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Streamlined Routes to Phenacyl Azides and 2,5-Diarylpyrazines Enabled by Deep Eutectic Solvents

Paola Vitale,*[a] Luciana Cicco,[a] Francesco Messa,[b] Filippo Maria Perna,[a] Antonio Salomone,[b] and Vito Capriati*[a]

In memory of Professor Cinzia Chiappe.

Abstract: A Deep Eutectic Solvent like choline chloride/glycerol (1:2 mol mol^{-1}) proved to be an effective, sustainable reaction medium to easily synthesize both phenacyl azides and symmetrical 2,5-diarylpyrazines of interest in pharmacology and in coordination chemistry. Notable features of our report include: (i) nucleophilic substitution reactions of α-halo carbonyl compounds to the corresponding phenacyl azides compatible with the eutectic mixture, (ii) the reduction of phenacyl azides to α-amino carbonyl compounds, which undergo spontaneous dimerisation/cyclisation/aromatisation in the same eutectic mixture to provide valuable pyrazines. Telescoped, one-pot, two-steps stoichiometric/catalytic processes have also been successfully developed to furnish 2,5-diarylpyrazines in up to 95% yield.

Introduction

Pyrazine derivatives are an important class of heterocyclic compounds that can be isolated from natural sources or prepared by chemical synthesis. They have drawn much interest as dyes and light-emitting materials,[1] and have found wide applications in metal coordination chemistry[2] and especially in the field of medicine because of their pharmacological activity as antineoplatics, diuretics, neuroprotectors, antiviral, anti-infective and anti-inflammatory agents.[3] As a result, a variety of methods for the preparation of variously functionalised pyrazines have been developed throughout the years.[4] Of particular interest are 2,5-diarylpyrazines as they are known to bind with high selectivity and/or high affinity to Corticotropin Releasing Factor 1 (CFR1) receptors, and thus proven to be effective in the treatment of several central nervous system and peripheral disorders such as anxiety, stress, depression, cardiovascular and eating disorders.[5] An efficient synthesis for constructing 2,5-disubstituted pyrazines from easily accessible (*Z*)-β-haloenol acetates, employing ammonium formate as the nitrogen source and DMF as the solvent, has been recently described by Chen, Liu and co-workers (Scheme 1a).[6]

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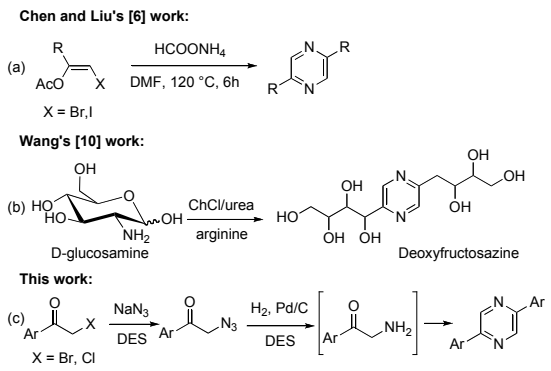
Deep Eutectic Solvents (DESs) are eutectic mixtures of safe and nature-inspired components that, upon mixing, show a large decrease in melting temperature compared to that of the initial components.[7] This is attributed to the hydrogen-bonding between the components, which decreases the lattice energy of the system. Typical DES components [e.g., choline chloride (ChCl), urea, glycerol (Gly), L-lactic acid (LA), natural carboxylic acids, polyalcohols) come from natural sources, and thus show a high biodegradability. An impressive number of eco-friendly protocols have been introduced for the synthesis of heterocycles, via condensation, cyclisation and multicomponent reactions, by exploiting the ability of DESs of playing multiple roles as reaction media, active catalysts and, in some cases, also as starting materials, thereby acting as non-innocent reaction media.[8]

As a part of our ongoing interest toward the synthesis of heterocyclic scaffolds by means of organo- and metal-catalysed, metal-mediated and condensation reactions using nonconventional reaction media with a minimal ecological footprint (DESs and water),[9] we became interested in developing an eco-friendly synthesis of pyrazine derivatives. Interestingly, D-glucosamine was recently found to undergo self-condensation in a ChCl/urea eutectic mixture to provide deoxyfructosazine in up to 30.1% yield in the presence of arginine (Scheme 1b).[10] Herein, we report a streamlined synthesis of symmetrical 2,5-diarylpyrazines in DESs. We started from commercially available α-halo ketones, which were first converted into phenacyl azides in DESs. The latter were then subjected to an in-situ catalytic reduction to α-amino ketones, which underwent spontaneous dimerisation/cyclisation in DESs, and final aromatisation to give 2,5-diarylpyrazines (Scheme 1c).

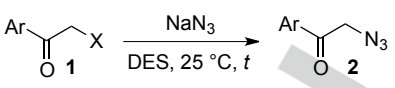


Scheme 1. (a) Formation of 2,5-disubstituted pyrazines from (*Z*)-β-haloenol acetates; (b) self-condensation of D-glucosamine to deoxyfructosazine in DES; (c) synthesis of 2,5-diarylpyrazines from α-halo ketones in DES.

Results and Discussion

In order to explore the viability of eutectic mixtures in the synthesis of pyrazines, we began our study by first investigating the synthesis of phenacyl azides in DESs by nucleophilic substitution of the corresponding α-substituted ketones having a good leaving group such as a halide. By using conventional solvents, these transformations are usually carried out in dipolar aprotic solvents (e.g., DMF, DMSO, acetone) or their mixtures with water.[11] Alternatively, ionic liquids have also been successfully employed,[12] and procedures set up with the support of ultrasounds[13] or phase-transfer catalysts[14] have allowed to work at room temperature (RT, 25 °C), thereby minimising the formation of by-products. As a bench reaction, we screened the transformation of phenacyl bromide **1a** (1.5 mmol) into phenacyl azide **2a** in three prototypical ChCl-based eutectic mixtures, namely ChCl/Gly (1:2 mol mol^{-1}), ChCl/urea (1:2 mol mol^{-1}), and ChCl/LA (1:2 mol mol^{-1}), using sodium azide as the azide source (1.65 mmol). When the reaction was performed in the eutectic mixture ChCl/Gly at RT, the reaction was complete within 4 h. After partitioning the crude between AcOEt and water, product **2a** could be isolated in 97% yield after column chromatography on silica gel (Table 1, entry 1). A similar yield (94%) was observed when phenacyl chloride **1b** was alternatively used, but only after 6 h (Table 1, entry 2). The employment of ChCl/urea as the eutectic mixture provided **2a** in 89% yield, whereas the use of LA as the hydrogen-bond donor in combination with ChCl was ineffective (Table 1, entries 3,4). Reaction time could be shortened to 1 h by warming the mixture up to 50 °C, however, with a slightly lower yield (**2a**: 89%) (Table 1, entry 5) owing to the appearance of by-products whose amounts increased by increasing the temperature. Of note, by changing the solvent to pure Gly the yield of **2a** dropped down to 23%, the remaining being starting material only (Table 1, entry 6). These results are consistent with a positive cooperative effect of the DES components with the reagents in promoting the described transformation. To examine the scope and limitation of this reaction, various functionalised phenacyl halides (**1c**–**i**) were tested (Table 1). Assorted aryl derivatives with "neutral" substituents (Me) (**1c**) or with electron-withdrawing (chloro) (**1d**) or electron-donating (methoxy, diethylamino) groups (**1e**,**f**), afforded the expected products **2b**–**e** in very good yields (80–91%) in 3–6 h (Table 1, entries 7–10). Phenacyl halides decorated with a fluoro or a free hydroxyl substituent (**1g**,**h**) as well as a bromomethyl 2-naphtyl ketone (**1i**) also participated smoothly in the nucleophilic substitution with NaN_3 to afford azides **2f**–**h** in 73–95% yield (Table 1, entries 11–13). This transformation also represents the first effective synthesis of valuable α-azido ketones in eutectic mixtures. Azides are widely used in synthetic organic chemistry as a masked amino functionality, potential sources of nitrene derivatives, and can also serve as dipoles in 1,3-dipolar cycloadditions and versatile "building blocks" to synthesize various heterocycles.[11b]

Table 1. Synthesis of azides **2** from α-halocarbonyl compounds **1** in DESs.[a]



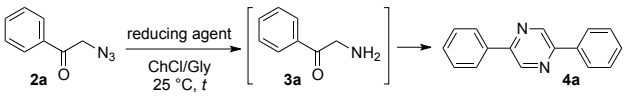
Entry	Substrate **1**	*t* [h]	X	DES	Azide **2** [%][b]
1	**1a** (Ar = Ph)	4	Br	ChCl/Gly	**2a** (97)
2	**1b** (Ar = Ph)	6	Cl	ChCl/Gly	**2a** (94)
3	**1a** (Ar = Ph)	4	Br	ChCl/urea	**2a** (89)
4	**1a** (Ar = Ph)	4	Br	ChCl/LA	NR[c]
5	**1a** (Ar = Ph)[d]	1	Br	ChCl/Gly	**2a** (89)
6	**1a** (Ar = Ph)	4	Br	[e]	**2a** (23)
7	**1c** (Ar = 4-MeC_6H_4)	6	Br	ChCl/Gly	**2b** (87)
8	**1d** (Ar = 4-ClC_6H_4)	4	Cl	ChCl/Gly	**2c** (91)
9	**1e** [Ar = 2,5-$(OMe)_2C_6H_3$]	4	Br	ChCl/Gly	**2d** (84)
10	**1f** (Ar = 4-$NEt_2C_6H_4$)	3	Br	ChCl/Gly	**2e** (80)
11	**1g** (Ar = 4-FC_6H_4)	3	Cl	ChCl/Gly	**2f** (93)
12	**1h** (Ar = 2-OHC_6H_4)	3	Br	ChCl/Gly	**2g** (95)
13	**1i** (Ar = 2-naphtyl)	3	Br	ChCl/Gly	**2h** (73)[f]

[a] Reaction conditions: 2.0 g DES per 1.5 mmol of **1** and 1.65 mmol of NaN_3; DES: ChCl/Gly (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}); ChCl/LA (1:2 mol mol^{-1}). [b] The yields reported are for products isolated and purified by column chromatography. [c] NR = no reaction; substrate **1a** was quantitatively recovered. [d] T = 50 °C. [e] Solvent: Gly. [f] The mixture was diluted with 10% v/v EtOH because of the low solubility of **1i** in the eutectic mixture.

Next, we examined as a benchmark reaction the chemoselective reduction of phenacyl azide **2a** to the corresponding primary amine **3a** in ChCl/Gly (Table 2). To the best of our knowledge, there is only one case of reduction reported in a low melting mixture: the catalytic hydrogenation of methyl α-cinnamate run in the melt citric acid-dimethyl urea using the Wilkinson's catalyst (15 mol%) (90 °C, 1 atm H_2).[15] A survey of conditions was undertaken to optimise this step in the above DES. A complex mixture always formed when azide **2a** was treated at RT with Zn/ammonium formate,[16] Zn/HCl,[17] Zn/NH_4Cl,[18] Ph_3P,[19] or D-glucose/KOH[20] as reducing agents (Table 2, entries 1–5). Pleasingly, when $SnCl_2{\cdot}2H_2O$ was alternatively used[21] the reduction of the azide moiety to the corresponding α-amino ketone this time took place, but the latter spontaneously underwent dimerisation/cyclisation in the same eutectic mixture leading to the isolation of 2,5-diphenylpyrazine **4a** as the sole product in 48% yield (Table 2, entry 6). In the 80s, the group of Anselme reported that the synthesis of substituted pyrazines could also be achieved by the catalytic reduction (10 mol% Pd/C, ca. 50 psi for 24 h) of α-azido ketones in a EtOH/AcOH mixture.[22] To our delight, the desired pyrazine **4a** could be straightforwardly isolated in 87% yield in ChCl/Gly by subjecting **2a** to a reduction using H_2 as the reducing agent (3 atm for 6 h) and Pd/C (10 mol%) as the

catalyst (Table 2, entry 7). Such a yield did not change by prolonging the time of reduction up to 24 h, but dropped down to 78% after 4 h reaction time. Notably, the effectiveness of this transformation was still maintained in the above DES (**4a**: 83%) even with a catalyst loading as low as 1 mol% (Table 2, entry 8). On the other hand, a lower pressure of H_2 (1 atm) almost completely suppressed the formation of **4a** (11% yield) (Table 2, entry 9). Switching ChCl/Gly for Gly, catalytic reduction of **2a** with Pd/C (1 mol%) led to **4a** in 71% yield after 6 h.

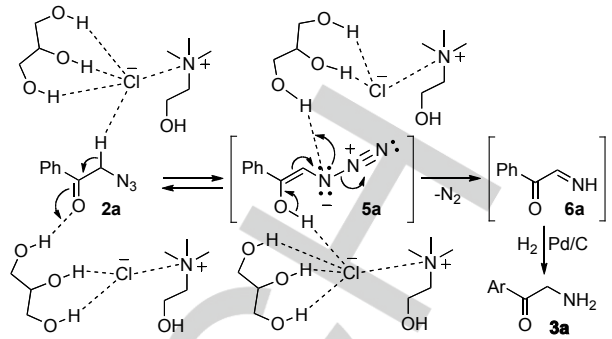
Table 2. Synthesis of pyrazine **4a** by reduction of azide **2a** through **3a**.[a]



Entry	Reducing agent	*t* [h]	**4a** yield [%][b]
1	Zn/HCO_2NH_4	15	–[c]
2	Zn/HCl	15	–[c]
3	Zn/NH_4Cl	1	–[c]
4	Ph_3P	15	–[c]
5	D-glucose/KOH	15	–[c]
6	$SnCl_2·H_2O$	15	**4a** (48)
7	H_2 (3 atm), Pd/C (10 mol%)	6	**4a** (87)[d]
8	H_2 (3 atm), Pd/C (1 mol%)	6	**4a** (83)[e]
9	H_2 (1 atm), Pd/C (1 mol%)	6	**4a** (11)

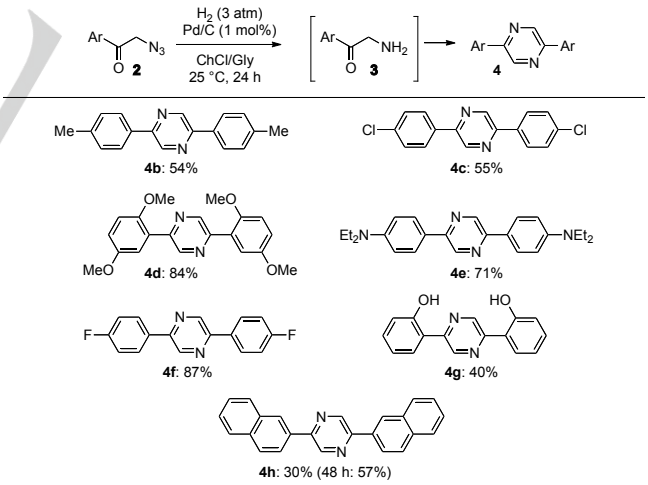
[a] Reaction conditions: 2.0 g DES per 1.5 mmol of **2a**. [b] Calculated via ^{1}H-NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: dibromomethane). [c] A complex mixture of unidentified products was detected in the crude along with the starting material. [d] The same yield was obtained after 24 h, whereas a reaction time of 4 h led to a recovery of **4a** in 78% yield only. [e] Catalytic reduction of **2a** with Pd/C (1 mol%) in Gly led to **4a** in 71% yield.

α-Aminoketone **3a**, *en route* to 2,5-diphenylpyrazine **4a**, is likely formed by catalytic reduction of in-situ generated α-imino ketone **6a** (Scheme 2). The formation of the latter can be ascribed to the loss of nitrogen from the azido group within the the key intermediate **5a**. In this context, DES components (ChCl and Gly) may play an active role in triggering acid-catalysed enolisation processes[23] ending up with the decomposition of **5a** to give **6a**, as depicted in Scheme 2. The role of DESs as catalytic active species has been suggested in several other transformations.[9a,24]



Scheme 2. Plausible mechanism for the formation of α-amino ketone **3a** from **2a**.

The scope of this reduction was then evaluated (Scheme 3). Under the conditions of Table 2 (entry 8), phenacyl azides **2b**–**g** yielded pyrazines **4b**–**g** in 40–87% yield after 24 h. Symmetrical 2,5-disubstituted pyrazines **4a**–**c**, and **4f** have also been synthesized in 85–91% yield by reacting (*Z*)-β-bromoenol acetates with ammonium formate in DMF at 120 °C for 6 h.[6] Of note, mononuclear and dinuclear Ru(II) complexes of pyrazine **4g**, which has been reported to be prepared via a three-step procedure from 4-hydroxycoumarin in overall 23% yield, have revealed interesting electronic properties.[25] 2-Naphtyl azido ketone **2h** also participated in the reduction process to afford pyrazine **4h** in up to 57% yield by prolonging the reaction time from 24 (30% yield) to 48 h (Scheme 3).

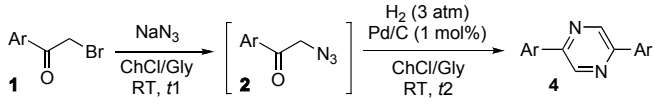


Scheme 3. Scope of the reduction reaction of phenacyl azides **2** and synthesis of pyrazines **4**. Yields refer to products isolated after column chromatography on silica gel or by crystallisation from AcOEt (see Experimental Section).

Finally, we targeted telescoped, one-pot processes in the same eutectic mixture for the preparation of functionalised pyrazine derivatives through multiple stoichiometric/catalytic

events. To this end, phenacyl bromide **1a** (1.5 mmol) was first treated with NaN_3 (1.65 mmol) in a ChCl/Gly mixture at RT for 4 h, and then the mixture was directly subjected to Pd/C catalytic hydrogenation (1 mol%; H_2, 3 atm) at RT for 15 h. After work-up procedure (see Experimental Section), pyrazine **4a** was isolated in an excellent 89% yield, as the sole product, after two steps in one pot (Table 3, entry 1). To showcase our system's synthetic utility, this protocol was similarly applied with regard to other representative phenacyl bromides such as **1c**, **1e** and **1i**. The corresponding desired pyrazines **4b**, **4d**, and **4h** were straightforwardly isolated in remarkable overall yields (64–95%) (Table 3, entries 2–4).

Table 3. One-pot, two-step synthesis of pyrazines **4** in DES.[a]



Entry	Substrate **1**	*t*1 [h]	*t*2 [h]	Pyrazine **4** [%][b]
1	**1a** (Ar = Ph)	4	15	**4a** (89)
2	**1c** (Ar = 4-MeC_6H_4)	6	24	**4b** (64)
3	**1e** [Ar = 2,5-$(OMe)_2C_6H_3$]	4	24	**4d** (95)
4	**1i** (Ar = 2-naphtyl)	4	48	**4h** (65)

[a] Reaction conditions: 2.0 g DES per 1.5 mmol of **1** and 1.65 mmol of NaN_3; Pd/C: 0.015 mmol. [b] The overall yields reported are for products isolated and purified by column chromatography on silica gel or by crystallisation from AcOEt (see Experimental Section).

Conclusions

In summary, the environmentally benign and biodegradable eutectic mixture ChCl/Gly (1:2) revealed to be an effective reaction medium for performing the synthesis of phenacyl azides from the corresponding commercially available phenacyl halides, and for promoting their direct transformation into valuable, symmetrical 2,5-disubstituted pyrazines after in-situ catalytic reduction with H_2 (3 atm) and using as little as 1 mol% Pd/C as catalyst. Telescoped, one-pot azidation/cyclisation processes, which are of great value to minimise chemical waste, are also feasible and allow the straightforward synthesis of functionalised pyrazine derivatives (a) without any halfway isolation/purification step, and (b) in overall chemical yields higher than those associated to the two single steps. Further applications of DESs as green and sustainable reaction media to synthesize other medicinally relevant heterocycles are underway and will be reported in due course.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz or 600 MHz spectrometers and chemical shifts are reported in parts per million (δ). Dibromomethane has been used as the internal standard for yield determination by ^{1}H NMR analysis on the crude reaction mixtures. FT-IR spectra were recorded on a Perkin-Elmer 681 spectrometer. GC analyses were performed on a HP 6890 model, Series II by using a HP1 column (methyl siloxane; 30 m x 0.32 mm x 0.25 μm film thickness). Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F_{254}; visualisation was accomplished by UV light (254 nm) or by spraying a solution of 5% (w/v) ammonium molybdate and 0.2% (w/v) cerium(III) sulphate in 100 mL 17.6% (w/v) aq. sulphuric acid and heating to 473 K until blue spots appeared. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM, using hexane/AcOEt mixtures as the eluent. High-resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. Deep Eutectic Solvents [choline chloride(ChCl)/lactic acid (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}) and ChCl/glycerol (1:2 mol mol^{-1})] were prepared by heating under stirring at 60–80 °C for 10–30 min the corresponding individual components until a clear solution was obtained. Compounds **2a**–**c**, **2f**–**h**, **4a**–**c, 4f**, and **4g** are known, and their spectroscopic data are in agreement with those reported in the literature (*vide infra*). Fully characterization data, including HRMS and copies of ^{1}H and ^{13}C NMR spectra (see Supporting Information) have been reported for the newly synthesized compounds (**2d**, **2e**, **4d**, **4e** and **4h**).

General Procedure for the Synthesis of α-Azido Ketones 2a–h. α-Halo carbonyl compound 1 (1.5 mmol) and NaN_3 (107 mg, 1.65 mmol) were sequentially added to the ChCl/Gly (1:2 mol mol^{-1}) (2.0 g) eutectic mixture. The reaction mixture was stirred at RT (25 °C) in air for 3–6 h until complete consumption of the starting material (monitored by thin layer chromatography). Then, water was added, and the mixture was extracted with AcOEt (3 x 10 mL). The collected organic layers were dried using anhydrous Na_2SO_4, filtered, and the volatile evaporated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (hexane/AcOEt 5:1–4:1) to provide the desired α-azido ketone **2** (73–97% yield; see Table 1).

2-Azido-1-phenylethanone (**2a**).[26] Yellow oil; yield 97%. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 7.92–7.91 (m, 2H), 7.65–7.62 (m, 1H), 7.52–7.50 (m, 2H), 4.57 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ= 193.2, 134.4, 134.1, 129.0, 127.9, 54.9. FT-IR (film, cm^{-1}): $\tilde{\nu}$= 3064, 2902, 2102, 1694, 1597, 1581, 1450, 1422, 1349, 1002, 909, 813, 755, 688; GC-MS (EI, 70 eV) *m/z* (%): 133 [(*M*-28)$^+$, 1], 105 (100), 77 (64), 51 (22), 50 (10). HRMS (ESI) *m/z* calcd for $C_8H_7N_3O$ [*M*+Na]$^+$: 184.0481; found: 184.0487.

2-Azido-1-*p*-tolylethanone (**2b**).[27] Yellow solid; yield 87%; m.p. 62-63 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 7.82 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.54 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ = 193.0, 145.3, 132.0, 129.8, 128.2, 54.9, 21.9. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3036, 2917, 2103, 1694, 1607, 1284, 1224, 912, 811. GC–MS (EI, 70 eV) *m/z* (%): 147 [(*M*-28)$^+$, 1], 119 (100), 91 (69), 65 (32). HRMS (ESI) *m/z* calcd for $C_9H_9N_3O$ [*M*+Na]$^+$: 198.0638; found: 198.0637.

2-Azido-1-(*p*-chlorophenyl)ethanone (**2c**).[14a] Yellow solid; yield 91%; m.p. 67-69 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ = 7.87 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 4.54 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 192.1, 140.7, 132.7, 129.37, 129.35, 54.8. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3371, 2920, 2104, 1693, 1593, 1092. GC-MS (EI, 70 eV) *m/z* (%): 167 [(*M*-28)$^+$, 2], 141 (33), 139 (100), 113 (14), 111 (41), 75 (22), 50 (9). HRMS (ESI) *m/z* calcd for $C_8H_6ClN_3O$ [*M*+Na]$^+$: 218.0092; found: 218.0083.

2-Azido-1-(2,5-dimethoxyphenyl)ethanone (**2d**). Pale yellow solid; yield 84%; m.p. 67-68°C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 7.48–7.47 (m, 1H), 7.13–7.11 (m, 1H), 6.96–6.94 (m, 1H), 4.54 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 194.0, 153.9, 153.8, 124.7, 122.2, 113.7, 113.1, 59.5, 56.0, 55.9. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3391, 2921, 2101, 1675, 1501, 1267, 1013. GC-MS (EI, 70 eV) *m/z* (%): 221 (M^+, 11), 165 (100), 107 (16), 92 (7), 77 (11). HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_3O_3$ [*M*+Na]$^+$: 244.0693; found: 244.0708.

2-Azido-1-[4-(diethylamino)phenyl]ethanone (**2e**). Yellow oil, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ= 7.77 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 4.44 (s, 2H), 3.42 (q, *J* = 7.0 Hz, 4H), 1.20 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 190.6, 151.8, 130.5, 121.4, 110.4, 54.1, 44.6, 12.4. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 332, 2974, 2102, 1596, 1409, 1187. GC-MS (EI, 70 eV) *m/z* (%): 232 (M^+, 5), 176 (100), 133 (12), 77 (7). HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N_4O$ [*M*+Na]$^+$: 255.1222; found: 255.1217.

2-Azido-1-(4-fluorophenyl)ethanone (**2f**).[14a] Orange solid; yield 93%; m.p. 54-55 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 7.96–7.93 (m, 2H), 7.19–7.16 (m, 2H), 4.54 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ= 191.7, 166.1 (d, $^1J_{C\text{-}F}$ = 257 Hz), 130.9 (d, $^4J_{C\text{-}F}$ = 5 Hz), 130.8 (d, $^3J_{C\text{-}F}$ = 9 Hz), 116.3 (d, $^2J_{C\text{-}F}$ = 22 Hz), 54.9. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3031, 2102, 1689, 1595, 1226, 1216, 832. GC-MS (EI, 70 eV) *m/z* (%): 151 [(*M*-28)$^+$, 2], 123 (100), 95 (52), 75 (19), 69 (5), 50 (4). HRMS (ESI) *m/z* calcd for $C_8H_6N_3FO$ [*M*+Na]$^+$ 202.0387; found 202.0387.

2-Azido-1-(2-hydroxyphenyl)ethanone (**2g**).[28] Pale yellow solid; yield 95%; m.p. 75-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 11.61 (s, 1H), 7.55–7.49 (m, 2H), 7.03–7.01 (m, 1H), 6.94–6.90 (m, 1H), 4.58 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ= 198.5, 162.2, 137.2, 128.4, 119.3, 118.7, 117.1, 54.0. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3429, 2115, 1651. GC-MS (EI, 70 eV) *m/z* (%): 177 (M^+, 3), 149 (9), 121 (100), 94 (18), 65 (23). HRMS (ESI) *m/z* calcd for $C_8H_7N_3O_2$ [*M*+H]$^+$: 178.0611; found: 178.0618.

2-Azido-1-(naphthalen-2-yl)ethanone (**2h**).[29] Pale yellow solid; yield 73%; m.p. 62-64 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 8.43–8.41 (m, 1H), 7.98–7.89 (m, 4H), 7.66–7.56 (m, 2H), 4.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ= 193.0, 135.9, 132.2, 131.5, 129.7, 129.5, 129.0, 128.9, 127.8, 127.1, 123.1, 54.9. FT-IR (film, cm^{-1}) $\tilde{\nu}$= 3062, 2980, 2905, 2099, 1676, 1624, 1466, 1355, 1274, 1215, 1003, 898, 850, 816, 772. GC-MS (EI, 70 eV) *m/z* (%): 211 (M^+, 5), 183 (11), 155 (92), 127 (100). HRMS (ESI) *m/z* calcd for $C_{12}H_9N_3NO$ [*M*+Na]$^+$ 234.0638; found 234.0631.

General Procedure for the Synthesis of 2,5-Diarylpyrazines 4a–h. In a 100 mL beker, Pd/C (1 mol%, 15 mg) was added to a suspension of α-azido ketone **2** (1.5 mmol) in the ChCl/Gly (1:2 mol mol^{-1}) (2.0 g) eutectic mixture in a Parr autoclave. The autoclave was closed, and 3 atm of H_2 was charged. The mixture was kept under stirring at RT for 6–24 h until complete consumption of the starting material (monitored by thin layer chromatography). After carefully releasing the hydrogen, the reaction mixture was diluted with AcOEt (MeOH in the case of pyrazines **4d** and **4h**) (10 mL), and filtered through a Celite pack. Then, water was added, and the mixture was extracted with AcOEt (3 x 10 mL). The collected organic layers were dried using anhydrous Na_2SO_4, filtered, and the volatile evaporated under reduced pressure to afford the crude product, which was crystallised from EtOAc (compounds **4d**, **4h**) or purified by column chromatography on silica gel (hexane/EtOAc 15:1) (compounds **4a**–**c**, **4e**–**g**) to afford pyrazine **4** (40–87% yield; see Table 2 and Scheme 3).

General Procedure for the One-pot, Two-step Synthesis of 2,5-Diarylpyrazines 4a, 4b, 4d, and 4h. α-Halo carbonyl compound **1** (**1a, 1c, 1e** or **1i**) (1.5 mmol) and NaN_3 (107 mg, 1.65 mmol) were sequentially added to the ChCl/Gly (1:2 mol mol^{-1}) (2.0 g) eutectic mixture. The reaction mixture was stirred at RT in air for 3–6 h until complete consumption of the starting material. Then, the mixture was transferred to a Parr autoclave, and Pd/C (1 mol%, 16 mg) was added. The autoclave was closed, and 3 atm of H_2 was charged. The mixture was kept under stirring at RT for 6–24h until complete consumption of the starting material. After carefully releasing the hydrogen, the reaction mixture was diluted with AcOEt (MeOH in the case of pyrazines **4d** and **4h**) (10 mL), and filtered through a Celite pack. Then, water was added, and the mixture was extracted with AcOEt (3 x 10 mL). The collected organic layers were dried using anhydrous Na_2SO_4, filtered, and the volatile evaporated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (hexane/EtOAc10:1) to provide pyrazine **4** (**4a, 4b, 4d** or **4h**) (64–95% yield; see Table 3).

2,5-Diphenylpyrazine (**4a**).[6] Pale yellow oil; yield 87%. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 9.09 (s, 2H); 8.08–8.07 (m, 4H), 7.55–7.47 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 150.8, 141.3, 136.4, 129.8, 129.1, 126.9. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 3060, 2929, 1694, 1620, 1450, 1288, 757, 698. GC-MS (EI, 70 eV) *m/z* (%): 232 (M^+, 100), 204 (5), 129 (6), 102 (86), 76 (16), 51 (5). HRMS (ESI) *m/z* calcd for $C_{16}H_{12}N_2$ [*M*+Na]$^+$: 255.0893; found: 255.0895.

2,5-Di-*p*-tolylpyrazine (**4b**).[6] Brown solid; yield 54%; m.p. 182-183 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 9.04 (s, 2H), 7.97 (d, *J* = 8.1 Hz, 4H), 7.34 (d, *J* = 8.1 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 151.7, 140.2, 139.4, 134.0, 129.9, 127.0, 21.4. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 3029, 2920, 1679, 1606, 1477, 1269, 1180, 819. GC-MS (EI, 70 eV) *m/z* (%): 260 (M^+, 100), 259 (15), 245 (4), 143 (2), 130 (4), 116 (37), 115 (46), 90 (3), 89 (6), 65 (2), 63 (2). HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_2$ [*M*+Na]$^+$: 283.1206; found: 283.1210.

2,5-Di(4-chlorophenyl)pyrazine (**4c**).[6] Orange solid; yield 55%; m.p. 173-174 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 9.05 (s, 2H), 8.04–8.02 (m, 4H), 7.52–7.51 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 149.7, 140.9, 136.2, 134.5, 129.3, 128.0. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 2922, 2852, 1466, 1409, 1159, 1098, 1017, 836, 825. GC-MS (EI, 70 eV) *m/z* (%): 304 [(*M*+4)$^+$, 11], 302 [(*M*+2)$^+$, 65], 300 (M^+, 100), 265 (13), 138 (27), 137 (17), 136 (78), 101 (18), 75 (12), 51 (4). HRMS (ESI) *m/z* calcd for $C_{16}H_{10}N_2Cl_2$ [*M*+Na]$^+$: 323.0113; found 323.0114.

2,5-Di(2,5-dimethoxyphenyl)pyrazine (**4d**). Pale yellow solid; yield 84%; m.p. 208-210 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 9.28 (s, 2H), 7.53–7.52 (m, 2H), 6.99–6.97 (m, 4H), 3.87 (s, 6H), 3.86 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 154.0, 151.5, 148.6, 145.3, 126.3, 116.7, 115.3, 112.9, 56.2, 55.8. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 2998, 2937, 2832, 1584, 1505, 1476, 1462, 1313, 1262, 1210, 1177, 1048, 1018, 881, 806, 733. GC-MS (EI, 70 eV) *m/z* (%): 352 (M^+, 100), 351 (38), 338 (11), 337 (57), 335 (23), 322 (12), 321 (32), 307 (34), 305 (12), 161 (21), 147 (14). HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_2O_4$ [*M*+Na]$^+$ 375.1315; found 375.1318.

2,5-Di[4-(*N*,*N*-diethylamino)phenyl]pyrazine (**4e**). Yellow waxy solid; yield 71%. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 8.90 (s, 2H), 7.92 (d, *J* = 8.5 Hz, 4H), 6.78 (d, *J* = 8.5 Hz, 4H), 3.44 (q, *J* = 6.4 Hz, 8H) 1.23 (t, *J* = 6.4 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 149.1, 148.6, 139.7, 127.6, 123.4, 111.7, 44.4, 12.6. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 2921, 1607, 1527, 1468, 1198, 817. GC-MS (EI, 70 eV) *m/z* (%): 374 (M^+, 100), 359 (79), 315 (80), 253 (15), 172 (35), 158 (13). HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_4$ [*M*+Na]$^+$: 397.2363; found 397.2366.

2,5-Di(4-fluorophenyl)pyrazine (**4f**).[6] Brown orange solid; yield 87%; m.p. 232-235 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 9.03 (s, 2H), 8.09–8.06 (m, 4H), 7.25–7.22 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$,

25 °C) δ= 164.0 (d, $^{1}J_{C\text{-}F}$= 250 Hz), 149.7, 140.8, 132.4, 128.6 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 116.1 (d, $^{2}J_{C\text{-}F}$ = 22 Hz). FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 2919, 1597, 1464, 1230, 1156, 834. GC-MS (EI, 70 eV) *m/z* (%): 268 (100, M^{+}), 267 (10), 245 (4), 240 (4), 147 (5), 121 (18), 120 (100), 100 (4), 94 (11), 75 (5), 74 (5), 70 (4), 63 (2). HRMS (ESI) *m/z* calcd for $C_{16}H_{10}F_2N_2$ [*M*+Na]$^{+}$ 291.0710; found 291.0714.

2,5-Di(2-hydroxyphenyl)pyrazine (**4g**).[25] Brown solid; yield 40%; m.p. 265-267 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ= 12.6 (s, 2H), 9.14 (s, 2H), 7.91–7.88 (m, 2H), 7.45–7.39 (m, 2H), 7.11–7.09 (m, 2H), 7.03–7.00 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ= 159.5, 150.1, 137.0, 132.6, 125.7, 119.7, 118.9, 116.7. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 3308, 2920, 1613, 1454, 1290, 1203, 1040, 751. GC-MS (EI, 70 eV) *m/z* (%): 264 (100, M^{+}), 263 (24), 236 (16), 144 (5), 133 (7), 132 (7), 118 (19), 90 (31), 89 (21), 63 (11). HRMS (ESI) *m/z* calcd for $[C_{16}H_{11}N_2O_2]^{-}$: 263.0821; found: 263.0867.

2,5-Di(naphthalen-2-yl)pyrazine (**4h**). Purple solid; yield 30% (57% after 48 h reaction time); mp 101-104 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 9.28 (s, 2H), 8.60 (s, 2H), 8.24–8.21 (m, 2H), 8.03–8.01 (m, 4H), 7.93–7.90 (m, 2H), 7.58–7.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ= 150.5, 141.5, 133.9, 133.5, 133.4, 128.9, 128.8, 127.7, 127.0, 126.6, 126.5, 123.9. FT-IR (KBr, cm^{-1}) $\tilde{\nu}$= 3053, 2925, 1626, 1596, 1278, 825, 740. GC-MS (EI, 70 eV) *m/z* (%): 332 (M^{+}, 100), 283 (12), 192 (9), 179 (11), 164 (12), 152 (76). HRMS (ESI) *m/z* calcd for $C_{24}H_{16}N_2$ [*M*+H]$^{+}$: 333.1386; found 333.1392.

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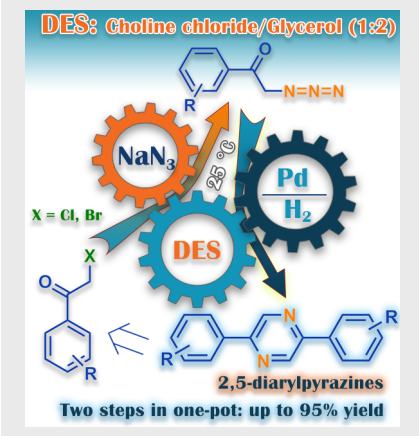
Heterocyclic Chemistry

FULL PAPER

A valuable approach for the preparation of phenacyl azides and 2,5-diarylpyrazines, under mild reaction conditions and in Deep Eutectic Solvents (DESs) as environmentally responsible reaction media, is illustrated. Telescoped, one-pot, two-steps processes have also been successfully accomplished.



Nitrogen heterocycles

Paola Vitale, Luciana Cicco, Francesco Messa, Filippo Maria Perna, Antonio Salomone, Vito Capriati**

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Streamlined Routes to Phenacyl Azides and 2,5-Diarylpyrazines in Deep Eutectic Solvents