A straightforward microwave method for rapid synthesis of N-1, C-6 functionalized 3,5-dichloro-2(1*H*)-pyrazinones†

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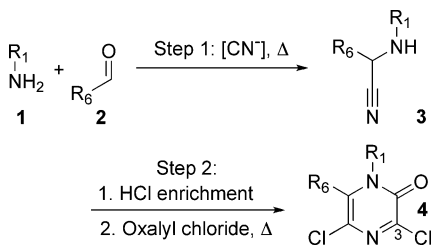
A rapid and versatile one-pot, 2 × 10 min microwave protocol for the preparation of N-1 and C-6 decorated 3,5-dichloro-2(1*H*)-pyrazinones was developed. Comparable reaction sequences using classical conditions require about 1–2 days of heating. The α-aminonitrile was first generated in a Strecker reaction and thereafter cyclized under microwave heating. The microwave approach developed offers the possibility of efficiently generating and utilizing functionalized 3-amino-5-chloro-2(1*H*)-pyrazinone-N-1-carboxylic acids as β-strand inducing core structures in a medicinal chemistry context. To illustrate the usefulness of the method, the synthesis of two novel 2(1*H*)-pyrazinone-containing Hepatitis C virus NS3 protease inhibitors is reported.

Introduction

Derivatives of 2(1*H*)-pyrazinones have wide-spread biological activities[1–3], are classified as important drug scaffolds, and are known β-strand[4,5] conformation inducers.[6,7] Thus, these heterocyclic systems are of general interest to medicinal chemists. However, there are only a few synthetic approaches to N-1, C-3, C-6-trisubstituted 2(1*H*)-pyrazinones in the literature.[6,7] A powerful synthetic procedure reported by Hoornaert *et al.*[8] employs a primary amine (**1**), an aldehyde (**2**) and a cyanide source to give an intermediate α-aminonitrile (**3**) in a Strecker type reaction (Scheme 1, Step 1). The reaction mixture is thereafter treated with HCl and oxalyl chloride, and the resulting chlorinated oxamoyl derivative is slowly cyclized at room temperature for two days,[9] or under traditional heating at 80–100 °C for 4–6 h,[8] to afford the desired N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinone (**4**) in moderate to good yields (Scheme 1, Step 2). The use of formaldehyde as the C-6 source also provides the opportunity to keep this ring position unfunctionalized. Although Hoornaert's reaction sequence suffers from the requirement of prolonged reaction times, a hazardous cyanide source and a purification procedure for the intermediates, it is the only versatile protocol available for the preparation of N-1, C-6-disubstituted 3,5-dichloro-pyrazinones **4**. Furthermore, different functionalities might be introduced at the C-3 position of **4** using the reactive imidoyl chloride moiety.[6,7,10]



Scheme 1 Two-step synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4**).

The development of new high-speed chemistry procedures continues to be a prioritized area for modern drug discovery.[11,12] Heterocyclic systems of interest in drug discovery projects must be rapidly constructed, purified, characterized, and evaluated. In this area, controlled microwave radiation has proven to be a valuable tool for enhancing reaction rates and synthetic productivity, especially for the straightforward generation of functionalized azaheterocycles.[13–15]

In this short article, we present the successful application of high-density microwave heating for: (1) the fast one-pot, two-step synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4**); (2) the rapid 10 min ring-closure of α-aminonitriles **3** to provide synthetically demanding products of class **4**; and (3) the preparation and biological testing of two new peptidomimetic Hepatitis C virus NS3 protease inhibitors comprising a N-1, C-3, C-6 functionalized 2(1*H*)-pyrazinone structure.

Results and discussion

The first aim of this investigation was to develop a fast and convenient one-pot, two-step microwave procedure for synthesis of 3,5-dichloro-2(1*H*)-pyrazinones **4**. Initially, 10 min microwave-assisted Strecker experiments were carried out in sealed vessels using 1.0 mmol primary amine, 1.2 equiv. aldehyde, and 1.1 equiv. trimethylsilyl cyanide[16] in 1,2-dimethoxyethane (DME) to assess the appropriate reaction temperature for each individual step 1 reaction (Scheme 2). The choice of reaction temperature was not self-evident but varied considerably between different reactant combinations. The temperature optimization was performed using at least three different reaction temperatures with 20 °C difference. To qualitatively compare the outcome of the reactions, all reaction mixtures were analyzed by RP-HPLC/UV at 254 nm, and the peak

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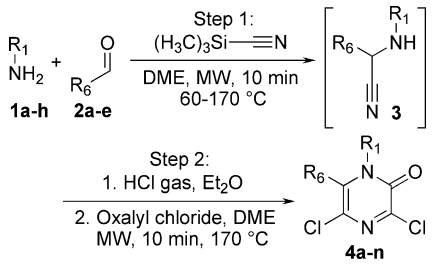
† Electronic supplementary information (ESI) available: Experimental details, UV/ELSD, ESI-MS, ^{1}H and ^{13}C NMR spectra of products. See DOI: 10.1039/b905501k

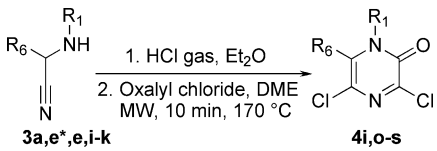


Scheme 2 One-pot, two-step microwave synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4**).

area ratio between **3** and **1** was used as the productivity response. If the starting amine **1** did not have a useful UV absorption, ELSD detection or MS detection was applied. The results obtained during these studies provided the selected temperatures for the Step 1 Strecker transformation. In successful reactions with full consumption of amine **1**, intermediate **3** was not purified but instead the solvent was evaporated and the crude material was dissolved in diethyl ether and directly treated with HCl gas. Thereafter, the solvent was again evaporated, the solid HCl salt of **3** was suspended in DME and 2.5 equiv. of oxalyl chloride was added to the reaction mixture. The reaction vial was sealed and the content was heated by controlled microwave irradiation at 170 °C for 10 min (Scheme 2, Step 2).

By using a purpose built microwave synthesizer, together with the appropriate 5 mL reaction vials, the protocol is safe and convenient to carry out. In all cases, the maximum reaction pressure (<20 bar) during step 2 did not disturb the microwave processing. The preparative results of the two-step methodology are depicted in Table 1. In those cases where it was difficult to identify a suitable temperature for producing aminonitrile **3**, several temperatures were employed and the preparative results were evaluated by completing the ring closure and determining the isolated yield of pure pyrazinone product **4** (Table 1, entries 2, 5, 6, 9, 10, 11 and 13). Entry 5 provides an illustrative example in which intermediate **3e** was produced *in situ* by heating for 10 min at 60 °C, 80 °C, or 100 °C, and then cyclized to afford the isolated product **4e** in 79%, 74%, and 74% yield, respectively. Generally, complete conversions of **1** and **3** were efficiently achieved with reactive primary amines **1a–d**, **1f–h**, and acetaldehyde (**2a**), providing products **4a**,**e–g**,**j**,**k**,**m** in 41–79% two-step isolated yields. Benzaldehyde (**2b**) and the brominated derivatives **2c** and **2d** furnished somewhat lower yields of **4** (43–58%) compared with analogous reactions of **2a** (compare *e.g.* entry 1 with entries 2–4). A similar trend was also noted when comparing **2a** with the formaldehyde source **2e**[17,18] as the electrophile (Table 1, entry 12 and 14). The use of the weak nucleophile aniline (**1e**) afforded only low yields of **4i** (27–29%), while the ester protected amino acids **1f–h** served as more efficient nucleophiles (38–63%, entries 9–14). Importantly, the valine derivative **1f** and the protected phenylalanine **1h** reacted without any detected racemization despite the high temperature and acidic reaction conditions (entries 10,13,14).[19] Please note that the hydrochloride salt of **1h** was used in entry 14. The one pot two-step protocol could also be performed on a 2 mmol scale (entry 10) and on a 5 mmol scale (entry 13). In the 5 mmol reaction, a 20 mL sealed vessel was used instead of the previously employed 5 mL vial and the temperature and time were modified in step 2 to 145 °C for 25 min in order to reduce the maximum reaction pressure (<20 bar). The isolated yields were more or less identical regardless of whether they were determined from 1.0, 2.0 or 5.0 mmol scale reactions (45–51%, 53% and 55%). When comparing the results from Table 1 with the available literature data,[8,9,20–22] the one-pot, two-step microwave protocol developed provides the same or a slightly improved outcome with respect to the isolated yield of pyrazinone **4** using classical heating.

In the case of preparative handling and reaction speed, the microwave protocol is superior with reaction times being reduced from days or hours down to 2 × 10 min. In the case of weakly nucleophilic aniline (**1e**, Table 1, entry 9), amino acid derivatives, and formaldehyde (**2e**), it was advantageous to either purify aminonitrile **3**, or use commercially available **3**, before HCl enrichment, addition of oxalyl chloride and subsequent ring-closing (Scheme 3).



Scheme 3 One-step microwave synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4**) starting from pure α-aminonitriles (**3**).

Thus, when LC-MS analysis indicated the formation of by-products, degradation of starting materials, or incomplete conversion from **1** to **3** in the Strecker reaction, the crude reaction mixtures were passed through a short column of silica gel before the final cyclization. The pure α-aminonitriles **3** were enriched with HCl gas in diethyl ether and thereafter smoothly cyclized with oxalyl chloride in DME, employing microwave heating at 170 °C for 10 min, proving good one-step yields of pyrazinone products **4i**, **4o-s** (Table 2, 56–86%). As expected, the one-step protocol gave better yields than the one-pot, two step method, see entry 9, Table 1 (27–29% of **4i**) and entry 1, Table 2 (70% of **4i**). When compared with reported cyclizations under classical conditions, the microwave approach gave improved or at least similar isolated yields (Table 2).[8,23–25]

Proteases are involved in many pathological conditions, and consequently, these enzymes are also important drug targets. The natural substrates of proteases are generally assumed to adopt an extended conformation prior to binding the enzymes (Chart 1, I), and 2(1*H*)-pyrazinones substituted by an RNH group in the C-3 position and with an amino acid C-terminal incorporated in the N-1, are known β-strand conformation inducers (Chart 1, II).[4,5] Since pre-organizing and rigidifying inhibitors in the proper conformation for binding to the target is a way to increase their activity, this is a very interesting aspect of the pyrazinone core from a medicinal chemistry point of view. In the case of Hepatitis C virus (HCV) NS3 protease inhibitors, there are earlier examples of rigidification by macrocyclization[26] as well as by incorporation of heterocycles[4,27,28] in the inhibitor backbone. We have previously reported on the discovery of *p*-substituted phenylglycine as a promising P2 residue (standard nomenclature according to Schechter and Berger[29]) in tripeptide (HCV) NS3 protease inhibitors.[30] Aiming at inhibitors with increased rigidity, decreased peptide character and decreased molecular weight, we became interested in introducing the pyrazinone-phenylglycine

Table 1 Microwave-accelerated one-pot, two-step synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4a–n**) according to Scheme 2[a]

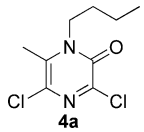
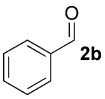
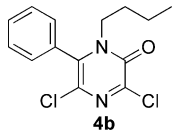
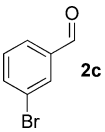
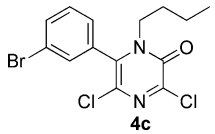
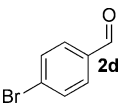
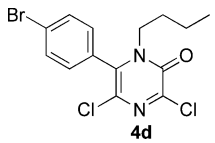
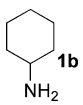
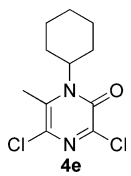
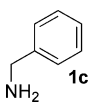
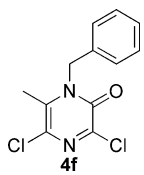
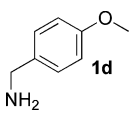
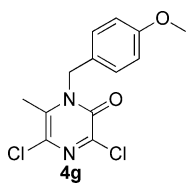
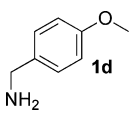
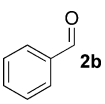
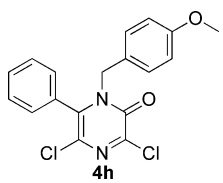
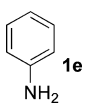
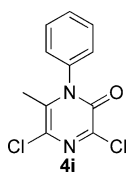
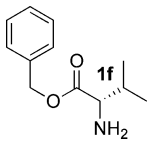
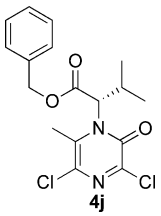
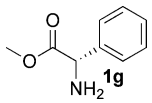
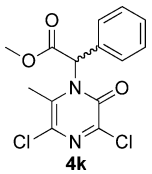
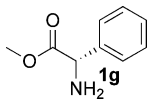
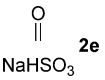
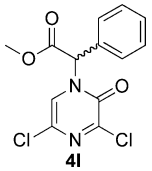
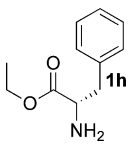
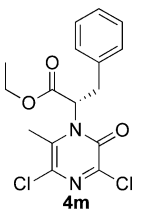
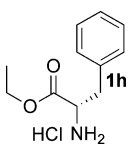
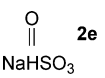
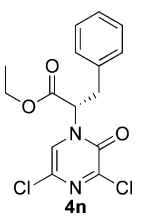
Entry	Amine	Aldehyde	Temp Step 1 (°C)	Product	Isolated yield[b]
1	 **1a**	 **2a**	60	 **4a**	72%
2	 **1a**	 **2b**	60 80	 **4b**	58% 56%
3	 **1a**	 **2c**	60	 **4c**	57%
4	 **1a**	 **2d**	80	 **4d**	43%
5	 **1b**	 **2a**	60 80 100	 **4e**	79% 74% 74%
6	 **1c**	 **2a**	60 80	 **4f**	67% 62%
7	 **1d**	 **2a**	80	 **4g**	55%
8	 **1d**	 **2b**	80	 **4h**	38%
9	 **1e**	 **2a**	80 100	 **4i**	29% 27%

Table 1 *(Contd.)*

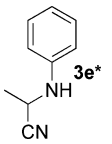
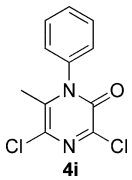
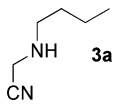
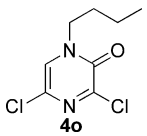
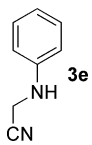
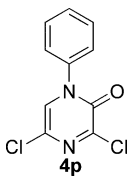
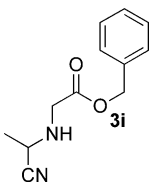
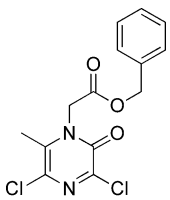
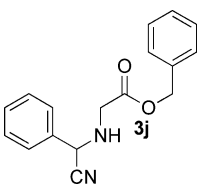
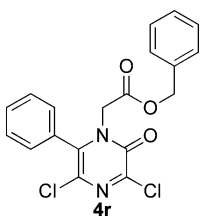
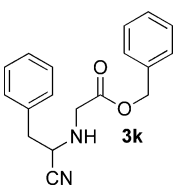
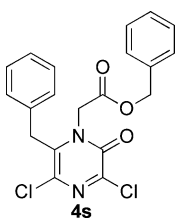
Entry	Amine	Aldehyde	Temp Step 1 (°C)	Product	Isolated yield[b]
10	 **1f**	 **2a**	80 100 80	 **4j**	45% 51% 53%[c]
11	 **1g**	 **2a**	80 100	 **4k**	44% 41%
12	 **1g**	 **2e**	170	 **4l**	38%
13	 **1h**	 **2a**	80 100 80	 **4m**	56% 63% 55%[d]
14	 **1h**	 **2e**	170	 **4n**	54%

[a] Step 1 was performed with 1.0 mmol of **1**, 1.2 equiv. of **2**, and 1.1 equiv. of trimethylsilyl cyanide in 3.0 mL of DME with microwave heating in a sealed 5 mL vial for 10 min at the stated temperature. Step 2 was carried out, after cooling and exchange of DME for 5.0 mL Et_2O, by enrichment with HCl gas, evaporation, and addition of 3.0 mL DME and 2.5 equiv. oxalyl chloride. The sealed reaction vial was microwave heated to 170 °C for 10 min. [b] Isolated yield. Purity >95% by LC-ELSD. [c] Reaction was performed on 2.0 mmol scale. [d] Reaction was performed on 5.0 mmol scale in a 20 mL vial. The temperature and time in step 2 was changed to 145 °C for 25 min.

scaffold as a P3–P2 building block instead of a traditional dipeptide motif. We hoped that the rigidity conferred by the pyrazinone system would compensate, at least to some extent, for the use of an unsubstituted phenylglycine, and result in a new type of inhibitors to be considered as a starting point for further structural optimization.

The 3,5-dichloro-pyrazinone core **4k** was smoothly prepared as described in Table 1. Next, we were interested in the substitution of the C-3 chloro group with a Boc-protected primary amino group (Scheme 4). To accomplish this, we decided to employ a palladium-catalyzed amide N-arylation reaction using *tert*-butylcarbamate as the nucleophile to afford the Boc-protected aniline derivative **5**. By slightly modifying the conditions reported by Yin and Buchwald[31] a successful microwave version was developed.[32] Thus, the protected N-monoarylated product **5** was obtained in 51% isolated yield after only 30 min of heating at 100 °C using 5 equiv. of *tert*-butylcarbamate as the nucleophile, 5% $Pd(OAc)_2$ as the Pd source, 8% Xantphos as the ligand, and 2 equiv. caesium carbonate as the base in dry DME (Scheme 4). Full conversion of **4k** was also obtained at higher temperatures but competing cleavage of the Boc group complicated product isolation and diminished the yield. All attempts to further reduce the reaction time to avoid the cleavage of pyrazinone **5** failed, despite investigating different solvents (1,4-dioxane or THF) and an alternative base (K_3PO_4). Ester hydrolysis of **5** followed by standard solution phase peptide coupling, furnished compound **6** as a 50:50 L- and D-Phg epimeric

Table 2 Microwave-accelerated one-step synthesis of N-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones (**4i**,**o–s**) according to Scheme 3[a]

Entry	Aminonitrile	Product	Isolated yield[b]	Literature yield
1	 **3e***	 **4i**	70%	45%[c]
2	 **3a**	 **4o**	64%	—
3	 **3e**	 **4p**	80%	56%[c]
4	 **3i**	 **4q**	86%	56%[c]
5	 **3j**	 **4r**	65%	60%[d]
6	 **3k**	 **4s**	56%	38%[d]

[a] The cyclization was carried out with 1.0 mmol **3** in 5.0 mL Et_2O, by enrichment of HCl gas, and thereafter a change of solvent to 3.0 mL DME and addition of 2.5 equiv. oxalyl chloride. The sealed reaction vial was thereafter microwave heated to 170 °C for 10 min. [b] Isolated yield. Purity >95% by LC/ELSD. [c] Literature yield: **4i**,[23] **4p**,[8] **4q**.[24] [d] Literature yield reported for the two-step process.[25]

mixture in 29% two-step isolated yield (Scheme 4). LiOH-mediated ester hydrolysis of ethyl ester **6** and purification by RP-HPLC gave the final inhibitors **7a** and **7b** as pure epimers. When evaluated in an *in vitro* assay comprising the full-length NS3 protein,[33] the β-strand mimic containing **7a** and **7b** were found to be fairly potent inhibitors with K_i-values of 11.0 ± 1.1 μM for **7a** and 12.5 ± 2.4 μM for **7b**, respectively (Scheme 4). Considering the use of a C-terminal carboxylic acid and an unsubstituted phenylglycine in **7a** and **7b**, the new P3 pyrazinone-based peptidomimetics are of similar potencies as structurally related, tripeptide inhibitors previously reported by us.[30]

Conclusion

We have demonstrated that N-1, C-6-functionalized 3,5-dichloro-2(1*H*)-pyrazinones can be generated in a one-pot, two-step protocol from the corresponding primary amine and aldehyde using a cyanide source, oxalyl chloride, and HCl utilizing

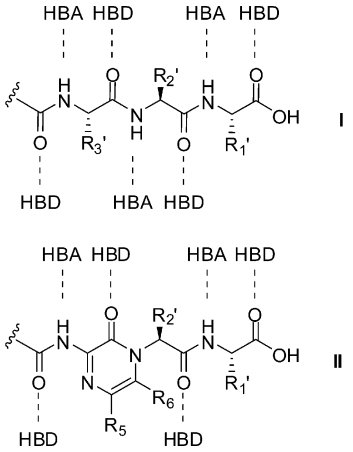
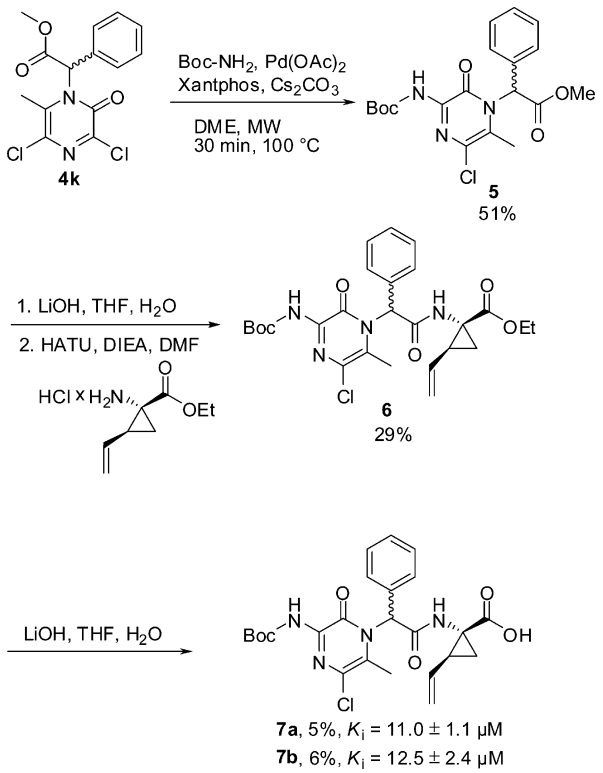


Chart 1 β-Strand peptide (**I**), and anticipated β-strand formation for a C-5-, C-6-disubstituted 2-(1*H*)-pyrazinone β-strand mimic containing structure (**II**). HBA—hydrogen bond acceptor, HBD—hydrogen bond donator.



Scheme 4 Synthesis of Hepatitis C Virus NS3 protease inhibitors **7a** and **7b**.

2 × 10 min of high density microwave heating. Compared to the previously reported protocols, this microwave methodology not only increases the reaction speed but actually makes it possible to take advantage of this protocol for modern drug discovery. In the case of sluggish amines, the α-aminonitrile intermediate was purified before microwave-induced cyclization with HCl and oxalyl chloride. A new 3-Boc-amino, N-1-carboxylic acid 2(1*H*)-pyrazinone unit was constructed by palladium(0)-catalyzed microwave-assisted Boc-NH_2 substitution of the chloro group at C-3. Due to the beneficial alignment of the CO- and NH-groups coupled with the rigidity of the pyrazinone ring, the 3-amino-5-chloro-2-(1*H*)-pyrazinone N-1-carboxylic acid scaffold was used as a β-strand inducer in two new Hepatitis C Virus NS3 protease inhibitors. The potency of the inhibitors was evaluated in an enzymatic assay (K_i = 11.0 and 12.5 μM, respectively). In view of the speed and robustness of the presented protocols, we anticipate that our work will increase the utilization of the 2(1*H*)-pyrazinone ring system in various medicinal chemistry related applications.

Experimental

General one-pot, two-step procedure for preparation of 2(1*H*)-pyrazinones 4a–n. Method A. A 2.0–5.0 mL Smith microwave vial was charged with amine (**1a–h**, 1.0 mmol) and was dissolved in 3.0 mL DME. The aldehyde (**2a–e**, 1.2 mmol) was added and the mixture was stirred for 30 s before adding trimethylsilyl cyanide (1.1 mmol, 138 μL). The vial was sealed and irradiated with microwaves for 10 min at the stated temperatures (step 1, Table 1). The solvent was removed under a stream of nitrogen gas and the residue was dissolved in 5.0 mL diethyl ether. HCl gas was bubbled through the reaction mixture for 5 min followed by evaporation under a stream of nitrogen gas. DME (3.0 mL) and oxalyl chloride (2.5 mmol, 214 μL) were added and the vial was sealed. After 30 s of stirring, the overpressure was released with a needle before irradiation with microwaves for 10 min at 170 °C (creating a pressure of 10–17 bar). Purification by flash chromatography yielded pure products **4a–n** (>95% by LC-ELSD).

General procedure for preparation of α-aminonitrile 3e*,i–k. Method B. A 2.0–5.0 mL Smith microwave vial was charged with 1 equiv. amine **1e,i–j**and 3.0 mL DME. (Diisopropylamine (1.2 equiv.) was added if the amine was a HCl salt). Addition of 1.2 equiv. aldehyde **2a,b**, or phenylacetaldehyde (**2f**) was followed by 30 s stirring before addition of 1.1 equiv. trimethylsilyl cyanide. The vial was sealed and irradiated with microwaves for 10 minutes at the stated temperatures. The solvent was evaporated in vacuum and the crude residue purified by flash chromatography yielding pure products **3e*,i–k** (>95% by LC-ELSD).

General procedure for preparation of 2(1*H*)-pyrazinones 4i,o–s from pure α-aminonitriles. Method C. A 2.0–5.0 mL Smith microwave vial was loaded with 1 mmol α-aminonitrile **3a,e*,i–k** and 5.0 mL diethyl ether. HCl gas was bubbled through the reaction mixture for 5 min followed by removal of the diethyl ether under a stream of nitrogen gas. DME (3.0 mL) and oxalyl chloride (2.5 mmol, 214 μL) were added and the vial was sealed. After 30 s stirring the overpressure was released and the reaction irradiated by microwaves for 10 min at 170 °C (creating a pressure of 10–17 bar). Purification by flash chromatography yielded pure products **4i,o–s**, (>95% by LC-ELSD).

1-Butyl-3,5-dichloro-6-methylpyrazin-2(1*H*)-one (4a). The compound was prepared according to method A, using a 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. Pale yellow oil, 72% yield. ^{1}H NMR ($CDCl_3$) δ 4.06 (m, 2H), 2.49 (s, 3H), 1.66 (m, 2H), 1.43 (qm, J= 7.4 Hz, 2H), 0.97 (t, J= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 143.5, 135.6, 123.8, 47.4, 29.9, 20.2, 16.6, 13.7. ESI-MS (m/z) 235 (M + H$^+$), 471 (2M + H$^+$). Anal. Calcd for $C_9H_{12}Cl_2N_2O$: C, 45.98; H, 5.14; N, 11.91. Found: C, 46.14; H, 5.25; N, 12.04.

Benzyl 2-(1-cyanoethylamino)acetate (3i)[24]. The compound was prepared according to method B, using HCl×HGlyOBn (2.0 mmol, 0.402 g), diisopropylamine (2.3 mmol, 400 μL), acetaldehyde **2a** (2.5 mmol, 140 μL), trimethylsilyl cyanide (2.2 mmol, 280 μL) and a temperature of 100 °C. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 30:70 to 75:25. Colorless oil, 68% yield. ^{13}C-NMR (CD_3OD) δ 172.5, 137.3, 129.7, 129.5 (two peaks), 121.7, 67.8, 49.2, 45.8, 19.6.

Benzyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)acetate (4q)[24]. The compound was prepared according to method C. Purification by flash chromatography, eluent ethyl acetate:iso-hexane 20:80 to 35:65. Pale yellow solid, 86% yield. ^{13}C-NMR ($CDCl_3$) δ 166.1, 152.7, 143.8, 135.2, 134.6, 129.1, 129.0, 128.7, 124.0, 68.4, 47.6, 16.9. ESI-MS (*m*/*z*) 327 ($M + H^+$), 655 ($2M + H^+$).

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Notes and references

1 C. D. Haffner, C. J. Diaz, A. B. Miller, R. A. Reid, K. P. Madauss, A. Hassell, M. H. Hanlon, D. J. T. Porter, J. D. Becherer and L. H. Carter, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4360–4363.
2 J. I. Trujillo, H. C. Huang, W. L. Neumann, M. W. Mahoney, S. Long, W. Huang, D. J. Garland, C. Kusturin, Z. Abbas, M. S. South and D. B. Reitz, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4568–4574.
3 C. R. Hopkins, K. Neuenschwander, A. Scotese, S. Jackson, T. Nieduzak, H. Pauls, G. Y. Liang, K. Sides, D. Cramer, J. Cairns, S. Maignan and M. Mathieu, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4819–4823.
4 X. J. Zhang, A. C. Schmitt, W. Jiang, Z. Wasserman and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1157–1160.
5 J. J. Parlow, B. L. Case, T. A. Dice, R. L. Fenton, M. J. Hayes, D. E. Jones, W. L. Neumann, R. S. Wood, R. M. Lachance, T. J. Girard, N. S. Nicholson, M. Clare, R. A. Stegeman, A. M. Stevens, W. C. Stallings, R. G. Kurumbail and M. S. South, *J. Med. Chem.*, 2003, **46**, 4050–4062.
6 V. G. Pawar and W. M. De Borggraeve, *Synthesis*, 2006, 2799–2814.
7 N. Kaval, P. Appukkuttan, and E. Van der Eycken, in *Microwave-Assisted Synthesis of Heterocycles*, Springer-Verlag, Berlin, 2006, vol. 1, pp. 267–304.
8 J. Vekemans, C. Pollerswieers and G. Hoornaert, *J. Heterocycl. Chem.*, 1983, **20**, 919–923.
9 W. M. De Borggraeve, B. M. P. Verbist, F. J. R. Rombouts, V. G. Pawar, W. J. Smets, L. Kamoune, J. Alen, E. V. Van der Eycken, F. Compernolle and G. J. Hoornaert, *Tetrahedron*, 2004, **60**, 11597–11612.
10 S. V. Pawar, V. G. Pawar, W. Dehaen and W. M. De Borggraeve, *Org. Lett.*, 2008, **10**, 4473–4476.
11 M. Larhed and A. Hallberg, *Drug Discov. Today*, 2001, **6**, 406–416.
12 J. Wannberg, K. Ersmark and M. Larhed, *Top. Curr. Chem.*, 2006, **266**, 167–198.
13 E. Suna and I. Mutule, *Top. Curr. Chem.*, 2006, **266**, 49–101.
14 E. V. Van der Eycken and C. O. Kappe, *Microwave-Assisted Synthesis of Heterocycles*, Springer-Verlag, Berlin, 2006.
15 V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629–639.
16 J. E. Reiner, D. V. Siev, G. L. Araldi, J. R. J. Cui, J. Z. Ho, K. M. Reddy, L. Mamedova, P. H. Vu, K. S. S. Lee, N. K. Minami, T. S. Gibson, S. M. Anderson, A. E. Bradbury, T. G. Nolan and J. E. Semple, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1203–1208.
17 D. A. Evans and S. A. Biller, *Tetrahedron Lett.*, 1985, **26**, 1907–1910.
18 S. Dong and P. K. Dasgupta, *Atmos. Environ.*, 1986, **20**, 1635–1637.
19 A 2.0 mL microwave vial was loaded with 2(1*H*)-pyrazinones **4j–n** (0.05–0.15 mmol), (1*S*,2*R*)-*cis*-1-amino-2-indanol (3 equiv.) and acetonitrile (2.0 mL). The reactions were then irradiated by microwaves: **4j** at 150 °C for 1.5 h; **4k** at 140 °C for 2 h; **4l** at 140 °C for 0.5 h; **4m** at 160 °C for 2 h; **4n** at 160 °C for 1.5 h. The diastereomeric ratios were determined by ^{1}H-NMR or by HPLC separation with ELSD and ESI-MS detection.
20 B. M. P. Verbist, W. M. De Borggraeve, S. Toppet, F. Compernolle and G. J. Hoornaert, *Eur. J. Org. Chem.*, 2005, 2941–2950.
21 F. J. R. Rombouts, W. M. De Borggraeve, D. Delaere, M. Froeyen, S. M. Toppet, F. Compernolle and G. J. Hoornaert, *Eur. J. Org. Chem.*, 2003, 1868–1878.
22 K. J. Buysens, D. M. Vandenberghe, S. M. Toppet and G. J. Hoornaert, *Tetrahedron*, 1995, **51**, 12463–12478.
23 S. M. Vandenberghe, K. J. Buysens, L. Meerpoel, P. K. Loosen, S. M. Toppet and G. J. Hoornaert, *J. Org. Chem.*, 1996, **61**, 304–308.
24 P. E. J. Sanderson, T. A. Lyle, K. J. Cutrona, D. L. Dyer, B. D. Dorsey, C. M. McDonough, A. M. Naylor-Olsen, I. W. Chen, Z. G. Chen, J. J. Cook, C. M. Cooper, S. J. Gardell, T. R. Hare, J. A. Krueger, S. D. Lewis, J. H. Lin, B. J. Lucas, E. A. Lyle, J. J. Lynch, M. T. Stranieri, K. Vastag, Y. W. Yan, J. A. Shafer and J. P. Vacca, *J. Med. Chem.*, 1998, **41**, 4466–4474.
25 M. S. South, B. L. Case, R. S. Wood, D. E. Jones, M. J. Hayes, T. J. Girard, R. M. Lachance, N. S. Nicholson, M. Clare, A. M. Stevens, R. A. Stegeman, W. C. Stallings, R. G. Kurumbail and J. J. Parlow, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2319–2325.
26 D. Lamarre, P. C. Anderson, M. Bailey, P. Beaulieu, G. Bolger, P. Bonneau, M. Bos, D. R. Cameron, M. Cartier, M. G. Cordingley, A. M. Faucher, N. Goudreau, S. H. Kawai, G. Kukolj, L. Lagace, S. R. LaPlante, H. Narjes, M. A. Poupart, J. Rancourt, R. E. Sentjens, R. St George, B. Simoneau, G. Steinmann, D. Thibeault, Y. S. Tsantrizos, S. M. Weldon, C. L. Yong and M. Llinas-Brunet, *Nature*, 2003, **426**, 186–189.
27 X. J. Zhang, A. C. Schmitt and C. P. Decicco, *Tetrahedron Lett.*, 2002, **43**, 9663–9666.
28 P. W. Glunz, B. D. Douty and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 785–788.
29 I. Schechter and A. Berger, *Biochem. Biophys. Res. Commun.*, 1967, **27**, 157–162.
30 P. Örtqvist, S. D. Peterson, E. Åkerblom, T. Gossas, Y. A. Sabnis, R. Fransson, G. Lindeberg, U. H. Danielson, A. Karlén and A. Sandström, *Bioorg. Med. Chem.*, 2007, **15**, 1448–1474.
31 J. J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 6043–6048.
32 J. Wannberg, D. Dallinger, C. O. Kappe and M. Larhed, *J. Comb. Chem.*, 2005, **7**, 574–583.
33 A. Poliakov, I. Hubatsch, C. F. Shuman, G. Stenberg and U. H. Danielson, *Protein Expr. Purif.*, 2002, **25**, 363–371.