Access to $N$-Alkylpyrazin-2-ones via C–O to C–N Rearrangement of Pyrazinyl Ethers

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Abstract The reaction of tosylated 2-alkoxypyrazines with potassium halides led to the unexpected formation of $N$-alkylated pyrazinones. Such rare example of substitutive C–O $\rightarrow$ C–N rearrangement on pyrazines was then scrutinised by using various nucleophiles to afford the respective products in moderate to good yields. This method provides a direct access to $N$-alkylated-$1H$-pyrazin-2-ones. The formation of the rearranged products is conveniently and reliably determined by characteristic NMR shifts of their heteroaromatic protons.

Key words pyrazinones, rearrangement, $S_N$ reaction, NMR spectroscopy, X-ray crystal structure analysis

$N$-Alkylated-$1H$-pyrazin-2-ones belong to a family of heterocycles that exhibit interesting and potentially useful pharmacological properties, including antiviral$^1$ or antitumor$^{2,3}$ activity. Typically, these compounds are prepared by direct N-alkylation (mostly N-methylation) of pyrazinones under basic conditions.$^2$ However, due to their ambident nucleophilic nature, this traditional method often suffers from competitive O-alkylation, generating undesired side products, and thus diminishing the yield of target compounds.$^{1,3}$ To circumvent such difficulties, activation/protection$^5$ of the respective substrates is necessary prior to the desired N-alkylation. However, this approach undesirably extends the synthetic pathway. Alternatively, 2-hydroxy-1,4-oxazin-3-ones can be transformed into $1H$-pyrazin-2-ones, but in low to moderate yields only.$^3$ Clearly, there is a need for more efficient and atom-economical methods to generate the title compounds, particularly when access to N-alkylated derivatives other than with a methyl substituent is required.

During our ongoing project dealing with the synthesis of galbazine analogues, we have attempted the preparation of iodide 2 via nucleophilic displacement of tosylate 1.

![Scheme 1](image-url)

While the MS spectrum ($m/z$ 293.0 [M + H]$^+$, 165.2 [M + H – I]$^+$) of the product would fit to either iodide 2 or 3, detailed HMBC and NOESY NMR analyses clearly suggested the exclusive formation of 3. Definitive proof of the structure of the isolated product being the pyrazinone 3 was obtained by single-crystal X-ray analysis (Figure 1, see the Supporting Information).

We reasoned that the unexpected formation of pyrazinone 3 can be explained as follows: thermally initiated $S_N$ displacement of the tosyl group with the proximal nitrogen in pyrazine 1, significantly aided by the Thorpe–Ingold effect of the gem-dimethyl group,$^6$ generates the intermediate...
salt 4. This is re-opened in situ at the electrophilic methylene group by the I– nucleophile, thus forming the final aromatic pyrazinone 3 (Scheme 2, path a). Alternatively, initial intermolecular tosylate displacement might generate iodide 2, which subsequently cyclises in situ to the intermediate salt 5, which is then analogously re-opened to the observed product 3 (Scheme 2, path b).

A literature search revealed that such C–O → C–N rearrangement on pyrazines is rare and, to our knowledge, there are only three examples7–9 for an analogous transformation.10 However, except for the benzopyrazine derived mesylate,8 these are restricted either to phenolic nucleophiles used via phosphine mediated Mitsunobu type rearrangement,7 or rely on transition-metal catalysis.9

Therefore, we decided to explore this useful reaction for the atom-economical synthesis of various pyrazinones and possibly gain an insight into the mechanistic scenario of the transformation.

The preparation of tosylate 1 started from the commercially available chloropyrazine 6, which was etherified11 in the first step to afford alcohol 7 along with the undesired (but readily chromatographically separable) bis-ether 8 as a minor side product. The structures of the two latter compounds were determined by single-crystal X-ray analysis (Figure 2 and Figure 3, and the Supporting Information). Alcohol 7 was subsequently activated12 to the tosylate 1 in good yield (Scheme 3).

With pure tosylate 1 in hand, we performed the screening of its C–O → C–N rearrangement with various nucleophiles by heating the substrate in anhydrous DMF (Scheme 4, Table 1).
Except for sodium cyanide, all nucleophilic systems used, including potassium halides, sodium azide, and potassium thiocyanate furnished the corresponding N-alkyl-pyrazin-2-ones \(3, 9-12\) in moderate to good yields after flash chromatographic purification (Table 1, entries 1–5). Even DMF used as both the solvent and nucleophile afforded the C–O → C–N rearranged product 13 after aqueous work-up of the reaction mixture (entry 6). On the other hand, the use of NaCN led to the formation of the corresponding O-alkylated nitrile 14, which was, however, isolated in low yield from a complex mixture (Scheme 4, b). This result suggests the direct S_N2 replacement of tosylate 1 with cyanide as the initial step (equivalent to path b in Scheme 2) with the formation of a strong C–C bond, and thus, with the latter having only a very poor leaving group (–CN), this with the formation of a strong C–C bond, and thus, with the nitrile as the initial step (equivalent to path b in Scheme 2).

All chemicals and reagents were purchased from commercial sources (Alfa Aesar, Sigma–Aldrich) and were used without further purification, unless otherwise noted. All solvents were distilled prior to use. Anhydrous solvents were prepared either by filtration through a column of activated alumina or by standing over activated 4Å molecular sieves and stored under argon atmosphere. ‘Hexanes’ refers to a mixture of C-6 alkanes (bp 60–80 °C). Yields refer to chromatographically and spectrophotometrically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on aluminium sheets pre-coated with silica gel 60 F254 (Merck) or aluminium oxide 60 F254 (neutral, Merck). Visualisation was performed using shortwave UV light followed by dipping TLC plates in either a basic solution of KMnO₄, an acidic solution of vanillin or an acidic solution of ceric ammonium nitrate followed by heating with a heat gun. Flash column chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm), NMR spectra were recorded in CDCl₃ with a Varian INOVA 300 (300 MHz for 1H, 75 MHz for 13C nuclei) or a Varian VNMRS 600 (600 MHz for 1H, 151 MHz for 13C nuclei) NMR spectrometer using residual non-deuterated solvent or tetramethylsilane as an internal reference [CHCl₃; \( \delta_N = 7.26 \) ppm, \( \delta_C = 77.00 \) ppm (central peak of the 1:1:1 triplet), TMS: \( \delta_N = \delta_C = 0.00 \) ppm]. Chemical shifts (δ) are quoted in ppm. Liquid chromatography–mass spectrometry (LC-MS) analyses were performed with an Agilent 1200 Series instrument equipped with a multimode MS detector using the MM ESI/APCI ionisation method (column Zorbax Eclipse XDB-18, 150 × 4.6 mm, particle size 5 μm, eluent water with 0.1% HCO₃⁻/CH₃CN, 70:30, flow 1.5 mL/min). High-resolution mass spectra (HRMS) were recorded with a Thermo Scientific Orbitrap Velos mass spectrometer with a heated electrospray ionisation (HESI) source in positive and/or negative mode. FTIR spectra were obtained with a Nicolet 5700 spectrophotometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory using the reflection technique (4000–400 cm⁻¹).

### 2,2-Dimethyl-3-(pyrazin-2-yloxy)propan-1-ol (7) and 2,2-Dimethyl-1,3-bis(pyrazin-2-yloxy)propane (8)

To a cooled (0 °C) solution of 2,2-dimethylpropan-1,3-diol (910 mg, 8.73 mmol) and 2-chloropyrazine (1000 mg, 0.78 mL, 8.73 mmol) in anhydrous DMF (87 mL, 0.1 M) was added NaH (385 mg, 60% dispersion in mineral oil, first washed with hexanes (4 × 10 mL) and dried in vacuo) in portions over 15 min under Ar. After stirring the resulting white suspension at r.t. for 24 h, water (70 mL) was added and the mixture was extracted with Et₂O (3 × 70 mL). The combined organic extracts were washed with brine (100 mL) dried over anhydrous Na₂SO₄, filtered and evaporated in vacuo. The crude product was purified by flash chromatography (58 g SiO₂, gradient elution: hexanes–EtOAc, 8:1 → 6:1 → 4:1 → 2:1 → 1:1) to afford alcohol 7 (1211 mg, 76%) and bis-ether 8 (159 mg, 14%) as colourless solids.

### Alcohol (7)

Mp 37–38 °C; \( R_f = 0.22 \) (EtOAc–hexanes, 1:2). IR (ATR): 3385, 3161, 2960, 1530, 1474, 1418, 1390, 1383, 1286, 1153, 1052, 1007, 986, 857, 609 cm⁻¹.

### Table 1 Screening of C–O to C–N Rearrangement of 1 (Scheme 4)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Reaction conditions</th>
<th>Product (FLC yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KI</td>
<td>0.5 M, 2.5 h</td>
<td>3 (58%), Nu = I</td>
</tr>
<tr>
<td>2</td>
<td>KBr</td>
<td>0.5 M, 5.5 h</td>
<td>9 (70%), Nu = Br</td>
</tr>
<tr>
<td>3</td>
<td>KCl</td>
<td>0.25 M, 6 h</td>
<td>10 (58%), Nu = Cl</td>
</tr>
<tr>
<td>4</td>
<td>KSCN</td>
<td>0.34 M, 5 h</td>
<td>11 (50%), Nu = SCN</td>
</tr>
<tr>
<td>5</td>
<td>NaN₂</td>
<td>0.5 M, 4.5 h</td>
<td>12 (65%), Nu = N₃</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>0.5 M, 4 h</td>
<td>13 (52%), Nu = OCHO</td>
</tr>
</tbody>
</table>

Regarding the NMR properties of N-alkyl-pyrazin-2-ones \(3, 9-13\), these exhibit a typical upfield shift (ca. 1 ppm) of two heteroaromatic CH-protons (δ = 7.3–7.0 ppm) in comparison to their respective pyrazinyl ethers \(1, 7, 8, 14\) (δ = 8.2–8.0 ppm). Thus, such a characteristic spectroscopic pattern can be conveniently used for the confident determination of C–O → C–N rearrangement.

In conclusion, we have shown that C–O → C–N substitutive rearrangement of readily accessible pyrazinyl ethers can provide a simple access to N-alkylated 1H-pyrazin-2-ones in moderate to good yields. Moreover, their formation is conveniently demonstrated by typical NMR shifts of the aromatic protons of the respective products.

[Diagram and Table 1 as mentioned in the original text]
1H NMR (300 MHz, CDCl3): δ = 8.23 (d, J = 1.3 Hz, 1 H, H-3‘), 8.10 (d, J = 2.8 Hz, 1 H, H-6‘), 8.02 (dd, J = 2.8, 1.3 Hz, 1 H, H-5‘), 4.16 (s, 2 H, H-3), 3.36 (s, 2 H, H-1), 2.84 (s, 1 H, OH, D2O excl.), 1.00 (s, 6 H, 2 × Me).

13C NMR (75 MHz, CDCl3): δ = 160.5 (Cq, C-2), 140.1 (CH, C-3‘), 136.5 (CH, C-6‘), 136.2 (CH, C-5‘), 71.6 (CH3, C-3), 67.9 (CH3, C-1), 36.7 (Cq, C-2), 21.5 (CH2, 2 × Me).

LCMS (APCI): m/z (%) = 183.2 (100) [M + H]+ \( t_r = 2.1 \text{ min} \).


Bis-ether (8)

Toluene-4-sulfonic Acid 2,2-Dimethyl-3-(pyrazin-2-yl)propyl Ester (1)

To a chilled (0 °C) solution of alcohol 7 (479 mg, 2.63 mmol) in anhydrous pyridine (5.3 mL, 0.5 M), tosyl chloride (551 mg, 2.89 mmol) was added in portions over 15 min under argon. After stirring at r.t. for 24 h, the mixture was extracted with toluene (3 × 12 mL) and volatiles were co-evaporated in vacuo (80 °C, 10 mbar). The crude product was adsorbed onto a small amount of silica gel and purified by flash chromatography (44 g, SiO2; gradient elution: hexanes–EtOAc, 4:1 → 2:1) to furnish tosylate 1 as a white solid (779 mg, 88%).

Mp 107–108 °C; Rf 0.43 (EtOAc–hexanes, 1:2).

IR (ATR): 3396, 3068, 2966, 1584, 1533, 1463, 1318, 1294, 1282, 1190, 1180, 1060, 1004, 843, 607 cm−1.

1H NMR (300 MHz, CDCl3): δ = 8.14 (d, J = 1.2 Hz, 1 H, H-3‘), 7.29 (d, J = 4.4 Hz, 1 H, H-6‘), 7.17 (dd, J = 4.4, 1.2 Hz, 1 H, H-5‘), 3.93 (s, 2 H, H-1), 3.17 (s, 2 H, H-3), 1.13 (s, 6 H, 2 × Me).

13C NMR (75 MHz, CDCl3): δ = 156.6 (Cq-C-2), 150.2 (CH, C-3‘), 129.1, 123.3 (2 × CH-C-5′−C-6′), 55.3 (CH3, C-1), 36.8 (CH3, C-2), 25.5 (CH2, 2 × Me), 20.0 (CH3, C-3).

LCMS (APCI): m/z (%) = 293.0 (100) [M + H]+ \( t_r = 1.8 \text{ min} \).


1-(3-Iodo-2,2-dimethylpropyl)-1H-pyrazine-2-one (9)

To a chilled (0 °C) solution of alcohol 10 (100 mg, 0.298 mmol), KBr (71 mg, 0.595 mmol), DMF (0.6 mL), 120 °C, 5.5 h, then H2O (10 mL) and Et2O (3 × 10 mL), brine (10 mL), flash chromatography (1.4 g SiO2; hexanes–EtOAc, 3:1), brownish solid 9 (51 mg, 76%).

Mp 47–48 °C; Rf 0.38 (EtOAc–hexanes, 1:2).

IR (ATR): 3086, 2964, 2939, 2872, 1655, 1591, 1570, 1498, 1450, 1270, 1252, 1184, 1121, 1094, 1038, 897, 866, 852, 802, 647, 626 cm−1.

1H NMR (300 MHz, CDCl3): δ = 8.17 (s, 1 H, H-3‘), 7.30 (d, J = 4.2 Hz, 1 H, H-6‘), 7.21 (d, J = 4.2 Hz, 1 H, H-5‘), 3.96 (s, 2 H, H-1), 3.31 (s, 2 H, H-3), 1.12 (s, 6 H, 2 × Me).

13C NMR (75 MHz, CDCl3): δ = 156.7 (Cq-C-2), 150.2 (CH, C-3‘), 129.2 (CH3-C-6′), 123.3 (CH-C-5′), 54.3 (CH3, C-1), 43.0 (CH3, C-3), 37.9 (Cq-C-2), 24.5 (CH3, 2 × Me).

LCMS (APCI): m/z (%) = 245.0 (100) [M+H]+ \( t_r = 2.1 \text{ min} \).


1-(3-Chloro-2,2-dimethylpropyl)-1H-pyrazine-2-one (10)

To a chilled (0 °C) solution of alcohol 10 (70 mg, 0.208 mmol), KCl (31 mg, 0.417 mmol), DMF (0.8 mL), 120 °C, 6 h, then H2O (10 mL) and Et2O (6 × 10 mL), brine (10 mL), flash chromatography (1 g SiO2; gradient elution: hexanes–EtOAc, 3:1→1:1), brownish solid 10 (24 mg, 58%).

Mp 76–77 °C; Rf 0.40 (EtOAc–hexanes, 1:2).

IR (ATR): 2986, 2873, 1655, 1587, 1492, 1471, 1452, 1367, 1245, 1189, 1156, 1104, 926, 897, 773, 744, 719, 627 cm−1.

1H NMR (300 MHz, CDCl3): δ = 8.16 (s, J = 1.1 Hz, 1 H, H-3‘), 7.29 (d, J = 4.4 Hz, 1 H, H-6‘), 7.17 (dd, J = 4.4, 1.1 Hz, 1 H, H-5‘), 3.94 (s, 2 H, H-1), 3.38 (s, 2 H, H-3), 1.07 (s, 6 H, 2 × Me).

13C NMR (75 MHz, CDCl3): δ = 156.7 (Cq-C-2), 150.2 (CH, C-3‘), 129.3 (CH, C-6), 123.4 (CH-C-5′), 53.7 (CH3, C-1), 52.4 (CH3, C-3), 38.5 (Cq-C-2), 23.8 (CH3, 2 × Me).

LCMS (APCI): m/z (%) = 201.2 (100) [M + H]+ \( t_r = 1.8 \text{ min} \).
1-(2,2-Dimethyl-3-thiocyanatopropyl)-1H-pyrazin-2-one (11)

Tosylate 1 (200 mg, 0.595 mmol), KSCN (116 mg, 1.19 mmol), DMF (0.9 mL), 120 °C, 5 h, then H₂O (60 mL) and EtO₂ (6 × 20 mL), brine (20 mL), flash chromatography (4 g SiO₂; gradient elution: hexanes–EtOAc, 3:1–1:1–0:1), orange solid 11 (68 mg, 50%). Mp 106–107 °C; Rf 0.24 (EtOAc–hexanes, 2:1).

IR (ATR): 2962, 2875, 1720, 1651, 1592, 1474, 1453, 1371, 1364, 1283, 1263, 1184, 1157, 1118, 1045, 920, 850, 813, 785, 774, 627 cm⁻¹.

LCMS (APCI): m/z (%) = 224.0 (100) [M + H]+ {tᵣ = 1.7 min}.

HRMS (ESI): m/z [M⁺].calcld for C₁₀H₁₄N₅O: 223.0772; found: 223.0772.

3,3-Dimethyl-4-(pyrazin-2-yl)butyronitrile (14)

Tosylate 1 (200 mg, 0.595 mmol), NaCN (58 mg, 1.19 mmol), DMF (0.6 mL), 120 °C, 4.5 h, then H₂O (70 mL) and EtO₂ (6 × 20 mL), brine (20 mL), flash chromatography (5 g SiO₂; gradient elution: hexanes–EtOAc, 4:1–3:1–2:1–1:1–0:1), pale-yellow oil 14 (24 mg, 21%). Rf 0.6 (EtOAc–hexanes, 1:1).

IR (ATR): 2965, 2245, 1727, 1694, 1537, 1471, 1427, 1417, 1396, 1319, 1306, 1287, 1062, 1006, 858 cm⁻¹.

LCMS (APCI): m/z (%) = 192.2 (100) [M + H]+ {tᵣ = 2.4 min}.


Crystallography

Data collection and cell refinement for 3, 7 and 8 were carried out with a Stoe StadiVAR diffractometer with Dectris PILATUS3R 300K detector at 100 K, using Ag-Kα radiation (λ = 0.65803 Å, microfocused source Incoatec μS 2.0 HB) or Cu-Kα radiation (λ = 1.54186 Å, microfocused source Xenocs Genix3D Cu HF) for measurement. The software SHELXT, SHELXL (version 2018/3), Olex2.refine and OLEX2 were used for single-crystal X-ray analysis.¹³

CCDC 1920210 (3), 1920211 (7) and 1920212 (3) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Crystal Data for 3

C₁₀H₁₀N₃O (M = 292.21 g/mol), triclinic, space group P-1 (no. 2), a = 6.3878(4) Å, b = 6.9198(6) Å, c = 17.1748(10) Å, α = 87.106(5)°, β = 83.579(5)°, γ = 88.942(5)°, V = 1047.34(11) Å³, Z = 4, T = 100 K, μ(AgKα) = 1.607 mm⁻¹, Dcalc = 1.853 g/cm³. The final R₁ = 0.0472 (I > 2σ(I)) and wR₂ was 0.0109 (all data). Data for 3 show non-merohedral twinning.

Crystal Data for 7

C₁₀H₁₀N₃O (M = 202.30 g/mol), orthorhombic, space group P2₁/c (no. 14), a = 12.0331(3) Å, b = 18.1659(8) Å, c = 9.8862(4) Å, β = 113.585(2)°, V = 1908.52(13) Å³, Z = 8, T = 100 K, μ(CuKα) = 0.716 mm⁻¹, Dcalc = 1.222 g/cm³. The final R₁ was 0.0460 (I > 2σ(I)) and wR₂ was 0.1291 (all data).

Crystal Data for 3

C₁₀H₁₅N₃O₂ (M = 260.30 g/mol), monoclinic, space group P2₁/c (no. 14), a = 10.0358(2) Å, b = 6.5456(2) Å, c = 20.2698(5) Å, V = 1331.53(6) Å³, Z = 4, T = 100 K, μ(CuKα) = 0.745 mm⁻¹, Dcalc = 1.298 g/cm³. The final R₁ was 0.0892 (I > 2σ(I)) and wR₂ was 0.1638 (all data).
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Supporting Information

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