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Denitrative imino-diaza-Nazarov cyclization: synthesis of pyrazoles†

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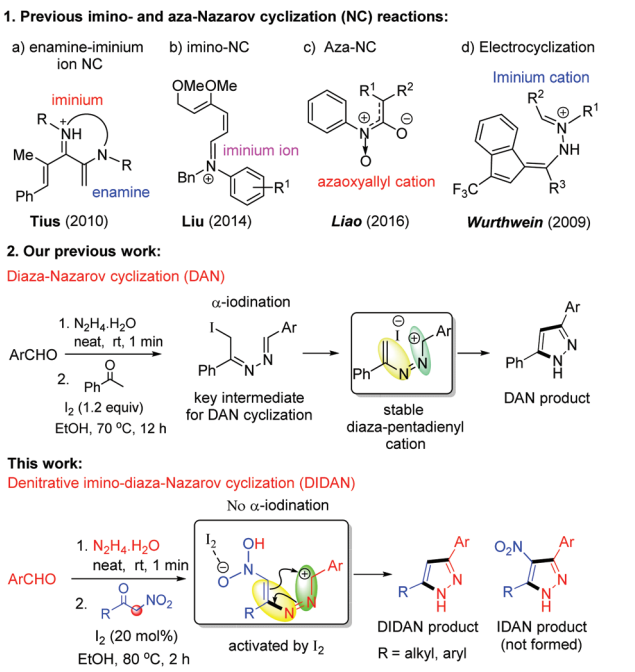
An iodine-catalyzed denitrative imino-diaza-Nazarov cyclization (DIDAN) methodology has been developed for the synthesis of pyrazoles with high to excellent yields by using α-nitroacetophenone derivatives and *in situ* generated hydrazones. The key transformation of this oxidative 4π-electrocyclization proceeds through an enamine–iminium ion intermediate. This rapid one-pot DIDAN protocol results in the selective generation of C–C and C–N bonds and cleavage of a C–N bond.

Five-membered nitrogen containing heterocyclic rings are excellent auxiliary structures that broadly exist in natural products, biologically active compounds, and functional materials.[1] Of particular note is the pyrazole unit that forms the core scaffold of bioactive molecules displaying antibacterial,[2] antiinflammatory,[3] antimicrobial[4] and analgesic activities. They also form the core structural architectures of valuable therapeutic agents[5] that have been successfully commercialized, such as the bestseller drugs Viagra, Celebrex, and Acomplia.[6] Apart from these applications, pyrazoles can also be used as ligands in various transition metal-catalyzed cross-coupling reactions.[7] As a result, numerous synthetic routes have been investigated for the preparation of pyrazoles *via* the cyclization process.[8] Routinely, these pyrazoles can be synthesized by the 1,3-dipolar cycloaddition of hydrazines with alkenes/alkynes[9] and by the condensation of 1,3-diketones/α,β-unsaturated carbonyls[10] and β-nitrostyrenes[11] with hydrazine derivatives. With the developing enthusiasm for the construction of pyrazoles, several transition metal-mediated[12] and metal-free[13] approaches have been explored over the past few decades.

Despite the sizeable work presented in the literature,[8–14] new and sustainable synthetic techniques for the synthesis of pyrazoles with high selectivity under mild and economic conditions are still in high demand. Among them the Nazarov-type cyclization reaction is one of the most versatile and efficient methods for C–C and C–N bond formation in the construction of 5-membered heterocyclic compounds.[15,16] In the beginning of the twentieth century, the concept of imino/aza-Nazarov cyclization has been introduced. The Nazarov reaction that proceeds through an imino/enamine–imino intermediate, instead of the classical ketone functionality, is called the imino-Nazarov reaction (Scheme 1).

The Frontier,[5a,16b,d] Tius,[17] Klumpp,[18] Hsung,[19] West,[20] Liao,[21a] Liu[21b] and Würthwein[22] research groups explored the advancement of the Nazrov cyclization reactions. We successfully established a new approach for the synthesis of polysub-



Scheme 1 Nazarov-type cyclizations.

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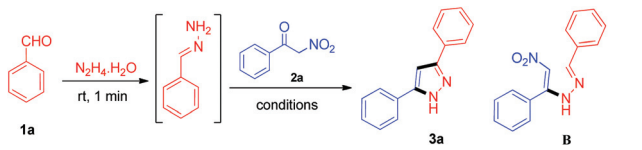
stituted pyrazoles *via* the diaza-Nazarov (DAN) cyclization involving a 2,3-diazapentadienyl cation using a stoichiometric amount of iodine.[23] It occurred to us that the *in situ* generated aldehyde hydrazones would undergo molecular Lewis acid-catalyzed imino-diaza-Nazarov (IDAN) cyclization and/or DIDAN cyclization with α-nitroacetophenones to provide the corresponding pyrazoles (Scheme 1). Thus, in continuation of our endeavours to develop green conventions,[24] we carried out the reaction of *in situ* generated aldehyde hydrazones with α-nitroacetophenones in the presence of a catalytic amount of iodine leading to diversely substituted pyrazoles and herein, we present our results.

To probe the conceived objective, in a pilot experiment, we inspected the reaction between benzaldehyde (**1a**), hydrazine hydrate and α-nitroacetophenone (**2a**) under solvent-free conditions. The reaction afforded the pyrazole product **3a** only in a trace amount (entry 1, Table 1). The *in situ* generated hydrazone underwent the reaction with α-nitroacetophenone (**2a**) in the presence of equimolar molecular iodine in EtOH at 80 °C. The reaction was accomplished in 6 h to afford a complex mixture of products from which the major denitrative pyrazole derivative **3a** was isolated in 67% yield along with uncyclized compound **B** in 20% yield (entry 2). When 50 mol% of molecular iodine was used in the reaction, product **3a** was obtained in an improved yield of 78% (entry 3). A perfect isolation of **3a** in 94% yield was achieved in 2 h when the reaction was carried out in the presence of 20 mol% iodine (entry 4). No improvement in the yield of **3a** was observed on lowering the amount of iodine (entry 5). Screening of the reaction temperature was also carried out, and 80 °C was found to be the optimal temperature to obtain the products in better yields (entries 4, 6 and 7). To investigate the effect of the solvent on the reaction, we performed the reaction in solvents such as MeOH, CH_3CN, THF, and DCE. These reactions afforded pyrazole **3a** in 76, 77, 57, and 64% yields, respectively, along with uncyclized product **B** in about 20% yield (entries 8–11). EtOH was considered to be the best solvent for this transformation (entry 4). Furthermore, catalysts such as PTSA, $BF_3{\cdot}OEt_2$ and TFA were screened. No improvement in the yield of product **3a** was observed with these promoters (entries 12–14). On the basis of the above findings, we recognised that iodine (20 mol%) in EtOH with model substrates at 80 °C was optimum in terms of the reaction efficiency and yield (entry 4). The uncyclized **B**, under optimization conditions, could be transformed into pyrazole **3a** in 61% yield.

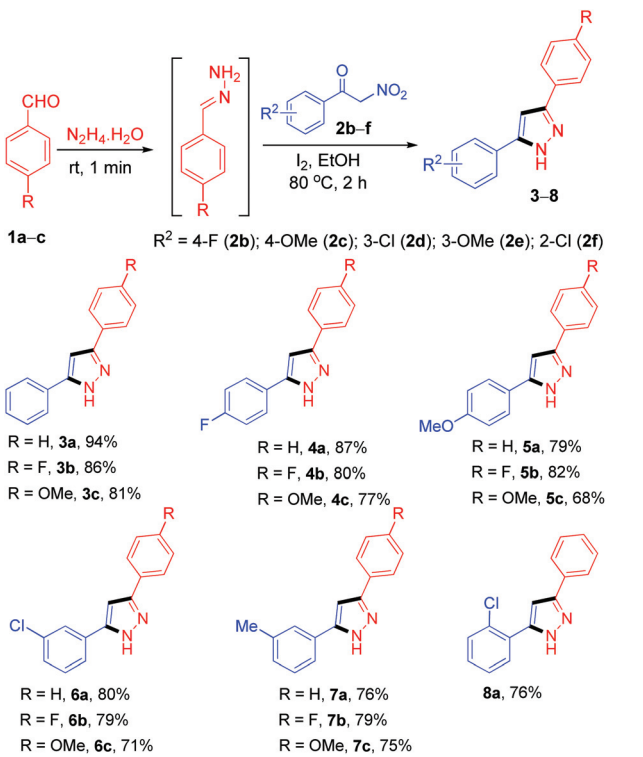
With the optimized reaction conditions in hand, we scrutinized the generality of this one-pot, iodine-catalysed denitrative-imino-diaza-Nazarov-type (DIDAN) cyclization. In this direction, we have chosen different benzaldehydes **1a–c** and performed the reaction with α-nitroacetophenones **2a–f** under the above mentioned conditions. In these cases, substrates **1** and **2** bearing electron-donating as well as electron-withdrawing substituents provided the corresponding pyrazole derivatives **3–8** in high to excellent yields of 68–94% (Scheme 2). The structures of the cyclized products were assigned on the basis of their ^1H (400 MHz) and ^{13}C (100 MHz) NMR data and DEPT spectroscopic and ESI-MS spectrometric analysis. The structure of pyrazole **7c** was further confirmed by its single-crystal

Table 1 Optimization of reaction conditions[a]



Entry	Reagent (mol%)	Solvent	Temp. (°C)	Time (h)	% yield[b] **3a**/**B**
1	I_2 (0)	Neat	80	6	Traces
2	I_2 (100)	EtOH	80	6	67/20
3	I_2 (50)	EtOH	80	6	78/12
4	I_2 (20)	EtOH	80	2	94/traces
5	I_2 (10)	EtOH	80	4	91/traces
6	I_2 (20)	EtOH	90	2	90/traces
7	I_2 (20)	EtOH	70	2	86/traces
8	I_2 (20)	MeOH	80	24	76/19
9	I_2 (20)	ACN	80	24	77/20
10	I_2 (20)	THF	80	24	57/16
11	I_2 (20)	DCE	80	24	64/23
12	PTSA (20)	EtOH	80	24	86/traces
13	$BF_3{\cdot}OEt_2$ (20)	EtOH	80	24	71/15
14	TFA (20)	EtOH	80	24	78/traces

[a] Reaction conditions: **1a** (0.6 mmol), hydrazine hydrate 80% (1 mmol), **2a** (0.4 mmol), reagent. [b] Isolated yield.



Scheme 2 Substrate scope for the DIDAN cyclization reaction of α-nitroacetophenones **2**.

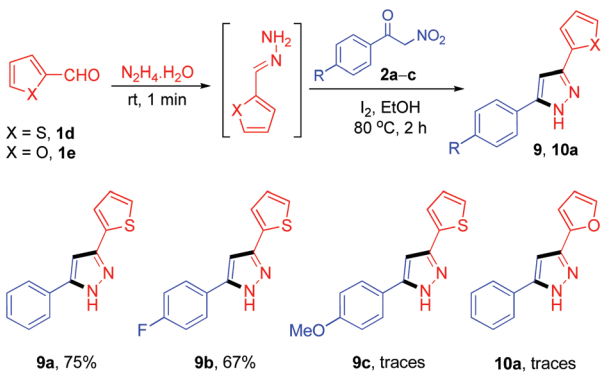
X-ray diffraction analysis (see the ESI, Fig. S1†). The NMR spectra of products **3b** & **4a** are identical. Similarly, each product of the other two sets **3c** & **5a** and **4c** & **5b** has identical spectral data. This indicates that, most likely, the proton in the pyrazole ring is delocalized between the two nitrogen atoms of the heterocycle. Although the position of the proton in the pyrazole ring is shown in the structures on one nitrogen atom, in principle, it can be on either of the two nitrogen atoms due to prototropic tautomerism.[25]

The reaction presumably proceeds through regioselective denitrative imino-diaza-Nazarov (DIDAN) cyclization. The oxidative cyclization reaction occurs between easily accessible *in situ* generated aldehyde hydrazones with α-nitroacetophenone derivatives through the enamine–iminium ion intermediate to furnish various substituted pyrazoles in excellent yields (*vide supra*). To the best of our knowledge, α-nitroacetophenones were not accounted for the construction of pyrazoles.

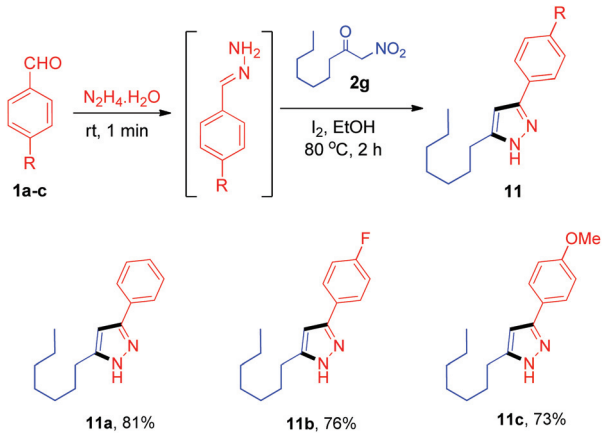
Further to investigate the extent of this metal-free DIDAN protocol, we tested heteroaromatic aldehydes such as 2-formylthiophene (**1d**) and furfural (**1e**). Notably, the reaction of **2a**,**b** with **1d** afforded products **9a** and **9b** in 2 h in 75 and 67% yields, respectively. In the case of **2c**, the reaction afforded the pyrazole product **9c** only in trace amounts. Similarly, when we performed the reaction between **1e** and **2a**, the pyrazole derivative **10a** was obtained in trace amounts (Scheme 3).

The functionalization of the aliphatic compounds is a more challenging task than functionalizing aromatic compounds due to the less reactivity of the former compounds. Our previous DAN approach failed to provide the cyclized product in the case of aliphatic ketones.[23] Remarkably, this current one-pot, three-component DIDAN strategy was successful with easily accessible aliphatic 1-nitrononan-2-one **2g** with aldehydes **1a–c**. To our delight, the cyclized products **11a–c** were obtained in 2 h in high yields of 73–81% (Scheme 4).

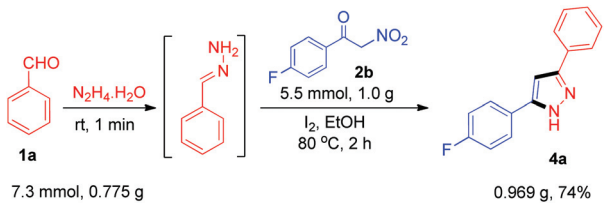
To scrutinize the scalability of the established protocols, the synthesis of **2b** on a gram-scale was carried out under the optimal conditions, and the product **4a** was isolated in 74% yield (Scheme 5).



Scheme 3 Scope of the DIDAN cyclization reaction of heteroaromatic aldehydes **1**.



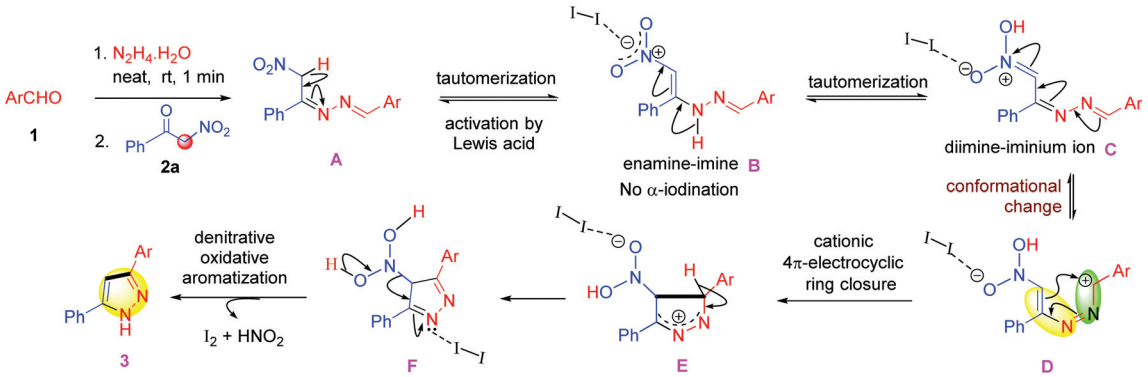
Scheme 4 Scope of the DIDAN cyclization reaction for aliphatic α-nitroketone **2g**.



Scheme 5 Gram-scale preparation.

The DDIAN cyclization reaction is successful in the case of Lewis acid catalysts such as PTSA, $BF_3{\cdot}OEt_2$ and TFA. Only a catalytic amount of molecular iodine was used to activate the reaction. The reaction would require a stoichiometric amount of I_2 to proceed through an α-iodinated intermediate. This indicates that there is no C–I bond formation in the reaction and I_2 simply acted as a Lewis acid promoter for the synthesis of pyrazoles *via* activating the diamine–iminium ion intermediate **C** (Scheme 6). ^{1}H NMR evidence for intermediate **B**/**C** supports this assumption (see the ESI†). These observations suggest that the cyclization takes place without α-iodination, unlike in the diaza-Nazarov cyclization of acetophenones, where iodine was used in a stoichiometric amount.[23]

Based on the above findings and previous literature studies,[14,22,23,26] a plausible mechanism for the DIDAN cyclization is proposed in Scheme 6. Initially the hydrazone, generated from aldehyde **1** and hydrazine hydrate, undergoes condensation with α-nitroacetophenone **2a** to produce intermediate **A** which tautomerizes to enamine–imine **B**. Next the molecular iodine activates the nitro group of **B** to deliver diimine–iminium ion intermediate **C**. The conformational variation of s-*trans* diimine **C** to s-*cis* diimine subsequently leads to 2,3-diaza-pentadienyl cation **D**, which is stabilized by the delocalization of the positive charge. The cation **D** then undergoes 4π-electrocyclization ring closure to produce diaza-allyl cation



Scheme 6 Possible reaction mechanism.

E, which upon denitrative aromatization provides exclusively five-membered heterocycle **3**.

Conclusions

In summary, we have delineated an unprecedented iodine-catalyzed denitrative-imino-diaza-Nazarov cyclization for the synthesis of pyrazoles using *in situ* generated hydrazones and α-nitroacetophenones. This one-pot, three-component protocol provided pyrazoles in good to excellent yields under eco-friendly conditions. The transformation proceeds through the enamine–imino diaza-Nazarov 4π-electrocyclization. The simplicity of the experimental procedure and the ready accessibility of the precursors thus make this an experimentally attractive technique for the construction of nitrogenous heterocycles.

General information

Unless otherwise noted, chemicals were purchased from commercial suppliers at the highest purity grade available and were used without further purification. Thin layer chromatography was performed on 0.25 mm silica gel plates (60F-254) using UV light as the visualizing agent. Silica gel (100–200 mesh) was used for column chromatography. Melting points were determined on capillary point apparatus equipped with a digital thermometer and were uncorrected. Nuclear magnetic resonance spectra were recorded on 400 and 500 MHz spectrometers, and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak) and DMSO-d_6 (δ 39.5 ppm, the middle peak). Coupling constants were expressed in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, brs = broad singlet. In some cases, DMSO-d_6 (about 5%) was added as a co-D-solvent to $CDCl_3$ to solubilise the compound.

General procedure for the synthesis of α-nitroketones 2[27]

To a DMSO (25 mL) solution of KO^{t}Bu (3.1 g, 27.5 mmol) was added nitromethane (1.48 mL, 27.5 mmol) at RT and stirred for 1 h and then phenyl benzoate (2.0 g, 10.1 mmol) was added. The reaction contents were further stirred at RT for 2 h. The reaction mixture was poured in ice water and 2 mol L^{-1} aq. HCl solution was added to neutralise the mixture. The resulting solid substance was filtered and dried to obtain α-nitroketone product **2** as a white solid in quantitative yield. This was used for the next step without purification.

General procedure for the synthesis of substituted pyrazoles 3–10

To a benzaldehyde derivative **1** (0.4 mmol) was added hydrazine hydrate (80% in water, 0.033 g, 1.0 mmol) under solvent-free conditions. After the addition of hydrazine hydrate, a yellow solid was formed within a minute which indicated the formation of the hydrazone derivative. To the thus formed hydrazone derivative was added the above synthesized α-nitroketone **2** (0.3 mmol) in EtOH (4 mL) followed by iodine (0.016 g, 0.06 mmol, 20 mol%). Then the reaction mixture was refluxed at 80 °C on a pre-heated oil bath for 2 h. After completion of the reaction, as judged by TLC, the reaction mixture was quenched with a saturated sodium thiosulfate solution and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate in hexanes as the eluent to afford a pure pyrazole derivative.

Characterization data

3,5-Diphenyl-1*H*-pyrazole (3a)

Yield: 0.062 g (94%) as a brown solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 5.6 Hz, 4H), 7.33–7.29 (m, 6H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 131.2, 128.8, 128.1, 125.6, 100.0; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{12}N_2$, 221.1073; found, 221.1041.

3-(4-Fluorophenyl)-5-phenyl-1*H*-pyrazole (3b)

Yield: 0.061 g (86%) as a brown solid; mp: 189–190 °C; ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 7.76–7.72 (m, 4H), 7.36–7.33 (m, 2H), 7.27–7.23 (m, 1H), 7.05–7.01 (m, 2H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 161.6 (d, $^1J_{C,F}$ = 245 Hz), 146.9 (d, $^2J_{C,F}$ = 39 Hz), 130.7, 128.1, 127.2, 126.6, 126.5, 124.8, 114.9, 114.7, 98.6; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{12}FN_2$, 239.0979; found, 239.0986.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrazole (3c)

Yield: 0.061 g (81%) as a brown solid; mp: 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.37–7.30 (m, 3H), 6.87 (d, J = 8.0 Hz, 2H), 6.72 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 149.0, 148.2, 131.5, 128.8, 128.0, 126.9, 126.8, 125.7, 114.2, 99.4, 55.3; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{15}N_2O$, 251.1179; found, 251.1178.

5-(4-Fluorophenyl)-3-phenyl-1*H*-pyrazole (4a)

Yield: 0.062 g (87%) as a brown solid; mp: 188–190 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.74–7.71 (m, 4H), 7.34 (t, J = 9.0 Hz, 2H), 7.26–7.23 (m, 1H), 7.05–7.01 (m, 2H), 6.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6 + CD_3OD): δ 161.7 (d, $^1J_{C,F}$ = 245 Hz), 147.1, 130.6, 128.1, 127.3, 126.6, 126.6, 124.8, 115.0, 114.8, 99.7.

3,5-Bis(4-fluorophenyl)-1*H*-pyrazole (4b)

Yield: 0.062 g (80%) as a brown solid; mp: 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.67 (t, J = 6.0 Hz, 4H), 7.10 (t, J = 8.6 Hz, 4H), 6.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 162.2 (d, $^1J_{C,F}$ = 244 Hz), 127.7, 127.1, 127.0, 115.5, 115.3, 99.0; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{11}F_2N_2$, 257.0885; found, 257.0862.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (4c)

Yield: 0.062 g (77%) as a brown solid; mp: 205–206 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (q, J = 5.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.56 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (d, $^1J_{C,F}$ = 247 Hz), 159.5, 148.7, 147.5, 128.0, 127.2, 127.1, 126.7, 123.2, 115.6, 115.4, 114.1, 98.9, 55.1; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{14}FN_2O$, 269.1085; found, 269.1088.

5-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazole (5a)

Yield: 0.060 g (79%) as a brown solid; mp: 153–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.69 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 9.2 Hz, 2H), 7.32–7.23 (m, 3H), 6.81 (t, J = 9.2 Hz, 2H), 6.69 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.4, 148.9, 147.9, 131.6, 128.6, 127.8, 126.8, 125.5, 123.8, 114.0, 99.1, 55.1.

3-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (5b)

Yield: 0.066 g (82%) as a brown solid; mp: 128–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.66 (q, J = 14.4 Hz, 2H), 7.58 (d, J = 9.2 Hz, 2H), 6.97 (t, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.61 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 162.2 (d, $^1J_{C,F}$ = 244 Hz), 159.3, 148.2, 147.1, 128.2, 127.1, 127.0, 115.4, 115.2, 113.9, 98.6, 55.0; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{14}FN_2O$, 269.1085; found, 269.1082.

3,5-Bis(4-methoxyphenyl)-1*H*-pyrazole (5c)

Yield: 0.057 g (68%) as a brown solid; mp: 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.61 (d, J = 9.2 Hz, 4H), 6.83 (d, J = 9.2 Hz, 4H), 6.60 (s, 1H), 3.75 (s, 6H (2-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.2, 148.0, 126.7, 124.3, 113.9, 98.2, 55.0; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{17}N_2O_2$, 281.1285; found, 281.1297.

5-(3-Chlorophenyl)-3-phenyl-1*H*-pyrazole (6a)

Yield: 0.061 g (80%) as a brown solid; mp: 208–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.73–7.58 (m, 4H), 7.32–7.14 (m, 5H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 134.2, 129.7, 128.5, 127.7, 127.3, 125.2, 125.4, 99.4; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{11}ClN_2$, 255.0684; found, 255.0683.

5-(3-Chlorophenyl)-3-(4-fluorophenyl)-1*H*-pyrazole (6b)

Yield: 0.065 g (79%) as a brown solid; mp: 202–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.66 (d, J = 6.8 Hz, 2H), 7.31–7.22 (m, 4H), 7.16 (d, J = 4.0 Hz, 1H), 6.97 (s, 1H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 162.4 (d, $^1J_{C,F}$ = 247 Hz), 134.5, 133.6, 129.9, 127.6, 127.4, 127.2, 127.1, 125.4, 123.5, 115.7, 115.5, 99.6; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{10}ClFN_2$, 273.0589; found, 273.0600.

(3-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (6c)

Yield: 0.061 g (71%) as a brown solid; mp: 128–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.74 (s, 1H), 7.59 (d, J = 8.4 Hz, 3H), 7.26–7.16 (m, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.56 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.2, 148.1, 146.5, 134.2, 129.7, 127.3, 126.6, 125.3, 123.4, 123.3, 113.9, 99.8, 55.0; HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}ClN_2O$, 285.0789; found, 285.0785.

3-Phenyl-5-(*m*-tolyl)-1*H*-pyrazole (7a)

Yield: 0.053 g (76%) as a brown solid; mp: 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71–7.69 (m, 2H), 7.49–7.47 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 138.2, 131.3, 130.1, 128.6, 128.5, 127.8, 126.2, 125.5,

122.7, 99.7, 21.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{16}H_{14}N_2$, 235.1230; found, 235.1222.

3-(4-Fluorophenyl)-5-(*m*-tolyl)-1*H*-pyrazole (7b)

Yield: 0.060 g (79%) as a brown solid; mp: 158–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.66 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.02 (t, J = 8.8 Hz, 2H), 6.74 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, $^1J_{C,F}$ = 246 Hz), 148.6, 148.0, 138.4, 130.5, 128.9, 128.7, 127.8, 127.2, 126.2, 122.6, 115.7, 99.7, 21.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{16}H_{13}FN_2$, 253.1136; found, 253.1134.

3-(4-Methoxyphenyl)-5-(*m*-tolyl)-1*H*-pyrazole (7c)

Yield: 0.060 g (75%) as a brown solid; mp: 127–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 3.77 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 148.9, 148.0, 138.1, 131.4, 128.5, 126.8, 126.2, 123.9, 122.7, 113.9, 99.0, 55.0, 21.2; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{17}H_{16}N_2O$, 265.1335; found, 265.1344.

5-(2-Chlorophenyl)-3-phenyl-1*H*-pyrazole (8a)

Yield: 0.058 g (76%) as a brown solid; mp: 218–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.39–7.30 (m, 3H), 7.27–7.11 (m, 2H), 6.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8, 131.3, 130.4, 130.2, 129.8, 129.2, 128.7, 128.0, 127.0, 125.7, 103.6; HRMS: *m*/*z* calculated for $C_{15}H_{11}ClN_2$ $(M + H)^+$: 255.0684; found, 255.0690.

5-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazole (9a)

Yield: 0.051 g (75%) as a brown solid; mp: 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.76 (s, 1H), 7.69 (q, J = 8.0 Hz, 2H), 7.62 (t, J = 7.6 Hz, 3H), 7.31–7.27 (m, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.05 (t, J = 8.4 Hz, 1H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 146.3, 144.4, 135.3, 130.4, 128.5, 127.8, 127.3, 125.3, 124.2, 123.5, 99.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{13}H_{11}N_2S$, 227.0637; found, 227.0679.

5-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole (9b)

Yield: 0.050 g (67%) as a brown solid; mp: 183–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.55–7.52 (m, 2H), 7.1 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 4.8 Hz, 1H), 6.90–6.84 (m, 3H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8 (d, $^1J_{C,F}$ = 244 Hz) 127.0, 126.8, 126.7, 124.0, 123.2, 115.2, 115.0, 98.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{13}H_{10}N_2S$, 245.0543; found, 245.0579.

5-Heptyl-3-phenyl-1*H*-pyrazole (11a)

Yield: 0.059 g (81%) as a brown solid; mp: 222–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.32–7.28 (m, 1H), 6.36 (s, 1H), 2.62 (t, J = 8.4 Hz, 2H), 1.69–1.61 (m, 2H), 1.32–1.27 (m, 8H), 0.88 (t, J = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 147.9, 132.7, 128.6, 127.7, 125.7, 101.0, 31.8, 29.2, 29.0, 26.4, 22.6, 14.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{16}H_{22}N_2$, 243.1856; found, 243.1860.

3-(4-Fluorophenyl)-5-heptyl-1*H*-pyrazole (11b)

Yield: 0.059 g (76%) as a brown solid; mp: 214–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, J = 6.8 Hz, 2H), 7.07 (t, J = 8.0 Hz, 2H), 6.31 (s, 1H), 2.63 (t, J = 7.6 Hz, 2H), 1.69–1.61 (m, 2H), 1.32–1.27 (m, 8H), 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, $^1J_{C,F}$ = 245 Hz) 149.9, 147.3, 129.1, 127.3, 127.3 115.7, 115.4, 100.8, 31.7, 29.2, 29.0, 26.2, 22.6, 14.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{16}H_{22}FN_2$, 261.1762; found, 261.1735.

5-Heptyl-3-(4-methoxyphenyl)-1*H*-pyrazole (11c)

Yield: 0.060 g (73%) as a brown solid; mp: 207–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 6.27 (s, 1H), 3.81 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.66–1.60 (m, 2H), 1.28–1.26 (m, 8H), 0.88 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 149.5, 148.1, 126.9, 125.4, 114.0, 100.3, 55.2, 31.7, 29.3, 29.0, 26.5, 22.6, 14.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calculated for $C_{17}H_{24}N_2O$, 273.1961; found, 273.1947.

Conflicts of interest

There are no conflicts to declare.

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