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Highly regio- and diastereoselective three-component reaction of acyclic/cyclic donor–acceptor carbenoids for the synthesis of angularly fused furocoumarins and spirooxindolylfurocoumarins

Govindaraju Karthik [a], Tamilselvan Rajasekaran [a], B. Sridhar [b], B.V. Subba Reddy [a,*]

[a] Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A highly regio- and stereoselective method has been developed for the synthesis of spiro[furo[3,4-*c*]chromene-1,3′-indoline]-2′,4(9b*H*)-dione derivatives via a three component reaction of cyclic diazoamide and aldehyde with methyl 2-oxo-2*H*-chromene-3-carboxylate, 3-acetyl-2*H*-chromen-2-one and 3-benzoyl-2*H*-chromen-2-one using 3 mol % of $Rh_2(OAc)_4$. Similarly, acyclic diazoesters also undergo smooth coupling with carbonyl compounds and 3-substituted coumarin in the presence of 1 mol % of $Rh_2(OAc)_4$ to afford a novel series of tetrahydro-1*H*-furo[3,4-*c*]chromene-1-carboxylates in 78–88% yield with high regio- and stereo-selectivity for the first time.

1. Introduction

1,3-Dipolar cycloaddition of carbonyl ylides, generated from α-diazocarbonyl compounds and aldehydes with activated olefins is a powerful method for the construction of highly substituted five-membered heterocycles such as tetrahydrofurans and pyrrolidines.[1] For the last two decades, a great attention has been paid to intramolecular carbonyl ylide cycloaddition for the synthesis of complex natural products[2] but not on the intermolecular ylide cycloaddition. The scope of intermolecular carbonyl ylide cycloaddition is generally limited to highly activated dipolarophiles due to the competing side reactions such as dioxolane or epoxide formation, and also the formation of a mixture of regio- and stereoisomers, which are often observed with unsymmetrical olefins.[3] Jamison and co-workers reported an efficient method for the construction of dihydro- and tetrahydro-furan derivatives via Rh(II)-catalyzed three-component reaction of trimethylsilyldiazomethane dicobalt hexacarbonyl complexes with propargyl aldehydes and electron deficient olefins such as dimethyl acetylenedicarboxylate, dimethyl maleate and dimethyl fumarate affording good stereoselectivity but with poor regioselectivity in many of cases.[4a] Subsequently, Muthusamy et al. reported the Rh(II)-catalyzed synthesis of spirooxindolyl furans using cyclic diazoamides, aldehydes, and dimethyl acetylenedicarboxylate with high diastereoselectivity, whereas low regioselectivity was observed with ethyl acrylate.[4c]

Later on, Fox and co-workers demonstrated the (Rh_2Piv_4)-catalyzed three component reaction of α-alkyl-α-diazoesters, aldehydes and unsymmetrical olefins such as methyl vinyl ketone and ethyl acrylate for the synthesis of highly substituted tetrahydrofurans with high regio- and diastereoselectivity. However, this method is limited to α-alkyl-α-diazoesters. They also reported a three component reaction with methyl phenyldiazoacetate to produce the furan derivatives in poor yield along with undesired epoxide and unreacted aldehyde as side products.[4d] However, to the best of our knowledge, there are no reports on the regioselective cycloaddition of carbonyl ylides, which were generated from donor–acceptor diazo compounds and aldehydes with unsymmetrical cyclic olefinic esters and ketones as dipolarophiles.

Inspired by the versatility of diazo chemistry in generating structural diversity and our ongoing work on diazo chemistry[5] we sought to develop a three-component reaction between cyclic diazoamide, aldehydes and coumarins. We assumed that 3-substitued coumarin can trap the ylide formed from 3-diazooxindoles and aromatic aldehyde efficiently to produce a series of furocoumarins and spirooxindolyl furans, which are common structural motifs in many biologically active natural products such as triFA1, Rubioncolin B and growth inhibitor of hepatocellular carcinoma (HepG2) cells (Fig. 1).[6]

* Corresponding author. Fax: +91 40 27160512; e-mail address: basireddy@iict.res.in (B.V. Subba Reddy).

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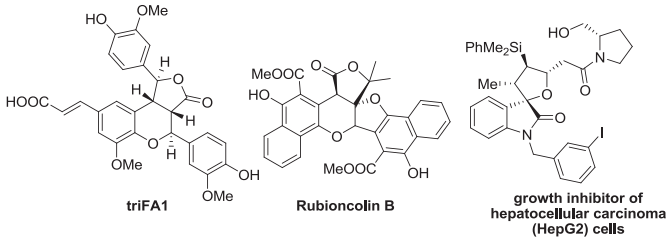


Fig. 1. Biologically active furocoumarin and spirofuran skeleton.

Accordingly, we performed the coupling of 1.2 equiv of coumarin methyl ester **1a** with 1 equiv of *N*-methyl-3-diazooxindole **2a** and 1.1 equiv of benzaldehyde **3a** using 5 mol % $Rh_2(OAc)_4$ in dry dichloromethane. To our delight, the desired product **4a** was obtained as a single diastereomer in 78% yield with complete regioselectivity. The structure of **4a** was confirmed by NMR, IR and HRMS analysis. Furthermore, the structure of **4f** was confirmed unambiguously by a single crystal X-ray analysis as shown in Fig. 2 (Table 1, entry f).

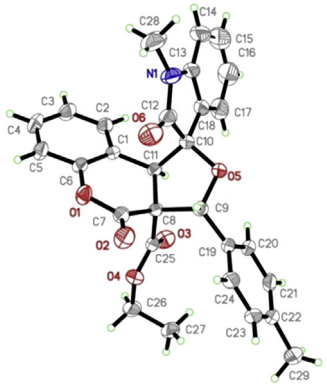
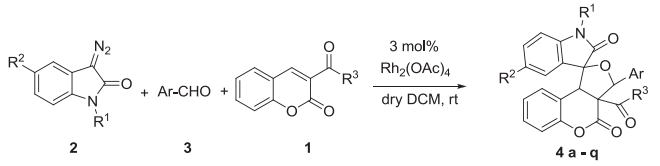


Fig. 2. ORTEP diagram of **4f** (Table 1 entry f).

Table 1
Three component coupling of 3-diazooxindole (**2**), aldehyde (**3**) and coumarin (**1**)[a]



Entry	R^1/R^2	Ar	R^3	Yield %[b]
a	CH_3/H (**2a**)	C_6H_5 (**3a**)	OCH_3 (**1a**)	76 (**4a**)
b	Boc/H (**2b**)	*p*-Cl–C_6H_4 (**3b**)	OCH_3 (**1a**)	86 (**4b**)
c	Boc/H (**2b**)	*o*-OCH_3–C_6H_4 (**3c**)	OCH_3 (**1a**)	88 (**4c**)
d	CH_3/H (**2a**)	*p*-OCH_3–C_6H_4 (**3d**)	OEt (**1b**)	88 (**4d**)
e	CH_3/H (**2a**)	*p*-Br–C_6H_4 (**3e**)	OEt (**1b**)	80 (**4e**)
f	CH_3/H (**2a**)	*p*-CH_3–C_6H_4 (**3f**)	OEt (**1b**)	87 (**4f**)
g	Boc/H (**2b**)	*p*-CH_3–C_6H_4 (**3f**)	OEt (**1b**)	86 (**4g**)
h	CH_3/H (**2a**)	C_6H_5 (**3a**)	CH_3 (**1c**)	78 (**4h**)
i	CH_3/H (**2a**)	*p*-OCH_3–C_6H_4 (**3d**)	CH_3 (**1c**)	86 (4i)
j	CH_3/H (**2a**)	*p*-Br–C_6H_4 (**3e**)	CH_3 (**1c**)	84 (**4j**)
k	Bn/H (**2c**)	*p*-Br–C_6H_4 (**3e**)	CH_3 (**1c**)	88 (**4k**)
l	CH_3/H (**2a**)	*m*-CH_3–C_6H_4 (**3g**)	CH_3 (**1c**)	82 (**4l**)
m	CH_3/Cl (**2d**)	*p*-OCH_3–C_6H_4 (**3d**)	CH_3 (**1c**)	86 (**4m**)
n	CH_3/Br (**2e**)	*p*-CH_3–C_6H_4 (**3f**)	CH_3 (**1c**)	88 (**4n**)
o	Boc/H (**2b**)	C_6H_5 (**3a**)	CH_3 (**1c**)	78 (**4o**)
p	Boc/H (**2b**)	C_6H_5 (**3a**)	C_6H_5 (**1d**)	76 (**4p**)
q	Boc/H (**2b**)	*p*-Br–C_6H_4 (**3e**)	C_6H_5 (**1d**)	88 (**4q**)

[a] Unless otherwise noted, all the reactions were performed using $Rh_2(OAc)_4$ (3 mol %), diazo compound **2** (1 equiv), aldehyde **3** (1.1 equiv) and coumarin **1** (1.2 equiv) in dry DCM at rt.
[b] Yields refer to pure products after column chromatography.

By minimizing the catalyst loading to 3 mol %, the corresponding product **4a** was still obtained in 76% yield as a single diastereomer (Table 1 and entry a). We also screened various solvents such as dry dichloroethane, dichloromethane, benzene and toluene. Of these, dicholoromethane was found to be the best in terms of yield and reaction time.

Encouraged by these initial results, we focused our attention to explore the electronic effect of substituents on aromatic aldehydes. Accordingly, the reaction of *N*-methyldiazooxindole with aromatic aldehydes bearing electron releasing and electron withdrawing substituents and coumarin-3-carboxylate in the presence of 3 mol % $Rh_2(OAc)_4$ performed. Interestingly, electron-rich aromatic aldehydes such as anisaldehyde (Table 1, entries c, d, i and m) and tolualdehyde (Table 1, entries f, l and n) gave the products in excellent yields. Conversely, the reaction did not proceed with electron-deficient aromatic aldehyde like *p*-nitrobenzaldehyde. However, the presence of halides such as chloro and bromo substituents on aromatic ring also furnished the required products in good yields (Table 1, entries b and e).

Furthermore, the reactivity of various 3-diazooxindoles possessing substituents on aromatic ring and *N*-protecting groups were also investigated. The halo substituents such as chloro and bromo at 5-position of diazooxindole did not show any significant electronic effect on the conversion and affording the product in 86% and 88% yields, respectively (Table 1, entries m and n). Similarly, *N*-substituted 3-diazooxindoles such as *N*-methyl, *N*-benzyl and *N*-Boc derivatives also participated well in this reaction under present conditions (Table 1, entries h, k and o). It is noteworthy to mention that the keto functionality at 3-position of the coumarin ring is well tolerated under the reaction conditions affording the products in excellent yields with high chemoselectivity (Table 1, entries h–q).

The cycloaddition of simple olefinic esters with aryl diazoacetate and aldehyde is less studied due to the predominant formation of the epoxide from aldehyde and aryl diazoacetate. To our delight, the cycloaddition of coumarin methyl ester **1a** with methyl diazophenylacetate **5a** and benzaldehyde **3a** was successful using 3 mol % $Rh_2(OAc)_4$. The desired product **6a** was isolated in 79% yield as a single diastereomer with complete regioselectivity. The relative configuration of **6c** was unambiguously confirmed by X-ray single crystal analysis (Fig. 3). Upon screening the catalyst loading, we found the formation of **6a** in 78% yield even with 1 mol % $Rh_2(OAc)_4$. Having optimized reaction conditions in hand for diazoester, the scope of this 3CC reaction was further extended to other aromatic aldehydes. The results are summarized in Table 2.

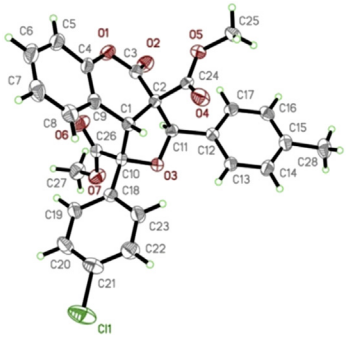


Fig. 3. ORTEP diagram of the product **6c** (Table 2, entry c).

As expected, the electron releasing groups on aromatic ring show significant increase in yield. Moreover, the halo substituted aryldiazoacetates also participated well in the reaction and