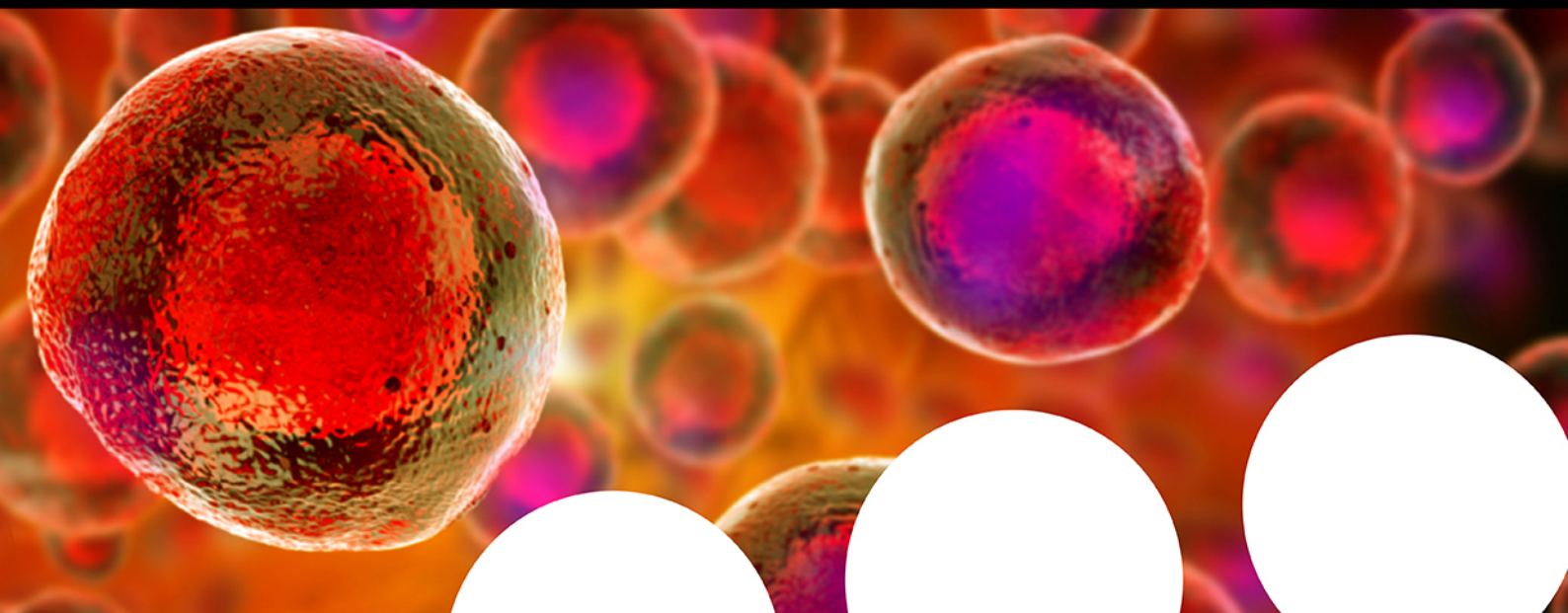


# Your research is important and needs to be shared with the world



## Benefit from the Chemistry Europe Open Access Advantage

- Articles published open access have higher readership
- Articles are cited more often than comparable subscription-based articles
- All articles freely available to read, download and share.

**Submit your paper today.**



[www.chemistry-europe.org](http://www.chemistry-europe.org)

Special  
Collection

# Ruthenium-Catalyzed Decarboxylative Rearrangement of 4-Alkenyl-isoxazol-5-ones to Pyrrole Derivatives

Letizia Molteni,<sup>[a]</sup> Camilla Loro,<sup>[b]</sup> Michael S. Christodoulou,<sup>[a]</sup> Marta Papis,<sup>[b]</sup>  
Francesca Foschi,<sup>[b]</sup> Egle M. Beccalli,<sup>\*[a]</sup> and Gianluigi Broggini<sup>\*[b]</sup>*Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday*

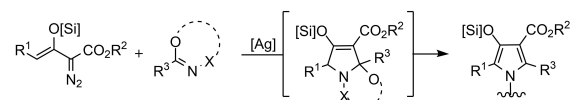
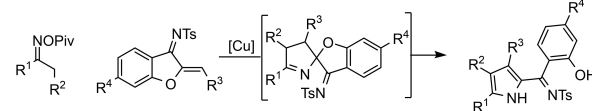
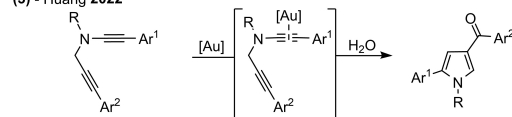
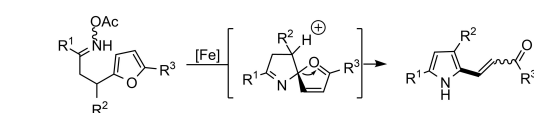
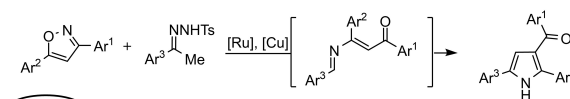
Easily accessible isoxazol-5(4*H*)-ones are useful precursors of heterocycles. In this context, we report the ruthenium-catalyzed transformation of 4-alkenyl-substituted isoxazol-5-ones to afford 1*H*-pyrrole derivatives. The operative conditions were proven to be effective also on cyclohexane-fused isoxazolones giving

4,5,6,7-tetrahydroindoles. The reactions, which allow for access to tri- and tetra-substituted pyrroles in moderate to high yields, occur through decarboxylative ring-opening/ring-closure involving C–H functionalization of the alkenyl moiety.

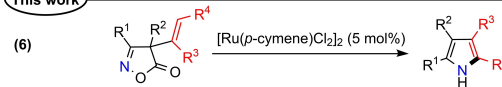
## Introduction

Among the most important heterocyclic compounds, pyrroles represent the structural core in a wide range of natural products and synthetic compounds endowed with various pharmacological and physicochemical properties.<sup>[1]</sup> Consequently, since the pioneering Knorr, Paal-Knorr and Hantzsch reactions,<sup>[2]</sup> their synthesis has always aroused interest in the most important research areas of synthetic chemistry.<sup>[3]</sup> To avoid approaches based on the use of strong operating conditions, which are incompatible with many functional groups and a wide scope of the reaction, transition metal-promoted synthetic protocols have been developed to access pyrroles under mild reaction conditions.<sup>[4]</sup> In this context, more recently Doyle and co-workers described a silver-catalyzed coupling reaction between enol diazoacetates and imino ethers providing fully substituted pyrroles at room temperature (Scheme 1, reaction 1).<sup>[5]</sup> A copper-catalyzed process through [3+2] spiroannulation of oximes and azadienes followed by aromatization of the first-obtained 3*H*-pyrroles was reported by the Jiang and Wei group (Scheme 1, reaction 2).<sup>[6]</sup> Huang and co-workers developed a gold-catalyzed cycloisomerization of 1,5-dienes to afford 1,2,4-trisubstituted pyrroles (Scheme 1, reaction 3).<sup>[7]</sup>

### Previous works

(1) - Doyle 2021<sup>5</sup>(2) - Wei 2021<sup>6</sup>(3) - Huang 2022<sup>7</sup>(4) - Makarov 2021<sup>8</sup>(5) - Kapur 2021<sup>9</sup>

### This work



**Scheme 1.** Recent transition metal-catalyzed procedures for the synthesis of pyrroles.

Two interesting procedures to access pyrrole skeleton by conversion of heterocyclic compounds have been recently achieved using iron or ruthenium catalysis. The former, reported by Makarov, is a rearrangement of furyl-tethered *O*-acetyl oximes, which undergoes 5-*exo-trig* cyclization to generate spiro-intermediates susceptible of aromatization by dihydrofur-

[a] L. Molteni, Dr. M. S. Christodoulou, Prof. E. M. Beccalli  
DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini"  
Università degli Studi di Milano  
Via Venezian 21, 20133, Milano, Italy  
E-mail: egle.beccalli@unimi.it

[b] C. Loro, M. Papis, Dr. F. Foschi, Prof. G. Broggini  
Dipartimento di Scienza e Alta Tecnologia  
Università dell'Insubria  
via Valleggio 11, 22100 Como, Italy  
E-mail: gianluigi.broggini@uninsubria.it

Supporting information for this article is available on the WWW under  
<https://doi.org/10.1002/ejoc.202200496>

Part of the "Cesare Gennari's 70th Birthday" Special Collection.

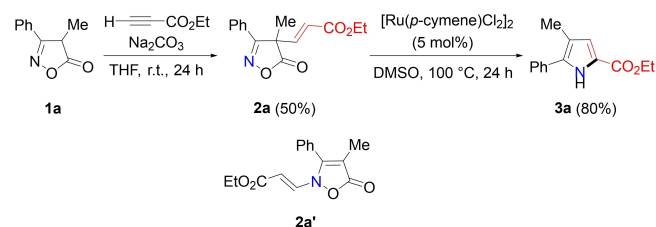
© 2022 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

an ring-opening (Scheme 1, reaction 4).<sup>[8]</sup> In the second-one, the treatment of isoxazoles with sulfonylhydrazones in ruthenium-catalyzed copper-mediated conditions was proven to be a convenient procedure to the synthesis of trisubstituted pyrroles (Scheme 1, reaction 5).<sup>[9]</sup>

Exploitation of isoxazol-5-ones as building blocks in organic synthesis has attracted considerable attention not only due to their easy availability, but also to the versatile reactivity of the generated nitrenoid active species arising from the N–O bond cleavage, depending on their substituents.<sup>[10]</sup> Also in this field, transition metal catalysis by palladium,<sup>[11]</sup> ruthenium,<sup>[12]</sup> iron,<sup>[13]</sup> iridium<sup>[14]</sup> and rhodium<sup>[15]</sup> complexes has proved a powerful tool for widening processes to obtain various types of heterocycles, mainly through decarboxylative reactions. As regards the catalysis with ruthenium, assuming that the generation of a Ru-vinylidene intermediate by decarboxylative opening of isoxazolones in the presence of ruthenium(II) complexes is a general behavior, it is possible to design new strategies for heterocyclic synthesis by modulating the substituent at C4-position. Having long-standing interest toward the investigation of synthetic protocols for nitrogen-containing compounds by carbon-nitrogen bond forming reactions,<sup>[16]</sup> as well as toward the reactivity of the isoxazol-5-ones,<sup>[12d,e,17]</sup> herein we describe a ruthenium(II)-catalyzed reaction for the transformation of 4-alkenyl-substituted isoxazolones to tri- and tetrasubstituted NH-pyrroles (Scheme 1, reaction 6).

## Results and Discussion

At the beginning of our study, we examined the behaviour of the model substrate **2a**, synthesized from the isoxazolone **1a** and ethyl propiolate (Scheme 2). The preparation of **2a** deserves some considerations. Performing the reaction with TEA as catalyst in DCM, a mixture of 4- and 2-alkenyl isoxazolin-5-ones (**2a** and **2a'**), each of them as a mixture of *E/Z* isomers on the double bond, were obtained. Better results in term of regioselectivity were observed by switching the reaction conditions to Na<sub>2</sub>CO<sub>3</sub> as base (1 equiv.) in THF as solvent, reporting a widely favourable ratio for the product **2a** vs **2a'** (from 3:1 to 5:1 *E/Z* ratio), from which the *E* isomer was isolated in 50% yield.<sup>[18]</sup> When **2a** was treated with catalytic [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> in DMSO at 100 °C, that are the same conditions successfully used by us for the conversion of 4-(1,4-naphthoquinone)-substituted isoxazol-5-ones to benzo[*f*]indole-

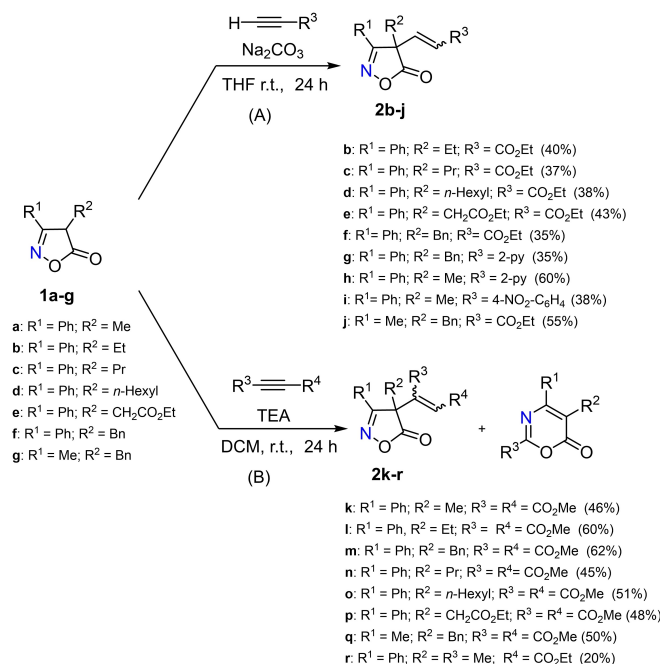


**Scheme 2.** Preparation and ruthenium-catalyzed treatment of the isoxazol-5(4*H*)-one **2a**.

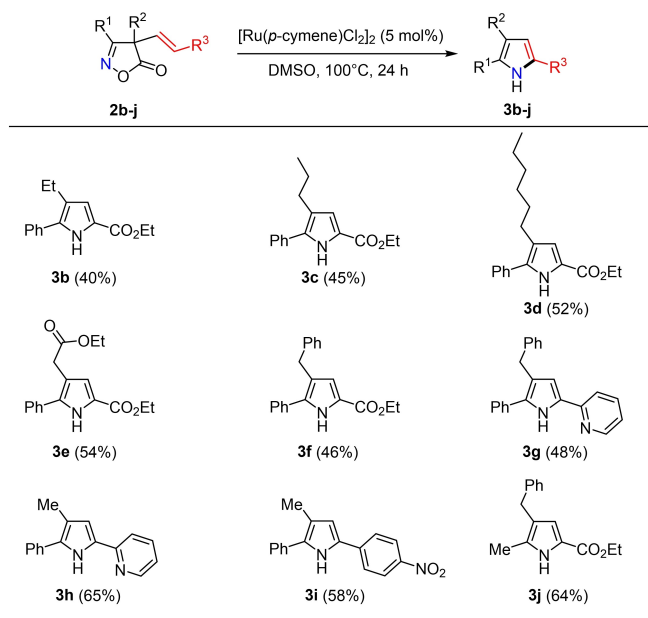
4,9-diones,<sup>[12d]</sup> the total conversion to the pyrrole **3a** as the sole product was achieved. The reaction has been repeated starting from the crude mixture obtained preparing **2a**. Gratifyingly, both *E* and *Z* isomers of compound **2** undergo the rearrangement under Ru-catalysis, albeit with different reaction times due to the *in situ* conversion of the *Z* isomers into the more reactive *E* species. Conversely, the 2-alkenyl derivative **2a'** didn't react under the same reaction conditions. This allows to directly employ the crude **2a/2a'** mixture making as whole the procedure easier, also in terms of separation of the undesired compound **2a'**.

Given the satisfactory results in terms of preparation and transformation of substrate **2a**, a number of isoxazol-5-ones were synthesized to evaluate the scope of the rearrangement conditions. For this purpose, the **1a–g** precursors were treated with a series of alkynes bearing electron-withdrawing substituents. The functionalization with ethyl propiolates was carried out following the conditions used for the preparation of compound **2a**, *i.e.* with Na<sub>2</sub>CO<sub>3</sub> as base in THF as solvent, giving products **2b–j** mainly as isomers *E* (Scheme 3, reaction A). These conditions were unsuccessfully applied to the reaction between isoxazolones **1** and dimethyl acetylenedicarboxylate (DMAD). Access to compounds **2k–r** was achieved by operating with catalytic triethylamine in DCM (Scheme 3, reaction B). An excess of DMAD (4 equiv.) was proven to be necessary to minimize the competitive formation of the substituted 1,3-oxazin-6-ones.<sup>[19]</sup>

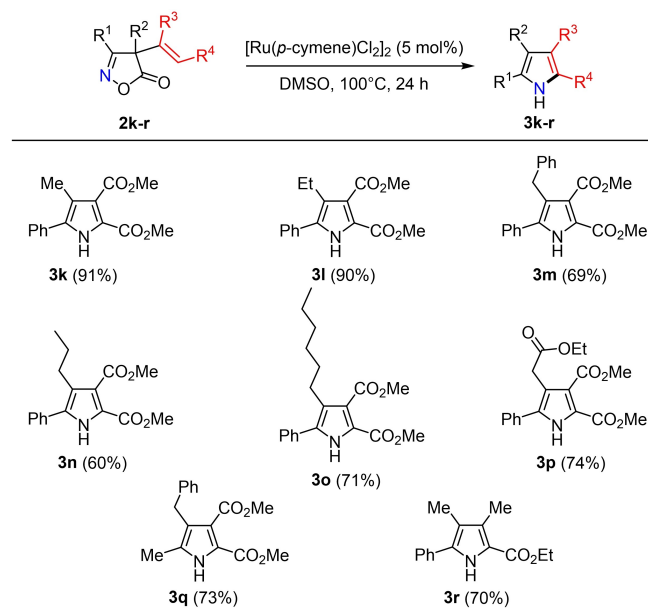
To evaluate the robustness of the methodology, the isoxazol-5-ones **2b–j** were submitted to the treatment with [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> in DMSO at 100 °C (Scheme 4). As in the case of substrate **2a**, the reactions were carried out directly on the crude mixture of the starting isoxazolone and ethyl propiolate. The expected 2,3,5-trisubstituted pyrroles were obtained in all



**Scheme 3.** Preparation of the isoxazol-5(4*H*)-ones **2b–r**.



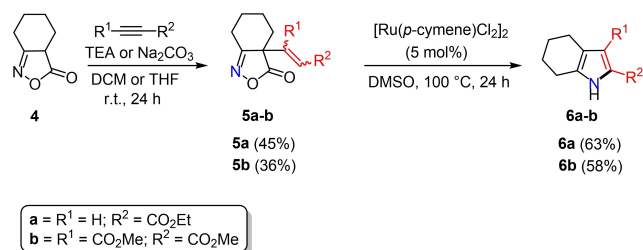
**Scheme 4.** Conversion of the isoxazol-5(4*H*)-ones **2b–j** into the trisubstituted pyrroles.



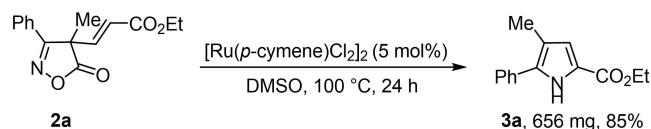
**Scheme 5.** Conversion of the isoxazol-5(4*H*)-ones **2k–r** into the tetrasubstituted pyrroles.

cases through a similar reaction outcome in terms of selectivity and yields beside the unreactive regioisomeric material. In addition to the carbethoxy group, the catalytic system is tolerant towards electron-poor (hetero)aromatic rings. Indeed, pyridin-2-yl and 4-nitrophenyl isoxazolone derivatives yielded the corresponding pyrroles (**3g**, **3h** and **3i**, respectively) through satisfactory outcomes.

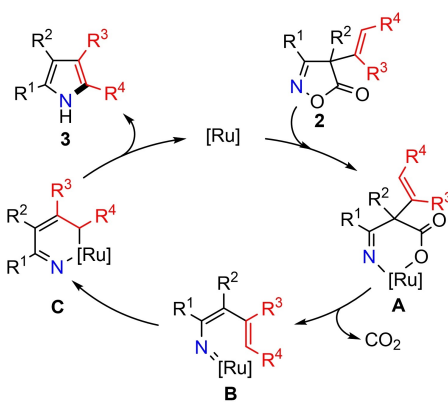
Then, the applicability of this synthetic path was applied to the synthesis of tetrasubstituted pyrroles. Using the isoxazol-5-



**Scheme 6.** Preparation of 4,5,6,7-tetrahydroindoles.



**Scheme 7.** Gram-scale synthesis of product **3a**.



**Scheme 8.** Proposed mechanism for the decarboxylative conversion of the isoxazol-5(4*H*)-ones **2** into pyrroles **3**.

ones **2k–r** as substrates, after 24 h at 100 °C the reactions were completed and the 2,3,4,5-tetrasubstituted pyrroles **3k–r** were obtained in satisfactory to good yields (Scheme 5). It should be emphasized that the reactions were particularly clean, as evidenced by the <sup>1</sup>H-NMR of the crude mixture.

To improve the versatility of the reaction, isoxazolone **4** was synthesized and functionalized at C4-position with methyl propiolate and dimethyl acetylene dicarboxylate, yielding compounds **5a** and **5b** (Scheme 6). Their treatment under the standard conditions provided the formation of the 4,5,6,7-tetrahydroindoles **6a** and **6b**, isolated in 63 % and 58 %, respectively.

Furthermore, the practical utility of this approach to pyrrole synthesis was demonstrated by performing a gram-scale reaction on substrate **2a**, which provided product **3a** in 85 % yield (Scheme 7).

A plausible mechanism is depicted in Scheme 8. First step should involve cleavage of the N–O bond by oxidative addition of the ruthenium complex giving the intermediate **A**, which undergoes decarboxylation to generate the ruthenium-nitre-



noid intermediate **B**. Then, **B** evolves to the ruthenacycle **C** by an electrocyclic reaction. Finally, reductive elimination delivers the product **3** and the regeneration of the active ruthenium catalyst.

## Conclusions

In summary, we have developed a procedure for the preparation of tri- and tetrasubstituted NH-pyrroles based on the rearrangement of 4-alkenyl-isoxazol-5-ones. The reaction proceeds under thermal conditions in the presence of a ruthenium(II) catalyst without the need for additional additives. This synthetic protocol implies an electrocyclic reaction that occurs after the cleavage of a nitrogen-oxygen bond and the formation of a new carbon-nitrogen bond in the final reductive elimination step of a ruthenacycle intermediate. This methodology for the synthesis of 1H-pyrroles confirms the versatility of the isoxazolones treated under ruthenium catalysis for the conversion in different heterocyclic systems.

## Experimental Section

**General information.** Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected. IR spectra were measured with a Jasco FT/IR 5300 spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded with: Varian Oxford 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts are given as  $\delta$  values in ppm relative to residual solvent peaks (CHCl<sub>3</sub>) as the internal reference. <sup>13</sup>C NMR spectra are <sup>1</sup>H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. Elemental analyses were executed on Perkin-Elmer CHN Analyzer Series II 2400. Thin-layer chromatographic separations were performed on Merck silica-gel 60-F<sub>254</sub> precoated. Preparative separations were performed by flash chromatography by using Merck silica gel 0.035-0.070 mm.

**General procedure for the preparation of 4-alkenyl-isoxazol-5-ones 2a-l and 5a:** To a stirred solution of the appropriate isoxazol-5-one **1a-l** or **4** (1.0 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol, 105.9 mg) in DCM (10 mL) the appropriate alkyne (1.0 mmol) was added. After 24 hours the solvent was removed under reduced pressure. The crude reaction was used as such for the subsequent reaction. For the characterization of the compounds **2a-l** and **5a**, a column chromatography was made. The characterization of products **2k,l**<sup>[19]</sup> are consistent with those reported in the literature.

**General procedure for the preparation of 4-alkenyl-isoxazol-5-ones 2m-r and 5b:** To a stirred solution of the appropriate isoxazol-5-one **1a-g** or **4** (1.0 mmol), DMAD (4.0 mmol, 568 mg), triethylamine (100  $\mu$ L) in DCM (10 mL) were added. After 24 hours the solvent was removed under reduced pressure. The residue was purified by FCC.

**General procedure for the preparation of pyrroles 3a-r and 6a-b.** The crude mixture arising from the previous reaction to obtain isoxazolones **2a-r** or **5a,b** (1.0 mmol) was solved in DMSO (6 mL) and [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (30.6 mg, 0.05 mmol) was added in a sealed tube. The resulted solution was magnetically stirred at 100 °C for 24 hours in oil bath. The reaction mixture was washed with brine (5 mL  $\times$  3) and extracted with AcOEt (5 mL  $\times$  3), dried over MgSO<sub>4</sub> and filtered. The solvent was removed under reduced pressure. The residue was purified by FCC. The characterization of products

**3a,h,i**,<sup>[20]</sup> **3k,l**,<sup>[21]</sup> **3o**,<sup>[22]</sup> **6b**<sup>[23]</sup> and **6a**<sup>[24]</sup> are consistent with that reported in the literature.

**Gram-scale synthesis for the preparation of pyrrole 3a.** In a sealed tube, [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (0.17 mmol, 103 mg) was added to a solution of substrate **3a** (3.37 mmol, 920 mg) in DMSO (33 mL). The resulted solution was magnetically stirred at 100 °C for 24 hours. The reaction mixture was washed with brine (10 mL  $\times$  3) and the organic layer was extracted with AcOEt (10 mL  $\times$  3), dried over MgSO<sub>4</sub> and filtered. The solvent was removed under reduced pressure. The residue was purified by FCC (7/3 hexane/AcOEt) and **3a** was recovered as white solid with 85% yield (656 mg). The characterization of product **3a** is consistent with that reported in the literature.<sup>[19]</sup>

## Acknowledgements

We thank Università degli Studi dell'Insubria and Università degli Studi di Milano for financial support. Open Access Funding provided by Università degli Studi dell'Insubria within the CRUI-CARE Agreement.

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

Research data are not shared.

**Keywords:** Decarboxylation · Nitrogen heterocycles · Pyrroles · Rearrangement · Ruthenium

- [1] a) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264–287; b) I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep.* **2010**, *27*, 1801–1839; c) Y. Ding, Y. Tang, W. Zhu, Y. Xie, *Chem. Soc. Rev.* **2015**, *44*, 1101–1112; d) Y. Geng, A. Tang, K. Tajima, Q. Zeng, E. Zhou, *J. Mater. Chem. A* **2019**, *7*, 64–96; e) J. Cao, F. Du, L. Yang, W. Tang, *J. Mater. Chem. A* **2020**, *8*, 22572–22592; f) S. Peng, Q. He, G. I. Vargas-Zuniga, L. Qin, I. Hwang, S. K. Kim, N. J. Heo, C.-H. Lee, R. Dutta, J. L. Sessler, *Chem. Soc. Rev.* **2020**, *49*, 865–907; g) A. N. Bismillah, I. Aprahamian, *Chem. Soc. Rev.* **2021**, *50*, 5631–5649.
- [2] a) C. Paal, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756–2767; b) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863–2870; c) A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.
- [3] a) V. Estevez, M. Villacampa, J. C. Menendez, *Chem. Soc. Rev.* **2010**, *39*, 4402–4421; b) N. Yoshikai, Y. Wei, *Asian J. Org. Chem.* **2013**, *2*, 466–478; c) V. Estevez, M. Villacampa, J. C. Menendez, *Chem. Soc. Rev.* **2014**, *43*, 4633–4657; d) N.-N. Zhou, H.-T. Zhu, D.-S. Yang, Z.-H. Guan, *Org. Biomol. Chem.* **2016**, *14*, 7136–7149; e) J. S. S. Neto, G. Zeni, *ChemCatChem* **2020**, *12*, 3335–3408; f) N. Singh, S. Singh, S. Kohli, A. Singh, H. Asiki, G. Rathee, R. A. Anderson, *Org. Chem. Front.* **2021**, *8*, 5550–5573; g) Y. Wang, C. Zhang, S. Li, L. Liu, *Eur. J. Org. Chem.* **2021**, 3837–3849; h) S. C. Philkhana, F. O. Badmus, I. C. Dos Reis, R. Kartika, *Synthesis* **2021**, *53*, 1531–1555.
- [4] a) G. Bartolo, G. Salerno, A. Fazio, *J. Org. Chem.* **2003**, *68*, 7853–7861; b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339; c) G. Bartolo, L. Veltri, R. Mancuso, G. Salerno, S. Maggi, B. M. Aresta, *J. Org. Chem.* **2012**, *77*, 4005–4016; d) W. Geng, W. X. Zhang, W. Hao, Z. Xi, *J. Am. Chem. Soc.* **2012**, *134*, 20230–20233; e) B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett.* **2013**, *15*, 136–139;

- f) L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176–179; g) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem. Int. Ed.* **2013**, *52*, 6953–6957; *Angew. Chem.* **2013**, *125*, 7091–7095; h) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 6958–6961; *Angew. Chem.* **2013**, *125*, 7096–7099; i) L. Zhu, Y. Yu, Z. Mao, X. Huang, *Org. Lett.* **2015**, *17*, 30–33; j) T. Li, H. Yan, X. Li, C. Wang, B. Wan, *J. Org. Chem.* **2016**, *81*, 12031–12037; k) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2016**, *55*, 14373–14377; *Angew. Chem.* **2016**, *128*, 14585–14589; l) Y. Liu, H. Hu, X. Wang, S. Zhi, Y. Kan, C. Wang, *J. Org. Chem.* **2017**, *82*, 4194–4202; m) F. Kallmeier, B. Dudzic, T. Irgang, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 7261–7265; *Angew. Chem.* **2017**, *129*, 7367–7371; n) H. C. Chiu, I. A. Tonks, *Angew. Chem. Int. Ed.* **2018**, *57*, 6090–6094; *Angew. Chem.* **2018**, *130*, 6198–6202; o) M. N. Zhao, Z. H. Ren, D. S. Yang, Z. H. Guan, *Org. Lett.* **2018**, *20*, 1287–1290; p) Y. Liu, A. Parodi, S. Battaglioli, M. Monari, S. Protti, M. Bandini, *Org. Lett.* **2019**, *21*, 7782–7786; q) K. Kawakita, E. P. Beaumier, Y. Kakiuchi, H. Tsurugi, I. A. Tonks, K. Mashima, *J. Am. Chem. Soc.* **2019**, *141*, 4194–4198.
- [5] K. Dong, A. Humeidi, W. Griffith, H. Arman, X. Xu, M. P. Doyle, *Angew. Chem. Int. Ed.* **2021**, *60*, 13394–13400; *Angew. Chem.* **2021**, *133*, 13506–13512.
- [6] J. Lin, T.-Y. Zheng, N.-Q. Fan, P. Zhang, K. Jiang, Y. Wei, *Org. Chem. Front.* **2021**, *8*, 3776–3782.
- [7] Q. Wan, L. Xin, J. Zhang, X. Huang, *Org. Biomol. Chem.* **2022**, *20*, 1647–1651.
- [8] A. S. Makarov, A. A. Fadeev, M. G. Uchuskin, *Org. Chem. Front.* **2021**, *8*, 6553–6560.
- [9] P. Kumar, S. K. Keshri, M. Kapur, *Org. Biomol. Chem.* **2021**, *19*, 3428–3433.
- [10] a) A. F. da Silva, A. A. G. Fernandes, S. Thurow, M. L. Stivanin, I. D. Jurberg, *Synthesis* **2018**, *50*, 2473–2489; b) A. A. G. Fernandes, A. F. da Silva, S. Thurow, C. Y. Okada Jr, I. D. Jurberg, *Targets Heterocycl. Syst.* **2018**, *22*, 409–435.
- [11] a) K. Okamoto, T. Oda, S. Kohigashi, K. Ohe, *Angew. Chem. Int. Ed.* **2011**, *50*, 11470–11473; *Angew. Chem.* **2011**, *123*, 11672–11675; b) S. Rieckhoff, T. Hellmuth, R. Peters, *J. Org. Chem.* **2015**, *80*, 6822–6830; c) M. L. Stivanin, M. Duarte, C. Sartori, N. M. R. Capreti, C. F. F. Angiolini, I. D. Jurberg, *J. Org. Chem.* **2017**, *82*, 10319–10330; d) S. Rieckhoff, W. Frey, R. Peters, *Eur. J. Org. Chem.* **2018**, 1797–1805; e) K. Okamoto, T. Oda, G. Matsushita, T. Shimbayashi, K. Sasakura, K. Ohe, *Heterocycles* **2018**, *97*, 218–231; f) S. Rieckhoff, W. Frey, R. Peters, *Eur. J. Org. Chem.* **2018**, 1797–1805.
- [12] a) K. Okamoto, K. Sasakura, T. Shimbayashi, K. Ohe, *Chem. Lett.* **2016**, *45*, 988–990; b) S. Rieckhoff, M. Titze, W. Frey, R. Peters, *Org. Lett.* **2017**, *19*, 4436–4439; c) A. A. G. Fernandes, M. L. Stivanin, I. D. Jurberg, *ChemistrySelect* **2019**, *4*, 3360–3365; d) M. S. Christodoulou, S. Giofrè, E. M. Beccalli, F. Foschi, G. Broggin, *Org. Lett.* **2020**, *22*, 2735–2739; e) C. Loro, L. Molteni, M. Papis, L. Lo Presti, F. Foschi, E. M. Beccalli, G. Broggin, *Org. Lett.* **2022**, *24*, 3092–3096.
- [13] S. Rieckhoff, T. Hellmuth, R. Peters, *J. Org. Chem.* **2015**, *80*, 6822–6830.
- [14] K. Okamoto, T. Shimbayashi, M. Yoshida, A. Nanya, K. Ohe, *Angew. Chem. Int. Ed.* **2016**, *55*, 7199–7202; *Angew. Chem.* **2016**, *128*, 7315–7318.
- [15] a) I. D. Jurberg, H. M. L. Davies, *Org. Lett.* **2017**, *19*, 5158–5161; b) T. Shimbayashi, G. Matsushita, A. Nanya, A. Eguchi, K. Okamoto, K. Ohe, *ACS Catal.* **2018**, *8*, 7773–7780.
- [16] a) G. Broggin, E. M. Beccalli, T. Borelli, F. Brusa, S. Gazzola, A. Mazza, *Eur. J. Org. Chem.* **2015**, 4261–4268; b) F. Foschi, C. Loro, R. Sala, J. Obel, L. Lo Presti, E. M. Beccalli, G. Poli, G. Broggin, *Org. Lett.* **2020**, *22*, 1402–1406; c) C. Loro, R. Sala, M. Penso, F. Foschi, *Adv. Synth. Catal.* **2021**, *363*, 3983–3994; d) S. Giofrè, C. Loro, L. Molteni, C. Castellano, A. Contini, D. Nava, G. Broggin, E. M. Beccalli, *Eur. J. Org. Chem.* **2021**, 1750–1757; e) C. Loro, J. Obel, F. Foschi, M. Papis, E. M. Beccalli, S. Giofrè, G. Poli, G. Broggin, *Org. Chem. Front.* **2022**, *9*, 1711–1718; f) M. Papis, C. Loro, M. Penso, G. Broggin, F. Foschi, *Org. Chem. Front.* DOI: 10.1039/D2Q000400 C; g) C. Loro, L. Molteni, M. Papis, E. M. Beccalli, D. Nava, L. Lo Presti, S. Brenna, G. Colombo, F. Foschi, G. Broggin, *J. Org. Chem.* **2022**, *87*, 1032–1042.
- [17] a) E. M. Beccalli, A. Marchesini, *J. Org. Chem.* **1987**, *52*, 3426–3434; b) G. Abbiati, E. M. Beccalli, G. Broggin, C. Zoni, *Tetrahedron* **2003**, *59*, 9887–9893.
- [18] Regarding the alkenylation of the 3,4-disubstituted isoxazolones, a mixture of C- and N-alkenylation products was obtained, whereas no O-alkenylation product was observed. For the 3-methyl-4-benzyl-isoxazol-5-one, we reported the <sup>1</sup>H-NMR spectra of all the isolated single isomers: the C-alkenylation products (E and Z isomers) and N-alkenylation products (E and Z isomers) (see Supporting Info). The Ru-catalyzed reaction was investigated on the single stereoisomers obtaining the results reported in the text: the (Z) C-alkenylated isomers was less reactive than the (E), the N-alkenylated isomers were unreactive. Fortunately, it is possible to perform the Ru-catalyzed reaction on the mixture of the regio- and stereoselective isomers.
- [19] E. M. Beccalli, A. Marchesini, M. L. Gelmi, T. Pilati, *J. Org. Chem.* **1987**, *52*, 1666–1669.
- [20] H.-B. Yang, N. Selander, *Chem. Eur. J.* **2017**, *23*, 1779–1783.
- [21] X. Tang, L. Huang, C. Qi, W. Wu, H. Jiang, *Chem. Commun.* **2013**, *49*, 9597–9599.
- [22] S. Ngwerume, W. Lewis, J. E. Camp, *J. Org. Chem.* **2013**, *78*, 920–934.
- [23] S. Ngwerume, J. E. Camp, *Chem. Commun.* **2011**, *47*, 1857–1859.
- [24] X. Wang, J. Barbosa, P. Blomgren, M. C. Bremer, J. Chen, J. J. Crawford, W. Deng, L. Dong, C. Eigenbrot, S. Gallion, J. Hau, H. Hu, A. R. Johnson, A. Katewa, J. E. Kropf, S. H. Lee, L. Liu, J. W. Lubach, J. Macaluso, P. Maciejewski, S. A. Mitchell, D. F. Ortwein, J. DiPaolo, K. Reif, H. Scheerens, A. Schmitt, H. Wong, J.-M. Xiong, J. Xu, Z. Zhao, F. Zhou, K. S. Currie, W. B. Young, *ACS Med. Chem. Lett.* **2017**, *8*, 608–613.

Manuscript received: April 29, 2022  
Revised manuscript received: May 26, 2022  
Accepted manuscript online: June 5, 2022