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Synthesis of substituted 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones

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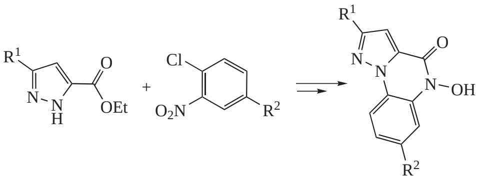
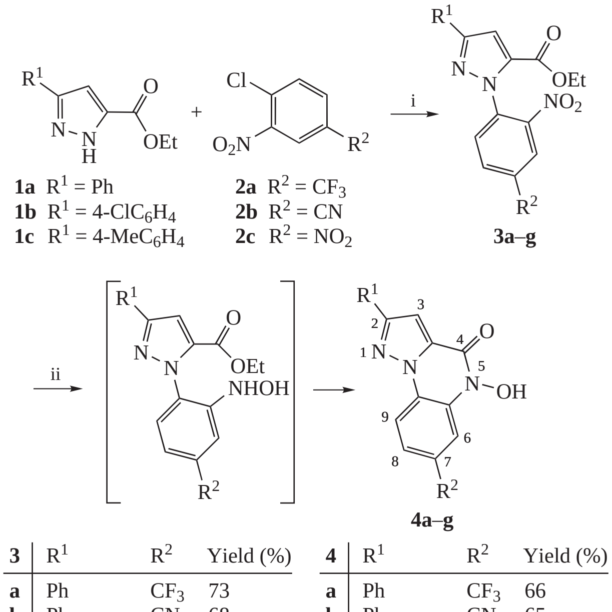
A two-stage selective synthesis of new substituted 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones from ethyl 3-arylpyrazole-5-carboxylates and activated *o*-chloronitroarenes substrates has been developed.



Recently much attention has been given to the syntheses of various pyrazole derivatives,[1] including heterocyclic fused systems.[2] Pyrazolo[1,5-*a*]quinoxalines that manifest different types of biological activity as inhibitors of various human enzymes[3,4] are interesting representatives of this class of compounds.

As a rule, approaches to pyrazolo[1,5-*a*]quinoxaline involve multiple stages. The preparative synthesis of pyrazolo[1,5-*a*]quinoxalin-4-one involves preliminary preparation of carbonylpyrazole dimer followed by cyclization into the target product *via* intramolecular nucleophilic substitution under drastic conditions.[5,6] Analysis of reported data has shown that there is a limited choice of methods for synthesizing pyrazolo[1,5-*a*]quinoxalin-4-ones and no methods to synthesize 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones, with the exception of a casual example[7] of a similar compound obtained in a low yield. Therefore, the purpose of this study was to develop a two-stage synthesis of substituted 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones based on the N-arylation of pyrazolecarboxylates with *o*-halonitroarenes followed by reductive cyclization of the resulting nitro compounds into the target products (Scheme 1).



1a R^1 = Ph
1b R^1 = 4-ClC_6H_4
1c R^1 = 4-MeC_6H_4

2a R^2 = CF_3
2b R^2 = CN
2c R^2 = NO_2

3a–g

4a–g

3	R^1	R^2	Yield (%)
a	Ph	CF_3	73
b	Ph	CN	68
c	Ph	NO_2	76
d	4-ClC_6H_4	CF_3	75
e	4-ClC_6H_4	CN	75
f	4-ClC_6H_4	NO_2	70
g	4-MeC_6H_4	CN	79

4	R^1	R^2	Yield (%)
a	Ph	CF_3	66
b	Ph	CN	65
c	Ph	NH_2	61
d	4-ClC_6H_4	CF_3	59
e	4-ClC_6H_4	CN	55
f	4-ClC_6H_4	NH_2	67
g	4-MeC_6H_4	CN	56

Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMF, 50–80 °C, 3–6 h; ii, $SnCl_2$, HCl, EtOH, 50 °C, 3–4 h.

3-Arylpyrazole-5-carboxylates **1a–c** (obtained by the known procedure[8]) were used as N-nucleophiles, and substituted *o*-chloronitroarenes **2a–c** activated by an additional electron-withdrawing group were used as substrates (see Scheme 1). The arylation of *NH*-pyrazoles was carried out in DMF in the presence of K_2CO_3 at 50–80 °C for 3–6 h, the yield of the target products **3a–g** was up to 79%.[†] The formation of the C–N bond in pyrazoles[9,10] implies that two structural isomers can be formed due to the prototropic tautomerism of the heterocycle, their ratio being affected by the reaction conditions, the nature and positions of substituents in the pyrazole ring, and the structure of the arylating substrate. To date, no regularities for the formation of a particular isomer have been rationalized, though experimental data on the regioselective formation of isomeric products in N-alkylation and N-arylation of various substituted pyrazoles are available.[11–13]

Pyrazolecarboxylates **1a–c** were found to exist as NH-tautomer mixtures, which followed from appearance of the signals in their ^{1}H NMR spectra as broad lines or double 1 : 1 sets. Therefore,

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[†] *Compounds* **3a–g** *(general procedure)*. Pyrazole **1a–c** (0.012 mol), the corresponding *o*-chloronitrobenzene **2a–c** (0.012 mol) and powdered K_2CO_3 (0.50 mg, 0.036 mol) were successively mixed in DMF (3 ml). The reaction mixture was stirred at 50–80 °C for 3–6 h (TLC monitoring). The mixture was cooled, and water (5 ml) was added with stirring. The precipitate that formed was filtered off and recrystallized from ethanol.

*Ethyl 1-[2-nitro-4-(trifluoromethyl)phenyl]-3-phenyl-1*H*-pyrazole-5-carboxylate* **3a**. Yield 410 mg (73%), yellow powder, mp 122–123 °C. IR (ν/cm^{-1}): 1715 (C=O), 1629 (Ar), 1545 (NO_2), 1323 (NO_2), 1244, 1124 (C–O), 1139 (C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (t, 3H, Me, *J* 7.3 Hz), 4.22 (q, 2H, CH_2, *J* 7.3 Hz), 7.41 (t, 1H, H-4′, *J* 7.4 Hz), 7.46 (t, 2H, H-3′, H-5′, *J* 7.4 Hz), 7.76 (s, 1H, H-4), 7.91 (d, 2H, H-2′, H-6′, *J* 7.4 Hz), 8.13 (d, 1H, H-6″, *J* 8.3 Hz), 8.42 (d, 1H, H-5″, *J* 8.3, 1.8 Hz), 8.81 (d, 1H, H-3″, *J* 1.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.68, 61.51, 109.93, 122.40 (q, $^3J_{C-F}$ 3.5 Hz), 125.58 (2C), 127.58 (q, $^1J_{C-F}$ 274 Hz), 128.89 (2C), 128.93, 129.69 (q, $^2J_{C-F}$ 33 Hz), 130.63 (q, $^3J_{C-F}$ 3.5 Hz), 130.92, 131.64, 135.58, 136.15 (br. s), 145.22, 152.40, 158.02. MS, *m/z* (%): 405 [M]$^+$ (26), 331 (51), 296 (31), 144 (20), 129 (71), 102 (53), 77 (100). Found (%): C, 56.13; H, 3.46; N, 10.33. Calc. for $C_{19}H_{14}F_3N_3O_4$ (%): C, 56.30; H, 3.48; N, 10.37.

one could expect formation of two products in their reactions with chloroarenes **2a–c**. In fact, the reaction afforded mainly 3-arylpyrazole-5-carboxylates **3a–g** (above 95%, NMR data), apparently due to negative charge localization on the nitrogen atom adjacent to the carboxy group.

At the second stage, nitroarylpyrazoles **3a–g** were reduced with divalent tin by a known technique.[14] The presence of the second electron-withdrawing substituent in the nitroaryl fragment caused intramolecular regioselective condensation into 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones **4a–g** in up to 67% yield (one-pot reaction). In the case of compounds **3c**,**f** ($R^2 = NO_2$), reduction of the second nitro group occurred due to application of two-fold excess $SnCl_2$ thus giving amino derivatives **4c**,**f** ($R^2 = NH_2$).

The structures of compounds **3** and **4** were confirmed by a combination of IR and NMR spectroscopic and mass spectrometric data. Intense molecular ion peaks (100 %) were observed for the target compounds **4a–g**. As a rule, subsequent fragmentation resulted in an $[M – OH]^+$ ion, which confirmed that *N*-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones were formed. In the ^1H NMR spectra, the proton signal of the OH group was observed as a broadened singlet in the range of 11.87–11.92 ppm. Furthermore, assignment of hydrogen and carbon atoms was made on the basis of HMBC spectroscopy data for compound **4f**, which manifested no signals of amino and hydroxy groups in the ^1H NMR spectrun owing to the exchange effect.

In conclusion, we have developed a simple and selective synthesis of new substituted 5-hydroxypyrazolo[1,5-*a*]quinoxalin-4-ones containing N–OH fragment. The obtained compounds can be regarded as tautomers of 4-hydroxypyrazolo[1,5-*a*]quinoxaline 5-oxides and are of interest for further studies of their biological properties.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.039.

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*Ethyl 1-(2,4-dinitrophenyl)-3-phenyl-1*H*-pyrazole-5-carboxylate* **3c**. Yield 381 mg (76%), yellow powder, mp 144–146 °C. IR (ν/cm^{-1}): 1716 (C=O), 1608 (Ar), 1531 (NO_2), 1344 (NO_2), 1240, 1105 (C–O). ^1H NMR (400 MHz, DMSO-d_6) δ: 1.22 (t, 3H, Me, *J* 7.1 Hz), 4.23 (q, 2H, CH_2, *J* 7.1 Hz), 7.41 (t, 1H, H-4′, *J* 7.4 Hz), 7.47 (t, 2H, H-3′, H-5′, *J* 7.4 Hz), 7.79 (s, 1H, H-4), 7.92 (d, 2H, H-2′, H-6′, *J* 7.4 Hz), 8.20 (d, 1H, H-6″, *J* 8.8 Hz), 8.71 (dd, 1H, H-5″, *J* 8.8/2.5 Hz), 8.93 (d, 1H, H-3″, *J* 2.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.74, 61.63, 110.26, 120.56, 125.62 (2C), 128.22, 128.90 (2C), 129.02, 130.79, 131.68, 135.64, 137.40, 144.72, 147.18, 152.68, 158.02. MS, *m*/*z* (%): 382 $[M]^+$ (82), 308 (100), 262 (29), 129 (42), 102 (24), 77 (26). Found (%): C, 56.24; H, 3.67; N, 14.61. Calc. for $C_{18}H_{14}N_4O_6$ (%): C, 56.55; H, 3.69; N, 14.65.

Compounds **4a–g** *(general procedure)*. Compound **3a–g** (0.01 mol) was added to a solution of $SnCl_2$ (3.5 mmol) (for **3c**,**f**, 7.0 mmol) in conc. HCl (2 ml) and EtOH (2 ml), and the mixture was stirred at 50 °C for 3–4 h. The precipitate formed upon cooling of the solution was filtered off and recrystallized from EtOH.

*5-Hydroxy-2-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]quinoxalin-4(5*H*)-one* **4a**. Yield 229 mg (66%), white powder, mp 284–285 °C (decomp.). IR (ν/cm^{-1}): 3200 (OH), 1659 (C=O), 1614, 1595 (Ar), 1130. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.45 (t, 1H, H-4′, *J* 7.6 Hz), 7.52 (t, 2H, H-3′, H-5′, *J* 7.6 Hz), 7.78 (dd, 1H, H-8, *J* 8.3/1.5 Hz), 7.85 (s, 1H, H-4), 7.93 (br. s, 1H, H-6), 8.11 (d, 2H, H-2′, H-6′, *J* 7.6 Hz), 8.44 (d, 1H, H-9, *J* 8.3 Hz), 11.91 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 104.82, 110.71 (q, ^3J 3.9 Hz), 116.05, 120.53 (q, ^3J 3.9 Hz), 122.00 (q, ^1J 273.0 Hz), 125.54, 126.07 (2C), 126.67 (q, $^2J_{C–F}$ 33 Hz), 128.91 (2C), 129.16, 129.61, 131.17, 134.64, 150.57, 153.47. MS, *m*/*z* (%): 345 $[M]^+$ (84), 328 $[M-17]^+$ (52), 300 (42), 183 (17), 170 (15), 103 (13), 77 (100). Found (%): C, 58.98; H, 2.90; N, 12.13. Calc. for $C_{17}H_{10}F_3N_3O_2$ (%): C, 59.14; H, 2.92; N, 12.17.

*7-Amino-5-hydroxy-2-phenylpyrazolo[1,5-*a*]quinoxalin-4(5*H*)-one* **4c**. Yield 178 mg (61%), white powder, mp 273–275 °C. IR (ν/cm^{-1}): 2605 (OH + NH), 1647 (C=O), 1606 (Ar). ^1H NMR (500 MHz, DMSO-d_6) δ: 6.88 (dd, 1H, H-8, *J* 8.8/1.0 Hz), 7.18 (d, 1H, H-6, *J* 1.0 Hz) 7.38 (t, 1H, H-4′, *J* 7.8 Hz), 7.47–7.50 (t, 2H, H-3′, H-5′, *J* 7.8 Hz), 7.63 (s, 1H, H-3), 8.03 (d, 2H, H-2′, H-6′, *J* 7.8 Hz), 8.07 (d, 1H, *J* 8.8 Hz), (NH_2 + OH, exchange). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 103.88, 106.00, 116.22, 116.70, 120.31, 125.96 (2C), 128.91, 128.93 (2C), 130.17, 131.55, 133.61, 135.28, 150.80, 152.46. MS, *m*/*z* (%): 293 $[M]^+$ (18), 292 $[M]^+$ (100), 276 (29), 275 $[M – 17]^+$ (57), 247 (58), 172 (26), 117 (24), 105 (25), 90 (20), 77 (89). LCMS (ESI), *m*/*z*: 291 $[M – H]^-$. Found (%): C, 65.61; H, 4.11; N, 19.12. Calc. for $C_{16}H_{12}N_4O_2$ (%): C, 65.75; H, 4.14; N, 19.17.

For characteristics of compounds **3b**,**d–g** and **4b**,**d–g**, see Online Supplementary Materials.