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A [3 + 2] Dipolar Cycloaddition Route to 3-Hydroxy-3-alkyl Oxindoles: An Approach to Pyrrolidinoindoline Alkaloids

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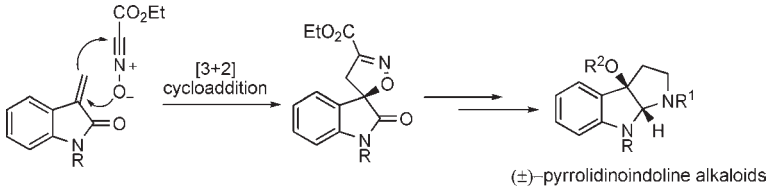
ABSTRACT



A [3 + 2] cycloaddition approach to the 3-hydroxy-3-alkyl oxindole scaffold is described. Isoxazolines obtained by cycloaddition of nitrile oxide 3 with 3-methylene oxindoles were elaborated to 3-hydroxy-3-cyanomethyl oxindoles employing a one-pot protocol en route to the pyrrolidinoindoline moiety which is found in many natural products. The total syntheses of alkaloids (±)-alline and (±)-CPC-1 were achieved using this methodology.

Oxindole-based molecules are ubiquitous in the realm of natural products and pharmaceuticals. A significant subset of these compounds contains the spirooxindole[1] and the 3-hydroxy-3-alkyl-oxindole moieties. Such motifs represent the substructures of many natural products which have garnered interest owing to their wide spectrum of biological activities including antioxidant, anticancer, and neuroprotective properties (Figure 1).[2] Additionally, a remarkable array of bioactive scaffolds can be generated from these molecules,

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and consequently, they have been the subject of numerous drug discovery programs in addition to being employed as valuable synthetic intermediates.[3] Although aza-spirooxindoles have inspired many studies, the structural diversity and approaches toward oxygen containing spirooxindoles remain limited. Synthetic efforts toward the 3-hydroxy-3-alkyl-2-oxindole scaffold focus on arylation and allylation of isatin[4] en route to the constituent natural products and medicinally relevant compounds. Efficient access to synthetic alternatives that can provide additional functional diversity would represent an advance over the aforementioned methods. We report a [3 + 2] dipolar cycloaddition reaction between 3-methylene oxindoles and nitrile oxides as a unified approach toward novel spirocyclic isoxazolines and 3-alkyl-3-hydroxy oxindole derivatives. The versatility of these intermediates was demonstrated by their elaboration to the tricyclic pyrrolidinoindoline natural products (±)-alline and (±)-CPC-1 in order to explore their bioactivity.

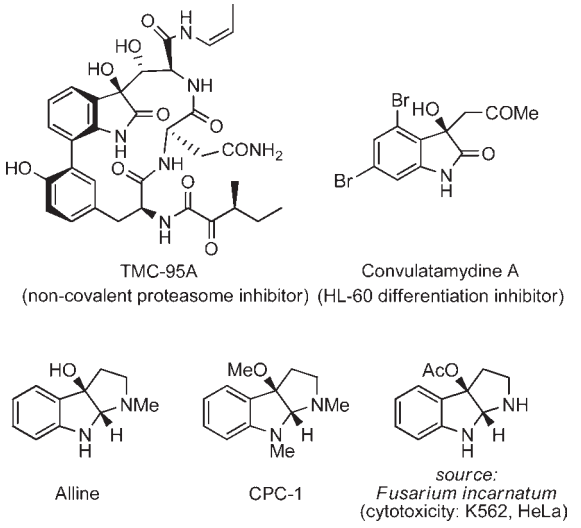

Figure 1. Examples of natural products containing (or derived from) 3-alkyl-3-hydroxy oxindoles.

3-Methylene oxindoles are valuable building blocks; however their use has been sporadic in the literature, presumably due to their relative instability.[5,6] We envisioned that another substantially reactive species, such as the nitrile oxides, would be ideal reaction partners, and we could achieve fruitful reactivity between them. Our objective was to harness their reactivity in a productive manner and couple it with the chemistry of isoxazolines in order to furnish functionalized, versatile intermediates with brevity.[7]

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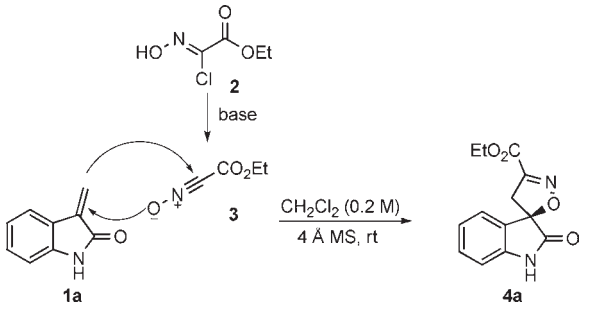
Treatment of 3-methylene oxindole with the *in situ* generated nitrile oxide **3** demonstrated that the desired product could be isolated as a single regioisomer, albeit in low yield. Investigation into the nature of the base indicated that the reaction provided the best results when the dipole species was generated with a basic resin (Amberlyst A21) and introduced directly into the reaction as a solution in dichloromethane (Table 1).[8] Due to the propensity of the dipole to dimerize, it was necessary to employ an excess (3 equiv) to achieve good yields. The addition of copper salts decreased the yield presumably by causing the decomposition of the oxindole. The cycloaddition reaction was highly regioselective (>20:1), affording the desired product in good yield. The regiochemistry of carbon−carbon bond formation was unambiguously proved through single crystal X-ray diffraction of a derivative obtained *via* hydrogenolysis (Figure 2).

Table 1. Optimization of the [3 + 2] Cycloaddition Reaction



entry[a]	dipole eqiv	base	time[b] (h)	yield[c] (%)
1	1	TBAF	5	0
2	1	Et_3N	5	10
3	1	DIPEA	5	15
4	1	Pyridine	5	13
5	1	Amberlyst A21	5	28
6	2	Amberlyst A21	5	49
7	2	Amberlyst A21	15	66
8	3	Amberlyst A21	15	80

[a] For entries 3−6, a solution of the dipole precursor was added to the reaction through a syringe filled with the basic resin. [b] Reaction time after the addition of the dipole. [c] Isolated yields. The other regioisomer was not detected by ^{1}H NMR.

Table 2 illustrates the scope of the cycloaddition reaction. A variety of substituted 3-methylene oxindoles underwent smooth cycloaddition to afford spiroadducts in good yields. Substitutions at the 5, 6, or 7 positions did not impact the reactivity and/or regioselectivity. Both electron-rich and -deficient oxindoles were well tolerated. In the case of the 7-iodo derivative, the lower yield is at least in part due to the instability of the dipolarophile. While the applicability of the unsubstituted *N*-H oxindoles is a positive outcome, we confirmed that the corresponding

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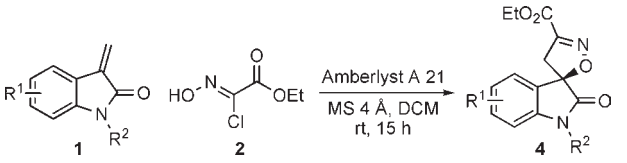
N-methyl dipolarophile also underwent the cycloaddition in a facile manner.

Table 2. Reaction Scope: Electronically Distinct Dipolarophiles in the Cycloaddition Reaction



entry	R^1		R^2	yield[a] (%)	regioselectivity[b]
1	H	**a**	H	80	>20:1
2	5-CI	**b**	H	79	>20:1
3	5-OMe	**c**	H	76	>20:1
4	5-Me	**d**	H	82	>20:1
5	5-F	**e**	H	84	>20:1
6	5-OCF_3	**f**	H	79	>20:1
7	6-Br	**g**	H	77	>20:1
8	7-Br	**h**	H	66	>20:1
9	7-I	**i**	H	50	>20:1
10	7-Ph	**j**	H	83	>20:1
11	7-CI	**k**	H	81	>20:1
12	H	**l**	Me	81	>20:1

[a] Isolated yields after column chromatography. [b] Regioisomer ratios were measured using ^{1}H NMR. All reactions performed at 0.2 M. See Supporting Information for details.

We initially envisioned elaborating the isoxazolines to two scaffolds, namely β-hydroxynitriles (available by decarboxylation/elimination) and the corresponding amino alcohols (*via* reduction). While several reduction protocols have been developed for the reduction of unfunctionalized isoxazolines, the chemoselectivity of the oxindole and ester moieties limited our options. Treatment of isoxazoline **4a** with $NaBH_4$ and Zn/HCl failed to reduce the imine and N−O bonds. We discovered that hydrogenation using Pd/C resulted in an unprecedented ring-opening yielding the corresponding amino acid oxime **7** in excellent yield (Figure 2). The identity of the product was unambiguously confirmed by X-ray diffraction. Given the weak nature of N−O bonds, this outcome was surprising, although the benzylic nature of the C−O bond being broken (in addition to the formation of amide-enolate **6**) provides a plausible explanation of the sequence of events taking place. We believe that this reaction proceeds *via* the reduction of the isoxazoline **4** to the corresponding isoxazolidine **5**, which then undergoes ring-opening to yield the enolate-nitrone **6**.[9] Subsequent protonation and enolization provided the observed product. A reaction performed in CD_3OD as solvent resulted in deuterium incorporation at the benzylic position thereby providing support to our proposed mechanism.

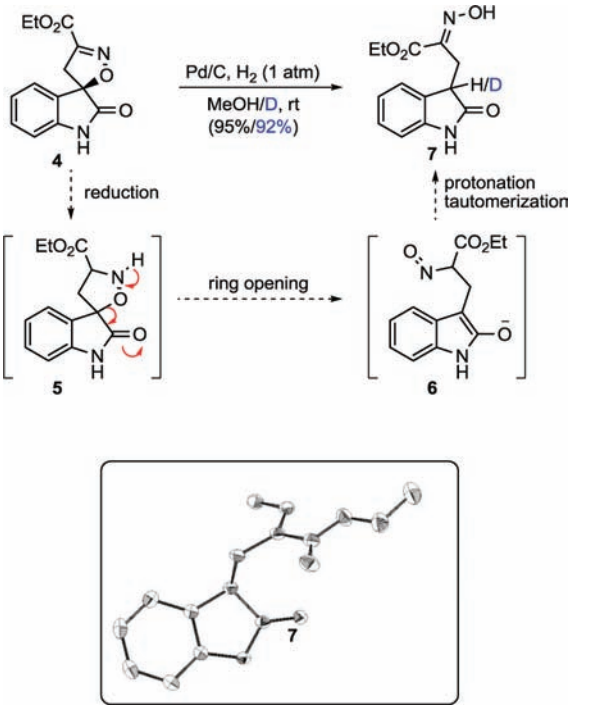
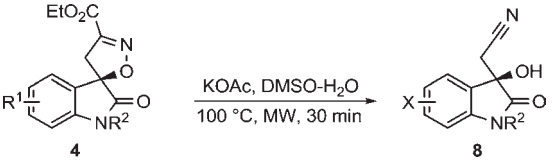


Figure 2. Mechanistic rationale for the formation of **7**.

The synthetic utility of these novel isoxazolines was demonstrated by their conversion to β-hydroxynitrile derivatives by employing a microwave assisted, one-pot sequence of hydrolysis/decarboxylation (Table 3). The ring-opening

Table 3. One-Pot Conversion of Isoxazolines to Hydroxynitriles



entry	R^1	R^2		yield[a] (%)
1	H	H	**a**	95
2	5-OMe	H	**c**	86
3	5-F	H	**e**	90
4	5-OCF_3	H	**f**	88
5	6-Br	H	**g**	82
6	7-CI	H	**k**	81
7	H	Me	**9**	83

[a] Isolated yields.

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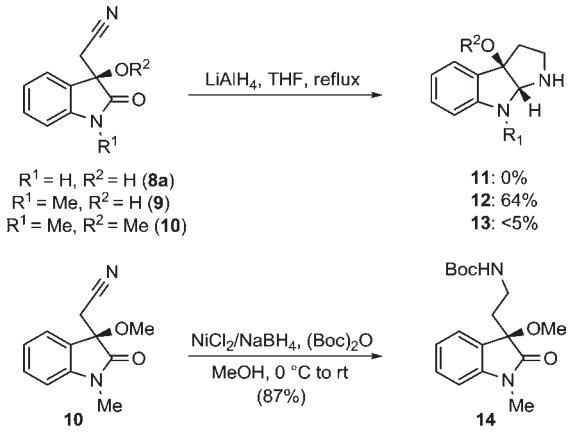
proceeded smoothly leading to the 3-hydroxy-3-cyanomethyl oxindole derivatives in good yield. During our optimization studies, we discovered that potassium acetate was uniquely effective in this transformation and the use of other bases such as sodium hydroxide resulted in complex mixtures.

The nitrile functionality provides an opportunity to access either the oxidized tryptamine derivatives or the pyrrolidinoindoline scaffold by modulating the reduction conditions. We discovered that the treatment of nitrile **8a** with $LiAlH_4$ did not provide the desired tricyclic compound although the starting material was consumed. Attributing this failure to the excess negative charge on the deprotonated *N*-H, we next evaluated this reduction with the *N*-methyl and *N*,*O*-dimethyl derivatives. While the *N*-methyl derivative **9** provided the desired product **12** in good yield, the *N*,*O*-dimethyl derivative **10** suffered extensive decomposition under the reaction conditions. Successful reduction of the nitrile functionality to the amine was accomplished by a nickel chloride/sodium borohydride ($NiCl_2/NaBH_4$) system which promotes the reduction under mild conditions while concomitantly protecting the resulting amine as the Boc-derivative (Scheme 1).

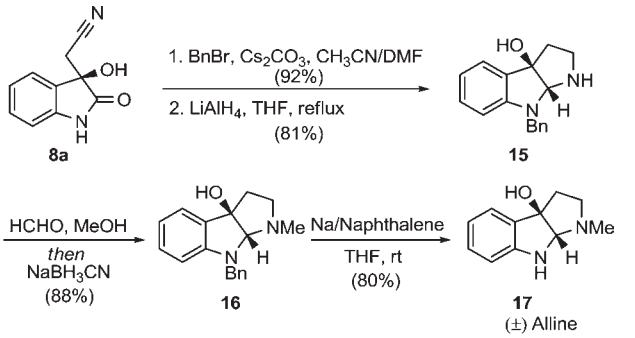
Scheme 1. Controlled Reduction of Hydroxynitriles to 1,3-Aminoalcohols



Using the cyclization/annulation of the hydroxynitrile **8a** as the key step, we targeted the concise syntheses of alkaloids (±)-alline and (±)-CPC-1. The synthesis of alline started with the chemoselective benzyl protection of the cyanoalcohol **8a** to afford the *N*-benzyl derivative in 92% yield. $LiAlH_4$ promoted reductive cyclization cleanly afforded the fused tricyclic intermediate **15** in excellent yield. Subsequent reductive monomethylation using $HCHO/NaCNBH_3$ furnished alcohol **16** (Scheme 2). The debenzylation of the aryl amine proved nontrivial as hydrogenolysis attempts employing palladium catalysts failed to provide the desired product under a variety of conditions. We discovered that the use of sodium naphthalenide smoothly effected the debenzylation at room temperature leading to (±)-alline.

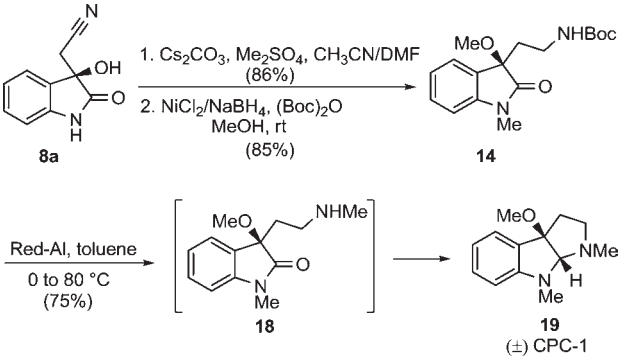
The synthesis of (±)-CPC-1 commenced with the bis-methylation of **8a** to provide the *N*,*O*-dimethyl derivative **10**

Scheme 2. Synthesis of (±)-Alline



(93%) which was then converted to the Boc-protected amine using $NiCl_2/NaBH_4$. Our strategy was to employ the Boc group as a latent methyl moiety. Treatment of the amine **14** with Red-Al in toluene resulted in the formation of the *N*-methyl derivative **18** *in situ* which then cyclized with the oxindole functionality to afford the desired alkaloid (±)-CPC-1 (Scheme 3).

Scheme 3. Synthesis of (±)-CPC-1



In summary, we have described the efficient synthesis of novel oxa-spirooxindoles resulting from the [3 + 2] dipolar cycloaddition of 3-methylene oxindoles with nitrile oxide **3**. The N−O bond in the resulting isoxazoline adducts was found to be remarkably stable to homolytic cleavage and exhibited a unique mode of ring-opening. The cycloadducts were converted to the corresponding 3-hydroxy-3-cyanomethyl oxindoles which were successfully elaborated to the pyrrolidinoindoline alkaloids (±)-alline and (±)-CPC-1.

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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.