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A convenient microwave-assisted desulfitative dimethylamination of the 2(1*H*)-pyrazinone scaffold using *N*,*N*-dimethylformamide

Anuj Sharma, Vaibhav Pravinchandra Mehta, Erik Van der Eycken*

Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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Abstract

A convenient microwave-assisted methodology is developed for the generation of 5-chloro-3-(dimethylamino)pyrazin-2(1*H*)-ones. The method entails a chemoselective desulfitative removal of a phenylthioether bond upon DMF/H_2O treatment in the presence of sodium carbonate, yielding the desired compounds in 73–96%.

Keywords: Microwave-assisted organic synthesis (MAOS); 2(1*H*)-Pyrazinone; Dimethylamination; Desulfitative; DMF

1. Introduction

There is no dearth of compounds containing a dimethylamino functionality in nature as well as in the organic chemist's arsenal.[1] For example, taxoids, a series of anti-cancer drugs, which inhibit cell growth by interacting with microtubules, often contain a dimethylamino moiety as part of the pharmacophore.[2] The dimethylamino moiety is also found in a number of active tetracyclines.[3] Similarly, a compound like austrospicatine, bearing a dimethylamino function, has shown promising insecticidal activity.[4] Moreover, many of the dimethylamino substituted heterocyclic compounds represent important drugs like, e.g., ampyzine, triampyzine, and methadone.[5] 6-Dimethylamino-purine is useful as inhibitor of cyclin dependent kinase and in cloning of animals via nuclear transfer from adult somatic cells.[6] A convenient method for the introduction of a dimethylamino group in (hetero-)aromatic compounds is the reaction of halogenated substrates with DMF at elevated temperature in the presence of a base,[7] as this avoids the handling of low boiling dimethylamine. Mostly the reaction proceeds slowly although resulting in rather good yields. It is also reported that thioethers could be used in amination reactions applying a two-step protocol involving previous oxidation to the sulfoxide followed by substitution with a suitable amine.[8] However, direct amination without prior oxidation of the thioether, has rarely been described[9] and, to the best of our knowledge, dimethylamination using DMF as the amine source applying thioether compounds, has only been mentioned once as a side reaction upon treatment of a 2-methylthiotetrahydroquinazolinone with morpholine in DMF at 180 °C, without further exploring the scope and limitations of this coversion.[10] Here we will comment on an unprecedented and convenient microwave-assisted dimethylamination of 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones applying a mixture of DMF/H_2O (1:1) in the presence of sodium carbonate.

We have previously explored a number of transition metal catalyzed cross-coupling reactions, at the reactive imidoyl chloride moiety in C3-position as well as at the unreactive C5-position of the 3,5-dichloro-2(1*H*)-pyrazinone scaffold applying microwave-assisted protocols.[11] During our endeavors to perform microwave-assisted Suzuki-arylation at the unreactive C5-position[11a] of 5-chloro-1-(4-methoxybenzyl)-3-(phenylsulfanyl)pyrazin-2(1*H*)-one (**1a**) with phenylboronic acid

* Corresponding author. Tel.: +32 16 327406; fax: +32 16 327990.
E-mail address: erik.vandereycken@chem.kuleuven.be (E. Van der Eycken).

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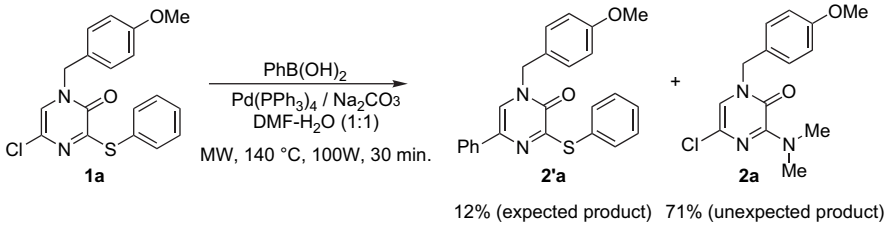


Scheme 1. Attempted arylation of 5-chloro substituted pyrazin-2(1*H*)-one (**1a**).

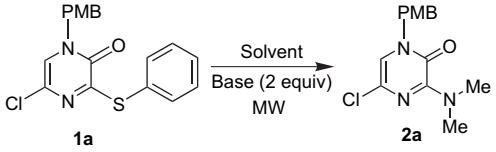
in the presence of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) and sodium carbonate as the base, we evaluated a solvent mixture of DMF/H_2O (1:1) (Scheme 1). To our surprise, only 12% of the desired C5-arylated compound **2′a** was obtained. Instead, the reaction proceeded chemoselectively to produce 71% of the C3-aminated 5-chloro-3-(dimethylamino)-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**2a**).

These results prompted us to explore further this desulfitative dimethylamination reaction using DMF as amine source, and an optimization study was undertaken. All inorganic bases explored, resulted in the formation of **2a** in good to excellent yields (Table 1, entries 1–3 and 6–8). On the contrary, when no base was added, the reaction did not proceed (Table 1, entry 4). Also the presence of water seemed to be crucial for the amination (Table 1, entry 5). This might be attributed to a better solvation of the inorganic base. Best conditions were found to be focused microwave irradiation for 30 min at 150 W maximum power and a ceiling temperature of 140 °C of a mixture of compound **1a** together with 2 equiv of Na_2CO_3 in DMF/water (1:1) yielding compound **2a** in 96% (Table 1, entry 2).

After having an efficient protocol for dimethylamination at hand, we next investigated the scope and limitations of the optimized protocol. A series of differently substituted 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones[11f] (**1b–h**) was subjected to amination reaction (Table 2). The respective dimethylamino products **2b–h** were obtained in good to excellent yields.

Next, we were interested to see if an alkylthio substituent in C3-position, instead of a phenylthio substituent, would allow the same transformation. Therefore the ethylthio-substituted pyrazinone **1i** was subjected to the optimized protocol. Gratifyingly the reaction proceeded smoothly upon irradiation for

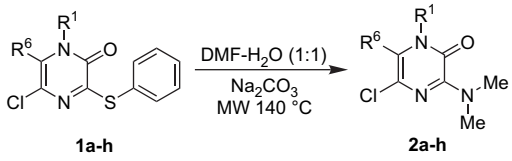
Table 1
Optimization of the desulfitative dimethylamination of **1a**[a]

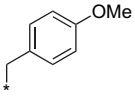
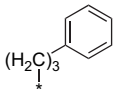
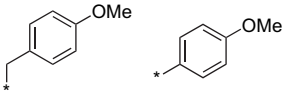
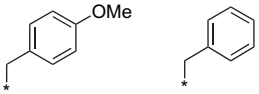
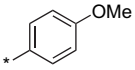


Entry	Base	Solvent (1:1)	Time (min)	Yield[b] (%)
1	Na_2CO_3	DMF/H_2O	20	71
2	Na_2CO_3	DMF/H_2O	30	96
3	Na_2CO_3	DMF/H_2O	45	94
4	—	DMF/H_2O	60	0[c]
5	Na_2CO_3	DMF	60	63 (30)[d]
6	NaOH	DMF/H_2O	30	85
7	K_2CO_3	DMF/H_2O	30	91
8	KOH	DMF/H_2O	30	87

[a] Reactions were run on a 0.3 mmol scale of **1a** in DMF/H_2O (1:1) (3 mL) with 2 equiv of base (0.6 mmol). The mixture was irradiated in a sealed tube at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time.
[b] Isolated yield.
[c] All starting materials recovered.
[d] Value in parenthesis indicate yield of unreacted starting material.

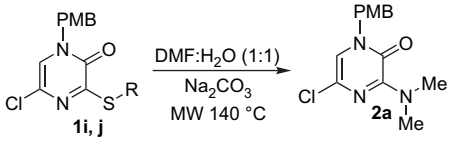
Table 2
Evaluation of the scope of dimethylamination for different pyrazinones (**1a–h**)[a]



Entry	R^1	R^6	Compd.	Time (min)	Yield[b] (%)
1		H	**2a**	30	96
2		Me	**2b**	30	91
3	Me	Me	**2c**	60[c]	73[d]
4		H	**2d**	30	81
5		H	**2e**	60[c]	85
6			**2f**	30	92
7			**2g**	30	94
8		H	**2h**	30	83

[a] Reactions were run on a 0.3 mmol scale of **1a–h** in DMF/H_2O (1:1) (3 mL) with 2 equiv of base (0.6 mmol). The mixture was irradiated in a sealed tube at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time.
[b] Isolated yield.
[c] As some unreacted starting material was observed by GC–MS, the reaction mixture was subsequently run for another 30 min.
[d] Around 15–20% starting material still remained based on GC analysis.

Table 3
Extension of the procedure to alkylthio-substituted and solid phase linked pyrazinones[a]



Entry	R	Compd.	Time (min)	Yield[b] (%)
1	Ethyl	**2a**	60	62
2[c]	— 	**2a**	30	71

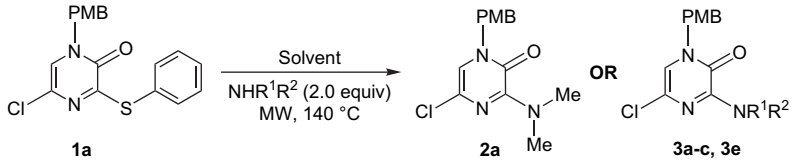
[a] Reactions were run on a 0.3 mmol scale of **1i**, **j** in DMF/H_2O (1:1) (3 mL) with 2 equiv of base (0.6 mmol). The mixture was irradiated in a sealed tube at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time.
[b] Isolated yield.
[c] The calculated loading of the pyrazinone bound to the mercapto phenylpropionyl AM resin was found to be 0.84 mmol/g.

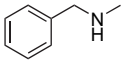
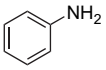
60 min, yielding the desired compound in 62% (Table 3, entry 1). Moreover, to broaden the scope of our protocol, a pyrazinone **1j** linked with a commercially available mercapto phenylpropionyl AM resin (loading 0.88 mmol/g) via a thioether bond at its C3-position, was subjected to the same procedure. To our delight we notified that, applying the standard conditions, the aminated pyrazinone **2a** was isolated in 71% yield, after an irradiation time of only 30 min (Table 3, entry 2). To the best of our knowledge, there are no precedents described in literature, where a desulfitative amination protocol is used as traceless linking concept for solid phase organic synthesis.[11e] This interesting extension of our methodology opens the way for the fast generation of small combinatorial libraries of valuable C3-dimethylaminated pyrazinones, which will be investigated in due course.

Finally, we decided to investigate the possibility to introduce amines other than dimethylamine using our desulfitative protocol. Obviously, a possible competition with dimethylamination could be expected. Therefore we decided to perform the experiments applying three different conditions: (i) standard conditions using DMF/H_2O (1:1) and Na_2CO_3, (ii) DMF, and (iii) dioxane/H_2O (1:1) and Na_2CO_3 (Table 4).

When DMF/H_2O (1:1) with Na_2CO_3 was used (Table 4, entries 1, 4, 7, 10, 13, and 16) a strong preference for the formation of the dimethylaminated compound was observed, which is consistent with the conclusions drawn from Table 1. However, when solely DMF was used, the amines reacted

Table 4
Evaluation of other amines for the desulfitative protocol[a]

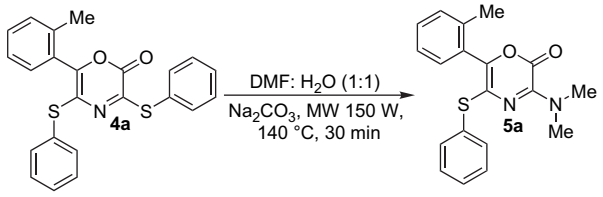


Entry	NHR^1R^2	Solvent	Time (min)	Product yield[b] (%)	
1		DMF/H_2O	30	**2a** (81)	**3a** (12)
2		DMF	30	**2a** (5)	**3a** (91)
3		Dioxane/H_2O	30	—	**3a** (96)
4		DMF/H_2O	30	**2a** (79)	**3b** (14)
5		DMF	30	**2a** (5)	**3b** (91)
6		Dioxane/H_2O	30	—	**3b** (95)
7		DMF/H_2O	60	**2a** (68)	**3c** (12)[c]
8		DMF	60	**2a** (15)	**3c** (72)[c]
9		Dioxane/H_2O	60	**2a** (0)	**3c** (15)[c,d]
10	$NH(hex)_2$	DMF/H_2O	60	**2a** (81)	**3d** (traces)
11		DMF	60	**2a** (0)	**3d** (0)[e]
12		Dioxane/H_2O	60	**2a** (0)	**3d** (traces)[c,d]
13	Isobutyl amine	DMF/H_2O	30	**2a** (75)	**3e** (5)
14		DMF	30	**2a** (38)	**3e** (55)
15		Dioxane/H_2O	30	**2a** (0)	**3e** (26)[d]
16		DMF/H_2O	60	**2a** (83)	**3f** (0)
17		DMF	60	**2a** (0)	**3f** (0)[e]
18		Dioxane/H_2O	60	**2a** (0)	**3f** (0)[c,d]
19	$NH(CH_3)_2$	Dioxane/H_2O	60	**2a** (25)[c]	—

[a] Reactions were run on a 0.3 mmol scale of **1a** in DMF/H_2O (1:1) or dioxane/H_2O (1:1) (3 mL) with 2 equiv of amine (0.6 mmol) and 2.0 equiv of Na_2CO_3 (0.6 mmol). Alternatively, reactions were run on a 0.3 mmol scale of **1a** in DMF (3 mL) with 2 equiv of amine (0.6 mmol). The mixture was irradiated in a sealed tube at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time.
[b] Isolated yield.
[c] Some unreacted starting material was recovered despite an extended irradiation time.
[d] Unidentified side product formed.
[e] Only starting material recovered.

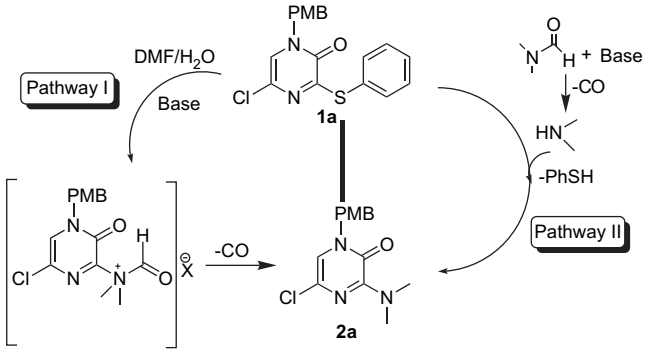
preferentially forming compounds **3a**, **3b**, **3c**, and **3e** (Table 4, entries 2, 5, 8, and 14). In the case of the strongly basic piperidine and morpholine, only traces of the dimethylaminated product were formed while the respective aminated product was isolated in excellent yield (Table 4, entries 2 and 5). Similarly, the respective aminated products **3c** and **3e** formed in better yield than the dimethylaminated product **2a** in case of benzylmethylamine and isobutyl amine (Table 4, entries 8 and 14). However, in the case of the weakly basic amines dihexylamine and aniline, neither the aminated nor the dimethylaminated product formed (Table 4, entries 11 and 17). Finally, when dioxane/H_2O (1:1) was used as alternative solvent mixture, with the exception of piperidine and morpholine (Table 4, entries 3 and 6), the amines reacted very poorly (Table 4, entries 9, 12, 15, and 18). It is worth mentioning that in the latter cases, little or no starting material could be recovered as some unidentified side products were formed. Conclusively, the DMF method can be successfully applied as an amination tool for strongly basic amines. Next we were interested in comparing the potential of DMF as a dimethylamination source with the direct use of dimethylamine (Table 4, entry 19). When a mixture of **1a** and 2.0 equiv of an aqueous solution of dimethylamine (40%) was irradiated at 140 °C (150 W) for 30 min in presence of 2.0 equiv of Na_2CO_3 and 3 mL of dioxane/H_2O (1:1), surprisingly, a poor yield of only 25% of the dimethylaminated product was obtained. This clearly underscores the importance of our DMF-protocol as a better aminating source than dimethylamine itself.

Finally, the usefulness of this methodology was also investigated on an alternative heterocyclic system different from pyrazinones. Oxazinone **4a** was reacted in a DMF/H_2O (1:1) mixture under the optimized conditions, and to our delight, the product **5a** was formed in 72% yield (Scheme 2).



Scheme 2. Dimethylamination of oxazinone **4a**.

Regarding the mechanism of the developed amination protocol, there are two possibilities as shown in Scheme 3.



Scheme 3. Plausible mechanisms for the amination protocol.

According to Agarwal et al.,[7f] the reaction should start with a nucleophilic attack of DMF on the C3-position of the pyrazinone followed by loss of carbon monoxide resulting in the dimethylaminated product (Pathway I). However, more likely the reaction starts with a base assisted cleavage of DMF to form the required dimethylamine,[12] which is acting as the nucleophile for the formation of the required product (Pathway II).

To get some hint for the actual mechanism, we performed a blank run, irradiating a DMF/H_2O (1:1) mixture in the presence of Na_2CO_3 applying exactly the same conditions as used in our experiments but without the addition of the pyrazinone. GC–MS analysis at low temperature[13] as well as FTIR analysis revealed that this crude reaction mixture contained dimethylamine, suggesting a reaction Pathway II.[14]

In conclusion, we have elaborated a convenient and fast, microwave-assisted chemoselective procedure for the desulfitative dimethylamination of variously substituted 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones using a DMF/water mixture in the presence of sodium carbonate. The aminated compounds are obtained in excellent yields. The merits of the protocol are (i) DMF as an easy to handle substitute for dimethylamine, (ii) a one-step desulfitative amination without the necessity of prior oxidation of the thioether, and (iii) short reaction times and high yields applying microwave irradiation. We have demonstrated that the method could be extended to alkylthio-substituted pyrazinones as well as to solid phase linked pyrazinones providing a way of traceless linking.

2. Experimental section

2.1. General experimental methods

^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10,000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70–230 mesh silica gel (E. M. Merck)) were used. Melting points of the compounds were determined using a Reichert-Jung Thermovar apparatus and are uncorrected.

2.2. Microwave irradiation experiments

All microwave irradiation experiments were carried out in a dedicated CEM Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. Initially, microwave irradiation of required watts was used and the temperature is

being ramped from room temperature to the desired temperature. Once this was reached the reaction mixture was held at this temperature for the required time. The reaction mixture was continuously stirred during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, gas jet cooling cooled the reaction vessel rapidly to ambient temperature.

2.3. General procedure for preparation of compounds **2a–h**, **3a–c**, **3e**, **5a**

In a 10 mL reaction glass vial containing a stirring bar were added successively sulfanyl pyrazinone (0.3 mmol), Na_2CO_3 (0.60 mmol, 2 equiv), amine (0.6 mmol, 2.0 equiv), and/or DMF/H_2O (1:1) (3 mL). Alternatively, in case of **3c**, sulfanyl pyrazinone (0.3 mmol), amine (0.6 mmol, 2.0 equiv) in 3 mL of DMF is taken. The vial was sealed tightly with a Teflon septum and irradiated for the stipulated time using 150 W maximum power at a ceiling temperature of 140 °C (CEM Discover® monomode instrument, 2.45 GHz with a power limit of 300 W). The temperature was ramped from room temperature to 140 °C in 2 min. After completion of the reaction, the vial was cooled with gas jet cooling to ambient temperature. The mixture was extracted with ethyl acetate (3×15 mL) and the organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was chromatographed over silica gel (40% EtOAc/heptane) to yield the products.

2.3.1. 1-(4-Methoxybenzyl)-5-chloro-3-(dimethylamino)-pyrazin-2(1H)-one (**2a**)

Yield 96%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J=9.4 Hz, 2H), 6.87 (d, J=9.3 Hz, 2H), 6.53 (s, 1H), 4.88 (s, 2H), 3.79 (s, 3H, −OMe), 3.31 (s, 6H, N−$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 151.5, 129.9, 127.5 (×2), 126.0, 114.4 (×2), 113.5, 55.4, 51.6, 40.4. HRMS (EI): $C_{14}H_{16}ClN_3O_2$ calcd 293.0931, found 293.0933.

2.3.2. 1-Benzyl-5-chloro-3-(dimethylamino)-6-methylpyrazin-2(1H)-one (**2b**)

Yield 73%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.30 (m, 2H), 7.24−7.21(m, 3H), 4.89 (s, 2H), 3.30 (s, 6H, N−$(CH_3)_2$), 2.34 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 151.5, 139.9, 130.1, 128.6, 128.4, 127.5, 126.4, 125.9, 114.1, 51.5, 40.1, 16.4. HRMS (EI): $C_{14}H_{16}ClN_3O$ calcd 277.0982, found 277.0989.

2.3.3. 5-Chloro-3-(dimethylamino)-1,6-dimethylpyrazin-2(1H)-one (**2c**)

Yield 73%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (s, 3H), 3.24 (s, 6H, N−$(CH_3)_2$), 2.33 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 149.6, 124.7, 121.5, 40.1, 32.4, 16.3. HRMS (EI): $C_8H_{12}ClN_3O$ calcd 201.0669, found 201.0674.

2.3.4. 5-Chloro-3-(dimethylamino)-1-(3-phenylpropyl)-pyrazin-2(1H)-one (**2d**)

Yield 81%, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.26 (m, 2H), 7.22−7.17(m, 3H), 6.48 (s, 1H), 3.77 (t, J=8.3 Hz, 2H), 3.30 (s, 6H, N−$(CH_3)_2$), 2.68 (t, J=8.3 Hz, 2H, −C−CH_2), 2.10−2.00 (m, 2H, −C−CH_2−C). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 151.4, 140.6, 128.6, 128.4, 126.3, 125.9, 114.0, 49.3, 40.4, 32.9, 29.9. HRMS (EI): $C_{15}H_{18}ClN_3O$ calcd 291.1138, found 291.1140.

2.3.5. 5-Chloro-1-(cyclohexylmethyl)-3-(dimethylamino)pyrazin-2(1H)-one (**2e**)

Yield 85%, light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 3.58 (d, J=7.96 Hz, 2H), 3.30 (s, 6H, N−$(CH_3)_2$), 1.79−1.66 (m, 6H), 1.24−1.17 (m, 3H), 1.02−0.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.6, 151.5, 140.6, 125.5, 114.9, 55.8, 40.4, 36.9, 30.7, 26.3, 25.7. HRMS (EI): $C_{13}H_{20}ClN_3O$ calcd 269.1295, found 269.1290.

2.3.6. 1-(4-Methoxybenzyl)-5-chloro-3-(dimethylamino)-6-(4-methoxyphenyl)pyrazin-2(1H)-one (**2f**)

Yield 92%, dark brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J=9.3 Hz, 2H), 6.87 (d, J=9.3 Hz, 2H), 6.80 (d, J=9.6 Hz, 2H), 6.72 (d, J=9.4 Hz, 2H), 4.90 (s, 2H), 3.84 (s, 3H, −OMe), 3.76 (s, 3H, −OMe), 3.34 (s, 6H, N−$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 159.3, 158.0, 153.7, 135.3, 133.0, 131.4, 129.5, 129.4, 129.3, 128.0, 127.6, 127.5, 123.1, 113.9, 113.8, 55.4, 55.3, 49.0, 40.4. HRMS (EI): $C_{21}H_{22}ClN_3O_3$ calcd 399.1350, found 399.1347.

2.3.7. 1-(4-Methoxybenzyl)-6-benzyl-5-chloro-3-(dimethylamino)pyrazin-2(1H)-one (**2g**)

Yield 94%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.26 (m, 3H), 7.13 (d, J=8.1 Hz, 2H), 7.02 (d, J=9.3 Hz, 2H), 6.85 (d, J=9.3 Hz, 2H), 4.96 (s, 2H), 3.98 (s, 2H, −Ph−CH_2), 3.79 (s, 3H, −OMe), 3.33 (s, 6H, N−$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 152.8, 150.4, 136.9, 129.2, 128.1, 127.6, 127.5, 127.1, 126.9, 122.9, 114.5, 55.4, 47.5, 40.3, 34.9. HRMS (EI): $C_{21}H_{22}ClN_3O_2$ calcd 383.1401, found 383.1406.

2.3.8. 5-Chloro-3-(dimethylamino)-1-(4-methoxyphenyl)pyrazin-2(1H)-one (**2h**)

Yield 83%, brown solid, mp 70−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J=9.8 Hz, 2H), 6.97 (d, J=9.8 Hz, 2H), 6.63 (s, 1H), 3.83 (s, 3H, −OMe), 3.33 (s, 6H, N−$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 151.5, 132.6, 127.3, 125.9, 114.9, 114.7, 55.7, 40.6. HRMS (EI): $C_{13}H_{12}ClN_3O_2$ calcd 279.0775, found 279.0778.

2.3.9. 3-(Dimethylamino)-5-(phenylthio)-6-o-tolyl-2H-1,4-oxazin-2-one (**5a**)

Yield 72%, yellow crystalline, mp 87−89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J=8.3 Hz, 1H), 7.38 (t, J=7.4 Hz, 1H), 7.29 (m, 4H), 7.16 (t, J=5.6 Hz, 3H), 3.30 (s, 6H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1, 160.3, 148.9, 138.9, 136.5, 135.9, 131.4, 130.9, 129.2, 126.5, 126.1, 125.8, 125.4, 125.1, 102.7, 39.4, 20.6. HRMS (EI): $C_{19}H_{18}N_2O_2S$ calcd 338.1089, found 338.1093.

*2.3.10. 1-(4-Methoxybenzyl)-5-chloro-3-(piperidin-1-yl)pyrazin-2(1H)-one (**3a**)*

Yield 98%, orange crystalline, mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J=9.1 Hz, 2H), 6.86 (d, J=10.1 Hz, 2H), 6.60 (s, 1H), 4.89 (s, 2H), 3.83 (s, 4H, $-N-(CH_2)_2$), 3.77 (s, 3H, $-OMe$), 1.64 (s, 6H, $-C-(CH_2)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 151.3, 151.2, 129.8, 127.3, 125.6, 114.3, 114.2, 55.3, 51.6, 47.9, 26.1, 24.7. HRMS (EI): $C_{17}H_{20}ClN_3O_2$ calcd 333.1244, found 333.1241.

*2.3.11. 1-(4-Methoxybenzyl)-5-chloro-3-morpholino-pyrazin-2(1H)-one (**3b**)*

Yield 91%, brown crystalline, mp 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J=9.4 Hz, 2H), 6.88 (d, J=9.4 Hz, 2H), 6.67 (s, 1H), 4.89 (s, 2H), 3.93–3.90 (m, 4H, $-N-(CH_2)_2$), 3.79 (s, 3H, $-OMe$), 3.70 (d, 4H, $-O-(CH_2)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 151.2, 150.8, 130.0, 127.1, 125.5, 115.4, 114.4, 66.8, 55.4, 51.7, 47.2. HRMS (EI): $C_{17}H_{20}ClN_3O_2$ calcd 335.1037, found 335.1046.

*2.3.12. 1-(4-Methoxybenzyl)-3-(N-benzyl-N-methylamino)-5-chloropyrazin-2(1H)-one (**3c**)*

Yield 72%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.23 (m, 7H), 6.87 (d, J=9.1 Hz, 2H), 6.59 (s, 1H), 5.12 (s, 2H), 4.91 (s, 2H), 3.79 (s, 3H), 3.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 151.3, 151.1, 142.7, 138.2, 129.8, 128.0, 127.7, 127.4, 126.8, 125.9, 114.1, 54.9, 51.6, 51.2, 38.3. HRMS (EI): $C_{20}H_{20}ClN_3O_2$ calcd 369.1244, found 369.1248.

*2.3.13. 1-(4-Methoxybenzyl)-5-chloro-3-(isobutyl-amino)pyrazin-2(1H)-one (**3e**)*

Yield 26%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J=9.1 Hz, 2H), 6.86 (d, J=10.1 Hz, 2H), 6.45 (s, 1H), 6.41 (br s, 1H), 4.93 (s, 2H), 3.80 (s, 3H), 3.24 (t, J=7.0 Hz, 2H), 1.92 (m, 1H), 0.97 (d, 6H, $-CH-(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 150.6, 130.0, 127.3, 127.0, 114.5, 114.4, 55.4, 51.5, 48.6, 28.1, 20.4. HRMS (EI): $C_{17}H_{20}ClN_3O_2$ calcd 321.1244, found 321.1241.

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Supplementary data

Detailed description of the spectral data (NMR, HRMS) is included in the supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.030.

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13. The GC–LRMS experiment was performed at 160 °C instead of 250 °C as routinely kept for all GC–LRMS experiments.
14. *Conditions*: Na_2CO_3 (5 mmol) and DMF/H_2O (1:1) (3 mL) were irradiated in a sealed vial at a ceiling temperature of 140 °C and a maximum power of 150 W for 40 min (CEM Discover®). The crude mixture was evaluated with GC–LRMS at 180 °C. GC–MS analysis of pure DMF did not show any traces of dimethylamine clearly indicating in situ generation of dimethylamine under the conditions used.