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# Dual Behavior of Isatin-Based Cyclic Ketimines with Dicarbomethoxy Carbene: Expedient Synthesis of Highly Functionalized Spirooxindolyl Oxazolidines and Pyrrolines

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## ABSTRACT


**A highly stereo-, regio-, and chemoselective method has been devised for the synthesis of a wide range of spirooxindolyl oxazolidines via an intermolecular 1,3-dipolar cycloaddition of carbonyl ylides generated from dimethyl diazomalonate and aromatic aldehydes, with cyclic ketimines using 5 mol % of $Rh_2(OAc)_4$ under mild conditions. Similarly, highly functionalized spirooxindolyl pyrrolines have also been prepared through 1,3-dipolar cycloaddition of azomethine ylides generated from dimethyl diazomalonate and cyclic ketimines, with dimethyl acetylenedicarboxylate.**

Over the last few decades, great efforts have been focused on catalytic multicomponent reactions (CMCRs) as they offer rapid access to biologically relevant complex molecules with wide structural diversity, high atom economy, and excellent bond-forming efficiency in a single-step process.[1] A multicomponent reaction of α-diazocarbonyl compounds is one of the attractive methods for the rapid production of the highly functionalized five-membered heterocycles.[2] Notably, a 1,3-dipolar cycloaddition of carbonyl ylides and azomethine ylides generated from α-diazocarbonyl compounds with dipolarophiles has been employed for the stereoselective synthesis of oxygen- and

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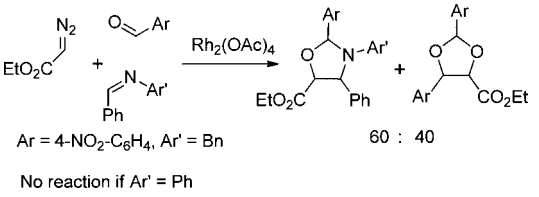
nitrogen-containing heterocycles.[3] However, an intermolecular cycloaddition of ylides with dipolarophiles is known to be synthetically unsuitable in CMCRs because of their low selectivity and the competitive side reactions such as epoxidation, dioxolane formation. Furthermore, the cycloaddition of carbonyl ylides with imines to produce oxazolidines has received limited attention because of their low dipolarophilicity. Recently, an elegant approach has been reported by Somfai et al. for the cycloaddition of a carbonyl ylide generated from ethyl diazoacetate and aromatic aldehyde with aldimine.[4] However, this method suffers from low conversion and moderate diastereoselectivity with respect to substrate. Competitive dioxolane formation reduces the efficiency of this method (Scheme 1).

**Scheme 1**




Like carbonyl ylide, the generation of azomethine ylide from *N*-benzylideneaniline and diazo compound has also been reported to facilitate cycloaddition with diplorophiles to produce the pyrrolidines and pyrroles.[5] But *N*-benzylideneaniline fails to undergo cycloaddition with carbonyl ylide (Scheme 1). Therefore, there is still a need to find a suitable imine that can trap the carbonyl ylide effectively without the formation of any epoxide and dioxolane and also to generate the azomethine ylide.

As a part of our research program on diazocarbonyl compounds, we recently reported the synthesis of spirooxindolyl lactams and oxazinones through the trapping of acylketenes with isatin-based cyclic ketimines.[6] We initially envisaged that the cyclic ketimines derived from isatin could be interesting if they act as good dipolarophiles to trap the carbonyl ylides and also to generate azomethine ylides from carbenoids. Therefore, the cyclic ketimines could be used to produce the spirooxindolyl-1,3-oxazolidines and spirooxindolyl-1,3-pyrrolidines. Such spirooxindoles, oxazolidines, and pyrrolidines have emerged as attractive synthetic targets because of their prevalence in biologically active natural products and drugs[7] (Figure 1).

Herein, we report a novel approach for the construction of spirooxindolyl-1,3-oxazolidines and spirooxindolyl-1,3-pyrrolines via the coupling of diazomalonate and ketimine with aldehyde or with dimethyl acetylenedicarboxylate, respectively.

Accordingly, the three-component coupling (3CC) of dimethyl diazomalonate with benzaldehyde and *N*-methylisatin-3-arylimine in the presence of 5 mol % of $Rh_2(OAc)_4$ afforded the spirooxindolyl-1,3-oxazolidine **4a** in 86% yield (entry **a**, Table 1). The $^1H$ NMR analysis of a crude sample indicates the exclusive formation of cycloadduct **4a** as a single diastereomer. The product was purified by flash column chromatography on silica gel and characterized by spectroscopic analysis.

The spectral data evidently confirm the proposed structure for **4a**. The relative stereochemistry of spirooxindolyl-1,3-oxazolidine **4q** was determined on the basis of X-ray crystallography (see the Supporting Information).

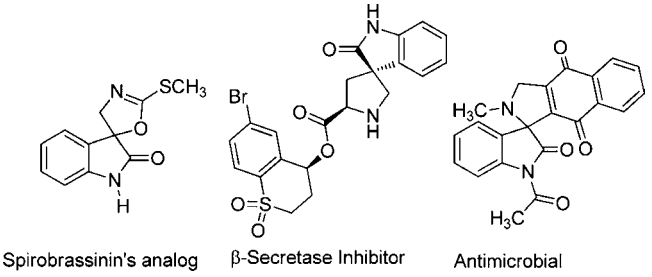



**Figure 1.** Biologically active spirooxindolyl oxazole and pyrroline derivatives.

Encouraged by the initial results, we further examined the reactivity of ketimines with various carbonyl ylides generated from diazomalonate and electron-rich as well as electron-deficient aryl aldehydes (Table 1). In order to investigate the competitive side reactions such as epoxidation and 1,3-dioxolane formation, we performed the 3CC reaction with electron-deficient aryl aldehydes which usually serve as dipolarophiles in the formation of dioxolanes. Surprisingly, no such formation of dioxolane was observed with *p*-nitrobenzaldehyde under the present reaction conditions. Inspired by this observation, we extended its effectiveness to the preparation of spirooxazolidine with a highly electron-deficient substrate, i.e., 2,4-dinitrobenzaldehyde. Remarkably, the corresponding oxazolidine was obtained in good yield under the present reaction conditions without the formation of dioxolane (entries **d** and **r**, Table 1) although 2,4-dinitrobenzaldehyde is known to act as an excellent dipolarophile in carbonyl ylide cycloadditions.

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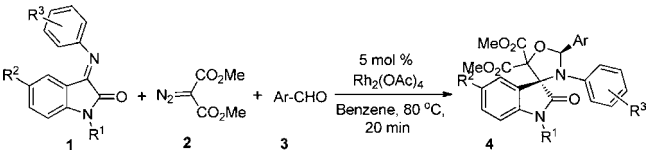
**Table 1.** Three-Component Synthesis of Spirooxindolyl Oxazolidines[a]




1 2 3 4

| entry | $R^1$ | $R^2$ | $R^3$ | Ar | yield[b] (%) of **4a**–**x** |
|---|---|---|---|---|---|
| **a** | $CH_3$ | H | H | Ph | 86 |
| **b** | $CH_3$ | H | H | *p*-$NO_2C_6H_4$ | 82 |
| **c** | $CH_3$ | H | H | *p*-$CNC_6H_4$ | 84 |
| **d** | $CH_3$ | H | H | *o*,*p*-$(NO_2)_2C_6H_3$ | 78 |
| **e** | $CH_3$ | $CH_3$ | H | Ph | 86 |
| **f** | $CH_3$ | Br | H | Ph | 90 |
| **g** | $CH_3$ | Cl | H | Ph | 88 |
| **h** | $CH_3$ | $NO_2$ | H | Ph | 88 |
| **i** | $CH_3$ | H | m-Cl | Ph | 84 |
| **j** | allyl | H | H | *p*-$CH_3C_6H_4$ | 86 |
| **k** | allyl | H | H | *p*-$BrC_6H_4$ | 88 |
| **l** | allyl | H | H | *p*-$FC_6H_4$ | 86 |
| **m** | allyl | H | H | *p*-$CNC_6H_4$ | 84 |
| **n** | allyl | H | H | *p*-$NO_2C_6H_4$ | 84 |
| **o** | allyl | H | H | *m*-$NO_2C_6H_4$ | 85 |
| **p** | allyl | H | *p*-Br | *p*-$NO_2C_6H_4$ | 86 |
| **q** | allyl | H | *p*-$CH_3$ | *p*-$NO_2C_6H_4$ | 85 |
| **r** | allyl | H | H | *o*,*p*-$(NO_2)_2C_6H_3$ | 76 |
| **s** | propargyl | H | H | *p*-$NO_2C_6H_4$ | 82 |
| **t** | Bn | H | H | Ph | 90 |
| **u** | Bn | H | H | p-$CNC_6H_4$ | 86 |
| **v** | Bn | H | H | p-$NO_2C_6H_4$ | 85 |
| **w** | Bn | H | *p*-$CH_3$ | *p*-$NO_2C_6H_4$ | 88 |
| **x** | Bn | H | *p*-Br | *p*-$NO_2C_6H_4$ | 88 |

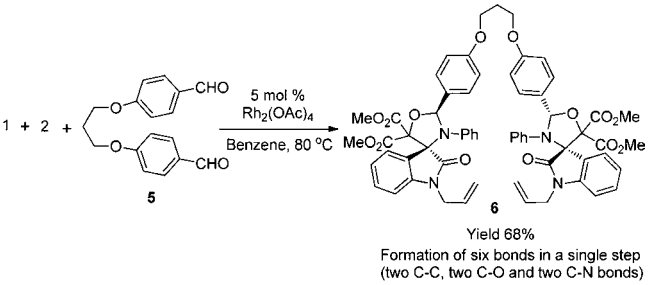
[a] Unless otherwise noted, all reactions were performed using $Rh_2(OAc)_4$ (5 mol %), imine **1** (1.2 equiv), dimethyl diazomalonate **2** (1 equiv), and aromatic aldehydes **3** (1 equiv) in dry benzene at 80 °C. [b] Yield refers to pure products after column chromatography.

This is due to high dipolarophilicity of ketimines over nitrobenzaldehydes. Furthermore, it is inevitable to note that no oxazole (which is known to form from diazomalonate and cyano group) or dioxolane was formed with *p*-cyanobenzaldehyde (entries **c**, **m**, and **u**, Table 1). Further, the bond-forming efficiency of this method is exemplified by making six bonds (two C–C bonds, two C–O bonds, and two C–N bonds) with bis-aldehyde **5** in a single-step process (Scheme 2).

To study the electronic effect of substituents on the aromatic ring, we prepared several ketimines with both electron-rich and electron-deficient substrates. Remarkably, *N*-substituted isatin-3-arylimines such as allyl, propargyl, and benzyl are well tolerated without participating in side reactions such as cyclopropanation, furan formation, and C–H insertion, respectively, which shows the high chemoselectivity of this protocol.

Mechanistically, the reaction was proposed to proceed via Huisgen's cycloaddition of carbonyl ylide, formed in situ from diazomalonate and aromatic aldehyde, with

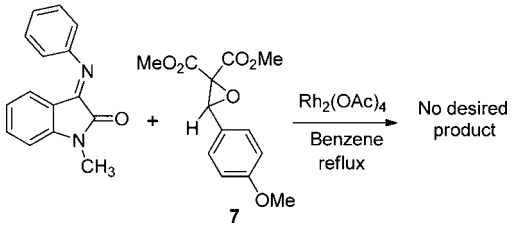
**Scheme 2.** Formation of Bis-spirooxindolyl Oxazolidine




5 6

ketimine. Isatin-based ketimine, being a very good dipolarophile, can trap the carbonyl ylide effectively via endo attack (Scheme 4). The reaction does not proceed through the formation of epoxide from diazomalonate and aromatic aldehyde as this was confirmed by reacting the ketimine with epoxide which was prepared independently from diazomalonate and anisaldehyde. With this evidence, we excluded the possibility of involving a stepwise mechanism (Scheme 3).

**Scheme 3.** Reaction of Isatin-3-arylimine with Epoxide

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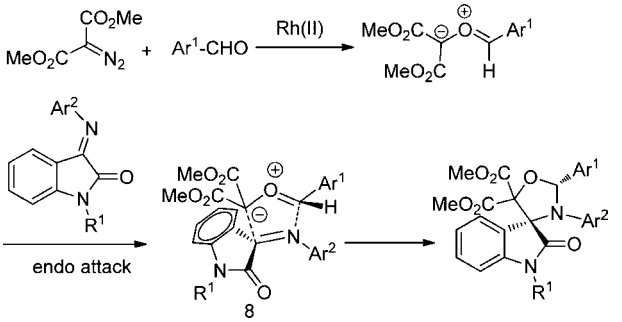
**Scheme 4.** Plausible Reaction Pathway for the Formation of Spirooxindolyl Oxazolines

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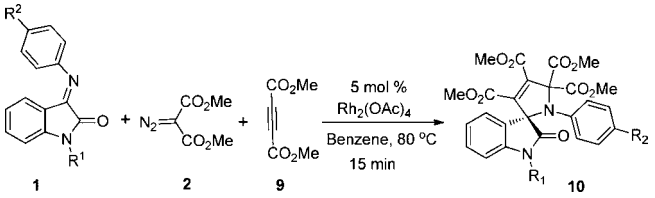
To the best of our knowledge, there is no report on the generation of azomethine ylide from diazomalonate and imine. Therefore, we were curious to extend our approach to azomethine ylides generated from diazomalonate and ketimines. Accordingly, treatment of azomethine ylides with dimethyl acetylenedicarboxylate afforded a highly substituted spirooxindolyl dihydropyrroline in

**Table 2.** Three-Component Synthesis of Spirooxindolyl Pyrrolines[a]




1 2 9 10

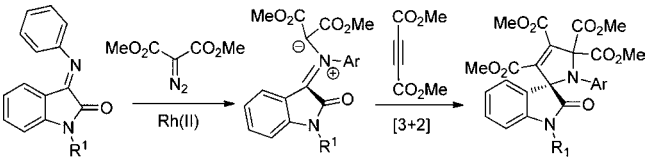
| entry | $R^1$ | $R^2$ | yield[b] (%) of **10a**–**k** |
|---|---|---|---|
| **a** | $CH_3$ | H | 80 |
| **b** | $CH_3$ | $CH_3$ | 84 |
| **c** | $CH_3$ | Br | 82 |
| **d** | $CH_3$ | $OCH_3$ | 80 |
| **e** | Bn | H | 85 |
| **f** | Bn | $CH_3$ | 86 |
| **g** | Bn | $OCH_3$ | 85 |
| **h** | allyl | H | 80 |
| **i** | allyl | $CH_3$ | 85 |
| **j** | allyl | $OCH_3$ | 84 |
| **k** | allyl | Cl | 86 |

[a] Unless otherwise noted, all reactions were performed using $Rh_2(OAc)_4$ (5 mol %), imine **1** (1.2 equiv), dimethyl diazomalonate **2** (1 equiv), and dimethyl acetylenedicarboxylate **9** (1.2 equiv) in dry benzene at 80 °C. [b] Yield refers to pure products after column chromatography.

good to excellent yields without the formation of aziridines (Table 2).

The structure of **10e** was unambiguously determined by single-crystal X-ray analysis (see the Supporting Information). The reaction was assumed to proceed via formation of azomethine ylide from diazomalonate and ketimine. The ylide is trapped with dimethyl acetylenedicarboxylate via the Huisgen's cycloaddition to produce the desired spirooxindolyl pyrroline (Scheme 5).

**Scheme 5.** Plausible Reaction Pathway for the Formation of Spirooxindolyl Pyrroline




In conclusion, we have developed a highly efficient approach for the synthesis of a novel class of highly substituted spirooxindolyl oxazolidines via a 1,3-dipolar cycloaddition of carbonyl ylides with ketimines and also spirooxindolyl pyrrolines through the cycloaddition of dimethyl acetylenedicarboxylate with azomethine ylides generated from ketimines and diazomalonate. These spirocycles may find significant application in medicinal chemistry since the concept of hybrid drugs is gaining popularity in medicine. The bond-forming efficiency of this method is exemplified by making six bonds (two C–C bonds, two C–O bonds, and two C–N bonds) with bis-aldehyde in a single-step operation.

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**Supporting Information Available.** Experimental details, characterization data of the products, copies of $^1H$ and $^{13}C$ NMR spectra of the products, and X-ray crystallography data of **4q** and **10e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.