

## A novel synthesis of oxazino derivatives from an efficient one-pot three-component reaction of isoquinoline and dimethylacetylene dicarboxylate (DMAD) in the presence of arylaldehyde derivatives

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Received: August 2011; Revised: August 2011; Accepted: August 2011

**Abstract:** The 1,4-dipolar derived from isoquinoline and DMAD has been shown to react readily with arylaldehyde derivatives in the diastereoselective synthesis of (2*S*,2*R*)-dimethyl-2,11*b*-dihydro-2-(3-nitrophenyl)-[1,3]-oxazino-[2,3-*a*]-isoquinoline-3,4-dicarboxylate (**4a**), dimethyl-2-(4-bromophenyl)-2,11*b*-dihydro-[1,3]-oxazino[2,3-*a*]-isoquinoline-3,4-dicarboxylate (**4b**), dimethyl-2-(furan-2-yl)-2,11*b*-dihydro-[1,3]oxazino[3,2-*a*] isoquinoline-3,4-dicarboxylate (**4c**) and dimethyl-2,11*b*-dihydro-2-(5-nitrofuran-2-yl)-[1,3]-oxazino-[2,3-*a*]-isoquinoline-3,4-dicarboxylate (**4d**) in the moderate to good yield. The reaction was carried out in the room temperature or solvent free in microwave.

**Keywords:** DMAD; Isoquinoline; Arylaldehyde; Oxazino.

### Introduction

The pronounced reactivity of nitrogen-containing heterocycles towards DMAD, is well documented [1]. The monumental work of Huisgen has established 1, 3-dipolar cycloaddition [2,3] as the most important methodology for the construction of a wide range of five-member heterocycles.

A noteworthy development in this area has been the reaction of 1, 4-dipoles incorporated in to cross-conjugated betaines by Padwa [4]. The formation of a 1, 4-dipolar from isoquinoline and dimethylacetylene dicarboxylate (DMAD) and its trapping by phenyl isocyanate, diethyl mesoxalate and dimethylazodicarboxylate were reported by Huisgen [5] and the utility of this reaction for the synthesis of six-member heterocycles and Spiro compounds has been reported by V. Nair. In the context of our general investigations on heterocyclic compounds via dipolar

intermediates derived from nucleophilic species and DMAD [6], we were intrigued by the possibility of trapping the zwitterionic intermediate derived from isoquinoline and dimethylacetylene dicarboxylate with arylaldehydes.

A mixture of isoquinoline and dimethylacetylene dicarboxylate with arylaldehydes, at room temperature, affords the products **4a-4d** as mixtures of regioisomers in the ratio 2:1 in about 56-70 % yield (Scheme 1)

### Results and discussion

Isoquinoline **1** with dimethylacetylene dicarboxylate **2** in presence of derivatives of arylaldehyde **3**, undergo a smooth 1:1 addition-reaction in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, to produce **4a-4d** in excellent yields (Scheme 1).

The structures of **4a-4d** were deduced from their IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra. The diastereomeric ratio was determined 2:1 by <sup>1</sup>H NMR.

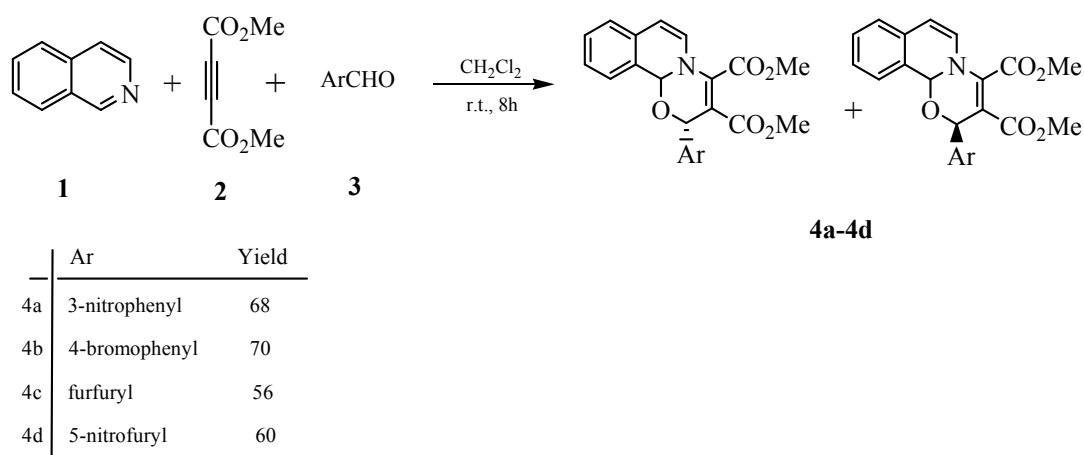
NMR data for major isomer (66%); <sup>1</sup>H NMR spectrum of **4a**, showed two singlets at δ=4.03 and

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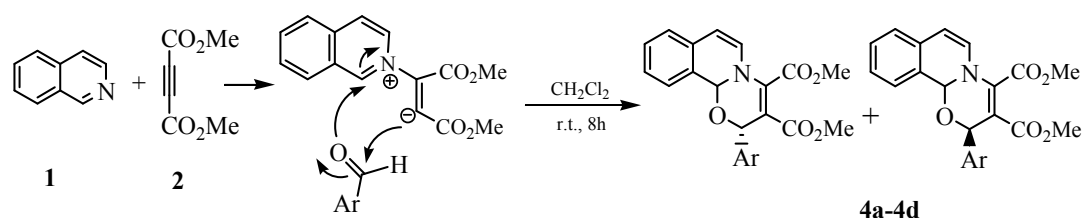
$\delta=3.64$  ppm for the methoxy protons. The ring junction proton of **4a**, was observed as a singlet at  $\delta=5.80$  and the other proton displayed a singlet at  $\delta=5.86$  ppm. In the  $^{13}\text{C}$  NMR spectra **4a**, the two methoxy resonated at about  $\delta=52.3$  and  $53.9$  and two ester carbonyls resonated at  $\delta=165.2$  and  $168.1$ . NMR data for minor isomer (33%);  $^1\text{H}$  NMR spectrum of minor isomer **4a** showed two singlets at  $\delta=3.99$  and  $\delta=3.56$  ppm for the methoxy protons. The ring junction proton, was observed as a singlet at  $\delta=6.07$  and the other proton

displayed a singlet at  $\delta=6.25$  ppm. In the  $^{13}\text{C}$  NMR spectrum of minor isomer **4a**, the two methoxy resonated at about  $\delta=52.3$  and  $54.0$  and two ester carbonyls resonated at  $\delta=164.1$  and  $165.2$  ppm.

Mechanistically, the reaction can be considered to proceed via the initial formation of the 1, 4-dipolar intermediate from isoquinoline and DMAD, followed by its trapping with the solution of arylaldehyde derivatives, to give the corresponding **4a-4d** as shown in Scheme 2.



**Scheme 1:** The reaction of isoquinoline and dimethylacetylene dicarboxylate with arylaldehydes, at room temperature and affords the products **4a-4d**.



**Scheme 2:** Mechanism of the reaction of 1, 4-dipolar intermediate from isoquinoline and DMAD with the arylaldehyde derivatives.

## Conclusion

In conclusion, we have developed a simple method for the synthesis of novel diastereoselective oxazino derivatives from an efficient one-pot three-component reaction of isoquinoline and DMAD in the presence of 3-nitrobenzaldehyde under room temperature it gave two isomer of **4a** in the ratio 2:1. However, when the reaction was carried out between 1, 4-dipolar intermediate and other arylaldehyde derivatives under room temperature it gave one isomer of **4b-4d** in 8 h. But when the same reaction was carried out (solvent free) in microwave reactor between 1, 4-dipolar

intermediate and 3-nitrobenzaldehyde or *p*-bromobenzaldehyde, it gave the desired product 90-80% yield in 20-25 minutes (Table 1).

## Experimental

All compounds in these reactions were obtained from Merck co. and were used without further purification. Mp: Thomas-Hoover capillary. FT-IR spectra: Bruker VERTEX-70.  $^1\text{H}$  and  $^{13}\text{C}$ NMR spectra: Bruker DRX-500 or 300 Avance instrument; in  $\text{CDCl}_3$  or DMSO at 500 or 300 and 125.7 or 75 MHz, respectively;  $\delta$  in part per million, J in Hz.

**Typical experimental procedure:**

To a stirred solution of isoquinoline **1** (1.3, 1 mmol), dimethylacetylene dicarboxylate **2** (1.2 cc, 1 mmol) in the presence of CH<sub>2</sub>Cl<sub>2</sub> (3 ml), was added *m*-nitrobenzaldehyde (1.5, 2 mmol) at room temperature. The resulting mixture was stirred for 8 h. The formed precipitate was isolated by filtration. To the filtrate was added ethanol (4 ml), which resulted in the crystallization of the product. When the same reaction was carried out (solvent free) in microwave reactor, it gave the desired product 90% yield in 25 minutes and for the reaction of *p*-bromobenzaldehyde it gave the desired product 85% yield in 20 minutes (Table 1).

**Table 1:** The reaction of isoquinoline and DMAD in presence of *m*-nitro or *p*-bromobenzaldehyde under room temperature or in microwave reactor

	Reactants	Reaction time	Yield
Room Temperature	isoquinoline+ <i>m</i> -nitrobenzaldehyde	8 h	70 %
Macro wave	isoquinoline+ <i>m</i> -nitrobenzaldehyde	25 min	90 %
Room Temperature	isoquinoline+ <i>p</i> -bromobenzaldehyde	8 h	60 %
Macro wave	isoquinoline+ <i>p</i> -bromobenzaldehyde	20 min	85 %

*Dimethyl -2,11b dihydro-2-(3-nitrophenyl)-[1,3]oxazinof[3,2-a]isoquinoline-3,4-dicarboxylate (4a):*

Orange crystals: yield: 70% mp: 92-93°C; The ratio of two isomers is 1:2, IR: (KBr) (Vmax/cm<sup>-1</sup>): 3087(CH, aromatic), 2955(CH), 1702 (C=O), 1595 and 1437(NO<sub>2</sub>). NMR data for major isomer (66%) <sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>): The ratio of two isomers is 2:1, **major 4a**: 3.63 (3 H, *s*, OCH<sub>3</sub>), 4.03 (3 H, *s*, OCH<sub>3</sub>), 5.70 (1 H, *d*, *J*=7.8 Hz, CH), 5.80 (*s*, CH), 5.86 (*s*, CH), 6.27 (*d*, *J*=7.8 Hz, CH), 6.96 (*d*, *J*=7.8 Hz, CH), 7.02 (*d*, *J*=7.6 Hz, CH), 7.15 (*t*, *J*=7.6 and 7.6 Hz, CH), 7.23 (*d*, *J*=7.6 Hz, CH), 7.63 (*t*, *J*=7.8 and 7.8 Hz, CH), 7.79(*t*, *J*=7.6, CH), 8.34 (*s*, CH); <sup>13</sup>CNMR (75 MHz, CDCl<sub>3</sub>); **major 4a**: 52.3 (OCH<sub>3</sub>), 53.9 (OCH<sub>3</sub>), 73.1 (C ring junction), 78.6 (C), 102.9 105.5, 123.7, 123.9, 124.1, 124.8, 125.5, 127.1, 127.6, 128.9, 129.9, 130.7, 135.1, 135.5, 143.5 and 148.8 (16 C), 164.1 (C=O), 165.2 (C=O); NMR data for **minor isomer 4a** (33%); <sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>): 3.56 (*s*, OCH<sub>3</sub>), 3.99 (*s*, OCH<sub>3</sub>), 5.81 (*d*, *J*=7.8 Hz, CH), 6.07 (*s*, H ring junction), 6.25 (*s*, CH), 6.40 (*d*, *J*=7.8 Hz, CH), 7.09 (*d*, *J*=7.6 Hz, CH), 7.40 (*d*, *J*=7.6 Hz, CH), 7.48 (*t*, *J*=7.8 and 7.8 Hz, CH), 7.73 (*d*, *J*=7.8 Hz, CH), 7.79 (*t*, *J*=7.6 Hz, CH), 8.11 (*d*, *J*=7.8 Hz, CH) 8.28 (*s*, CH); <sup>13</sup>CNMR (75 MHz, CDCl<sub>3</sub>) for **minor isomer 4a**:

52.3 (OCH<sub>3</sub>), 54.0 (OCH<sub>3</sub>), 68.5 (C), 73.1 (C), 78.6 (C), 102.9 105.5, 123.7, 123.9, 124.1, 124.8, 125.5, 127.1, 127.6, 128.9, 129.9, 130.7, 135.1, 135.5, 143.5 and 148.8 (16 C), 164.1 (C=O), 165.2 (C=O) ppm.

*Dimethyl-2-(4-bromophenyl)-2, 11b-dihydro-[1, 3]-oxazino-[2, 3-a]-isoquinoline-3, 4-dicarboxylate (4b):*

Yellow crystals, yield: 60% mp: 97-98°C; IR: (KBr) (Vmax/cm<sup>-1</sup>): 3086 (CH, aromatic), 2951(CH), 1743 (C=O), 1698 and 1590 (C=C); <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>), 3.65 (*s*, OCH<sub>3</sub>), 4.04 (*s*, OCH<sub>3</sub>), 5.71 (*d*, <sup>3</sup>*J*=7.6 Hz, CH), 5.72 (*s*, H ring junction), 5.89 (*s*, H benzyl), 6.30 (*d*, <sup>3</sup>*J*=7.6 Hz, HC=CH ring), 7.01 (*d*, <sup>3</sup>*J*=7.6 Hz, CH), 7.04 (*d*, <sup>3</sup>*J*=7.6 Hz, CH), 7.17 (*t*, <sup>3</sup>*J*=7.5 and 7.6 Hz, CH), 7.27 (*t*, <sup>3</sup>*J*=7.5 Hz, CH), 7.35 (*d*, <sup>3</sup>*J*=8.4 Hz, HC=CH ph), 7.58 (*d*, <sup>3</sup>*J* = 8.4 Hz, CH=CH ph). <sup>13</sup>CNMR (125MHz, CDCl<sub>3</sub>); 52.2 (OCH<sub>3</sub>), 53.8 (OCH<sub>3</sub>), 73.5 (C-O), 78.2 (C-O), 104.3, 105.1, 123.0, 124.1, 125.4, 126.9, 127.3, 127.5, 129.8, 130.2, 131.1, 132.1, 140.5 and 143.9 (14 C, aromatic), 164.3 (C=O), 165.5 (C=O).

*Dimethyl -2-(furan-2-yl)-2, 11b-dihydro-[1, 3]-oxazino-[3,2-a] isoquinoline-3,4-dicarboxylate(4c):*

Brown crystals: yield: 65%, mp: 87-89°C; IR: (KBr), (Vmax/cm<sup>-1</sup>): 3087 (CH, aromatic), 2955(CH), 1702 (C=O). <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>): 3.68 (*s*, OCH<sub>3</sub>), 4.02 (*s*, OCH<sub>3</sub>), 5.33 (*d*, <sup>3</sup>*J*=7.8 Hz, HC=CH ring), 5.75 (*s*, CH), 6.13 (*s*, CH), 6.30 (*s*, *d*, <sup>3</sup>*J*=7.8 Hz, HC=CH-N ring), 6.38 (CH furan), 6.42 (CH furan), 7.52 (CH furan), 7.07 (CH), 7.18 (CH), 7.23 (CH), 7.52 (C H). <sup>13</sup>CNMR (125MHz, CDCl<sub>3</sub>); 52.2 (OCH<sub>3</sub>), 53.8 (OCH<sub>3</sub>), 67.84 (C), 78.83 (C), 104.2, 104.9, 110.8, 111.4, 124.2, 125.3, 127.1, 127.4, 127.6, 129.7, 130.2, 143.1, 143.6 and 154.3 (14 C, *sp*<sup>2</sup>), 164.2 (C=O), 165.4 (C=O).

*Dimethyl-2-11b-dihydro-2-(5-nitrofurane-2-yl)-[1,3]-oxazino-[2,3-a]-isoquinoline-3, 4-dicarboxylate (4d):*

Brown crystals: yield: 65%, mp 90-92°C; IR: (KBr) (Vmax/cm<sup>-1</sup>): 3087(CH, aromatic), 2955 (CH), 1702 (C=O), 1595 and 1437(NO<sub>2</sub>).

<sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>); 3.71 (*s*, OCH<sub>3</sub>), 3.94 (*s*, OCH<sub>3</sub>), 5.31 (*s*, CH ring junction), 5.80 (*s*, CH), 6.44 (*d*, <sup>3</sup>*J*=7.2 Hz, CH furan), 6.51 (*d*, <sup>3</sup>*J*=7.2 Hz, HC=CH furan), 6.99 and 7.15 (*t*, <sup>3</sup>*J* = 4.7 and 3.6 Hz, CH ph), 7.17 (*d*, <sup>3</sup>*J* = 3.6 Hz, CH ph). <sup>13</sup>CNMR (125MHz, CDCl<sub>3</sub>); 52.5 (OCH<sub>3</sub>), 53.7 (OCH<sub>3</sub>), 53.9 (C ring junction), 57.5 (C), 120.7-150.8 (14 C of aromatic), 164.7 (C=O), 165.2 (C=O).

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