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SHORT COMMUNICATIONS

Regioselective Alkylation of Substituted 1*H*-Pyrazolo[3,4-*c*]isoquinolin-1-ones

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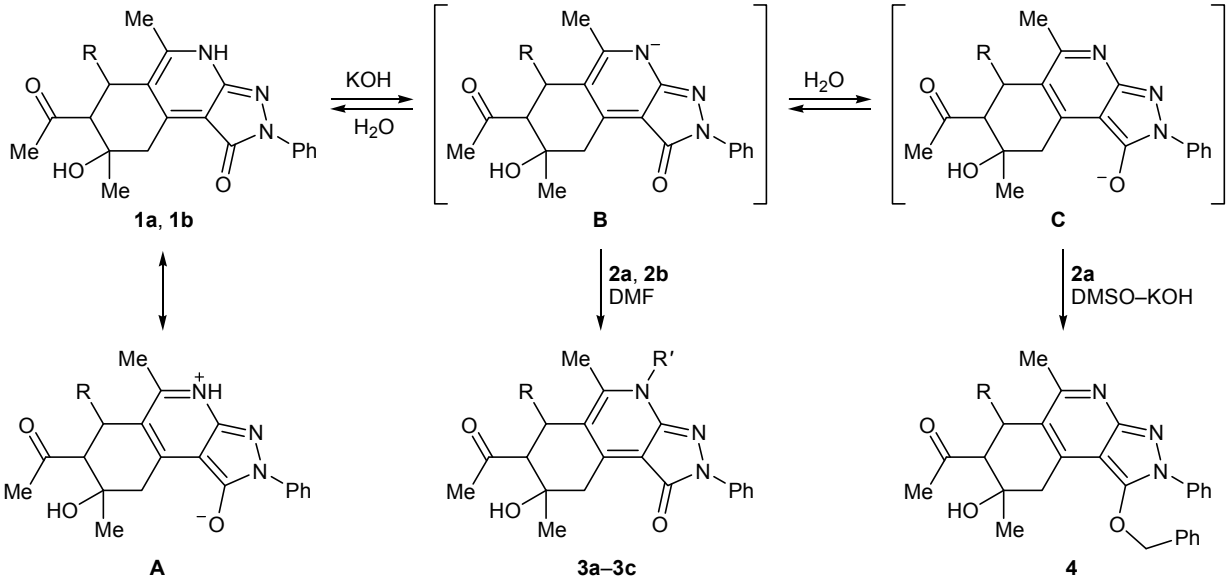
Substituted 1*H*-pyrazolo[3,4-*c*]isoquinolin-1-ones can be synthesized by condensation of 2-acetylcyclohexanones with 3-amino-1-phenyl-1*H*-pyrazol-5(4*H*)-one [1] or via nucleophilic vinylic substitution (S_NVin) in reactions of 1-[2-(morpholin-4-yl)cyclohexyl]alkanones with the same pyrazolone [2]. The alkylation of pyrazoloisoquinolines containing no functional substituents in the cyclohexane ring with alkyl halides in DMF in the presence of aqueous potassium hydroxide gave the corresponding N^3-alkyl derivatives [2]. No other examples of alkylation of this heterocyclic system have been reported.

We have found that variation of the reaction conditions makes it possible to obtain both N^4- and 1-*O*-alkyl-substituted pyrazolo[3,4-*c*]isoquinolines, i.e., the regioselectivity of the alkylation can be controlled. According to the X-ray diffraction data [1], molecules **1a** and **1b** in crystal are largely contributed by zwitterionic structure **A**. Compounds **1a** and **1b** in DMF in the presence of aqueous potassium hydroxide are likely to generate anion **B** which exists in tautomeric equilibrium with oxygen-centered anion **C**. The reaction of anion **B** with alkyl halides **2a** and **2b** yields *N*-alkylpyrazolo[3,4-*c*]isoquinolines **3a**–**3c**. When aqueous alkali was replaced by a superbase [3] (a solution of anhydrous potassium hydroxide in DMSO), other conditions being equal, the reaction direction changed toward the formation of 1-*O*-benzyl derivative **4**. The mechanism of the described reaction and its scope are now under study.



1, R = Ph (**a**), furan-2-yl (**b**); **2**, $PhCH_2Cl$ (**a**), MeI (**b**); **3**, R = Ph, R′ = $PhCH_2$ (**a**); R = furan-2-yl, R′ = $PhCH_2$ (**b**); R = furan-2-yl, R′ = Me (**c**).

4-Alkylpyrazolo[3,4-*c*]isoquinolin-1-ones 3a–3c (*general procedure*). Pyrazoloisoquinoline **1a** or **1b**, 2 mmol, was dissolved in 10 mL of DMF, 1.12 mL (2 mmol) of a 10% aqueous solution of potassium hydroxide and 2 mmol of alkyl halide **2a** or **2b** were added under stirring at 20°C, and the mixture was heated for 30 min at 50°C and left to stand for 2 days. The mixture was then diluted with an equal volume of water and left to stand for 24 h, and the precipitate was filtered off and washed with ethanol and hexane.

7-Acetyl-4-benzyl-8-hydroxy-5,8-dimethyl-2,6-diphenyl-2*H*-6,7,8,9-tetrahydropyrazolo[3,4-*c*]isoquinolin-1(4*H*)-one (3a). Yield 0.55 g (63%), white powder, mp 198°C (from AcOH). IR spectrum, ν, cm^{-1}: 3419 (OH); 1689, 1673 (C=O). ^1H NMR spectrum, δ, ppm: 1.24 s (3H, CH_3), 2.08 s (3H, CH_3), 2.10 s (3H, CH_3), 2.89 d (1H, 7-H, J = 10.0 Hz), 3.03 d and 3.46 d (1H each, 9-H, ^2J = 18.1 Hz), 4.53 d (2H, 6-H, OH, J = 9.4 Hz), 4.78 d and 5.15 d (1H each, NCH_2, ^2J = 14.9 Hz), 6.75 d (2H, H_{arom}, J = 7.2 Hz), 6.97 d (2H, H_{arom}, J = 7.1 Hz), 7.11 t (2H, H_{arom}, J = 7.2 Hz), 7.18 t (2H, H_{arom}, J = 6.9 Hz), 7.25 t (2H, H_{arom}, J = 7.2 Hz), 7.35 d (1H, H_{arom}, J = 7.1 Hz), 7.44 d (2H, H_{arom}, J = 7.6 Hz), 7.53 t (2H, H_{arom}, J = 7.4 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 517 (87) $[M]^+$, 516 (42) $[M - H]^+$, 499 (7) $[M - H_2O]^+$, 474 (8) $[M - CH_3C{=}O]^+$, 455 (28) $[M - H - CH_3C{=}O - H_2O]^+$, 425 (33) $[M - PhCH_2]^+$, 383 (10), 365 (42) $[M - CH_3C{=}O - H_2O - PhCH_2]^+$, 91 (84) $[C_7H_7]^+$, 77 (46) $[Ph]^+$, 44 (100) $[CH_3C{=}OH]^+$. Found, %: C 76.50; H 5.89; N 7.99. $C_{33}H_{31}N_3O_3$. Calculated, %: C 76.57; H 6.04; N 8.12.

7-Acetyl-4-benzyl-6-(furan-2-yl)-8-hydroxy-5,8-dimethyl-2-phenyl-2*H*-6,7,8,9-tetrahydropyrazolo-[3,4-*c*]isoquinolin-1(4*H*)-one (3b). Yield 0.35 g (58%), white powder, mp 160°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 3420 (OH); 1709, 1679 (C=O). ^1H NMR spectrum, δ, ppm: 1.22 s (3H, CH_3), 2.22 s (3H, CH_3), 2.78 s (3H, CH_3), 2.98–3.04 m (2H, 7-H, 9-H), 3.37 d (1H, 9-H, ^2J = 18.1 Hz), 4.66 d (1H, 6-H, J = 8.6 Hz), 4.71 br.s (1H, OH), 4.82 d and 5.15 d (1H each, NCH_2, ^2J = 15.0 Hz), 5.91 s (1H, 3′-H), 6.31 s (1H, 4′-H), 6.76 d (2H, H_{arom}, J = 7.7 Hz), 7.11 t (2H, H_{arom}, J = 7.4 Hz), 7.18 t (1H, H_{arom}, J = 7.3 Hz), 7.33 t (1H, H_{arom}, J = 7.3 Hz), 7.39–7.43 m (3H, H_{arom}, 5′-H), 7.52 t (2H, H_{arom}, J = 7.6 Hz). Mass spectrum: *m*/*z* 508 (I_{rel} 100%) $[M + H]^+$. Found, %: C 73.20; H 5.48; N 8.14. $C_{31}H_{29}N_3O_4$. Calculated, %: C 73.35; H 5.76; N 8.28.

7-Acetyl-6-(furan-2-yl)-8-hydroxy-4,5,8-trimethyl-2-phenyl-2*H*-6,7,8,9-tetrahydropyrazolo-[3,4-*c*]isoquinolin-1(4*H*)-one (3c). Yield 0.38 g (73%), red powder, mp 235°C (from AcOH). IR spectrum, ν, cm^{-1}: 3392 (OH), 1709 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 s (3H, CH_3), 2.17 s (3H, CH_3), 2.22 s (3H, CH_3), 3.07–3.22 m (5H, 7-H, 9-H, NCH_3), 3.54 d (1H, 9-H, ^2J = 17.9 Hz), 4.59 d (1H, 6-H, J = 8.0 Hz), 4.79 br.s (1H, OH), 5.96 s (1H, 3′-H), 6.30 s (1H, 4′-H), 7.15 t (1H, H_{arom}, J = 7.1 Hz), 7.41 t (3H, H_{arom}, J = 6.9 Hz), 7.95–8.02 m (2H, H_{arom}, 5′-H). Mass spectrum, *m*/*z* (I_{rel}, %): 361 (38), 360 (100), 359 (90), 276 (11), 180 (7), 84 (10); no molecular ion peak was observed. Found, %: C 69.48; H 5.70; N 9.65. $C_{25}H_{25}N_3O_4$. Calculated, %: C 69.59; H 5.84; N 9.74.

1-(1-Benzyloxy-8-hydroxy-5,8-dimethyl-2,6-diphenyl-2*H*-6,7,8,9-tetrahydropyrazolo[3,4-*c*]isoquinolin-7-yl)ethanone (4) was synthesized as described above for compounds **3a**–**3c** but using 10 mL of DMSO as solvent, 0.06 g (1 mmol) of potassium hydroxide, and 0.12 mL (1 mmol) of benzyl chloride (**2a**). Yield 0.4 g (77%), yellow powder, mp 160–162°C (from EtOH). IR spectrum, ν, cm^{-1}: 3422 (OH), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 1.42 s (3H, CH_3), 2.08 s (3H, CH_3), 2.32 s (3H, CH_3), 2.67–2.73 m (2H, 7-H, 9-H), 3.75 d (1H, 9-H, ^2J = 18.2 Hz), 4.72–4.86 m (2H, 6-H, OH), 5.11 d and 5.28 d (1H each, OCH_2, ^2J = 14.5 Hz), 6.72–7.48 m (15H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 19.48, 20.41, 21.22, 34.58, 44.02, 45.79, 65.72, 70.04, 95.63, 115.23, 116.41, 118.83, 119.55, 120.87, 125.80, 127.29 (4C), 127.54, 129.15, 129.30 (4C), 129.59, 135.15, 142.66, 144.60, 144.86, 145.91, 148.73, 209.57 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 519 (16) $[M + 2H]^+$, 474 (2) $[M - CH_3C{=}O]^+$, 457 (27) $[M - H - H_2O - CH_3C{=}O]^+$, 366 (21) $[M + H - H_2O - CH_3C{=}O - PhCH_2]^+$, 276 (27), 199 (8), 105 (17), 91 (100) $[C_7H_7]^+$, 79 (9), 77 (41) $[Ph]^+$, 65 (13), 44 (30) $[CH_3C{=}OH]^+$, 33 (37) $[H_2O + CH_3]^+$. Found, %: C 76.42; H 5.92; N 7.95. $C_{33}H_{31}N_3O_3$. Calculated, %: C 76.57; H 6.04; N 8.12.

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum One spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance instrument at 399.95 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The mass spectra were obtained on MKh-1321 (electron impact, 70e V; direct sample admission into the ion source; compounds **3a**, **3c**, and **4**) and Agilent 1100 LC/MSD SL instruments (CF_3COOH

matrix, electron impact; **3b**). The elemental analyses were obtained on a Perkin Elmer CHN analyzer. The melting points were determined on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3 : 5) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

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