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Article

Streamlined Synthesis of 6-((1*H*-1,2,3-Triazol-4-yl)methyl)-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one System via Sequential *N*-Alkylation, CuAAC, and [4 + 2] Cyclization Reactions

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An efficient sequential three-step reaction methodology for the synthesis of three new series-1-(prop-2-yn-1-yl)-1*H*-pyrroles, methyl 4-acetyl-1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole-3-carboxylates and 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones-is reported. The methodology comprises: (*i*) *N*-alkylation reactions of polyfunctionalized 1*H*-pyrroles-which were previously obtained from (*E*)-methyl 2-azido-3-arylacrylates-with propargyl bromide in order to obtain 1*H*-pyrroles; (*ii*) standard copper-catalyzed azide-alkyne cycloaddition (CuAAC) involving organic azides (benzyl-, 4-methoxybenzyl- and 4-chlorobenzyl, as well as *n*-octyl azide) and N-propargylated 1*H*-pyrroles to give triazolyl derivatives, as methyl 1*H*-pyrrole-3-carboxylates (click chemistry); and (*iii*) [4 + 2] cyclocondensation reactions of the ketoesters in the presence of hydrazine hydrochloride in order to furnish the desired series of pyrrolo[3,4-*d*]pyridazin-1-ones at total yields up to 54%.

Keywords: pyrroles, triazoles, pyrrolo[3,4-*d*]pyridazinones, *N*-alkylation, CuAAC, cyclocondensation reaction

Introduction

Heterocyclic compounds play a significant role in synthetic chemistry. In particular, the pyrrolo[3,4-*d*]pyridazinone system has been extensively explored in the literature, due to its anticancer activity and being a strong analgesic agent and used in the treatment of autoimmune and immunologically mediated diseases.[1-6] Thus, the addition, fusion, or derivatization of pyrrolo-pyridazinones to or from other heterocycles is an important way of obtaining new molecules with high potential for biological activity.[7-11]

Polysubstituted pyrroles[12-14] are widely used in the treatment of several important diseases. For example, atorvastatin is a drug used to prevent cardiovascular diseases and it has become one of world's best-selling drugs.[13,14]

In this context, due to the high metabolic stability, propensity to make hydrogen bond, dipole-dipole, and π stacking interactions with biological targets, 1,2,3-triazole nucleus has become one of the most promising pharmacological scaffolds for the development of new drugs. In the last few decades, triazole derivatives have been used in the development of new pharmaceutical agents possessing anti-cancer, anti-fungal, anti-malarial, anti-diabetic, anti-leishmanial, anti-tripanossomal and acetylcholinesterase inhibitory properties (Figure 1).[15-23] 1,2,3-Triazoles are generally obtained through a copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, which is an easy and widely used synthetic methodology.[24-27] Figure 1 shows examples of synthetic heterocycles containing polysubstituted pyrrole, triazole and pyrrolo[3,4-*d*]pyridazinone rings with pharmacological activity.

Despite all the studies, documents and patents mentioning the numerous biological properties of pyrrolo[3,4-*d*]pyridazinone derivatives and 1,2,3-triazoles, no methodology has been developed in recent decades for the combination of these heterocycles as diheteroaryl methylene-spacer systems. Thus, due to our background in the synthesis of pyrroles[28-32] and

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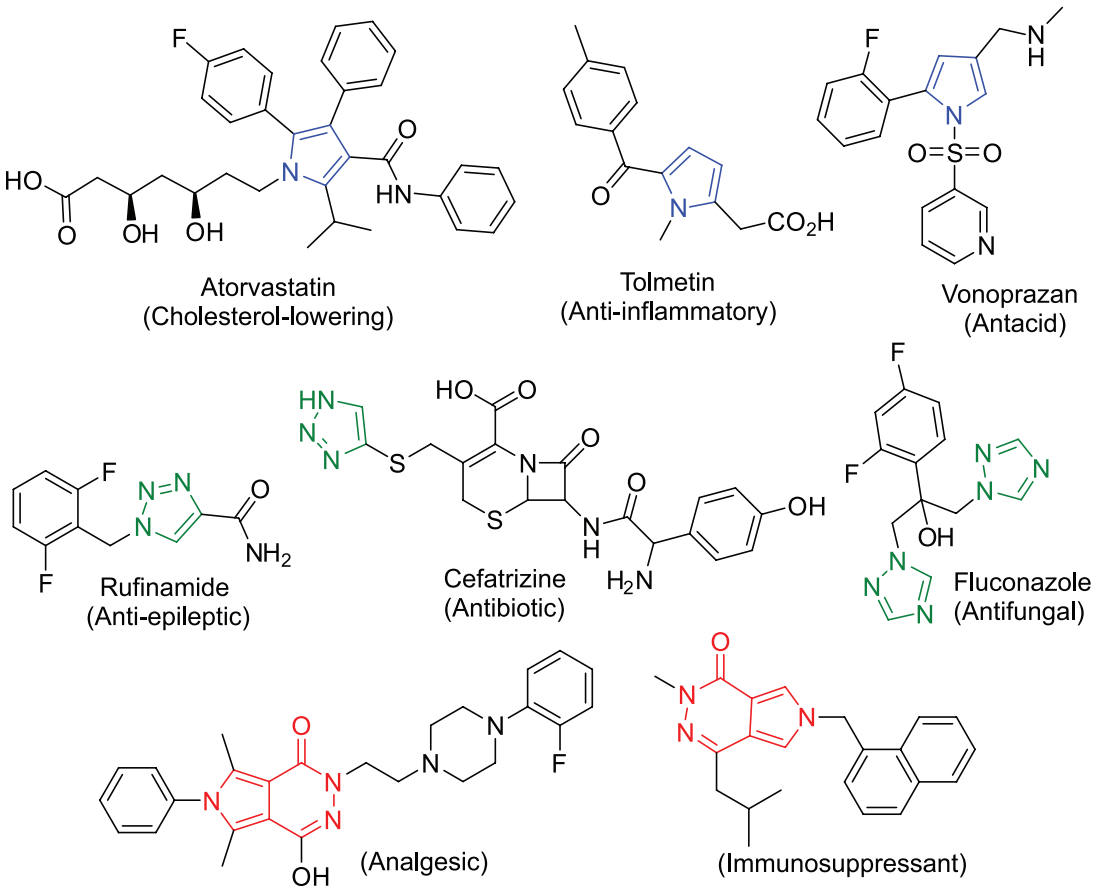


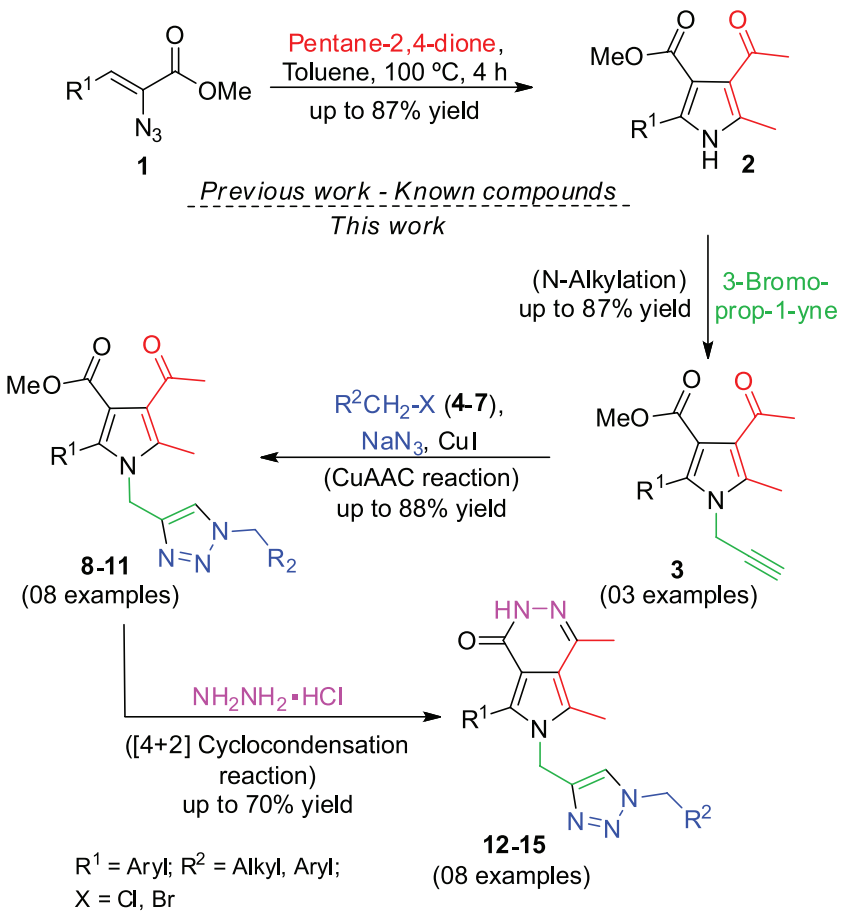
Figure 1. Known synthetic heterocycles containing polysubstituted pyrrole, triazole, and pyrrolo[3,4-*d*]pyridazinone nuclei with pharmacological activity.

pyrrolo[3,4-*d*]pyridazinones,[33] we envisioned the possibility of using an efficient methodology for the synthesis of a new series of a more complex heterocyclic system, which could have a wide range of biological activities for further applications.

In this work the concise sequential three-step reaction methodology for the synthesis of new series of 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones (**12**-**15**) is disclosed. The method starts from an *N*-alkylation reaction of polyfunctionalized pyrroles (**2**)-previously obtained from (*E*)-methyl 2-azido-3-arylacrylates (**1**)-with propargyl bromide, in order to obtain 1-(prop-2-yn-1-yl)-1*H*-pyrroles (**3**). Subsequently, a standard CuAAC reaction involving organic azides (generated *in situ*) and pyrroles **3** gives the methyl 4-acetyl-1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole-3-carboxylates **8**-**11**, and, finally, a [4 + 2] cyclocondensation reaction of the triazolyl methylene-spacer pyrroles **8**-**11** with hydrazine hydrochloride furnishes the desired pyrrolo[3,4-*d*]pyridazin-1-one system **12**-**15** at total yields of up to 54%. Scheme 1 shows an overview of the synthetic strategy for obtaining all the novel heterocycles proposed in this work.

Experimental

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) or Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz), 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. All melting points were determined using coverslips on an Microquímica MQAPF-302 apparatus and are uncorrected. For the ^{13}C NMR experiments, the chemical shifts were calibrated using a residual non-deuterated solvent as an internal reference. All results are reported as follows: chemical shift (δ) (multiplicity, integration, coupling constant). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet, dd = doublet of doublets. All NMR chemical shifts are reported in parts *per* million relative to the internal reference. Gas chromatography-mass spectrometry (GC-MS) analyses



Scheme 1. An overview of the synthetic strategy for the proposed work.

were registered with a split-splitless injector, autosampler, capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a PerkinElmer 2400 CHN elemental analyzer (Universidade de Santa Cruz do Sul, Brazil).

High-resolution mass spectra (HRMS) were obtained for all compounds on an LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific). This hybrid system combines an LTQ XL linear ion-trap mass spectrometer and an Orbitrap mass analyzer. The experiments were performed via direct infusion of the sample (flow rate 10 μL min^{-1}) in positive-ion mode using electrospray ionization (ESI). Elemental composition calculations were executed using the specific tool included in the Qual Browser module of the Xcalibur (Thermo Fisher Scientific, release 2.0.7) software.

X-ray diffraction data for a white single crystal of 1-(prop-2-yn-1-yl)-1*H*-pyrrole (**3a**) and for a white single crystal of 1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole (**8a**) were performed on a Bruker D8 QUEST and on a Bruker D8 VENTURE, equipped with a PHOTON 100 CMOS detector and, a $Cu_{K\alpha}$ Iμs micro-focus source (λ = 1.54178 Å) and a $Ag_{K\alpha}$ Iμs micro-focus source (λ = 0.56086 Å), respectively. Indexing was performed using APEX3 software package.[34] Data integration and reduction were executed using SAINTPLUS 6.01 program.[35] Absorption correction was performed by multi-scan method implemented in SADABS program.[36] Respective space groups of the crystal systems of **3a** and **8a** were determined using XPREP program integrated in APEX3.[34] The structure of both compounds were solved by direct methods contained in Sir2014 v. 17.01[37] and refined on F^2 with anisotropic temperature parameters for all non H atoms using SHELXL version 2016/6[38] integrated in WinGX version 2014.1 system.[39] Hydrogen atoms were located in geometrically calculated positions (aromatic group: C–H = 0.93 Å for C_{sp^2} atoms; methyl groups: C–H = 0.96 Å for C_{sp^3} atoms; propargyl group: C–H = 0.93 Å for C_{sp} atom) and treated as riding on their respective C atoms, with U_{iso}(H) values set at $1.2U_{eq}C_{sp^2}$ (aromatic and propargyl fragments) and $1.5U_{eq}C_{sp^3}$ (methyl substituents). The crystallographic parameters and details of data collection and refinement are listed on Tables S1 and S4 (Supplementary Information (SI) section). Selected bond and angles are listed on Tables S2 and S5 (SI section).

Graphical representations involved the DIAMOND program version 3.1a.[40]

General procedure for the synthesis of 1-(prop-2-yn-1-yl)-1*H*-pyrroles (**3a**-**b**)

In a round-bottomed flask, the respective pyrrole (**2a**-**b**) (1 mmol) and K_2CO_3 (4 mmol, 0.55 g) were solubilized in dimethylformamide (DMF, 5 mL) at room temperature. Pure propargyl bromide (1.2 mmol, 0.14 g) was then added slowly under ice bath at 0-5 ºC. The mixture was magnetically stirred at 65 ºC for 5 h. After this time, 40 mL of water was added at room temperature to the reaction mixture, and this mixture was then washed with ethylacetate (3 × 20 mL). The combined organic fractions were washed with water (3 × 20 mL) and then with NaCl aqueous saturated solution (20 mL). The organic solution was dried with anhydrous Na_2SO_4 and then filtered, and the solvent was then evaporated under reduced pressure. The crude solid products **3a**-**b** were obtained at good purity grade at 85-87% yields, and were used for the next reaction without previous purification.

Methyl 4-acetyl-5-methyl-2-phenyl-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**3a**)

White solid; yield 85%; mp 120-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5H), 4.35 (d, 2H), 3.58 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H), 2.37 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 165.4, 136.8, 133.2, 130.6, 130.3, 129.0, 128.3, 123.4, 113.2, 77.6, 73.7, 51.4, 34.3, 31.0, 11,2; GC-MS (EI, 70 eV) *m/z* (%) 295 (M^+, 30), 280 (32), 262 (100), 220 (25), 206 (21), 192 (20), 181 (9); HRMS (ESI-TOF) *m/z*, calcd. for $C_{18}H_{18}NO_3$ $[M + H]^+$: 296.1287; found: 296.1277.

Methyl 4-acetyl-5-methyl-2-(4-methoxyphenyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**3b**)

Orange solid; yield 87%; mp 119-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 6.99-6.97 (m, 2H), 4.38 (d, 2H), 3.86 (s, 3H), 3.63 (s, 3H), 2.50 (s, 3H), 2.43 (s, 3H), 2.40 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 165.5, 160.0, 136.8, 132.9, 132.0, 123.3, 122.2, 113.7, 112.9, 77.7, 73.6, 55.3, 51.4, 34.2, 31.0, 11.2; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{20}NO_4$ $[M + H]^+$: 326.1392; found: 326.1379.

General procedure for the synthesis of methyl 4-acetyl-1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole-3-carboxylates (**8-11**)

To a stirred solution of H_2O/*t*-BuOH 1:1 v/v (12 mL) at room temperature, the respective pyrrole (**3a**-**b**, 1 mmol), alkyl halide (**4**-**7**, 1.2 mmol), and NaN_3 (1.2 mmol, 0.078 g) were added as one portion. After 30 min under magnetic stirring, CuI (15 mmol%) was also added at room temperature. The reaction mixture was then heated at 80 °C for 4 h. Water (40 mL) was then added to the reaction mixture at room temperature and this mixture was then washed with ethylacetate (3 × 20 mL). The combined organic fractions were washed with water (3 × 20 mL) and then with NaCl aqueous saturated solution (20 mL). The organic solution was dried with anhydrous Na_2SO_4 and then filtered, and the solution was then concentrated under reduced pressure. The products **8**-**11** were purified by column chromatography on silica gel, using a solution of ethyl acetate (30%) in hexane as eluent. Complete spectral data for compounds **8**-**11** are available at SI section.

Methyl 4-acetyl-1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**8a**)

White solid; yield 77%; mp 130-134 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.31-7.26 (m, 2H), 7.20-7.16 (m, 4H), 6.77 (s, 1H), 5.43 (s, 2H), 4.98 (s, 2H), 3.57 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 165.4, 144.2, 143.4, 137.0, 133.3, 130.8, 130.7, 129.3, 129.0, 128.3, 128.1, 123.5, 121.8, 113.4, 54.3, 51.5, 40.1, 31.2, 11.6; GC-MS (EI, 70 eV) *m/z* (%) 429 (M^+, 18), 355 (32), 281 (46), 221 (23), 147 (29), 133 (10); calcd. for $C_{25}H_{24}N_4O_3$: C 70.08, H 5.65, N 13.08%, found: C 70.35, H 5.69, N 13.10%.

Methyl 4-acetyl-1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (**8b**)

Yellow solid; yield 86%; mp 124-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 4H), 7.20 (s, 2H), 7.09-7.08 (m, 2H), 6.87 (s, 1H), 6.81-6.80 (m, 1H), 5.44 (s, 2H), 4.99 (s, 2H), 3.80 (s, 3H), 3.58 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 165.5, 160.1, 137.0, 134.4, 133.1, 132.0, 129.8, 129.3, 129.1, 128.1, 123.4, 122.7, 121.9, 113.8, 113.4, 55.4, 54.4, 51.4, 39.9, 31.1, 11.6; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{27}N_4O_4$ $[M + H]^+$: 459.2032; found: 459.2032.

Methyl 4-acetyl-1-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**9a**)

White solid; yield 60%; mp 135-136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 3H), 7.16-7.10 (m, 4H), 6.87 (d, 2H), 6.79 (s, 1H), 5.32 (s, 2H), 4.94 (s, 2H), 3.77 (s, 3H), 3.53 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 165.6, 160.0, 159.9, 146.9, 137.7, 133.6, 132.2, 132.1, 129.5, 126.1, 123.3, 122.8,

114.3, 113.8, 113.3, 55.4, 53.9, 51.4, 40.5, 31.2, 11.8; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{27}N_4O_4$ $[M + H]^+$: 459.2032; found: 459.2040.

Methyl 4-acetyl-1-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (**9b**)

Yellow solid; yield 70%; mp 120-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 4H), 6.93 (s, 1H), 6.90 (d, 2H), 6.81 (d, 2H), 5.49 (s, 2H), 4.90 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 165.6, 159.9, 159.8, 137.7, 133.6, 132.2, 132.1, 129.5, 126.1, 123.3, 122.8, 114.3, 113.9, 113.8, 113.3, 55.3, 55.1, 53.9, 51.4, 40.5, 31.2, 11.8; HRMS (ESI-TOF) *m/z*, calcd. for $C_{27}H_{29}N_4O_5$ $[M + H]^+$: 489.2138; found: 489.2154.

Methyl 4-acetyl-1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**10a**)

Yellow oil; yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 7.24-7.21 (m, 2H), 7.00-6.96 (m, 2H), 6.92 (s, 1H), 5.52 (s, 2H), 4.98 (s, 2H), 3.57 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 165.4, 162.5, 160.1, 143.8, 137.0, 133.4, 131.8, 131.7, 130.7, 130.0, 129.0, 128.3, 123.4, 122.0, 113.3, 51.4, 41.5, 39.8, 31.1, 11.5; HRMS (ESI-TOF) *m/z*, calcd. for $C_{25}H_{24}ClN_4O_3$ $[M + H]^+$: 463.1537; found: 463.1550.

Methyl 4-acetyl-1-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (**10b**)

Yellow oil; yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 4H), 7.15-7.10 (m, 4H), 6.86 (s, 1H), 5.41 (s, 2H), 4.99 (s, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 165.4, 160.0, 136.8, 134.2, 133.9, 133.0, 132.8, 131.9, 129.5, 129.4, 129.0, 123.4, 122.6, 113.7, 113.4, 55.3, 53.5, 51.3, 39.8, 31.0, 11.5; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{26}ClN_4O_4$ $[M + H]^+$: 493.1643; found: 493.1654.

Methyl 4-acetyl-1-((1-octyl-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**11a**)

Yellow oil; yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 3H), 7.29-7.27 (m, 2H), 6.89 (s, 1H), 5.02 (s, 2H), 4.25 (t, 2H), 3.59 (s, 3H), 2.43 (s, 3H) 2.42 (s, 3H), 1.70 (s, 2H), 1.27-1.25 (m, 10H), 0.87 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 165.5, 143.8, 137.0, 133.4, 130.8, 130.7, 129.1, 128.4, 123.5, 121.5, 113.4, 51.5, 50.6, 40.2, 31.8, 31.1, 30.3, 29.1, 29.0, 26.5, 22.7, 14.2, 11.6; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{35}N_4O_3$ $[M + H]^+$: 451.2709; found: 451.2726.

Methyl 4-acetyl-1-((1-octyl-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (**11b**)

Yellow oil; yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.18 (m, 2H), 6.95 (s, 1H), 6.91-6.89 (m, 2H), 5.0 (s, 2H), 4.24-4.23 (m, 2H), 3.82-3.80 (m, 3H), 3.60-3.58 (m, 3H), 2.40-2.39 (m, 6H), 1.82-1.80 (m, 2H), 1.24 (bs, 10H), 0.87-0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 165.5, 160.1, 143.8, 137.0, 133.1, 132.0, 123.5, 122.7, 121.6, 113.8, 113.4, 55.3, 51.4, 50.6, 40.1, 31.7, 31.1, 30.3, 29.1, 29.0, 26.5, 22.6, 14.1, 11.5; HRMS (ESI-TOF) *m/z*, calcd. for $C_{27}H_{37}N_4O_4$ $[M + H]^+$: 481.2815; found: 481.2842.

Complete spectral data for compounds **8**-**11** are available in the SI section.

General procedure for the synthesis of 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones (**12**-**15**)

Ethanol (10 mL), the respective methyl 4-acetyl-1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole-3-carboxylate **8-11** (1 mmol), and hydrazine hydrochloride (1.5 mmol, 0.103 g) were added to a round-bottomed flask at room temperature. The reaction mixture was magnetically stirred under reflux (80 °C) for 4 h. Subsequently, ethanol and other volatile components were evaporated under reduced pressure, and the resulting solid was purified by recrystallization from ethanol (**12**-**15**).

6-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-phenyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (**12a**)

White solid; yield 58%; mp 175-181 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.38-7.29 (m, 8H), 7.18-7.16 (m, 2H), 6.68 (s, 1H), 5.41 (s, 2H), 5.28 (s, 2H), 2.71 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 143.8, 142.2, 134.2, 132.2, 131.0, 130.1, 129.2, 129.0, 128.9, 128.3, 128.0, 125.4, 121.8, 116.6, 111.70, 54.3, 40.3, 21.0, 12.1; HRMS (ESI-TOF) *m/z*, calcd. for $C_{24}H_{23}N_6O$ $[M + H]^+$: 411.1933; found: 411.1944.

6-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-(4-methoxyphenyl)-2,6-dihydro-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one (**12b**)

White solid; yield 50%; mp 178-181 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.20-7.18 (m, 2H), 7.10 (d, 2H), 6.91-6.88 (m, 1H), 6.83 (s, 1H), 6.82 (d, 2H), 5.44 (s, 2H), 4.98 (s, 2H), 3.81 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160, 144.3, 134.4, 133.1, 132.0, 131.5, 129.3, 129.1, 128.7, 128.1, 127.0, 123.4, 122.7, 121.8, 114.0, 113.80, 55.4, 54.4, 40.0,

27.9, 11.6; HRMS (ESI-TOF) *m/z*, calcd. for $C_{25}H_{25}N_6O_2$ $[M + H]^+$: 441.2039; found: 441.2050.

6-((1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-4,5-dimethyl-7-phenyl-2,6-dihydro-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one (**13a**)

White solid; yield 50%; mp 153-159 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 7.14 (d, 2H), 6.89 (d, 2H), 6.72 (s, 1H), 5.34 (s, 2H), 5.26 (s, 2H), 3.81 (s, 3H), 2.70 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.0, 143.8, 142.3, 132.2, 131.0, 130.1, 129.8, 128.9, 128.4, 126.12, 125.5, 121.6, 116.7, 114.6, 111.70, 55.5, 53.9, 40.35, 21.17, 12.26; HRMS (ESI-TOF) *m/z*, calcd. for $C_{25}H_{25}N_6O_2$ $[M + H]^+$: 441.2039; found: 441.2042.

6-((1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-(4-methoxyphenyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (**13b**)

White solid; yield 66%; mp 145-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H), 7.16-7.12 (m, 2H), 6.90-6.86 (m, 2H), 6.73 (s, 1H), 5.41 (s, 2H), 4.99 (s, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160, 144.3, 134.4, 133.1, 132.0, 131.5, 129.3, 129.1, 128.7, 128.1, 127.0, 123.4, 122.7, 121.8, 114.0, 113.80, 55.5, 55.4, 53.9, 40.35, 21.17, 12.26; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{27}N_6O_3$ $[M + H]^+$: 471.2145; found: 471.2157.

6-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-phenyl-2,6-dihydro-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one (**14a**)

Yellow oil; yield 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 7H), 7.14 (d, 2H), 6.79 (s, 1H), 5.40 (s, 2H), 5.30 (s, 2H), 2.73 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.2, 134.0, 132.8, 131.4, 131.1, 129.8, 129.7, 129.6, 129.5, 129.2, 128.8, 128.5, 122.0, 54.2, 53.7, 40.5, 29.8, 20.9, 12.4; HRMS (ESI-TOF) *m/z*, calcd. for $C_{24}H_{22}ClN_6O$ $[M + H]^+$: 445.1544; found: 445.1556.

6-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-(4-methoxyphenyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (**14b**)

Yellow oil; yield 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 4H), 7.15 (d, 2H), 7.11 (d, 2H), 6.86 (s, 1H), 5.41 (s, 2H), 4.99 (s, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 135.0, 134.2, 133.9, 132.8, 132.0, 131.9, 129.5, 129.4, 129.3, 129.0, 122.6, 114.32, 113.7, 113.4, 55.3, 53.5, 39.8, 29.7, 11.5; HRMS (ESI-TOF) *m/z*, calcd. for $C_{25}H_{24}ClN_6O_2$ $[M + H]^+$: 475.1649; found: 475.1677.

6-((1-Octyl-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-phenyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (**15a**)

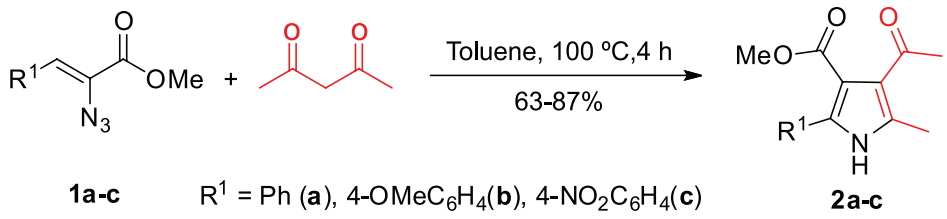
Yellow oil; yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 5H), 6.83 (s, 1H), 5.32 (s, 2H), 4.25 (t, 2H), 2.71 (s, 3H), 2.53 (s, 3H), 1.27-1.24 (m, 12H), 0.87 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 143.6, 142.4, 132.5, 131.5, 131.2, 129.1, 128.6, 128.6, 121.6, 116.9, 50.7, 40.6, 31.8, 30.3, 29.8, 29.2, 29.0, 26.5, 22.7, 21.1, 14.2, 12.3; HRMS (ESI-TOF) *m/z*, calcd. for $C_{25}H_{33}N_6O$ $[M + H]^+$: 433.2716; found: 433.2729.

6-((1-Octyl-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-dimethyl-7-(4-methoxyphenyl)-2,6-dihydro-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one (**15b**)

Yellow oil; yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 2H), 7.01-6.97 (m, 1H), 6.95 (d, 2H), 5.30 (d, 2H), 4.26 (t, 2H), 3.82 (s, 3H), 2.26 (s, 3H), 2.51 (s, 3H), 1.84-1.81 (m, 10H), 0.86 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.3, 152.4, 143.7, 141.8, 132.8, 132.8, 132.4, 122.2, 121.7, 116.6, 114.0, 111.4, 55.4, 50.7, 40.7, 31.8, 31.8, 30.3, 29.2, 29.0, 26.5, 22.7, 21.0, 14.2, 12.3; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{35}N_6O_2$ $[M + H]^+$: 463.2821; found: 463.2837.

Results and Discussion

We started our research by using a convenient methodology for the synthesis of tetrasubstituted 1*H*-pyrroles **2a**-**c**, which are the starting material for our proposed synthesis. Although many methodologies have been developed for the synthesis of pyrroles, it is still difficult to prepare tetrasubstituted 1*H*-pyrroles from easily accessible reagents.[41] Thus, vinyl azides appear to be versatile precursors, as well as an alternative to classical methodologies,[42-44] for obtaining the pyrroles considered herein. Firstly, following a well-known procedure,[45] the three selected vinyl azides **1a**-**c** were prepared from the reaction of methyl 2-azidoacetate with three arylaldehydes, and this resulted in substitution patterns in the phenyl rings due to the introduction of activating and deactivating groups to modulate opposite electronic effects. Subsequently, the pyrroles **2a**-**c** (Scheme 2) could be obtained by refluxing a mixture of vinyl azides **1a**-**c** and acetylacetone in toluene at 100 ºC for 4 h.[45] Similar to the literature, the pyrroles **2a** and **2b** were obtained at a yield of 87 and 72%, respectively, and by using the same methodology, the unpublished 2-(4-nitrophenyl)pyrrole **2c** was synthesized at 63% yield. It is important to mention that the vinyl azide **1c** decomposed in about a week, even when stored in a refrigerator.



Scheme 2. Synthetic route to the tetrasubstituted 1*H*-pyrroles **2a**-**c**.

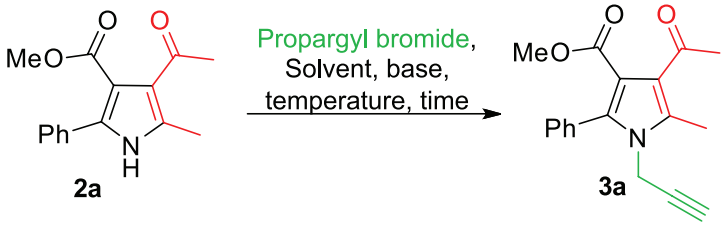
With the starting materials **2a**-**c** in hand, compound **2a** was selected as the standard pyrrole for optimization of the step-by-step reaction conditions. We initially turned our attention towards targeting an expedient protocol for the *N*-alkylation reaction of **2a** with propargyl bromide, in order to obtain the N-propargylated pyrrole **3a** (see Scheme 3). A survey in the literature showed that a base would be necessary to promote the N-deprotonation reaction of the 1*H*-pyrrole and solvents, and that temperature and reaction time must be optimized. It was found that KOH in acetone[46] or K_2CO_3 in DMF[47-49] could be used to achieve the desired product **3a**.

When the N-propargylation reaction was conducted for **2a** (1.0 mmol), using propargyl bromide (1.2 mmol) in KOH/acetone medium at room temperature, product **3a** was isolated at only 10% yield (Table 1, entry 1). However, reactions conducted in DMF were the most suitable choice when combined with K_2CO_3 as base. The base K_2CO_3 was evaluated in 2.0, 4.0 and 6.0 equiv. It was found that the ratio of 4.0 equiv. of K_2CO_3 provided the best reaction condition. Thus, the reaction in DMF as solvent with either 4.0 or 6.0 equiv. of K_2CO_3, at room temperature for 14 h, furnished the product **3a** at the same yield of 87% (Table 1, entries 2 and 4). The conversion to **3a** was followed by thin-layer chromatography (TLC) until complete consumption of the starting material **2a**. However, when the same reaction conditions were tested at 65 ºC,[48] the yield remained similar (85%) to that obtained at room temperature, but the reaction time could be decreased to 5 h (Table 1, entry 5). Moreover, the reaction at 80 ºC gave a very similar yield (86%)-see Table 1, entry 6.

Thus, considering the good thermal stability of **3a** at 65 ºC, we chose the *N*-alkylation reaction condition using DMF as solvent and 4.0 equiv. of K_2CO_3, at 65 °C for 5 h. Under this optimized condition, the new pyrroles **3a**-**c** were obtained at a yield of 85-87% (Scheme 3).

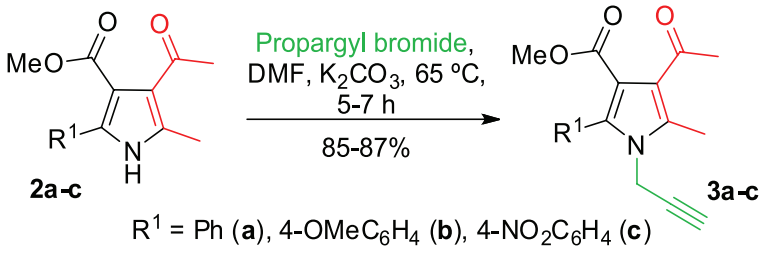
After establishing the best reaction condition for the first reaction step, we next turned our attention to the CuAAC reaction. From the independent discovery of Sharpless and co-workers[24] in 2002 regarding the ability of CuI to catalyze the 1,3-dipolar cycloaddition reaction between a terminal alkyne and an organic azide, with regiospecific formation of 1,4-disubstituted 1,2,3-triazoles, the number of publications involving the synthesis of 1,2,3-triazoles has grown exponentially in several areas of chemistry.[24,25] Many of these successful and versatile cycloaddition reactions have been catalyzed by CuI using 5 to 20 mmol%, at reaction temperatures of 20-25 ºC to

Table 1. Optimization of reaction conditions[a] for the *N*-alkylation of pyrrole **2a**



entry	Solvent	Volume / mL	time / h	Base (number of mols / mmol)	Temperature / ºC	Yield[b] / %
1	acetone	10	14	KOH (6)	rt	10
2	DMF	5	14	K_2CO_3 (6)	rt	87
3	DMF	5	22	K_2CO_3 (2)	rt	73
4	DMF	5	14	K_2CO_3 (4)	rt	87
5	DMF	5	5	K_2CO_3 (4)	65	85
6	DMF	5	5	K_2CO_3 (4)	80	86

[a]Reaction conditions: pyrrole **2a** (1.0 mmol) and propargyl bromide (1.2 mmol); [b]isolated yields; rt: room temperature; DMF: dimethylformamide.



Scheme 3. Synthetic route to 1-(prop-2-yn-1-yl)-1*H*-pyrroles **3a-c**.

around 120 °C.[50-54] Thus, in order to attain triazole synthesis, similar processes in the literature related to our objective were investigated. Many of them use *t*-BuOH/H_2O mixtures as the solvent for this type of reaction,[50-54] whereas others use the *in situ* formation of the organic azide to substitute the use of pre-formed organic azide, in order to avoid an additional reaction step.[55,56] Thus, sodium azide and benzyl chloride were selected to be used for the *in situ* formation of the benzyl azide, and equimolar quantities of both compounds to the reactions were added. The reactions were calculated so that the amount of benzyl azide formed gave a 1:1.2 molar ratio between the pyrrole **3** and the benzyl azide.

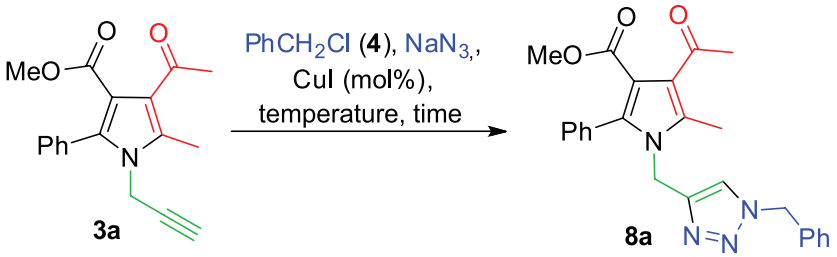
In order to optimize the derivatization of pyrroles **3** for the triazolylmethyleno pyrrole system **8-11** via CuAAC reactions, pyrrole **3a** was selected together with the standard reaction conditions described in the literature.[52] The conversion of **3a** to **8a** was followed by TLC, until complete consumption of the starting material **3a**-see Table 2.

Table 2 shows that for reactions carried out using 5 mmol% CuI at either 20-25 or 80 °C, and with reaction times of 5-12 h, the reaction yield did not exceed 61% (Table 1, entries 1-3). The best yields were obtained when the amount of catalyst (CuI) was increased to 10 and 15 mmol% in reactions conducted at temperatures of 80-95 °C, which enabled reduction of the reaction time from 12 h to either 5 or 4 h (Table 2, entries 4-6).

Thus, when the reactions were performed at 80 °C in a mixture of *tert*-butanol and water (1:1 v/v) as solvent, with 15 mmol% of CuI as catalyst, 1.0 mmol of **3a**, 1.2 mmol of sodium azide, and 1.2 mmol of benzyl chloride, **8a** was obtained at a yield of 77% after 4 h of reaction; however, depending on the substituents, reactions times of up to 5 h were necessary.

After establishing the best reaction condition for the second reaction step (CuAAC), the scope of the pyrroles (**3a-c**) and organic azides (**4-7**) was expanded, varying the R^1-position with phenyl (**3a**) and 4-methoxyphenyl (**3b**), and the R^2-position with a phenyl (**4**), 4-methoxyphenyl (**5**), 4-chlorophenyl (**6**), and *n*-C_8H_{17} group (**7**), in order to analyze the behavior of these electron-donating or electron-withdrawing and a long alkyl side chain substrates in this new protocol. Unfortunately, pyrrole **3c** was excluded due to the chemical instability of the vinyl azide **1c**. As a result, the desired 4-acetyl-1-((1-aryl-1*H*-1,2,3-triazol-4-yl) methyl)-5-methyl-2-aryl-1*H*-pyrrole-3-carboxylates **8a-b**,

Table 2. Optimization of reaction conditions[a] for obtaining pyrrole **8a**

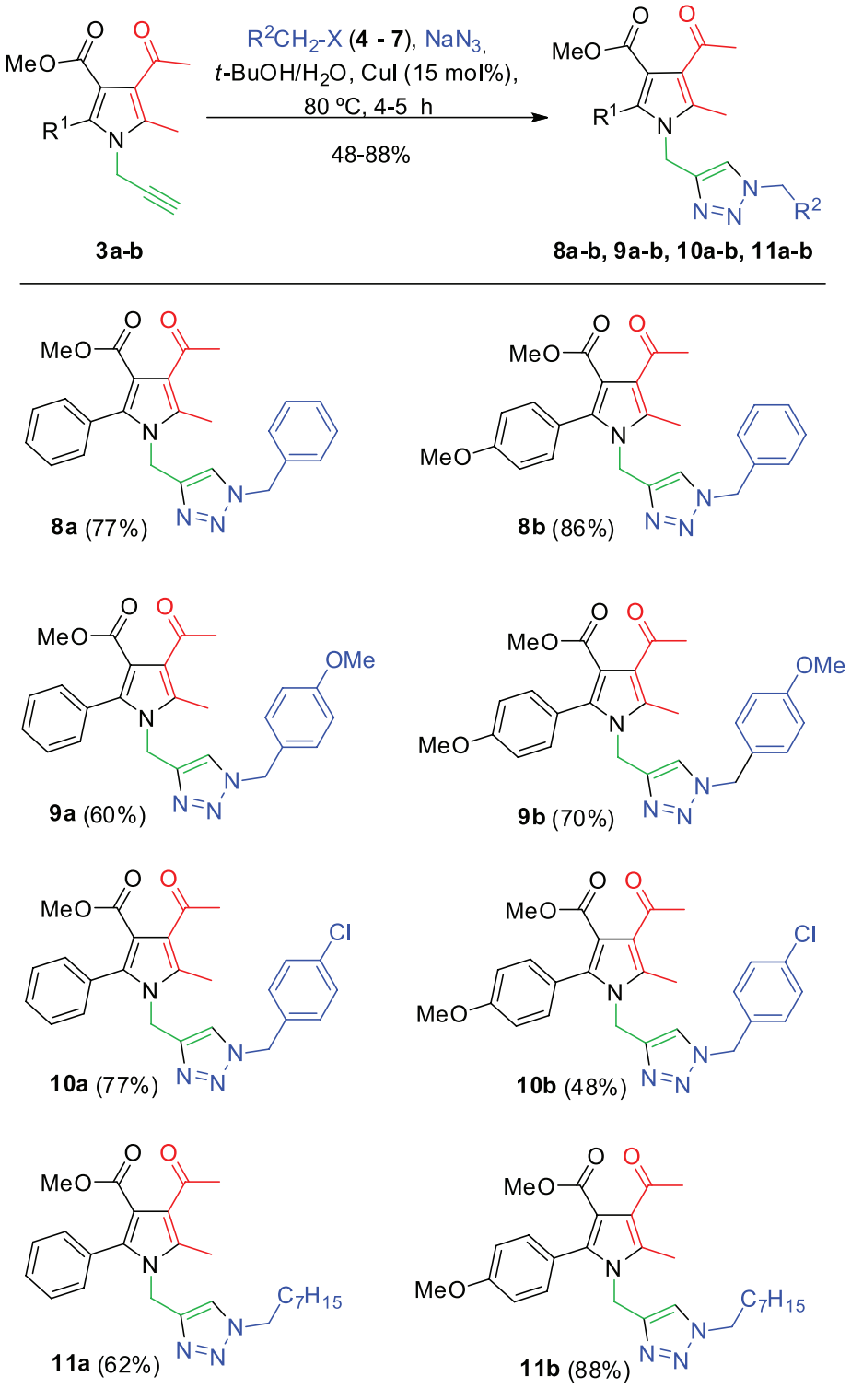


entry	NaN_3 / mmol	CuI / mmol%	Temperature / °C	time / h	Yield[b] / %
1	1.2	5	rt	12	60
2	2.0	5	rt	12	61
3	1.2	5	80	5	60
4	1.2	10	80	5	65
5	1.2	15	80	4	77
6	1.2	15	95	4	78

[a]Reaction conditions: pyrrole (1.0 mmol), benzyl chloride (1.2 mmol) and H_2O/*t*-BuOH (1:1, 12 mL); [b]isolated yields; rt: room temperature.

9a-b, **10a-b** and **11a-b** were obtained at moderate to good yields of 48-88% (see Scheme 4).

For the subsequent and last reaction step, the methyl 4-acetyl-1-((1-aryl(alkyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-2-aryl-1*H*-pyrrole-3-carboxylates (**8**-**11**) were reacted with hydrazine monohydrochloride, in order to obtain the pyrrolo[3,4-*d*]pyridazin-1-one system (**12**-**15**). Many protocols for the synthesis of [3,4-*d*]pyridazin-1-ones have used hydrazine hydrate or its hydrochloride salt in refluxing methanol or ethanol as the standard



Scheme 4. Novel methyl 4-acetyl-1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole 3-carboxylates (**8a-b**-**11a-b**).

condition.[57-59] Thus, the tests were performed using one of these solvents. The reaction of **8a** and hydrazine hydrochloride in the appropriate solvent under reflux was followed by TLC until conversion to pyrrole **8a** was verified. After some initial tests, we found that when the reaction of **8a** with hydrazine hydrochloride at a 1:1.5 molar ratio was carried out in ethanol at reflux for 4 h, it furnished the pyrrolo[3,4-*d*]pyridazin-1-one **12a** at a satisfactory yield (58%).

Knowing the optimized conditions for the third reaction step ([4 + 2] cyclocondensation reaction), and in order to analyze the behavior of the electron-donating or electron-withdrawing and the long *n*-alkylated chain substrates in this method, the scope for the final pyrrole system (**12**-**15**) was also expanded. As a result, the desired 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones **12a**-**b**, **13a**-**b**, **14a**-**b** and **15a**-**b** were also obtained at moderate to good yields of 40-70% (Scheme 5). Again, it was observed that the reaction time to convert compounds **8-11** into **12-15** was dependent on the substituents attached to both rings, which resulted in reaction times of 4 to 5 h. In summary, the yields of the reactions can not be predict because different products can be obtained from the methodology developed in this work due to structural variation of the starting materials.

Complementary, to demonstrate that the pyrrolo [3,4-*d*]pyridazin-1-ones **12**-**15** could be obtained regiospecifically and directly from the reaction of pyrroles **2**, the synthesis of the selected pyridazinone **12a** was also attempted by a one-pot three-steps reaction without the isolation of the propargylated pyrrole **3a** and the triazole derivative **8a**, starting from pure **2a** (Scheme 6).

Unfortunately and after several attempts, it became clear for us that only the first two reaction steps are feasible in DMF as optimized solvent, which led to the isolation of triazole **8a** in only 40% yield from **2a**, without the isolation of **3a**. Sequential one-pot reactions to obtain **12a** directly from **2a** or from **3a**, without the isolation of **8a**, resulted in mixtures of by-products of impossible separation through column chromatography.

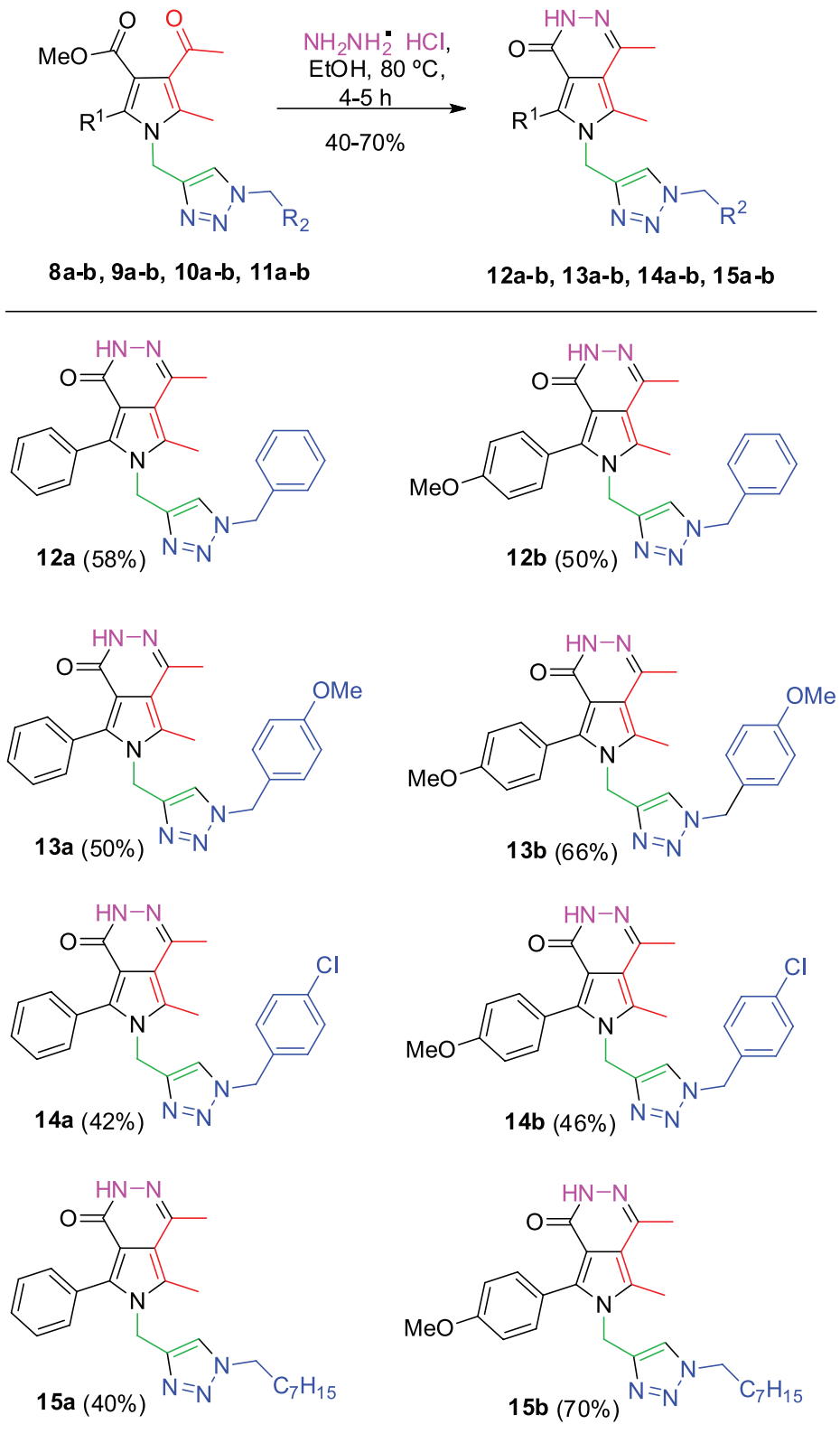
All the new products **2c**, **3a-c**, and **8-15** were fully characterized based on GC-MS and $^{1}H/^{13}C$ NMR spectroscopic data, as well as elemental analysis or HRMS data.

The structures of **3a** and **8a** were also unequivocally confirmed by single crystal X-ray diffraction, as shown in Figures 2 and 3, respectively.[37,40] Crystal data and structure refinement parameters for molecules **3a** and **8a** are listed on Tables S1 and S4 (SI section), selected bond distances and angles observed are listed on Tables S2 and S5 (SI section) and interplanar angles between selected molecular fragments are listed on Tables S3 and S6, respectively (SI section).

Crystals of compound **3a** and **8a** are monoclinic and triclinic with respective space groups *Cc* and *P*(-1). The structure analysis reveals both molecules with the respective site symmetry 1. In the particular case of compound the acentric space group *Cc* was unequivocally determined and the attempt to solve the structure with the centrosymmetric space group *C*2/*c* was not successful. Since the absolute structure parameter deviates from zero, racemic twinning in the crystal structure of is present. Due to the fact that the correct configuration of the molecular structure is not certain, the authors decided by the structure refinement considering the crystal to be twinned, using the TWIN command and thus eliminating the value corresponding to the absolute structure parameter while the batch scale factor parameter converges to the 0.19207 value (Table S1, SI section).

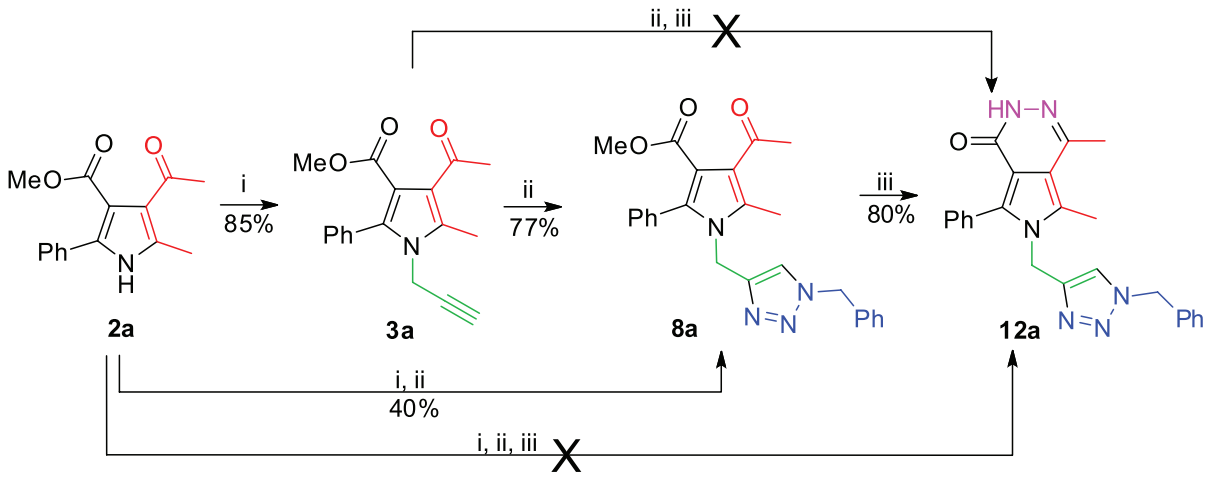
Geometrically, molecules **3a** and **8a** shows that the interplanar angles between that planes corresponding to the substituents, respectively, attached to the N(1), C(2), C(3) and C(4) atoms with the plane of the central pyrrole ring deviate significantly from the co-planarity (Tables S3 and S6, SI section). In this context, it is noteworthy in the molecule that the carbonyl group of the acetyl substituent connected to the C(4) atom of the central pyrrole ring is oriented in the same direction of the methyl substituent attached to the C(5) atom whereas in the molecule the carbonyl group of the acetyl substituent is oriented in opposite direction of the methyl substituent. This observation can be explained by the fact that in molecule **8a**, the oxygen atom of the acetyl substituent involves an interaction with a carbon atom of the phenyl substituent of the π-π O···C type [C(25)··O(411)$^{\#3}$ distance = 3.382(3) Å; symmetry code (#3): 1 + *x*, *y*, *z*]. This interaction contributes to the formation of a one-dimensional chain by translation of the molecule along the [100] crystallographic direction in the unit cell in *Cc* of compound in the solid state, as well as explains the non-coplanarity of the phenyl substituent with the central pyrrole ring (interplanar angle of 44.61(7)º, Table S3 (SI section) and Figure 4).

On the other hand, after the "click-reaction" on the ethynyl substituent of with phenyl-methylene-azide giving raise to the molecule, a terminal phenyl substituent results in the structure [(C(152)-C(157)-ring]. This phenyl ring is responsible for the observation of π-π C···C interactions including carbon atoms belonging to the central pyrrole ring and the phenyl substituent attached to its C(2) atom [C(2)···C(155)$^{\#7}$ distance = 3.411(2) Å; C(3)···C(155)$^{\#7}$ distance = 3.475(2) Å; C(22)···C(156)$^{\#7}$



Scheme 5. Novel 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones (**12**-**15**).

distance = 3.493(2) Å; symmetry code (#7): 1 + *x*, 1 + *y*, *z*]. As a consequence of this preferential interaction, the O(412) atom of the acetyl group was excluded from an interaction with the phenyl ring attached to C(2) atom of the central pyrrole ring, allowing its rearrangement by turning around the C(4)-C(41) bond in the same direction



Reagents and Conditions: (i) = Propargyl bromide, DMF, K_2CO_3, 65 ºC, 5 h; (ii) = $PhCH_2Cl$, NaN_3, DMF, CuI (15 mol%), 80 °C, 4 h; (iii) = $NH_2NH_2 \cdot HCl$, DMF, 80 °C, 5 h.

Scheme 6. Sequential three-steps one-pot reaction to obtain 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one **12a**.

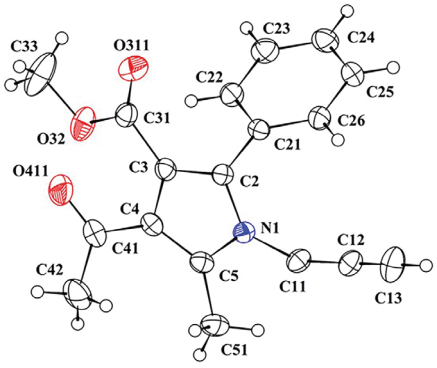


Figure 2. Projection of the molecular structure with atom-labeling scheme of 1-(prop-2-yn-1-yl)-1*H*-pyrrole (**3a**) (CCDC 1056078, SI section). Displacement ellipsoids at the 30% level. H atoms involve arbitrary radii.

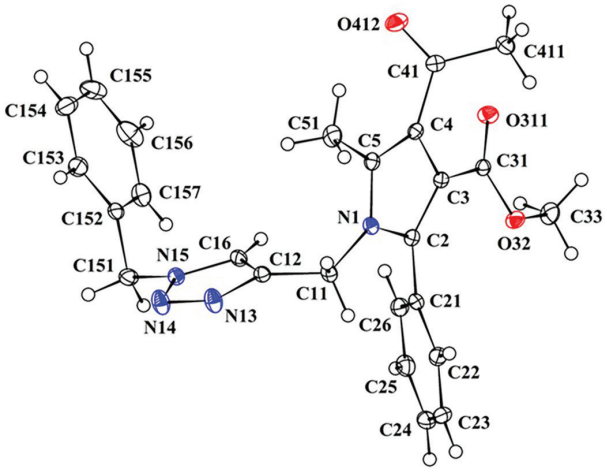


Figure 3. Projection of the molecular structure with atom-labeling scheme of 1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole (**8a**) (CCDC 1574331, SI section).Displacement ellipsoids at the 50% level. H atoms involve arbitrary radii.

to the methyl substituent attached to the C(5) atom of the central ring of molecule (Figure 5).

Conclusions

In summary, we successfully developed a streamlined new three-step methodology for the synthesis of a series of eight examples of polysubstituted 6-((1*H*-1,2,3-triazol-4-yl)methyl)-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-ones, through the use of: sequential *N*-alkylation reactions of tetrasubstituted NH-pyrroles, which furnished a series of three examples of 1-(prop-2-yn-

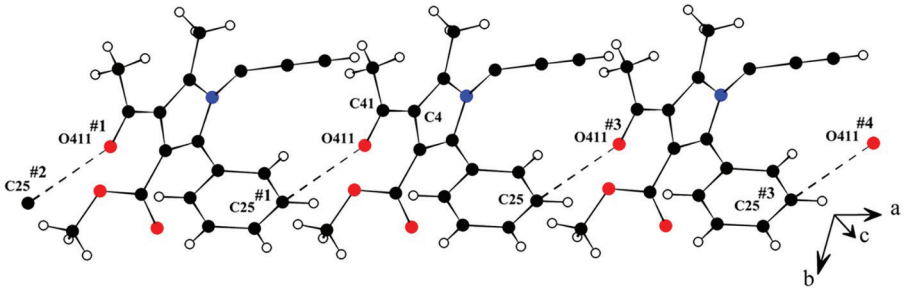


Figure 4. Section of the crystal structure packing of involving the one-dimensional arrangement by translation of molecules along the [100] crystallographic direction highlighting the π-π O···C interactions. Symmetry codes #1: −1 + *x*, *y*, *z*; #2: −2 + *x*, *y*, *z*; #3: 1 + *x*, *y*, *z*; #4: 2 + *x*, *y*, *z*.

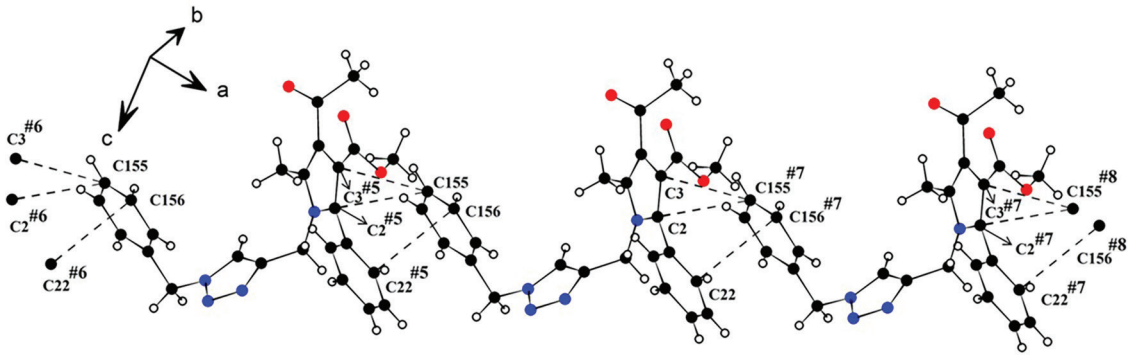


Figure 5. Section of the crystal structure packing of involving the one-dimensional arrangement by translation of molecules along the [110] crystallographic direction highlighting the π-π C···C interactions. Symmetry codes #5: −1 + *x*, −1 + *y*, *z*; #6: −2 + *x*, −2 + *y*, *z*; #7: 1 + *x*, 1 + *y*, *z*; #8: 2 + *x*, 2 + *y*, *z*.

1-yl)-1*H*-pyrroles; standard CuAAC "click chemistry", which involved some alkyl and aryl organic azides and N-propargylated pyrroles to give eight examples of methyl 1-((1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrrole-3-carboxylates; and [4 + 2] cyclocondensation reactions of the respective ketoesters with hydrazine hydrochloride to furnish the pyrrolo[3,4-*d*]pyridazin-1-one system under mild reaction conditions and at moderate to satisfactory yields. The aforementioned protocol could be applicable to a range of substrates and provide more complex and stable heterocyclic structures at yields up to 54%, thus demonstrating the generality of this methodology. Other advantages of this synthetic route are smooth reaction conditions and readily available raw materials. The novel compounds obtained are currently being evaluated for their biological activity.

Supplementary Information

The crystallographic data for the structures of pyrroles **3a** and **8a** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 1056078 and 1574331, respectively. Copies of the data can be obtained free of charge, upon application to: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44 1223 336033 or deposit@ccdc.com.ac.uk).

Supplementary information (NMR spectral and X-ray diffraction data) is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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