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Multicomponent Synthesis of Fused Benzimidazolopiperazines

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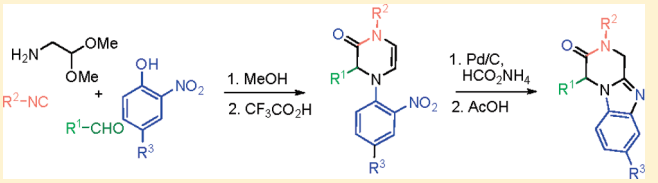
Supporting Information

ABSTRACT: We present a novel protocol for the efficient synthesis of fused benzimidazolo piperazines starting from a four-component Ugi−Smiles reaction and a subsequent three-step cascade involving an acid-catalyzed cyclization, an intramolecular reductive cyclization, and an oxidation.



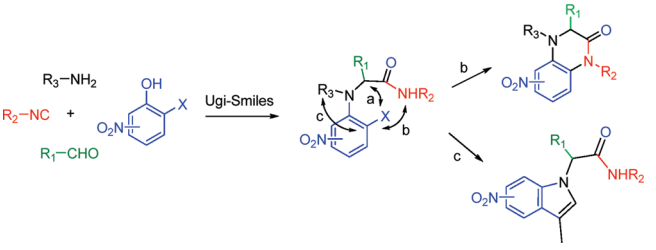
In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, multicomponent reactions (MCRs)[1] have become an essential tool in organic and medicinal chemistry. The potential of MCRs coupled with postcondensation transformations to generate highly diverse scaffolds within a few steps was mainly highlighted by the synthetic developments made around the Ugi reaction.[2] Recently, our research group reported an extension of this four-component coupling by replacing carboxylic acids with electron-deficient phenols as acidic inputs.[3] In this reaction, a final irreversible Smiles rearrangement leads to the formation of *N*-arylcarboxamide (Scheme 1).

The potential of Ugi−Smiles couplings was highlighted by several syntheses of various fused heterocyclic systems.[4] All these studies involved cyclization between the aryl moiety and functionalities present on the nitrogen substituents of the aniline Ugi framework (paths a, b, or c, Scheme 1).

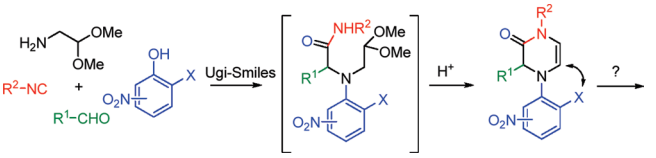
Searching for more complex cyclizations involving the aromatic moiety, we considered the use of aminoacetaldehyde acetal as amine input in the Ugi−Smiles reaction. The latter has been already used in the Ugi reaction to afford piperazine derivatives under acidic treatment of the intermediate Ugi adducts.[5] Applying a similar strategy with Ugi−Smiles couplings, we surmised that the newly created double bond could give us some opportunies to observe further cyclization between the aromatic subsituents and the intermediate enamine (Scheme 2). Herein, we report the preparation of various fused polycyclic piperazinones using Ugi−Smiles reaction of 2-nitrophenol with aminoacetaldehyde dimethyl acetal.

Using aminoacetaldehyde dimethyl acetal with 2-nitrophenol in the Ugi−Smiles reaction, we decided to study the direct four-component formation of ketopiperazinones **1** under a one-pot procedure. Thus, after completion of the Ugi−Smiles reaction (performed under standard conditions in methanol), trifluoroacetic acid was added and the mixture heated for few hours. Following this procedure, we could obtain the ketopiperazinones **1a**−**k** in moderate to good yields with a set of various nitrophenols, isocyanides, and carbonyl (Table 1, entries 1−11). Similar

Scheme 1. Strategies for Heterocyclic Syntheses



Scheme 2. Piperazinones from Ugi−Smiles Couplings



conditions applied to 2-hydroxypyridine (or 2-hydroxy-3-nitropyridine), cyclohexyl isocyanide, and isovaleraldehyde failed to give any piperazine because of the inefficiency of the second step.

The *N*-arylpiperazinones prepared according to this sequence are related to the *N*-acyl analogues obtained from traditional Ugi reaction of aminoacetaldehyde dimethyl acetal followed by acid-triggered cyclization.[5] These intermediates have been trapped further in Pictet−Spengler reactions.[6]

In order to increase the synthetic potential of the new *N*-aryl analogues, we envisioned similar formation of complex polycyclic piperazines. Therefore, cyclizations involving the nitro and enamines moieties were next considered. We postulated that a reduction of the nitro, acid-triggered addition of the resulting amine on the enamine followed by oxidation could afford some

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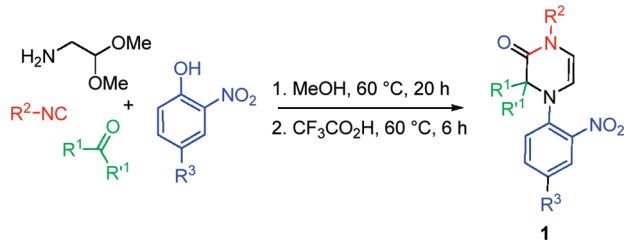
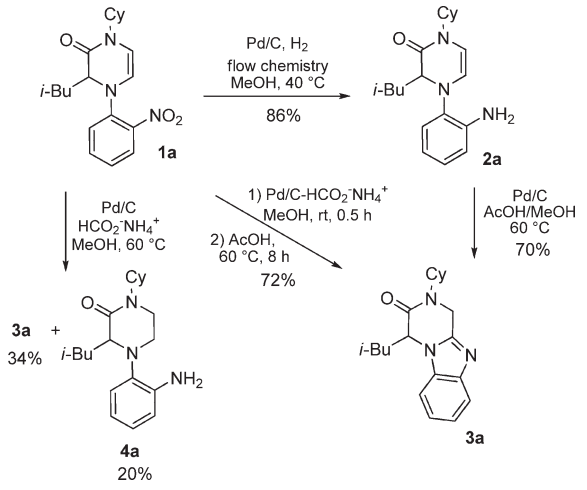
Table 1. Ugi–Smiles/Acidic Cyclization Cascade



1

entry	R^1	R'^1	R^2	R^3	reaction time (h)	product	yield (%)
1	*i*-Bu	H	Cy	H	32	**1a**	54
2	Ph	H	Cy	H	32	**1b**	66
3	*i*-Bu	H	Cy	Cl	32	**1c**	55
4	$(CH_2)_4$	H	Cy	H	34	**1d**	58
5	*i*-Bu	H	Cy	CH_3	24	**1e**	51
6	$(CH_2)_4$		Cy	OCH_3	22	**1f**	54
7	$(CH_2)_4$		4-ClBn	Cl	34	**1g**	62
8	$(CH_2)_4$		4-ClBn	CH_3	32	**1h**	57
9	4-ClPh	H	4-ClBn	H	32	**1i**	41
10	Et	H	4-ClBn	H	32	**1j**	47
11	Et	Et	CH_2CO_2Me	Cl	30	**1k**	60

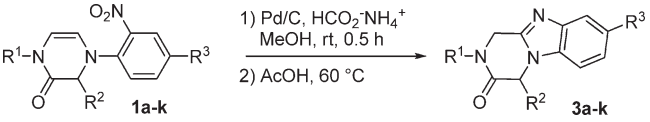
Scheme 3. Reductive Cyclization of Piperazinones



stable fused benzimidazole systems. Related formation of fused piperazinobenzimidazoles from thermal degradation of naphthoquinone azide gives positive indications on aniline addition on the enamine moiety.[7]

Hydrogenolysis of piperazine **1a** under flow chemistry gave the aniline **2a** efficiently. Although the latter could be converted into benzimidazole **3a** under heating in acetic acid with palladium on charcoal (Scheme 3), we preferred conditions that might allow the two steps in the same pot. Still working with palladium in the presence of ammonium formate, we thought that the acidity of the medium could allow the reduction–cyclization cascade. Indeed, the reduction of the nitro was observed at room temperature, and the oxidative cyclization proceeded smoothly when the temperature of the medium was raised to 60 °C to afford **3a** (Scheme 3). However, under these conditions, the over-reduced piperazine **4a** was obtained as a byproduct due to partial reduction of the piperazine before its cyclization. Acetic acid was then added before the mixture was heated. This more acidic medium ensured a faster cyclization and a better selectivity. Various piperazines **1** were converted into benzimidazoles **3** under this set of conditions (Table 2).

Table 2. Scope of Fused System Synthesis



Entry	Reactant	Reaction time(h)	Product	Yield(%)
1	**1b**	8	**3b**	69
2	**1c**	5	**3c**	53
3	**1d**	5	**3d**	81
4	**1e**	6	**3e**	52
5	**1f**	6	**3f**	65
6	**1g**	8	**3g**	66
7	**1h**	7	**3h**	67
8	**1i**	12	**3i**	46
9	**1j**	8	**3j**	59
11	**1k**	8	**3k**	80

In conclusion, a new synthesis of complex fused benzimidazo piperazines based on a Ugi–Smiles four-component strategy is reported.[8] Piperazines and benzimidazoles are considered as

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privilege scaffolds in medicinal chemistry.[9] Indeed, these rings may be found in a number of biologically active compounds, including several marketed drugs. The Ugi−Smiles reaction with nitrophenols allows the coupling of both scaffolds in fused systems and in a multicomponent fashion.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a 400 MHz spectrometer, using $CDCl_3$ solvent as reference and/or internal deuterium lock. ^{13}C NMR spectra were recorded on a 100.6 MHz spectrometer. Two-dimensional NMR spectroscopy [^{1}H−^{1}H COSY spectra, ^{1}H−^{13}C COSY spectra (HSQC), and long-range ^{1}H−^{13}C COSY spectra (HMBC)] was carried out to determine the correlation between ^{1}H and ^{13}C. The chemical shifts for all NMR spectra are expressed in parts per million to high frequency of TMS reference. Coupling constants (J) are quoted in hertz and are recorded to the nearest 0.1 Hz. The IR spectra were obtained using ATR accessories. High-resolution (HR) mass spectra were performed on a GC/MS system spectrometer. TLC was carried out using precoated plates of silica gel 60F254.

General Procedure for the Synthesis of 3,4-Dihydropyrazin-2(1*H*)-ones (1a−k). To a 1 M solution of carbonyl derivative (1.0 equiv) in methanol were added successively 2,2-dimethoxyethylamine (1.0 equiv), isocyanide (1.0 equiv) and *o*-nitrophenol (1 equiv). The reaction mixture was stirred at 60 °C until completion of the Ugi−Smiles coupling and then cooled to room temperature. TFA (15 equiv) was added and the mixture heated at 60 °C. After completion of the reaction, the mixture was evaporated and purified by flash chromatography on silica gel.

*1-Cyclohexyl-3-isobutyl-4-(2-nitrophenyl)-3,4-dihydropyrazin-2(1H)-one (**1a**).* The typical procedure performed on a 1.0 mmol scale afforded **1a** as a brown oil (petroleum ether/diethyl ether 80/20): yield 54% (193 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 1H, J = 8.3 Hz), 7.47 (t, 1H, J = 7.8 Hz), 7.12 (d, 1H, J = 8.3 Hz), 7.04 (t, 1H, J = 7.8 Hz), 5.82 (d, 1H, J = 5.3 Hz), 5.35 (d, 1H, J = 5.3 Hz), 4.46−4.33 (m, 2H), 1.91−1.76 (m, 4H), 1.75−1.65 (m, 3H), 1.54−1.36 (m, 5H), 1.19−1.13 (m, 1H), 1.09 (d, 3H, J = 6.3 Hz), 0.95 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.7, 141.7, 138.7, 133.2, 126.3, 121.7, 120.9, 112.6, 110.3, 61.5, 52.1, 37.6, 31.5, 30.5, 25.6, 25.4, 24.7, 23.5, 22.2; IR (ATR) 2931, 2861, 1672, 1605, 1523, 1488, 1456, 1425, 1351, 1257, 1210 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_3O_3$ 357.2052, found 357.2050.

*1-Cyclohexyl-4-(2-nitrophenyl)-3-phenyl-3,4-dihydropyrazin-2(1H)-one (**1b**).* The typical procedure performed on a 1.0 mmol scale afforded compound **1b** as a yellow oil (petroleum ether/diethyl ether 60/40): yield 66% (250 mg); R_f 0.4 (60:40 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, 1H, J = 8.3 Hz), 7.44 (d, 2H, J = 7.3 Hz), 7.41−7.32 (m, 4H), 7.07 (t, 1H, J = 7.8 Hz), 6.97 (d, 1H, J = 8.3 Hz), 5.71 (d, 1H, J = 5.0 Hz), 5.59−5.56 (m, 2H), 4.43−4.34 (m, 1H), 1.93 (br d, 1H, J = 11.1 Hz), 1.86−1.75 (m, 2H), 1.66 (br d, 1H, J = 13.4 Hz), 1.57−1.52 (m, 1H), 1.45−1.40 (m, 1H), 1.39−1.30 (m, 3H), 1.15−1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 161.9, 141.3, 138.5, 135.4, 133.3, 128.8, 128.3, 126.2, 126.0, 122.0, 120.9, 113.7, 109.2, 66.0, 52.6, 31.4, 30.1, 25.6, 25.5, 25.4; IR (ATR) 2931, 2857, 1668, 1609, 1523, 1491, 1452, 1429, 1347, 1261, 1214 cm^{-1}; HRMS calcd for $C_{22}H_{23}N_3O_3$ 377.1739, found 377.1730.

*4-(4-Chloro-2-nitrophenyl)-1-cyclohexyl-3-isobutyl-3,4-dihydropyrazin-2(1H)-one (**1c**).* The typical procedure performed on a 1.0 mmol scale afforded **1c** as a reddish oil (petroleum ether/diethyl ether 90/10): yield 55% (215 mg); R_f 0.1 (90:10 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 1H, J = 2.5 Hz), 7.43 (dd, 1H, J = 2.5, 8.8 Hz), 7.06 (d, 1H, J = 8.8 Hz), 5.85 (d, 1H, J = 5.6 Hz), 5.29 (dd, 1H, J = 2.0, 5.6 Hz), 4.42−4.32 (m, 2H), 1.90−1.79 (m, 3H), 1.77−1.74 (m, 1H), 1.73−1.66 (m, 3H), 1.52−1.37 (m, 6H), 1.08 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.6, 141.4, 137.4, 133.3, 126.5, 126.0, 122.0, 112.0, 111.0, 61.6, 52.2, 37.6, 31.5, 30.5, 25.6, 25.4, 24.7, 23.5, 22.2; IR (ATR) 2928, 2861, 1671, 1609, 1527, 1488, 1433, 1351, 1261, 1214, 1119 cm^{-1}; HRMS calcd for $C_{20}H_{26}ClN_3O_3$ 391.1663, found 391.1658.

*9-Cyclohexyl-6-(2-nitrophenyl)-6,9-diazaspiro[4.5]dec-7-en-10-one (**1d**).* The typical procedure performed on a 1.0 mmol scale afforded **1d** as a reddish oil (petroleum ether/diethyl ether 90/10): yield 56% (200 mg); R_f 0.1 (90:10 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, J = 8.1 Hz), 7.48 (t, 1H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.8 Hz), 7.20 (d, 1H, J = 8.1 Hz), 5.73 (d, 1H, J = 5.3 Hz), 5.71(d, 1H, J = 5.3 Hz), 4.45−4.36 (m, 1H), 2.16−2.03 (m, 2H), 1.87−1.77 (m, 4H), 1.76−1.62 (m, 7H), 1.49−1.34 (m, 4H), 1.17−1.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 165.9, 149.5, 138.0, 132.5, 131.5, 127.0, 124.2, 118.0, 109.2, 70.8, 52.6, 34.6, 31.0, 25.7, 25.4, 24.7; IR (ATR) 2930, 2857, 1665, 1603, 1530, 1405, 1357, 1252, 1211, 1193 cm^{-1}; HRMS calcd for $C_{20}H_{25}N_3O_3$ 355.1896, found 355.1845.

*1-Cyclohexyl-3-isobutyl-4-(4-methyl-2-nitrophenyl)-3,4-dihydropyrazin-2(1H)-one (**1e**).* The typical procedure performed on a 1.0 mmol scale afforded **1e** as a brown oil (petroleum ether/diethyl ether 80/20): yield 51% (190 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (s, 1H), 7.27 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 8.6 Hz), 5.77 (d, 1H, J = 5.3 Hz), 5.35 (d, 1H, J = 5.3 Hz), 4.41−4.32 (m, 2H), 2.33 (s, 3H), 1.91−1.77 (m, 3H), 1.76−1.64 (m, 4H), 1.52−1.34 (m, 5H), 1.17−1.09 (m, 1H), 1.06 (d, 3H, J = 6.3 Hz), 0.93 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.6, 141.8, 136.6, 134.0, 132.3, 126.1, 121.6, 112.9, 109.6, 61.7, 52.0, 37.7, 31.5, 30.5, 25.6, 25.4, 24.6, 23.4, 22.2, 20.3; IR (ATR) 2933, 2857, 1668, 1620, 1526, 1498, 1432, 1404, 1347, 1263, 1206 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_3O_3$ 371.2209, found 371.2202.

*9-Cyclohexyl-6-(4-methoxy-2-nitrophenyl)-6,9-diazaspiro[4.5]dec-7-en-10-one (**1f**).* The typical procedure performed on a 1.0 mmol scale afforded **1f** as a yellow oil (petroleum ether/diethyl ether 80/20): yield 54% (208 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (d, 1H, J = 2.8 Hz), 7.11(d, 1H, J = 8.8 Hz), 7.01 (dd, 1H, J = 3.0, 9.1 Hz), 5.70 (d, 1H, J = 5.3 Hz), 5.66 (d, 1H, J = 5.3 Hz), 4.46−4.35 (m, 1H), 3.83 (s, 3H), 2.19−2.07 (m, 1H), 2.05−1.93 (m, 1H), 1.88−1.77 (m, 4H), 1.73−1.61 (m, 7H), 1.49−1.37 (m, 4H), 1.17−1.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 165.8, 158.0, 150.2, 132.9, 130.5, 118.9, 118.5, 108.5, 108.3, 70.9, 55.9, 52.6, 35.1, 34.0, 31.0, 25.7, 25.5, 24.7; IR (ATR) 2933, 2857, 1658, 1531, 1498, 1399, 1225, 1037 cm^{-1}; HRMS calcd for $C_{21}H_{27}N_3O_4$ 385.2002, found 385.2007.

*6-(4-Chloro-2-nitrophenyl)-9-(4-chlorobenzyl)-6,9-diazaspiro[4.5]dec-7-en-10-one (**1g**).* The typical procedure performed on a 1.0 mmol scale afforded **1g** as a yellow oil (petroleum ether/diethyl ether 80/20): yield 62% (267 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (br s, 1H), 7.45 (dd, 1H, J = 2.5, 8.6 Hz), 7.31 (d, 2H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 7.13 (d, 1H, J = 8.6 Hz), 5.67 (d, 1H, J = 5.3 Hz), 5.57 (d, 1H, J = 5.3 Hz), 4.70 (br s, 2H), 2.27−2.05 (br s, 2H), 1.79−1.61 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.3, 149.5, 136.1, 135.4, 133.3, 132.8, 132.6, 129.0, 128.8, 124.5, 118.0, 112.4, 71.0, 49.0, 35.1, 33.9, 24.6; IR (ATR) 2957, 2874, 1666, 1600, 1534, 1481, 1398, 1556, 1259, 1176, 1110, 1013 cm^{-1}; HRMS calcd for $C_{21}H_{19}Cl_2N_3O_3$ 431.0803, found 431.0812.

*9-(4-Chlorobenzyl)-6-(4-methyl-2-nitrophenyl)-6,9-diazaspiro[4.5]dec-7-en-10-one (**1h**).* The typical procedure performed on a 1.0 mmol scale afforded **1h** as a brown oil (petroleum ether/diethyl ether 80/20): yield 45% (183 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 1H), 7.32 (d, 2H, J = 8.3 Hz), 7.29 (dd, 1H, J = 1.8, 8.1 Hz), 7.23 (d, 2H, J = 8.3 Hz) 7.07 (d, 1H, J = 8.1 Hz), 5.72 (d, 1H, J = 5.0 Hz), 5.51 (d, 1H, J = 5.0 Hz), 4.71 (br s, 2H), 2.40 (s, 3H), 2.29−2.00 (m, 2H), 1,80−1.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.5, 149.4, 138.3, 135.6, 134.9, 133.4, 133.3, 131.6, 129.1, 128.8, 124.5, 119.0, 111.2, 71.0, 49.0, 35.3, 33.7, 24.6, 20.8; IR (ATR)

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2959, 2873, 1668, 1652, 1531, 1495, 1401, 1359, 1261, 1178, 1096, 1022 cm^{-1}; HRMS calcd for $C_{22}H_{22}ClN_3O_3$ 411.1350, found 411.1352.

*1-(4-Chlorobenzyl)-3-(4-chlorophenyl)-4-(2-nitrophenyl)-3,4-dihydropyrazin-2(1H)-one (**1i**).* The typical procedure performed on a 1.0 mmol scale afforded **1i** as a colorless oil (petroleum ether/diethyl ether 80/20): yield 41% (185 mg); R_f 0.2 (80:20 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 1H, J = 8.3 Hz), 7.30−7.25 (m, 3H), 7.21 (d, 2H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.3 Hz), 7.01−6.94 (m, 3H), 6.79 (d, 1H, J = 8.3 Hz), 5.48 (dd, 1H, J = 1.8, 5.3 Hz), 5.45 (s, 1H), 5.41 (d, 1H, J = 5.3 Hz), 4.64 (d, 1H, J = 15.4 Hz), 4.45 (d, 1H, J = 15.4 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.1, 141.5, 138.1, 134.6, 134.4, 133.5, 133.4, 129.1, 128.8, 128.6, 127.5, 126.3, 122.8, 121.0, 114.1, 112.2, 65.3, 48.7; IR (ATR) 2928, 2857, 1679, 1644, 1613, 1495, 1413, 1351, 1280, 1175, 1096, 1018 cm^{-1}; HRMS calcd for $C_{23}H_{17}Cl_2N_3O_3$ 453.0647, found 453.0661.

*1-(4-Chlorobenzyl)-3-ethyl-4-(2-nitrophenyl)-3,4-dihydropyrazin-2(1H)-one (**1j**).* The typical procedure performed on a 1.0 mmol scale afforded **1j** as a brown syrup (petroleum ether/diethyl ether 65/35): yield 47% (174 mg); R_f 0.35 (65:35 petroleum ether/diethyl ether); ^1H NMR-($CDCl_3$, 400 MHz) δ 7.76 (d, 1H, J = 8.3 Hz), 7.50 (t, 1H, J = 7.8 Hz), 7.33 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.3 Hz), 7.15 (d, 1H, J = 8.3 Hz), 7.08 (t, 1H, J = 7.8 Hz), 5.63 (d, 1H, J = 5.3 Hz), 5.40 (dd, 1H, J = 1.8, 5.3 Hz), 4.76 (d, 1H, J = 15.2 Hz), 4.69 (d, 1H, J = 15.2 Hz), 4.37 (t, 1H, J = 7.3 Hz), 1.98−1.79 (m, 2H), 1.07 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.4, 141.9, 138.5, 134.9, 133.5, 133.3, 129.0, 128.9, 126.4, 122.2, 121.3, 113.4, 112.8, 64.0, 48.2, 22.5, 10.3; IR (ATR) 2971, 2931, 2857, 1675, 1620, 1523, 1488, 1456, 1401, 1351, 1272, 1096, 1018 cm^{-1}; HRMS calcd for $C_{19}H_{18}ClN_3O_3$ 371.1037, found 371.1011.

*Methyl 2-(4-(4-Chloro-2-nitrophenyl)-3,3-diethyl-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetate (**1k**).* The typical procedure performed on a 1.0 mmol scale afforded **1l** as a pale yellow oil (petroleum ether/diethyl ether 70/30): yield 60% (230 mg); R_f 0.3 (70:30 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.45 (dd, 1H, J = 2.5, 8.8 Hz), 7.38 (d, 1H, J = 8.8 Hz), 5.47 (d, 1H, J = 5.3 Hz), 5.30 (d, 1H, J = 5.3 Hz), 4.57−3.97 (m, 2H), 3.77 (s, 3H), 2.25−2.06 (m, 1H), 2.02−1.88 (m, 2H), 1.33−1.20 (m, 1H), 1.00−0.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.8, 165.7, 146.1, 136.3, 132.2, 129.9, 128.7, 125.7, 115.5, 70.0, 52.3, 47.8, 8.6; IR (ATR) 2942, 2886, 1747, 1667, 1531, 1484, 1437, 1394, 1277, 1211, 1178, 1112 cm^{-1}; HRMS calcd for $C_{17}H_{20}ClN_3O_5$ 381.1091, found 381.1097.

General Procedure for the Synthesis of Fused Benzimidazolopiperazines (3a−l). To a 0.5 M solution of dihydroketopiperazine (**1a−l**) (1.0 equiv) in methanol were added ammonium formate (5.0 equiv) and Pd−C (10% Pd−C, 2.0 equiv) under argon. The reaction mixture was stirred at room temperature for 30 min, and then it was acidified by addition of 6.0 equiv of CH_3COOH and stirred at 60 °C until completion of the reaction. The residue was filtered through a Celite pad, and the solvent was evaporated. The crude mixture was purified by flash chromatography on silica gel to get the required product.

*2-Cyclohexyl-4-isobutyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazin-3-one (**3a**).* The typical procedure was followed with **1a** (100 mg, 0.28 mmol). Purification by flash chromatography (petroleum ether−diethyl ether, 40:60) afforded **3a** as a colorless oil: yield 72% (65 mg); R_f 0.6 (40:60 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77−7.71 (m, 1H), 7.38−7.33 (m, 1H), 7.32−7.27 (m, 2H), 5.03 (t, 1H, J = 6.6 Hz), 4.75 (d, 1H, J = 16.7 Hz), 4.59 (d, 1H, J = 16.7 Hz), 4.57−4.49 (m, 1H), 1.99−1.79 (m, 5H), 1.74−1.61 (m, 3H), 1.56−1.41 (m, 4H), 1.21−1.11 (m, 1H), 0.96 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.0, 145.6, 143.5, 133.3, 122.8, 119.7, 109.3, 56.4, 53.1, 42.3, 39.8, 29.7, 29.2, 25.6, 25.4, 25.3, 24.5, 22.7, 22.6; IR (ATR) 2929, 2856, 1653, 1539, 1466, 1443, 1368, 1297, 1283, 1256, 1233, 1183, 1169 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_3O$ 325.2154, found 325.2141.

*2-Cyclohexyl)-4-phenyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine (**3b**).* The typical procedure was with **1b** (100 mg, 0.26 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 50:50) afforded **3b**> as a white solid: mp = 181−183 °C; yield 69% (63 mg); R_f 0.5 (50:50 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 1H, J = 8.1 Hz), 7.33−7.28 (m, 4H) 7.20 (t, 1H, J = 7.8 Hz), 7.16−7.11 (m, 3H), 6.05 (s, 1H), 4.82 (d, 1H, J = 16.9 Hz), 4.67 (d, 1H, J = 16.9 Hz), 4.54−4.45 (m, 1H), 1.91−1.79 (m, 2H), 1.75−1.65 (m, 3H), 1.58−1.31 (m, 4H), 1.19−1.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.1, 145.7, 143.6, 135.1, 133.0, 129.1, 128.8, 126.0, 123.1, 123.0, 119.6, 109.9, 60.8, 53.6, 39.9, 29.6, 29.1, 25.5, 25.4, 25.3; IR (ATR) 2926, 2857, 1655, 1569, 1456, 1373, 1292, 1256, 1234 cm^{-1}; HRMS calcd for $C_{22}H_{23}N_3O$ 345.1841, found 345.1843.

*2-Cyclohexyl-4-isobutyl-1,2-dihydro-4-chlorobenzo[4,5]imidazo[1,2-a]pyrazin-3-one (**3c**).* The typical procedure was followed with **1c** (100 mg, 0.26 mmol. Purification by flash chromatography (petroleum ether/diethyl ether 25:75) afforded **3c** as a white solid: mp = 115−116°C; yield 53% (48 mg); R_f 0.75 (25:75 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77−7.73 (m, 1H), 7.38−7.34 (m, 1H), 7.31−7.28 (m, 1H), 5.03 (t, 1H, J = 6.3 Hz), 4.75 (d, 1H, J = 16.7 Hz), 4.60 (d, 1H, J = 16.7 Hz), 4.57−4.49 (m, 1H), 1.99−1.79 (m, 6H), 1.75−1.62 (m, 3H), 1.56−1.45 (m, 3H), 1.21−1.11 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.92 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.1, 145.6, 143.5, 133.3, 125.5, 122.8, 119.7, 109.3, 56.4, 53.2, 42.3, 39.8, 30.3, 29.7, 29.2, 25.6, 25.4, 25.3, 24.5, 22.8, 22.6; IR (ATR) 2928, 2856, 1652, 1539, 1465, 1439, 1297, 1232, 1183 cm^{-1}; HRMS calcd for $C_{20}H_{26}ClN_3O$ 359.1764, found 359.1772.

*2-Cyclohexyl-4-cyclopentyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine (**3d**).* The typical procedure was followed with **1d** (100 mg, 0.28 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 40:60) afforded **3d** as a white solid: mp = 133−134 °C; yield 81% (73 mg); R_f 0.6 (40:60 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.28 (t, 1H, J = 7.3 Hz), 7.23 (t, 1H, J = 7.3 Hz), 4.71 (s, 2H), 4.57−4.49 (m, 1H), 2.57−2.48 (m, 2H), 2.46−2.37 (m, 2H), 2.22−2.10 (m, 4H), 1.90−1.83 (m, 2H), 1.80−1.68 (m, 3H), 1.58−1.8 (m, 4H), 1.22−1.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.2, 145.5, 143.9, 132.1, 122.6, 122.3, 119.7, 111.5, 69.5, 53.7, 40.1, 38.1, 29.3, 27.1, 25.6, 25.3; IR (ATR) 2931, 2856, 1644, 1544, 1472, 1452, 1427, 1332, 1297, 1180, 764, 702 cm^{-1}; HRMS calcd for $C_{20}H_{25}N_3O$ 323.1998, found 323.2001.

*2-Cyclohexyl-4-isobutyl-1,2-dihydro-4-methylbenzo[4,5]imidazo[1,2-a]-pyrazin-3-one (**3e**).* The typical procedure was followed with **1c** (100 mg, 0.27 mmol). Purification by flash chromatography (petroleum ether−diethyl ether 40:60) afforded **3e** as a colorless oil: yield 52% (47 mg); R_f 0.6 (40:60 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 1H), 7.23 (d, 1H, J = 8.3 Hz), 7.11 (d, 1H, J = 8.3 Hz), 4.99 (t, 1H, J = 6.6 Hz), 4.73 (d, 1H, J = 16.7 Hz), 4.58 (d, 1H, J = 16.7 Hz), 4.57−4.49 (m, 1H), 2.48 (s, 3H), 1.97−1.79 (m, 5H), 1.74−1.62 (m, 3H), 1.55−1.41 (m, 4H), 1.21−1.09 (m, 1H), 0.95 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.1, 145.5, 143.9, 132.6, 131.4, 124.2, 119.5, 108.8, 56.4, 53.2, 42.3, 39.9, 29.7, 29.2, 25.6, 25.4, 25.3, 24.5, 22.8, 22.6, 21.5; IR (ATR) 2930, 2857, 1656, 1537, 1464, 1450, 1294, 1186 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_3O$ 339.2311, found 339.2313.

*1-Cyclohexyl-3-cyclopentyl-5,6-dihydrobenzo-4-methoxy[4,5]imidazo[1,2-a]pyrazin-2-one (**3f**).* The typical procedure was followed with **1f** (200 mg, 0.52 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 20:80) afforded **3f** as a colorless oil: yield 65% (119 mg); R_f 0.8 (20:80 petroleum ether/diethyl ether); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 1H, J = 8.8 Hz), 7.18 (s, 1H), 6.87 (dd, 1H, J = 8.8 Hz), 4.68 (s, 2H), 4.57−4.48 (m, 1H), 3.85 (s, 3H), 2.56−2.47 (m, 2H), 2.41−2. 32 (m, 2H), 2.22−2.06 (m, 4H), 1.91−1.83 (m, 2H), 1.79−1.67 (m, 3H), 1.58−1.37 (m, 4H), 1.22−1.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.2, 156.2, 145.6, 144.9,

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126.5, 112.1, 111.8, 101.8, 69.4, 55.7, 53.6, 40.1, 38.2, 29.3, 27.1, 25.6, 25.3; IR (ATR) 2937, 2857, 1648, 1540, 1479, 1446, 1277, 1197, 1183, 1154, 1121, 1037 cm^{-1}; HRMS calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2104.

*2-(4-Chlorobenzyl)-4-cyclopentyl-1,2-dihydro-4-chlorobenzo[4,5]imidazo-[1,2-a]pyrazin-2-one (**3g**).* The typical procedure was followed with **1g** (100 mg, 0.23 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 20:80) afforded **3g** as a white solid: mp = 139−141 °C; yield 66% (61 mg); R_f 0.8 (20:80 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 7.6 Hz), 7.27−7.21 (m, 4H), 7.20−7.15 (m, 1H), 4.69 (s, 2H), 4.61 (s, 2H), 2.53−2.45 (m, 2H), 2.42−2.34 (m, 2H), 2.20−2.06 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.8, 144.6, 143.9, 135.4, 131.9, 128.9, 128.2, 128.0, 122.7, 122.3, 119.8, 111.4, 69.4, 50.6, 44.7, 38.3, 27.1; IR (ATR) 2954, 1652, 1454, 1426, 1332, 1266, 1186, 735, 700 cm^{-1}; HRMS calcd for $C_{21}H_{19}Cl_2N_3O$ 399.0905, found 399.0886.

*1-(4-chlorobenzyl)-3-cyclopentyl-5,6-dihydrobenzo-4-methyl[4,5]imidazo [1,2-a]-pyrazin-2-one (**3h**).* The typical procedure was followed with **1h** (150 mg, 0.36 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 50:50) afforded **3h** as a colorless oil: yield 67% (92 mg); R_f 0.5 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.37 (d, 2H, J = 8.3 Hz), 7.34−7.31 (m, 3H), 7.06 (d, 1H, J = 8.3 Hz), 4.78 (s, 2H), 4.67 (s, 2H), 2.60−2.52 (m, 2H), 2.46 (s, 3H), 2.48−2.40 (m, 2H), 2.27−2.18 (m, 3H), 1.94−1.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.0, 144.5, 144.4, 135.4, 132.5, 130.0, 129.0, 128.3, 128.1, 123.8, 119.6, 110.9, 69.4, 50.7, 44.8, 38.4, 27.2, 21.4; IR (ATR) 2955, 1652, 1543, 1480, 1439, 1327, 1266, 1185, 791, 733, 699 cm^{-1}; HRMS calcd for $C_{22}H_{22}ClN_3O$ 379.1451, found 379.1460.

*2-(4-Chlorobenzyl)-4-(4-chlorophenyl)-1,2-dihydrobenzo[4,5]imidazo-[1,2-a]pyrazin-3-one (**3i**).* The typical procedure was followed with **1i** (100 mg, 0.22 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 50:50) afforded **3i** as a pale yellow oil: yield 46% (43 mg); R_f 0.5 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 1H, J = 8.1 Hz), 7.35−7.28 (m, 6H), 7.24−7.21 (m, 2H), 7.19−7.15 (m, 2H), 7.10 (d, 1H, J = 7.8 Hz), 6.12 and its rotamer 6.08 (s, 1H), 4.86 (dd, 1H, J = 6.1, 14.6 Hz), 4.77 (s, 2H), 4.64 (d, 1H, J = 14.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz, rotamers observed) δ 164.6 (164.1), 143.5 (144.9), 135.1, 135.0 (134.8), 133.6, 129.4 (129.2), 129.0 (128.9), 128.3, 128.2 (128.1), 127.6, 126.2 (125.5), 123.2 (123.4), 123.2 (123.1), 119.7 (119.6), 110.0 (109.9), 60.7 (60.1), 50.7 (50.6), 30.3 (29.7); IR (ATR) 2923, 2853, 1659, 1541, 1454, 1440, 1324, 1295, 1261 cm^{-1}; HRMS calcd for $C_{23}H_{17}Cl_2N_3O$ 421.0749, found 421.0756.

*2-(4-Chlorobenzyl)-4-ethyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazin-2-one (**3j**).* The typical procedure was followed with **1j** (100 mg, 0.27 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 10:90) afforded **3j** as a colorless oil: yield 59% (54 mg); R_f 0.9 (10:90 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.71 (m, 1H), 7.41−7.29 (m, 7H), 5.15 (t, 1H, J = 4.8 Hz), 4.87 (d, 1H, J = 14.4 Hz), 4.76 (d, 1H, J = 14.4 Hz), 4.70 (d, 1H, J = 16.9 Hz), 4.64 (d, 1H, J = 17.9 Hz), 2.38−2.25 (m, 2H), 0.77 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.0, 144.8, 143.6, 135.2, 132.8, 129.0, 128.5, 128.2, 123.0, 122.8, 119.7, 109.7, 58.0, 50.5, 44.7, 26.6, 8.4; IR (ATR) 2964, 2929, 1670, 1507, 1494, 1454, 1376, 1304, 1276, 1177, 1077 cm^{-1}; HRMS calcd for $C_{19}H_{18}ClN_3O$ 339.1138, found 339.1138.

*1-(Carbomethoxymethyl)-3,3-diethyl-5,6-dihydrobenzo-4-chloro[4,5]-imidazo[1,2-a]pyrazin-2-one (**3k**).* The typical procedure was followed with **1k** (100 mg, 0.27 mmol). Purification by flash chromatography (petroleum ether/diethyl ether 10:90) afforded **3l** as a colorless oil: yield 80% (280 mg); R_f 0.7 (30:70 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (br s, 1H), 7.56 (d, 1H, J = 8.1 Hz), 7.32 (t, 1H, J = 7.9 Hz), 4.92 (s, 2H), 4.32 (s, 2H), 3.80 (s, 3H), 2.52−2.35 (m, 4H), 0.63 (t, 6H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.1, 168.4, 144.8, 131.9, 122.9, 122.5, 119.9, 112.1, 70.2, 52.5, 48.9, 46.8, 31.3, 8.2; IR (ATR) 2928, 2857, 1752, 1658, 1437, 1333, 1281, 1206, 1173, 1018, 957 cm^{-1}; HRMS calcd for $C_{17}H_{20}ClN_3O_3$ 349.1193, found 349.1194.

*4-(2-Aminophenyl)-1-cyclohexyl-3-isobutylpiperazin-2-one (**4a**).* To a 0.5 M solution of **1a** (100 mg, 0.28 mmol) in methanol were added ammonium formate (90 mg, 1.40 mmol) and 10% Pd−C (60 mg, 0.56 mmol) under argon. The reaction mixture was stirred at room temperature for 30 min, and then it was stirred at 60 °C for 12 h. The residue was filtered through a Celite pad, and the solvent was evaporated. The crude mixture was purified by flash chromatography on silica gel; the products were **4a** (18 mg, 20%) and **3a** (31 mg, 34%): R_f for **4a** 0.2 (80:20 petroleum ether/diethyl ether); R_f for **3a** 0.6 (40:60 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (t, 1H, J = 7.6 Hz), 6.89 (d, 1H, J = 7.8 Hz), 6.74 (d, 1H, J = 7.8 Hz), 6.69 (t, 1H, J = 7.6 Hz), 4.56−4.48 (m, 1H), 3.97 (br s, 2H), 3.75 (dd, 1H, J = 5.6, 7.6 Hz), 3.35−3.27 (m, 1H), 3.23−3.15 (m, 1H), 3.12−3.05 (m, 2H), 1.84−1.76 (m, 3H), 1.75−1.62 (m, 5H), 1.48−1.31 (m, 4H), 1.11−0.99 (m, 1H), 0.88 (d, 3H, J = 6.3 Hz), 0.78 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.8, 141.8, 136.0, 125.2, 122.4, 118.4, 115.3, 61.2, 52.2, 43.4, 40.3, 38.5, 29.4, 29.3, 25.6, 25.5, 25.3, 22.9, 21.8; IR (ATR) 2933, 2862, 1620, 1503, 1451, 1272, 1183, 1051, 900 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures with characterization data and copies of C^{13} and H^1 NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For some reviews, see: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (d) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (f) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *50*, 1741–1743.

(3) (a) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *117*, 7961–7164. (b) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180. (c) Barthelon, A.; El Kaim, L.; Gizolme, M. *Eur. J. Org. Chem.* **2008**, 5974–5987.

(4) (a) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835–5838. (b) Oble, J.; El Kaim, L.; Gizzi, M.; Grimaud, L. *Heterocycles* **2007**, *73*, 503–517. (c) El Kaim, L.; Grimaud, L.; Gizzi, M. *Org. Lett.* **2008**, *10*, 3417–3419. (d) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 995–997. (e) Barthelon, A.; Legoff, X.-F.; El Kaim, L.; Grimaud, L. *Synlett* **2010**, 153–157. (f) El Kaïm, L.; Grimaud, L. *Mol. Div.* **2010**, *14*, 855–867. (g) El Kaim, L.; Grimaud, L.; Wagschal, S. *J. Org.*

Chem. **2010**, *75*, 5343–5346. (h) El Kaim, L.; Grimaud, L.; Legoff, X.-F.; Schiltz, A. *Org. Lett.* **2011**, *13*, 534–536. (i) El Kaim, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887–1889.

(5) Cheng, J.-F.; Chen, M.; Arrhenius, T.; Nadzan, A. *Tetrahedron Lett.* **2002**, *43*, 6293–6295.

(6) (a) Liu, H. X.; Domling, A. *J. Org. Chem.* **2009**, *74*, 6895–6898. (b) Wang, W.; Olliot, S.; Herdtweck, E.; Domling, A. *Chem. Commun.* **2010**, *46*, 770–772. Wang, W.; Olliot, S.; Herdtweck, E.; Domling, A. *J. Org. Chem.* **2011**, *76*, 637–644.

(7) Berezhnaya, V. N.; Shishkina, R. P.; Fokin, E. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, *12*, 2822–2826. For related benzimidazole formation, see: Schmutz, J.; Künzle, F. *Helv. Chim. Acta* **1956**, *39*, 1144–1154.

(8) For reviews on piperazine and ketopiperazine formation, see: (a) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron Lett.* **2002**, *58*, 3297–3312. For isocyanide-based preparation of piperazines, see: (b) Domling, A.; Huang, Y. *Synthesis* **2010**, 2859–2883. For a review on the synthesis of fused benzimidazole hetrocycles, see: (c) Dawood, K. M.; Abdel-Wahab, B. F. *ARKIVOC* **2010**, 333–389.

(9) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.