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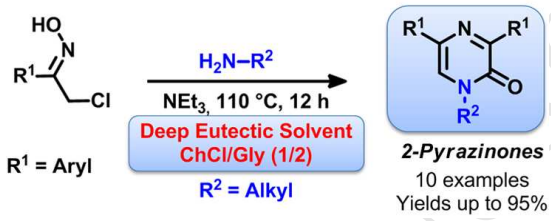

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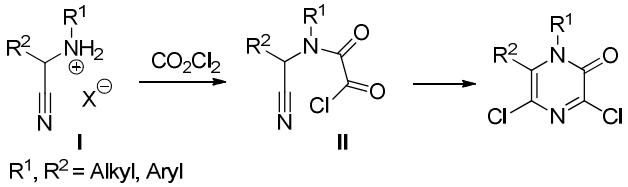
ABSTRACT

A novel and green synthesis of 2-pyrazinones in deep eutectic solvents (DESs) is described. Treatment of aromatic α-chloro oximes with aliphatic amines at 110 °C in choline chloride based DESs resulted in a straightforward and efficient assembly of 1,3,5-trisubstituted-2(*1H*)-pyrazinones. The protocol, featuring mild reaction conditions and avoiding common volatile organic solvents, affords a safe and sustainable approach to original peptidomimetic scaffolds.

1. Introduction

In the last few years, *2(1H)*–pyrazinones have aroused considerable interest since they may represent a significant scaffold in peptidomimetic chemistry. Recently the use of pyrazinones as a part of a number of macromolecular peptidomimetic ligands acting as protease inhibitors has been reported. In particular, the introduction of a pyrazinone in the caspase-3,[1] thrombin[2a-e] and tryptase[3] peptide-like inhibitors leads to a reduction of the peptidyl nature of these compounds, while preserving their binding potency and selectivity to modulate protease activity. Inhibition of specific proteases may offer significant opportunity for therapeutic intervention in several diseases such as neurodegenerative diseases and autoimmune disorders. A pyrazinone unit also replaced a disulfide portion in a somatostatin derivative leading to a compound with high anti-proliferative activity.[4] Moreover, investigations of a tunicate-derived actinomycete *Streptomyces sp*. afforded new *2(1H)*–pyrazinone-based molecules providing further understanding about the chemistry and bioactivities of the alkylated *2(1H)*–pyrazinone derivatives.[5]

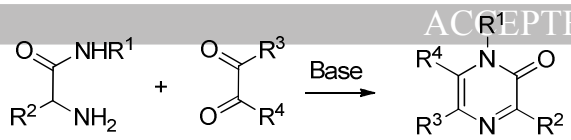
Considering the importance of the above-mentioned applications and activities, methods for the synthesis of the *2(1H)*–pyrazinone core are of great interest. As previously reported by Hoornaert and coworkers,[6] the treatment of hydrohalides of 2-*sec*-aminoalkanenitriles (**I**) with an excess of oxalyl chloride, using *o*-dichlorobenzene (ODCB) as reaction solvent, afforded intermediate (**II**) and then 3,5-dihalo-2(*1H*)-pyrazinones, of which the 3-halo substituent is easily replaced by nucleophiles (Scheme 1).[7]



Scheme 1. Synthesis of 3,5-dichloro-2(1*H*)-pyrazinones from *α*-amino nitriles and oxalyl chloride.

The reactive 3-Cl position of 3,5-dichloro-2(*1H*)-pyrazinones can be easily functionalized with (hetero)aryl, alkyl and alkenyl groups by means of Suzuki cross-coupling reactions using organoboron reagents. Furthermore, Heck coupling of vinyl compounds at C-3 of 2(*1H*)-pyrazinones provides 3-alkenyl-5-cloro-*2(1H)*-pyrazinones.[7] The 5-Cl position is inert towards Suzuki and Heck cross-coupling reactions and its functionalization is proved to be more difficult. Indeed, before carrying out cross coupling reactions, a prior trans-halogenation of the 5-Cl substituent to produce a 5-Br or 5-I-*2(1H)*-pyrazinones is required.[7]

Alternatively, 5-alkyl and 5-aryl-2(*1H*)-pyrazinones can be prepared, using H_2O/MeOH as solvent, via a direct condensation of carboxamide derivatives with dicarbonyl compounds producing a pyrazinone product when R^3 and R^4 are the same, or a mixture of regioisomers when R^3 and R^4 are different from each other (Scheme 2).[8]



Scheme 2. Synthesis of 5-substituted 2(*1H*)-pyrazinones from *α*-amino amides.

In terms of the reactivity of 2(*1H*)-pyrazinones, several heterocycles containing a 2-azadiene moiety are subject to cycloaddition reactions. The 2-azadiene system of *2(1H)*–pyrazinones has been shown to be involved in [4+2] cycloaddition reactions with a variety of dienophiles such as singlet oxygen, 1,2,4-triazoline-3,5-diones, olefins and acetylenic compounds.[9a-b] Furthermore, *2(1H)*–pyrazinones with either a 3- or 4- alkynyloxy side chain in the 3-position underwent intramolecular Diels-Alder reactions providing furo/pyrano-pyridines and/or –pyridinones.[10]

Therefore, development of new approaches for the synthesis of *2(1H)*–pyrazinones could be relevant from both chemical and biological viewpoints. In addition, it should also be noted how the methods previously reported are performed in toxic, hazardous volatile organic solvents (VOCs, e.g. ODCB, DMF, toluene, etc.).

In this paper, we describe a novel synthetic method for the assembly of the *2(1H)*–pyrazinone core by means of a coupling reaction between aromatic *α*-chloro oximes and aliphatic amines. Moreover, this process, representative of a direct and straightforward methodology to obtain 1-alkyl-3,5-aryl trisubstituted *2(1H)*-pyrazinones, was successfully accomplished in "green" reaction media such as DESs (deep eutectic solvents).[11a-c] DESs represent an emerging class of unconventional and bio-renewable solvents that could satisfactorily replace any common VOC solvents in organic reactions. They are generally composed of two or three safe and inexpensive components, which are involved in hydrogen bond interactions with each other to obtain a eutectic mixture with a melting point much lower than that of each component species. Since their typical components [e.g., choline chloride (ChCl), urea, glycerol (Gly), natural carboxylic acids, amino acids and carbohydrates, polyalcohols, etc.] come from natural sources, DESs display low toxicity, high thermal stability, high biodegradability, high recyclability, low inflammability and volatility, avoiding many disadvantages of common hazardous organic solvents (VOCs).

2. Results and discussion

In the recent past, our research group has been interested in the study of the reactivity of halides characterized by a π C–C,C–O or C–N bond such as allyl, benzyl halides, *α*-chloro-ketones and -imines.[12,13] These unsaturated halides, via a Pd-catalyzed carbonylation process, were efficiently coupled with a variety of nucleophiles to afford a wide range of carbonyl-containing organic molecules such as functionalized *β*-lactams,[12a-c] imides,[12d] esters,[12e] acetylenic ketones,[12f] amides,[12g-i] pyranones,[13a] uracil,[13b] pyrazolone derivatives,[13c] and isocytosine analogues.[13d]

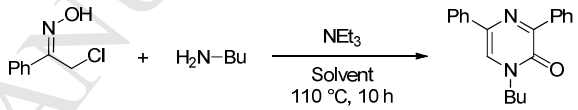
In line with our research work, we then started an investigation of the reactivity *α*-chloro oximes towards primary amines as nucleophiles. *α*-Chloro oximes are highly reactive and unstable molecules, the utility of which in organic synthesis has remained little explored. In particular, *α*-chloro oximes are known to undergo a base-induced condensation to provide both alkynyl oxime ethers with lithium diisopropylamide[14] and 2,4,6-trisubstituted pyrimidines in the presence of Grignard reagents.[15]

Moreover, *α*-chloro oximes have been involved in umpolung carbon sulfur bond-forming reactions by nucleophilic addition of thiolate and sulfinate ions.[16] However, no application of *α*-chloro oximes in the synthesis of the 2(*1H*)-pyrazinone core has been reported.

Here we describe a novel, safe and convenient coupling reaction of *α*-chloro oximes with primary amines to furnish *2(1H)*-pyrazinone derivatives. The *α*-chlorinated oximes used were easily prepared according to a known protocol based on direct condensation of the *α*-chloroketones with hydroxylamine hydrochloride.[17] At first, the reaction of 2-chloro-1-phenylethanone oxime **1a** with butan-1-amine **2a**, under Pd–catalyzed carbonylation conditions previously reported,[12-13] was carried out. (Table 1, entry 1).

After a reaction time of 10 h, GC-MS and ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the formation of a new coupling molecule as main reaction product. ^{1}H, ^{13}C NMR spectroscopic analysis and NOESY experiments performed on the product, after its isolation by column chromatography on silica gel, proved that coupling between oxime **1a** and amine **2a** occurred to provide the 1-butyl-3,5-diphenylpyrazin-2(*1H*)-one **3a** in 32% yield.

Table 1. Optimization of the experimental conditions for the coupling between 2-chloro-1-phenylethanone oxime and butan-1-amine[a]



1a **2a** **3a**

Entry	Oxime **1a** (equiv.)	Amine **2a** (equiv.)	Solvent	**3a** Yield (%)[b]
1	1.0	1.3	THF[c]	32
2	1.0	1.3	THF[d]	39
3	1.0	1.3	Toluene	traces
4	1.0	1.3	DMF	58
5	1.0	1.3	Gly/ChCl[e]	70
6	1.0	1.3	urea/ChCl[e]	68
7	1.0	1.0	Gly/ChCl	43
8	2.0	1.0	Gly/ChCl	55
9	1.0	1.3	THF/H_2O[f]	22
10	1.0	1.3	DMF/H_2O[f]	35

[a] Reagents and conditions on 1 mmol scale: 2-chloro-1-phenylethanone oxime (1.5 to 3.0 mmol), 1-butanamine (1.5 to 2.0 mmol), Et_3N (3.0 mmol), common volatile organic solvents (THF, toluene, DMF, 10 mL) or DES (3 mL), 110 °C, 10 h. All reactions were run in duplicate.

[b] Isolated yield.

[c] Reaction carried out in autoclave at a temperature of 110 °C under CO pressure (27.0 atm) with 5 mol% of $Pd(PPh_3)_4$.

[d] Reaction carried out in autoclave at a temperature of 110 °C.

[e] DES mixture: Gly–ChCl, 2:1 mol mol^{-1} or urea–ChCl, 2:1 mol mol^{-1}.

[f] Solvents were mixed in a 1:1 ratio.

The analysis of the atomic connectivity in **3a** prompted us to perform the same reaction without carbon monoxide and Pd-source; the pyrazinone nucleus was again obtained in a similar yield, highlighting how the Pd-catalysis is not necessary in such a reaction (Table 1, entry 2).

Indeed, to improve the coupling process yield, an optimization of reaction conditions was carried out by changing some parameters such as the reaction solvent as well as the amounts of oxime and amine used. As shown in Table 1, the nature of the solvent was proven to be crucial for the final product yield, and good results were achieved using polar common organic solvents with an increase in the yield as the solvent polarity increases from toluene to DMF (Table 1, entries 2-4).

However, to our delight the best product yields were obtained when the experiments were run, under air, in environmentally friendly solvents (DESs). In particular, Gly/ChCl and urea/ChCl were tested (Table 1, entries 5-8) as eutectic solvents. The reaction proved to be very clean, in both cases, without the detection of other byproducts. The pyrazinone **3a** was easily isolated in 70% and 68% yield, respectively (Table 1, entries 5 and 6), after a simple reaction workup involving dilution of the crude reaction with an equal volume of water and AcOEt, separation of the organic layer followed by chromatography on silica gel (see Experimental Section). In addition, it was possible to recover and recycle Gly/ChCl and urea/ChCl DES mixtures. Indeed, a further addition of water (2 mL) to the aqueous layer containing the DES leads to the precipitation of the unreacted reagents and small amounts of other organic byproducts that were removed by filtration. Subsequent evaporation of water under reduced pressure, afforded a DES mixture that was successfully reused for the synthesis of **3a** without a significant drop in the chemical yield (67%) after three experiments. As far as we are aware, this represents the first example of the preparation of 2(*1H*)-pyrazinones performed in low melting green mixtures.

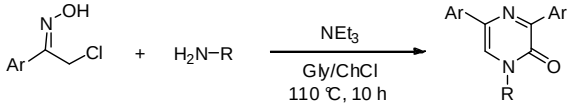
Moreover, a brief screening about the relative amounts of reagents revealed that formation of the *2(1H)*-pyrazinone **3a** was higher when an excess of the primary amine was employed (Table 1, entry 5); if an equimolar amount of **1a** and **2a**, or an excess of oxime were used, the pyrazinone yield dropped considerably (Table 1, entries 7-8). In addition, we experimented with two mixed solvents containing an equal volume of a polar aprotic solvent (THF, DMF) and water. This was done in order to check if the addition of water, as a proton source, to a VOC solvent could be equivalent to using DES. Although the product **3a** could be isolated in both cases (22 and 35% yield, Table 1, entries 9-10), the use of DESs resulted far more efficient.

Once the optimal experimental conditions were identified (Table 1, entry 5), the coupling reaction of various aromatic *α*-chloro oximes with aliphatic primary amines, under the same conditions, was examined (Table 2). In particular, we synthesized in high yields (78-93%) 1-alkyl-3,5-phenyl trisubstituted *2(1H)*-pyrazinones **3b-e** starting from 2-chloro-1-phenylethanone oxime **1a** and the aliphatic amines **2b-e** as nucleophiles. Notably, the methodology works efficiently also with sterically demanding amines, as proved with the synthesis of 1-*tert*-butyl and 1-phenylethyl substituted derivatives **3d** and **3e** obtained in excellent yields (Table 2, entries 3-4).

The same experimental procedure was also efficiently applied to the *p*-Cl- and *p*-F- substituted oximes **1b** and **1c**; in fact, they proved to be good partners with aliphatic amines affording the corresponding 1-alkyl-3,5-aryl trisubstituted *2(1H)*-pyrazinones **3f**-**3j** in high yield (88-95%, Table 2, entries 5-9).

However, any attempts to perform coupling between aliphatic *α*-chlorinated oximes (e.g. 2-chlorocyclohexanone oxime or 1-chloropropan-2-one oxime) and aromatic (such as aniline) or aliphatic amines resulted in a complex mixture of unidentified products.

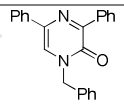
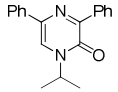
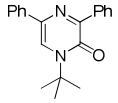
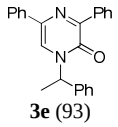
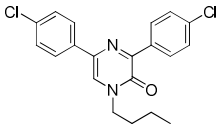
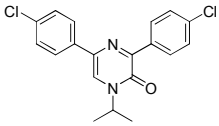
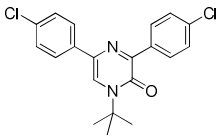
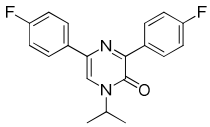
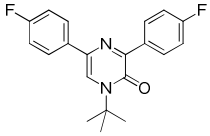
Table 2. Synthesis of *2(1H)*–pyrazinone derivatives **3b-j** in Deep Eutectic Solvents



1a-c **2a-e** **3b-j**

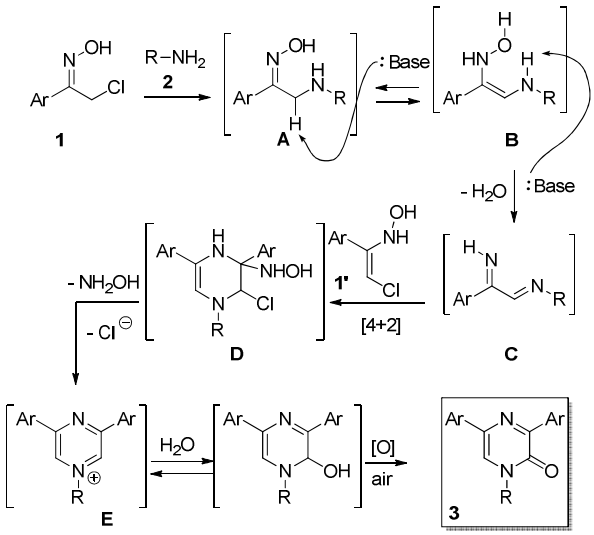
[a] Reagents and conditions: oxime (1.5 mmol), primary amine (2.0 mmol), Et_3N (3.0 mmol), DES (Gly/ChCl, 3 mL), 110 °C, 10 h. All reactions were run in duplicate.

[b] After isolation by column chromatography on silica gel.

Entry	Oxime **1**	Ar	Amine **2**	R	2-Pyrazinone **3** (Yield %)
1	**1a**	Ph	**2b**	Bn	 **3b** (78)
2	**1a**	Ph	**2c**	*i*-Pr	 **3c** (89)
3	**1a**	Ph	**2d**	*t*-Bu	 **3d** (91)
4	**1a**	Ph	**2e**		 **3e** (93)
5	**1b**	4-ClC_6H_4	**2a**	*n*-Bu	 **3f** (88)
6	**1b**	4-ClC_6H_4	**2c**	*i*-Pr	 **3g** (89)
7	**1b**	4-ClC_6H_4	**2d**	*t*-Bu	 **3h** (95)
8	**1c**	4-FC_6H_4	**2c**	*i*-Pr	 **3i** (93)
9	**1c**	4-FC_6H_4	**2d**	*t*-Bu	 **3j** (92)

Furthermore, in the reactions between aromatic α-chlorinated oximes and aniline no coupling product was obtained, pointing out how this synthetic procedure works well with the use of aromatic oximes and aliphatic amines.

Although the chemical impact of our method relies basically on its synthetic utility as a fast, green and simple way to 2-pyrazinones, some considerations about the reaction mechanism are needed. On the basis of a recent investigation on the reactivity of α-chloro oximes in DESs,[16] we hypothesize that the first step of our domino process should be the nucleophilic attack of the amine **2** to the oxime **1** affording the α-amino oxime intermediate **A** (Scheme 3).



Scheme 3. Mechanistic hypothesis for the formation of 1-alkyl-3,5-trisubstituted 2(*1H*)-pyrazinones from α-chloro oximes and amines.

The absence of a N-O bond in the final product prompted us to consider that an elimination of the OH group from the nitrogen atom must occur. This process may consist of two steps: firstly, a base-catalyzed tautomerism could promote the formation of **B**, the enaminic form of **A**, favored by the extensive electronic conjugation. A subsequent base-catalyzed elimination and NO bond breaking, should afford the intermediate **C.**

Once formed, the 1,4-diaza-1,3-diene **C** could undergo a [4+2] cycloaddition with **1'**, the enolic form of **1**, to assemble the six-membered ring **D**.[18] The subsequent elimination of the hydroxylamine and the chloride ion should afford the aromatic pyrazinium **E** that, after the nucleophilic attack of a molecule of water and air-promoted dehydrogenation/aromatization,[19] should give the 1-alkyl-3,5-diaryl trisubstituted 2-pyrazinone product **3**.

3. Conclusions

A direct and easy method for the synthesis of 1-alkyl-3,5-aryl trisubstituted *2(1H)*-pyrazinones, biologically valuable products like peptidomimetics, is described. In particular, we have found that aromatic α-chloro oximes can be safely and conveniently coupled with aliphatic primary amines using DESs as privileged and green solvents for the reactions. This methodology, by which *2(1H)*-pyrazinones are obtained with high yields, has the advantage of working in biodegradable and cost-effective reaction solvents so avoiding the use of toxic and hazardous volatile organic solvents.

4. Experimental section

4.1. General Information

Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. THF was purified by distillation from sodium/benzophenone before use. Petroleum ether refers to the 40−60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded with a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as the solvent and TMS as an internal standard (δ = 7.26 ppm for ^{1}H spectra; δ = 77.0 ppm for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. Gas chromatography (GC) was conducted on an Rtx-5 30-m fused silica capillary column (split ratio 100:1). The following program was used: method A = initial temperature of 100 °C for 0.0 min, ramp 10 °C/min to 280 °C, and hold for 15 min; the standard operating conditions were 300 °C injector temperature and 290 °C detector temperature. GC-MS analyses, conducted using method A temperature programme, were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenylpolymethylsiloxane capillary column, 30 m, 0.25 mmi.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV. The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion-spray ionization source. MS (+) spectra were acquired by direct infusion (5 mL min^{-1}) of a solution containing the appropriate sample (10 pmol mL^{-1}) dissolved in a solution 0.1% acetic acid, methanol/water (50:50) at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm) or p-anisaldehyde and phosphomolybdic acid staining solution. Chromatographic separations were performed on silica gel (63−200 mesh) using petroleum ether/ethyl acetate (AcOEt) mixture as the eluent. All reactions involving air-sensitive reagents were performed under an atmosphere of nitrogen in oven-dried glassware by using syringe/septum cap techniques. The deep eutectic solvents ChCl–Gly (1:2 mol.mol-1) and ChCl–urea (1:2 mol.mol-1) were prepared by gently heating under stirring at 70 °C for 5 min the corresponding individual components until a clear solution was obtained.

*4.2. General procedure for the synthesis of α-chlorinated oximes **1a-c***

To a stirred mixture of α-chlorinated aromatic ketone (38 Mmol) and hydroxylamine hydrochloride (115 mmol) in water (8 mL), methanol was added (60 mL) to yield a clear solution that was stirred overnight at room temperature. Subsequently, water (80 mL) was added and the oxime product precipitated out as a solid. The solid was filtered out, washed several times with water and dried over $CaCl_2$ in a vacuum desiccator. Spectroscopic data for 2-chloro-1-phenylethanone oxime **1a**, obtained in 91% yield, were in agreement with those reported in the literature.[17] Spectroscopic data for oximes **1b** and **1c** are reported below.

*2-Chloro-1-(4-chlorophenyl)ethanone oxime (**1b**)*: white solid (7.1 g, 92%), m.p. 100-102 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.59 (s, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 9.36 (broad s, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ =32.0, 127.5, 129.0, 131.6, 136.0, 153.4 ppm. FT-IR ($CHCl_3$): ν = 3574, 3289 (broad), 1604, 1512, 1496, 1442, 1291, 1263, 1096 cm^{-1}.GC-MS (70 eV): m/z (%) = 207 (7) [M+4], 205 (47) [M+2], 203 (70) $[M]^{+}$, 154 (65), 137 (100), 111 (68), 75 (60), 51 (30).

HRMS (ESI): calcd. for $C_8H_8Cl_2NO$ $[M+H]^+$ 203.9984; found 220 (100), 116 (26), 89 (29). HRMS (ESI): calcd. for 203.9987.

*2-Chloro-1-(4-fluorophenyl)ethanone oxime (**1c**)*: pale yellow solid (6.4 g, 90%), m.p. 64-66 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ =4.59 (s, 2 H), 7.09-7.13 (m, 2 H), 7.66-7.69 (m, 2 H), 9.39 (broad s, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 32.2, 115.8 (d, *J* = 22 Hz), 128.2 (d, *J* = 8 Hz), 129.1, 153.4, 163.7 (d, *J* = 251 Hz) ppm. FT-IR ($CHCl_3$): 3575, 3300 (broad), 1602, 1513, 1442, 1281, 1159 cm^{-1}. GC-MS (70 eV): m/z (%) = 189 (18) [M+2], 187 (53) $[M]^+$, 138 (34), 121 (100), 95 (51), 75 (27). HRMS (ESI): calcd. for C_8H_8FClNO $[M+H]^+$188.0279; found 188.0281.

*4.3. General procedure for the preparation of pyrazin-2(1H)-one derivatives **3a-j***

In a round bottomed flask, aromatic *α*-chlorinated oxime **1** (1.5 mmol), aliphatic primary amine **2** (2.0 mmol) and Et_3N (3.0 mmol) were mixed in 3 mL of DES (Gly/ ChCl 2:1 mol/mol or urea/ ChCl 2:1 mol/mol) for 10 hour at 110 °C. After dilution of the crude reaction with an equal volume of water, the reaction mixture was extracted with AcOEt (3 x 5 mL). The combined organic phases were dried over dry Na_2SO_4 and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography over silica gel using a mixture of 90:10 to 70:30 petroleum ether/AcOEt as the eluent, to give the corresponding pyrazin-2(1*H*)-one derivative **3**.

Spectroscopic data for *1-Benzyl-3,5-diphenylpyrazin-2(1H)-one (**3b**)*, obtained in 78% yield (395 mg), were in agreement with those reported in the literature.[7]

Spectroscopic data for compounds **3a,c-j** are reported below.

*1-Butyl-3,5-diphenylpyrazin-2(1H)-one (**3a**)*: pale yellow oil (388 mg, 85%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ =8.50 – 8.57 (m, 2 H), 7.86 – 7.89 (m, 2 H), 7.56 (s, 1 H), 7.44 – 7.47 (m, 5 H), 7.34 – 7.37 (m, 1 H), 4.03–4.10 (m, 2 H), 1.86 (dt, *J* = 15.2, 7.4 Hz, 2 H), 1.46 (dq, *J* = 14.8, 7.4 Hz, 2 H), 1.00 (t, *J* = 7.4 Hz, 3 H). ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 154.7, 151.6, 136.2, 136.0, 132.7, 129.9, 129.3, 128.8, 128.0, 127.9, 125.0, 124.1, 50.6, 30.9, 20.0, 13.7 ppm. FT-IR ($CHCl_3$): ν= 3027, 3009, 2961, 2931, 2874, 1728, 1645, 1595, 1455 cm^{-1}.GC-MS (70 eV): m/z (%) = 304 (100) $[M]^+$, 287 (35), 262 (21), 248 (53), 233 (70), 220 (50), 116 (30), 103 (45), 89 (40), 77 (15). HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ $[M+H]^+$ 305.1655; found 305.1657.

*1-Isopropyl-3,5-diphenylpyrazin-2(1H)-one (**3c**)*: pale yellow oil (387 mg, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ =8.45–8.47 (m, 2 H), 7.87–7.89 (m, 2 H), 7.61 (s, 1 H), 7.44 – 7.48 (m, 5 H), 7.34–7.38 (m, 1 H), 5.35 (hept, *J* = 6.8 Hz, 1 H), 1.49 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C-NMR (100 MHz, CDCl3): δ = 154.3, 151.5, 136.4 (2 x C), 133.2, 129.8, 129.3, 128.8, 128.0, 127.9, 125.0, 119.3, 47.7, 29.7, 21.6 ppm. FT-IR ($CHCl_3$): ν = 3026, 3009, 2963, 2935, 2872, 1726, 1644, 1596, 1455 cm^{-1}.GC-MS (70 eV): m/z (%) = 290 (93) $[M]^+$, 348 (40), 220 (100), 116 (30), 89 (36).HRMS (ESI): calcd. for $C_{19}H_{19}N_2O$ $[M+H]^+$291.1498; found 291.1499.

*1-(tert-butyl)-3,5-Diphenylpyrazin-2(1H)-one (**3d**)*: yellow oil (415 mg, 91%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ= 8.33 – 8.36 (m, 2 H), 7.84 - 7.86 (m, 2 H), 7.79 (s, 1 H), 7.43 – 7.47 (m, 5 H), 7.32 – 7.36 (m, 1 H), 1.80 (s, 9 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.8, 153.4, 136.8, 136.6, 132.3, 129.6, 129.4, 128.8, 127.9, 127.6, 125.0, 120.4, 62.7, 28.1 ppm. FT-IR ($CHCl_3$): ν = 3027, 3008, 2962, 2931, 2873, 1728, 1644, 1596, 1455 cm^{-1}.GC-MS (70 eV): m/z (%) = 304 (30) $[M]^+$, 248 (99), 220 (100), 116 (26), 89 (29). HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ $[M+H]^+$ 305,1655; found 305,1653.

(±)-*3,5-Diphenyl-1-(1-phenylethyl)pyrazin-2(1H)-one (**3e**)*: yellow oil (491 mg, 93%).^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.50–8.52 (m, 2 H), 7.72–7.76 (m, 2 H), 7.29 – 7.51 (m, 12 H), 6.52 (q, *J* = 7.1 Hz, 1 H), 1.84 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.5, 151.5, 139.0, 136.3, 133.1, 130.0, 129.4, 129.1, 128.8, 128.0, 127.9, 127.6, 126.0, 125.0, 120.5, 53.9, 18.9 ppm. FT-IR ($CHCl_3$): ν = 3033, 3011, 2960, 2929, 2855, 1729, 1644, 1593, 1454 cm^{-1}.GC-MS (70 eV): m/z (%) = 353(44) $[M]^+$, 248 (100), 220 (83), 116 (35), 105 (88), 89 (49), 77 (33). HRMS (ESI): calcd. for $C_{24}H_{21}N_2O$ $[M+H]^+$353.1655; found 353.1659.

*1-Butyl-3,5-bis(4-chlorophenyl)pyrazin-2(1H)-one (**3f**)*: yellow oil (491 mg, 88%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.46–8.48 (m, 2 H), 7.77–7.79 (m, 2 H), 7.55 (s, 1 H), 7.41 – 7.44 (m, 4 H), 4.00 – 4.09 (m, 2 H), 1.84 (dt, *J* = 15.2, 7.6 Hz, 2 H), 1.45 (td, *J* = 14.8, 7.6 Hz, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl^3$): δ = 154.5, 150.4, 136.2, 134.4, 134.3, 133.9, 131.6, 130.6, 129.0, 128.2, 126.2, 124.3, 50.7, 30.9, 29.7, 13.6 ppm. FT-IR ($CHCl_3$): ν = 3026, 3011, 2960, 2931, 2874, 1727, 1645, 1594, 1451 cm^{-1}.GC-MS (70 eV): m/z (%) = 376 (11) [M+4], 374 (66) [M+2], 372 (100) $[M]^+$,355 (45), 316 (50), 301 (53), 288 (47), 150 (43), 137 (48), 123 (45). HRMS (ESI): calcd. for$C_{20}H_{19}Cl_2N_2O[M+H]^+$ 373.0875; found 373.0876.

*3,5-Bis(4-chlorophenyl)-1-isopropylpyrazin-2(1H)-one (**3g**)*: pale yellow oil (478 mg, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.6 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 7.60 (s, 1 H), 7.42 – 7.44 (m, 4 H), 5.33 (hept, *J* = 6.8 Hz, 1 H), 1.49 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.1, 150.2, 136.1, 134.7, 134.6, 133.9, 132.1, 130.6, 129.0, 128.2, 126.2, 119.6, 47.9, 21.6 ppm. FT-IR ($CHCl_3$): ν = 3028, 3011, 2961, 2930, 2876, 1727, 1645, 1592, 1450 cm^{-1}.GC-MS (70 eV): m/z (%) = 362 (8) [M+4], 360 (51) [M+2], 358 (77) $[M]^+$, 315 (60), 288 (100), 150 (39), 123 (43), 89 (23). HRMS (ESI): calcd. for $C_{19}H_{17}Cl_2N_2O$ $[M+H]^+$ 359.0719; found 359.0721.

*1-(tert-butyl)-3,5-Bis(4-chlorophenyl)pyrazin-2(1H)-one (**3h**)*: pale yellow oil (530 mg, 95%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ =8.34 (d, *J* = 8.7 Hz, 2 H), 7.75 – 7.78 (m, 3 H), 7.40 – 7.43 (m, 4 H), 1.79 (s, 9 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.6, 152.1, 135.8, 135.1, 134.8, 133.6, 131.3, 130.8, 129.0, 128.1, 126.2, 120.7, 63.1, 28.0 ppm.FT-IR ($CHCl_3$): ν = 3027, 3010, 2962, 2929, 2875, 1724, 1645, 1592, 1450 cm^{-1}.GC-MS (70 eV): m/z (%) = 376 (2) [M+4], 374 (13) [M+2], 372 (20) $[M]^+$, 316 (100), 288 (75), 207 (23), 150 (30), 123 (35), 89 (23). HRMS (ESI): calcd. for $C_{20}H_{19}Cl_2N_2O[M+H]^+$373.0875; found 373.0873.

*3,5-Bis(4-fluorophenyl)-1-isopropylpyrazin-2(1H)-one (**3i**)*: pale yellow oil (455 mg, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.49 – 8.52 (m, 2 H), 7.80 – 7.83 (m, 2 H), 7.54 (s, 1 H), 7.11 – 7.15 (m, 4 H), 5.32 (hept, *J* = 6.8 Hz, 1 H), 1.47 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.9 (d, *J* = 250 Hz), 162.7 (d, *J* = 248 Hz), 154.1, 150.3, 132.4 (2 x C), 132.3, 131.4 (d, *J* = 8 Hz), 126.8 (d, *J* = 8 Hz), 118.9, 115.7 (d, *J* = 21 Hz), 114.9 (d, *J* = 21 Hz), 47.8, 21.6 ppm. FT-IR ($CHCl_3$): ν = 3026, 3012, 2965, 2927, 2870, 1723, 1643, 1591, 1452 cm^{-1}. GC-MS (70 eV): m/z (%) = 326 (85) $[M]^+$, 284 (51), 256 (100), 229 (11), 134 (23), 107 (32). HRMS (ESI): calcd. for $C_{19}H_{17}F_2N_2O$ $[M+H]^+$327.1310; found 327.1308.

*1-(tert-butyl)-3,5-Bis(4-fluorophenyl)pyrazin-2(1H)-one (**3j**)*: pale yellow oil (469 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.38 – 8.41 (m, 2 H), 7.77 – 7.80 (m, 2 H), 7.72 (s, 1 H), 7.10 –

7.15 (m, 4 H), 1.78 (s, 9 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.7 (d, *J* = 250 Hz), 162.5 (d, *J* = 250 Hz), 155.6, 152.2, 132.9, 132.5, 131.5 (d, *J* = 8 Hz), 126.7 (d, *J* = 8 Hz), 120.1, 115.7 (d, *J* = 21 Hz), 114.8 (d, *J* = 21 Hz), 62.9, 28.0 ppm.FT-IR ($CHCl_3$): ν = 3027, 3015, 2963, 2926, 2871, 1724, 1643, 1591, 1450 cm^{-1}.GC-MS (70 eV): m/z (%) = 340 (22) $[M]^+$, 284 (97), 256 (100), 229 (12), 134 (25), 107 (32), 57 (15). HRMS (ESI): calcd. for $C_{20}H_{19}F_2N_2O[M+H]^+$341.1466; found 341.1464.

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