studies with analogous isoxazolines, the ring opening of pyrazolines proceeded at significantly higher temperatures. We observed that pyrazolines with a *N*-Bn group (**6b** and **6c**) could be successfully cleaved at lower temperatures than **6a** which contains a *N*-Ph moiety.

Scheme 1. Decarboxylative Ring Opening of Pyrazolines to Aminonitriles **6a**−**c**



Scheme 2. Elaboration of Amino Nitriles to 1,3-Diamine **7** and Pyrrolo[2,3-*b*]indoline **8**



The nitrile moiety offers opportunities to employ stepwise reduction to generate 3-amino-3-alkyl oxindole derivatives.[10] In order to access orthogonally protected 1,3-diamines, the β-amino nitrile derivative **6b** was subjected to a $NiCl_2/NaBH_4$ reduction protocol (Scheme 2). The resulting primary amine could be concomitantly protected as the carbamate by performing the reaction in the presence of $(Boc)_2O$. By employing more aggressive reduction conditions, the generation of amino substituted pyrrolo[2,3-*b*]indoline derivative **8** was accomplished by performing a one-pot reductive cyclization. Treatment of amino nitrile **6c** with lithium aluminum hydride in refluxing THF afforded the tricyclic derivative in 79% yield. These 3-amino oxindole derivatives generated from spirocyclic

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pyrazolines represent substructures of natural products and bioactive synthetic molecules that are of current interest to the scientific community.[11] Additionally, they are versatile synthetic building blocks that can be transformed into a plethora of motifs that will enrich the chemical space relevant to medicinal chemistry research.

In summary, nitrile imines were employed in a [3 + 2] cycloaddition reaction with 3-alkylidene oxindoles to generate novel oxindole-based spiro-pyrazolines. The cycloadditions were regio- and diastereoselective, affording adducts in high yields. Application of these heterocycles toward generating a variety of 3-amino oxindole-derived synthetic building blocks was demonstrated. Studies are underway to expand the utility of this method for the efficient synthesis of complex molecular architectures.

Acknowledgment. We thank SBMRI for financial support to GPR, Dr. Maren Pink (Indiana University) for determining the crystal structure of **5g**, and Dr. David Terry (SBMRI) for obtaining accurate mass data.

Supporting Information Available. Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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