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Ambient-Temperature Synthesis of (*E*)-*N*-(3-(*tert*-Butyl)-1-methyl-1*H*-pyrazol-5-yl)-1-(pyridin-2-yl)methanimine

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Abstract: We report the ambient-temperature synthesis of novel (*E*)-*N*-(3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-yl)-1-(pyridin-2-yl)methanamine **3** in 81% yield by a condensation reaction between 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine **1** and 2-pyridinecarboxaldehyde **2** in methanol using magnesium sulfate as a drying agent. The *N*-pyrazolyl imine **3** was full characterized by IR, 1D, and 2D NMR spectroscopy, mass spectrometry, and elemental analysis.

Keywords: 5-aminopyrazole; *N*-pyrazolyl imine; condensation reaction

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1. Introduction

Pyrazole is a five-membered heterocyclic system containing three carbon atoms and two nitrogen atoms in adjacent positions [1]. Pyrazole and its derivatives have attracted a great deal of attention in organic and medicinal chemistry due to their wide range of pharmacological and biological activities [2–7]. For example, apixaban is employed to prevent blood clots [7], sildenafil is a cyclic GMP-specific phosphodiesterase inhibitor to treat erectile dysfunction [8], benzydamine hydrochloride is a non-steroidal anti-inflammatory drug [9], and axitinib is a selective tyrosine kinase inhibitor to treat advanced renal cell carcinoma [10], among others marketed drugs possessing this pyrazole structural motif, as shown in Figure 1.

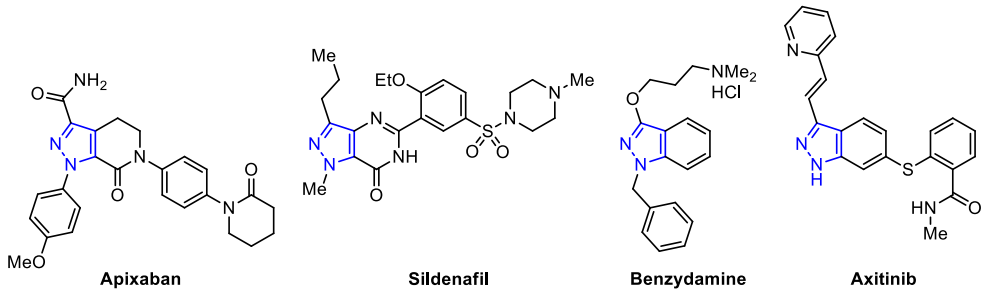


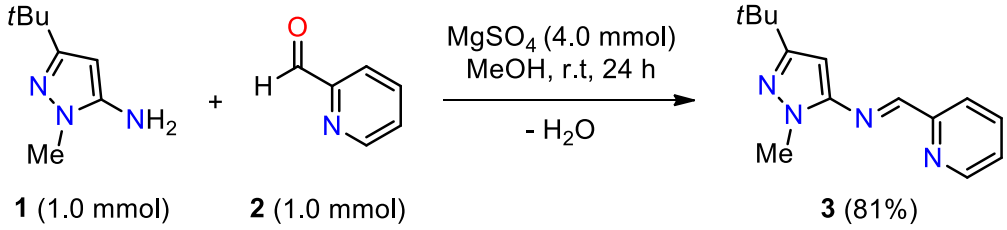
Figure 1. Pyrazole-containing marketed drugs.

In particular, 5-aminopyrazole has been extensively employed as an important aza-heterocyclic template for the preparation of a variety of bicyclic *N*-heterocycles with interesting applications in medicinal chemistry [11] and material science [12,13]. In this context, we have recently employed *N*-(5-pyrazolyl)imines in the aza-Diels–Alder cycloaddition reaction using electrophilic α-oxoketene and aryne intermediates for the expeditious syntheses of pyrazolopyrid-4-ones [14] and isoquinolines [15], respectively. Due to the considerable interest of 5-aminopyrazole as an important aza-heterocyclic template for the preparation of *N*-(5-pyrazolyl)imines, and its application in the formation of pyrazole-containing

heterocycles [14–16], we herein report the synthesis and full characterization of novel *N*-pyrazolyl imine **3** through the uncatalyzed condensation reaction of 5-aminopyrazole **1** with hetaryl aldehyde **2** under mild reaction conditions.

2. Results and Discussion

We describe the synthesis of *N*-pyrazolyl imine **3** by a condensation reaction between equimolar amounts of 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine **1** and pyridinecarboxaldehyde **2** in methanol (HPLC grade, ≥99.9%) under stirring at ambient temperature for 24 h, using an excess of magnesium sulfate as a drying agent (Scheme 1). After the specified reaction time, the mixture was filtered, and the solvent was removed by a rotary evaporator under vacuum. The resulting crude product was purified by flash chromatography on silica gel using a mixture of DCM/MeOH (40:1, *v*/*v*) as an eluent to afford *N*-pyrazolyl imine **3** in an 81% yield. As expected, the water released in the condensation process was trapped by the drying agent to displace the equilibrium towards the imine product. It should be noted that a complete spectroscopic and analytical characterization was performed in this work (Materials and Methods). Initially, the structure of *N*-pyrazolyl imine **3** was determined by IR, 1D NMR spectroscopy, mass spectrometry, and elemental analysis (Figures S1–S6, Figure 2A). Then, the examination of 2D NMR spectra, including HSQC (Figure S7), HMBC (Figures S8–S9), and COSY (Figure S10), allowed structure assignment without ambiguity (Figure 2B).



Scheme 1. Ambient-temperature synthesis of *N*-pyrazolyl imine **3**.

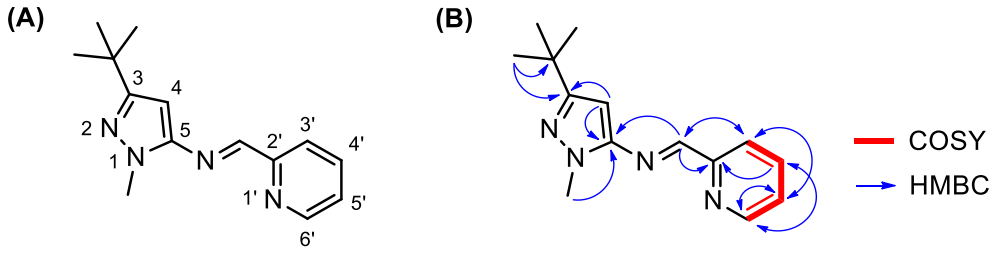


Figure 2. (**A**) Structure of *N*-pyrazolyl imine **3**. (**B**) Connectivities of **3** based on COSY (bold red line) and HMBC (from H to C, blue arrow) data.

In the IR spectrum, the absorption bands at 1588 and 1568 cm^{-1} were assigned to C = N stretching vibrations. It should be noted that C=N stretching modes are mostly depicted as combinational bands with C=C stretching vibrations. In addition, C–N stretching vibrations were observed at 1245 and 1290 cm^{-1}. In the MS spectrum, the molecular ion peak was observed at 242 *m*/*z* with a 58% intensity, while the base peak was detected at 227 *m*/*z* with a 100% intensity, corresponding to the elimination of a methyl group. The ^{1}H NMR spectrum of **3** recorded in $CDCl_3$ showed the existence of two methyl groups at 1.32 and 3.94 ppm, as well as one methine of the pyrazole ring at 6.17 ppm (Table 1). In the downfield region, four methines of the pyridine ring appeared in a range between 7 and 8 ppm. The signal of the azomethine group was observed as a singlet at 8.66 ppm, indicating that the condensation process was successful. The $^{13}C\{^{1}H\}$ NMR and DEPT spectra of **3** showed 12 carbon signals, consisting of one azomethine, four quaternary carbons, five aromatic methines, and two methyls (Table 1 and Figure 2A). The HSQC

spectrum recorded in $CDCl_3$ enabled the assignment of all protons to the directly bonded carbons. Thus, the signals of $C(CH_3)_3$, NCH_3, and CH=N groups were assigned at 30.6, 34.8, and 159.1 ppm, respectively. Moreover, the C-4 signal was observed at 88.7 ppm, which is in good agreement with the high electron density of the carbon atom at position **4** of π-excedent pyrazole systems [14–16]. In Table 1 and Figure 2B, the correlation C-H observed in the HMBC experiment for quaternary carbons C-3, C-5, and C-2′ is summarized, highlighting the correlation at ^2J for CH=N to C-2′ (154.7 ppm). Other important correlations were the *tert*-butyl group with C-3 (161.4 ppm) at ^3J, while NCH_3 and CH=N signals correlated with C-5 (148.9 ppm) at ^3J. The quaternary carbon of the *tert*-butyl group was observed in the upfield region at 32.4 ppm. Ultimately, the COSY experiment helped to identify the four aromatic methines of the pyridine ring C-3′, C-4′, C-5′, and C-6′ at 121.5, 136.7, 125.3, and 149.9 ppm, respectively.

Table 1. ^1H and $^{13}C\{^1H\}$ NMR assignments, COSY and HMBC correlations of **3** [a].

Number	δ_H (Mult, *J* in Hz)	δ_C (ppm)	COSY (^1H-^1H)	HMBC (^1H-^{13}C)
CH_3, *t*-Bu	1.32 (s)	30.6	–	–
Cq, *t*-Bu	–	32.4	–	CH_3, *t*-Bu (^2J)
NCH_3	3.94 (s)	34.8	–	–
3	–	161.4	–	H-4 (^2J) CH_3, *t*-Bu (^3J)
4	6.17 (s)	88.7	–	–
5	–	148.9	–	CH=N (^3J) H-4 (^2J) NCH_3 (^3J)
2′	–	154.7	–	CH=N (^2J) H-4′ (^3J)
3′	8.21 (dt, *J* = 7.6, 1.0)	121.5	H-4′ (^3J)	CH=N (^3J) H-5′ (^3J)
4′	7.78 (dddd, *J* = 7.8, 7.6, 1.6, 0.8)	136.7	H-3′ (^3J) H-5′ (^3J)	H-6′ (^3J)
5′	7.34 (ddd, *J* = 7.6, 4.8, 1.2)	125.3	H-4′ (^3J) H-6′ (^3J)	H-6′ (^2J) H-3′ (^3J)
6′	8.68 (ddd, *J* = 4.8, 1.6, 0.8)	149.9	H-5′ (^3J)	H-4′ (^3J) H-5′ (^2J)
CH=N	8.66 (s)	159.1	–	H-3′ (^3J)

[a] Measured at 400 MHz (^1H) and 101 MHz (^{13}C) in $CDCl_3$.

In summary, we report the ambient-temperature synthesis of *N*-pyrazolyl imine **3** in good yield through an uncatalyzed condensation reaction between 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine **1** and 2-pyridinecarboxaldehyde **2** in the presence of magnesium sulfate as a drying agent. This protocol is distinguished by its ease of operation, high atom economy, simple isolation of the imine, and clean reaction profile. It should be noted that *N*-pyrazolyl imine **3** could be employed as an aza-heterocyclic template for obtaining fused pyrazole derivatives with potential applications in medicinal chemistry and materials science.

3. Materials and Methods

3.1. General Information

The 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine **1** was synthesized using a known method [14]. 2-pyridinecarboxaldehyde **2** was acquired from Sigma–Aldrich (CAS 1121-60-4) and used without previous purification. The starting materials were weighed and

handled in air at ambient temperature. Silica gel aluminum plates (Merck 60 F_{254}, Darmstadt, Germany) were used for analytical TLC. A Shimadzu FTIR 8400 spectrophotometer (Scientific Instruments Inc., Seattle, WA, USA) equipped with an attenuated reflectance accessory was used for acquiring the IR absorption spectrum. A Bruker Avance 400 spectrophotometer (Bruker BioSpin GmbH, Rheinstetten, Germany) was used to record ^{1}H and ^{13}C{^{1}H} NMR spectra at 25 °C using frequencies of 400 and 101 MHz, respectively. The chemical shifts of ^{1}H and ^{13}C{^{1}H} NMR spectra were referenced with tetramethylsilane (δ = 0.0 ppm). Alternatively, the chemical shifts of ^{1}H and ^{13}C{^{1}H} NMR experiments could be referenced with the residual non-deuterated signal (δ = 7.26 ppm) and the deuterated solvent signal (δ = 77.16 ppm), respectively. The assignment of carbon signals was performed using the DEPT-135 experiment. The chemical shifts (δ) are given in ppm, while coupling constants (*J*) are given in Hz. The following abbreviations are used to indicate the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The 2D HSQC, HMBC, and COSY experiments were performed using the standard Bruker pulse sequence. 1D and 2D NMR spectra were processed in MestReNova 12.0.0 (2017) software. A SHIMADZU-GCMS 2010-DI-2010 spectrometer (Scientific Instruments Inc., Columbia, WA, USA) equipped with a direct input probe at 70 eV was used for acquiring the mass spectrum. The microanalysis was performed on a CHNS elemental analyzer (Thermo Fischer Scientific Inc., Madison, WI, USA) and the values are within ±0.4% of the theoretical values.

3.2. Synthesis of (E)-N-(3-(tert-Butyl)-1-methyl-1H-pyrazol-5-yl)-1-(pyridin-2-yl)methanamine **3**

A mixture of 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine **1** (153 mg, 1.0 mmol), 2-pyridinecarboxaldehyde **2** (95 µL, 1.0 mmol, CAS 1121-60-4), and anhydrous magnesium sulphate (481 mg, 4.0 mmol, CAS 7487-88-9) in methanol (5.0 mL, HPLC grade, ≥99.9%, CAS 67-56-1) was stirred at ambient temperature for 24 h. After a complete disappearance of the starting materials, as monitored by thin-layer chromatography (TLC), the reaction mixture was filtered, and the solvent was evaporated by a rotary evaporator under vacuum. The resulting crude product was purified by flash chromatography on silica gel using a mixture of DCM/MeOH (40:1, *v*/*v*) as an eluent to afford *N*-pyrazolyl imine **3** as a brown solid (196 mg, 81% yield). Rf (DCM/MeOH: 20/1) = 0.25. M.p 162–163 °C. FTIR–ATR: ν = 2953, 2895, 2861, 1588 (ν C=N), 1568 (ν C=N), 1537, 1469, 1432, 1360, 1290 (ν C–N), 1245 (ν C–N), 1180, 1057, 993, 747, 699, 593 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H, *t*-Bu), 3.94 (s, 3H, NCH_3), 6.17 (s, 1H, H-4), 7.34 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H-5′), 7.78 (dddd, *J* = 7.8, 7.6, 1.6, 0.8 Hz, H-4′), 8.21 (dt, *J* = 7.6, 1.0 Hz, 1H, H-3′), 8.66 (s, 1H, CH=N), 8.68 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H, H-6′) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 30.6 (CH_3, *t*-Bu), 32.4 (Cq, *t*-Bu), 34.8 (NCH_3), 88.7 (CH, C-4), 121.5 (CH, C-3′), 125.3 (CH, C-5′), 136.7 (CH, C-4′), 148.9 (Cq, C-5), 149.9 (CH, C-6′), 154.7 (Cq, C-2′), 159.1 (CH, CH=N), 161.4 (Cq, C-3) ppm. Anal. calcd. for $C_{14}H_{18}N_4$ (242.15): C, 69.39; H, 7.49; N, 23.12. Found: C, 69.53; H, 7.44; N, 23.21. MS (EI, 70 eV) *m*/*z* (%): 242 (58) [$M^{+\bullet}$], 227 ($M^{+\bullet}$–CH_3, 100), 200 (14), 183 (6), 143 (7), 131 (6), 118 (5), 92 (10).

Supplementary Materials: The following are available online. Figure S1: MS spectrum of the compound **3**; Figure S2: IR spectrum of the compound **3**; Figure S3: 1H NMR spectrum of the compound **3**; Figure S4: Expansion 1H NMR spectrum of the compound **3**; Figure S5: 13C{1H} NMR and DEPT-135 spectra of the compound **3**; Figure S6: Expansion 13C{1H} NMR and DEPT-135 spectra of the compound **3**; Figure S7: HSQC 2D C–H correlation spectrum of the compound **3**; Figure S8: HMBC 2D C–H correlation spectrum of the compound **3**; Figure S9: Expansion HMBC 2D C–H correlation spectrum of the compound **3**; Figure S10: COSY 2D H–H correlation spectrum of the compound **3**.

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Conflicts of Interest: The authors declare not conflicts of interest.

Sample Availability: Not available.

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