A practical oxidative conversion of aldehydes into *N*-chloroaldimines

Can Jin[a,c]*, Feng Wang[a], Bin Sun[b] and Xiaohui Zhuang[a]

[a]*College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P.R. China*
[b]*Collaborative Innovation Centre of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P.R. China*
[c]*Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P.R. China*

A novel method for the preparation of *N*-chloroaldimines from commonly available aromatic aldehydes has been developed. The reaction proceeded effectively by two steps: aldehydes were initially transformed into imines and then chloro-substitution with $NaClO_2$ gave the *N*-chloroaldimines. This simple protocol allows for the preparation of a variety of aromatic *N*-chloroaldimines in moderate to excellent yields without the isolation of the imine intermediate. We also found that 3-nitrobenzaldehyde and 4-cyanobenzaldehyde were converted into the related benzonitrile directly under the standard conditions.

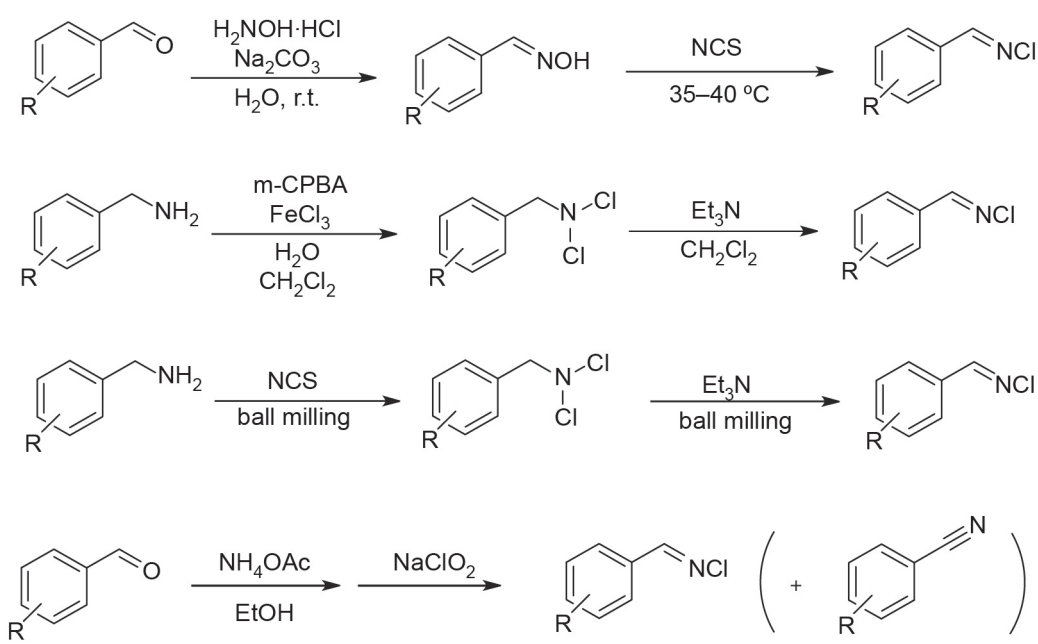
Keywords: aromatic *N*-chloroaldimines, nitriles, aldehydes, febuxostat

N-chloroaldimines are important compounds not only because of their interesting chemical and biological properties,[1] but also because they have been widely used as versatile starting materials for the synthesis of many important compounds. For example, *N*-chloroaldimines can be converted into oximes, amines[2] and nitriles[3] by hydroxylation, hydrogenation and dehydrochlorination respectively. In addition, isoxazole, an important structural feature of nucleozin, which is an effective anti-influenza drug, can be prepared by the ring formation between *N*-chloroaldimines and ethyl acetoacetate.[4–6]

Due to the extensive applications of *N*-chloroaldimines, studying efficient strategies for their synthesis is considered highly desirable. The traditional method for preparation of *N*-chloroaldimines involved chloro-substitution of an aromatic oxime, which could be prepared by condensation between an aldehyde and hydroxylamine [Scheme 1, Eqn (1)].[5] In the past decades, some research groups have reported novel methods for the synthesis of *N*-chloroaldimines. For example, in 2014, Liu *et al.* described a facile two-step method for the synthesis of *N*-chloroaldimines by chlorination of phenylmethanamine, followed by dehydrochlorination with Et_3N in dichlomethane to yield the final products [Scheme 1, Eqn (2)].[6] Another facile method for the synthesis of *N*-chloroaldimines was developed by Gaspa's group.[2] The chlorination of phenylmethanamine and the consequent dehydrochlorination proceeded well under ball-milling conditions [Scheme 1, Eqn (3)].[7] It is true that progress has been made in the preparation of *N*-chloroaldimines but some drawbacks remain, such as use of a high boiling point solvent, tedious work-up and low atom economy. Therefore, developing mild and environmentally friendly methods for the synthesis of *N*-chloroaldimines is still important. We envisaged that the synthesis of *N*-chloroaldimines could also be achieved by chlorination of aldimines, which could be easily prepared by the condensation of aldehydes and amines. We report here a novel and convenient method for the transformation of aldehydes to *N*-chloroaldimines. Firstly, aromatic aldehydes were reacted with NH_4OAc in ethanol at 50 °C for 1 h, forming the corresponding imine. Then $NaClO_2$ (80%) was added directly to the mixture and the *N*-chloroaldimine was obtained after stirring for a few hours [Scheme 1, Eqn (4)].

Results and discussion

To begin our study, benzaldehyde (**1a**) was chosen as a model substrate. The initial reaction of benzaldehyde with NH_4OAc and $NaClO_2$ (added in simultaneously) in ethanol resulted in a poor yield, which could be attributed to the inevitable oxidation of benzaldehyde to benzoic acid. This result might indicate



Scheme 1 Formation of *N*-chloroaldimines from aldehydes.

* Correspondent. E-mail: jincan@zjut.edu.cn

that benzaldehyde should be transformed into the aldimine first in order to avoid direct oxidation by $NaClO_2$. A range of solvents for this condensation was originally studied and the results showed that ethanol was the best choice compared with the other screened solvents (toluene, methanol, acetonitrile and acetone). Subsequently, for the complete conversion of aldehyde **1**, it was observed that the use of 2.0 equiv. of NH_4OAc in ethanol at 50 °C for 1 h is necessary.

Next, the aldimine was transformed into the *N*-chloroaldimine. Without any prior isolation of the aldimine, $NaClO_2$ (1.0 equiv.) was directly added and the mixture was stirred in ethanol for 1.5 h. However, only a 10% yield of product was obtained. Then the effect of different amounts of $NaClO_2$ on chlorination was studied. A generally increasing trend was observed when the amount of $NaClO_2$ was increased from 1.0 equiv. to 1.6 equiv. The highest yield was obtained when 1.6 equiv. of $NaClO_2$ was used (Table 1, entry 3) and improvement was not observed beyond this (Table 1, entry 4). Subsequently, our attention was focused on searching for a suitable temperature for the chloro-substitution reaction. It was observed that the highest yield was obtained when the reaction was carried out at 50 °C (Table 1, entry 7) and increasing or decreasing the temperature all showed a negative effect (Table 1, entries 5, 6, 8). We also found that appropriately extending the reaction time could contribute to a higher yield of desired product (Table 1, entries 9–11) and a slightly lower yield was obtained when the time was prolonged over 2 h (Table 1, entry 12). Thus, it can be concluded that the optimised reaction should be performed at 50 °C in EtOH for 2 h using $NaClO_2$ (1.6 equiv.) as chlorination reagent.

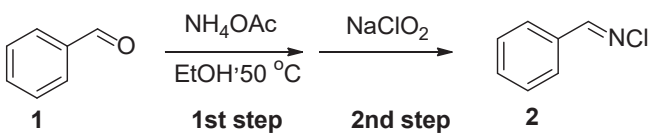
Under the optimised conditions, different sets of experiments were carried out to investigate the scope and limitations of this reaction. It was found to be applicable to a wide range of aromatic aldehydes (**1a**–**n**), which were able to undergo the condensation and chlorination to give the corresponding *N*-chloroaldimines[12–13] in yields of 54–77% (Table 2). The results demonstrated that aryl aldehydes with either electron-donating groups such as *tert*-butyl or hydroxyl or electron-withdrawing substituents like fluoro, chloro, bromo, nitro, cyano or trifluoromethyl all afforded satisfactory yields (Table 2, entries 2–13). Furthermore, substituents at different positions of the benzene ring showed no effect on this reaction. For example, 2-chloro- or 3-chloro-benzaldehyde gave the corresponding products in yields of 67 and 72% respectively. Gratifyingly, a heterocyclic aldehyde, 5-bromo-2-furaldehyde, also showed excellent tolerance for this transformation and gave the chloro-product in 62% yield.

Unexpectedly, some of the aromatic aldehydes gave not only the corresponding *N*-chloroaldimines, but also the aromatic nitrile **2′** by dehydrochlorination.[8,9] For example, under the optimised conditions, 3-nitrobenzaldehyde (**1o**) yielded the *N*-chloroaldimine and nitrile with yields of 15 and 54% respectively (Table 2, entry 15). With respect to the 4-formylbenzonitrile, the situation is similar (Table 2, entry 16).

A possible mechanism for formation of *N*-chloroaldimines **2** and nitriles **2′** is proposed in Scheme 2. Initially, the aldehyde reacts with ammonium acetate to form the aldimine **3**, along with AcOH and H_2O. Next, the acidified $NaClO_2$ can immediately release chlorine and the aldimine **3** can be transformed into the *N*-chloroaldimine **2** by chloro-substitution. Further dehydrochlorination can afford the benzonitrile product **2′**, in the cases of **2o** and **2p**, which were both unstable and easy to transform into the cyano compounds.

Febuxostat, a nonpurine xanthine oxidase inhibitor, is widely used for the treatment of hyperuricemia. Because of its inhibition of the formation of uric acid, with relatively few side effects, it plays an increasingly important role in the treatment of gout. As the key intermediate for the synthesis of febuxostat, compound **2q′** can be transformed into febuxostat by Williamson synthesis and subsequent hydrolysis reactions. The aldehyde **1q**, which was prepared by the Duff reaction using hexamethylenetetramine as the formylation reagent,[10] was used as the starting material to prepare **2q′**. The traditional method

Table 1 Evaluation of various reaction conditions[a]

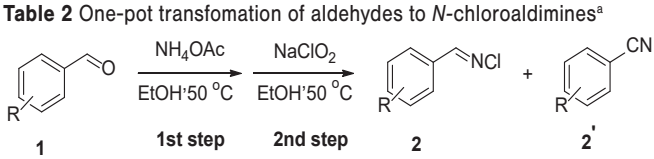


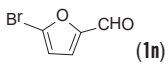
Entry	$NaClO_2$ (equiv.)	Temperature (°C)	Time (h)	Yield[b] (%)
1	1	45	1.5	10
2	1.2	45	1.5	32
3	1.6	45	1.5	56
4	2	45	1.5	53
5	1.6	35	1.5	48
6	1.6	40	1.5	50
7	1.6	50	1.5	62
8	1.6	60	1.5	21
9	1.6	50	0.5	25
10	1.6	50	1.0	60
11	1.6	50	2.0	75
12	1.6	50	2.5	72

[a]Reaction conditions: 1st step, aldehyde (2 mmol), EtOH (15 mL), NH_4OAc (4 mmol), 50 °C, 1 h.

[b]Isolated yields.

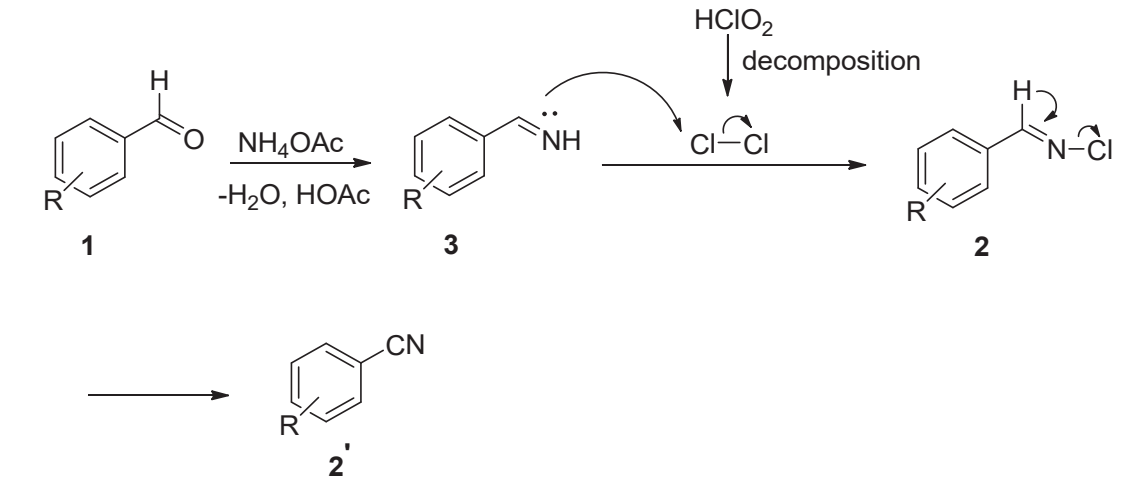
Table 2 One-pot transfomation of aldehydes to *N*-chloroaldimines[a]



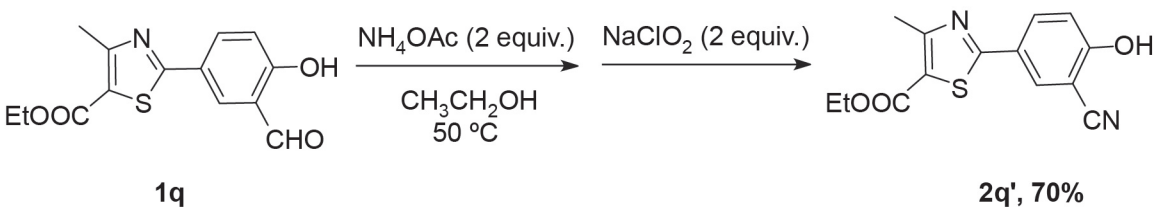
Entry	Substrate	Yield[b] (%) 2	2′
1	R = H (**1a**)	75	–
2	R = 4-^{t}Bu (**1b**)	68	–
3	R = 3-OH (**1c**)	77	–
4	R = 2-F (**1d**)	66	–
5	R = 4-F (**1e**)	65	–
6	R = 2-Cl (**1f**)	67	–
7	R = 3-Cl (**1g**)	72	–
8	R = 2-Br (**1h**)	55	–
9	R = 4-Br (**1i**)	58	–
10	R = 2-NO_2 (**1j**)	55	–
11	R = 4-NO_2 (**1k**)	54	–
12	R = 2-CN (**1l**)	55	–
13	R = 4-CF_3 (**1m**)	57	–
14	 (**1n**)	62	–
15	R = 3-NO_2 (**1o**)	15	54
16	R = 4-CN (**1p**)	22	40

[a]Reaction conditions: 1st step, aldehyde (2 mmol), EtOH (15 mL), NH_4OAc (4 mmol), 50 °C, 1 h; 2nd step, $NaClO_2$ (80%, 3.2 mmol), 50 °C, 2 h.

[b]Isolated yields.



Scheme 2 A possible mechanism.



Scheme 3 Synthesis of febuxostat intermediate.

for the synthesis of **2q′** was by the condensation between **1q** and $NH_2OH{\cdot}HCl$, followed by dehydration with HCOOH/HCOONa.[11] However, the excessive amount of HCOOH may prevent its further application. Employing our procedure it was possible that the transformation of aldehyde into nitrile directly could occur directly, such as in the cases of **2o′** and **2p′**. Gratifyingly, employing our methods, the compound **1q** was successfully transformed into the desired product **2q′** by condensation and chlorination on treatment with NH_4OAc and $NaClO_2$ in a total yield of 70%, as shown in Scheme 3. Thus it may provide a more convenient, environmentally friendly and high atom economy method for preparation of **2q′**.

Conclusion

In conclusion, we have developed a novel efficient two-step method for the synthesis of *N*-chloroaldimines. A variety of aromatic aldehydes were smoothly converted into the corresponding aromatic *N*-chloroaldimines by treatment with NH_4OAc in ethanol, followed by chlorination with $NaClO_2$. Under the same reaction conditions, 3-nitrobenzaldehyde and 4-cyanobenzaldehyde were converted into the related benzonitrile directly. In addition, applying this novel strategy, the key intermediate for febuxostat (**2q′**) could be obtained by condensation and chlorination of **1q** in 70% yield, which extended its application in the pharmaceutical industry. To the best of our knowledge, there are no examples describing the synthesis of aromatic *N*-chloroaldimines **2a–p** and nitriles **2o′**, **2p′** and **2q′** employing the new strategy.

Experimental

Melting points were determined using a digital melting point apparatus (Büchi B-540) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on two Varian spectrometers (Bruker Avance III HD Ascend 600 MHz and Bruker Avance III 500MHz) at working frequencies 600 and 150 MHz (or 500 and 125 MHz) respectively in $CDCl_3$ (or DMSO) using TMS as internal standard. All chemical shifts are reported as δ values (ppm) relative to TMS and observed coupling constants (*J*) are given in Hertz (Hz). Mass spectra were measured with an HRMS–EI (Waters GCT Premier) and ESI (Agilent 1200) instrument or a low-resolution MS instrument using EI (Thermo Fisher ITQ1100) and ESI (Thermo Fisher LCQ™ Deca XP plus). All reagents were purchased from Aladdin Industrial Corporation and used without prior purification. Column chromatography was performed on silica gel (200–300 mesh) and the elution was performed with *n*-hexane/ethyl acetate.

Synthesis of N*-chloro aldimines and nitriles; general procedure*

A suspension of an aldehyde **1** (2 mmol) and NH_4OAc (0.308 g, 4 mmol) in ethanol (15 mL) was stirred for 1 h at 50 °C. $NaClO_2$ (80%, 0.36 g, 3.2 mmol) was then added and the mixture was stirred strongly for 2 h. After cooling, the filtrates were rotary-evaporated to dryness and the residues were purified by column chromatography on silica gel (ethyl acetate/*n*-hexane, 1:100) to afford compounds **2a–p** and compounds **2o′–q′**.

Benzalchloroimine (**2a**)*:*[12] Colourless oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.71–7.69 (m, 2H), 7.54–7.51 (m, 1H), 7.48–7.45 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 133.2, 132.1, 128.9, 128.0; HRMS (EI) calcd for C_7H_6NCl: [M (^{35}Cl)]$^+$: 139.0189; found: 139.0198 (100%); [M (^{37}Cl)]$^+$: 141.0159; found: 141.0168 (31.5%).

4-tert-Butylbenzalchloroimine (**2b**): Colourless oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.64–7.63 (m, 2H), 7.49–7.48 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 155.8, 130.5, 127.9, 125.9, 35.1, 31.1; HRMS (EI) calcd for $C_{11}H_{14}NCl$: [M (^{35}Cl)]$^+$: 195.0815; found: 195.0821 (100.0%); [M (^{37}Cl)]$^+$: 195.0785; found: 197.0816 (31.7%).

3-Hydroxybenzalchloroimine (**2c**): Colourless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.33 (t, J = 9.8 Hz, 1H), 7.23–7.22 (m, 1H), 7.20 (d, J = 9.8 Hz, 1H), 7.03 (dd, J_1 = 8.0 Hz, J_2 = 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 156.1, 134.4, 130.4, 121.5, 119.7, 113.7; HRMS (ESI) calcd for C_7H_7NClO: [M (^{35}Cl) + H]$^+$: 156.0211; found: 156.0209 (100.0%); [M (^{37}Cl) + H]$^+$: 158.0187; found: 158.0184 (32.0%).

2-Fluorobenzalchloroimine (**2d**): Colourless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.92–7.89 (m, 1H), 7.53–7.48 (m,

1H), 7.23 (t, J = 0.8 Hz, 1H), 7.16–7.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4 (d, J_{C-F} = 5.0 Hz), 161.2 (d, J_{C-F} = 253.7 Hz), 133.9 (d, J_{C-F} = 8.8 Hz), 127.4 (d, J_{C-F} = 1.8 Hz), 124.7 (d, J_{C-F} = 3.6 Hz), 121.0 (d, J_{C-F} = 9.9 Hz), 116.2 (d, J_{C-F} = 20.8 Hz); HRMS (EI) calcd for C_7H_5NFCl: [M (^{35}Cl)]$^+$: 157.0095; found: 157.0086 (100.0%); [M (^{37}Cl)]$^+$: 159.0065; found: 157.0067 (31.8%).

4-Fluorobenzalchloroimine (**2e**): Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.73–7.70 (m, 2H), 7.17–7.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.2, 165.0 (d, J_{C-F} = 252.2 Hz), 130.2 (d, J_{C-F} = 8.9 Hz), 129.5 (d, J_{C-F} = 3.3 Hz), 116.3 (d, J_{C-F} = 22.1 Hz); HRMS (EI) calcd for C_7H_5NFCl: [M (^{35}Cl)]$^+$: 157.0095; found: 157.0100 (100.0%); [M (^{37}Cl)]$^+$: 159.0065; found: 159.0081 (31.9%).

2-Chlorobenzalchloroimine (**2f**):[13] Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.27 (s, 1H), 7.98–7.97 (m, 1H), 7.59–7.54(m, 1H), 7.45–7.44 (m, 1H), 7.36–7.33 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6, 134.7, 133.0, 130.7, 130.1, 128.0, 127.3; MS (EI) *m/z* (%) = 173.0 ([M (^{35}Cl)]$^+$, 100.0%), 175.0 ([M (^{37}Cl)]$^+$, 32.0%); HRMS (EI) calcd for $C_7H_5NCl_2$: [M (^{35}Cl)]$^+$: 172.9799; found: 172.9810 (100.0%); [M (^{35}Cl + ^{37}Cl)]$^+$: 174.9770; found: 174.9783 (63.9%).

3-Chlorobenzalchloroimine (**2g**): Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.72 (t, J = 0.3 Hz, 1H), 7.57–7.55 (m, 1H), 7.50–7.48 (m, 1H), 7.41 (t, J = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.3, 135.2, 134.7, 132.1, 130.3 127.7, 126.3; MS (EI) *m/z* (%) = 173.0 ([M (^{35}Cl)]$^+$, 100.0%), 175.0 ([M (^{37}Cl)]$^+$, 31.9 %); HRMS (EI) calcd for $C_7H_5NCl_2$: [M (^{35}Cl) – HCl]$^+$: 137.0032; found: 137.0037 (100.0%); [M(^{37}Cl) – HCl]$^+$: 139.0005; found: 139.0003 (31.9%).

2-Bromobenzalchloroimine (**2h**): Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.97–7.96 (m, 1H), 7.64–7.63 (m, 1H), 7.41–7.36 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 133.4, 133.2, 132.3, 128.5, 127.9, 124.5; MS (EI) *m/z* (%) = 218.9 ([M (^{35}Cl) (^{81}Br)]$^+$ & [M (^{37}Cl) (^{79}Br)]$^+$, 100.0 %), 216.9 ([M (^{35}Cl) (^{79}Br)]$^+$, 77.6 %), 220.9 ([M (^{37}Cl) (^{81}Br)]$^+$, 24.0 %); HRMS (EI) calcd for C_7H_5NClBr: [M (^{35}Cl) (^{81}Br)]$^+$ & [M(^{37}Cl) (^{79}Br)]$^+$: 218.9271; found: 218.9285 (100.0%); [M(^{35}Cl) (^{79}Br)]$^+$: 216.9294; found: 216.9306 (77.3%); [M (^{37}Cl) (^{81}Br)]$^+$: 220.9244; found: 220.9267 (24.2%).

4-Bromobenzalchloroimine (**2i**): Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.61–7.58 (m, 2H), 7.56–7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 132.6, 132.3, 129.3, 126.9; MS (EI) *m/z* (%) = 218.9 ([M (^{35}Cl) (^{81}Br)]$^+$ & [M (^{37}Cl) (^{79}Br)]$^+$, 100.0%), 216.9 ([M (^{35}Cl) (^{79}Br)]$^+$, 76.6%), 220.9 ([M(^{37}Cl) (^{81}Br)]$^+$, 24.4%); HRMS (EI) calcd for C_7H_5NClBr: [M (^{35}Cl) (^{81}Br)]$^+$ & [M(^{37}Cl) (^{79}Br)]$^+$: 218.9271; found: 218.9298 (95.0%); [M (^{35}Cl) (^{79}Br)]$^+$: 216.9294; found: 216.9309 (100%); [M (^{37}Cl) (^{81}Br)]$^+$: 220.9245; found: 216.9267 (20.1%).

2-Nitrobenzalchloroimine (**2j**): Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.17 (dd, J_1 = 1.0 Hz, J_2 = 3.2 Hz, 1H), 7.98–7.97 (dd, J_1 = 3.0 Hz, J_2 = 1.5 Hz, 1H), 7.78–7.74 (td, J_1 = 0.8 Hz, J_2 = 3.0 Hz, 1H), 7.72–7.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 147.5, 134.1, 132.2, 129.7, 128.3, 124.9; MS (EI) *m/z* (%) = 184.0 ([M (^{35}Cl)]$^+$, 100.0%), 186.0 ([M (^{37}Cl)]$^+$, 32.0%); HRMS (EI) calcd for $C_7H_5N_2O_2Cl$: [M (^{35}Cl)]$^+$: 184.0040; found: 184.0033 (100.0%); [M (^{37}Cl)]$^+$: 186.0010; found: 185.9986 (29.5%).

4-Nitrobenzalchloroimine (**2k**): Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.33 (d, J = 11.3 Hz, 2H), 7.91–7.89 (d, J = 10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 149.7, 138.3, 128.8, 124.2; MS (EI) *m/z* (%) = 184.0 ([M (^{35}Cl)]$^+$, 100.0%), 186.0 ([M (^{37}Cl)]$^+$, 31.7%); HRMS (EI) calcd for $C_7H_4N_2O_2$: [M – HCl]$^+$: 148.0273; found: 148.0276.

2-Cyanobenzalchloroimine (**2l**): Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.90–7.86 (m, 2H), 7.68–7.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 147.1, 138.5, 132.5, 132.4, 124.5, 124.0, 122.5; HRMS (EI) calcd for $C_8H_5N_2Cl$; [M (^{35}Cl)]$^+$: 164.0141; found: 164.0150 (100.0%); [M (^{37}Cl)]$^+$: 166.0112; found: 166.0103 (32.2%).

4-Trifluoromethylbenzalchloroimine (**2m**): Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.74–7.72 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.3, 136.1, 133.5 (q, J_{C-F} = 32.6 Hz), 128.3, 126.0 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 270.9 Hz); HRMS (EI) calcd for $C_8H_4NF_3$: [M – HCl]$^+$: 171.0296; found: 171.0310.

5-Bromofuran-2-N-*chloroaldimine* (**2n**): Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (s, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$): δ 159.6, 149.6, 128.0, 118.2, 114.2; HRMS (EI) calcd for C_5H_2NOBr: [M (^{79}Br) – HCl]$^+$: 170.9320; found: 170.9316; [M (^{81}Br) – HCl]$^+$: 172.9299; found: 172.9302.

3-Nitrobenzalchloroimine (**2o**):[13] Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.55 (t, J = 1.8 Hz, 1H), 8.39–8.37 (m, 1H), 8.07 (d, J = 6.6 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 148.6, 134.6, 133.2, 130.2, 126.4, 122.9; MS (EI) *m/z* (%) = 184.0 ([M (^{35}Cl)]$^+$, 100.0%), 186.0 ([M (^{37}Cl)]$^+$, 32.1%); HRMS (EI) calcd for $C_7H_5N_2O_2Cl$: [M (^{35}Cl)]$^+$: 184.0040; found: 184.0047 (100%); [M (^{37}Cl)]$^+$: 186.0010; found: 186.0022 (31.8%).

3-Nitrobenzonitrile (**2o′**): Pale yellow solid; m.p. 115.3–117.0 °C (lit. [14] 116 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.51–8.50 (m, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.78–7.76 (t, J = 8.4Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.3, 137.6, 130.7, 127.5, 127.2, 116.5, 114.2; MS (EI) *m/z* = 148.0 [M]$^+$ (lit. MS (EI) *m/z* = 148.0 [M]$^+$).

4-Cyanobenzalchloroimine (**2p**): Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.82 (d, J = 10.5 Hz, 2H), 7.77 (d, J = 10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 136.7, 132.7, 128.4, 117.9, 115.4; HRMS (EI) calcd for $C_8H_5N_2Cl$: [M (^{35}Cl)]$^+$: 164.0141; found: 164.0148 (100%); [M (^{37}Cl)]$^+$: 166.0112; found: 166.0110 (32.0%).

Terephthalonitrile (**2p′**): White solid; m.p. 222.5–223.6 °C (lit.[15] 224 °C); ^{1}H NMR (500 MHz, DMSO): δ 8.10 (s, 4H); ^{13}C NMR (125 MHz, DMSO): δ 133.2, 117.5, 115.7; MS (EI) *m/z* = 128.0 [M]$^+$ (lit.[15] MS (EI) *m/z* = 128.0 [M]$^+$).

*Synthesis of ethyl 2-(3-cyano-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (***2q′***)*

A solution of **1q** (1.00 g, 3.4 mmol) and NH_4OAc (0.54 g, 6.8 mmol) in ethanol (15 mL) was stirred for 30 min at 50 °C. $NaClO_2$ (80%, 0.62 g, 5.4 mmol) was then added and the mixture was stirred for 2 h under nitrogen (TLC control, petroleum ether [boiling range: 60–90 °C)/EtOAc (3:1, v/v)]. After cooling, the filtrate was rotary-evaporated to dryness and the residues were purified by column chromatography on silica gel (ethyl acetate/*n*-hexane, 1:8) to afford **2q′** [yield 0.69 g (70%)].

Ethyl 2-(3-cyano-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**2q′**): Pale yellow solid; m.p. 184.5–185.5 °C (lit.[11] 184.7–185.4 °C); ^{1}H NMR (600 MHz, DMSO): δ 11.89 (s, 1H), 8.15 (d, J = 2.4 Hz, 1H), 8.05 (dd, J_1 = 2.4 Hz, J_2 = 4.2 Hz, 1H), 7.11–7.09 (m, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.63 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO): δ 167.5, 162.9, 161.7, 160.5, 133.3, 131.9, 124.3, 121.3, 117.4, 116.4, 100.3, 61.6, 17.6, 14.6; MS (ESI): 289.1 [M + H]$^+$ (lit.[11] MS (ESI): 286.9 [M – H]$^-$).

Acknowledgements

We are grateful to the National Natural Science Foundation of China (21606202) and the Collaborative Innovation Centre of Yangtze River Delta Region Green Pharmaceuticals for financial help.

Received 23 March 2018; accepted 18 August 2018
Paper 1805338
https://doi.org/10.3184/174751918X15403084696731
Published online: 29 October 2018

References

1 R. Kupfer and U.H. Brinker, *J. Org. Chem.,* 1996, **61**, 4185.
2 S. Gaspa, A. Porcheddu, A. Valentoni, S. Garroni, S. Enzo and L.D. Luca, *Eur. J. Org. Chem.,* 2017, **37**, 5519.
3 J.W. Lemaistre, A.E. Rainsford and C.R. Hauser, *J. Org. Chem.,* 1939, **4**, 106.

4 D. Sun, Z. Wang, Y. Di, J.C. Jaen, M. Labelle, J. Ma, S. Miao, A. Sudom, L. Tang, C.S. Tomooka, H. Tu, S. Ursu, N. Walker, X. Yan, Q. Ye and J.P. Powers, *Bioorg. Med. Chem. Lett.,* 2008, **18**, 3513.
5 O. Okamoto, K. Kobayashi, H. Kawamoto, S. Ito, T. Yoshizumi, I. Yamamoto, M. Hashimoto, A. Shimizu, H. Takahashi, Y. Ishii, S. Ozaki and H. Ohta, *Bioorg. Med. Chem. Lett.,* 2008, **18**, 3282.
6 J. Liu, J. Xu, J. Ren and B.B. Zeng, *Chem. Lett.,* 2014, **43**, 190.
7 X. Xiong, X. Xu, Y. Zhou and C. Weng, *Russ. J. Gen. Chem.,* 2013, **83**, 2402.
8 J. Liu, H.-X. Zheng, C.-Z. Yao, B.-F. Sun and Y.-B. Kang, *J. Am. Chem. Soc.,* 2016, **138**, 3294.
9 Y. Kawagoe, K. Moriyama and H. Togo, *Eur. J. Org. Chem.,* 2014, **19**, 4115.
10 M. Hasegawa, *Heterocycles*, 1998, **47**, 857.
11 X.L. Li, R. Qiu, W.L. Wan, X. Cheng, L. Hai and Y. Wu, *Lett. Org. Chem.*, 2015, **12**, 217.
12 J.L. Zhang, *Gaodeng Xuexiao Huaxue Xuebao*, 1987, **8**, 246; *Chem. Abstr.,* 1988, **108**, 37295
13 C.R. Hauser, M.L. Hauser and A. Gillaspie, *J. Am. Chem. Soc.,* 1930, **52**, 4158.
14 M.V. Roux, P. Jiménez, J.Z. Dávalos, M. Temprado and J.F. Liebman, *J. Chem. Thermodyn.*, 2003, **35**, 803.
15 R.J. Abraham and M. Reid, *Magn. Reson. Chem.*, 2000, **38**, 570.