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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Abstract: The 1,4-dipolar derived from isoquinoline and DMAD has been shown to react readily with arylaldehyde derivatives in the diastereoselective synthesis of (2S,2R)-dimethyl-2,11b-dihydro-2-[3-nitrophenyl]-[1,3]-oxazino-[2,3-a]-isoquinoline-3,4-dicarboxylate (4a), dimethyl-2-(4-bromophenyl)-2,11b-dihydro-[1,3]-oxazino[2,3-a]-isoquinoline-3,4-dicarboxylate (4b), dimethyl-2-(furan-2-yl)-2,11b-dihydro-[1,3]oxazino[3,2-a] isoquinoline-3,4-dicarboxylate (4c) and dimethyl-2,11b-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 CH2Cl2 at room temperature, to produce 4a-4d in excellent yields (Scheme 1).

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

NMR data for major isomer (66%); 1H NMR spectrum of 4a, showed two singlets at δ=4.03 and
δ=3.64 ppm for the methoxy protons. The ring junction proton of 4a, was observed as a singlet at δ=5.80 and the other proton displayed a singlet at δ=5.86 ppm. In the $^{13}$C NMR spectra 4a, the two methoxy resonated at about δ=52.3 and 53.9 and two ester carbonyls resonated at δ=165.2 and 168.1. NMR data for minor isomer (33%); $^{1}$H NMR spectrum of minor isomer 4a showed two singlets at δ=3.99 and δ=3.56 ppm for the methoxy protons. The ring junction proton, was observed as a singlet at δ=6.07 and the other proton displayed a singlet at δ=6.25 ppm. In the $^{13}$C NMR spectrum of minor isomer 4a, the two methoxy resonated at about δ=52.3 and 54.0 and two ester carbonyls resonated at δ=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.

**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. $^{1}$H and $^{13}$C NMR spectra: Bruker DRX-500 or 300 Avance instrument; in CDCl$_3$ or DMSO at 500 or 300 and 125.7 or 75 MHz, respectively; δ 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 CH₂Cl₂ (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 I).

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

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Reaction time</th>
<th>Yield</th>
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<tbody>
<tr>
<td>Isoquinoline + m-nitrobenzaldehyde</td>
<td>8 h</td>
<td>70%</td>
</tr>
<tr>
<td>Isoquinoline + m-nitrobenzaldehyde</td>
<td>25 min</td>
<td>90%</td>
</tr>
<tr>
<td>Isoquinoline + p-bromobenzaldehyde</td>
<td>8 h</td>
<td>60%</td>
</tr>
<tr>
<td>Isoquinoline + p-bromobenzaldehyde</td>
<td>20 min</td>
<td>85%</td>
</tr>
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</table>

Dimethyl-2,11b dihydro-2-(3-nitrophenyl)-[1,3]oxazino[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⁻¹): 3087 (CH, aromatic), 2955(CH), 1702 (C=O), 1595 and 1437(NO2). NMR data for major isomer (33%): ¹HNMR (500MHz, CDCl3); 3.63 (3 H, s, OCH3), 4.03 (3 H, s, OCH3), 5.70 (1 H, d, J=7.8 Hz, CH), 5.80 (s, CH), 5.86 (s, CH), 6.47 (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); ¹³CNMR (75 MHz, CDCl3); major 4a: 52.3 (OCH3), 53.9 (OCH3), 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, 131.5, 135.5 and 148.6 (16 C, 164.1 (C=O), 165.2 (C=O); NMR data for minor isomer 4a (33%): ¹HNMR (500MHz, CDCl3); 3.56 (s, OCH3), 3.99 (s, OCH3), 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); ¹³CNMR (75 MHz, CDCl3) for minor isomer 4a: 52.3 (OCH3), 54.0 (OCH3), 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, 131.5, 135.5 and 148.8 (16 C, 164.1 (C=O), 165.2 (C=O).
References


