# Synthesis of 4*H*-Pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones and Imidazo[1,2-*a*]pyrazin-8(7*H*)-ones

Piotr Raubo,*[a,b] Neal Ladwa[a,c]

[a] AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK
E-mail: piotr.raubo@astrazeneca.com

[b] AstraZeneca R&D, Alderley Park, Macclesfield, SK10 4TG, UK

[c] Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK

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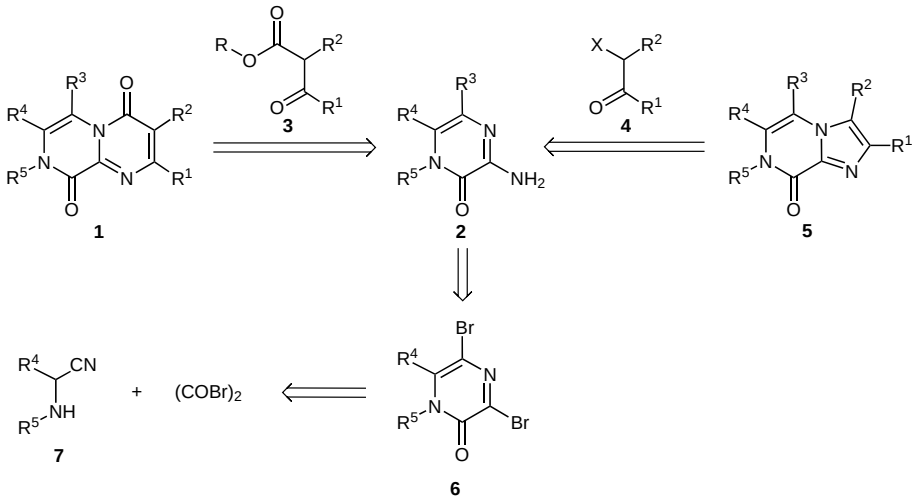
**Abstract:** A facile method of synthesis of 4*H*-pyrazino[1,2-*a*]-pyrimidine-4,9(8*H*)-diones and imidazo[1,2-*a*]pyrazin-8(7*H*)-ones from the corresponding 3-amino-2(1*H*)-pyrazinones is described.

**Key words:** heterocyclic compounds, bicyclic compounds, Conrad–Limpach condensation, parallel synthesis

Small aromatic heterocyclic ring systems play a pivotal role in the development of new drug candidates. To date, from the chemical space of 23,895 unique small hetero-aromatic rings only about 7% have been synthesised.[1] As part of one of our ongoing medicinal chemistry programmes we were interested in examining bicyclic heterocyclic ring systems such as **1** (Scheme 1). To our surprise a literature search revealed only one patent mentioning preparation of a single compound having such a heterocyclic ring system.[2] To support our medicinal chemistry project, we were interested in a facile synthesis of diverse analogues of **1**. In this paper, we would like to report results of our work on the development of the synthesis of 4*H*-pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-dione (**1**) and imidazo[1,2-*a*]pyrazin-8(7*H*)-one (**5**) ring systems.

Conceptually, **1** can be disconnected into two fragments, a 3-amino-2(1*H*)-pyrazinone **2** and a β-keto ester **3** in a retro Conrad–Limpach condensation (Scheme 1).[3] We postulated that the 3-amino-2(1*H*)-pyrazinone **2** might be accessible by the selective manipulation of 3,5-dibromo-2(1*H*)-pyrazinone **6** capitalising on differences in reactivity of both halogen atoms in the 3,5-dibromopyrazinone ring.[4] In turn, **6** should be easily synthesised in one step from the α-aminonitrile **7**, a product of the three-component Strecker reaction between the corresponding amine, aldehyde and hydrogen cyanide. This short sequence would allow a straightforward diversification at the 1- and 6-positions of the pyrazinone ring (Scheme 1).

As a starting material for our model studies we chose commercially available substituted α-aminonitriles **8a–c** (**8a**: $R^4$ = H; **8b**: $R^4$ = Ph; **8c**: $R^4$ = *i*-Pr) which, on treatment with an excess of oxalyl bromide in dichloromethane in the presence of a catalytic amount of DMF, provided the corresponding 3,5-dibromo-2(1*H*)-pyrazinones **9a–c** in 47–53% yield (Scheme 2). Regioselective nucleophilic substitution of the imidoyl bromine at the 3-position of the pyrazinone ring in **9a–c** using a 35% aqueous solution of ammonia in 1,4-dioxane gave the expected




**Scheme 1** Diversification of the pyrazinone ring; since two different heterocyclic ring systems are discussed here, R group numbering has been set to allow straightforward reading and do not reflect IUPAC numbering of the corresponding heterocycle

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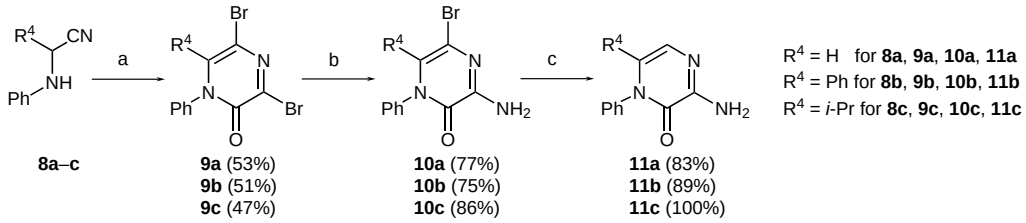
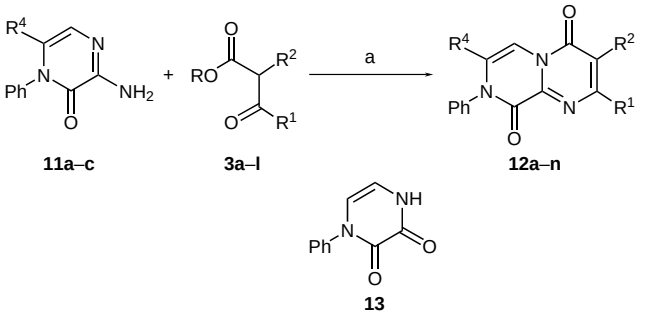



**Scheme 2** *Reagents and conditions*: (a) $(COBr)_2$, $CH_2Cl_2$, cat. DMF (47–53%); (b) $NH_3$, 1,4-dioxane–$H_2O$, r.t. (75–86%); (c) $HCOONH_4$, Pd/C, *i*-$Pr_2NEt$, EtOH, reflux, (83–100%).

3-amino-5-bromo-2(1*H*)-pyrazinones **10a–c** in good yields (75–86%). Subsequent hydrogenation of the vinylic bromine at the 5-position under hydrogen transfer conditions using ammonium formate in the presence of a catalytic amount of palladium on charcoal smoothly afforded the required 3-amino-2(1*H*)-pyrazinone derivatives **11a–c** in excellent yields (83–100%).

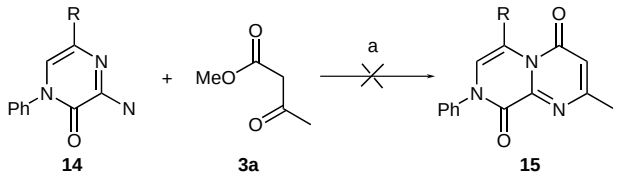
The Conrad–Limpach condensation of β-keto esters and various amino heterocycles is a well-established reaction.[3] The standard procedure for this transformation involves heating a β-keto ester with a corresponding amino heterocycle in acidic medium (e.g. acetic acid or polyphosphoric acid).[5] When we subjected 3-amino-2(1*H*)-pyrazinone **11a** to reaction with methyl 3-oxopentanoate (**3a**) in glacial acetic acid we were pleased to observe formation of the expected bicyclic product **12a** with good conversion (Scheme 3). However, when the more sterically demanding methyl 4-methyl-3-oxopentanoate (**3b**) was used, the reaction was less effective leading to a significant proportion of 1-phenylpyrazine-2,3(1*H*,4*H*)-dione (**13**) which results from hydrolysis of the starting pyrazinone **11a**. We assumed that this side reaction is proceeding via initial N-acetylation of the amino group in **11a** making the 3-position more susceptible towards nucleophilic substitution. To avoid this side reaction, we optimised reaction conditions by screening a range of acidic promoters [acetic acid, methanesulfonic acid, Amberlyst 15 resin, Montmorillonite K 10, zinc(II) bromide, trimethylsilyl chloride, pyridinium *p*-toluenosulfonate, polyphosphoric acid, scandium(III) trifluoromethanesulfonate] and solvents (acetic acid, acetonitrile, DMF, ethanol, 1,4-dioxane, DMSO, 1,2-dichlorobenzene, *N*-methylpyrrolidine, 1,2-dichloroethane] in addition to varying reaction temperature and stoichiometry of reagents. As a result of this optimisation, we found that heating the 3-amino-2(1*H*)-pyrazinone **11a** with ten equivalents of **3b** in anhydrous acetonitrile in the presence of one equivalent of methanesulfonic acid under microwave irradiation at 180 °C afforded the required 4*H*-pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-dione **12b** in 63% isolated yield (Scheme 3, Table 1, entry 2).[6] When a catalytic amount of methanesulfonic acid was used the reaction did not proceed to completion.

To investigate the scope of this cyclisation, a range of β-keto esters **3a–l** was employed using these conditions providing the corresponding 4*H*-pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones **12a–n** in moderate to excellent isolated yields (Table 1). In general, the reaction was completed after 30 minutes. However, for more sterically hindered β-keto esters (**3b**, **3g**) prolonged reaction times were required to achieve good conversions. For pyrazinones bearing a substituent at the 6-position (**11b**, **11c**) better cyclisation yields were achieved in comparison to unsubstitued analogue **11a** (e.g. 83% for the product **12l** versus 63% for the product **12b**). For the less accessible β-keto ester **3l**, 5.4 equivalents of β-keto ester were employed, giving a significantly lower isolated yield of the corresponding product **12n** (25%). Heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple bond coherence (HMBC) and NOE NMR experiments were used to confirm the proposed structures of **12a** and **12b**.




**Scheme 3** *Reagents and conditions*: (a) β-keto ester **3a–l** (10 equiv), MsOH (1 equiv), MeCN, MW, 180 °C, (25–100%).

Unfortunately, our attempts to perform the condensation of 5-substituted 3-amino-1-phenylpyrazin-2(1*H*)-ones **14** ($R^3$ = Br, Ph)[7] with **3a** under these conditions failed to provide the requisite cyclisation product **15** (R = Br, Ph; Scheme 4). This might be due to reduced nucleophilicity and/or increased steric hindrance of 5-substituted 3-amino-1-phenylpyrazin-2(1*H*)-ones.




**Scheme 4** *Reagents and conditions*: (a) **14** (R = Br, Ph), β-keto ester **3a** (10 equiv), MsOH (1 equiv), MeCN, MW, 180 °C.



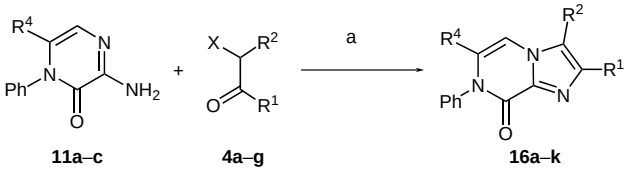
 

**Table 1** Synthesis of 4*H*-Pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones **12a**–**n** (Scheme 3)

| β-Keto ester | R | $R^1$ | $R^2$ | **11** | $R^4$ | Product | Reaction time (min) | Yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| **3a** | Me | Me | H | **11a** | H | **12a** | 30 | 89 |
| **3b** | Me | *i*-Pr | H | **11a** | H | **12b** | 90 | 63 |
| **3c** | Me | $CF_3$ | H | **11a** | H | **12c** | 30 | 61 |
| **3d** | Me | Ph | H | **11a** | H | **12d** | 30 | 64 |
| **3e** | Me | Me | Ph | **11a** | H | **12e** | 30 | 60 |
| **3f** | Me | *c*-Pr | H | **11a** | H | **12f** | 30 | 47 |
| **3g** | Me | *t*-Bu | H | **11a** | H | **12g** | 90 | 48 |
| **3h** | Me | 2-furyl | H | **11a** | H | **12h** | 30 | 46 |
| **3i** | Me | Me | Bn | **11a** | H | **12i** | 30 | 51 |
| **3j** | Et | Me | H | **11b** | Ph | **12j** | 30 | 93 |
| **3j** | Et | Me | H | **11c** | *i*-Pr | **12k** | 30 | 100 |
| **3b** | Me | *i*-Pr | H | **11c** | *i*-Pr | **12l** | 30 | 83 |
| **3k** | Me | $-(CH_2)_3-$ | | **11a** | H | **12m** | 30 | 58 |
| **3l**[b] | Me | $-CH_2SCH_2-$ | | **11a** | H | **12n** | 45 | 25 |

[a] Isolated yield.
[b] Amount of **3l** used was 5.4 equiv.

In parallel, we also examined the reaction of **11a** with α-halo ketones **4a**–**g** (Scheme 5, Table 2). We found that treatment of **11a** with 1-bromo-3,3-dimethylbutanone (**4a**) in acetonitrile under microwave irradiation at 170 °C in the presence of triethylamine provided the expected imidazo[1,2-*a*]pyrazin-8(7*H*)-one **16a** in 63% yield (Table 2, entry 1).




**11a–c** **4a–g** **16a–k**

**Scheme 5** *Reagents and conditions*: (a) α-halo ketone **4a**–**g** (1.2 equiv), $Et_3N$ (1.2 equiv), MeCN, MW, 170 °C

**Table 2** Synthesis of Imidazopyrazin-8(7*H*)-ones **16a**–**k** from **11a** and **11c** (Scheme 5)

| α-Halo ketone | X | $R^1$ | $R^2$ | **11** | $R^4$ | Product | Reaction time (min) | Yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| **4a** | Br | *t*-Bu | H | **11a** | H | **16a** | 45 | 63 |
| **4b** | Br | Ph | H | **11a** | H | **16b** | 45 | 55 |
| **4c** | Br | *c*-Pr | H | **11a** | H | **16c** | 45 | 63 |
| **4c** | Br | *c*-Pr | H | **11c** | *i*-Pr | **16d** | 60 | 44 |
| **4d** | Br | 4-$MeOC_6H_4$ | H | **11a** | H | **16f** | 30 | 65 |
| **4e** | Cl | 3-THP[b] | H | **11a** | H | **16g** | 60 | 72 |
| **4f** | Cl | Me | H | **11a** | H | **16h** | 60 | 56 |
| **4f** | Cl | Me | H | **11c** | *i*-Pr | **16i** | 60 | 51 |
| **4g** | Br | Ph | Me | **11a** | H | **16j** | 60 | 62 |
| **4g** | Br | Ph | Me | **11c** | *i*-Pr | **16k** | 60 | 91 |

[a] Isolated yield.
[b] Tetrahydro-2*H*-pyran-3-yl.

Several imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **16a**–**k** were prepared by condensation of **11a** and **11c** with selected α-halo ketones **4a**–**g** using the procedure described above to afford the corresponding substituted imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **16a**–**k** in moderate to excellent yields (44–91%).[8] Since two regioisomers are possible, the structures of compounds **16a**, **16h** and **16j** were confirmed using HMQC, HMBC and NOE NMR experiments.[9] Imidazo[1,2-*a*]pyrazin-8(7*H*)-ones are found in a number of biologically active compounds[10] and have previously been prepared using different routes.[10a,b,11]

In conclusion, a facile method of synthesis of 4*H*-pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones **1** from the corresponding 3-amino-2(1*H*)-pyrazinone and β-keto ester has been developed. The condensation of 3-amino-2(1*H*)-pyrazinones with α-halo ketones provided imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **5**. Procedures developed for both condensation reactions fit well the requirements of parallel synthesis coupled with automated purification techniques allowing the rapid generation of a diverse set of analogues for biological evaluation. 4*H*-Pyrazino[1,2-*a]*pyrimidine-4,9(8*H*)-dione and imidazo[1,2-*a*]pyrazin-8(7*H*)-one can serve as useful templates in the search for new drug candidates.

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(6) **Representative Procedure for the Preparation of 4*H*-Pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones 12a–n; 2-Methyl-8-phenyl-4*H*-pyrimido[1,2-*a*]pyrazine-4,9(8*H*)-dione (12a)**: 3-Amino-1-phenylpyrazin-2(1*H*)-one **(11a**; 100 mg, 0.53 mmol), methyl 3-oxobutanoate (**3a**; 0.576 mL, 5.34 mmol) and methanesulfonic acid (0.035 mL, 0.53 mmol) were dissolved in anhyd MeCN (1.2 mL) and sealed into a microwave tube. The reaction was heated at 180 °C over a period of 30 min within the microwave reactor (see ref. 12). The crude product was purified by flash silica chromatography (elution gradient 0–100% EtOAc in isohexane) to afford 2-methyl-8-phenyl-4*H*-pyrimido[1,2-*a*]pyrazine-4,9(8*H*)-dione (**12a**) as a white solid (124 mg, 89%); mp 238.5–239.2 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 6.55 (s, 1 H), 6.90 (d, *J* = 6.4 Hz, 1 H), 7.35–7.60 (m, 5 H), 7.76 (d, *J* = 6.4 Hz, 1 H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ = 24.49, 103.58, 111.92, 120.18, 125.78, 129.08, 129.71, 139.20, 144.66, 154.61, 157.54, 164.56. HRMS (ESI+): *m*/*z* [M + H$^+$] calcd for $C_{14}H_{11}N_3O_2$: 254.0924; found: 254.0938.
(7) 3-Amino-1,5-diphenylpyrazin-2(1*H*)-one (**14**; R = Ph) was obtained in a Suzuki cross-coupling reaction between 3-amino-5-bromo-1-phenylpyrazin-2(1*H*)-one (**10a**) and phenylboronic acid in 42% yield.
(8) **A Representative Procedure for the Preparation of Imidazo[1,2-*a*]pyrazin-8(7*H*)-ones 16a–k**; **2,7-Diphenylimidazo[1,2-*a*]pyrazin-8(7*H*)-one (16b)**: 3-Amino-1-phenylpyrazin-2(1*H*)-one (**11a**; 100 mg, 0.53 mmol), 2-bromo-1-phenylethanone (**4b**; 133 mg, 0.67 mmol) and $Et_3N$ (0.093 mL, 0.67 mmol) were dissolved in anhyd MeCN (1.2 mL) and sealed into a microwave tube. The reaction was heated to 170 °C over a period of 45 min in the microwave reactor (see ref. 12). The solid was filtered off, washed with $Et_3N$ and recrystallised from MeCN to afford 2,7-diphenylimidazo[1,2-*a*]pyrazin-8(7*H*)-one (**16b**) as white crystals (85 mg, 55%); mp 304.9–306.9 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.20 (d, *J* = 5.9 Hz, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.43–7.59 (m, 7 H), 7.65 (d, *J* = 5.9 Hz, 1 H), 7.94 (dd, *J* = 8.2, 1.0 Hz, 2 H), 8.33 (s, 1 H). HRMS (ESI+): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{13}N_3O$: 288.1131; found: 288.1134.
(9) For example, in a NOE experiment irradiation of the proton at the 5-position of imidazo[1,2-*a*]pyrazin-8(7*H*)-one ring in **16a** and **16j** resulted in enhancement of $R^2$ proton signal in compound **16a** ($R^2$ = H) and in the case of **16j** ($R^2$ = Me) the protons of the methyl group.
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(12) Single-mode CEM Explorer and Biotage Initiator automated microwave reactors were used.



 