Convenient One Pot Synthesis of 5-Unsubstituted Pyrazolo[3,4-*c*]isoquinolines

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The convenient one pot synthesis of pyrazolo[3,4-*c*]isoquinolines **1** from 5-aminopyrazoles **2** and paraformaldehyde in formic or trifluoroacetic acids is described.

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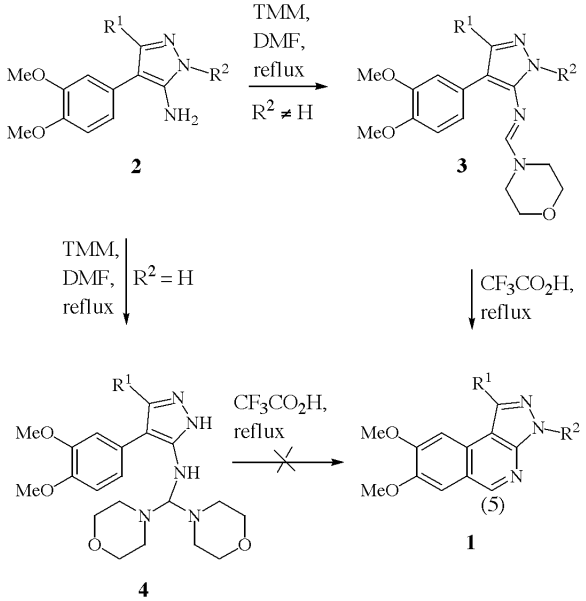
Pyrazolo[3,4-*c*]isoquinolines are a structurally rare but biologically promising class of heterocyclic compounds containing the pyrazolopyridine core. Closely related pyrazolopyridine derivatives have been extensively studied due to their wide ranging biological activity, such as anxyolitic [1] and antidepressant activities [2], and platelet aggregation inhibition [3]. Therefore, new convenient synthetic routes to similar systems are of considerable interest, and a one-pot transformation of 6-nitroquinoline into pyrazolo[3,4-f]quinolines by the action of aromatic hydrazones/NaH in N,N-dimethylformamide was recently reported [4].

Earlier we described [5] the synthesis of 5-unsubstituted pyrazolo[5,4-*c*]isoquinolines **1** by reaction of 5-aminopyrazoles **2** with tris(morpholino)methane (TMM) in DMF resulting in amidines **3** which underwent cyclization in trifluoroacetic acid (Scheme 1).

Scheme 1

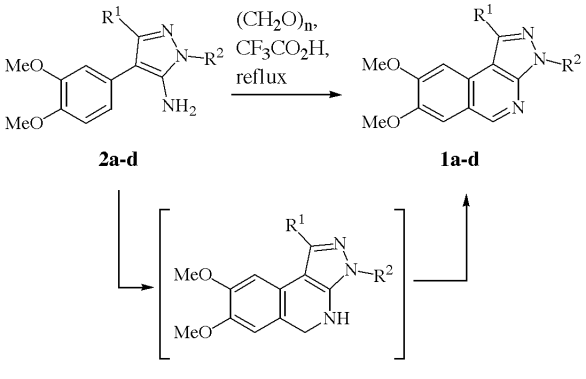


2 **3** **4** **1**

This method has been found to be very sensitive to the purity of starting compounds. We have also noted that the presence of traces of water in the azolylformamidines cyclization step (**3** → **1**) results in their facile hydrolysis to **2** which substantially decreases the yield and purity of the products **1**. Moreover, this method (Scheme 1) is unsuitable for cyclization of 1-unsubstituted 5-aminopyrazole derivatives (**2**, R^2 = H): the final products in this case are tris(amino)methanes **4** which are stable in acidic conditions and do not undergo further cyclization [6].

As a part of our contribution to poly(aza)heterocyclic systems with potential biological activity [5,7], we describe here a new, convenient, one pot method for the synthesis of 5-unsubstituted pyrazolo[3,4-*c*]isoquinolines **1** from 5-amino-4-arylpyrazoles **2**. We have found that 5-amino-4-(3,4-dimethoxyphenyl)pyrazoles **2a-d** readily react with paraformaldehyde at reflux in trifluoroacetic or formic acid to provide intermediate 4,5-dihydropyrazolo[3,4-*c*]isoquinolines **5**, which, however, are unstable (reactive) in these conditions and are oxidized to pyrazolo[3,4-*c*]isoquinolines **1a-d**, which are the only isolated products. (Scheme 2).

Scheme 2



2a-d **1a-d**

5

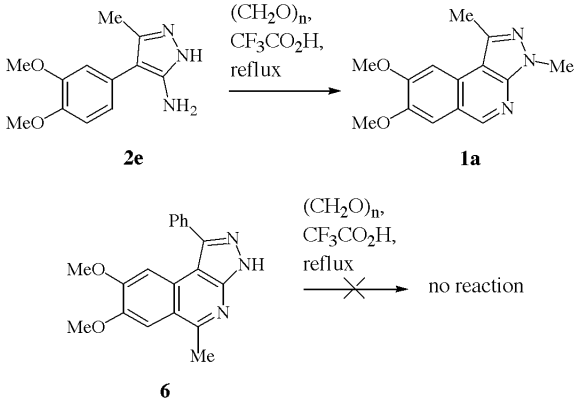
a: $R^1 = R^2$ = Me
b: R^1 = Me, R^2 = Ph
c: R^1 = H, R^2 = Ph
d: $R^1 = CH_2Ph$, R^2 = Ph

The structures of compounds **1** were confirmed by ^{1}H and ^{13}C nmr spectroscopy, and supported by MS and satisfactory elemental analyses data. The characteristic feature of compounds **1** is the low-field absorption of the H(5) proton (*ca.* 9 ppm) in their ^{1}H nmr spectra.

3,4-Dimethoxy-substituents in **2** increase the activity of C(6) atom of the phenyl ring to intramolecular electrophilic attack providing intermediate **5** [8]. However, although the reaction proceeds under the conditions of Pictet-Spengler tetrahydroisoquinoline synthesis, an annelation of the pyrazole moiety has a drastic effect on the resulting products. We were unable to isolate the corresponding dihydroisoquinolines **5** which are, presumably, very reactive in these conditions and are easily oxidized/dehydrogenated into **1**. As the reaction was carried out in air, oxygen is responsible for this transformation. However, when the reaction was carried out in the same conditions but in an inert atmosphere, only starting materials were isolated or tag(resin) (if the mixture was refluxed for a long time) was formed due to polymerization/condensation processes.

An interesting transformation, which we observed, was the reaction of 1-unsubstituted 5-aminopyrazoles. As mentioned above, 1-unsubstituted pyrazoles **2** (R^2 = H) do not yield pyrazolo[3,4-*c*]isoquinolines but tris(amino)-methanes **4** instead. In contrast to that, the reaction with paraformaldehyde allows the formation of the pyrazolo-[3,4-*c*]isoquinoline core. Thus, for the reaction of aminopyrazole **2e** with paraformaldehyde, concomitant with cyclization, the reductive methylation of N(1) atom of the pyrazole ring occurs (Scheme 3). The isolated 7,8-dimethoxy-1,3-dimethylpyrazolo[3,4-*c*]isoquinoline

Scheme 3



(**1a**) is identical to the sample of **1a** which was obtained from pyrazole **2a**. When an equimolar ratio of pyrazole **2e** and paraformaldehyde was used in the reaction, compound **1a** was isolated with the yield of 27%; for a 1:2 ratio of **2e**:paraformaldehyde, the yield increased to 38-40% (quoted yields are after recrystallization).

We have also established that hydroxymethylation of the N(1)-pyrazole atom occurs before formation of the pyrazolo[3,4-*c*]isoquinoline ring because 7,8-dimethoxy-5-methyl-1-phenylpyrazolo[5,4-*c*]isoquinoline (**6**) [9] does not react with paraformaldehyde under these conditions, and was almost quantitatively recovered from the reaction mixture. So, we suggest that in this case the aromatization step of 4,5-dihydropyrazolo[3,4-*c*]isoquinoline **5** and the reduction of the *N*-hydroxymethyl substituent proceeds *via* abstraction of hydride ion from the C(5) atom in **5**.

For the reaction of 5-amino-4-(3,4-dimethoxyphenyl)-isoxazoles with paraformaldehyde under these conditions destruction of the isoxazole ring (low stability of isoxazole ring in acidic media is documented in the literature [10]) yielded a complex mixture of products, which were not identified.

In summary, we have developed a convenient straightforward method for construction of the 5-unsubstituted pyrazolo[3,4-*c*]isoquinoline framework in an one-pot synthesis which involves direct cyclocondensation of 5-amino-4-arylpyrazoles with paraformaldehyde in trifluoroacetic or formic acids. The intermediate dihydroisoquinoline system **5** reacts further under the reaction conditions, due to the annelated pyrazole moiety, and readily undergoes dehydrogenation yielding the target products.

EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded on a Varian MERCURY (200 MHz), Bruker AC-250 (250 MHz), and Varian UNITY 300 (300 MHz) spectrometers in dimethyl sulfoxide-d_6 solutions with Me_4Si as an internal standard (for ^{1}H) and referenced to the solvent (for ^{13}C; δ = 39.52 ppm [11]). Mass spectra (electron impact) were recorded on a VG7070E spectrometer operating at 70 eV. Melting points were determined on a Kofler-type hot-stage apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 881 spectrophotometer in potassium bromide pressed pellets. Starting 5-amino-1-R^2-3-R^1-4-(3,4-dimethoxyphenyl)pyrazoles **2a-e** and 7,8-dimethoxy-5-methyl-1-phenylpyrazolo[5,4-*c*]isoquinoline **6** were prepared as described previously [9].

General Procedure for the Pyrazolo[3,4-*c*]quinoline Derivatives (**1a-d**).

5-Aminopyrazole **2a-d** (5 mmol) and paraformaldehyde (5 mmol) were refluxed in trifluoroacetic or formic acid (20 mL) for 10–12 hours or 25–30 hours, respectively. The solvent was removed *in vacuo*, the residue was crushed with 5% aqueous ammonia solution, filtered off, washed with water, dried and recrystallized from acetonitrile (yields after recrystallization are given in parentheses).

7,8-Dimethoxy-1,3-dimethylpyrazolo[3,4-*c*]isoquinoline (**1a**).

This compound was obtained within the yields of 72 (61)% and 65 (55)% for the reaction in trifluoroacetic and formic acid, respectively; mp 211–212 °C (decomp.); ^{1}H nmr (200 MHz): δ

2.82 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.35 (s, 3H, N–CH_3,), 7.49 (s, 1H, H–9), 7.56 (s, 1H, H–6), 8.94 (s, 1H, H–5); ^{13}C nmr (63 MHz): δ 14.72, 55.71, 56.07, 100.90, 108.59, 110.39, 115.24, 131.73, 140.80, 141.44, 145.20, 147.30, 156.49 ppm (N–*C*H_3 is not recognized due to possible overlapping by the solvent and/or its low intensity as the result of splitting on nitrogen); ms: m/z (%) 257 (M^+, 100.0), 242 (M^+-CH_3, 8.7), 228 (M^+-N–CH_3, 12.6), 214 (M^+-N–N–CH_3, 12.5), 199 (214-CH_3, 11.9), 186 (8.4), 171 (6.1); ir: 1630, 1615 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.36; H, 5.88; N, 16.33. Found: C, 65.24; H, 6.00; N, 16.20.

Compound **1a** was also obtained from **2e** by the above procedure in trifluoroacetic acid using 10 mmol of paraformaldehyde. Yield 50 (38) %. In formic acid yields were somewhat lower.

7,8-Dimethoxy-1-methyl-3-phenylpyrazolo[3,4-*c*]isoquinoline (**1b**).

This compound was obtained within the yields of 74 (65)% and 60 (50)% for the reaction in trifluoroacetic and formic acid, respectively; mp 166–166.5 °C (decomp.); ^{1}H nmr (300 MHz): δ 2.78 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.30 (tt, 1H, ^{3}J = 7.4 Hz, ^{4}J = 1.2 Hz, *p*-phenyl), 7.43 (s, 1H, H–9), 7.54 (t, 2H, ^{3}J = 7.8 Hz, *m*-phenyl), 7.61 (s, 1H, H–6), 8.26 (dd, 2H, ^{3}J = 7.8 Hz, ^{4}*J* = 1.2 Hz, *o*-phenyl), 8.93 ppm (s, 2H, H–5); ^{13}C nmr (75 MHz): δ 15.12, 55.56, 55.68, 101.43, 108.24, 108.64, 120.04, 120.53 (2C), 125.37, 126.58, 129.01 (2C), 139.41, 142.11, 147.17, 147.93, 151.02, 153.71 ppm; ms: m/z (%) 319 (M^+, 100.0), 304 (M^+-CH_3, 25.0), 276 (16.1), 259 (5.5), 246 (6.7), 232 (7.7), 160 (7.4), 152 (5.7), 77 (C_6H_5, 8.0); ir: 1630, 1610 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_3O_2$ (319.36): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.45; H, 5.22; N, 13.20%.

7,8-Dimethoxy-3-phenylpyrazolo[3,4-*c*]isoquinoline (**1c**).

This compound was obtained within the yields of 70 (62)% and 60 (51)% for the reaction in trifluoroacetic and formic acid, respectively; mp 209.5–211 °C (decomp.); ^{1}H nmr (200 MHz): δ 3.95 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.37 (t, 1H, ^{3}J = 7.3 Hz, *p*-phenyl), 7.60 (t, 2H, ^{3}J ≈ 7.8 Hz, *m*-phenyl), 7.72 (s, 1H, H–6), 7.91 (s, 1H, H–9), 8.33 (d, 2H, ^{3}J = 8.2 Hz, *o*-phenyl), 8.85 (s, 1H, H–1), 9.08 ppm (s, 1H, H–5); ^{13}C nmr (50 MHz): δ 55.61, 56.09, 102.65, 108.09, 111.06, 120.07, 120.81 (2C), 125.85, 126.07, 129.04 (2C), 133.26, 139.40, 146.48, 148.46, 150.94, 154.00 ppm; ms: m/z (%) 305 (M^+, 100.0), 290 (M^+-CH_3, 15.0), 262 (13.8), 247 (6.5), 231 (12.6), 218 (17.3), 192 (8.2), 115 (8.1), 100 (9.2), 88 (14.9), 77 (C_6H_5, 77.7), 63 (15.0), 51 (42.1); ir: 1630, 1615 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$ (305.34): C, 70.81; H, 4.95; N, 13.76. Found: C, 70.75; H, 4.84; N, 13.95.

1-Benzyl-7,8-dimethoxy-3-phenylpyrazolo[5,4-*c*]isoquinoline (**1d**).

This compound was obtained within the yields of 63 (57)% and 60 (50)% for the reaction in trifluoroacetic and formic acid, respectively; mp 200–201 °C (decomp.); ^{1}H nmr (200 MHz): δ 3.77 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2), 7.18–7.40 (m, 7H, H–9 + *p*-phenyl–N + $C_6H_5CH_2$), 7.60 (t, 2H, ^{3}J = 8.2 Hz, *m*-phenyl–N), 7.68 (s, 1H, H–6), 8.35 (d, 2H, ^{3}J = 8.2 Hz, *o*-phenyl–N), 9.05 ppm (s, 1H, H–5); ^{13}C nmr (50 MHz): δ 34.53, 55.58, 55.76, 102.53, 108.30, 108.37, 120.15, 120.94 (2C), 125.68, 125.93, 126.42, 128.24 (2C), 128.64 (2C), 129.04 (2C), 138.30, 139.28, 144.31, 147.65, 147.97, 151.34, 153.53 ppm; ms: m/z (%) 395 (M^+, 100.0), 380 (M^+-CH_3, 9.9), 318 (M^+-C_6H_5, 6.1), 198 (5.9), 91 (C_6H_5–N, 7.8), 77 (C_6H_5, 4.5); ir: 1630, 1610 cm^{-1}.

Anal. Calcd. for $C_{25}H_{21}N_3O_2$ (395.46): C, 75.93; H, 5.35; N, 10.63. Found: C, 75.80; H, 5.17; N, 10.77.

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