Ring-closing metathesis as a key step to construct the 2,6-dihydropyrano[2,3-c]pyrazole ring system

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Received 11-25-2017 Accepted 02-17-2018 Published on line 07-07-2018

Abstract

A simple and efficient synthetic route to the 2,6-dihydropyrano[2,3-c]pyrazole ring system was developed by employing ring-closing metathesis (RCM) as a key step. The required diene substrate for the RCM reaction was prepared by a three-step procedure starting form 1-phenyl-1H-pyrazol-3-ol. Treatment of the obtained 4-ethenyl-1-phenyl-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole with Grubbs’ first-generation catalyst afforded the target 2-phenyl-2,6-dihydropyrano[2,3-c]pyrazole. 2-(4-Fluorophenyl)- and 2-(4-bromophenyl)-2,6-dihydropyrano[2,3-c]pyrazole were synthesized by an analogous way. The structures of the obtained heterocyclic products were unequivocally confirmed by detailed 1H, 13C, 15N and 19F NMR spectroscopic experiments and HRMS measurements. The optical properties of 2-phenyl-2,6-dihydropyrano[2,3-c]pyrazole were studied by UV–Vis and fluorescence spectroscopy.

Keywords: 1-Phenylpyrazol-3-ol, Wittig olefination, Ring-closing metathesis, 2,6-Dihydropyrano[2,3-c]pyrazole

DOI: https://doi.org/10.24820/ark.5550190.p010.407
Introduction

The pyrano[2,3-c]pyrazole ring system (Figure 1, A) is present in a wide variety of biologically active compounds.\(^1\) In recent years, there has been increasing interest in the chemistry of its dihydro analogues. The 1,4- and 2,4-dihydropyrano[2,3-c]pyrazole ring systems, which correspond to tautomeric forms B and C (Figure 1), often appear as the main structural motifs of anticancer,\(^2\)-\(^5\) anti-inflammatory,\(^6\) and anti-diabetic agents.\(^7\) The known numerous methods for the preparation of these compounds are generally based on a multicomponent reaction of an aromatic aldehyde, 3-oxobutanoate, hydrazine hydrate, and malononitrile in the presence of a suitable catalyst.\(^8\) However, access to derivatives of 1,6- and 2,6-dihydropyrano[2,3-c]pyrazole isomers D and E (Figure 1) is very limited, and their chemistry and biological properties remain largely unexplored. Derivatives of pyrano[2,3-c]pyrazol-6(1H)-one\(^9\) (Figure 1, F) are structurally similar and are known as analgesic, anti-inflammatory\(^10\) and antiviral agents.\(^11\)

![Figure 1. Pyrano[2,3-c]pyrazole and its hydro derivatives.](image)

In the present work, we describe a method for the construction of the 2,6-dihydropyrano[2,3-c]pyrazole ring system (Figure 1, E) via a ring-closing metathesis (RCM) reaction. RCM reactions catalyzed by ruthenium alkylidene complexes\(^12,13\) have proven to be one of the most powerful tools for the construction of non-aromatic (hetero)carbocyclic compounds\(^14-16\), in particular, oxygen heterocycles.\(^17-19\) For example, treatment of 2-allyloxy-1-ethenylbenzene with Grubb’s first-generation catalyst, \([\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]),\(^20\) afforded 2\(H\)-1-benzopyran in 95% yield.\(^21\)

Results and Discussion

The synthetic strategy designed to construct the 2,6-dihydropyrano[2,3-c]pyrazole ring system employs a diene substrate that contains an ethene unit attached to an allyloxy unit onto the pyrazole core, which can participate in the RCM reaction (Scheme 1). As a starting material, we used 1-phenylpyrazol-3-ol (1a), which is readily accessible from the oxidation of 1-phenyl-3-pyrazolidinone.\(^22-24\) Recently, we applied this scaffold to
obtain the novel pyrazolo[4,3-ß][1,2,3]triazolo[5,1-c][1,4]oxazepine and pyrazolo[4',3':3,4]pyrido[1,2-ß]benzimidazole ring systems\textsuperscript{25,26} and to prepare building blocks for the preparation of optoelectronic materials and fluorescent organic nanoparticles.\textsuperscript{27-30}

The O-allylation of 1a with allyl bromide in the presence of NaH gave O-allylated pyrazole 2a.\textsuperscript{31} To introduce a formyl group at the 4-position of the pyrazole ring, we employed a previously reported procedure based on the Vilsmeier-Haack reaction.\textsuperscript{32} Heating compound 2a with POCl\textsubscript{3} in N\textsubscript{2}N-dimethylformamide (DMF) at 60 °C resulted in the formation of the desired pyrazole-4-carbaldehyde 3a in 91% yield (Scheme 1). The characteristic signals of aldehyde 3a in the \textsuperscript{1}H NMR spectrum were the singlets at 8.25 (5-H) and 9.88 ppm (CHO). The \textsuperscript{13}C NMR spectrum contained the signal of a formyl carbon at 183.4 ppm.

Next, we investigated the conversion of aldehyde 3a into 4-ethenylpyrazole 4a. One of the most popular methods for the synthesis of alkenes from aldehydes and ketones is the Wittig reaction, which is based on the coupling of carbonyl compounds with single-substituted phosphonium ylides.\textsuperscript{33} To introduce a methylene group, methylenetriphenylphosphorane (Ph\textsubscript{3}P=CH\textsubscript{2} \rightleftharpoons Ph\textsubscript{3}P\textsuperscript{+}CH\textsubscript{2} \textsuperscript{-}) generated by the addition of a base to a solution of methyltriphenylphosphonium bromide or iodide is typically used as an ylide source.\textsuperscript{34,35} For example, the Wittig reaction of benzaldehyde with methyltriphenylphosphonium iodide in the presence of K\textsubscript{2}CO\textsubscript{3} in DME provided styrene in 90% yield.\textsuperscript{35} In our case, the reaction of aldehyde 3a with methyltriphenylphosphonium iodide in the presence of KOTBu in toluene resulted in the formation of 4-ethenylpyrazole 4a in 89% yield. The \textsuperscript{13}C NMR spectrum of 4a exhibited the corresponding signals of the newly formed vinyl carbon atoms at 113.4 and 125.1 ppm.

\begin{center}
\begin{tabular}{c|c|c|c|c|c}
 & 1a & 2a & 3a & 4a & 5a \\
R & H; & H (78%); & H (91%); & H (89%); & H (42%); \\
1b & R = F; & R = F (48%); & R = F (70%); & R = F (39%); & R = F (56%); \\
1c & R = Br; & R = Br (52%); & R = Br (75%); & R = Br (46%); & R = Br (39%); \\
\end{tabular}
\end{center}

\textbf{Scheme 1.} Synthetic route to the 2,6-dihydropyrano[2,3-c]pyrazole ring system.

Having prepared the required diene 4a, we further investigated its RCM reaction in order to convert the latter into the target compound 5a. When 4a was heated with Grubbs’ first-generation catalyst in dichloromethane, no RCM reaction occurred. However, the replacement of the solvent with THF gave the desired 2-phenyl-2,6-dihydropyrano[2,3-c]pyrazole 5a in 42% yield. The application of microwave heating allowed to shorten the RCM reaction time from 48 h to 3 h, but the isolated yield of 5a was only 34%.

The heterocyclic compounds of type 5 represent dihydropyrano[2,3-c]pyrazole substructures related to important functional organic molecules with wide biomedical applications. Because popular NMR prediction programs, such as ACD C+H predictor,\textsuperscript{36} depend on high-quality data with unambiguously assigned resonances, we carried out NMR studies with compound 5a in an attempt to fully map all the NMR signals for \textsuperscript{1}H, \textsuperscript{13}C and \textsuperscript{15}N as accurately as possible (Figure 1). The desired results were achieved through a combination
of standard NMR techniques, such as DEPT, gs-HSQC, gs-HMBC, COSY, TOCSY, NOESY\textsuperscript{37}, H2BC\textsuperscript{38} and 1,1-ADEQUATE\textsuperscript{39} experiments. The broad-band decoupled $^{13}$C NMR spectrum of compound 5a showed resonances for 10 carbon atoms. The DEPT-90 and 135 spectra indicated the presence of 1 methylene and 6 methine carbon atoms. Comparison of the DEPT spectrum with the broad-band decoupled $^{13}$C NMR spectrum revealed the presence of 3 quaternary carbons. The multiplicity-edited $^{1}H$-$^{13}$C HSQC spectrum indicated that the methylene protons H-6 have one-bond connectivity with the C-6 carbon at 68.8 ppm. Moreover, this also revealed heteronuclear interactions between the protons of two pairs of chemically equivalent methine groups (7.36-7.40 and 7.54-7.58 ppm), with their respective carbons, which resonated at 129.4 and 117.6, respectively. The data from the $^{1}H$-$^{13}$C HMBC spectrum revealed long-range correlations of the methylene protons with the quaternary carbon C-7a (at 161.9 ppm) and protonated carbons C-5 (at 119.0 ppm) and C-4 (118.1 ppm). The aforementioned protonated carbon C-4 showed correlation with quaternary carbon C-3a in the 1,1-ADEQUATE spectrum, which was also supported by the correlation of C-3 with C-3a. The $^{15}$N NMR data were obtained via a $^{1}H$-$^{15}$N HMBC experiment. Both nitrogen atoms showed appropriate couplings to H-3, and in the case of N-2, it had strong coupling with the aromatic protons 2-H and 6-H. The TOCSY spectrum showed that there were two distinct spin systems in the molecule. The $^{1}H$-$^{1}H$ connectivities within each spin system were confirmed using the data from the COSY, TOCSY and NOESY spectra.

![Diagram of chemical shifts](image)

**Figure 2.** (a) $^{13}$C and $^{15}$N (in bold) NMR chemical shifts of compound 5a. (b) Characteristic $^{1}H$-$^{13}$C HMBC, H2BC and 1,1-ADEQUATE correlations are represented by arrows. (c) Characteristic $^{1}H$-$^{1}H$ NOESY correlations are represented by arrows.

Compounds 5b,c were obtained analogously to compound 5a. Although the preparation of the starting compound 1b was reported in a patent application,\textsuperscript{40,41} neither a detailed synthesis description nor spectroscopic data of the product were provided. The O-allylation of 1b and 1c\textsuperscript{42} and the subsequent formylation of 2b,c produced aldehydes 3b,c which after conversion to the corresponding ethenyl derivatives afforded the diene substrates 4b and 4c. Treatment of 4b,c with Grubbs’ first-generation catalyst resulted in the formation of the target compounds 5b and 5c in 56% and 39% yield, respectively.

The optical properties of compound 5a were investigated by UV–Vis spectroscopy and fluorometric measurements. The electronic absorption spectra of compound 5a in THF did not show absorption bands in the visible region of the electronic spectra, and it showed an absorption maximum at 310 nm (Figure 3, a). Upon excitation of compound 5a at 320 nm (in THF solution), the fluorescence spectrum exhibited three peaks at 360, 381 and 395 nm (Figure 3, b). The fluorescence quantum yield ($\Phi_f$) of the solution was estimated by the integrating sphere method and gave a $\Phi_f$ value of ca. 1%.
Figure 3. (a) Absorption spectrum of 5a in THF (0.1 mM, 298 K); (b) fluorescence emission spectrum of 5a in THF (\(\lambda_{\text{ex}} = 320\) nm).

Conclusions

In summary, an efficient route to access the 2,6-dihydropyrano[2,3-c]pyrazole ring system was developed by employing ring-closing metathesis (RCM) as the key step. The structures of the synthesized 2-phenyl-, 2-(4-bromophenyl)- and 2-(4-fluorophenyl)-2,6-dihydropyrano[2,3-c]pyrazoles were characterized by \(^1\text{H}\), \(^{13}\text{C}\), \(^{15}\text{N}\) and \(^{19}\text{F}\) NMR spectroscopy, UV–Vis and fluorescence spectroscopy and HRMS measurements.

Experimental Section

General. Microwave reactions were conducted using a CEM Discovery Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The reactions were performed in glass vessels (capacity 10 mL) sealed with septum. In the case of an open vessel conditions the reactions were performed in a round bottom flask (capacity 25 mL) connected to a reflux condenser. All experiments were performed using a stirring option. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Silica gel 60 F\(_{254}\)) were employed. The purification of the products was performed using flash chromatography on a glass column with silica gel (high purity grade 9385, pore size 60 A, 230-400 mesh particle size). The melting points were determined in capillary tubes, on a capillary melting point apparatus Büchi Melting Point M-565 and are uncorrected. The \(^1\text{H}\), \(^{13}\text{C}\) and \(^{15}\text{N}\) NMR spectra were recorded in CDCl\(_3\) solutions at 25 °C on a Bruker Avance III 700 (700 MHz for \(^1\text{H}\), 176 MHz for \(^{13}\text{C}\), 71 MHz for \(^{15}\text{N}\)) spectrometer equipped with a 5 mm TCI \(^1\text{H}-{^{13}}\text{C}/^{15}\text{N/D} \) z-gradient cryoprobe. The chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). The \(^{15}\text{N}\) NMR spectra were referenced to neat, external nitromethane (coaxial capillary). \(^{19}\text{F}\) NMR spectra (376.46 MHz, absolute referencing via \(\delta\) ratio) were obtained on a Bruker Avance III 400 instrument with a ‘directly’ detecting broadband observe probe (BBO). The full and unambiguous assignments of the \(^1\text{H}\), \(^{13}\text{C}\), \(^{15}\text{N}\) and \(^{19}\text{F}\) NMR resonances were achieved using standard Bruker software and a combination of standard NMR spectroscopic
techniques, such as DEPT, COSY, TOCSY, NOESY, gs-HSQC, gs-HMBC, H2BC and 1,1-ADEQUATE. The infrared spectra were recorded on a Bruker Vertex v70 FTIR spectrometer equipped with a diamond ATR accessory. The UV-vis spectra were recorded using 0.1 mM solutions of the compounds in THF on a Shimadzu 2600 UV/Vis spectrometer. The fluorescence spectra were recorded on a FL920 fluorescence spectrometer from Edinburgh Instruments. The PL quantum yields were measured from dilute solutions by an absolute method using Edinburgh Instruments integrating sphere excited with a Xe lamp. Optical densities of the sample solutions were ensured to be below 0.1 to avoid reabsorption effects. All optical measurements were performed at rt under ambient conditions. HRMS spectra were recorded with a Bruker maXis or Bruker micrOTOF-QII spectrometers.

1-(4-Fluorophenyl)-1H-pyrazol-3-ol (1b). An intensively stirred suspension of 4-fluorophenylhydrazine hydrochloride (8.13 g, 50 mmol) in dry toluene/methanol (1/1, 100 mL) was kept under inert atmosphere, and the potassium tert-butoxide (16.83 g, 150 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 30 min. Then it was subsequently raised to 50°C and the ethyl acrylate (150 mmol, 16.36 mL) was added dropwise over the 15 min. The reaction mixture was stirred at 50°C for 24 h, diluted with 100 mL of water and the organic layer was separated. The aqueous phase was adjusted to a pH of 6 and extracted with ethyl acetate. The organic layers were combined, dried over Na2SO4, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with dichloromethane/methanol 100:3, v/v. To yield the 1-(4-fluorophenyl)pyrazolidin-3-one. Yield 6.31 g (70%), white crystals, m.p. 109–111 °C. IR (neat, νmax cm\(^{-1}\)): 3135, 2918, 1601, 1500, 1356, 1221, 1118. \(^1\)H NMR (700 MHz, CDCl\(_3\)): δ (ppm) 2.56 (t, J 8.0 Hz, 2H, 4-CH\(_2\)), 3.86 (t, J 8.0 Hz, 2H, 5-CH\(_2\)), 7.00 (d, J 6.4 Hz, 4H, Ph 2,3,5,6-H), 9.14 (s, 1H, NH). \(^13\)C NMR (176 MHz, CDCl\(_3\)): δ (ppm) 29.9 (C-4), 55.9 (C-5), 116.0 (d, \(^2\)J\(_{CF}\) 22.7 Hz, Ph C-3,5), 118.1 (d, \(^3\)J\(_{CF}\) 7.9 Hz, Ph C-2,6), 147.6 (d, \(^4\)J\(_{CF}\) 2.3 Hz, Ph C-1), 158.9 (d, \(^5\)J\(_{CF}\) 241.6 Hz, Ph C-4), 175.7 (C-3). \(^15\)N NMR (71 MHz, CDCl\(_3\)): δ (ppm) -278.3 (N-1), -230.2 (N-2). \(^19\)F NMR (376 MHz, CDCl\(_3\)): δ (ppm) -120.8. HRMS (ESI TOF): [M+H]+ found 181.0771. \([\text{C}_{9}\text{H}_{10}\text{F}_{2}\text{O}]^+\) requires 181.0772.

The obtained 1-(4-fluorophenyl)pyrazolidin-3-one (6.13 g, 34 mmol) and FeCl\(_3\)-H2O (2.3 g, 8.5 mmol) were dissolved in dimethylformamide (50 mL). The reaction mixture was heated to 80 °C, and gassed with oxygen for 2 h. After gassing was stopped, the mixture was stirred for further 10 h maintaining at 80 °C. Then it was poured into water (100 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine, dried over Na2SO4, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethylacetate 2:1, v/v, to yield the title compound 1b. Yield 4.91 g (81%), bright orange crystals, m.p. 152–154 °C. IR (neat, νmax cm\(^{-1}\)): 3139, 2938, 1556, 1510, 1393, 1230, 1158. \(^1\)H NMR (700 MHz, CDCl\(_3\)): δ (ppm) 5.88 (d, J 2.6 Hz, 1H, 4-H), 7.11 – 7.18 (m, 2H, Ph 3,5-H), 7.43 – 7.48 (m, 2H, Ph 2,6-H), 7.58 (d, J 2.6 Hz, 1H, 5-H). \(^13\)C NMR (176 MHz, CDCl\(_3\)): δ (ppm) 94.4 (C-4), 116.6 (d, \(^2\)J\(_{CF}\) 23.0 Hz, Ph C-3,5), 120.8 (d, \(^3\)J\(_{CF}\) 8.3 Hz, Ph C-2,6), 129.5 (C-5), 136.0 (d, \(^4\)J\(_{CF}\) 2.8 Hz, Ph C-1), 160.9 (d, \(^5\)J\(_{CF}\) 245.8 Hz, Ph C-4), 164.1 (C-3). \(^15\)N NMR (71 MHz, CDCl\(_3\)): δ (ppm) -191.8 (N-1), -135.2 (N-2). \(^19\)F NMR (376 MHz, CDCl\(_3\)): δ (ppm) -116.2. HRMS (ESI TOF): [M+H]+ found 179.0615. \([\text{C}_{9}\text{H}_{8}\text{F}_{2}\text{O}]^+\) requires 179.0615.

General procedure for the allylation of 1H-pyrazol-3-oles giving 3-[(prop-2-en-1-yl)oxy]-1H-pyrazoles (compounds 2a-c). The solution of 1a-c (10 mmol) in dry DMF (15 mL) was cooled to 0 °C under inert atmosphere and NaH (60% dispersion in mineral oil, 400 mg, 10 mmol) was added portionwise. After mixing for 15 min at 0 °C, the mixture was gradually warmed up to 40°C temperature and stirred for additional 15 min. Then it was subsequently raised to 60°C and an allyl bromide (12 mmol, 1.0 mL) was added dropwise over
the 10 min. The mixture was stirred at 60°C for 8 h, diluted with 60 ml of water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethylacetate 15:1, v/v. To yield compounds 2a-c.

1-Phenyl-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole (2a). Yield 1.56 g (78%), yellow oil. IR (neat, ν<sub>max</sub>, cm<sup>-1</sup>): 3132, 2927, 1541, 1505, 1396, 1236, 985, 936. <sup>1</sup>H NMR (700 MHz, CDCl₃): δ (ppm) 4.79 (dt, J 5.6, 1.4 Hz, 2H, O-CH₂-CH=CH₂), 5.26 – 5.32 (m, 1H, O-CH₂-CH=CH₂), 5.42 – 5.48 (m, 1H, O-CH₂-CH=CH₂), 5.91 (d, J 2.6 Hz, 1H, 4-H), 6.09 – 6.17 (m, 1H, O-CH₂-CH=CH₂), 7.19 – 7.22 (m, 1H, Ph 4-H), 7.39 – 7.42 (m, 2H, Ph 3.5-H), 7.59 – 7.62 (m, 2H, Ph 2.6-H), 7.73 (d, J = 2.6 Hz, 1H, 5-H). <sup>13</sup>C NMR (176 MHz, CDCl₃): δ (ppm) 70.0 (O-CH₂-CH=CH₂), 94.1 (C-4), 117.9 (O-CH₂-CH=CH₂), 118.0 (Ph C-2,6), 125.4 (Ph C-4), 127.8 (C-5), 129.5 (Ph C-3,5), 133.4 (O-CH₂-CH=CH₂), 140.3 (Ph C-1), 164.3 (C-3).<sup>15</sup>N NMR (71 MHz, CDCl₃): δ (ppm) -186.0 (N-1), -119.3 (N-2).<sup>30</sup>

1-(4-Fluorophenyl)-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole (2b). Yield 1.05 g (48%), bright yellow oil. IR (neat, ν<sub>max</sub>, cm<sup>-1</sup>): 3098, 2915, 1547, 1516, 1392, 1217, 1175, 991, 942. <sup>1</sup>H NMR (700 MHz, CDCl₃): δ (ppm) 4.77 (dt, J 5.6, 1.3 Hz, 2H, O-CH₂-CH=CH₂), 5.26 – 5.31 (m, 1H, O-CH₂-CH=CH₂), 5.41 – 5.48 (m, 1H, O-CH₂-CH=CH₂), 5.90 (d, J 2.6 Hz, 1H, 4-H), 6.07 – 6.15 (m, 1H, O-CH₂-CH=CH₂), 7.07 – 7.11 (m, 2H, Ph 3.5-H), 7.52 – 7.56 (m, 2H, Ph 2.6-H), 7.65 (d, J 2.6 Hz, 1H, 5-H).<sup>13</sup>C NMR (176 MHz, CDCl₃): 69.9 (O-CH₂-CH=CH₂), 94.0 (C-4), 116.1 (d, 7<sub>JC</sub>F 23.0 Hz, Ph C-3,5), 118.0 (O-CH₂-CH=CH₂), 119.6 (d, 7<sub>JC</sub>F 8.2 Hz, Ph C-2,6), 127.9 (C-5), 133.3 (O-CH₂-CH=CH₂), 136.6 (d, 4<sub>JC</sub> 2.7 Hz, Ph C-1), 160.5 (d, 4<sub>JC</sub> 244.5 Hz, Ph C-4), 164.3 (C-3).<sup>15</sup>N NMR (71 MHz, CDCl₃): δ (ppm) -187.8 (N-1), -118.7 (N-2). HRMS (ESI TOF): [M+Na]<sup>+</sup> found 241.0748. [C<sub>12</sub>H<sub>11</sub>FN<sub>2</sub>NaO]<sup>+</sup> requires 241.0748.

1-(4-Bromophenyl)-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole (2c). Yield 1.45 g (52%), colorless oil. IR (neat, ν<sub>max</sub>, cm<sup>-1</sup>): 3154, 2916, 1547, 1498, 1385, 1236, 1179, 982, 932. <sup>1</sup>H NMR (700 MHz, CDCl₃): δ (ppm) 4.77 (dt, J 5.6, 1.3 Hz, 2H, O-CH₂-CH=CH₂), 5.26 – 5.31 (m, 1H, O-CH₂-CH=CH₂), 5.42 – 5.46 (m, 1H, O-CH₂-CH=CH₂), 5.92 (d, J 2.6 Hz, 1H, 4-H), 6.06 – 6.15 (m, 1H, O-CH₂-CH=CH₂), 7.47 – 7.53 (m, 4H, Ph 2,3,5,6-H), 7.70 (d, J 2.6 Hz, 1H, 5-H).<sup>13</sup>C NMR (176 MHz, CDCl₃): δ (ppm) 70.0 (O-CH₂-CH=CH₂), 94.7 (C-4), 118.1 (O-CH₂-CH=CH₂), 118.3 (Ph C-4), 119.3 and 132.4 (Ph C-2,3,5,6), 127.8 (C-5), 133.3 (O-CH₂-CH=CH₂), 139.3 (Ph C-1), 164.4 (C-3).<sup>15</sup>N NMR (71 MHz, CDCl₃): δ (ppm) -188.1 (N-1), N-2 was not found. HRMS (ESI TOF): [M+Na]<sup>+</sup> found 300.9947. [C<sub>12</sub>H<sub>11</sub>BrN<sub>2</sub>NaO]<sup>+</sup> requires 300.9947.

**General procedure for the formulation of 3-[(prop-2-en-1-yl)oxy]-1H-pyrazoles giving 3-[(prop-2-en-1-yl)oxy]-1H-pyrazole-4-carbaldehydes (compounds 3a-c).** Phosphorus oxychloride (1.86 mL, 20 mmol) was added dropwise to dry DMF (1.55 mL, 20 mmol) at -10°C and the resulting mixture was stirred at the same temperature for 10-20 min until the Vilsmeier-Haack complex formed. Then, the appropriate 3-[(prop-2-en-1-yl)oxy]-1H-pyrazole 2a-c (5 mmol) in DMF (15 mL) was added to the Vilsmeier-Haack complex and the temperature was slowly raised to 70°C and maintained for 12 h. The reaction mixture was cooled in an ice bath, cautiously quenched with ice-cold water (100 mL), and basified with 10% NaHCO₃ solution. The precipitate was filtered off. The filtrate was extracted with ethyl acetate which was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel with hexane/ethylacetate 3:1, v/v. To yield compounds 3a-c.

**1-Phenyl-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole-4-carbaldehyde (3a).** Yield 1.04 g (91%), bright yellow crystals, m.p. 107–109°C. IR (neat, ν<sub>max</sub>, cm<sup>-1</sup>): 3126, 2938, 1665, 1552, 1501, 1391, 1222, 1205, 993, 943. <sup>1</sup>H NMR (700 MHz, CDCl₃): δ (ppm) 4.92 (dt, J 5.7, 1.3 Hz, 2H, O-CH₂-CH=CH₂), 5.30 – 5.35 (m, 1H, O-CH₂-CH=CH₂), 5.45 – 5.50 (m, 1H, O-CH₂-CH=CH₂), 6.11 – 6.18 (m, 1H, O-CH₂-CH=CH₂), 7.32 (t, J 7.4 Hz, 1H, Ph 4-H), 7.44 – 7.49 (m, 2H, Ph 3.5-H), 7.62 – 7.66 (m, 2H, Ph 2.6-H), 8.25 (s, 1H, 5-H), 9.88 (s, 1H, CHO). <sup>13</sup>C NMR (176 MHz, CDCl₃): δ (ppm) 70.2 (O-CH₂-CH=CH₂), 111.6 (C-4), 118.7 (O-CH₂-CH=CH₂), 118.9 (Ph C-2,6), 127.4 (Ph C-4), 129.5 (C-5), 132.0 (Ph C-1), 158.3 (C-3).
129.7 (Ph C-3,5), 132.6 (O-CH₂-CH₂), 139.1 (Ph C-1), 163.6 (C-3), 183.4 (CHO). ¹⁵N NMR (71 MHz, CDCl₃): δ (ppm) -179.2 (N-1), -118.0 (N-2). HRMS (ESI TOF): [M+Na]+ found 229.0974. [C₁₃H₁₃N₂O₂]⁺ requires 229.0972.

1-(4-Fluorophenyl)-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole-4-carbaldehyde (3b). Yield 0.86 g (70%), bright brown crystals, m.p. 134–136 °C. IR (neat, ν max cm⁻¹): 3126, 2946, 1669, 1564, 1502, 1390, 1224, 1209, 989, 941. ¹H NMR (700 MHz, CDCl₃): δ (ppm) 4.89 (dt, J 5.7, 1.3 Hz, 2H, O-CH₂-CH=CH₂), 5.30 – 5.34 (m, 1H, O-CH₂-CH=CH₂), 5.44 – 5.48 (m, 1H, O-CH₂-CH=CH₂), 6.09 – 6.16 (m, 1H, O-CH₂-CH=CH₂), 7.12 – 7.17 (m, 2H, Ph 3,5-H), 7.57 – 7.64 (m, 2H, Ph 2,6-H), 8.19 (s, 1H, 5-H), 9.86 (s, 1H, CHO). ¹³C NMR (176 MHz, CDCl₃): δ (ppm) 70.2 (O-CH₂-CH=CH₂), 111.6 (C-4), 116.6 (d, ²JC₁₁ 23.2 Hz, Ph C-3,5), 118.8 (O-CH₂-CH=CH₂), 120.7 (d, ²JC₁₂ 8.4 Hz, Ph C-2,6), 129.6 (C-5), 132.5 (O-CH₂-CH=CH₂), 133.4 (d, ²JC₁₂ 2.8 Hz, Ph C-1), 161.6 (d, ²JC₁₁ 247.4 Hz, Ph C-4), 163.6 (C-3), 183.4 (CHO). ¹⁵N NMR (71 MHz, CDCl₃): δ (ppm) -181.2 (N-1), -117.3 (N-2). HRMS (ESI TOF): [M+Na]+ found 269.0696. [C₁₃H₁₁FN₂NaO₂]⁺ requires 269.0697.

1-(4-Bromophenyl)-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole-4-carbaldehyde (3c). Yield 1.15 g (75%), bright brown crystals, m.p. 125–127 °C. IR (neat, ν max cm⁻¹): 3124, 2923, 1665, 1554, 1496, 1418, 1221, 1207, 988, 939. ¹H NMR (700 MHz, CDCl₃): δ (ppm) 4.90 (dt, J 5.8, 1.2 Hz, 2H, O-CH₂-CH=CH₂), 5.31 – 5.35 (m, 1H, O-CH₂-CH=CH₂), 5.45 – 5.50 (m, 1H, O-CH₂-CH=CH₂), 6.10 – 6.17 (m, 1H, O-CH₂-CH=CH₂), 7.50 – 7.66 (m, 4H, Ph 2,3,5,6-H), 8.23 (s, 1H, 5-H), 9.87 (s, 1H, CHO). ¹³C NMR (176 MHz, CDCl₃): δ (ppm) 70.3 (O-CH₂-CH=CH₂), 111.9 (C-4), 118.9 (O-CH₂-CH=CH₂), 120.3 and 132.8 (Ph C-2,3,5,6), 120.7 (Ph C-4), 129.5 (C-5), 132.4 (O-CH₂-CH=CH₂), 138.1 (Ph C-1), 163.6 (C-3), 183.4 (CHO). ¹⁵N NMR (71 MHz, CDCl₃): δ (ppm) -181.5 (N-1), -118.3 (N-2). HRMS (ESI TOF): [M+Na]+ found 328.9897. [C₁₃H₁₁⁷⁹BrN₂NaO₂]⁺ requires 328.9896.

General procedure for the Wittig olefination of 3-[(prop-2-en-1-yl)oxy]-1H-pyrazole-4-carbaldehydes giving 4-ethyl-1-phenyl-3-[(prop-2-en-1-yl)oxy]-1H-pyrazoles (compounds 4a-c). To a suspension of methyltriphenylphosphonium iodide (1.83 g, 4.5 mmol) in dry toluene (60 mL) under inert atmosphere, the potassium tert-butoxide (1.01 g, 9 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 30 min and subsequently refluxed for another 30 min. Formation of the ylide can be visibly observed by its persistent yellow color. After refluxing, the reaction mixture was allowed to come to room temperature and kept in an ice bath, followed by dropwise addition of an appropriate aldehyde 3a-c (3 mmol) dissolved in dry toluene (30 mL). Then the reaction was carried out in room temperature for 3-5 hours, and the progress was monitored by TLC. Upon completion, the reaction was quenched by saturated solution of ammonium chloride and the organic layer was extracted with ethyl acetate several times. The organic layers were combined, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethylacetate 15:1, v/v to yield compounds 4a-c.

4-Ethyl-1-phenyl-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole (4a). Yield 0.60 g (89%), colorless oil. IR (neat, ν max cm⁻¹): 3081, 2928, 1564, 1500, 1396, 1235, 1205, 989, 940. ¹H NMR (700 MHz, CDCl₃): δ (ppm) 4.89 (dt, J 5.5, 1.5 Hz, 2H, O-CH₂-CH₂), 5.18 (dd, J 11.3, 1.7 Hz, 1H, Pyr 4-CH=CH₂), 5.28 – 5.31 (m, 1H, O-CH₂-CH=CH₂), 5.45 – 5.50 (m, 1H, O-CH₂-CH=CH₂), 5.74 (dd, J 17.7, 1.7 Hz, 1H, Pyr 4-CH=CH₂), 6.12 – 6.20 (m, 1H, O-CH₂-CH=CH₂), 6.55 (dd, J 17.7, 11.3 Hz, 1H, Pyr 4-CH=CH₂), 7.18 – 7.22 (m, 1H, Ph 4-H), 7.39 – 7.43 (m, 2H, Ph 3,5-H), 7.57 – 7.61 (m, 2H, Ph 2,6-H), 7.75 (s, 1H, 5-H). ¹³C NMR (176 MHz, CDCl₃): δ (ppm) 69.7 (O-CH₂-CH₂), 108.7 (C-4), 113.4 (Pyr 4-CH=CH₂), 117.6 (O-CH₂-CH=CH₂), 117.7 (Ph C-2,6), 125.1 (Pyr 4-CH=CH₂), 125.2 (C-5), 125.3 (Ph C-4), 129.5 (Ph C-3,5), 133.4 (O-CH₂-CH=CH₂), 140.0 (Ph C-1), 161.7 (C-3). ¹⁵N NMR (71 MHz, CDCl₃): δ (ppm) -189.4 (N-1), -119.6 (N-2). HRMS (ESI TOF): [M+Na]+ found 249.1000. [C₁₄H₁₄N₂O]⁺ requires 249.0998.

4-ethyl-1-(4-fluorophenyl)-3-[(prop-2-en-1-yl)oxy]-1H-pyrazole (4b). Yield 0.29 g (39%), colorless oil. IR (neat, ν max cm⁻¹): 3086, 2929, 1564, 1511, 1396, 1226, 1205, 989, 941. ¹H NMR (700 MHz, CDCl₃): δ (ppm) 4.86
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(5a–c) had become deactivated, another portion of it (41 mg, 0.05 mmol) was added (total catalyst loading 10 mol%). The reaction mixture was refluxed for another 24 h. Subsequently the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel with hexane/ethylacetate 6:1, v/v. The yields of compounds 5a (83 mg, 42%), 5b (121 mg, 56%) and 5c (108 mg, 39%).

Method B. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (41 mg, 0.05 mmol) was added to a solution of diene 4a (99 mg, 0.5 mmol) in dry degassed tetrahydrofuran (5 mL). The reaction mixture was heated in a microwave reactor (150 W) to 65 °C for 3 h. Standard workup and purification according to the Method A yielded compound 5a (23 mg, 23%).

Method C. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (82 mg, 0.1 mmol) was added to a solution of diene 4a (198 mg, 1.0 mmol) in dry degassed tetrahydrofuran (10 mL). The reaction mixture was refluxed in a microwave reactor (150 W) for 3 h, under open vessel conditions with an inert gas sparging. Glass capillary for Ar purging were immersed through the reflux condenser into the solution maintaining the inert gas introduction. The solvent was kept at the constant volume. Standard workup and purification according to the Method A yielded compound 5a (67 mg, 34%).

2-Phenyl-2,6-dihydropyrano[2,3-c]pyrazole (5a). Pale crystals, m.p. 88–90 °C. IR (neat, \( v_{\text{max}} \) cm\(^{-1} \)): 3116, 2927, 1581, 1502, 1406, 1202. \(^1\)H NMR (700 MHz, CDCl\(_3\)): \( \delta \) (ppm) 5.03 (dd, J 3.3, 2.0 Hz, 2H, 6-H), 5.56 (dt, J 9.8, 3.4 Hz, 1H, 5-H), 6.47 (dt, J 9.8, 1.9 Hz, 1H, 4-H), 7.18 (t, J 7.4 Hz, 1H, Ph 4-H), 7.37 – 7.41 (m, 2H, Ph 3.5-H), 7.53 (s, 1H, 3-H), 7.55 – 7.58 (m, 2H, Ph 2,6-H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \( \delta \) (ppm) 68.8 (C-6), 104.8 (C-3a), 117.6 (Ph C-2,6), 118.2 (C-4), 119.1 (C-5), 121.1 (C-3), 125.3 (Ph C-4), 129.4 (Ph C-3,5), 140.1 (Ph C-1), 161.9 (C-7a). \(^{15}\)N NMR (71 MHz, CDCl\(_3\)): \( \delta \) (ppm) -188.7 (N-2), -120.2 (N-1). HRMS (ESI TOF): [M+H\(^+\)]\(^{\text{+}}\) found 199.0864. [C\(_{12}\)H\(_{15}\)N\(_2\)O\(^\text{+}\)] requires 199.0866.
2-(4-Fluorophenyl)-2,6-dihydropyrano[2,3-c]pyrazole (5b). Pale crystals, m.p. 104–107 °C. IR (neat, ν_{max} cm^{-1}): 3133, 2927, 1590, 1510, 1399, 1206. 1H NMR (700 MHz, CDCl₃): δ (ppm) 5.01 (dd, J 3.2, 1.7 Hz, 2H, 6-H), 5.54 (dt, J 9.8, 3.4 Hz, 1H, 5-H), 6.44 (dt, J 9.8, 1.5 Hz, 1H, 4-H), 7.04 – 7.09 (m, 2H, Ph 3,5-H), 7.44 (s, 1H, 3-H), 7.48 – 7.52 (m, 2H, Ph 2,6-H). 13C NMR (176 MHz, CDCl₃): δ (ppm) 68.8 (C-6), 104.9 (C-3a), 116.2 (d, 2J_C,F 160.4 (d, J_H,F 33, 2927, 1592, 1495, 1398, 1207. 1H NMR (700 MHz, CDCl₃): δ (ppm) 5.03 (dd, J 3.3, 2.0 Hz, 2H, 6-H), 5.57 (dt, J 9.8, 3.4 Hz, 1H, 5-H), 6.45 (dt, J 9.8, 1.9 Hz, 1H, 4-H), 7.42 – 7.50 (m, 5H, 3-H and Ph-2,3,5,6). 13C NMR (176 MHz, CDCl₃): δ (ppm) 68.9 (C-6), 105.3 (C-3a), 117.9 (C-4), 118.1 (Ph C-4), 119.0 and 132.4 (Ph C-2,3,5,6), 119.6 (C-5), 120.9 (C-3), 139.1 (Ph C-1), 162.0 (C-7a). 15N NMR (71 MHz, CDCl₃): δ (ppm) -190.6 (N-2), -119.7 (N-1). 19F NMR (376 MHz, CDCl₃): δ (ppm) -117.7. HRMS (ESI TOF): [M+Na]^+ found 239.0591. [C₁₂H₁₀₇BrN₂O]⁺ requires 239.0591.

2-(4-Bromophenyl)-2,6-dihydropyrano[2,3-c]pyrazole (5c). White crystals, m.p. 133–135 °C. IR (neat, ν_{max} cm^{-1}): 3134, 2927, 1592, 1495, 1398, 1207. 1H NMR (700 MHz, CDCl₃): δ (ppm) 5.03 (dd, J 3.3, 2.0 Hz, 2H, 6-H), 5.57 (dt, J 9.8, 3.4 Hz, 1H, 5-H), 6.45 (dt, J 9.8, 1.9 Hz, 1H, 4-H), 7.42 – 7.50 (m, 5H, 3-H and Ph-2,3,5,6). 13C NMR (176 MHz, CDCl₃): δ (ppm) 68.9 (C-6), 105.3 (C-3a), 117.9 (C-4), 118.1 (Ph C-4), 119.0 and 132.4 (Ph C-2,3,5,6), 119.6 (C-5), 120.9 (C-3), 139.1 (Ph C-1), 162.0 (C-7a). 15N NMR (71 MHz, CDCl₃): δ (ppm) -190.8 (N-2), -120.5 (N-1). HRMS (ESI TOF): [M+H]^+ found 276.9973. [C₁₂H₁₀₇BrN₂O]⁺ requires 276.9971.

Supplementary Material

NMR spectra (1H, 13C, DEPT-135 13C, 1H-15N HMBC, 1H-13C, gs-HSQC, and 60 Hz 1,1 gs-COSY) of compound 5a are available in the Supplementary material file.

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