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Additional Information
Regio- and Stereoselective Synthesis of 3-Pyrazolylidene-2-oxindole Compounds by Nucleophilic Vinylic Substitution of (E)-3-(Nitromethylene)indolin-2-one.

Carlos Vila,a* Sophie Slack,a Gonzalo Blay,a M. Carmen Muñozb and José R. Pedroa*

a Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain). E-mail: jose.r.pedro@uv.es, carlos.vila@uv.es.

b Departament de Física Aplicada, Universitat Politècnica de València, Camino de Vera s/n, 46022 València (Spain).

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Abstract. A highly regio- and stereoselective synthesis of 3-alkylidene-2-oxindoles has been described through a nucleophilic vinylic substitution (SnV) of (E)-3-(nitromethylene)indolin-2-one using pyrazol-3-ones as nucleophiles and Et3N as a base. The reaction affords selectively the Z-isomer when pyrazol-3-ones without substituents at the 4 position are used. While the reaction is E-selective with 4-substituted pyrazolones. The stereoselectivity (up to >20:1) and the yields (up to 98%) are very high under mild reaction conditions.

Keywords: regioselectivity; pyrazolone; 2-oxindole; stereoselectivity; vinylic substitution

Nitrogen-containing aromatic heterocycles are omnipresent in agrochemicals, pharmaceuticals and natural products.[1] In this context, oxindole scaffold represents one of the most important structure for medicinal chemistry, due to the large number of biologically active compounds that have this scaffold in their structure.[2] Therefore, oxindole have become in the last decades a privileged skeleton for library design and drug discovery.

As an important 2-oxindole structure, unsymmetrical 3-alkylidene-2-oxindoles[3] are present in various natural products[4] and are considered as significant pharmacophores (Figure 1). For example, Tenidap is an antirheumatic drug,[5] SU4984[6] and Sunitinib[7] are tyrosine kinase inhibitors, and Semaxanib[8] and Sunitinib are drugs for the treatment of renal cell carcinoma. In view of the great importance of the 3-alkylidene-2-oxindole skeleton, the regio- and stereoselective synthesis of such compounds have become an attractive goal for organic synthesis. There are several reported synthetic methods to access to 3-alkylidene-2-oxindoles compounds, such as the aldol condensation of 3-unsubstituted oxindoles and carbonyl compounds,[9] Wittig reaction of isatins,[10] palladium-catalyzed C-H activation-cyclization of N-aryl-propiolamide,[11] palladium catalyzed cyclization reaction of 2-(alkynyl)aryl isocyanates,[12] among others.[13] Although these methods are efficient, they suffer from some difficulties such as the use of hazardous or toxic reagents, generate a lot of waste, present poor atom economy or use expensive transition metal catalysts. We envisioned that the synthesis of unsymmetrical 3-alkylidene-2-oxindoles could be achieved by nucleophilic vinylic substitution (SnV)[14] of (E)-3-(nitromethylene)indolin-2-one (Scheme 1). However, this reaction has been scarcely studied in nitroolefins. Moreover, when (E)-3-(nitromethylene)indolin-2-one is used as an electrophile,[15] several challenges have to be addressed. First, the regioselectivity[16] of the addition step must be controlled since the nucleophile can attack the β-position of the nitroolefin (path A) or the α-position (path B). Second, in this last path, the addition product can progress through a nitrous acid elimination reaction whose stereoselectivity must be controlled. Xue and Tang, have described the use of (E)-3-(nitromethylene)indolin-2-one as an olefination reagent for the synthesis of 3-alkenyldiones using as nucleophiles alcohols, thiols and amines with good yields and excellence diastereoselectivities to the E isomer.[17] They also tried carbon nucleophiles, with only one successful example using ethyl cyclopentanone-2-carboxylate as nucleophile, however with a moderate yield.

Figure 1. Examples of bioactive 3-alkylideneoxindoles
Scheme 1. Nucleophilic addition of pyrazolones to isatin-derived nitroalkenes.

In view of the bibliographic antecedents on the use of carbon nucleophiles against \((E)-3-(\text{nitromethylene})\text{indolin-2-one}\) in nucleophilic vinylic substitution we decided to test pyrazol-3-ones as nucleophiles. The pyrazolone is a prominent nitrogen heterocycle,\(^{[18]}\) which is present in numerous biologically active compounds with antiinflammatory, antiviral, antitumor or antibacterial properties;\(^{[19]}\) moreover, pyrazol-3-ones are present in several pharmaceutical compounds such as edaravone,\(^{[20]}\) metamizole\(^{[21]}\) or remogliflozin etabonate\(^{[22]}\). Given the relevance of pyrazol-3-ones and 3-alkyl idene-2-oxindoles, it was anticipated that the incorporation of both structural motifs into one molecule could result in novel 3-alkylidene-2-oxindoles bearing a pyrazol-3-one ring with potentially interesting biological properties (Scheme 2). As a part of our ongoing interest in the nucleophilic addition of pyrazol-3-ones\(^{[23]}\) here we described the highly regio- and stereoselective addition of pyrazol-3-ones to \((E)-3-(\text{nitromethylene})\text{indolin-2-one}\) 1a, providing novel 3-alkylidene-2-oxindole adducts. The reaction is \(Z\)- or \(E\)-stereoselective depending of the substitution pattern at the 4 position of the pyrazol-3-one.

We initiated our study by using the \((E)-1\text{-benzyl}-3-(\text{nitromethylene})\text{indolin-2-one}\) 1a and 5-methyl-2-phenyl-2,4-dihydro-3\(H\)-pyrazol-3-one (2a) as model substrates to study the nucleophilic vinylic substitution (S\(\text{N}_\text{V}\)) in toluene and in the presence of Et\(\text{N}\) (50 mol\%) at room temperature (Table 1). To our delight, after 1 hour, 1-benzyl-3-((5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one 3aa was obtained regioselectively with 59\% yield and with excellent stereoselectivity to the \(Z\) isomer.\(^{[24]}\) This is remarkable, because in the report of Tang\(^{[17]}\) the S\(\text{N}_\text{V}\) with 1a was stereoselective to the \(E\) isomer. We attribute the \(Z\) stereoselectivity to the presence of a hydrogen bonding between the carbonyl of the oxindole and the enol form of the pyrazolone. Subsequently, a survey of solvents were screened, obtaining the best yield (79\%) when THF was used as a solvent (entry 5, Table 1). Increasing the amount of Et\(\text{N}\) (entry 6) or using DBU (entry 7) as a base did not improved the yield of product 3aa. After the reaction was performed at 0 °C, although the yield of 3aa was slightly lower (entry 8). The reaction did not work without the presence of a base (entry 9).

With the optimized reaction conditions in hand (entry 5, Table 1), we proceeded to study the scope of the nucleophilic vinylic substitution of 1 with different pyrazol-3-ones 2 (Scheme 3), obtaining excellent regio- and stereoselectivities to the \(Z\) isomer (\(>20:1\)), and moderate to good yields (57-81\%). First we tested different nitroalkenes derived from isatines with pyrazol-3-one 2a. Initially, \(N\)-substitution of the oxindole nitrogen was evaluated (Scheme 1, 3aa-3fa). Groups such as benzyl, methyl, allyl, propargyl or –CH\(_2\)CO\(_2\)Me were well accommodated, obtaining the corresponding adducts with good yields (65-79\%). In

Scheme 2. 3-Alkylidene-2-oxindole adducts bearing a pyrazol-3-one moiety.

Table 1. Optimization of the reaction conditions.\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>E:Z (%)(^b)</th>
<th>Y. (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>rt</td>
<td>1</td>
<td>&gt;1:20</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>4</td>
<td>&gt;1:20</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>Et(_2)O</td>
<td>rt</td>
<td>5</td>
<td>&gt;1:20</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>rt</td>
<td>1</td>
<td>&gt;1:20</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>rt</td>
<td>1</td>
<td>&gt;1:20</td>
<td>79</td>
</tr>
<tr>
<td>6(^d)</td>
<td>THF</td>
<td>0 °C</td>
<td>1</td>
<td>&gt;1:20</td>
<td>72</td>
</tr>
<tr>
<td>7(^e)</td>
<td>THF</td>
<td>rt</td>
<td>1</td>
<td>&gt;1:20</td>
<td>55</td>
</tr>
<tr>
<td>8(^f)</td>
<td>THF</td>
<td>0 °C</td>
<td>1</td>
<td>&gt;1:20</td>
<td>74</td>
</tr>
<tr>
<td>9(^f)</td>
<td>THF</td>
<td>rt</td>
<td>30</td>
<td>n.d</td>
<td>n.d</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 0.1 mmol 1a, 0.2 mmol 2a, and Et\(\text{N}\) (50 mol\%) in solvent (2 mL).\(^b\) Determined by \(^1\)H NMR.\(^c\) Isolated yield after column chromatography.\(^d\) With 100 mol\% Et\(\text{N}\).\(^e\) With 50 mol\% DBU.\(^f\) Without Et\(\text{N}\).
addition, non-protected free NH on the oxindole ring was also tolerated (3Fa), which allows easy potential N-substitutions on demand. Electron-donating (MeO, Me) or electron-withdrawing (Cl or Br), were tolerated at the 5, 6 or 7 positions of the isatin-derived nitroalkene, affording the corresponding products (3ga-3ka) with excellent regio- and stereoselectivity and good yields (57-77% yield). Different pyrazol-3-ones were also evaluated in the reaction with nitroalkene 1a. So, 2,5-dimethyl-pyrazol-3-one 2b was tested with nitroalkene 1a and 1b, leading to the corresponding products 3ab and 3bb, with lower yields than product 3aa. Moreover, when 2,5-diaryl-pyrazol-3-ones were tested with nitroalkene 1a, the corresponding product 3ac was obtained with 70% yield and a ratio (>20:1) in product 5aa, which allows easy potential N-substitutions on demand. Electron-donating (Me or MeO) or electron-withdrawing (Cl or Br), were tolerated at 5, 6 or 7 positions of the isatin-derived nitroalkene 1a. So, 2,5-dimethyl-pyrazol-3-one 1a, and 2,5-diaryl-pyrazol-3-ones were tested the corresponding product 3ad and 3ae, leading to the corresponding products 3af and 3ag were afforded with good yields (65-71%). The configuration of the double bond in product 3ka, was determined unambiguously by X-ray crystallography.[25]

Having established the optimal reaction conditions (entry 5, Table 1), the scope of the SnV reaction using several 4-substituted-pyrazol-3-ones was evaluated (Scheme 4). First, in the case of 4-substituted-pyrazolones, the N-substitution of oxindole was investigated (Scheme 4, 5aa-5fa). Groups such as benzyl, methyl, allyl, propargyl or CH2=CHCH3 were well tolerated, and the corresponding products 5 were obtained with excellent yields (76-96% yield) and excellent E:Z ratio, although the unprotected 5fa was gained with lower yield (67%). Next, the effect of substitution in the benzene ring of the N-benzyl protected isatin-derived nitroalkenes was studied (1g-1k). Different electron-donating (Me or MeO) or electron-withdrawing (Cl or Br), were tolerated at different positions of the isatin-derived nitroalkenes.
affording the corresponding products 5 with good yields (62-87% yield) and excellent E stereoselectivity. Next, the substrate scope with respect to other 4-substituted pyrazol-3-ones 4 was evaluated (5ab-5af) obtaining excellent values of \(E:Z\) ratios, with high yields (69-95%). The configuration of the double bond in product 5aa, was determined unambiguously by X-ray crystallography.\[26\]

![Scheme 4](image)

Scheme 4. Substrate scope of the \(\text{S}_{\text{N}}\text{V}\) reaction. Reaction conditions: 0.1 mmol 1, 0.2 mmol 4, and Et\(_3\)N (100 mol%) in CHCl\(_3\) (2 mL) at rt.

On the basis of the experimental results, we propose a plausible mechanism for the regio- and stereoselective \(\text{S}_{\text{N}}\text{V}\) reaction as is depicted in the Scheme 5. By the action of a base, the intermediate 6 is generated after the regioselective nucleophilic addition of the pyrazol-3-one to the \(\alpha\)-position of nitroalkene 1. We believe that the addition of the pyrazol-3-one, occurs at this carbon due to the steric effects. When the pyrazolone does not have substituents at 4 position, the intermediate 6 switches to the intermediate 7, favored by an intramolecular hydrogen bond between the carbonyl of the oxindole and the enol form of the pyrazolone moiety (intermediate 7). The hydrogen bond prompts a fast 1,2-trans-elimination in the presence of a base to afford the Z-3-alkenyl-2-oxindole 3aa. However, when the pyrazolone have a substituent at 4-position, the intermediate 6 switches to an eclipsed conformation, (intermediate 8), which is favored by an intramolecular hydrogen bond between the nitro group and the hydrogen of the C-3 of oxindole through a five-membered ring.\[17\] In this case, in the presence of a base, the hydrogen bond prompts a fast 1,2-cis-elimination to afford the \(E\)-3-alkenyl-2-oxindole 5aa. The base, in this \(\text{S}_{\text{N}}\text{V}\) reaction, assists the regioselective nucleophilic addition, as well as the stereoselective elimination.

![Scheme 5](image)

Scheme 5. Plausible mechanism for the \(\text{S}_{\text{N}}\text{V}\) reaction.

In conclusion, we have developed a nucleophilic vinylic substitution of pyrazol-3-ones to isatin-derived nitroalkenes, using Et\(_3\)N as a base, obtaining stereoselectively 3-alkenyl-2-oxindole bearing a pyrazolone moiety. The stereoselectivity towards the \(E\) or \(Z\) double bond formation depends of the substitution pattern of the pyrazol-3-one at 4 position. If the pyrazolone does not have a substituent at 4 position, the corresponding products 3, are obtained with good yields (up to 81%) and \(1:20\ E:Z\) ratio. While, with 4-substituted pyrazol-3-ones the reaction affords 3-alkenyl-2-oxindoles adducts 5 with excellent yields (up to 96%) and up to \(20:1\ E:Z\) ratio. The present methodology represents a powerful synthetic tool for the stereoselective synthesis of potentially bioactive 3-alkenyl-2-oxindole adducts bearing a pyrazolone moiety.

Experimental Section

General procedure for the \(\text{S}_{\text{N}}\text{V}\) reaction with nitroalkenes 1 and pyrazolones 2.

In a 10 mL round bottom flask, 3-nitromethylene-2-indolinone 1 (0.1 mmol) and pyrazol-3-one 2 (0.2 mmol) were dissolved in THF (2 mL). Triethylamine (50 mol%, 0.05 mmol, 7 µL) was added. The mixture was stirred at room temperature until completion (TLC). The THF was removed under reduced pressure and the residue was purified by column chromatography being eluted with hexane/EtOAc 98:2 to hexane/EtOAc 95:5, affording product 3.
General procedure for the S$_3$N$_3$V reaction with nitroalkenes 1 and pyrazolones 4.

In a 10 mL round bottom flask, 3-nitromethylene-2-indolione 1 (0.1 mmol) and 4-substituted pyrazol-3-one 4 (0.2 mmol) were dissolved in CHCl$_3$ (2 mL). Triethylamine (100 mol%, 0.1 mmol, 15 µL) was added. The mixture was stirred at room temperature until completion (TLC). Finally, the reaction mixture was directly poured into a column for chromatography, and the crude product was purified using hexane/EtOAc 95:5 or DCM/EtOAc 100:0 to 95:5, affording product 5.

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References


[24] CCDC 1889981 (3ka) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

[25] CCDC 1890014 (5aa) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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