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N-Heterocyclic Carbene Catalyzed Aroylation of 3,5-Dichloro-2(1*H*)-pyrazinones

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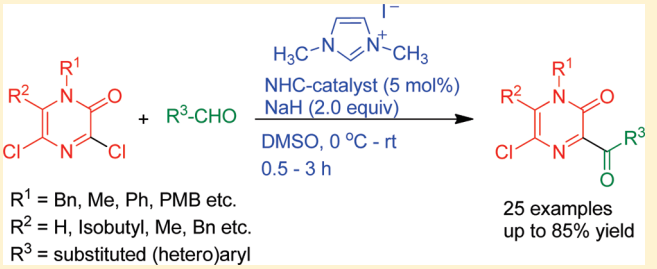
Supporting Information

ABSTRACT: The *N*-heterocyclic carbene catalyzed chemoselective C3-aroylation of 3,5-dichloro-2(1*H*)-pyrazinones with various aldehydes is reported. We herein describe results of this remarkable mild and efficient procedure.



In the past two decades 2(1*H*)-pyrazinones emerged as useful starting materials for the elaboration of different types of skeletons of biologically interesting compounds.[1] The 2(1*H*)-pyrazinone scaffold allows the easy introduction of a wide range of pharmacologically active groups with the ability to address a diverse set of biological targets.[2] A versatile synthesis of the 2(1*H*)-pyrazinone scaffold was developed,[3] and simultaneously we have shown that microwave-assisted cross-coupling reactions constitute a very mild method to introduce different alkyl and aryl groups to the most active C3-position of the pyrazinone ring.[4]

We became interested in investigating the possible bioactivity of C3-aroylated 2(1*H*)-pyrazinones. This was inspired by the fact that related 3-aroylquinoxalin-2(1*H*)-ones **I** have been described as late sodium channel inhibitors[5] and 3-benzoyl-2-piperazinyl-quinoxalines **II** have been reported as potential antitumor agents[6] (Figure 1). Although the synthesis of highly functionalized 3-carboxamide 2(1*H*)-pyrazinone derivatives has been recently reported,[7] to the best of our knowledge the selective aroylation of the C3-position of the 2(1*H*)-pyrazinone system has not yet been described. Preliminary experiments using a Stille protocol, combining the C3-stannylated pyrazinone with a suitable aroyl chloride, failed to give acceptable yields in our hands.[8] In light of the possible medicinal use of our aroylated compounds, we decided to avoid the use of transition metal catalysis and explored a carbene-catalyzed protocol.

By far the most studied members of nucleophilic carbenes are the *N*-heterocyclic carbenes (NHCs).[9,10] The term NHC came into use only recently, but the existence of such species was clearly established half a century ago when Breslow[11] postulated in 1958 that the thiazolium moiety in thiamine, a coenzyme that catalyzes decarboxylation of pyruvic acid, is acidic enough to be deprotonated under mildly basic conditions, resulting in the generation of a thiazolydinene species. Since then an increasing interest in the application of nucleophilic carbenes as organocatalysts has emerged. Metal-free catalyzed processes are interesting alternatives to organometal-catalyzed processes since they are often more economical and have a benign environmental impact. Initially primarily studied to promote the benzoin condensation,[12] a tremendous increase of the scope of NHCs was reported through the years, resulting in an ever-increasing number of reactions that can be promoted, for example, the Stetter reaction,[13,14] hydroacylation reactions,[15] homoenolate generation,[16] 1,2-additions,[17] polymerizations,[18] etc.

Of particular interest in the light of solving our problem is the application of NHCs for performing aroylation reactions. Although this process has been scarcely described with activated halides such as benzyl halides,[19] *p*-nitrofluorobenzenes,[20] and heteroaryl-chlorides[21] as electrophilic substrates, to the best of our knowledge there is no single report regarding the coupling of a Breslow intermediate with the imidoylchloride system of a 3-chloro-2(1*H*)-pyrazinone. We were therefore keen to know whether the Breslow intermediate, which is generated *in situ* from an aromatic aldehyde and a suitable NHC, can react with the 3-chloro-2(1*H*)-pyrazinone to afford the desired and hitherto unknown aroylated system (Figure 2).

To our satisfaction, when model substrate 3,5-dichloro-1-(4-methoxybenzyl)-6-methylpyrazin-2(1*H*)-one (**1a**) was subjected to aroylation with 4-methoxybenzaldehyde (**2a**) using NHC catalyst A and NaH as base in DMF as described in the literature,[20] the desired aroylated product 5-chloro-3-(4-methoxybenzoyl)-1-(4-methoxybe-

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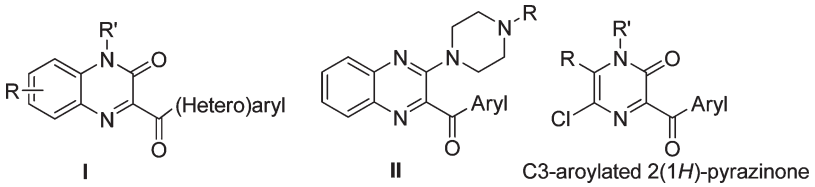
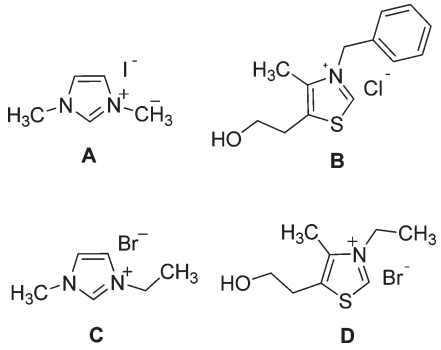


Figure 1. Bioactive 3-aroylquinoxalin-2(1*H*)-ones **I** and 3-benzoyl-2-piperazinylquinoxalines **II**.

nzyl)-6-methylpyrazin-2(1*H*)-one (**3a**) was obtained in 62% isolated yield (Table 1, entry 1). Screening further different organic and inorganic bases either gave no reaction with decomposition of starting materials or traces of the corresponding product as was determined via GC/MS or TLC analysis (Table 1, entries 2−5). However, changing the solvent from DMF to DMSO resulted in a major improvement of the reaction outcome yielding product **3a** in 83% (Table 1, entry 7). No improvement was seen when switching to less polar solvents or different NHCs (B, C, and D) (Table 1, entries 8−13). Lowering the catalyst loading to 5 mol % did not affect the reaction outcome and the product was isolated in 84% yield. The best condition was obtained using catalyst A (5 mol %), NaH (2.0 equiv) as base and DMSO (4 mL) as solvent and stirring the reaction mixture at rt for 0.5 h (Table 1, entry 14).



With this optimized condition in hand, the scope of the NHC-catalyzed aroylation of 3,5-dichloro-2-(1*H*)-pyrazinones **1b**−**k** was investigated (Table 2). It was found that most of the reactions proceeded well with good to excellent yield. The nature of the C6-substituent of the pyrazinone does not seem to play a significant role for the outcome of the reaction (Table 2, entries 1−9). Only when a benzyl group was present at the C6-position, the yield dropped to 52% (Table 2, entry 10).

Next the optimized protocol was explored for variously substituted (hetero)aromatic aldehydes as well as some aliphatic aldehydes. The desired aroylated products **3l**−**y** were obtained in good yields (Scheme 1).

When aliphatic aldehydes were used, the reaction did not proceed at all, and the corresponding starting materials were decomposed.[22] Interestingly, *ortho*-substituted benzaldehydes also give good yields. When furfural was employed as heteroaromatic aldehyde, the corresponding aroylated product was formed in mere 36% isolated yield (Scheme 1).

In summary, we have successfully elaborated an organo-catalyzed chemoselective procedure for the C3-aroylation of 3,5-dichloro-2-(1*H*)-pyrazinones using NHCs. This method is mild and efficient, and different substituents on the pyrazinone scaffold are tolerated, as well as variously substituted benzaldehydes. To the best of our knowledge this is the first report regarding the coupling of a Breslow intermediate with the imidoylchloride system of a 3,5-dichloro-2(1*H*)-pyrazinone.

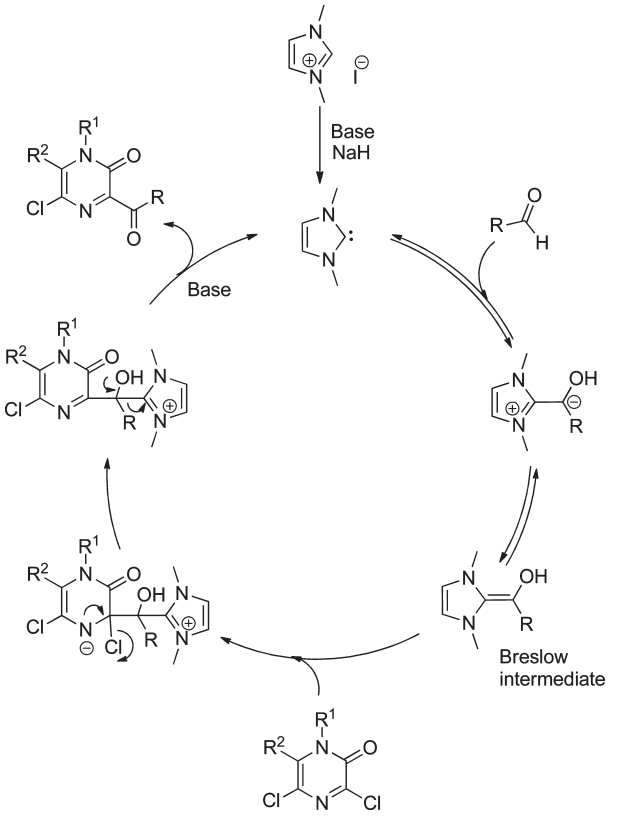


Figure 2. Proposed approach to 3-aroyl-2(1*H*)-pyrazinones applying a Breslow intermediate.

EXPERIMENTAL SECTION

General Procedure for *N*-Heterocyclic Carbene Catalyzed Aroylation of 3,5-Dichloro-2(1*H*)-pyrazinone 1a−l (Tables 1 and 2, and Scheme 1). To a oven-dried two-necked flask equipped with rubber septum and stir bar were added 3,5-dichloro-2(1*H*)-pyrazinone **1a**−**l** (0.33 mmol, 1 equiv), NHC catalyst A (5 mol %), corresponding aldehyde **2a**−**o** (0.4 mmol, 1.2 equiv), and DMSO (4 mL) as solvent. The resulting solution was flushed with argon (3 times), stirred for 10 min, and then cooled to 0 °C. Then NaH (2.0 equiv, 60% in mineral oil) was added in one shot, and the reaction mixture was allowed to warm to room temperature and was further stirred for 0.5−3 h. The reaction was monitored via TLC analysis, and conversion was determined via GC/MS and TLC analysis. After the reaction was complete, H_2O (20 mL) was added, and the mixture was extracted by CH_2Cl_2 (3 × 50 mL). The combined organic layers were extracted with brine (25 mL) and H_2O (20 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The resulting crude product was purified by silica gel column chromatography using (hexane/EtOAc 9:1 to 7:3) to afford corresponding C3-aroylated products **3a**−**y** in the below mentioned yields.

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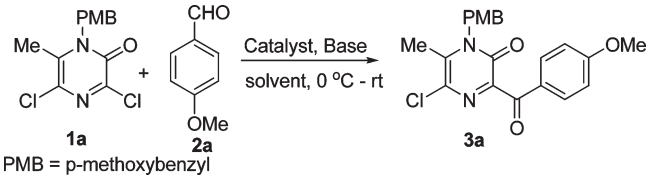
Table 1. Preliminary Study for NHC-Catalyzed Aroylation of 3,5-Dichloro-2(1*H*)-pyrazinone 1a[a]



PMB = p-methoxybenzyl

entry	catalyst (mol %)	base (equiv)	time (h)	solvent	yield[b] (%)
1	A (30)	NaH (2.0)	0.5	DMF	62
2	A (30)	DIEA (1.2)	1	DMF	NR[c]
3	A (30)	Cs_2CO_3 (1.2)	24	DMF	NR[c]
4	A (30)	Et_3N (1.2)	1	DMF	traces[d]
5	A (30)	DBU (1.2)	1	DMF	NR[c]
6	A (30)	LiHMDS (1.2)	0.5	DMF	36
7	A (30)	NaH (2.0)	0.5	DMSO	83
8	A (30)	NaH (2.0)	4	THF	traces[d]
9	A (30)	NaH (2.0)	4	dioxane	traces[d]
10	A (30)	NaH (2.0)	4	CH_3CN	traces[d]
11	B (30)	NaH (2.0)	1	DMSO	NR[c]
12	C (30)	NaH (2.0)	1	DMSO	traces[d]
13	D (30)	NaH (2.0)	1	DMSO	NR[c]
14	**A (5)**	**NaH (2.0)**	**0.5**	**DMSO**	**84**
15	A (5)	NaH (2.0)	0.5	DMA	75
16	A (5)	NaH (2.0)	0.5	NMP	71
17	A (1)	NaH (2.0)	0.5	NMP	traces[d]
18	A (1)	NaH (2.0)	0.5	DMSO	traces[d]

[a] See Experimental Section. [b] Isolated yields. [c] NR = no reaction with decomposition of starting materials was observed. [d] Detected via GC/MS and/or TLC analysis.

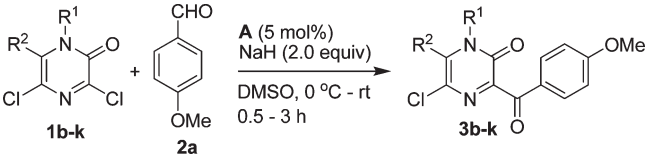
5-Chloro-3-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-6-methyl-pyrazin-2(1*H*)-one (3a). Yellow solid, mp 172−174 °C, yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 8.85 Hz, 2H), 7.21 (d, J = 8.46 Hz, 2H), 6.94 (d, J = 8.85 Hz, 2H), 6.87 (d, J = 8.67 Hz, 2H), 5.30 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 164.3, 159.5, 154.3, 148.6, 139.2, 132.5, 128.1, 126.1, 125.8, 114.50 113.9, 55.5, 55.3, 48.5, 17.3. HRMS (EI): calcd for $C_{21}H_{19}ClN_2O_4$ 398.1033, found 398.1044.

5-Chloro-6-isobutyl-3-(4-methoxybenzoyl)-1-(4-ethoxybenzyl)-pyrazin-2(1*H*)-one (3b). Brown viscous oil, yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 8.85 Hz, 2H), 7.15 (d, J = 8.46 Hz, 2H), 6.94 (d, J = 8.85 Hz, 2H), 6.87 (d, J = 8.67 Hz, 2H), 5.32 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.79 (d, J = 7.32 Hz, 2H), 2.20−2.11(m, 1H), 1.08 (d, J = 6.57 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 164.3, 159.4, 154.3, 148.9, 142.0, 132.5, 128.5, 128.0, 126.6 (x 2), 114.4, 113.9, 55.5, 55.3, 48.1, 38.3, 28.9, 22.5. HRMS (EI): calcd for $C_{24}H_{25}ClN_2O_4$ 440.1503, found 440.1497.

5-Chloro-3-(4-methoxybenzoyl)-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3c). Yellow solid, mp 124−125 °C, yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.67 Hz, 2H), 7.33−7.29 (m, 3H), 6.96−6.91 (m, 4H), 5.04 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 164.5, 160.2, 153.1, 152.5, 132.6, 132.3, 130.8, 128.1, 127.7, 125.8, 125.3, 114.8, 114.0, 113.7, 55.5, 55.3, 52.3. HRMS (EI): calcd for $C_{20}H_{17}ClN_2O_4$ 384.0877, found 384.0884.

6-Benzyl-5-chloro-3-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-pyrazin-2(1*H*)-one (3d). Yellow solid, mp 107−108 °C, yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.80 Hz, 2H), 7.40−7.34 (m, 3H), 7.17−7.12 (m, 4H), 6.97 (d, J = 8.80 Hz, 2H), 6.88 (d, J = 8.56 Hz, 2H), 5.13 (s, 2H), 4.23 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 164.4, 159.5, 154.4, 150.2, 140.1, 133.8, 132.6, 129.5, 128.0, 127.8, 127.5, 127.1, 126.5, 114.6, 114.0, 55.5, 55.3, 48.0, 35.6. HRMS (EI): calcd for $C_{27}H_{23}ClN_2O_4$ 474.1346, found 474.1360.

Table 2. Investigation of the Substrate Scope[a]



entry	R^1	R^2	product	yield[b] (%)
1	PMB	isobutyl **1b**	**3b**	78
2	PMB	H **1c**	**3c**	70
3	PMB	Bn **1d**	**3d**	67
4	PMB	4-MeO-Ph **1e**	**3e**	81
5	Ph	4-MeO-Ph **1f**	**3f**	66
6	Me	Ph **1g**	**3g**	84
7	Ph	Me **1h**	**3h**	79
8	Me	Me **1i**	**3i**	75
9	Ph	2-MeO-Ph **1j**	**3j**	82
10	2-MeO-Bn	Bn **1k**	**3k**	52

[a] See Experimental Section [b] Isolated yields.

5-Chloro-3-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)pyrazin-2(1*H*)-one (3e). Yellow solid, mp 147−148 °C, yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 9.04 Hz, 2H), 7.09 (d, J = 8.80 Hz, 2H), 7.01−6.96 (m, 4H) 6.83 (d, J = 8.56 Hz, 2H), 6.72 (d, J = 8.80 Hz, 2H), 5.07 (s, 2H), 3.89 (s, 6H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 164.4, 161.0, 159.3, 154.1, 151.0, 141.0, 132.6, 130.7, 129.5, 128.0, 127.2, 126.6, 122.6, 114.4, 113.9, 113.8, 55.5, 55.4, 55.2, 49.5. HRMS (EI): calcd for $C_{27}H_{23}ClN_2O_5$ 490.1295, found 490.1318.

5-chloro-3-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-1-phenylpyrazin-2(1*H*)-one (3f). Yellow solid, mp 101−102 °C, yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 8.85 Hz, 2H), 7.30−7.23 (m, 3H), 7.09−7.03 (m, 4H) 6.98 (d, J = 8.85 Hz, 2H), 6.77 (d, J = 8.85 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 164.4, 160.2, 153.6, 151.7, 140.6, 136.6, 132.6, 131.2, 129.1, 128.9, 128.0, 125.9, 122.8, 113.9, 113.8, 55.5, 55.2. HRMS (EI): calcd for $C_{25}H_{19}ClN_2O_4$ 446.1033, found 446.1048.

5-Chloro-3-(4-methoxybenzoyl)-1-methyl-6-phenylpyrazin-2(1*H*)-one (3g). Yellow viscous oil, yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.85 Hz, 2H), 7.60−7.58 (m, 3H), 7.38−7.35 (m, 2H), 6.98 (d, J = 8.85 Hz, 2H), 3.89 (s, 3H), 3.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 164.5, 153.9, 150.1, 141.2, 132.7, 130.8, 130.6, 129.5, 128.5, 127.9, 125.5, 113.9, 55.6, 35.1. HRMS (EI): calcd for $C_{19}H_{15}ClN_2O_3$ 354.0771, found 354.0768.

5-Chloro-3-(4-methoxybenzoyl)-6-methyl-1-phenylpyrazin-2(1*H*)-one (3h). Brown solid, mp 105−106 °C, yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 8.85 Hz, 2H), 7.59−7.47 (m, 3H), 7.23−7.21 (m, 2H), 6.95 (d, J = 8.85 Hz, 2H), 3.87 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.5, 164.3, 153.9, 149.6, 139.0, 136.6, 132.6, 130.2, 129.9, 128.0, 127.0, 125.2, 113.9, 55.5, 18.7. HRMS (EI): calcd for $C_{19}H_{15}ClN_2O_3$ 354.0771, found 354.0774.

5-Chloro-3-(4-methoxybenzoyl)-1,6-dimethylpyrazin-2(1*H*)-one (3i). Yellow solid, mp 151−152 °C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.56 Hz, 2H), 6.94 (d, J = 8.80 Hz, 2H), 3.87 (s, 3H), 3.63 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

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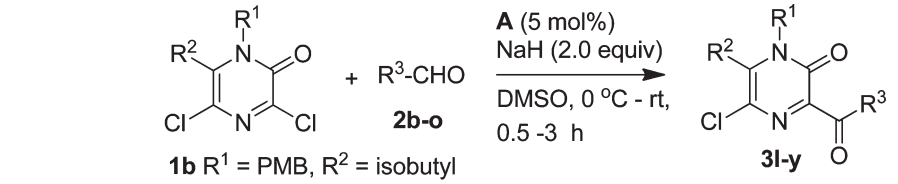
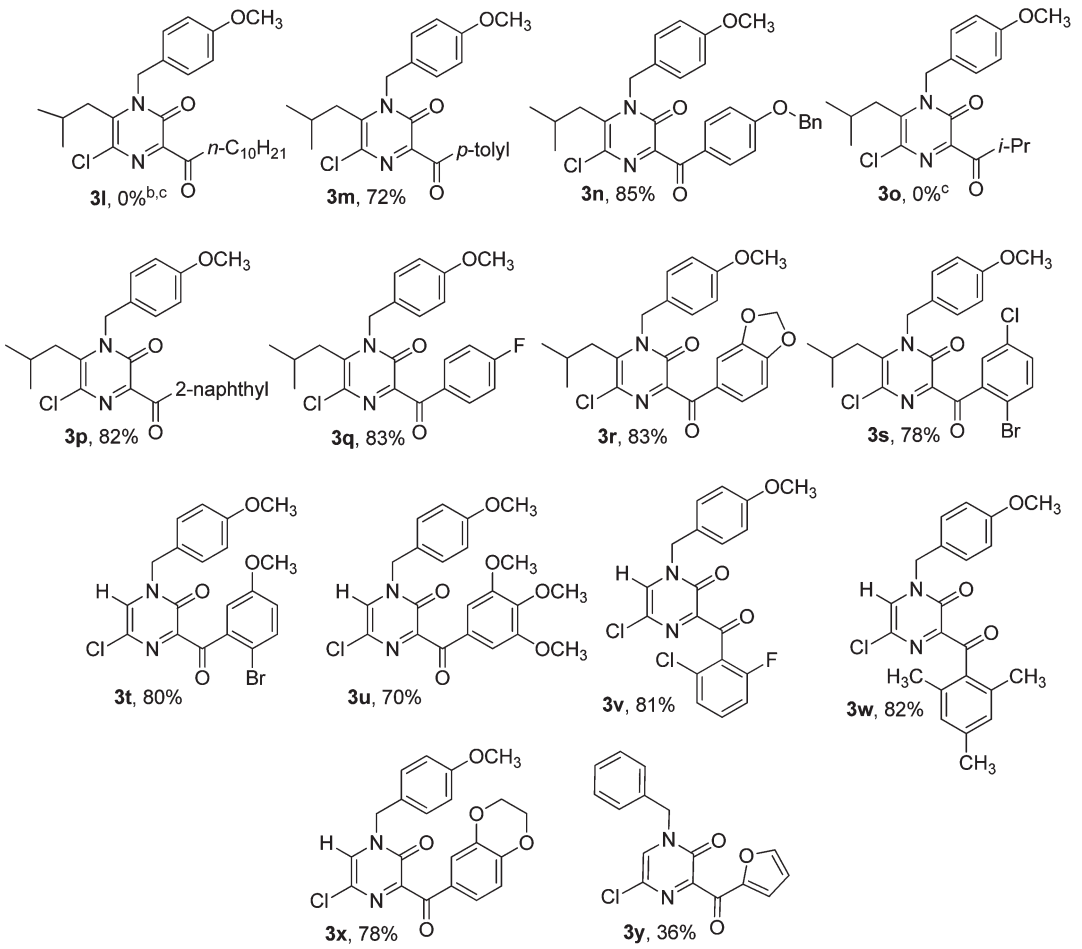
Scheme 1. Evaluation of the Scope with Variously Substituted Aldehydes[a]





[a] See Experimental Section. All yields are isolated after column chromatography. [b] NR = no reaction and only decomposition of starting materials was observed. [c] Determined via GC/MS and TLC analysis.

188.8, 164.3, 154.0, 147.8, 139.2, 132.5, 128.1, 125.3, 113.8, 55.5, 32.7, 17.5. HRMS (EI): calcd for $C_{14}H_{13}ClN_2O_3$ 292.0615, found 292.0597.

5-Chloro-3-(4-methoxybenzoyl)-1,6-dimethylpyrazin-2(1*H*)-one (3j). Yellow solid, mp 177−178 °C, yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.80 Hz, 2H), 7.28−7.23 (m, 2H), 7.20−7.18 (m, 3H), 7.11 (dd, J = 1.24, 7.56 Hz, 1H), 6.99−6.97 (m, 3H) 6.88 (t, J = 7.52 Hz, 1H), 6.72 (d, J = 8.28 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 164.4, 156.0, 153.7, 151.8, 138.7, 136.5, 132.7, 131.8, 130.7, 129.0, 128.5 (x 2), 128.0, 127.7, 127.2, 126.2, 120.4, 120.0, 113.9, 110.9, 55.5, 55.3. HRMS (EI): calcd for $C_{25}H_{19}ClN_2O_4$ 446.1033, found 446.1033.

5-Benzyl-5-chloro-3-(4-methoxybenzoyl)-1-(2-methoxy-benzyl) pyrazin-2(1*H*)-one (3k). Yellow solid, mp 90−91 °C, yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.56 Hz, 2H), 7.37−7.27 (m, 4H), 7.13 (d, J = 7.28 Hz, 2H), 6.97- 6.87 (m, 5H), 5.25 (s, 2H), 4.19 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 164.4, 156.4, 154.5, 150.0, 140.6, 134.1, 132.5, 129.3, 129.1, 128.1, 127.7, 127.6, 127.4, 122.4, 121.1, 113.9, 110.6, 55.5, 55.3, 48.8, 35.7. HRMS (EI): calcd for $C_{27}H_{23}ClN_2O_4$ 474.1346, found 474.1360.

5-Chloro-6-isobutyl-1-(4-methoxybenzyl)-3-(4-methylbenzoyl)-pyrazin-2(1*H*)-one (3m). Yellow oil, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.04 Hz, 2H), 7.27−7.25 (m, 2H), 7.15 (d, J = 8.56 Hz, 2H), 6.87 (d, J = 8.56 Hz, 2H), 5.29 (s, 2H), 3.79 (s, 3H), 2.79 (d, J = 7.28 Hz, 2H), 2.41 (s, 3H), 2.20−2.13 (m, 1H), 1.09 (d, J = 6.80 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 159.5, 154.3, 148.6, 145.0, 142.3, 132.6, 130.2, 129.2, 128.5, 126.7, 126.6 114.5, 55.3, 48.1, 38.3, 28.9, 22.5, 21.8. HRMS (EI): calcd for $C_{24}H_{25}ClN_2O_3$ 424.1554, found 424.1538.

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3-(4-(Benzyloxy)benzoyl)-5-chloro-6-isobutyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3n). Yellow solid, mp 158−159 °C, yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.84 Hz, 2H), 7.42−7.33 (m, 5H), 7.15 (d, J = 8.56 Hz, 2H), 7.01 (d, J = 9.08 Hz, 2H), 6.86 (d, J = 8.80 Hz, 2H), 5.32 (s, 2H), 5.14 (s, 2H), 3.79 (s, 3H), 2.78 (d, J = 7.28 Hz, 2H), 2.21−2.11 (m, 1H), 1.09 (d, J = 6.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 163.5, 159.5, 154.3, 148.9, 142.1, 136.0, 132.5, 128.7, 128.5, 128.3, 128.2, 127.4, 126.6, 126.1, 114.7, 114.5, 70.2, 55.3, 48.1, 38.3, 28.9, 22.5. HRMS (EI): calcd for $C_{30}H_{29}ClN_2O_4$ 516.1816, found 516.1829.

3-(2-naphthoyl)-5-chloro-6-isobutyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3p). Yellow viscous oil, yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (d, J = 8.49 Hz, 1H), 8.05 (d, J = 8.28 Hz, 1H), 7.90 (d, J = 7.92 Hz, 1H), 7.77 (d, J = 6.60 Hz, 1H), 7.62 (t, J = 6.94 Hz, 1H), 7.55 (t, J = 6.96 Hz, 1H), 7.48 (t, J = 7.71 Hz, 1H), 7.13 (d, J = 8.64 Hz, 2H),6.87 (d, J = 8.46 Hz, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 2.80 (d, J = 7.35 Hz, 2H), 2.22−2.13 (m, 1H), 1.09 (d, J = 6.60 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6, 159.5, 154.3, 149.2, 148.6, 142.8, 134.1, 133.9, 132.5, 131.7, 131.0, 128.5, 128.4, 126.8, 126.6, 126.5, 125.9, 124.2, 114.5, 55.3, 48.1, 38.4, 28.9, 22.6. HRMS (EI): calcd for $C_{27}H_{25}ClN_2O_3$ 460.1554, found 460.1552.

5-Chloro-3-(4-fluorobenzoyl)-6-isobutyl-1-(4-methoxybenzyl)-pyrazin-2(1*H*)-one (3q). Yellow semisolid, yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.16−7.12 (m, 4H), 6.87 (d, J = 8.56 Hz, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 2.81 (d, J = 7.32 Hz, 2H), 2.21−2.14 (m, 1H), 1.09 (d, J = 6.52 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 167.5, 164.9, 159.5, 154.2, 147.5, 143.1, 132.9, 132.8, 128.5, 126.6, 126.4, 115.8, 115.6, 114.5, 55.3, 48.3, 38.4, 29.0, 22.5. HRMS (EI): calcd for $C_{23}H_{22}ClFN_2O_3$ 428.1303, found 428.1303.

3-(Benzo[*d*][1,3]dioxole-5-carbonyl)-5-chloro-6-isobutyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3r). Yellow semisolid, yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49−7.46 (m, 2H), 7.15 (d, J = 8.67 Hz, 2H), 6.89−6.83 (m, 3H), 6.06 (s, 2H), 5.32 (s, 2H), 3.79 (s, 3H), 2.79 (d, J = 7.35 Hz, 2H), 2.20−2.09 (m, 1H), 1.09 (d, J = 6.78 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 159.4, 154.2, 152.7, 148.6, 148.2, 142.2, 129.7, 128.5, 127.5, 126.6, 126.5, 114.5, 109.1, 108.0, 102.0, 55.3, 48.2, 38.3, 29.0, 22.6. HRMS (EI): calcd for $C_{24}H_{23}ClN_2O_5$ 454.1295, found 454.1301.

3-(2-Bromo-5-chlorobenzoyl)-5-chloro-6-isobutyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3s). Yellow viscous oil, yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 2.46 Hz, 1H), 7.49 (d, J = 8.67 Hz, 1H), 7.31 (dd, J = 2.64, 8.49 Hz, 1H,), 7.11 (d, J = 8.49 Hz, 2H), 6.86 (d, J = 8.64 Hz, 2H), 5.33 (s, 2H), 3.78 (s, 3H), 2.81 (d, J = 7.35 Hz, 2H), 2.22−2.13 (m, 1H), 1.07 (d, J = 6.57 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 159.5, 154.0, 145.8, 144.3, 140.9, 134.1, 134.0, 132.3, 130.6, 128.4, 127.3, 126.1, 118.1, 114.5, 55.3, 48.2, 38.7, 28.9, 22.5. HRMS (EI): calcd for $C_{23}H_{21}BrCl_2N_2O_3$ 522.0113, found 522.0114.

3-(2-Bromo-5-methoxybenzoyl)-5-chloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3t). Yellow solid, mp 147−148 °C, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.80 Hz, 1H), 7.31−7.27 (m, 3H), 7.24 (d, J = 2.46 Hz, 1H), 6.95−6.91 (m, 3H), 5.05 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 160.2, 159.0, 153.0, 149.6, 139.1, 134.1, 130.6, 130.3, 126.0, 125.4, 119.9, 115.8, 114.7, 111.3, 55.6, 55.3, 52.1. HRMS (EI): calcd for $C_{20}H_{16}BrClN_2O_4$ 461.9982, found 461.9992. **LCMS (ESI)**: 951.1 ($2M^+$+Na^++H^+)

5-Chloro-1-(4-methoxybenzyl)-3-(3,4,5-trimethoxybenzoyl)-pyrazin-2(1*H*)-one (3u). Yellow solid, mp 161−162 °C, yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.31 (m, 3H), 7.18 (s, 2H), 6.93 (d, J = 8.46 Hz, 2H), 5.06 (s, 2H), 3.93 (s, 3H), 3.86 (s, 6H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 160.3, 153.0, 151.8, 143.8, 130.7, 129.7, 128.6, 125.6, 125.3, 114.7, 107.7, 61.0, 56.3, 55.3, 52.5. HRMS (EI): calcd for $C_{22}H_{21}ClN_2O_6$ 444.1088, found 444.1084.

5-Chloro-3-(2-chloro-6-fluorobenzoyl)-1-(4-methoxybenzyl)pyrazine-2(1*H*)-one (3v). Yellow solid, mp 111−112 °C, yield 81%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.37 (dd, J = 2.25, 8.10 Hz, 1H), 7.31 (d, J = 8.67 Hz, 2H), 7.22 (d, J = 8.10 Hz, 1H), 7.05 (t, J = 8.67 Hz, 1H), 6.94 (d, J = 8.46 Hz, 2H), 5.09 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.3, 161.7, 160.3, 158.3, 152.5, 145.3, 132.6, 132.3, 132.2, 131.8, 131.7, 130.8, 127.2, 126.9, 125.6, 125.5 (x 2), 125.1, 114.8, 114.5, 114.2, 55.3, 52.5. HRMS (EI): calcd for $C_{19}H_{13}Cl_2FN_2O_3$ 406.0287, found 406.0305.

5-Chloro-1-(4-methoxybenzyl)-3-(2,4,6-trimethylbenzoyl)-pyrazin-2(1*H*)-one (3w). Yellow viscous oil, yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.28 (m, 3H), 6.93 (d, J = 8.46 Hz, 2H), 6.84 (s, 2H), 5.06 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H), 2.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 160.3, 149.0, 139.5, 136.2, 135.1, 130.7, 130.5, 128.6, 125.5, 125.3, 114.8, 55.3, 52.3, 21.2, 19.9. HRMS (EI): calcd for $C_{22}H_{21}ClN_2O_3$ 396.1241, found 396.1289.

5-Chloro-3-(2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonyl)-1-(4-methoxy-benzyl)pyrazin-2(1*H*)-one (3x). Yellow solid, mp 151−152 °C, yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.44 (m, 2H), 7.31 (d, J = 8.56 Hz, 2H), 7.25 (bs, 1H(merged with chloroform peak)), 6.94−6.90 (m, 3H), 5.03 (s, 2H), 4.33−4.31 (m, 2H), 4.28−4.26 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6, 160.2, 153.1, 152.4, 149.2, 143.4, 130.7, 128.4, 128.2, 125.7, 125.4, 124.5, 119.5, 117.5, 114.7, 64.7, 64.0, 55.3, 52.2. HRMS (EI): calcd for $C_{21}H_{17}ClN_2O_5$ 412.0826, found 412.0812.

5-Chloro-3-(furan-2-carbonyl)-1-benzylpyrazin-2(1*H*)-one (3y). Brown viscous oil, yield 36%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.42−7.35 (m, 7H), 6.59 (q, J = 1.52 Hz, 1H), 5.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 152.7, 150.8, 149.3, 148.4, 133.6, 130.1, 129.3, 129.2, 129.1, 125.4, 122.4, 112.7, 52.9. HRMS (EI): calcd for $C_{16}H_{11}ClN_2O_3$ 314.0458, found 314.0472.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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