Vila, C.; Slack, S.; Blay, G.; Muñoz Roca, MDC.; Pedro, JR. (16-0). Regio- and Stereoselective Synthesis of 3-Pyrazolylidene-2-oxindole Compounds by Nucleophilic Vinylic Substitution of (E)-3-(Nitromethylene)indolin-2-one. Advanced Synthesis & Catalysis. 361(8):1902-1907. https://doi.org/10.1002/adsc.201900048

# 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 Muñoz[b] and José R. Pedro[a]*

[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)

Received: ((will be filled in by the editorial staff))

**Abstract.** A highly regio- and stereoselective synthesis of 3-alkylidene-2-oxindoles has been described through a nucleophilic vinylic substitution ($S_NV$) of (*E*)-3-(nitromethylene)indolin-2-one using pyrazol-3-ones as nucleophiles and $Et_3N$ 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.

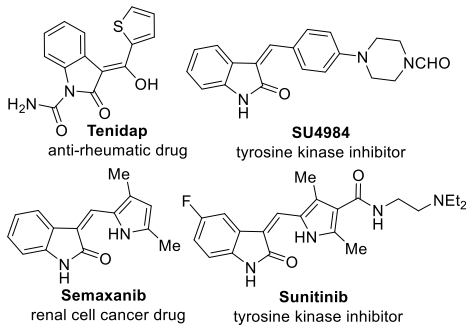
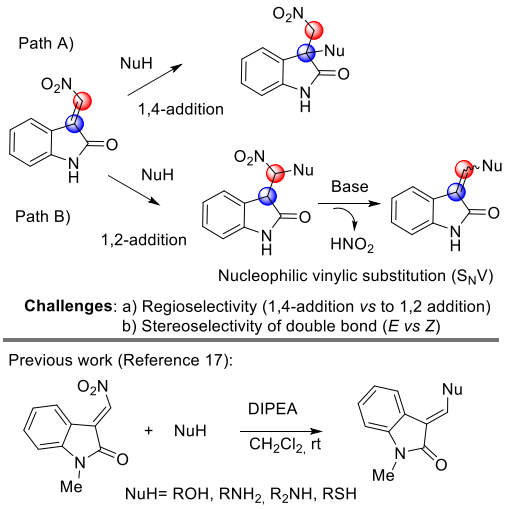


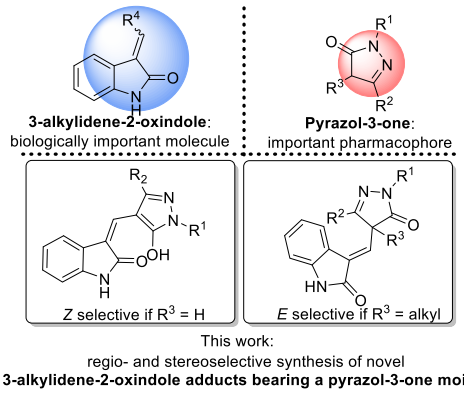

**Figure 1.** Examples of bioactive 3-alkylideneoxindoles

As an important 2-oxindole structure, unsymmetrical 3-alkylidene-2-oxindoles[3] are present in various natural products[4] and are considered as significant pharmacopheres (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 ($S_NV$)[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-alkenylindoles using as nucleophiles alcohols, thiols and amines with good yields and excellents 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.




**Scheme 1.** Nucleophilic addition of pyrazolones to isatin-derived nitroalkenes.

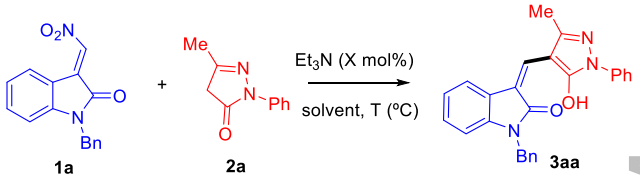
In view of the bibliographic antecedents on the use of carbon nucleophiles against (*E*)-3-(nitromethylene)indolin-2-one in nucleophilic vinylic substitution we decided to test pyrazol-3-ones as nucleophiles. The pyrazolone is a prominent nitrogen heterocycle,[18] which is present in numerous biologically active compounds with antiinflamatory, 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-alkylidene-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-(nitromethylene)indolin-2-ones, 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.




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

We initiated our study by using the (*E*)-1-benzyl-3-(nitromethylene)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 ($S_NV$) in toluene and in the presence of $Et_3N$ (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 $S_NV$ 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 $Et_3N$ (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 ºC, although the yield of **3aa** was slightly lower (entry 8). The reaction did not work without the presence of a base (entry 9).

**Table 1.** Optimization of the reaction conditions.[a]

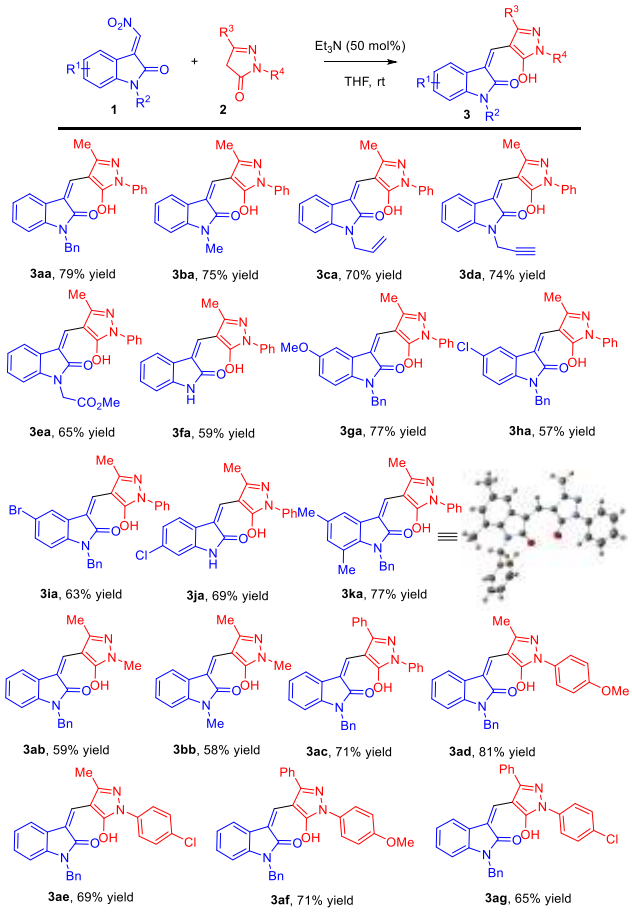



| Entry | Solvent | T (ºC) | t (h) | *E*:*Z* (%)[b] | Y. (%)[c] |
|---|---|---|---|---|---|
| 1 | toluene | rt | 1 | >1:20 | 59 |
| 2 | $CH_2Cl_2$ | rt | 4 | >1:20 | 47 |
| 3 | $Et_2O$ | rt | 5 | >1:20 | 62 |
| 4 | EtOAc | rt | 1 | >1:20 | 71 |
| 5 | THF | rt | 1 | >1:20 | 79 |
| 6[d] | THF | rt | 1 | >1:20 | 72 |
| 7[e] | THF | rt | 1 | >1:20 | 55 |
| 8 | THF | 0 ºC | 1 | >1:20 | 74 |
| 9[f] | THF | rt | 30 | n.d | n.d |

[a] Reaction conditions: 0.1 mmol **1a**, 0.2 mmol **2a**, and $Et_3N$ (50 mol%) in solvent (2 mL). [b] Determined by $^1H$ NMR. [c] Isolated yield after column chromatography. [d] With 100 mol% $Et_3N$. [e] With 50 mol% DBU. [f] Without $Et_3N$.

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 –$CH_2CO_2Me$ were well accommodated, obtaining the corresponding adducts with good yields (65-79%). In

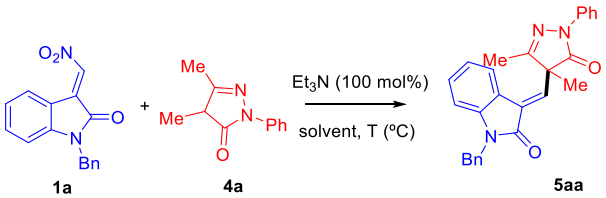
addition, non-protected free NH on the oxindole ring was also tolerated (**3fa**), which allows easy potential *N*-substitutions on demand. Electron-donating (MeO, Me) or electron-withdrawing (Cl or Br), were tolerated at the 5, 6 or 7 positions of the isatin-derived nitroalkene, affording the corresponding products (**3ga**-**3ka**) with excellent regio- and stereoselectivity and good yields (57-77% yield). Different pyrazol-3-ones **2** 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**. Nevertheless, the reaction proceeded efficiently with pyrazolones with diverse substituents (MeO or Cl) in the *N*-aryl group (**3ad**-**3ae**). Moreover, when 2,5-diaryl-pyrazol-3-ones were tested the corresponding product **3ac**, **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]




**Scheme 3.** Substrate scope of the $S_NV$ reaction. Reaction conditions: 0.1 mmol **1**, 0.2 mmol **2**, and $Et_3N$ (50 mol%) in THF (2 mL) at rt.

After having proved the efficiency of our methodology for the $S_NV$ reaction of isatin-derived nitroalkenes with pirazolones **2**, we decided to study the reaction of **1a** with pyrazol-3-ones bearing a substituent at 4 position. Our initial studies were focused on the addition of 4,5-dimethyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**4a**) to nitroalkene **1a** (Table 2). First, we evaluated the reaction in the initial conditions used in Table 1 (50 mol% $Et_3N$ in toluene as a solvent). The corresponding 3-alkylidene-2-oxindole **5aa** bearing a pyrazolone moiety was obtained with 70% yield and a good 10:1 *E*:*Z* ratio after 4 hours reaction time (entry 1, Table2). In this $S_NV$ reaction, the favoured product is the *E* product. At this point, we decided to use 1 eq. of $Et_3N$ as a base (entry 2), obtaining the product **5aa** with an improvement of the yield (98%) although with a slight decrease in stereoselectivity (9:1 *E*:*Z* ratio) after 0.5 hour of reaction time (entry 2, Table2). Different solvents such as THF, $CH_2Cl_2$, $CHCl_3$, $Et_2O$ or EtOAc were tested using 1 eq. of $Et_3N$. The best *E*:*Z* ratio (>20:1) in product **5aa**, was obtained when $CHCl_3$ was used as a solvent (entry 5), without compromising the yield (96%).

**Table 1.** Optimization of the reaction conditions.[a]

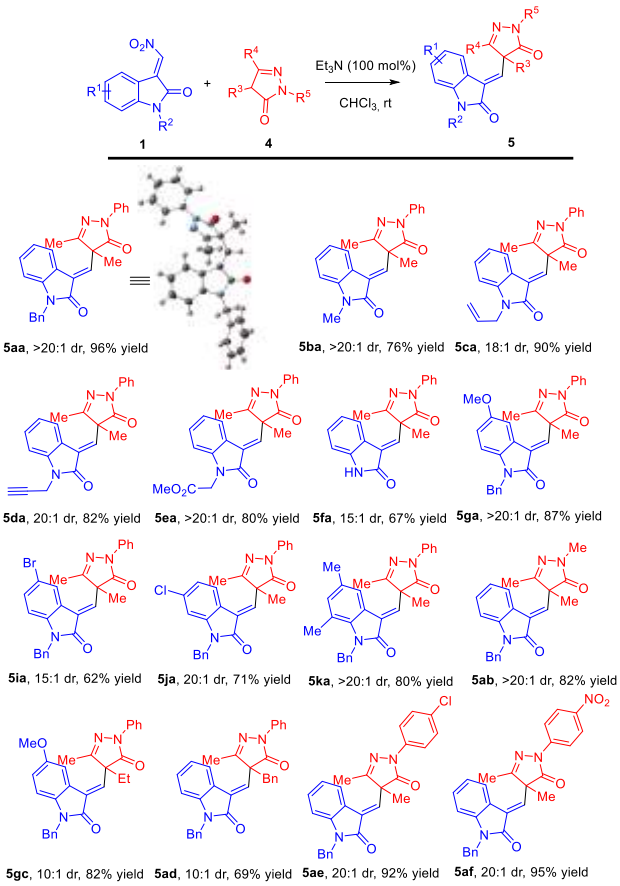



| Entry | Solvent | t (h) | *E*:*Z* (%)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1[d] | toluene | 4 | 10:1 | 70 |
| 2 | toluene | 0.5 | 9:1 | 98 |
| 3 | THF | 1 | 2:1 | 98 |
| 4 | $CH_2Cl_2$ | 1 | 13:1 | 94 |
| 5 | $CHCl_3$ | 1 | >20:1 | 96 |
| 6 | $Et_2O$ | 1 | 12:1 | 93 |
| 7 | EtOAc | 1 | 6:1 | 78 |

[a] Reaction conditions: 0.1 mmol **1a**, 0.2 mmol **4a**, and $Et_3N$ (100 mol%) in solvent (2 mL) at rt. [b] Determined by $^1H$ NMR. [c] Isolated yield after column chromatography. [d] With 50 mol% of $Et_3N$.

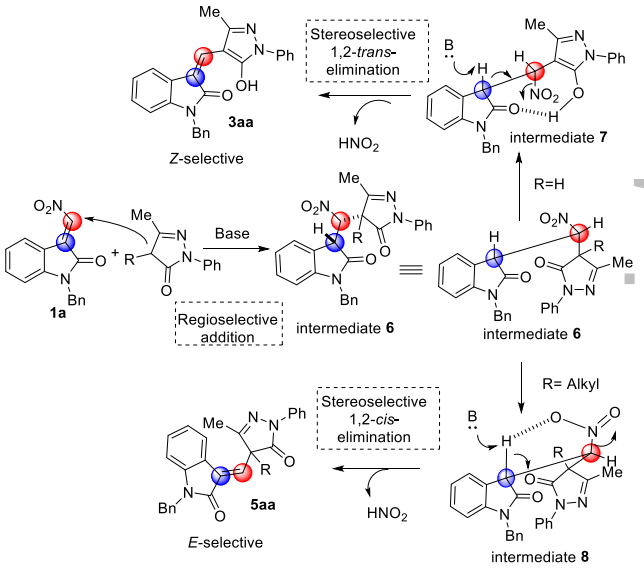
Having established the optimal reaction conditions (entry 5, Table 1), the scope of the $S_NV$ reaction using several 4-substituted-pyrazol-3-ones was evaluated (Scheme 4). First, in the case of 4-substituted-pyrazolones, the *N*-substitution of oxindole was investigated (Scheme 4, **5aa**-**5fa**). Groups such as benzyl, methyl, allyl, propargyl or $CH_2CO_2Me$ 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.** Substrate scope of the $S_NV$ reaction. Reaction conditions: 0.1 mmol **1**, 0.2 mmol **4**, and $Et_3N$ (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 $S_NV$ 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 α-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, 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 $S_NV$ reaction, assists the regioselective nucleophilic addition, as well as the stereoselective elimination.




**Scheme 5.** Plausible mechanism for the $S_NV$ reaction.

In conclusion, we have developed a nucleophilic vinylic substitution of pyrazol-3-ones to isatin derived nitroalkenes, using $Et_3N$ 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 $S_NV$ 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 $S_NV$ reaction with nitroalkenes 1 and pyrazolones 4.**

In a 10 mL round bottom flask, 3-nitromethylene-2-indolinone **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**.

## Acknowledgements

*Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (CTQ2017-84900-P) is acknowledged. C.V. thanks the Spanish Government for Ramón y Cajal contract (RYC-2016-20187). Access to NMR, MS and X-ray facilities from the Servei Central de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged.*

## References

[1] a) *Ring Nitrogen and Key Biomolecules: The Biochemistry of N-Heterocycles*, Ed.: E.G. Brown, Springer, **1998**; b) *Heterocyclic Chemistry*, Ed.: J. A. Joule, K. Mills, Wiley, Chichester, **2010**; c) *Modern Heterocyclic Chemistry*, Ed.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Wiley-VCH, Weinheim, **2011**.

[2] a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem*. **2003**, 2209-2219; b) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2007**, *46*, 8748-8758; c) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003-3025; d) J. Klein, R. Taylor, *Eur. J. Org. Chem*. **2011**, 6821-6841.

[3] A. Millemaggi, R. Taylor, *Eur. J. Org. Chem*. **2010**, 4527-4547.

[4] a) K. Hata, K. Baba, M. Kozawa, *Chem. Pharm. Bull*. **1978**, *26*, 2279-2280; b) B. Weniger, Y. Jiang, R. Anton, J. Bastida, T. Varea, J.-C. Quirion, *Phytochemistry* **1993**, *32*, 1587-1590; c) X. Wu, Y. Liu, W. Sheng , J. Sun, G. Qin, *Planta Med*. **1997**, *63*, 55-57; d) M. S. C. Pedras, P. B. Chumala, M. Suchy, *Phytochemistry* **2003**, *64*, 949-956; e) M. S. C. Pedras, J. L. Sorensen, F. J. Okanga, I. L. Zaharia, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3015-3020; f) L. Zhou, J.- S. Yang, X. Wu, J.- H. Zou, X.- D. Xu, G.- Z. Tu, *Heterocycles* **2005**, *65*, 1409-1414; g) I. Fatima, I. Ahmad, S. A. Nawaz, A. Malik, N. Afza, G. Luttfullah, M. I. Choudhary, *Heterocycles* **2006**, *68*, 1421-1428; h) I. Fatima, I. Ahmad, I. Anis, A. Malik, N. Afza, *Molecules* **2007**, *12*, 155-162.

[5] L. Xu, Y. Hao, X. Wu, P. Yu, G. Zhu, Z. Hong, *Neurolog. Res.* **2013**, *35*, 561-567.

[6] M. Mohammadi, G. McMahon, L. Sun, C. Tang, P. Hirth, B. Yeh, S. Hubbard, R. Schlessinger, *Science* **1997**, *276*, 955-960.

[7] T. Kimura, M. Uesugi, K. Takase, N. Miyamoto, K. Sawada, *Toxicol. Appl. Pharmacol.* **2017**, *329*, 282-292.

[8] T. Fong, L. K. Shawver, L. Sun, C. Tang, H. App, T. Powell, Y. Kim, R. Schreck, X. Wang, W. Risau, A. Ullrich, K. Hirth, G. McMahon, *Cancer Res.* **1999**, *59***,** 99-106.

[9] a) A. Wahl, P. Bayard, *Comptes Rend.***1909**, *148*, 716-719; b) L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon, C. Tang, *J. Med. Chem.* **1998**, *41*, 2588-2603.

[10] a) H. A. Brandman, *J. Heterocycl. Chem*. **1973**, *10*, 383-384; b) J. Azizian, M. R. Mohammadizadeh, Z. Kazemizadeh, N. Karimi, A. A. Mohammadi, A. R. Karimi, A. Alizadeh, *Lett. Org. Chem*. **2006**, *3*, 56-57.

[11] a) S. Tang, P. Peng, S. Pi, Y. Liang, N. Wang, J.-H. Li, *Org. Lett*. **2008**, *10*, 1179-1182; b) S. Tang, P. Peng, Z. Wang, B. Tang, C. Deng, J.-H. Li, P. Zhong, N. Wang, *Org. Lett.* **2008**, *10*, 1875-1878; c) A. Pinto, L. Neuville, P. Retailleau, J. Zhu, *Org. Lett*. **2006**, *8*, 4927-4930.

[12] a) S. Kamijo, Y. Sasaki, C. Kanazawa, T. Schüßeler, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 7718-7721; b) T. Miura, T. Toyoshima, Y. Takahashi, M. Murakami, *Org. Lett.* **2008**, *10*, 4887-4889; c) T. Miura, T. Toyoshima, Y. Takahashi, M. Murakami, *Org. Lett.* **2009**, *11*, 2141-2143; d) G. Cantagrel, B. de Carné-Carnavalet, C. Meyer, J. Cossy, *Org. Lett*. **2009**, *11*, 4262-4265.

[13] a) K. Hirao, N. Morii, T. Joh, S. Takahashi, *Tetrahedron Lett*. **1995**, *36*, 6243-6246; b) J. H. Park , E. Kim, Y. K. Chung, *Org. Lett.* **2008**, *10*, 4719-4721; c) Y. Kobayashi, H. Y. Kobayashi, H. Kamisaki, R. Yanada, Y. Takemoto, *Org. Lett*. **2006**, *8*, 2711-2713; d) M. R Fielding, R. Grigg, C. J. Urch, *Chem. Commun*. **2000**, 2239-2240; e) M. Inoue, T. Takahashi, H. Furuyama, M Hirama, *Synlett* **2006**, 3037-3040; f) B. Lu, D. Ma, *Org. Lett.* **2006**, *8*, 6115-6118; g) Z. Tu, J. Tan, Z. Chen, T. Tu, *Adv. Synth. Catal.* **2017**, *359*, 4294-4299; h) W.-K. Yuan, T. Cui, W. Liu, L.-R. Wen, M. Li, *Org. Lett*., **2018**, *20*, 1513-1516; i) K. F. Suzdalev, M. N. Babakova, V. G. Kartsev, K. A. Krasnov, *Heterocycles*, **2015**, *91*, 64-75; j) D. Qian, J. Zhang, *Chem. Commun*. **2012**, *48*, 7082-7084.

[14] F. C. Bernasconi, Z. Rappoport, *Acc. Chem. Res*. **2009**, *42*, 993-1003.

[15] G. Chen, X.-J. Hao, Q.-Y. Sun, J. Ding, *Chem. Pap*., **2010**, *64*, 673-677.

[16] T. Aria, Y. Yamamoto, A. Awata, K. Kamiya, M. Ishibashi, M. A. Arai, *Angew. Chem. Int. Ed*. **2013**, *52*, 2486-2490.

[17] H. Zhang, Y. Liu, R. Chen, J. Xue, Y. Li, Y. Tang, *Asian J. Org. Chem*. **2013**, *2*, 307-310.

[18] G. Varvounis, in *Pyrazol-3-ones. Part IV: Synthesis and Applications*, Ed. A. R. Katritzky, Advances in Heterocyclic Chemistry, Academic Press, New York, **2009**, vol. *98*, p. 143

[19] a) N. Yokoyama, B. Ritter, A. D. Neubert, *J. Med. Chem*. **1982**, *25*, 337-339; b) R. I. Fryer, P. Zhang, R. Rios, Z.-Q. Gu, A. S. Basile, P. Skolnick, *J. Med. Chem*. **1993**, *36*, 1669-1673; c) L. Savini, P. Massarelli, C. Nencini, C. Pellerano, G. Biggio, A. Maciocco, G. Tuligi,

A. Carrieri, N. Cinone, A. Carotti, *Bioorg. Med. Chem*. **1998**, *6*, 389-399; d) F. Caruso, M. Rossi, J. Tanski, R. Sartori, R. Sariego, S. Moya, S. Diez, E. Navarrete, A. Cingolani, F. Marchetti, C. Pettinari, *J. Med. Chem*. **2000**, *43*, 3665-3670; e) M. G. Ferlin, G. Chiarelotto, S. D. Acqua, E. Maciocco, M. P. Mascia, M. G. Pisu, G. Biggio, *Bioorg. Med. Chem*. **2005**, *13*, 3531-3541; e) A. Kimata, H. Nakagawa, R. Ohyama, T. Fukuuchi, S. Ohta, T. Suzuki, N. Miyata, *J. Med. Chem*. **2007**, *50*, 5053-5056.

[20] H. Yoshida, H. Yanai, Y. Namiki, K. Fukatsu-Sasaki, N. Furutani, N. Tada, *CNS Drug Rev*., **2006**, *12*, 9-20.

[21] *''Dipyrone''. Martindale: The Complete Drug Reference*, Ed. A. Brayfield, Pharmaceutical Press, **2014**.

[22] Y. Fujimori, K. Katsuno, I. Nakashima, Y. Ishikawa-Takemura, H. Fujikura, M Isaji, *J. Pharmacol. Exp. Ther*. **2008**, *327*, 268-276.

[23] a) C. Vila, F. I. Amr, G. Blay, M. C. Muñoz, J. R. Pedro, *Chem. Asian J*. **2016**, *11*, 1532-1536; b) F. I. Amr, C. Vila, G. Blay, M. C. Muñoz, J. R. Pedro, *Adv. Synth. Catal*., **2016**, *358*, 1583-1588.

[24] We have not observed on the crude $^{1}$H-NMR and $^{13}$C-NMR any product where the pyrazolone acts as an oxygen nucleophile. For a reference where the pyrazolone acts as a oxygen nucleophile, see: X. Tang, J. Chang, C. Liu, B. Zhang, *Tetrahedron Lett*. **2014**, *55*, 6534-6537.

[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.

[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.

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

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Carlos Vila,[a]* Sophie Slack,[a] Gonzalo Blay,[a] M. Carmen Muñoz,[b] and José R. Pedro[a]*