O-Pyrazolylpropynyl-Hydroxylamines as Versatile Intermediates in the Synthesis of Compounds of Pharmacological Interest

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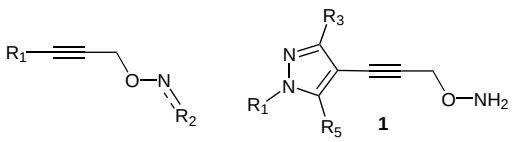
Abstract: Through an optimised Pd/Cu-catalysed cross-coupling reaction of 4-iodopyrazoles with 2-propyn-1-ol, followed by Mitsunobu transformation with *N*-hydroxyphthalimide and subsequent hydrazinolysis, *O*-[(pyrazol-4-yl)-prop-2-ynyl]-hydroxylamines were obtained in good yields. Their usefulness as intermediates in the synthesis of pharmaceuticals is exemplified by the first reported intramolecular cyclization of *O*-(2-propynyl)-hydroxylamines to yield 4,5-dihydro-isoxazoles.

Key words: *O*-pyrazolylpropynyl-hydroxylamines, 3-pyrazolyl-4,5-dihydro-isoxazoles, cross-coupling, Mitsunobu reaction, intramolecular cyclisation

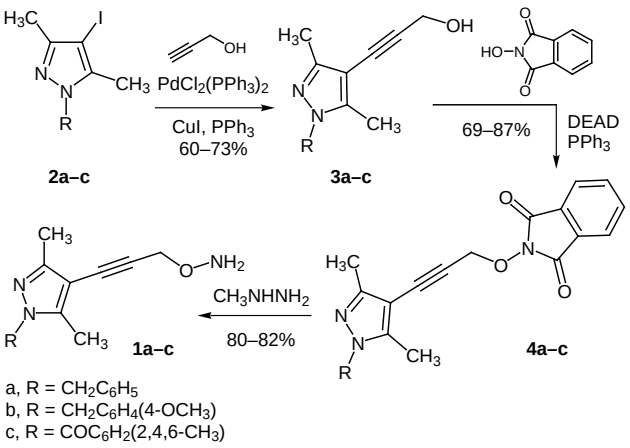
Since the *O*-alkynylhydroxylamine moiety is currently present in a wide variety of bioactive compounds (e.g., muscarinic agonists,[2] calcium antagonists,[3] antibiotics,[4] insecticides,[5] and fungicides[6]), its precursors represent valuable intermediates in Medicinal Chemistry.

As a result of our research on the synthesis of biologically active pyrazoles that showed muscarinic properties[7] or selective complexation of neurotransmitters,[8] we are now interested in the development of efficient synthetic pathways for *O*-pyrazolylpropynyl-hydroxylamines **1** (Figure) as useful intermediates in the synthesis of compounds of potential pharmacological interest. Herein, we describe the synthesis of the new pyrazolic intermediates **1** through an optimised Pd/Cu-catalysed cross-coupling reaction[9] of 4-iodopyrazoles with propargyl alcohol, followed by Mitsunobu transformation[10] with *N*-hydroxyphthalimide and subsequent hydrazinolysis. As a probe of the usefulness of **1** as intermediates of pharmaceuticals, the cyclisation of *O*-(2-propynyl)-hydroxylamines to give 4,5-dihydro-isoxazoles of potential interest as antithrombotic agents is also described.[11]



Figure

The synthetic route began with the iodination of 3,5-dimethyl-1*H*-pyrazole using elemental iodine in the presence of ceric ammonium nitrate [ammonium hexanitratocerate (IV): CAN] as the in situ oxidant, following the method recently reported by us,[12] obtaining 4-iodo-3,5-dimethyl-1*H*-pyrazole in very good yield (93%). This 4-iodopyrazole was treated with different alkylating agents to give the N-substituted 4-iodopyrazoles **2a**–**c**, which were then coupled with 2-propyn-1-ol (propargyl alcohol) using bis(triphenylphosphine)palladium dichloride and cuprous iodide as catalysts (Scheme 1).



Scheme 1

Preliminary experiments of these cross-coupling reactions were carried out using 1 equivalent of the corresponding 4-iodopyrazole, 1 equivalent of propargyl alcohol, 0.04 equivalents of $PdCl_2(PPh_3)_2$ and 0.04 equivalents of CuI, in diethylamine as solvent, as described for pyrazole derivatives in a precedent work.[13] Since under these experimental conditions little or no reaction was observed, and taking into account that an excess of the acetylenic compound in a more strongly basic solvent could give better results,[14] reactions were repeated using 2 equivalents of propargyl alcohol with piperidine as solvent. In these modified conditions only **3c** was obtained in moderate yield (30%), but when **2a** or **2b** were used as starting materials no reaction was observed. Instead, the reaction solution turned first brown and then black, due to the precipitation of uncomplexed metallic palladium, which is catalytically inactive.[15] This problem could be prevented by adding 2 moles of triphenylphosphine per mole of palladium, when the brown colour first appears, to regen-

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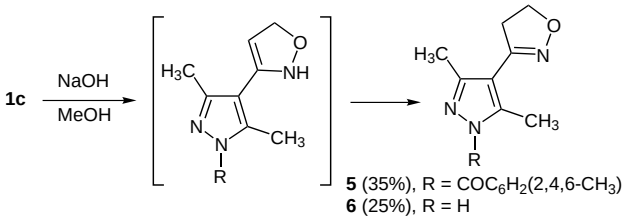
erate the active catalyst $Pd(PPh_3)_2$. Thus, the coupling of 4-iodopyrazoles **2a**–**c** (1 equivalent) with 2-propyn-1-ol (2 equivalents) in dry piperidine in the presence of bis(triphenylphosphine)palladium dichloride $[PdCl_2(PPh_3)_2]$ (0.04 equivalents), cuprous iodide (0.04 equivalents) and triphenylphosphine (0.08 equivalents), at room temperature for 24 hours, yielded the desired pyrazolylpropargyl alcohols in good yields (**3a**: 60%, **3b**: 73%, **3c**: 73%).

Following Mitsunobu's methodology, from the reaction of diethyl azodicarboxylate and triphenylphosphine (to form a betaine),[16] a pyrazolylpropargyl alcohol **3a**–**c**, and the nucleophilic *N*-hydroxyphthalimide,[17] the phthalimides **4a**–**c** were obtained in satisfactory yields (69–87%). Hydrazinolysis of the above protected intermediates **4a**–**c** with anhydrous methylhydrazine[18] gave the desired *O*-pyrazolylpropynyl-hydroxylamines **1a**–**c** in good yields (80–82%).

The *O*-[(pyrazol-4-yl)-prop-2-ynyl]-hydroxylamines **1a**–**c** are unstable intermediates that must be used immediately after their synthesis, or converted into the corresponding hydrochloride derivative for storage purposes. Standing at room temperature, they suffer a slow intramolecular addition of the hydroxylamine group to the triple bond, yielding isoxazolines. This reaction is faster in the presence of a base; the treatment of **1c** with sodium hydroxide in methanol at reflux for 3 hours gave a mixture of the N-substituted and N-unsubstituted isoxazolines **5** and **6**, as the result of an intramolecular addition of the amine group of the O-substituted hydroxylamine to the triple bond (Scheme 2). The reaction probably proceeds through the initial formation of an enamine, which then tautomerises to the more stable imine.[19]



Scheme 2

Although the intramolecular addition of amines to alkynes to yield pyrrolidines or piperidines is a well-known reaction, generally catalysed by transition[20] or lanthanide[21] metals, there are no examples of the analogous intramolecular transformations involving *O*-alkynylhydroxylamines. In fact, we found very few publications on the addition of the amino group belonging to an O-substituted hydroxylamine[22] or the hydroxylamine itself[23] to a triple bond, instead, in all cases, the examples were intermolecular additions yielding the corresponding linear oxime. Consequently, to our knowledge, this is the first example of the intramolecular addition of an O-substituted hydroxylamine to a triple bond to give an isoxazoline. Since some 3-(hetero)aryl-4,5-dihydroisoxazoles show pharmacological profiles (mainly antithrombotic,[24] antiinflammatory,[25] and antibacterial[26] activities) this reaction represents a new and convenient way to obtain these products under mild reaction conditions.

All new compounds showed combustion analysis and spectroscopic data in agreement with their structures. Unequivocal assignment of all chemical shifts (^1H and ^{13}C NMR) was undertaken using two-dimensional experiments such as HMQC for one-bond correlations, and HMBC for two and three bond correlations.

In conclusion, we have obtained *O*-[(pyrazol-4-yl)-prop-2-ynyl]-hydroxylamines in good yields, using an optimised Pd/Cu-catalysed cross-coupling reaction of 4-iodopyrazoles with 2-propyn-1-ol, followed by Mitsunobu transformation with *N*-hydroxyphthalimide and subsequent hydrazinolysis. We have also found the first example of the intramolecular addition of an O-substituted hydroxylamine to a triple bond, yielding the corresponding isoxazoline.

The analytical and synthetic methodologies were performed by using the facilities at our Institute as described in a recent work.[27] Most starting materials were commercially available products and were used without further purification. 2,4,6-Trimethylbenzoyl chloride was obtained by refluxing the commercially available acid with thionyl chloride for 8 h. 4-Iodo-3,5-dimethyl-1*H*-pyrazole (mp 136–137 °C (Lit.:[28] 137 °C) was obtained in 93% yield from 3,5-dimethyl-1*H*-pyrazole (Aldrich) by an oxidative iodination in the presence of ceric ammonium nitrate (CAN), as recently described by us.[12]

N-Alkylation of 4-Iodo-3,5-dimethyl-1*H*-pyrazole; General Procedure

To a mixture of 4-iodo-3,5-dimethyl-1*H*-pyrazole (1 equiv) and a base (NaH or Et_3N, 1 equiv), a solution of the corresponding alkylating agent (1 equiv) was added, and the reaction was stirred at r.t. or under reflux until completion. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 (25 mL), washed with H_2O (3 × 25 mL) and sat. NaCl (25 mL), dried (Na_2SO_4) and evaporated to dryness. The residual syrup was purified as described for individual compounds.

1-Benzyl-4-iodo-3,5-dimethyl-1*H*-pyrazole (2a)

Following the general procedure, from 4-iodo-3,5-dimethyl-1*H*-pyrazole (1.0 g, 4.5 mmol), NaH (60% dispersion in mineral oil, 198 g, 4.5 mmol), and benzyl bromide (0.5 mL, 4.5 mmol) in DMF (30 mL) at r.t. for 18 h, a syrup was obtained that was purified by silica gel flash chromatography (hexane–EtOAc, 3:1). The fractions of R_f = 0.3 afforded 840 mg (60%) of **2a** as a pure white solid.

Mp 85–86 °C.

^1H NMR ($CDCl_3$): δ = 7.02–7.28 (m, 5 H, Bn), 5.24 (s, 2 H, CH_2), 2.21 (s, 3 H, 3-CH_3), 2.14 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 149.4 (C-3 pyrazole), 140.7 (C-5 pyrazole), 136.6 (C-1 benzyl), 128.7 (C-2,-6 Bn), 127.7 (C-4 Bn), 126.6 (C-3,-5 Bn), 63.2 (C-4 pyrazole), 54.0 (CH_2), 14.0 (3-CH_3), 12.0 (5-CH_3).

MS (EI): *m/z* = 312 (M^+).

4-Iodo-1-(4-methoxybenzyl)-3,5-dimethyl-1*H*-pyrazole (2b)

From 4-iodo-3,5-dimethyl-1*H*-pyrazole (656 mg, 2.95 mmol), NaH (60% dispersion in mineral oil, 118 mg, 2.95 mmol), and 4-methoxy-benzyl bromide (0.4 mL, 2.95 mmol) in DMF (30 mL) at r.t. for 16 h, a syrup was obtained, which was purified by silica gel flash

chromatography (hexane–EtOAc, 6:1). From the fractions of R_f = 0.4, compound **2b** was isolated (713 mg, 71% yield), as a pure white solid.

Mp 43–44 °C.

^{1}H NMR ($CDCl_3$): δ = 6.99 (d, 2 H, *J* = 8.3 Hz, H-2,-6 Bn), 6.78 (d, 2 H, *J* = 8.3 Hz, H-3,-5 Bn), 5.15 (s, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.20 (s, 3 H, 3-CH_3), 2.14 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 158.9 (C-4 Bn), 148.8 (C-3 pyrazole), 140.0 (C-5 pyrazole), 128.5 (C-1 Bn), 127.9 (C-2,-6 Bn), 113.9 (C-3,-5 Bn), 63.0 (C-4 pyrazole), 54.9 (CH_2 Bn), 53.2 (OCH_3), 13.8 (3-CH_3), 11.8 (5-CH_3).

MS (EI): *m/z* = 342 (M^+).

4-Iodo-3,5-dimethyl-1-(2,4,6-trimethylbenzoyl)-1*H*-pyrazole (2c)

The reaction of 4-iodo-3,5-dimethyl-1*H*-pyrazole (3.8 g, 17 mmol), Et_3N (2.4 mL, 17 mmol), and 2,4,6-trimethylbenzoyl chloride (3.1 g, 17 mmol) in anhyd toluene (30 mL) under reflux for 8 h yielded a syrup, which was chromatographed (silica gel; hexane–EtOAc, 20:1). The fractions of R_f = 0.5 were collected and evaporated to dryness affording 5.8 g (92% yield) of **2c** as a pure white solid.

Mp 107–108 °C.

^{1}H NMR ($CDCl_3$): δ = 6.87 (s, 2 H, Bz), 2.71 (s, 3 H, 3-CH_3 pyrazole), 2.38 (s, 3 H, 4-CH_3 Bz), 2.17 (s, 3 H, 5-CH_3 pyrazole), 2.12 (s, 6 H, 2,6-CH_3 Bz).

^{13}C NMR ($CDCl_3$): δ = 169.3 (CO), 153.1 (C-3 pyrazole), 144.0 (C-5 pyrazole), 138.4 (C-4 Bz), 133.8 (C-2,-6 Bz), 132.1 (C-1 Bz), 127.5 (C-3,-5 Bz), 73.0 (C-4 pyrazole), 20.5 (4-CH_3 Bz), 18.8 (2,6-CH_3 Bz), 14.8 (3-CH_3 pyrazole), 13.8 (5-CH_3 pyrazole).

MS (EI): *m/z* = 368 (M^+).

3-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-prop-2-yn-1-ols (3a–c); General Procedure

Under a N_2 atm, to a stirred solution of the corresponding iodopyrazole **2a–c** (1 equiv) and 2-propyn-1-ol (2 equiv) in anhyd piperidine, catalytic amounts of bis(triphenylphosphine)palladium dichloride $PdCl_2(PPh_3)_2$ (0.04 equiv) and cuprous iodide (CuI, 0.04 equiv) were added. The light-yellow mixture was stirred at r.t. and, from the moment a brown colour began to develop (20–40 min), PPh_3 (0.08 equiv) was added, and the reaction was stirred under N_2 for an additional 24 h. Then the solvent was evaporated to dryness and the residue was redissolved in CH_2Cl_2 (25 mL), washed with H_2O (3 × 25 mL) and brine (25 mL). The organic solution was dried (Na_2SO_4) and evaporated to dryness to yield syrups that were purified by silica gel flash chromatography.

3-(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-prop-2-yn-1-ol (3a)

Following the general method, from **2a** (839 mg, 2.7 mmol), 2-propyn-1-ol (349 μL, 5.92 mmol), $PdCl_2(PPh_3)_2$ (64 mg, 0.11 mmol), CuI (21 mg, 0.11 mmol) and PPh_3 (64 mg, 0.22 mmol) in anhyd piperidine (5 mL), a syrup was obtained, which was chromatographed (silica gel; mixtures of hexane–EtOAc of increasing polarity, 5:1 to 2:1). From the fractions of R_f = 0.2 (hexane–EtOAc, 2:1), compound **3a** was isolated (388 mg, 60%) as a pure syrup.

^{1}H NMR ($CDCl_3$): δ = 7.10 (m, 5 H, Bn), 5.10 (s, 2 H, CH_2-Bn), 4.38 (s, 2 H, C≡C-C*H*$_2$-OH), 2.19 (s, 3 H, 3-CH_3), 2.09 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 149.9 (C-3 pyrazole), 142.3 (C-5 pyrazole), 136.3 (C-1 Bn), 128.6 (C-2,-6 Bn), 127.5 (C-4 Bn), 126.7 (C-3,-5 Bn), 101.8 (C-4 pyrazole), 91.3 (*C*≡C-CH_2OH), 77.8 (C≡*C*-CH_2OH), 52.9 (CH_2 Bn), 51.1 (C≡C-*C*H_2OH), 12.2 (3-CH_3), 10.3 (5-CH_3).

MS (EI): *m/z* = 240 (M^+).

3-[1-(4-Methoxybenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-prop-2-yn-1-ol (3b)

Following the general method, from **2b** (712 mg, 2.1 mmol), 2-propyn-1-ol (270 μL, 4.58 mmol), $PdCl_2(PPh_3)_2$ (46 mg, 0.08 mmol), CuI (16 mg, 0.08 mmol) and PPh_3 (46 mg, 0.16 mmol) in dry piperidine (4.5 mL), a syrup was obtained. Its purification on a silica gel column (mixtures of hexane–EtOAc, 6:1 to 1:2) yielded **3b** (408 mg, 73%) as a pure syrup (R_f = 0.1, hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 7.00 (d, 2H, *J* = 8.7 Hz, H-2,-6 Bn), 6.80 (d, 2H, *J* = 8.7 Hz, H-3,-5 Bn), 5.10 (s, 2H, CH_2 Bn), 4.46 (s, 2H, C≡C-C*H*$_2$-OH), 3.74 (s, 3H, OCH_3), 2.24 (s, 3H, 3-CH_3), 2.17 (s, 3H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 159.1 (C-4 Bn), 150.0 (C-3 pyrazole), 142.3 (C-5 pyrazole), 128.4 (C-1 Bn), 128.1 (C-2,-6 Bn), 114.1 (C-3,-5 Bn), 101.6 (C-4 pyrazole), 91.0 (*C*≡C-CH_2OH), 77.6 (C≡*C*-CH_2OH), 55.2 (CH_2 Bn), 52.5 (OCH_3), 51.6 (C≡C-*C*H_2OH), 12.4 (3-CH_3), 10.5 (5-CH_3).

MS (EI): *m/z* = 270 (M^+).

3-[3,5-Dimethyl-1-(2,4,6-trimethylbenzoyl)-1*H*-pyrazol-4-yl]-prop-2-yn-1-ol (3c)

From **2c** (582 mg, 1.6 mmol), 2-propyn-1-ol (0.2 mL, 3.4 mmol), $PdCl_2(PPh_3)_2$ (37 mg, 0.06 mmol), CuI (12 mg, 0.06 mmol) and PPh_3 (31 mg, 0.12 mmol) in anhyd piperidine (3 mL), a syrup was obtained, which was chromatographed (silica gel; mixtures of hexane–EtOAc of increasing polarity, 10:1 to 8:1). From the fractions of R_f = 0.2 (hexane–EtOAc, 7:1), compound **3c** was isolated (348 mg, 73%) as a white solid.

Mp 113–115 °C.

^{1}H NMR ($CDCl_3$): δ = 6.86 (s, 2H, Bz), 4.47 (s, 2H, C≡C-C*H*$_2$-OH), 2.69 (s, 3H, 3-CH_3), 2.29 (s, 3H, 4-CH_3 Bz), 2.18 (s, 3H, 5-CH_3), 2.11 (s, 6H, 2,6-CH_3 Bz).

^{13}C NMR ($CDCl_3$): δ = 171.2 (CO), 154.0 (C-3 pyrazole), 146.3 (C-5 pyrazole), 139.3 (C-4 Bz), 134.4 (C-2,-6 Bz), 132.8 (C-1 Bz), 128.1 (C-3,-5 Bz), 104.0 (C-4 pyrazole), 95.1 (*C*≡C-CH_2OH), 78.6 (C≡*C*-CH_2OH), 51.5 (C≡C-*C*H_2OH), 21.1 (4-CH_3 Bz), 19.3 (2,6-CH_3 Bz), 13.7 (3-CH_3), 12.7 (5-CH_3).

MS (EI): *m/z* = 296 (M^+).

2-[3-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-prop-2-ynyloxy]-isoindole-1,3-diones (4a–c); General Procedure

Diethyl azodicarboxylate (DEAD, 1.1 equiv) was added dropwise to a stirred solution of the corresponding pyrazolylpropargyl alcohol **3a–c** (1 equiv), *N*-hydroxyphthalimide (1 equiv) and PPh_3 (1 equiv) in dry THF under N_2, and the mixture was stirred for 48 h at r.t. The solvent was removed in vacuo and the product was purified as described for individual compounds.

2-[3-(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-prop-2-ynyloxy]-isoindole-1,3-dione (4a)

Following the general method, from **3a** (154 mg, 0.64 mmol), *N*-hydroxyphthalimide (105 mg, 0.64 mmol), PPh_3 (168 mg, 0.64 mmol) and DEAD (123 mg, 0.71 mmol) in THF (5 mL), compound **4a** was isolated as a pure colourless syrup (171 mg, 69%) after flash chromatography (hexane–EtOAc, 5:1 to 2:1), and two centrifugal circular TLC (hexane–EtOAc, 4:1 to 2:1).

^{1}H NMR ($CDCl_3$): δ = 7.70 (m, 4 H, phthalimide), 7.15 (m, 5 H, Bn), 5.14 (s, 2 H, CH_2-O), 5.10 (s, 2 H, CH_2), 2.15 (s, 3 H, 3-CH_3), 2.12 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 165.5 (CO), 149.8 (C-3 pyrazole), 142.1 (C-5 pyrazole), 136.3 (C-1 Bn), 133.5 (C-4,-5 phthalimide), 132.7 (C-2a,-6a phthalimide), 128.7 (C-2,-6 Bn), 127.4 (C-4 Bn), 126.9 (C-3,-5 Bn), 123.3 (C-3, -6 phthalimide), 101.5 (C-4 pyrazole), 91.0

(*C*≡C-CH_2), 77.8 (C≡*C*-CH_2), 52.9 (CH_2Ph), 51.0 (C≡C-*C*H_2), 12.2 (3-CH_3), 10.2 (5-CH_3).

MS (EI): *m/z* = 385 (M^+).

2-{3-[1-(4-Methoxybenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-prop-2-ynyloxy}-isoindole-1,3-dione (4b)

From **3b** (408 mg, 1.2 mmol), *N*-hydroxyphthalimide (195 mg, 1.2 mmol), PPh_3 (313 mg, 1.2 mmol) and DEAD (229 mg, 1.3 mmol) in THF (5 mL), a brown syrup was obtained, which was purified on a silica gel column (mixtures of hexane–EtOAc of increasing polarity, 8:1 to 2:1). The fractions of R_f = 0.5 (hexane–EtOAc, 1:1) were evaporated to dryness, yielding 403 mg (82%) of **4b**, as a pure colourless syrup.

^{1}H NMR ($CDCl_3$): δ = 7.65 (m, 4 H, phthalimide), 6.95 (d, 2 H, *J* = 8.7 Hz, H-2,-6 Bn), 6.74 (d, 2 H, *J* = 8.7 Hz, H-3,-5 Bn), 5.13 (s, 2 H, CH_2), 4.46 (s, 2 H, CH_2-O), 3.70 (s, 3 H, OCH_3), 2.25 (s, 3 H, 3-CH_3), 2.16 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 164.5 (CO), 159.0 (C-4 Bn), 150.2 (C-3 pyrazole), 142.6 (C-5 pyrazole), 133.8 (C-4,-5 phthalimide), 132.8 (C-2a, -6a phthalimide), 128.1 (C-1 Bn), 127.9 (C-2,-6 Bn), 123.0 (C-3,-6 phthalimide), 114.0 (C-3,-5 Bn), 101.8 (C-4 pyrazole), 91.1 (*C*≡C-CH_2), 77.2 (C≡*C*-CH_2), 55.2 (CH_2Ph), 52.3 (OCH_3), 51.7 (C≡C-*C*H_2), 12.2 (3-CH_3), 10.4 (5-CH_3).

MS (EI): *m/z* = 415 (M^+).

2-{3-[3,5-Dimethyl-1-(2,4,6-trimethylbenzoyl)-1*H*-pyrazol-4-yl]-prop-2-ynyloxy}-isoindole-1,3-dione (4c)

From **3c** (758 mg, 2.6 mmol), *N*-hydroxyphthalimide (418 mg, 2.6 mmol), PPh_3 (670 mg, 2.6 mmol) and DEAD (490 mg, 2.8 mmol) in THF (10 mL), a solid residue was obtained. Treatment with cold MeOH (10 mL) yielded **4c** as a white solid (mp 158–160 °C), which was isolated by filtration (985 mg, 87%).

^{1}H NMR ($CDCl_3$): δ = 7.70 (m, 4 H, phthalimide), 6.84 (s, 2 H, Bz), 5.13 (s, 2 H, CH_2-O), 2.61 (s, 3 H, 3-CH_3 pyrazole), 2.25 (s, 3 H, 4-CH_3 Bz), 2.08 (s, 9 H, 5-CH_3 pyrazole and 2,6-CH_3 Bz).

^{13}C NMR ($CDCl_3$): δ = 170.8 (CO Bz), 163.4 (CO phthalimide), 154.0 (C-3 pyrazole), 147.1 (C-5 pyrazole), 139.3 (C-4 Bz), 134.6 (C-4,-5 phthalimide), 134.4 (C-2,-6 Bz), 132.7 (C-1 Bz), 128.7 (C-2a,-6a phthalimide), 128.1 (C-3,-5 Bz), 123.6 (C-3,-6 phthalimide), 106.9 (C-4 pyrazole), 87.9 (*C*≡C-CH_2), 80.3 (C≡*C*-CH_2), 65.8 (C≡C-*C*H_2), 21.2 (4-CH_3 Bz), 19.3 (2,6-CH_3 Bz), 13.6 (3-CH_3 pyrazole), 12.7 (5-CH_3 pyrazole).

MS (EI): *m/z* = 441 (M^+).

***O*-[3-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-prop-2-ynyl]-hydroxylamines (1a–c); General Procedure**

Methylhydrazine (1 equiv) was added dropwise to a stirred and ice-cooled 0.1 N solution of the phathalimide derivative **4a**–**c** (1 equiv) in dry CH_2Cl_2. The reaction mixture was allowed to reach r.t. and stirred for an additional 1–5 h. Then, a white solid was separated by filtration, and the organic solution was evaporated to dryness, yielding the pyrazolyl propargyl hydroxylamines **1a**–**c**.

***O*-[3-(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-prop-2-ynyl]-hydroxylamine (1a)**

From methylhydrazine (20 mg, 0.44 mmol) and **4a** (171 mg, 0.44 mmol) in CH_2Cl_2 (5 mL, 1 h at r.t.), the hydroxylamine **1a** was obtained as a pure syrup (90 mg, 82%).

^{1}H NMR ($CDCl_3$): δ = 7.12 (m, 5 H, Bn), 4.76 (s, 2 H, CH_2-O), 5.09 (s, 2 H, CH_2), 2.16 (s, 3 H, 3-CH_3), 2.11 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 149.7 (C-3 pyrazole), 142.3 (C-5 pyrazole), 136.5 (C-1 Bn), 128.8 (C-2,-6 Bn), 127.2 (C-4 Bn), 126.7 (C-3,-5 Bn), 101.4 (C-4 pyrazole), 91.0 (*C*≡C-CH_2), 77.4 (C≡*C*-CH_2), 52.9 (CH_2Ph), 50.0 (C≡C-*C*H_2), 12.3 (3-CH_3), 10.1 (5-CH_3).

***O*-{3-[1-(4-Methoxybenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-prop-2-ynyl}-hydroxylamine (1b)**

Following the general method, **4b** (84 mg, 0.20 mmol) and methylhydrazine (9 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) (5 h at r.t.) yielded 46 mg (80%) of **1b**, as a pure colourless syrup.

^{1}H NMR ($CDCl_3$): δ = 7.00 (d, 2 H, *J* = 8.7 Hz, H-2,-6 Bn), 6.84 (d, 2 H, *J* = 8.7 Hz, H-3,-5 Bn), 5.10 (s, 2 H, CH_2), 4.10 (s, 2 H, CH_2-O), 3.70 (s, 3 H, OCH_3), 2.24 (s, 3 H, 3-CH_3), 2.16 (s, 3 H, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ = 159.0 (C-4 Bn), 150.3 (C-3 pyrazole), 142.8 (C-5 pyrazole), 128.1 (C-1 Bn), 127.9 (C-2,-6 Bn), 114.0 (C-3,-5 Bn), 101.5 (C-4 pyrazole), 91.5 (*C*≡C-CH_2), 77.5 (C≡*C*-CH_2), 55.2 (CH_2Ph), 52.3 (OCH_3), 51.2 (C≡C-*C*H_2), 12.4 (3-CH_3), 10.6 (5-CH_3).

***O*-{3-[3,5-Dimethyl-1-(2,4,6-trimethylbenzoyl)-1*H*-pyrazol-4-yl]-prop-2-ynyl}-hydroxylamine hydrochloride (1c·HCl)**

From **4c** (100 mg, 0.22 mmol) and methylhydrazine (10 mg, 0.22 mmol) in CH_2Cl_2 (2 mL, 4 h at r.t.), a syrup was obtained, which was dissolved in Et_2O (10 mL) and treated with HCl yielding **1c·HCl** as a white solid (62 mg, 81% yield, mp 104–105 °C).

^{1}H NMR (CD_3OD): δ = 7.10 (s, 2H, Bz), 5.26 (s, 2H, C≡C-C*H*$_2$), 5.13 (br s, 3H, NH_3^+), 2.92 (s, 3H, 3-CH_3), 2.50 (s, 3H, 5-CH_3), 2.39 (s, 3H, 4-CH_3 Bz), 2.29 (s, 6H, 2,6-CH_3 Bz).

^{13}C NMR (CD_3OD): δ = 172.2 (CO), 155.6 (C-3 pyrazole), 148.9 (C-5 pyrazole), 140.9 (C-4 Bz), 135.6 (C-2,-6 Bz), 134.0 (C-1 Bz), 129.1 (C-3,-5 Bz), 107.9 (C-4 pyrazole), 88.3 (*C*≡C-CH_2), 81.4 (C≡*C*-CH_2), 66.8 (C≡C-*C*H_2), 21.3 (4-CH_3 Bz), 19.3 (2,6-CH_3 Bz), 13.8 (3-CH_3), 12.5 (5-CH_3).

Intramolecular Cyclisation of 1c·HCl

To a solution of **1c·HCl** (38.3 mg, 0.11 mmol) in MeOH (3 mL), NaOH (80 mg, 2.0 mmol) was added and the solution was refluxed for 3 h. Then, the solvent was evaporated to dryness, the residue was redissolved in H_2O (2 mL), carefully neutralised with HCl (0.2 N), and extracted with CH_2Cl_2 (3 × 10 mL). The organic solution was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, yielding a mixture of products that were separated by preparative centrifugal circular TLC (mixtures of increasing polarity, from hexane–EtOAc, 12:1 to EtOAc–MeOH, 5:1).

From the fractions of R_f = 0.6 (hexane–EtOAc, 12:1), 3-[3,5-dimethyl-1-(2,4,6-trimethyl-benzoyl)-1*H*-pyrazol-4-yl]-4,5-dihydro-isoxazole (**5**) was isolated as a pure syrup (12 mg, 35% yield).

^{1}H NMR ($CDCl_3$): δ = 6.86 (s, 2 H, Bz), 4.41 (t, 2 H, *J* = 10.0 Hz, H-5 isoxazoline), 3.30 (t, 2 H, *J* = 10.0 Hz, H-4 isoxazoline), 2.82 (s, 3 H, 3-CH_3 pyrazole), 2.30 (s, 3 H, 4-CH_3 Bz), 2.26 (s, 3 H, 5-CH_3 pyrazole), 2.13 (s, 6 H, 2,6-CH_3 Bz).

^{13}C NMR ($CDCl_3$): δ = 164.1 (CO), 151.7 (C-3 isoxazoline), 150.9 (C-3 pyrazole), 142.8 (C-5 pyrazole), 139.3 (C-4 Bz), 134.4 (C-2,-6 Bz), 133.0 (C-1 Bz), 128.1 (C-3,-5 Bz), 107.2 (C-4 pyrazole), 68.4 (C-5 isoxazoline), 37.5 (C-4 isoxazoline), 21.2 (4-CH_3 Bz), 19.3 (2,6-CH_3 Bz), 14.8 (3-CH_3 pyrazole), 13.8 (3-CH_3 pyrazole).

MS (EI): *m/z* = 311 (M^+).

The fractions of R_f = 0.2 (hexane–EtOAc, 12:1) were evaporated to dryness, yielding 3-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-isoxazole (**6**) as a white solid (4.5 mg, 25% yield).

Mp 168–169 °C.

^{1}H NMR ($CDCl_3$): δ = 4.36 (t, 2 H, *J* = 9.8 Hz, H-5 isoxazoline), 3.29 (t, 2 H, *J* = 9.8 Hz, H-4 isoxazoline), 2.39 (s, 6 H, 3,5-CH_3 pyrazole).

^{13}C NMR ($CDCl_3$): δ = 152.0 (C-3 isoxazoline), 144.3 (C-3,-5 pyrazole), 107.2 (C-4 pyrazole), 67.8 (C-5 isoxazoline), 37.4 (C-4 isoxazoline), 13.2 (3,5-CH_3 pyrazole).

MS (EI): *m/z* = 165 (M^+).

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