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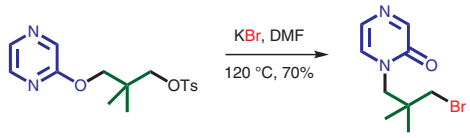
# Access to *N*-Alkylpyrazin-2-ones via C–O to C–N Rearrangement of Pyrazinyl Ethers

**Vladimír Dacho**[a]
**Dária Nitrayová**[a]
**Michal Šoral**[b]
**Andrea Machyňáková**[c]
**Ján Moncol**[d]
**Peter Szolcsányi***[a]

[a] Department of Organic Chemistry, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237 Bratislava, Slovakia
peter.szolcsanyi@stuba.sk
[b] Central Laboratories, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237 Bratislava, Slovakia
[c] Department of Analytical Chemistry, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237 Bratislava, Slovakia
[d] Department of Inorganic Chemistry, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237 Bratislava, Slovakia

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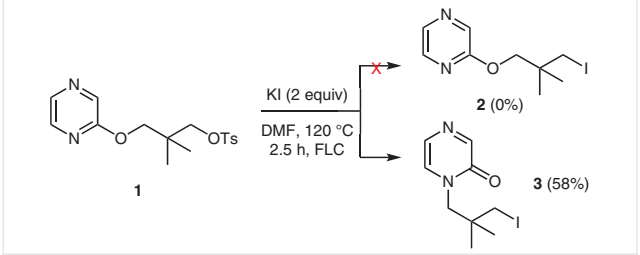
**Abstract** The reaction of tosylated 2-alkoxypyrazines with potassium halides led to the unexpected formation of N-alkylated pyrazinones. Such rare example of substitutive C–O → C–N rearrangement on pyrazines was then scrutinised by using various nucleophiles to afford the respective products in moderate to good yields. This method provides a direct access to N-alkylated-1*H*-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-1*H*-pyrazin-2-ones belong to a family of heterocycles that exhibit interesting and potentially useful pharmacological properties, including antiviral[1] or antitumor[2a,b] 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.[1,3,4] 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 sequence. Alternatively, 2-hydroxy-1,4-oxazin-3-ones can be transformed into 1*H*-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**. Rather surprisingly, instead of the expected product **2** we isolated only pyrazinone **3** in 58% yield after flash liquid chromatography of the crude reaction mixture (Scheme 1).




**Scheme 1** Unexpected formation of pyrazinone **3** instead of iodide **2** via nucleophilic displacement of tosylate **1**

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 $S_Ni$ 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

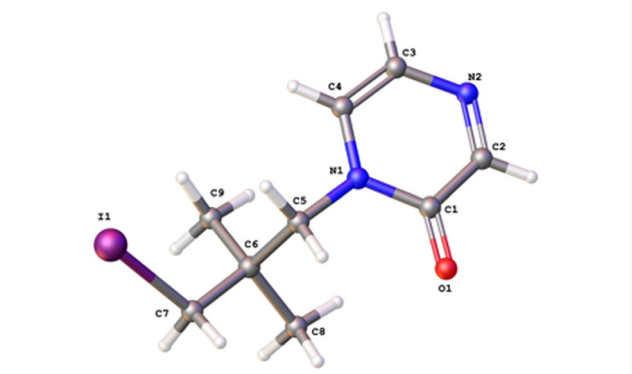
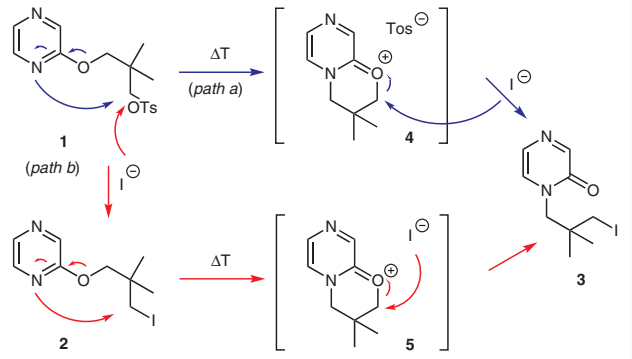



**Figure 1** Single-crystal structure of pyrazinone **3** obtained by X-ray analysis

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).

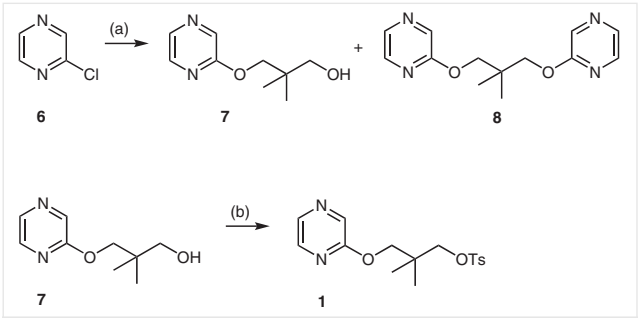



**Scheme 2** Possible scenarios for the formation of pyrazinone **3**

A literature search revealed that such C–O → C–N rearrangement on pyrazines is rare and, to our knowledge, there are only three examples[7–9] 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 etherified[11] 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 activated[12] to the tosylate **1** in good yield (Scheme 3).




**Scheme 3** *Reagents and conditions*: (a) 2,2-dimethyl-propan-1,3-diol, NaH (1.1 equiv), DMF (0.1 M), r.t., 24 h, FLC, **7** (76%) + **8** (14%); (b) TsCl (1.1 equiv), pyridine (0.5 M), r.t., 24 h, FLC, **1** (88%).

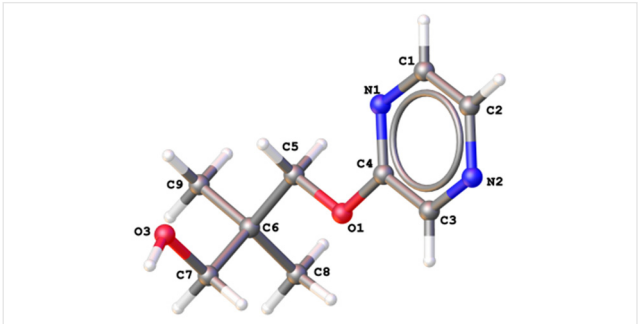



**Figure 2** Single-crystal structure of alcohol **7** obtained by X-ray analysis

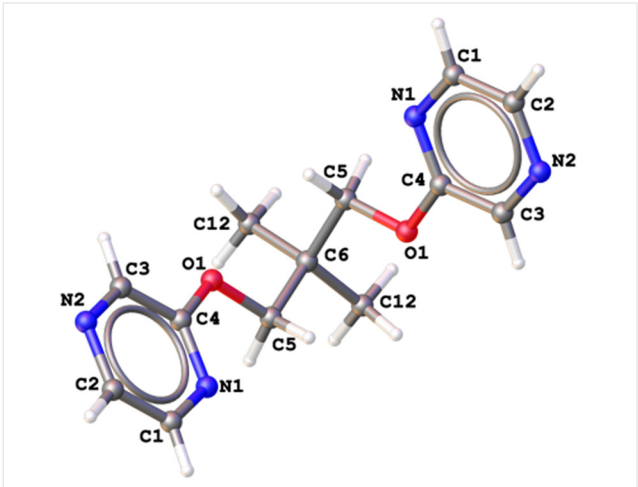
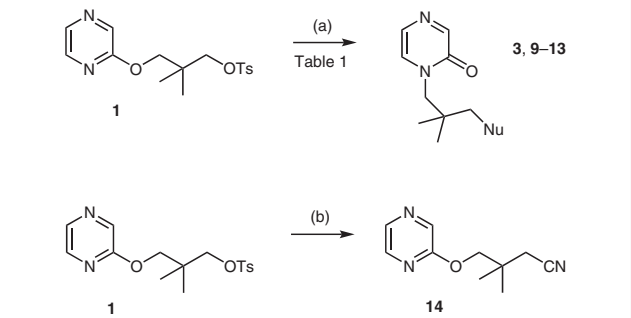



**Figure 3** Single-crystal structure of bis-ether **8** obtained by X-ray analysis

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).




**Scheme 4** *Reagents and conditions*: (a) nucleophile (2 equiv), anhydrous DMF (0.25–0.5 M), 120 °C, 2.5–6 h, FLC, 50–70%, see Table 1; (b) NaCN (2 equiv), DMF (0.43 M), 120 °C, 4.5 h, FLC, **14** (21%).

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 $S_N2$ displacement 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 would prevent any further rearrangement of such product generated in situ.

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

| Entry | Nucleophile | Reaction conditions | Product (FLC yield) |
|---|---|---|---|
| 1 | KI | 0.5 M, 2.5 h | **3** (58%), Nu = I |
| 2 | KBr | 0.5 M, 5.5 h | **9** (70%), Nu = Br |
| 3 | KCl | 0.25 M, 6 h | **10** (58%), Nu = Cl |
| 4 | KSCN | 0.34 M, 5 h | **11** (50%), Nu = SCN |
| 5 | $NaN_3$ | 0.5 M, 4.5 h | **12** (65%), Nu = $N_3$ |
| 6 | DMF | 0.5 M, 4 h | **13** (52%), Nu = OCHO |

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 1*H*-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.

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 spectroscopically ($^1$H 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 $F_{254}$ (Merck) or aluminium oxide 60 $F_{254}$ (neutral, Merck). Visualisation was performed using shortwave UV light followed by dipping TLC plates in either a basic solution of $KMnO_4$, 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 $CDCl_3$ with a Varian INOVA 300 (300 MHz for $^1$H, 75 MHz for $^{13}$C nuclei) or a Varian VNMRS 600 (600 MHz for $^1$H, 151 MHz for $^{13}$C nuclei) NMR spectrometer using residual non-deuterated solvent or tetramethylsilane as an internal reference [$CHCl_3$: $\delta_H$ = 7.26 ppm, $\delta_C$ = 77.00 ppm (central peak of the 1:1:1 triplet), TMS: $\delta_H = \delta_C$ = 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% $HCO_2H$ /$CH_3CN$, 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 reflectance 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 $Et_2O$ (3 × 70 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography (58 g $SiO_2$, 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$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): 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, $D_2O$ exch), 1.00 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.5 ($C_q$, C-2′), 140.1 (CH, C-3′), 136.5 (CH, C-6′), 136.2 (CH, C-5′), 71.6 ($CH_2$, C-3), 67.9 ($CH_2$, C-1), 36.7 ($C_q$, C-2), 21.5 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 183.2 (100) $[M + H]^+$ {$t_R$ = 2.1 min}.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_9H_{14}N_2O_2$: 182.1050; found: 182.1030.

**Bis-ether (8)**

Mp 52–53 °C; $R_f$ 0.43 (EtOAc–hexanes, 1:2).

IR (ATR): 3396, 3068, 2966, 1584, 1533, 1463, 1318, 1294, 1282, 1196, 1180, 1060, 1004, 843, 607 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 1.3 Hz, 2 H, 2 × H-3′), 8.09 (d, *J* = 2.8 Hz, 2 H, 2 × H-6′), 8.04 (dd, *J* = 2.8, 1.3 Hz, 2 H, 2 × H-5′), 4.23 (s, 4 H, H-1, H-3), 1.17 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.4 ($C_q$, 2 × C-2′), 140.4 (CH, 2 × C-3′), 136.5 (CH, 2 × C-6′), 136.0 (CH, 2 × C-5′), 71.1 ($CH_2$, C-1, C-3), 35.3 ($C_q$, C-2), 22.0 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 261.2 (100) $[M + H]^+$ {$t_R$ = 3.4 min}.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}N_4O_2$: 260.1268; found: 260.1255.

**Toluene-4-sulfonic Acid 2,2-Dimethyl-3-(pyrazin-2-yloxy)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, $SiO_2$; gradient elution: hexanes–EtOAc, 4:1→3:1→2:1→1:2) to furnish tosylate **1** as a white solid (779 mg, 88%).

Mp 107–108 °C; $R_f$ 0.45 (EtOAc–hexanes, 1:2).

IR (ATR): 3030, 2960, 2875, 1601, 1585, 1531, 1471, 1415, 1354, 1313, 1287, 1176, 1064, 1028, 965, 935, 875, 841, 818, 786, 665 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.8 Hz, 1 H, H-3′), 8.04 (dd, *J* = 2.8, 1.4 Hz, 1 H, H-5′), 7.99 (d, *J* = 1.4 Hz, 1 H, H-6′), 7.71 (d, *J* = 8.4 Hz, 2 H, $CH_o$-Ph), 7.21 (d, *J* = 8.6 Hz, 2 H, $CH_m$-Ph), 3.99 (s, 2 H, H-3), 3.91 (s, 2 H, H-1), 2.38 (s, 3 H, Ph-Me), 1.03 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 159.9 ($C_q$, C-2′), 144.7 ($C_q$-Tol), 140.4 (CH, C-3′), 136.5 (CH, C-5′), 135.7 (CH, C-6′), 132.6 ($C_q$-Tol), 129.6 (CH, 2 × $CH_o$-Ph), 127.8 (CH, 2 × $CH_m$-Ph), 74.3 ($CH_2$, C-3), 69.9 ($CH_2$, C-1), 35.2 ($C_q$, C-2), 21.6 ($CH_3$, Me-Ph), 21.5 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 337.0 (100) $[M + H]^+$ {$t_R$ = 3.1 min}.

HRMS (ESI): *m*/*z* $[M - Tos + H]^+$ calcd for $C_9H_{14}N_2O_2$: 182.1050; found: 182.1049.

**Reaction of Tosylate 1 with Nucleophiles; General Procedure**

To a solution of **1** in anhydrous DMF (0.25–0.5 M) the corresponding nucleophile (2 molar equiv) was added and the mixture was stirred in a glass pressure flask with Teflon screw-cap under argon at the specified temperature. After stirring for the specified time, water was added, and the mixture was repeatedly extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel.

**1-(3-Iodo-2,2-dimethylpropyl)-1*H*-pyrazin-2-one (3)**

Tosylate **1** (500 mg, 1.49 mmol), KI (494 mg, 2.97 mmol), DMF (3.3 mL), 120 °C, 2.5 h, then $H_2O$ (10 mL) and $Et_2O$ (8 × 10 mL), brine (40 mL), flash chromatography (11 g $SiO_2$; hexanes–EtOAc, 2:1), brownish solid **3** (251 mg, 58%).

Mp 55–57 °C; $R_f$ 0.40 (EtOAc–hexanes, 1:2).

IR (ATR): 2960, 2875, 1651, 1585, 1531, 1477, 1416, 1394, 1356, 1287, 1177, 1100, 1064, 1028, 966, 841, 818, 786, 666 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.15 (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).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 156.6 ($C_q$, C-2′), 150.2 (CH, C-3′), 129.1, 123.3 (2 × CH, C-5′↔C-6′), 55.3 ($CH_2$, C-1), 36.8 ($C_q$, C-2), 25.5 ($CH_3$, 2 × Me), 20.0 ($CH_3$, C-3).

LCMS (APCI): *m*/*z* (%) = 293.0 (100) $[M + H]^+$ {$t_R$ = 1.8 min}.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_9H_{13}IN_2O$: 292.0067; found: 292.0064.

**1-(3-Bromo-2,2-dimethylpropyl)-1*H*-pyrazin-2-one (9)**

Tosylate **1** (100 mg, 0.298 mmol), KBr (71 mg, 0.595 mmol), DMF (0.6 mL), 120 °C, 5.5 h, then $H_2O$ (10 mL) and $Et_2O$ (3 × 10 mL), brine (10 mL), flash chromatography (1.4 g $SiO_2$; hexanes–EtOAc, 3:1), brownish solid **9** (51 mg, 70%).

Mp 47–48 °C; $R_f$ 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 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): 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).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 156.7 ($C_q$, C-2′), 150.2 (CH, C-3′), 129.2 (CH, C-6′), 123.4 (CH, C-5′), 54.3 ($CH_2$, C-1), 43.0 ($CH_2$, C-3), 37.9 ($C_q$, C-2), 24.5 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 245.0 (100) $[M]^+$ {$t_R$ = 2.1 min}.

HRMS (ESI): *m*/*z* $[M - Br + H]^+$ calcd for $C_9H_{14}N_2O$: 166.1101; found: 166.1085.

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

Tosylate **1** (70 mg, 0.208 mmol), KCl (31 mg, 0.417 mmol), DMF (0.8 mL), 120 °C, 6 h, then $H_2O$ (10 mL) and $Et_2O$ (6 × 10 mL), brine (10 mL), flash chromatography (1 g $SiO_2$; gradient elution: hexanes–EtOAc, 3:1→1:1), brownish solid **10** (24 mg, 58%).

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

IR (ATR): 2968, 2873, 1656, 1587, 1492, 1471, 1452, 1367, 1342, 1267, 1189, 1156, 1104, 926, 897, 820, 773, 744, 719, 627 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *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).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 156.7 ($C_q$, C-2′), 150.2 (CH, C-3′), 129.3 (CH, C-6′), 123.4 (CH, C-5′), 53.7 ($CH_2$, C-1), 52.4 ($CH_2$, C-3), 38.5 ($C_q$, C-2), 23.8 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 201.2 (100) $[M + H]^+$ {$t_R$ = 1.8 min}.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_9H_{13}ClN_2O$: 200.0711; found: 200.0709.

### 1-(2,2-Dimethyl-3-thiocyanatopropyl)-1*H*-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 $H_2O$ (60 mL) and $Et_2O$ (6 × 20 mL), brine (20 mL), flash chromatography (4 g $SiO_2$; gradient elution: hexanes–EtOAc, 3:1→1:1→0:1), orange solid **11** (68 mg, 50%).

Mp 106–107 °C; $R_f$ 0.24 (EtOAc–hexanes, 2:1).

IR (ATR): 3068, 2972, 2935, 2873, 2184, 2148, 2098, 1649, 1588, 1496, 1471, 1431, 1418, 1388, 1364, 1283, 1263, 1184, 1157, 1118, 1045, 920, 850, 813, 785, 774, 627 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 1.1 Hz, 1 H, H-3′), 7.33 (d, *J* = 4.4 Hz, 1 H, H-6′), 7.01 (dd, *J* = 4.4, 1.1 Hz, 1 H, H-5′), 3.87 (s, 2 H, H-1), 2.94 (s, 2 H, H-3), 1.19 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 156.8 ($C_q$, C-2′), 150.1 (CH, C-3′), 129.6 (CH, C-6′), 123.7 (CH, C-5′), 114.5 ($C_q$, SCN), 56.6 ($CH_2$, C-1), 44.9 ($CH_2$, C-3), 38.5 ($C_q$, C-2), 24.8 ($CH_3$, 2 × Me).

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

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{13}N_3OS$: 223.0774; found: 223.0772.

### 1-(3-Azido-2,2-dimethylpropyl)-1*H*-pyrazin-2-one (12)

Tosylate **1** (200 mg, 0.595 mmol), $NaN_3$ (77 mg, 1.19 mmol), DMF (1.2 mL), 120 °C, 4.5 h, then $H_2O$ (40 mL) and $Et_2O$ (6 × 20 mL), brine (20 mL), flash chromatography (4 g $SiO_2$; hexanes–EtOAc, 3:1), orange solid (80 mg, 65%).

Mp 46–47 °C; $R_f$ 0.23 (EtOAc–hexanes, 1:1).

IR (ATR): 3089, 2968, 2957, 2095, 1655, 1585, 1578, 1489, 1467, 1369, 1313, 1269, 1205, 1149, 1113, 1007, 920, 891, 814, 650, 627 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, H-3′), 7.29 (d, *J* = 4.3 Hz, 1 H, H-6′), 7.07 (d, *J* = 4.3 Hz, 1 H, H-5′), 3.84 (s, 2 H, H-1), 3.20 (s, 2 H, H-3), 1.02 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 156.7 ($C_q$, C-2′), 150.0 (CH, C-3′), 129.7 (CH, C-6′), 123.2 (CH, C-5′), 59.5, 54.6 (2 × $CH_2$, C-1 ↔ C-3), 38.2 ($C_q$, C-2), 23.6 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 208.2 (100) [M + H]$^+$ {$t_R$ = 1.8 min}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}N_5O$: 208.1119; found: 208.1194.

### Formic Acid 2,2-dimethyl-3-(2-oxo-2*H*-pyrazin-1-yl)propyl Ester (13)

Tosylate **1** (90 mg, 0.208 mmol), DMF (1 mL), 120 °C, 4 h → 160 °C, 30 min, then $H_2O$ (20 mL) and $Et_2O$ (6 × 10 mL), DCM (3 × 10 mL), brine (10 mL), flash chromatography (1.5 g $SiO_2$; gradient elution: hexanes–EtOAc, 4:1→1:1), pale-yellow solid **13** (29 mg, 52%).

Mp 54–55 °C; $R_f$ 0.12 (EtOAc–hexanes, 1:1).

IR (ATR): 2962, 2875, 1720, 1651, 1592, 1474, 1453, 1371, 1271, 1151, 1114, 1056, 915, 801, 729 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 1.2 Hz, 1 H, H-3′), 8.12 (t, *J* = 0.9 Hz, 1 H, CHO), 7.27 (d, *J* = 4.4 Hz, 1 H, H-6′), 7.01 (dd, *J* = 4.4, 1.2 Hz, 1 H, H-5′), 3.97 (d, *J* = 0.9 Hz, 2 H, H-1), 3.89 (s, 2 H, H-3), 1.04 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.5 (CH, CHO), 156.7 ($C_q$, C-2′), 150.2 (CH, C-3′), 129.5, 123.2 (2 x CH, C-5′ ↔ C-6′), 69.0 ($C_q$, C-2), 54.6 ($CH_2$, C-3), 37.0 ($CH_2$, C-1), 22.9 ($CH_3$, 2 × Me).

LCMS (APCI): *m*/*z* (%) = 211.0 (100) [M + H]$^+$ {$t_R$ = 1.4 min}.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{14}N_2O_3$: 210.0999; found: 210.0991.

### 3,3-Dimethyl-4-(pyrazin-2-yloxy)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 $H_2O$ (70 mL) and $Et_2O$ (6 × 20 mL), brine (20 mL), flash chromatography (5 g $SiO_2$; gradient elution: hexanes–EtOAc, 4:1→3:1→2:1→1:1→0:1), pale-yellow oil **14** (24 mg, 21%).

$R_f$ 0.6 (EtOAc–hexanes, 1:1).

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

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 1.2 Hz, 1 H, H-3′), 8.16 (d, *J* = 2.8 Hz, 1 H, H-6′), 8.08 (dd, *J* = 2.8, 1.2 Hz, 1 H, H-5′), 4.15 (s, 2 H, H-4), 2.48 (s, 2 H, H-2), 1.22 (s, 6 H, 2 × Me).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 159.9 ($C_q$, C-2′), 140.5 (CH, C-3′), 137.0, 135.8 (2 × CH, C-5′↔ C-6′), 117.8 ($C_q$, C-1), 72.5 ($CH_2$, C-4), 34.2 ($C_q$, C-3), 27.6 ($CH_2$, C-2), 24.2 ($CH_3$, 2 × Me).

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

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{13}N_3O$: 191.1053; found: 191.1050.

### Crystallography

Data collection and cell refinement for **3**, **7** and **8** were carried out with a Stoe StadiVari diffractometer with Dectris PILATUS3R 300K detector at 100 K, using Ag-Kα radiation (λ = 0.56083 Å, microfocused source Incoatec IμS 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

$C_9H_{13}IN_2O$ (*M* = 292.11 g/mol), triclinic, space group *P*–1 (no. 2), *a* = 6.3878(4) Å, *b* = 9.6198(6) Å, *c* = 17.1748(10) Å, *α* = 87.106(5)°, *β* = 83.579(5)°, *γ* = 88.942(5)°, *V* = 1047.34(11) Å$^3$, *Z* = 4, *T* = 100 K, *μ*(AgKα) = 1.607 mm$^{-1}$, $D_{calc}$ = 1.853 g/cm$^3$. The final $R_1$ was 0.0472 ($I > 2\sigma(I)$) and w*R*2 was 0.1009 (all data). Data for **3** show non-merohedral twinning.

### Crystal Data for 7

$C_9H_{14}N_2O_2$ (*M* = 192.22 g/mol), monoclinic, space group $P2_1/c$ (no. 14), *a* = 12.0331(3) Å, *b* = 18.1659(8) Å, *c* = 9.8862(4) Å, *β* = 113.585(2)°, *V* = 1980.52(13) Å$^3$, *Z* = 8, *T* = 100 K, *μ*(CuKα) = 0.716 mm$^{-1}$, $D_{calc}$ = 1.222 g/cm$^3$. The final $R_1$ was 0.0460 ($I > 2\sigma(I)$) and w*R*2 was 0.1291 (all data).

### Crystal Data for 3

$C_{13}H_{16}N_4O_2$ (*M* = 260.30 g/mol), orthorhombic, space group *P*bcn (no. 60), *a* = 10.0358(2) Å, *b* = 6.5456(2) Å, *c* = 20.2698(5) Å, *V* = 1331.53(6) Å$^3$, *Z* = 4, *T* = 100 K, *μ*(CuKα) = 0.745 mm$^{-1}$, $D_{calc}$ = 1.298 g/cm$^3$. The final $R_1$ was 0.0892 ($I > 2\sigma(I)$) and w*R*2 was 0.1638 (all data).

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## Supporting Information

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