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Synthesis of 3-Aroyl-4-heteroarylpyrrole Derivatives by the Van Leusen Method

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Abstract: The synthesis and structural diversification of *N*-heterocycles systems have attracted much attention because of their potential applications. Three 6-aryl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** derivatives, in reaction with acetophenones **5**, via conventional Claisen–Schmidt condensation reactions, generated the respective enones. The enones were used as electron-deficient olefins in a "*formal*" [2+3] cycloaddition reaction using *p*-tosylmethyl isocyanide—TosMIC **7**. This protocol allows access to 3-(substituted aroyl)-4-heteroaryl pyrrole derivatives by the Van Leusen method.

Keywords: 3,4-substituted pyrrole synthesis; TosMIC; Van Leusen reaction

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1. Introduction

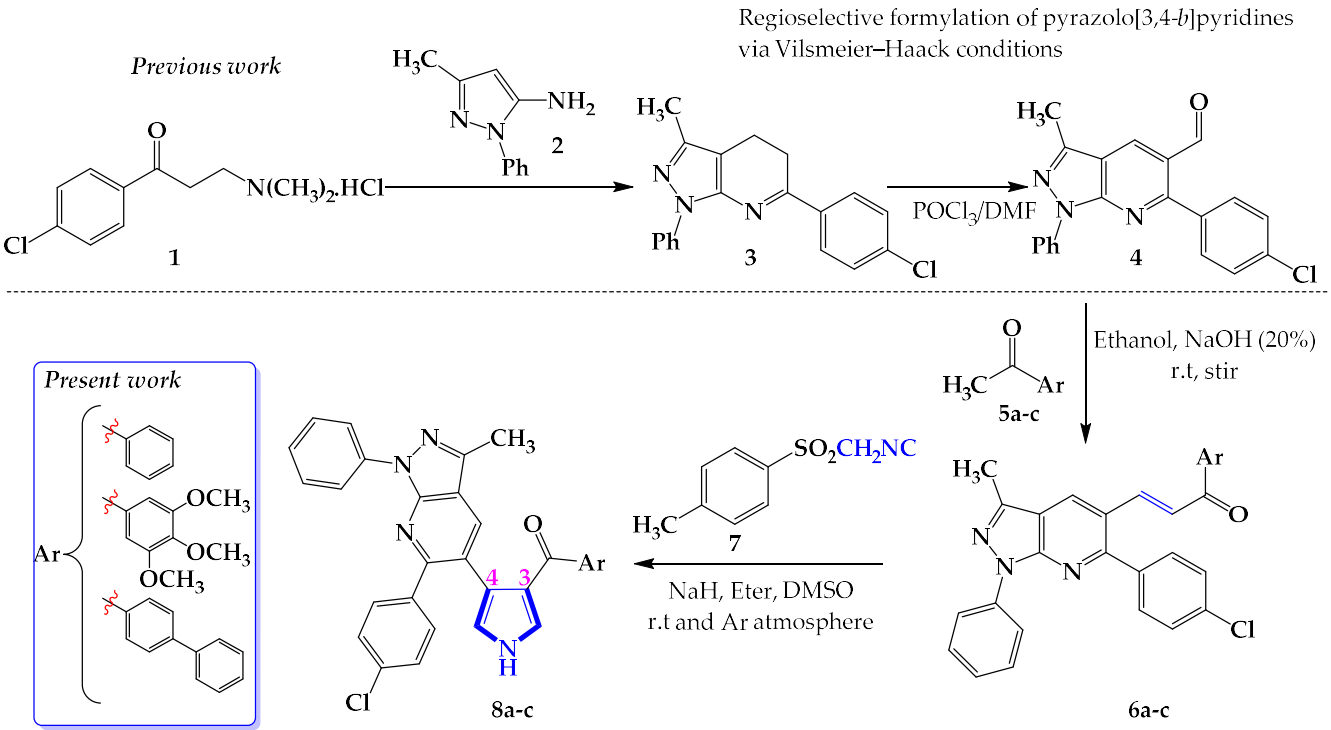
Pyrroles, π-excess *N*-heterocyclic systems, are found in nature, and several derivatives with interesting properties have been synthesized [1–5]. Because of the importance of pyrrole and its substituted derivatives as basic substructures in natural and synthetic products, the synthesis of these five-membered heterocycles is of interest to researchers. A variety of methodologies have been reported, including variations to the classical condensation reactions (*Hantzsch*, *Knorr*, and *Paal–Knorr*); heterocyclization reactions of alcohol, *N*-propargylamine, and α-iminodiazoacetates motifs [6]; the Barton–Zard procedure via coupling cyclization reaction between nitro-acetates and isocyanides; and the reaction of Van Leusen, starting with chalcones as electron-deficient olefins in a [2+3] heterocyclization with *p*-toluenesulfonyl methylisocyanide-TosMIC as a three-atom synthon and nitrogen source [6–8]. The TosMIC reagent is a versatile and powerful synthetic tool in heterocyclization reactions to build five- and six-membered heterocycles and heterofused systems. The chemical nature of TosMIC provides three different reactive sites because of the functional groups (an isocyanide group, a sulfonyl group, and an active methylene group). In reaction to the structural diversity of heterocyclic analogs of chalcones [9,10], TosMIC allows access to the polysubstituted or condensed pyrrole derivatives with different types of substituents—simple or complex—and has potential applications in the fields of chemistry and medicine [11–13].

In this sense, the Van Leusen reaction is a particularly attractive method for providing substituted pyrroles. In this work, we extend the scope for the synthesis of 3,4-disubstituted pyrrole derivatives from pyrazolo[3,4-*b*]pyridine-based chalcones.

2. Results

In previous work, the structural diversification of condensed *N*-heterocycles systems was reported, specifically in the preparation of dihydropyrazolo[3,4-*b*]pyridine derivatives

3 and subsequent changes via specific formylation on the pyridine (Scheme 1) [14]. Formylation on the pyridine ring offers the possibility to access a variety of heteroaryl chalcones through the Claisen–Schmidt condensation reaction between 6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** and substituted acetophenones **5a–c**, in the presence of a base. The heteroaryl chalcone was prepared by mixing equimolar amounts of reactants (**4** and **5a–c**) in a small amount of absolute ethanol (8.0 mL). Then, drops of a 20% NaOH solution were added. The reaction was carried out at room temperature, and, after NaOH addition and continuous stirring for 2 h, the reaction was completed, yielding the respective heteroaryl chalcones **6a–c** (Scheme 1) [15].



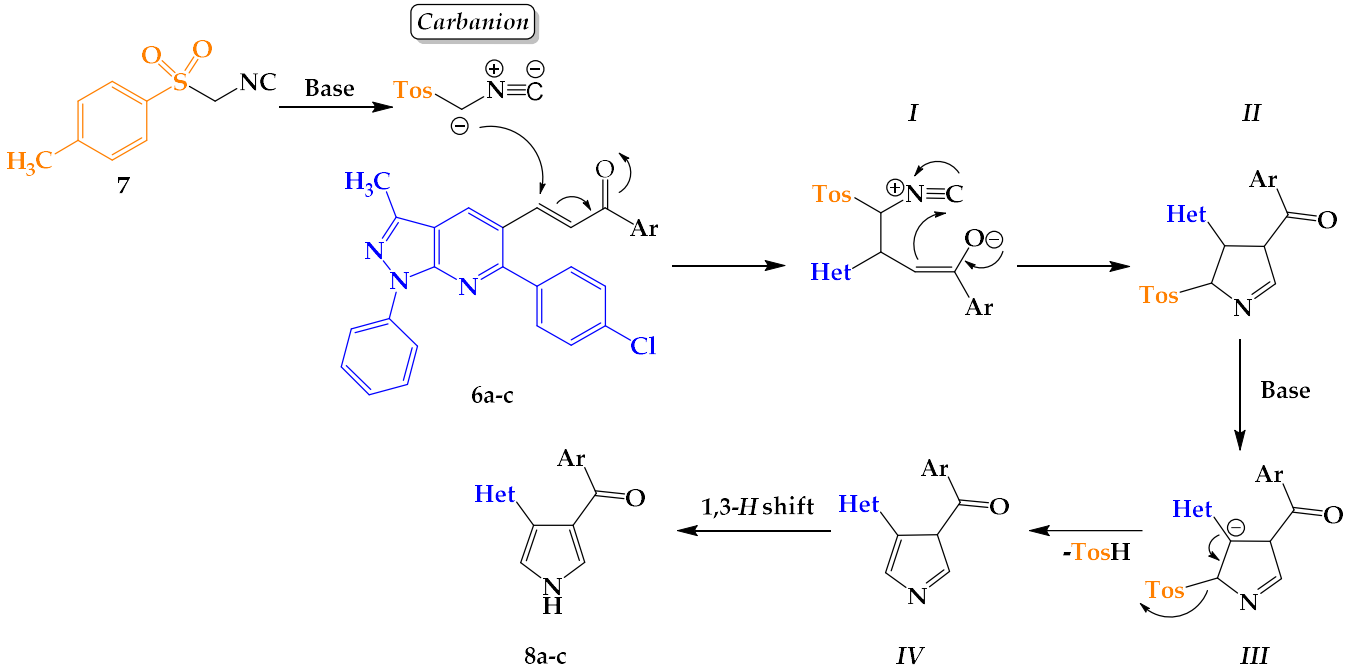
Scheme 1. Synthesis of 3–aroyl–4–heteroarylpyrrole derivatives **8a–c**.

The (*E*)-3-(6-(aryl-3-methyl-1-phenyl-1H-pyrazolo[3,4yridinedin-5-yl)-1-arylprop-2-en-1-one **6a–c**, α,β-unsaturated carbonyl compounds are also electron-deficient olefins with incorporated carbonyl groups (C=O). Therefore, the scope of this substrate as a Michael acceptor can be explored. The heteroaryl chalcones in reaction with TosMIC is a method that enriches the structural diversity of the 3,4-disubstituted pyrrole derivatives **8a-c**. The preparation of 3-aroyl-4-(6-aryl-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]yridine-5-yl)-1H-pyrrole derivatives **8a–c** includes physical and chemical characteristics of the Van Leusen pyrrole synthesis [6–8,16–18].

3. Discussion

The use of the heteroaryl chalcones **6a–c** as precursors did not present problems during the synthesis of the 3,4-disubstituted pyrrole derivatives **8a–c**. No influence of heterocyclic rings on the steric or solubility effects was observed in obtaining 3,4-disubstituted pyrrole derivatives **8a–c** with moderate yields. The olefin moiety included in **6** was exploited to develop five-membered heterocycles by regiospecific heterocyclization reactions with TosMIC, a known representative of the methylsulphurized isocyanide family that is commercially available. At the same time, the preparation of 3-aroyl-4-(6-aryl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4yridinedin-5-yl)-1*H*-pyrrole derivatives **8a–c** with this efficient method appears to be an alternative for obtaining new polycyclic heteroaromatics and for the future assessment of their applications. To construct 3,4-disubstituted pyrrole derivatives **8a–c**, the vinyl

carbons of the Michael acceptor **6a–c** provided the C3, C4, and respective substituents. The Cα-N-Cα moiety of TosMIC **7** complements the formation of the five-membered pyrrolic ring by incorporating the heteroatoms, C2 and C5. The plausible mechanism involves a base-assisted formal [2+3] cycloaddition between the Michael acceptor and TosMIC. According to the Van Leusen method, under the reaction conditions for synthesizing 3-aroyl-4-heteroarylpyrrole derivatives **8a–c**, the reaction sequence begins with the loss of the α-proton from the -CH_2 moiety in the TosMIC **7**, resulting in the formation of the carbanion. The acidity of these α-protons increases because of the electron-withdrawing effect of the sulfonyl and isocyanide groups. The Michael addition begins with the attack of the carbanion on the heteroaryl chalcone **6a–c**, generating intermediate I, which undergoes an intramolecular [2+3] cycloaddition reaction to form the intermediate II. The basic conditions of the reaction facilitate the removal of the tosyl group (intermediate III) and aromatization to obtain the final 3,4-disubstituted pyrrole derivatives **8a–c** (Scheme 2).



Scheme 2. Possible reaction mechanism for the formation of the 3-aroyl-4-heteroarylpyrrole derivatives **8a–c**.

The protonic spectra for each of the 3,4-disubstituted pyrrole derivatives **8a**, **8b**, and **8c** clearly present signals that correspond to the C2–H, C5–H, and N–H of the pyrrole rings, evidencing their formation. In the ^{1}H NMR spectrum for compound **8a**, the signals appeared at 7.02, 70.9, and 11.61 ppm; in **8b** at 7.04, 7.24, and 11.57 ppm; in **8c** at 7.04, 7.19, and 11.62 ppm. IR, ^{13}C-NMR, and HR-MS analyses further established the structures of all of the **8** compounds (Original spectra are available in the Supplementary Materials section).

4. Materials and Methods

4.1. General Information

Melting points (uncorrected) were determined with a Thermo Scientific melting point apparatus, model IA 9100/Capillary. Infrared spectra (FT-IR) were collected at a resolution of 2 cm^{-1} and 16 scans (transmission mode 4000–500 cm^{-1}) using a Shimadzu FTIR 8400 spectrophotometer (Scientific Instruments Inc., Seattle, WA, USA) and KBr disks. NMR spectra ^{1}H and ^{13}C (DEPT-135) were recorded on a Bruker Advance spectrophotometer operating at 400 and 100 MHz, respectively, using TMS as an internal standard (d, 0.0 ppm) and $CDCl_3$ and DMSO-d_6 as solvents. The NMR signals are reported in ppm and coupling constants (*J*) are reported in Hertz. Mass spectra were recorded in a Thermo Fisher Scientific

GC-MS spectrometer model DSQII (Thermo Fisher Scientific Inc., Waltham, MA, USA) using a direct insertion probe and the electron impact ionization technique (70 eV). HRMS was recorded in an Agilent Technologies QTOF 6520B spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA) coupled to an HPLC Agilent-1200 equipped with an Agilent Zorbax extend C18 (2.1 mm × 50 mm × 1.8 mm) PN 727700-902 column, via electrospray ionization (ESI), and analyzed in positive mode. HPLC method: 0.4 mL/min, gradient from acetonitrile/water (10%, with 0.1% of formic acid) to acetonitrile (with 0.1% of formic acid).

4.2. Synthesis and Characterization

Synthesis of (*E*)-3-(6-(aryl-3-methyl-1-phenyl-1k-pyrazolo[3,4-*b*]pyridin-5-yl)-1-arylprop-2-en-1-one compounds **6a–c**.

The synthesis of compounds **6a–c** followed the classical Claisen–Schmidt condensation reaction. Equimolar amounts of 6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** (1.0 mmol) [14], the respective substituted acetophenones **5a–c** (1.0 mmol) in ethanol (8.0 mL), and five drops of 20% sodium hydroxide (0.33 mL, 1.5 mmol) were added, and the mixture was stirred at room temperature for 2 h. The solid obtained was isolated and recrystallized from a DMF–ethanol mixture to produce a yellow solid [9,15].

(*E*)-3-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1-phenylprop-2-en-1-one **6a**. M.p. 210–212 °C, 65% yield. ^{1}H-NMR (400 MHz, $CDCl_3$ RT) δ (ppm): 2.72 (s, 3H, CH_3), 7.26 (t, 1H, H*p*, *J* = 7.4 Hz), 7.28 (t, 1H, H*p*, *J* = 7.2 Hz), 7.50 (m, 7H, CH, CH 6-aryl, CH, Hα), 7.61 (d, 2H, H*o*, 6-aryl, *J* = 8.4 Hz), 7.96 (d, 1H, Hβ, *J* = 15.5 Hz), 8.03 (d, 2H, H*o*, *J* = 7.0 Hz), 8.32 (d, 2H, H*o*, *J* = 7.6 Hz), 8.42 (s, 1H, CH). ^{13}C-NMR δ (ppm): 12.5 (CH_3), 116.4 (C3a pyrazolopyridine), 120.5 (C*o*, Ph), 123.0 (Cα), 123.4 (C5 pyrazolopyridine), 125.7 (C*p*, Ph), 128.6 (C*o*, Ph), 128.7 (C*p*, Ph), 128.9 (C*m*, 6-aryl), 129.1 (C*m*, Ph), 131.7 (C*o*, 6-aryl), 133.0 (C4, pyrazolopyridine), 135.5 (C*i*, Ph), 137.7 (C*i*, 6-aryl), 137.9 (C*p*, 6-aryl), 139.4 (C*i*, Ph), 143.4 (C3, pyrazolopyridine), 150.5 (C7a, pyrazolopyridine), 158.2 (C6 pyrazolopyridine), 189.7 (C=O). IR, KBr (cm^{-1}): 1657 (C=O, st). MS (70 eV) *m*/*z* (%): 451/449 (M^{+2}/M^{+}, 18/54), 346 (34), 344 (100), 343 (25), 308 (11), 105 (35). HR-MS calculated for $C_{28}H_{20}ClN_3O$ 449.1295, found 449.1289.

((*E*)-3-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **6b**. M.p. 212–214 °C, 60% yield. ^{1}H-NMR (400 MHz, $CDCl_3$ RT) δ (ppm): 2.74 (s, 3H, CH_3), 3.95 (s, 9H, OCH_3), 7.23 (t, 1H, H*p*, *J* = 7.4 Hz), 7.30 (s, 2H, H*o*, 1-aryl), 7.49 (d, 1H, Hα, *J* = 15.3 Hz), 7.50 (d, 2H, H*o*, 6-aryl, *J* = 8.68 Hz), 7.51 (t, 2H, H*m*, *J* = 7.5 Hz), 7.63 (d, 2H, H*m*, 6-aryl, *J* = 8.7 Hz), 8.00 (d, 1H, Hβ, *J* = 15.3 Hz), 8.35 (d, 2H, H*o*, *J* = 7.9 Hz), 8.43 (s, 1H, CH). ^{13}C-NMR δ (ppm): 12.7 (CH_3), 56.6 (OCH_3), 61.0 (OCH_3), 106.4 (C*o*, 1-aryl), 116.4 (C3a pyrazolopyridine), 120.5 (C*o*), 122.6 (Cα), 123.4 (C5 pyrazolopyridine), 125.7 (C*p*), 128.7 (C*m*, 6-aryl), 129.1 (C*m*), 129.2 (C4, pyrazolopyridine), 131.7 (C*o*, 6-aryl), 133.2 (C*i*, 6-aryl), 135.6 (C*i*, 1-aryl), 137.8 (C*p*, 6-aryl), 139.4 (C*i*), 143.1 (Cβ), 142.9 (C*p*, 1-aryl), 143.4 (C3, pyrazolopyridine), 150.5 (C7a, pyrazolopyridine), 153.3 (C*m*, 1-aryl), 158.2 (C6, pyrazolopyridine), 188.2 (C=O). IR, KBr (cm^{-1}): 1656 (C=O, st). MS (70 eV) *m*/*z* (%): 541/539 (M^{+2}/M^{+}, 4/10), 135 (100).

(*E*)-1-([1,1′-biphenyl]-4-yl)-3-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)prop-2-en-1-one **6c**. M.p. 218–220 °C, 80% yield. ^{1}H-NMR (400 MHz, DMSO-d_6 383 K) δ (ppm): 2.73 (s, 3H, CH_3), 7.29 (t, 1H, H*p*, *J* = 7.2 Hz), 7.43 (t, 1H, H*p*, *J* = 6.8 Hz), 7.50 (t, 2H, H*m*, *J* = 7.2 Hz), 7.52 (t, 2H, H*m*, *J* = 8.1 Hz), 7.61 (d, 2H, H*o*, 6-aryl, *J* = 8.3 Hz), 7.67 (d, 2H, H*m*, 6-aryl, J = 8.3 Hz), 7.74 (d, 2H, H*m*, 1-aryl, *J* = 7.0 Hz), 7.77 (d, 1H, Hα, *J* = 15.7 Hz), 7.83 (d, 2H, H*o*, 1-aryl, *J* = 7.0 Hz), 7.87 (d, 1H, Hβ, *J* = 14.7), 8.14 (d, 2H, H*o*, *J* = 7.2 Hz), 8.28 (d, 2H, H*o*, *J* = 8.1 Hz), 9.02 (s, 1H, CH). ^{13}C-NMR δ (ppm): 11.5 (CH_3), 115.9 (C3a pyrazolopyridine), 119.7 (C*o*), 122.3 (C5 pyrazolopyridine), 123.5 (Cα), 125.0 (C*p*), 126.2 (C*o*), 126.3 (C*o*, aryl), 127.6 (C*p*), 128.3 (C*m*, 6-aryl), 128.4 (C*m*), 128.5 (C4), 131.0

(C*o*, 6-aryl), 133.6 (C*i*, 6-aryl), 136.1 (C*p*, 6-aryl), 138.6 (C*i*), 140.5 (Cβ), 144.1 (C3), 149.4 (C7a), 157.3 (C6 pyrazolopyridine), 188.0 (C=O). IR, KBr (cm^{-1}): 1673 (C=O, st). MS (70 eV) *m*/*z* (%): 525 (M^+, 14), 344 (12), 181 (100). HR-MS calculated for C_{34} $H_{24}ClN_3O$ 525.1608, found 525.1595.

Synthesis of 3-aroyl-4-(6-aryl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrrole derivatives **8a**–**c**.

The synthesis of compounds **8** evidenced the scope of the chemistry of *p*-tosylmethyl isocyanide (TosMIC), known as Van Leusen's reagent, for the construction of simple/fused heterocycles [16,17]. The compounds **6** (1 mmol) and TosMIC **7** (1 mmol) were mixed in DMSO (1.5 mL). The reactant mixture was added dropwise to a suspension of the base (50 mg NaH in 20 mL Et_2O) at room temperature, under stirring and keeping the final reaction mixture under an Ar atmosphere. TLC was used to monitor the progress of the reaction. After one hour of stirring, the reaction mixture was poured onto a saturated NaCl solution (75 mL) and neutralized with 1N HCl. The precipitate formed was filtered and washed with water, and then dissolved in DCM. The water was separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from acetone–ethyl ether to generate the respective pyrrole derivative **8** as a yellow solid.

((4-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone **8a**. M.p. 225–227 °C, 60% yield. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H, CH_3), 7.02 (d, 1H, H5, pyrrole, *J* = 2.22 Hz), 7.09 (t, 1H, H2, pyrrole, *J* = 2.22 Hz), 7.23 (t, 2H, H*m*, *J* = 8.30 Hz), 7.26 (t, 1H, H*p*, *J* = 7.7 Hz), 7.34 (m, 4H, 6-aryl), 7.45–7.55 (m, 5H, 3-Aroyl), 8.23 (s, 1H, H4, pyrazolopyridine), 8.31 (d, 2H, H*o*, *J* = 8.5 Hz), 11.61 (s, 1H, NH). ^{13}C-NMR δ (ppm): 12.5 (CH_3), 116.1 (C-3a pyrazolopyridine), 120.3 (C*o*, Ph-pyrazolopyridine), 120.9 (C2, pyrrole), 122.8 (C5, pyrazolopyridine), 123.7 (C4, pyrrole), 125.3 (C3, pyrrole), 125.5 (C*p*, Ph-pyrazolopyridine), 127.5 (C*p*, 3-aroyl), 127.7 (C*m*, 3-aroyl), 128.2 (C*o*, 3-aroyl), 128.7 (C*m*, 6-aryl), 129.4 (C*m*, Ph-pyrazolopyridine), 131.7 (C*o*, 6-aryl), 132.3 (C4 pyrazolopyridine), 133.2 (C*i*, 3-aroyl), 140.1 (C*i*, Ph-pyrazolopyridine), 140.2 (C*i*, 6-aryl), 140.3 (C*p*, 6-aryl), 143.1 (C3, pyrazolopyridine), 157.2 (C6 pyrazolopyridine), 190.0 (C=O). IR, KBr (cm^{-1}): 3184 (NH, st), 1608 (C=O, st). MS (70 eV) *m*/*z* (%): 490/488 (M^{+2}/M^+, 2/6), 344/346 (11/31), 135 (10), 123 (14), 113/111 (6/19), 105 (100), 97 (39), 95 (28), 83 (43), 77 (28), 69 (53), 57 (59), 43 (52). HR-MS calculated for $C_{30}H_{21}ClN_4O$ 488.1404, found 488.1395.

(4-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone **8b**. M.p. 280–282 °C, 70% yield. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.64 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.74 (s, 6H, OCH_3), 6.59 (s, 2H, 3-aroyl), 7.04 (m, 1H, H5, pyrrole), 7.24 (m, 4H, H*p*, Ph-pyrazolopyridine; H*o*, 6-aryl; H2, pyrrole), 7.34 (d, 2H, H*m*, 6-aryl, *J* = 8.53 Hz), 7.51 (t, 2H, H*m*, Ph-pyrazolopyridine, *J* = 7.30 Hz), 8.24 (s, 1H, H4, pyrazolopyridine), 8.30 (d, 2H, H*o*, Ph-pyrazolopyridine, *J* = 8.5 Hz), 11.57 (s, 1H, NH). ^{13}C-NMR δ (ppm): 12.6 (CH_3), 56.1 (OCH_3), 60.3 (OCH_3), 106.5 (C*o*, 3-aroyl), 116.0 (C3a pyrazolopyridine), 119.2 (C*o*, Ph-pyrazolopyridine), 119.8 (C2, pyrrole), 122.2 (C5, pyrazolopyridine), 123.6 (C4, pyrrole), 125.1 (C3, pyrrole), 125.4 (C*p*, Ph-pyrazolopyridine), 126.9 (C5, pyrrole), 127.7 (C*m*, 6-aryl), 129.5 (C*m*, Ph-pyrazolopyridine), 131.5 (C4 pyrazolopyridine), 131.8 (C*o*, 6-aryl), 133.0 (C*i*, 6-aryl), 134.8 (C*i*, 3-aroyl), 139.7 (C*i*, Ph-pyrazolopyridine), 139.8 (C*p*, 3-aroyl), 140.6 (C*p*, 6-aryl-pyrazolopyridine), 143.1 (C3, pyrazolopyridine), 149.6 (C7a, pyrazolopyridine), 152.4 (C*m*, 3-aroyl), 157.0 (C6 pyrazolopyridine), 188.8 (C=O). IR, KBr (cm^{-1}): 3125 (NH, st), 1607 (C=O, st). MS (70 eV) *m*/*z* (%): 580/578 (M^{+2}/M^+, 38/98), 565/563 (8/22), 531 (12), 386/384 (3/12), 289 (16), 195 (100), 77 (10). HR-MS calculated for $C_{33}H_{27}ClN_4O_4$ 578.1721, found 578.1711.

[1,1′-biphenyl]-4-yl(4-(6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrrol-3-yl)methanone **8c**. M.p. 253–255 °C, 55% yield. ^{1}H-NMR (400 MHz, DMSO-

d_6) δ (ppm): 2.64 (s, 3H, CH_3), 7.04 (s, 1H, H5, pyrrole), 7.19 (s, 1H, H2, pyrrole), 7.24 (t, 2H, H*m*, 3-aroyl), 7.26 (t, 2H, H*p*, Ph-pyrazolopyridine, *J* = 7.5 Hz), 7.36–7.53 (m, 9H, H*m*, Ph-pyrazolopyridine; H*o*, H*m*, 3-aroyl; H*m*, H*p*, Ph-3-aroyl), 7.62 (d, 2H, H*o*, 6-aryl, *J* = 8.5 Hz), 7.65 (d, 2H, H*m*, 6-aryl, *J* = 8.5 Hz), 8.25 (s, 1H, H4, pyrazolopyridine), 8.31 (d, 2H, H*o* Ph-pyrazolopyridine, *J* = 8.5 Hz), 11.62 (s, 1H, NH). ^{13}C-NMR δ (ppm): 12.6 (CH_3), 116.0 (C3a pyrazolopyridine), 120.0 (C*o*, Ph-pyrazolopyridine), 120.8 (C2, pyrrole), 122.4 (C5, pyrazolopyridine), 123.5 (C4, pyrrole), 125.1 (C3, pyrrole), 125.5 (C*p*, Ph-pyrazolopyridine), 126.5 (C*p*, 3-aroyl), 127.3 (C*o*, 3-aroyl), 127.8 (C*o*, 3-aroyl), 128.5 (C*m*, 6-aryl), 129.5 (C*m*, 3-aroyl), 129.6 (C*m*, Ph-pyrazolopyridine), 129.7 (C*o*, 6-aryl), 131.8 (C4 pyrazolopyridine), 132.3 (C5, pyrrole), 133.1 (C*i*, 6-aryl), 138.5 (C*i*, Ph-pyrazolopyridine), 139.7 (C*i*, Ar-pyrazolopyridine), 139.8(C*i*, 3-aroyl), 139.9(C*i*, 3-aroyl), 143.1 (C*p*, 3-aroyl), 143.2 (C3, pyrazolopyridine), 149.7 (C7a, pyrazolopyridine), 157.0 (C6 pyrazolopyridine), 189.4 (C=O). IR, KBr (cm^{-1}): 3171 (NH, st), 1613 (C=O, st). MS (70 eV) *m*/*z* (%): 566/564 (M^{+2}/M^+, 39/100), 385/383 (18/52), 348 (14), 282 (15), 181 (87), 153 (34). HR-MS calculated for $C_{36}H_{25}ClN_4O$ 564.1717, found 564.1710.

5. Conclusions

The synthesis of 3,4-disubstituted pyrroles was carried out by the Van Leusen method under basic conditions. This transformation is regioselective and uses the Van Leusen reagent (TosMIC), considered a versatile synthetic tool because of its reactivity, selectivity, and ability to combine with substrates of different nature and structural diversity.

Exploring the scope of chalcones with scaffold pyrazolo[3,4-*b*]pyridine as substrates, we prepared three new 3-aroyl-4-(6-aryl-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-1H-pyrrole derivatives with reasonably good yields in a four-stage reaction sequence. The final stage consists of a heterocyclization reaction using NaH as a base and *p*-tosylmethyl isocyanide in a synthetic strategy known as Van Leusen pyrrole synthesis, which obtains pyrrole-ring-unsubstituted C2 and C5. Synthetic versatility studies of the pyrazolo[3,4-*b*]pyridine-based chalcones for the construction of polycyclic heteroaromatics are in progress.

Supplementary Materials: The following are available online: NMR and HR-MS spectra for compounds **8a**, **8b**, and **8c**.

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References

1. Petri, G.L.; Spanò, V.; Spatola, R.; Holl, R.; Raimondi, M.V.; Barraja, P.; Montalbano, A. Bioactive pyrrole-based compounds with target selectivity. *Eur. J. Med. Chem.* **2020**, *208*, 112783. [CrossRef]
2. Wang, P.; Nguyen, K.C.; Lindsey, J.S. Synthesis of the Ring C Pyrrole of Native Chlorophylls and Bacteriochlorophylls. *J. Org. Chem.* **2019**, *84*, 11286–11293. [CrossRef]
3. Zhan, X.-P.; Lan, L.; Wang, S.; Zhao, K.; Xin, Y.-X.; Qi, Q.; Wang, Y.-L.; Mao, Z.-M. Synthesis and Anticancer Activity of 3-(Substituted Aroyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole Derivatives. *Chem. Biodivers.* **2017**, *14*, e1600219. [CrossRef] [PubMed]

4. Domagala, A.; Jarosz, T.; Lapkowski, M. Living on pyrrolic foundations e Advances in natural and artificial bioactive pyrrole derivatives. *Eur. J. Med. Chem.* **2015**, *100*, 176–187. [CrossRef] [PubMed]
5. Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. Pyrrole: A resourceful small molecule in key medicinal heteroaromatics. *RSC Adv.* **2015**, *5*, 15233–15266. [CrossRef]
6. Philkhana, S.C.; Badmus, F.O.; Dos Reis, I.C.; Kartika, R. Recent Advancements in Pyrrole Synthesis. *Synthesis* **2021**, *53*, 1531–1555. [CrossRef] [PubMed]
7. Taghi Nazeri, M.; Shaabani, A. Synthesis of polysubstituted pyrroles via isocyanide-based multicomponent reactions as an efficient synthesis tool. *New J. Chem.* **2021**, *45*, 21967–22011. [CrossRef]
8. Kumar, K. TosMIC: A Powerful Synthon for Cyclization and Sulfonylation. *ChemistrySelect* **2020**, *5*, 10298–10328. [CrossRef]
9. Farooq, S.; Ngaini, Z. Recent synthetic methodologies for chalcone synthesis (2013–2018). *Curr. Organocatal.* **2019**, *6*, 184–192. [CrossRef]
10. Ardiansah, B. Chalcones bearing N, O, and S-heterocycles: Recent notes on their biological significances. *J. Appl. Pharm. Sci.* **2019**, *9*, 117–129. [CrossRef]
11. Manasa, K.L.; Visweswara Sastry, K.N.; Tangella, Y.; Babu, B.N. Tandem Synthesis of 3,4-Disubstituted Pyrroles from Aldehydes, 1,3-Diketones and TosMIC Under Metal-Free Conditions. *ChemistrySelect* **2018**, *3*, 2730–2733. [CrossRef]
12. Aitha, A.; Payili, N.; Rekula, S.R.; Yennam, S.; Anireddy, J.S. "One-Pot" Selective Synthesis of 3,4-Disubstituted Pyrroles and Benzo[*f*]indole-4,9-diones from 1,3-Indanedione, Aromatic Aldehydes and TosMIC. *ChemistrySelect* **2017**, *2*, 7246–7250. [CrossRef]
13. Zhan, X.; Lan, L.; Zhang, Y.; Chen, J.; Zhao, K.; Wang, S.; Xin, Y.; Mao, Z. Synthesis and Cytotoxicity Evaluation of New 3-substituted 4-(4-methyloxyphenyl)-1H-Pyrrole Derivatives. *Bull. Korean Chem. Soc.* **2016**, *37*, 200–206. [CrossRef]
14. Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. Regioselective formylation of pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine systems using Vilsmeier–Haack conditions. *Tetrahedron Lett.* **2008**, *49*, 2689–2691. [CrossRef]
15. Trilleras, J. Synthesis of *ortho*-Functionalized Heterocyclic Aldehydes and Study of Their Condensation, Cyclocondensation and S_NAr Reaction in the Preparation of α,β-Unsaturated and Fused Heterocyclic Systems. Ph.D. Thesis, Universidad del Valle, Cali, Colombia, 2009.
16. Van Leusen, D.; Van Leusen, A.M. Synthetic Uses of Tosylmethyl Isocyanide (TosMIC). *Org. React.* **2001**, *57*, 417–666. [CrossRef]
17. Van Leusen, A.M.; Siderius, H.; Hoogenboom, B.E.; Van Leusen, D. A new and simple synthesis of the pyrrole ring system from Michael acceptors and tosylmethylisocyanides. *Tetrahedron Lett.* **1972**, *13*, 5337–5340. [CrossRef]
18. Ma, Z.; Ma, Z.; Zhang, D. Synthesis of Multi-Substituted Pyrrole Derivatives Through [3+2] Cycloaddition with Tosylmethyl Isocyanides (TosMICs) and Electron-Deficient Compounds. *Molecules* **2018**, *23*, 2666. [CrossRef] [PubMed]