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Short Report

A Mild and Efficient Method for the Preparation of 3-(2'-Aminoaryl)pyrazoles from 4-Chloroquinolines

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Um método mais suave e eficiente é descrito para a síntese de 3-(2'-aminoaril)pirazóis, a partir das reações de 4-cloroquinolinas com hidrazina em excelentes rendimentos. Estas reações de abertura de anel heterocíclico ocorrem em condições mais suaves do que as descritas anteriormente.

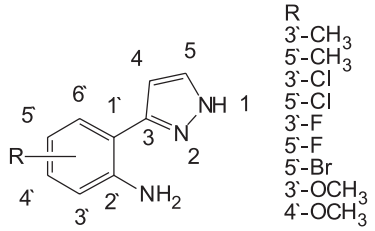
We describe a mild and efficient method for the formation of 3-(2'-aminoaryl)pyrazoles in excellent yields from reactions of 4-chloroquinolines with hydrazine. These heterocyclic ring opening reactions occur under much milder conditions then previously described.

Keywords: pyrazoles, 4-chloroquinolines, X-ray diffraction

Introduction

Pyrazoles and their derivatives are widely used as pharmaceutical[1-5] and agrochemical agents[6] and consequently a large number of synthetic routes to pyrazoles has been reported.[7-13] However, there is still great interest in finding milder and more efficient methods to these valuable compounds. Amino groups undergo various reactions, and as such are excellent and general starting points for the development of chemical libraries.[14] In particular, 3-(2`-aminoaryl)pyrazoles (**1**) are useful precursors of more elaborate pyrazolic molecules.[15] A preparation of 3-(2'-aminophenyl)pyrazoles was first described by Alberti[15] from 4-hydroxyquinolines. 4-Chloroquinolines[16,17] on treatment with substituted hydrazines gave 1-substituted-3-(2-aminophenyl)pyrazoles. All these reactions occurred under drastic conditions using autoclave or sealed tubes.[15,16] Later, other workers reported ring opening reactions of 4-hydroxyquinolines[13] and the preparation of the compound 3-(2'-aminophenyl)pyrazole by the reduction reaction of 3-(2-nitrophenyl)pyrazole.[18]

Our research group has developed a route to 3-(2'-aminoaryl)pyrazoles under mild conditions from 4-chloroquinolines (**2**) and hydrazine in a *one-pot* process.



(**1**)

Results and Discussion

The 4-chloroquinolines[19] (**3**) are readily prepared from 4-hydroxyquinolines (**2**) and can be stored for long periods. The 4-hydroxyquinolines,[20] in turn, can be readily made from quinolones *via* the Gould-Jacobs method.[21,22] Our *one-*

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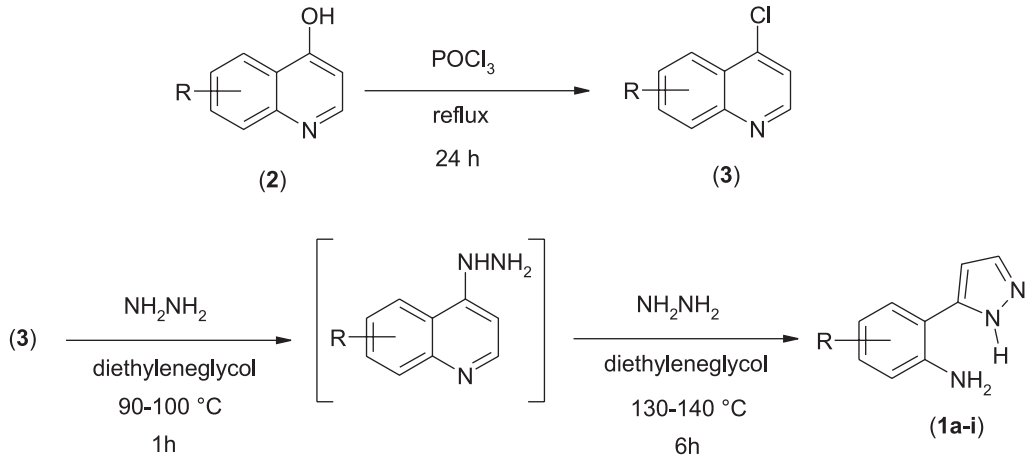

Scheme 1.

pot synthesis of (**1a-i**) involves reactions of 4-chloroquinolines with an excess of hydrazine in diethyleneglycol initally at 90-100 ºC for one hour. Substitutions of the chlorine atom in **3** by hydrazine occur in this temperature range to generate intermediate 4-hydrazinoquinolines, which on raising the temperature to 130-140 ºC, react further over a period of six hours to afford the desired products **1a-i**, see Scheme 1.

As shown in Table 1, isolated yields range from good to excellent, with electron withdrawing substituents resulting in the higher yields and electron donating substituents resulting in lower yields as expected for a nucleophilic aromatic substitution reaction.

Products were generally identified by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopies, mass spectrometry and elementary analysis. Specifically, confirmation of the structure of 1a was gained by X-ray diffraction.[23,24] Atom arrangements are shown in Figure 1.

Overall the molecules are nearly planar with the angles between the best planes of the two rings in the order of 12º and torsional angles ranging from 0.06 (0.40) to 12.34 (0.45)º. Intramolecular N3X-HAX…N1X (X=A or B) hydrogen bonds help to cement the planar arrangements of the two molecules. Intermolecular N2A-H2A…N3B and N2B-H2B…N3A hydrogen bonds link the two independent molecules, alternatively, into molA…molB…molA chains (Figure 2).

Table 1. Yields of compounds **1a-i**

Compound[b, c]	R	Yield / (%)[a]
1a	3'-CH_3	71
1b	5'-CH_3	65
1c	3'-Cl	91
1d	5'-Cl	80
1e	3'-F	94
1f	5'-F	87
1g[d]	5'-Br	80
1h	3'-OCH_3	70
1i	4'-OCH_3	67

[a]Isolated yields. [b]Identified by ^{1}H NMR, ^{13}C NMR, IR-FT, mass spectroscopy and elementary analysis. [c]All compounds were recrystalized in ethanol-H_2O (1:1). [d]Obtained as a white solid with mp of 83 ºC, in reference 13 as a brown oil.

Experimental

Preparation of the compounds 3-(2'-aminoaryl) pyrazoles: 0.8 g (0.004 mol) of the 4-chloroquinolines and 2.0 mL of hydrazine was stirred in 6.0 mL of diethyleneglycol at 90-100 ºC for 1 hour. Later the temperature was raised to 130-140 ºC for 6 hours. Finaly, the mixture was dropped in a beaker with ice and water and the crystals formed were filtered.

3-(2'-Amino-3'-methylphenyl)pyrazole, ***1a****; R = 3'-CH_3*

mp 111 ºC; FT-IR (KBr) ν_{max}/cm^{-1}: 3400, 3100, 1610, 1485, 765; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.55 (d; 2.4 Hz) H5 7.48 (d; 2.4 Hz); H4' 7.02 (dd; 7.5 and 2.4 Hz); H5' 6.70 (t; 7.5 Hz); H6' 7.35 (dd; 7.8 and 2.1 Hz); NH_2/NH 5.47 (s); CH_3 2.16 (s). ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.7; C4 103.7; C5 130.5; C1' 123.1; C2' 142.8; C3' 117.4; C4' 126.7; C5' 116.7; C6' 129.8; CH_3 17.8; MS: *m/z* 173.0949 (M^+, 100%). Anal. Calc. for $C_{10}H_{11}N_3$ (%): C 69.34; H 6.40; N 24.26. Found (%): C 69.16; H 6.21; N 23.98.

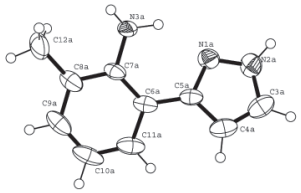

Figure 1. Molecular structure of **1a**. Ellipsoids, for non hydrogen atoms, are drawn at the 50% probability level: H atoms are drawn as arbitrary spheres.

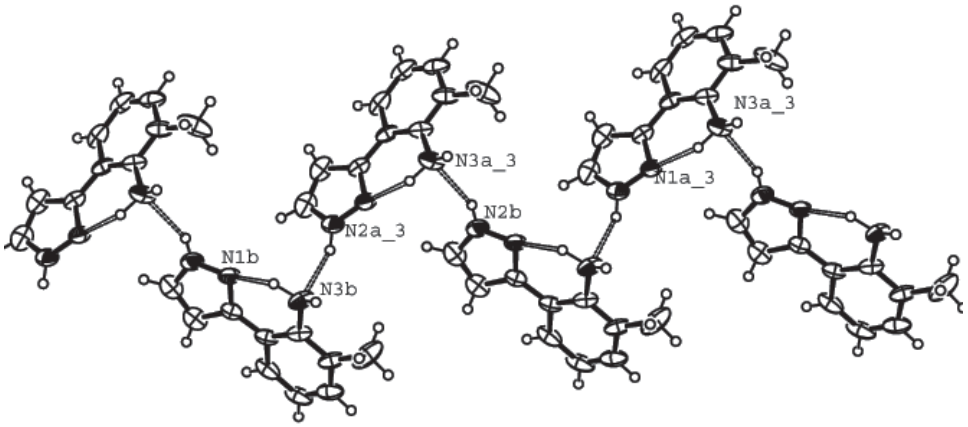

Figure 2. Hydrogen bonding of **1a**.

3-(2'-Amino-5'-methylphenyl)pyrazole, ***1b****; R = 5'-CH_3*

mp 87 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3400, 3190, 1620, 1590, 1510, 1450, 770; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.61 (s); H5 7.57 (s); H3' 6.69 (d; 8.1 Hz); H4' 6.94 (d; 7.2 Hz); H6' 7.30 (s); CH_3 2.27 (s); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 151.0; C4 103.2; C5 128.8; C1' 116.8; C2' 141.9; C3' 116.6; C4' 129.2; C5' 126.8; C6' 128.7; CH_3 20.3;MS: *m/z* 173.0876 (M^+, 100%). Anal. Calc. for $C_{10}H_{11}N_3$ (%): C 69.34; H 6.40 N 24.26. Found (%): C 69.23; H 6.55; N 24.01.

3-(2'-Amino-3'-chlorophenyl)pyrazole, ***1c****; R = 3'-Cl*

mp 94 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3420, 3080, 1610, 1585, 1490, 1425, 740; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.67 (d; 2.4 Hz); H5 7.62 (d; 2.4 Hz); H4' 7.24 (dd; 7.8 and 1.5 Hz); H5' 6.68 (t; 7.8 Hz); H6' 7.45 (dd; 1.5 and 7.8 Hz); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 151.2; C4 103.5; C5 129.4; C1' 120.0; C2' 141.1; C3' 117.5; C4' 128.4; C5' 117.0; C6' 126.8; MS: *m/z* 193.0375 (M^+, 100%). Anal. Calc. for $C_9H_8N_3Cl$ (%): C 55.83; H 4.16; N 21.70. Found (%): C 55.53; H 4.19; N 21.44.

3-(2'-Amino-5'-chlorophenyl)pyrazole, ***1d****; R = 5'-Cl*

mp 58 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3400, 3050, 1611, 1487, 765; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.63 (d; 2.4 Hz); H5 7.60 (d; 2.4 Hz); H3' 6.68 (d; 8.7 Hz); H4' 7.05 (dd; 8.4 and 2.4 Hz); H6' 7.48 (d; 2.4 Hz); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.3; C4 103.3; C5 129.6; C1' 117.7; C2' 143.1; C3' 117.5; C4' 128.2; C5' 121.9; 127.8; MS: *m/z* 193.0396 (M^+, 100%). Anal. Calc. for $C_9H_8ClN_3$ (%): C 55.83; H 4.16; N 21.70. Found (%): C 55.66; H 4.29; N 21.79.

3-(2'-Amino-3'-fluorophenyl)pyrazole, ***1e****; R = 3'-F*

mp 87 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3420, 3160, 1615, 1470, 1245, 755; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.65 (d; 2.1 Hz); H5 7.60 (d; 2.1 Hz); H4' 6.91-6.99 (m); H5' 6.67 (t; 8.4 Hz); H6' 7.31 (7.8 Hz); NH_2/NH 5.47 (s); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.8; C4 103.6; C5 129.5; C1' 118.4; C2' 133.3 (d; 13.6 Hz); C3' 152.1 (d; 236.6 Hz); C4' 113.7 (d; 18.4 Hz); C5' 116.4 (d; 7.8 Hz); C6' 123.3; MS: *m/z* 177.0623 (M^+, 100%). Anal. Calc. for $C_9H_8FN_3$ (%): C 61.01; H 4.55; N 23.72. Found (%): C 61.15; H 4.58; N 23.81.

3-(2'-Amino-5'-fluorophenyl)pyrazole, ***1f****; R = 5'-F*

mp 92 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3400, 3040, 1610, 1467, 810, 725; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.61 (d; 2.4 Hz); H5 7.60 (d; 2.4 Hz); H3' 6.70 (m); H4' 6.80 (m); H6' 7.20 (m); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.3; C4 103.4; C5 129.7; C1' 117.5; C2' 140.2; C3' 117.5 (d; 8.5 Hz); C4' 114.2 (d; 23.6 Hz); C5' 155.6 (d; 233,2 Hz); C6' 115.1 (d; 22.6 Hz); MS: *m/z* 177.0678 (M^+, 100%). Anal. Calc. for $C_9H_8FN_3$ (%): C 61.01; H 4.55; N 23.72. Found (%): C 61.09; H 4.58; N 23.77.

3-(2'-Amino-5'-bromophenyl)pyrazole, ***1g****; R = 5'-Br*

mp 83 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3400, 3000, 1610, 1462, 735; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.64 (s); H5 7.60 (s); H3' 6.64 (d; 7.5 Hz); H4' 7.18 (dd; 8.4 and 2.1 Hz); H6' 7.65 (d; 2,1 Hz); ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.7; C4 103.7; C5 128.8; C1' 109.4; C2' 143.9; C3' 118.8; C4' 131.1; C5' 118.8; C6' 131.0; MS: *m/z* 238.0811 (M^+, 100%). Anal. Calc. for $C_9H_8BrN_3$ (%): C 45.40; H 3.39; N 17.65. Found (%): C 45.37; H 3.36; N 17.61.

3-(2'-Amino-3'-methoxyphenyl)pyrazole, ***1h****; R = 3'-OCH_3*

mp 111 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3410, 3100, 2980, 1590, 1495, 1220, 725; ^{1}H NMR ($CDCl_3$, δ in ppm) H4 6.59 (d; 2.3 Hz); H5 7.53 (d; 2.3 Hz); OCH_3 3.88 (s); NH_2/NH 6.41 (s). ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.8; C4 103.5; C5 130.2; C1' 120.6; C2' 147.7; C3' 116.6; C4'

135.0; C5' 116.4; C6' 135.1; OCH_3 55.7; MS: *m/z* 189.2120 (M^+, 100%). Anal. Calc. for $C_{10}H_{11}N_3O$ (%): C 63.48; H 5.86; N 22.21. Found (%): C 63.21; H 6.02; N 22.48.

3-(2'-Amino-4'-methoxyphenyl)pyrazole, ***1i****; R = 4'-*OCH_3

mp 82 ºC; FT-IR (KBr) ν_{max} / cm^{-1}: 3410, 3090, 1610, 1510, 1210, 830, 770; ^1H NMR ($CDCl_3$, δ in ppm) H4 6.45 (d; 2.3 Hz); H5 7.43 (d; 2.3 Hz); OCH_3 3.70 (s); NH_2/NH 6.39 (s). ^{13}C NMR ($CDCl_3$, δ in ppm) C3 150.7; C4 103.4; C5 129.9; C1' 115.2; C2' 145.6; C3' 117.6; C4' 129.6; C5' 134.1; C6' 116.0; OCH_3 55.0; MS: *m/z* 189.2145 (M^+, 100%). Anal. Calc. for $C_{10}H_{11}N_3O$ (%): C 63.48; H 5.86; N 22.21. Found (%): C 63.46; H 5.87; N 22.35.

Conclusions

In conclusion we would like to reiterate that the method is a simple and efficient one, not requiring special equipment or harsh conditions. The respectable yields in these reactions also make it a viable method for the synthesis of 3-(2-amino-aryl/hetaryl)pyrazoles. Following this procedure, eight new compounds (**1a-f**, **1h-i**) were thus prepared.

Acknowledgments

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23. *Crystal data:* $C_{10}H_{11}N_3$, colourless, M = 173.22, T = 120 (2)K, monoclinic, space group c2, a = 25.9750(3), b =9.5820(6), c = 7.8299(7)Å, β = 107.541(3)º, V =1858.2(2) $Å^3$, Z = 8, D_x = 1.238 gcm^{-3}, monochromated Mo-Kα radiation, λ = 0.71073 Å, μ = 0.078 mm^{-1}.
24. *Data collection*. The unit cell and intensity data were collected on a Bruker-Nonius diffractometer. 5454 reflections were collected, of which 2925 [R(int) = 0.0489]were independent reflections, with the 2θ range for data collection of 2.28 to 24.99º.
25. *Structure Solution and Refinement*: Structure solution and refinement were achieved using SHELX97 and SHELXL97. Full matrix least squares on F^2 of data converged to R1=0.0437, wR2=0.0841 [I>2σI]. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Center, deposition number CCDC 635098.
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