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HIGHLY REGIOSELECTIVE SYNTHESIS OF 1-ACYL-5-HYDROXYPYRAZOLINES OR SYNTHESIS OF 3,5-DISUBSTITUTED PYRAZOLES FROM (*E*)-*β*-CHLOROVINYL KETONES AND BENZOHYDRAZIDES OR HYDRAZINE HYDRATE

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Abstract – Highly regioselective synthesis of 1-acyl-5-hydroxypyrazolines or synthesis of 3,5-disubstituted pyrazoles have been achieved through the cyclocondensation of (*E*)-*β*-chlorovinyl ketones with benzohydrazides/hydrazine hydrate under extremely mild reaction conditions. The mechanistic studies showed that diverse electrophilic pathways of (*E*)-*β*-chlorovinyl ketones could be observed by using different nucelophilic species. Moreover, the utility of the tandem reaction is further illustrated by the concise synthesis of 1-acyl-pyrazole and 3-pentyl-5-phenyl-1*H*-pyrazole.

INTRODUCTION

Pyrazoline and pyrazole derivatives are extremely important heterocyclic compounds in pharmaceutical science, which have been extensively studied in the past few decades and have exhibited a broad range of biological activities such as antitumor, antifungal, antidiabetic, antimicrobial, antiviral, and anti-inflammatory effects.[1] Specifically, 1-acyl-5-hydroxypyrazolines are acknowledged to possess antibacterial[2] and analgesic activities.[3] As shown in Figure 1, 5-nitro-2-furyl-substituted 1-acyl-5-hydroxypyrazoline displayed antibacterial activity against the strains *S. aureus*, *A. aerogenes*, *E. coli*, and *B. subtilis*,[2] whereas 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles have proven to be analgesics with a slightly improved pain-relieving efficacy than the standard drug.[3] 1-Acyl-5-hydroxypyrazolines bearing 3-fluoro-4-methoxyphenyl moiety also showed excellent activity in antioxidant studies and potent

anticancer activity against MCF-7 and MDA-MB-231 cell lines.[4] To date, the main methods for the construction of 1-acyl-5-hydroxypyrazolines are focused on the annulation of hydrazides with 1,3-dicarbonyl compounds,[5] alkynyl ketones,[6] alkynediones,[7] allenic ketones,[8] chalcone dibromides,[4,9] or 3-alkoxy-2-en-1-ones.[10] However, these methods are limited by the substrate scope, poor regioselectivity, and multistep sequences. On the other hand, a variety of clinical drugs containing a pyrazole pharmacophore such as Celecoxib,[11] Rimonabant,[12] Zoniporide,[13] Lersivirine,[14] and Difenamizole[15] have been developed (Figure 2). For example, the nonsteroidal anti-inflammatory drug Celecoxib is an inhibitor of COX-2[11] and Rimonabant as a selective CB1 receptor is used to treat obesity.[12] The common approaches for the construction of substituted pyrazoles involve the condensation of hydrazines with 1,3-dicarbonyl compounds[16] or 1,3-dielectrophile derivatives,[17] and 1,3-dipolar cycloaddition of diazo compounds with alkenes or alkynes.[18] Although efficient, these methods have some limitations including poor regioselectivity for highly substituted pyrazoles, use of expensive/toxic reagents, and harsh reaction conditions. Therefore, the rapid and regioselective construction of 1-acyl-5-hydroxypyrazolines or substituted pyrazoles from readily available starting materials would be more facile and efficient.

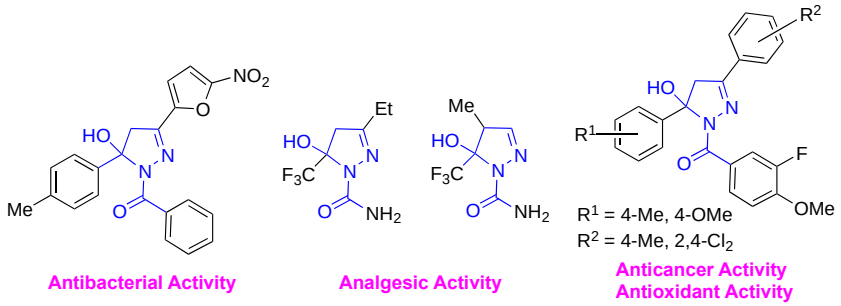


Figure 1. Selected 1-acyl-5-hydroxypyrazolines with biological activities

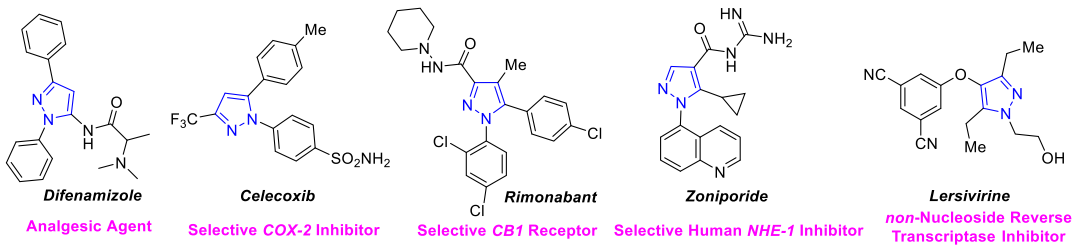


Figure 2. Selected pyrazole-containing drugs

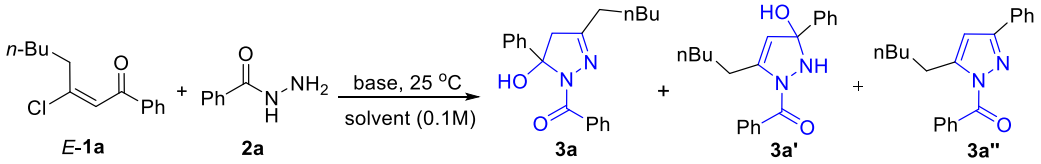
In 2013, the intrinsically electrophilic *β*-chlorovinyl ketones acting as either nucleophiles or electrophiles have been reported by Oh and co-workers.[19] However, the preparation of 1-acyl-5-hydroxypyrazolines or substituted pyrazoles via cyclocondensation of *β*-chlorovinyl ketones with benzohydrazides or hydrazine hydrate has not been reported to date. Inspired by our previous report on an *in situ* generated electrophilic allenone intermediate from *β*-chlorovinyl ketone in the presence of base for furan synthesis,[20] we

envisioned the base-promoted tandem reaction of *β*-chlorovinyl ketone with benzohydrazides or hydrazine hydrate to prepare the 1-acyl-5-hydroxypyrazolines or substituted pyrazoles. Herein, we report the diverse electrophilic pathways of (*E*)-*β*-chlorovinyl ketones in the synthesis of 1-acyl-5-hydroxypyrazolines and substituted pyrazoles.

RESULTS AND DISCUSSION

Our first attempt was to explore the synthesis of 1-acyl-5-hydroxypyrazoline **3a** by using (*E*)-**1a** and benzohydrazide **2a** as the model substrates (Table 1). Initial examinations focused on identifying the most suitable base for the dehydrochlorination/conjugate addition/cyclization/isomerization tandem process in MeCN. DABCO was proven to be the most suitable base in the tandem reaction (entries 1-5). Subsequently, some commonly used solvents were tested and MeCN was obviously chosen as optimal solvent for this reaction (entries 6-8). Upon decreasing the amount of DABCO to 100 mol% in MeCN, the reaction was markedly retarded and the yield slightly decreased to 87% (entry 9). Increasing the reaction temperature to 50 °C significantly accelerated the reaction and only led to a slight decline in the yield (entry 10). In addition, there was no difference in the reaction rates between (*E*)-**1a** and (*Z*)-**1a**, but a relatively lower isolated yield was produced by (*Z*)-**1a** (entry 11). It was noteworthy that the product **3a** was obtained exclusively without any recognizable structural information of regioisomers **3a'** and **3a''** in all the tested experiments (entries 1-11).

Table 1. Optimization of the tandem reaction of (*E*)-*β*-chlorovinyl ketones **1a** and benzohydrazide **2a**[a]

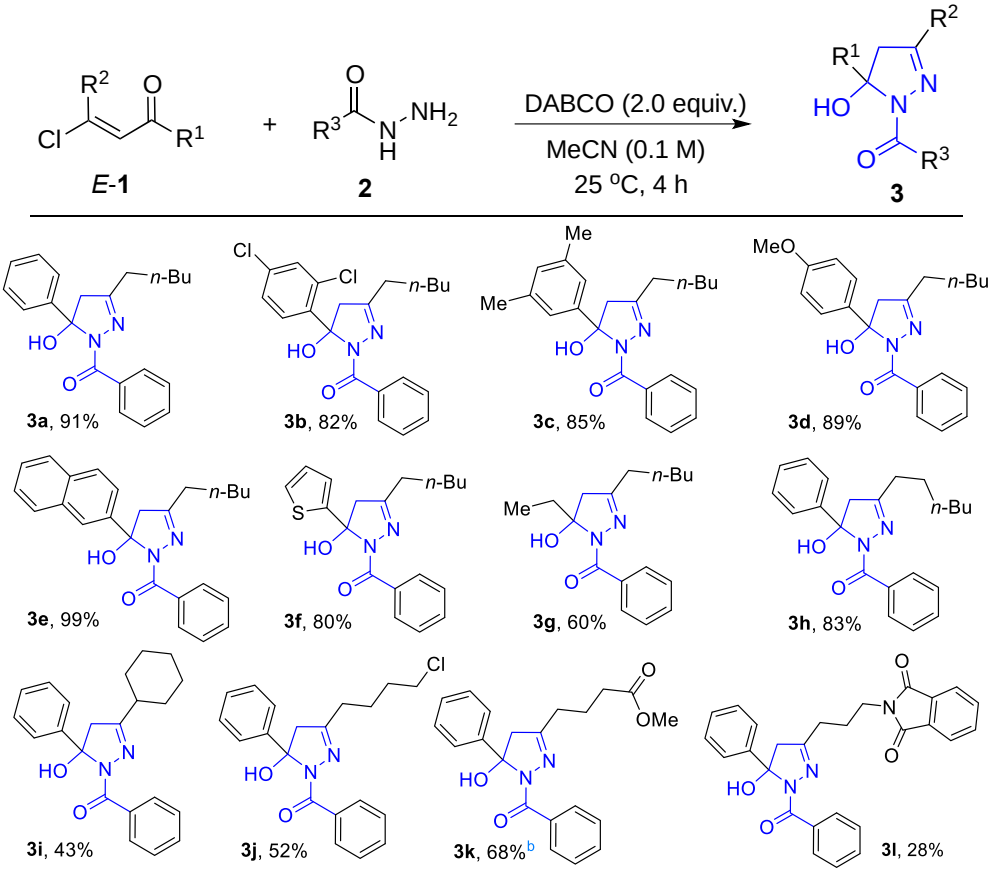


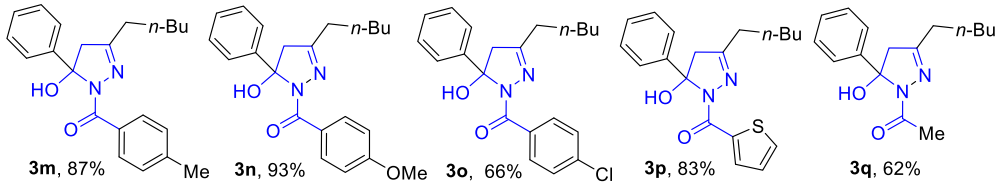
Entry	Base	Solvent	Time (h)	Yield of **3a** (%)[b]	Yield of **3a'** (%)[b]	Yield of **3a''** (%)[b]
1	Cs_2CO_3	MeCN	6	20	0	0
2	K_2CO_3	MeCN	15	50	0	0
3	DBU	MeCN	6	16	0	0
4	Et_3N	MeCN	9	78	0	0
5	DABCO	MeCN	4	91	0	0
6	DABCO	CH_2Cl_2	20	83	0	0
7	DABCO	EtOH	7	89	0	0
8	DABCO	THF	7	82	0	0
9[c]	DABCO	MeCN	25	87	0	0
10[d]	DABCO	MeCN	1	83	0	0
11[e]	DABCO	MeCN	4	74	0	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (2.0 equiv.), solvent (3.0 mL). [b]Isolated yields. [c]100 mol% DABCO was used. [d]Temperature = 50 °C. [e](*Z*)-**1a** was used as starting material.

The scope and generality of the formation of 1-acyl-5-hydroxypyrazoline **3** is shown in Table 2. Various phenyl-substituted aryl ketones and hereroaryl ketone were broadly tolerated, furnishing the desired product **3a-f** in 80-99% yields regardless of electronic nature, steric hindrances and substitution position on the aromatic ring. An aliphatic ketone with an ethyl substituent also smoothly underwent the sequential synthesis to provide **3g** in 60% yield. The effect of *n*-hexyl and cyclohexyl at the *β*-carbon of (*E*)-**1** was also assessed. The results indicated that *n*-hexyl substituent had a slight influence on the yield (**3h**, 83%), whereas cyclohexyl substituent resulted in a remarkable decline in the yield (**3i**, 43%). It was probably because it was more difficult to generate allenone intermediate from (*E*)-**1i**. In particular, (*E*)-**1** with various functional groups such as halide, ester, and phthalimide at the *β*-carbon led to the desired products **3j-l** in 28-68% yields. The scope of benzohydrazides was then surveyed. 4-Methylbenzohydrazide and 4-methoxylbenzohydrazide were tolerated with (*E*)-**1a**, delivering the expected products **3m** (87%) and **3n** (93%). However, the significantly reduced yield of **3o** (66%) was obtained when 4-chlorobenzohydrazide reacted with (*E*)-**1a**. Gratifyingly, the present methodology could also be extended to thiophene-2-carbohydrazide to give **3p** in 83% yield. In addition, acetohydrazide showed good reactivity and regioselectivity to afford **3q** in 62% yield.

Table 2. Scope of the formation of 1-acyl-5-hydroxypyrazolines[a]

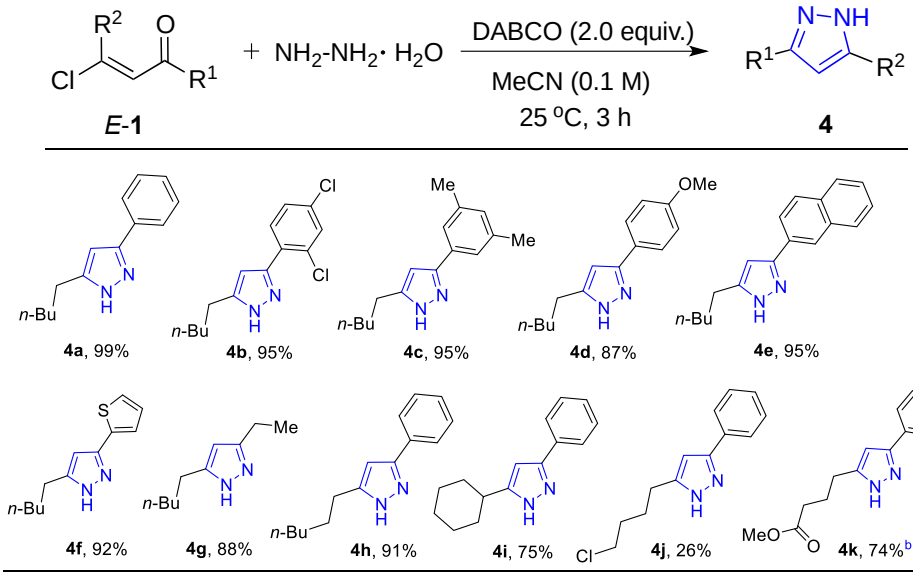




[a] Reaction conditions: (*E*)-**1** (0.3 mmol), **2** (0.6 mmol), DABCO (0.6 mmol) in MeCN (3.0 mL) at 25 °C for 4 h; Isolated yields. [b] (*Z*)-**1k** was the starting material.

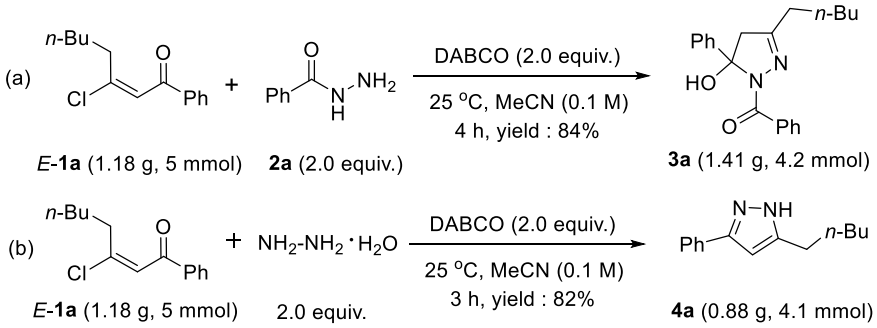
The formation of 3,5-disubstituted pyrazoles **4** using (*E*)-**1** and hydrazine hydrate as starting materials was then explored. We examined the cyclocondensation reaction of a variety of (*E*)-**1** with hydrazine hydrate in the presence of 2.0 equiv. DABCO in MeCN at 25 °C for 3 h and the results were summarized in Table 3. A variety of (*E*)-**1** reacted very well with hydrazine hydrate to provide 3,5-disubstituted pyrazoles **4a-h** in good to excellent yields (87-99%). (*E*)-**1i** with cyclohexyl at the *β*-carbon resulted in a marked decrease in the yield of **4i** (75%). The cyclocondensation reaction also tolerated functional groups such as halide and ester, however, the yield of **4j** was 26% only. It was probably because terminal chlorine elimination of (*E*)-**1j** resulted in a decreased yield. By comparison, **4k** was achieved in a yield of 74%.

Table 3. Cyclocondensation of (*E*)-*β*-chlorovinyl ketone **1** with hydrazine hydrate[a]



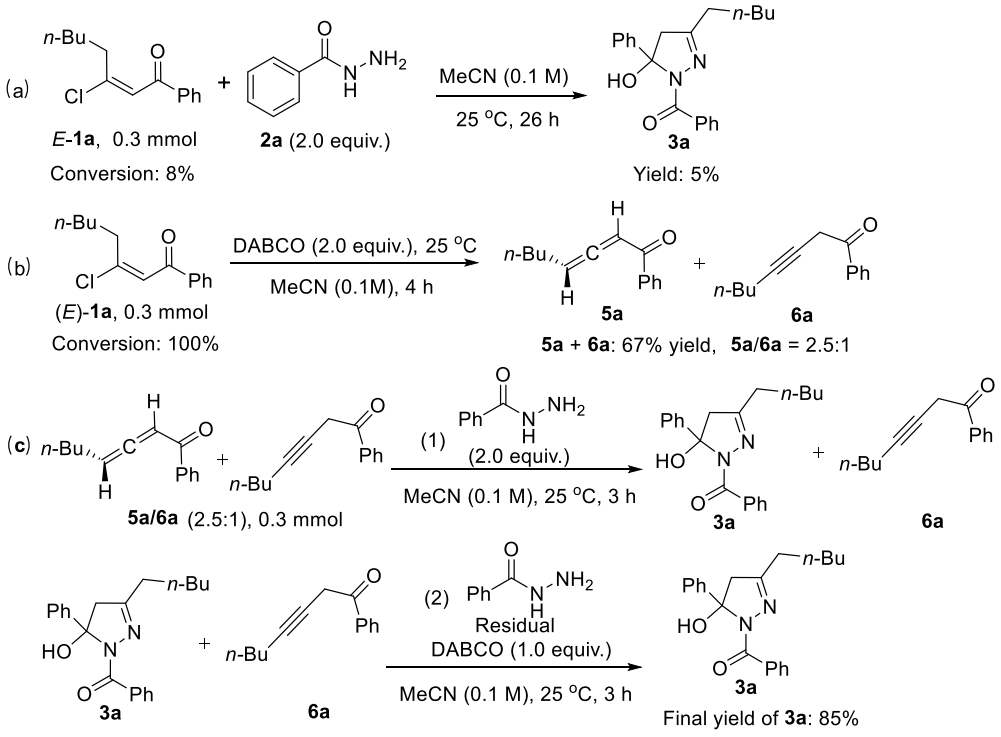
[a]Reaction conditions: (*E*)-**1** (0.3 mmol), hydrazine hydrate (0.6 mmol), DABCO (0.6 mmol) in MeCN (3.0 mL) at 25 °C for 3 h; Isolated yields. [b](*Z*)-**1k** was the starting material.

Subsequently, we confirmed that the tandem process leading to **3a** (4.2 mmol, 84%) was amenable to 16-fold scale-up without obvious loss of efficiency and cyclocondensation leading to **4a** (4.1 mmol, 82%) could still be achieved in very good yield in the gram-scale preparation (Scheme 1).



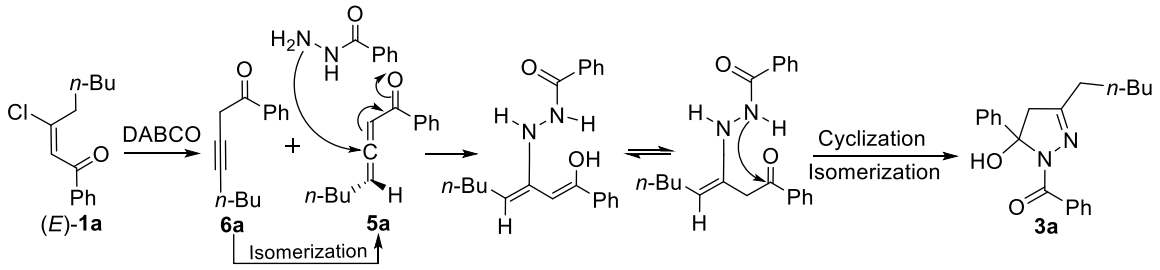
Scheme 1. Scale-up experiments

To obtain further insights into the reaction mechanisms, a series of control experiments were conducted (Scheme 2). It has been demonstrated that the starting materials are not easily converted into **3a** without using any base within 26 h (Scheme 2a). In the absence of benzohydrazide **2a**, the elimination product allenone **5a** and propargyl ketone **6a** were readily obtained in 67% yield with full conversion of (*E*)-**1a** (Scheme 2b). The tandem reaction of a mixture of **5a** and **6a** with benzohydrazide **2a** was then investigated. Firstly, allenone **5a** totally transformed into product **3a** in the absence of DABCO after three hours but propargyl ketone **6a** was still retained in the reaction; Upon adding 1.0 equiv. DABCO to the reaction system, **6a** was also fully converted into **3a** after another three hours (Scheme 2c). The results indicated sufficient evidences of allenone **5a** generated from the dehydrochlorination of (*E*)-**1a** as the electrophilic intermediate in the tandem reaction.



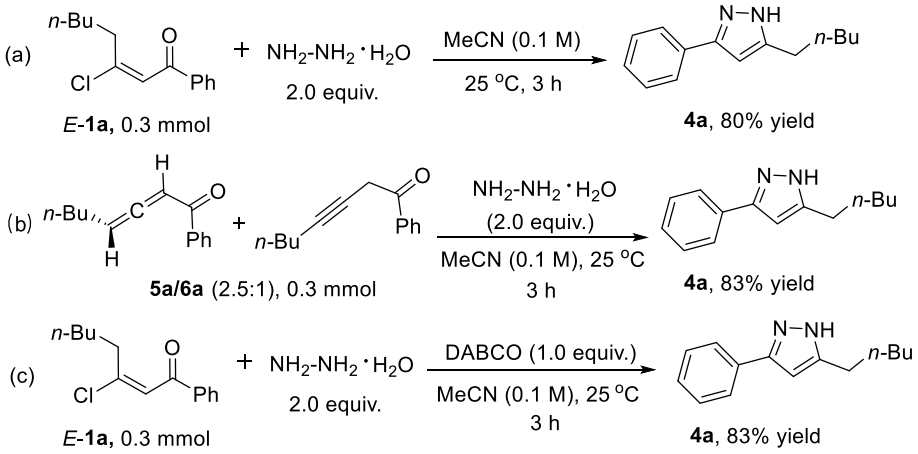
Scheme 2. Control experiments for the formation of **3a**

A possible mechanism for the formation of **3a** is proposed in Scheme 3. The reaction pathway illustrates that the conjugate addition of benzohydrazide **2a** to intermidate allenone **5a** generated from dehydrochlorination of (*E*)-**1a**, followed by a sequential cyclization/isomerization to get 1-acyl-5-hydroxypyrazoline **3a**.



Scheme 3. A plausible mechanism for the formation of 1-acyl-5-hydroxypyrazoline **3a**

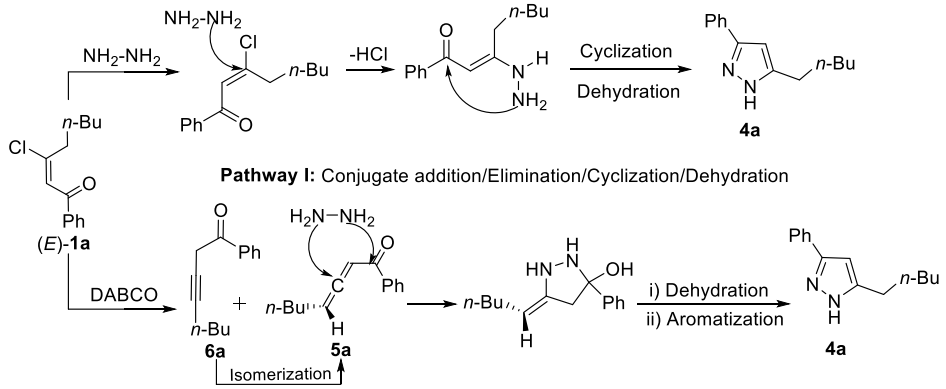
As for the cyclocondensation of (*E*)-**1a** and hydrazine hydrate, either (*E*)-**1a** or a mixture of **5a** and **6a** could readily react with hydrazine hydrate to afford **4a** in very good yield without DABCO (Scheme 4a-b). Moreover, compared to 2.0 equiv. DABCO used in the reaction, the yield of **4a** decreased from 99% to 83% when 1.0 equiv. DABCO was employed (Scheme 4c). These experimental results showed the following: (1) both (*E*)-**1a** and allenone **5a** could be used as the electrophilic species in the cyclocondensation reaction without DABCO; (2) excess DABCO was more conducive to the formation of **4a** with almost quantitative transformation of the starting materials.



Scheme 4. Control experiments for the formation of **4a**

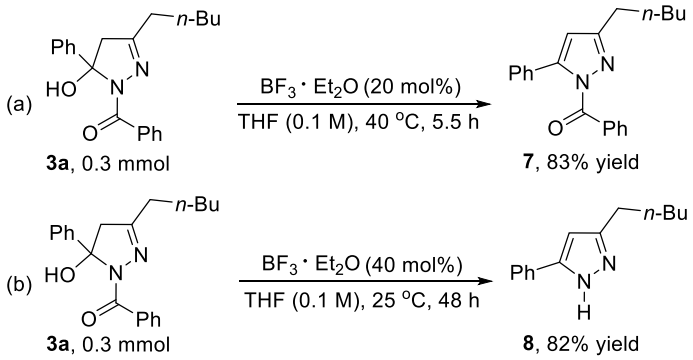
Two plausible pathways to account for the formation of **4a** are illustrated in Scheme 5. A direct 1,4-conjugate addition of hydrazine to (*E*)-**1a** followed by consecutive

elimination/cyclization/dehydration process is proposed in pathway **I**. By comparision with pathway **I**, pathway **II** is also capable of obtaining **4a** via a dehydrochlorination/conjugate addition/cyclization/dehydration/aromatization sequence in the presence of DABCO. According to the control experiments surveyed on the condensation reaction of (*E*)-**1a** and hydrazine, pathway **I** for the formation of **4a** is more likely to occur and pathway **II** may also be involved in the reaction.



Scheme 5. Plausible mechanisms for the formation of 3,5-disubstituted pyrazole **4a**

Lastly, as a useful synthetic application, we investigated the dehydration of **3a**. As shown in Scheme 6a, the corresponding pyrazole **7** was obtained in 83% yield when **3a** was treated with 20 mol% $BF_3 \cdot Et_2O$ in THF at 40 °C for 5.5 h. Interestingly, upon increasing the amount of $BF_3 \cdot Et_2O$ to 40 mol% and lowering the reaction temperature to 25 °C for 48 h, 3-pentyl-5-phenyl-1*H*-pyrazole **8** could be obtained via dehydration and debenzoylation of **3a** (Scheme 6b).



Scheme 6. Synthesis of pyrazoles **7** and **8**

In summary, we have developed a facile synthesis of 1-acyl-5-hydroxypyrazolines or 3,5-disubstituted pyrazoles via base-promoted annulation of readily available *β*-chlorovinyl ketones with benzohydrazides or hydrazine hydrate under extremely mild reaction conditions. This practical and easily handled protocol,

with great regioselectivity, easy scale-up and tolerating functional groups such as halide, ester and phthalimide, could occur under a broad substrate scope to give the product in up to 99% yield. Moreover, the utility of the cyclocondensation reaction is further illustrated by the concise synthesis of 1-acyl-pyrazole **7** and 3-pentyl-5-phenyl-1*H*-pyrazole **8**.

EXPERIMENTAL

All reactions were carried out with oven-dried glassware. The progress of all reactions was monitored by thin-layer chromatography on TLC silica gel 60 F_{254} plates and visualized by ultra-violet light or by staining with $KMnO_4$ stain. Unless otherwise noted, solvents and all reagents were purchased from commercial sources and used without further purification. IR spectra were recorded on a Bruker VERTEX 80v FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 500 spectrometer. ^{1}H and ^{13}C NMR chemical shifts were detemined relative to internal tetramethylsilane (TMS) at δ 0.0 and all coupling constants were reported in Hertz. High-resolution mass spectra were obtained on a Bruker micrOTOF-Q III MS using electrospray ionization (ESI).

General Procedure for the synthesis of 1-acyl-5-hydroxypyrazolines 3

β-Chlorovinyl ketones (**1**, 0.3 mmol, 1.0 equiv.), DABCO (0.6 mmol, 2.0 equiv., 67.3 mg), and hydrazide (**2**, 0.6 mmol, 2.0 equiv.) were added to a flame-dried vial with MeCN (3.0 mL). The vial was sealed with Teflon tape to stir at 25 °C until complete consumption of **1** as determined by thin layer chromatography. The reaction mixture was filtered through a plug of silica gel using EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by SiO_2-column chromatography (petroleum ether / EtOAc = 9/1-6/1) to afford 1-acyl-5-hydroxypyrazolines **3**.

(5-Hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (3a): yellow sticky solid; IR (neat, ν): 3428, 3062, 2955, 2928, 2862, 1686, 1573, 1421, 1325, 1178, 1063, 967, 847, 761, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 5.50 (s, 1H), 3.26 (d, *J* = 18.5 Hz, 1H), 2.94 (d, *J* = 18.5 Hz, 1H), 2.34 (t, *J* = 7.8 Hz, 2H), 1.60-1.50 (m, 2H), 1.35-1.27 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 158.7, 144.0, 133.9, 131.5, 130.2, 128.8, 128.0, 127.8, 124.0, 94.4, 52.2, 31.4, 30.3, 26.0, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{21}H_{25}N_2O_2$ $[M+H]^+$ 337.1911, found 337.1900.

(5-(2,4-Dichlorophenyl)-5-hydroxy-3-pentyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (3b): White soild; mp 70-71 °C; IR (neat, ν): 3359, 3065, 2952, 2926, 2860, 1616, 1579, 1427, 1366, 1291,1210, 1093, 1024, 851, 795, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz , 1H), 7.40-7.35 (m, 3H), 7.28 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H), 5.53 (s, 1H), 3.25 (d, *J* = 18.5 Hz, 1H), 3.09 (d, *J* = 18.5 Hz, 1H), 2.48-2.36 (m, 2H), 1.66-1.55 (m, 2H),

1.40-1.30 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 158.9, 138.3, 134.7, 133.2, 131.75, 131.67, 130.8, 130.4, 129.2, 127.7, 127.0, 91.9, 49.7, 31.5, 30.1, 26.1, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{21}H_{23}Cl_2N_2O_2$ $[M+H]^+$ 405.1131, found 405.1118.

(5-(3,5-Dimethylphenyl)-5-hydroxy-3-pentyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3c**)**:** Brown oil; IR (neat, ν): 3446, 3042, 2950, 2925, 2862, 1623, 1574, 1421, 1315, 1215, 1069, 853, 797, 702 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.41(t, *J* = 7.5 Hz, 2H), 7.07 (s, 2H), 6.91 (s, 1H), 5.39 (s, 1H), 3.25 (d, *J* = 18.5 Hz, 1H), 2.95 (d, *J* = 18.5 Hz, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 6H), 1.62-1.55 (m, 2H), 1.37-1.31 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 158.6, 143.9, 138.3, 133.9, 131.4, 130.2, 129.7, 127.7, 121.7, 94.4, 52.1, 31.4, 30.3, 26.0, 22.3, 21.5, 13.9; HRMS (ESI): *m/z* calcd. for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2213.

(5-Hydroxy-5-(4-methoxyphenyl)-3-pentyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3d**)**:** Brown soild; mp 91-92 ºC; IR (neat, ν): 3327, 2943, 2928, 2857, 1674, 1571, 1507, 1469, 1369, 1245, 1175, 1108, 1023, 845, 777, 695, 638 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.43-7.39 (m, 4H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.42 (s, 1H), 3.79 (s, 3H), 3.28 (d, *J* = 18.5 Hz, 1H), 2.96 (d, *J* = 18.5 Hz, 1H), 2.37 (t, *J* = 7.8 Hz, 2H), 1.61-1.55 (m, 2H), 1.36-1.31 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 159.3, 158.6, 136.1, 133.8, 131.4, 130.2, 127.7, 125.2, 114.0, 94.4, 55.3, 52.1, 31.4, 30.3, 26.0, 22.3, 13.9; HRMS (ESI): *m/z* calcd. for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ 367.2016, found 367.2021.

(5-Hydroxy-5-(naphthalen-2-yl)-3-pentyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3e**)**:** Brown soild; mp 102-103 ºC; IR (neat, ν): 3316, 3055, 2954, 2922, 2858, 1621, 1571, 1453, 1348, 1278, 1173, 1115, 1075, 903, 857, 813, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 3H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.45-7.41 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 2H), 5.67 (s, 1H), 3.32 (d, *J* = 18.5 Hz, 1H), 3.00 (d, *J* = 18.5 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.60-1.53 (m, 2H), 1.35-1.29 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.8, 141.2, 133.8, 133.2, 133.1, 131.6, 130.3, 128.9, 128.5, 127.8, 127.7, 126.5, 126.3, 123.1, 122.1, 94.6, 52.1, 31.5, 30.3, 26.0, 22.4, 14.1; HRMS (ESI): *m/z* calcd. for $C_{25}H_{26}N_2NaO_2$ $[M+Na]^+$ 409.1886, found 409.1881.

(5-Hydroxy-3-pentyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3f**)**:** Brown soild; mp 83-84 ºC; IR (neat, ν): 3147, 2952, 2924, 2858, 1665, 1575, 1521, 1452, 1415, 1280, 1239, 1193, 1090, 1025, 852, 809, 763, 704 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 2H), 7.47(d, *J* = 7.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 4.5 Hz, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.93 (t, *J* = 4.0 Hz, 1H), 5.67 (s, 1H), 3.35 (d, *J* = 18.5 Hz, 1H), 3.13 (d, *J* = 18.5 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.59-1.54 (m, 2H), 1.35-1.31 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 158.5, 148.0, 133.7, 131.6, 130.1, 127.8, 127.1, 125.1, 123.4, 92.7, 52.4, 31.4, 30.2, 25.9, 22.3, 14.0;

HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}N_2O_2S$ $[M+H]^+$ 343.1475, found 343.1478.

(5-Ethyl-5-hydroxy-3-pentyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3g**)**:** Pale yellow oil; IR (neat, ν): ν 3420, 3042, 2951, 2928, 2863, 1621, 1573, 1451, 1427, 1330, 1183, 1129, 1032, 853, 793, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 4.98 (s, 1H), 2.93 (d, *J* = 18.5 Hz, 1H), 2.86 (d, *J* = 18.5 Hz, 1H), 2.38-2.29 (m, 3H), 2.23 (dt, J_1 = 21.5 Hz, J_2 = 7.5 Hz, 1H), 1.61-1.51 (m, 2H), 1.36-1.29 (m, 4H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 158.9, 134.4, 131.1, 129.9, 127.6, 95.7, 46.3, 31.7, 31.4, 30.3, 25.9, 22.3, 13.9, 8.8; HRMS (ESI): *m/z* calcd. for $C_{17}H_{25}N_2O_2$ $[M+H]^+$ 289.1911, found 289.1905.

(3-Hexyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3h**)**:** Yellow oil; IR (neat, ν): 3420, 3061, 3030, 2925, 2858, 1625, 1448, 1422, 1331, 1261, 1180, 1065, 1027, 974, 849, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.48-7.46 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 5.45 (s, 1H), 3.28 (d, *J* = 18.5 Hz, 1H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.60-1.54 (m, 2H), 1.38-1.34 (m, 2H), 1.32-1.26 (m, 4H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.6, 143.9, 133.8, 131.5, 130.2, 128.7, 128.0, 127.7, 124.0, 94.4, 52.1, 31.5, 30.3, 28.9, 26.3, 22.5, 14.0; HRMS (ESI): *m/z* calcd. for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2067, found 351.2050.

(3-Cyclohexyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3i**)**:** Yellow sticky solid; IR (neat, ν): 3420, 3062, 2926, 2853, 1624, 1571, 1494, 1423, 1320, 1258, 1180, 1067, 1028, 977, 901, 848, 763, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.47 (dd, J_1 = 12.5 Hz, J_2 = 7.5 Hz, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 5.45 (s, 1H), 3.29 (d, *J* = 18.5 Hz, 1H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.42-2.38 (m, 1H), 1.91-1.85 (m, 2H), 1.82-1.75 (m, 2H), 1.71-1.66 (m, 1H), 1.36-1.29 (m, 4H), 1.26-1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 162.1, 144.0, 133.7, 131.5, 130.3, 128.7, 128.0, 127.7, 123.9, 94.3, 50.3, 39.3, 30.3, 30.2, 25.9, 25.7; HRMS (ESI): *m/z* calcd. for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1898.

(3-(4-Chlorobutyl)-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**3j**)**:** Pale yellow soild; mp 84-85 °C; IR (neat, ν): 3443, 3065, 2945, 2863, 1614, 1570, 1440, 1367, 1289, 1171, 1059, 1024, 985, 851, 704, 603 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.51-7.46 (m, 3H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 5.36 (s, 1H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.29 (d, *J* = 18.5 Hz, 1H), 2.98 (d, *J* = 18.5 Hz, 1H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.88-1.81 (m, 2H), 1.79-1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 157.6, 143.7, 133.6, 131.6, 130.1, 128.8, 128.1, 127.8, 124.0, 94.4, 52.1, 44.5, 31.9, 29.5, 23.4; HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}ClN_2O_2$ $[M+H]^+$ 357.1364, found 357.1356.

Methyl 4-(1-benzoyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)butanoate (**3k**)**:** Yellow oil;

IR (neat, ν): 3449, 3060, 3028, 2948, 1731, 1625, 1574, 1493, 1423, 1336, 1254, 1172, 1066, 978, 850, 762, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.49-7.45 (m, 3H), 7.41(t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 5.40 (s, 1H), 3.67 (s, 3H), 3.29 (d, *J* = 19.0 Hz, 1H), 2.99 (d, *J* = 18.5 Hz, 1H), 2.45-2.39 (m, 4H), 1.95 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 168.1, 157.3, 143.7, 133.7, 131.5, 130.1, 128.7, 128.0, 127.7, 124.0, 94.5, 52.2, 51.6, 33.2, 29.5, 21.4; HRMS (ESI): *m/z* calcd. for $C_{21}H_{22}N_2NaO_4$ $[M+Na]^+$ 389.1472, found 389.1472.

2-(3-(1-Benzoyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)propyl)isoindoline-1,3-dione (3l): White soild; mp 103-104 ºC; IR (neat, ν): 3189, 3057, 2923, 2852, 1770, 1707, 1633, 1542, 1443, 1398, 1363, 1284, 1181, 1067, 1028, 969, 848, 797, 761, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.81 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 1H), 7.70 (dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 1H), 7.50-7.46 (m, 3H), 7.42-7.38 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 2H), 5.37 (s, 1H), 3.84-3.75 (m, 2H), 3.29 (d, *J* = 18.5 Hz, 1H), 2.99 (d, *J* = 19.0 Hz, 1H), 2.50-2.39 (m, 2H), 2.08-2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 157.0, 143.6, 134.0, 132.0, 131.5, 130.2, 128.9, 128.73, 128.68, 128.0, 127.7, 127.2, 124.0, 123.3, 94.4, 52.3, 37.4, 27.8, 24.9; HRMS (ESI): *m/z* calcd. for $C_{27}H_{24}N_3O_4$ $[M+H]^+$ 454.1761, found 454.1748.

(5-Hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(*p*-tolyl)methanone (3m): Yellow oil; IR (neat, ν): 3432, 3062, 3031, 2952, 2926, 2862, 1614, 1571, 1425, 1322, 1263, 1177, 1110, 1063, 966, 836, 745, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 1H), 3.27 (d, *J* = 18.5 Hz, 1H), 2.96 (d, *J* = 18.5 Hz, 1H), 2.38 (s, 3H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.62-1.53 (m, 2H), 1.37-1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.3, 144.0, 142.0, 130.9, 130.3, 128.7, 128.5, 127.9, 124.0, 94.4, 52.0, 31.4, 30.3, 26.0, 22.4, 21.6, 14.0; HRMS (ESI): *m/z* calcd. for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2067, found 351.2069.

(5-Hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(4-methoxyphenyl)methanone (3n): Yellow oil; IR (neat, ν): 3433, 3060, 2954, 2928, 2861, 1605, 1508, 1427, 1312, 1253, 1172, 1111, 1063, 1028, 832, 759, 699 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.52 (s, 1H), 3.82 (s, 3H), 3.26 (d, *J* = 18.5 Hz, 1H), 2.95 (d, *J* = 18.5 Hz, 1H), 2.38 (t, *J* = 7.8 Hz, 2H), 1.63-1.53 (m, 2H), 1.37-1.31 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 162.3, 158.2, 144.1, 132.5, 128.7, 127.9, 125.9, 124.0, 113.0, 94.5, 55.4, 52.0, 31.4, 30.3, 26.0, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ 367.2016, found 367.2020.

(4-Chlorophenyl)(5-hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)methanone (3o): Orange soild; mp 72-73 ºC; IR (neat, ν): 3403, 3051, 2957, 2930, 2861, 1631, 1594, 1441, 1349, 1286,

1167, 1062, 1014, 911, 832, 753, 696, 658 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 (dd, J_1 = 14.3 Hz, J_2 = 8.3 Hz, 4H), 7.29 (t, *J* = 7.3 Hz, 1H), 5.39 (s, 1H), 3.28 (d, *J* = 18.5 Hz, 1H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.37 (t, *J* = 7.8 Hz, 2H), 1.63-1.53 (m, 2H), 1.37-1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.7, 159.1, 143.7, 137.7, 132.1, 131.7, 128.8, 128.1, 128.0, 123.9, 94.5, 52.1, 31.4, 30.3, 25.9, 22.3, 14.0; HRMS (ESI): *m/z* calcd. for $C_{21}H_{24}ClN_2O_2$ $[M+H]^+$ 371.1521, found 371.1508.

(5-Hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(thiophen-2-yl)methanone (**3p**)**:** Yellow soild; mp 69-70 °C; IR (neat, ν): 3417, 3063, 2952, 2927, 2859, 1604, 1511, 1445, 1369, 1331, 1291, 1174, 1067, 989, 863, 823, 724, 704 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J_1 = 3.8 Hz, J_2 = 1.3 Hz, 1H), 7.60 (dd, J_1 = 5.0 Hz, J_2 = 1.0 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.10 (dd, J_1 = 4.8 Hz, J_2 = 3.8 Hz, 1H), 5.26 (s, 1H), 3.32 (d, *J* = 18.5 Hz, 1H), 2.98 (d, *J* = 18.5 Hz, 1H), 2.44 (t, *J* = 8.0 Hz, 2H), 1.75-1.67 (m, 2H), 1.44-1.36 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 158.7, 143.7, 135.0, 134.9, 133.6, 128.8, 128.1, 126.8, 123.9, 94.4, 52.4, 31.4, 30.3, 25.7, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}N_2NaO_2S$ $[M+Na]^+$ 365.1294, found 365.1276.

1-(5-Hydroxy-3-pentyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one (**3q**)**:** Yellow oil; IR (neat, ν): 3422, 3031, 2928, 2862, 1651, 1416, 1320, 1255, 1164, 1072, 1042, 976, 914, 869, 763, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (m, 4H), 7.28 (dq, J_1 = 8.7 Hz, J_2 = 4.4 Hz, 1H), 5.11 (s, 1H), 3.26 (d, *J* = 19.0 Hz, 1H), 2.91 (d, *J* = 18.5 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 1.61-1.52 (m, 2H), 1.37-1.30 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 157.9, 144.0, 128.7, 128.0, 123.8, 93.2, 52.7, 31.4, 30.2, 26.0, 22.3, 22.2, 13.9; HRMS (ESI): *m/z* calcd. for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ 275.1754, found 275.1753.

General procedure for the synthesis of 3,5-disubstituted pyrazoles 4

β-Chlorovinyl ketones (**1**, 0.3 mmol, 1.0 equiv.), DABCO (0.6 mmol, 2.0 equiv., 67.3 mg), and hydrazine hydrate (0.6 mmol, 2.0 equiv., 30.0 mg) were added to a flame-dried vial with MeCN (3.0 mL). The vial was sealed with Teflon tape to stir at 25 °C until complete consumption of **1** as determined by thin layer chromatography. The reaction mixture was filtered through a plug of silica gel using EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by SiO_2-column chromatography (petroleum ether / EtOAc = 6/1-4/1) to afford 3,5-disubstituted pyrazoles **4**.

5-Pentyl-3-phenyl-1*H*-pyrazole (**4a**)**:** White soild; mp 74-75 °C; IR (neat, ν): 3232, 3062, 2953, 2921, 2857, 1570, 1455, 1264, 1229, 1137, 1070, 958, 763, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.72 (d, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.33 (s, 1H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.61 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.30-1.24 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 148.0, 132.8, 128.6, 127.7, 125.7, 100.9, 31.4, 29.0, 26.3, 22.4, 14.0;

HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1543, found 215.1548.

3-(2,4-Dichlorophenyl)-5-pentyl-1*H*-pyrazole (**4b**)**:** Yellow sticky solid; IR (neat, ν): 3190, 3105, 2926, 2859, 1588, 1552, 1444, 1373, 1252, 1198, 1152, 1101, 1035, 963, 805, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.44 (s, 1H), 7.21 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 6.48 (s, 1H), 2.57 (t, *J* = 7.8 Hz, 2H), 1.97 (dt, J_1 = 14.5 Hz, J_2 = 7.5 Hz, 2H), 1.35-1.27 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 146.5, 134.0, 132.8, 131.2, 130.4, 130.0, 127.1, 104.7, 31.5, 28.9, 26.2, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}Cl_2N_2[M+H]^+$ 283.0763, found 283.0753.

3-(3,5-Dimethylphenyl)-5-pentyl-1*H*-pyrazole (**4c**)**:** Yellow soild; mp 44-45 ºC; IR (neat, ν): ν 3169, 3086, 2923, 2852, 1603, 1577, 1463, 1339, 1256, 1152, 1016, 853, 778, 686 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.33 (s, 2H), 6.92 (s, 1H), 6.32 (s, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 6H), 1.67-1.60 (m, 2H), 1.33-1.28 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 148.3, 138.1, 132.4, 129.4, 123.6, 101.0, 31.5, 29.0, 26.5, 22.4, 21.3, 14.0; HRMS (ESI): *m/z* calcd. for $C_{16}H_{23}N_2$ $[M+H]^+$ 243.1856, found 243.1842.

3-(4-Methoxyphenyl)-5-pentyl-1*H*-pyrazole (**4d**)**:** White soild; mp 74-75 ºC; IR (neat, ν): 3238, 3028, 2950, 2923, 2859, 1611, 1574, 1519, 1439, 1243, 1175, 1106, 1023, 959, 828, 789, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.25 (s, 1H), 3.79 (s, 3H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.60 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.30-1.23 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 149.5, 148.2, 127.0, 125.5, 114.0, 100.4, 55.3, 31.5, 29.0, 26.4, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1648, found 245.1652.

3-(Naphthalen-2-yl)-5-pentyl-1*H*-pyrazole (**4e**)**:** White soild; mp 85-86 ºC; IR (neat, ν): 3238, 3047, 2954, 2920, 2858, 1567, 1427, 1347, 1269, 1133, 1038, 974, 896, 796, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.16 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.73 (m, 3H), 7.39 (dd, J_1 = 6.3 Hz, J_2 = 3.3 Hz, 2H), 6.44 (s, 1H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.57 (dt, J_1 = 15.0 Hz, J_2 = 7.6 Hz, 2H), 1.22-1.13 (m, 4H), 0.78 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 148.0, 133.6, 133.0, 130.3, 128.3, 128.2, 127.7, 126.2, 125.8, 124.4, 124.2, 101.2, 31.5, 29.0, 26.4, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{18}H_{21}N_2$ $[M+H]^+$ 265.1699, found 265.1702.

5-Pentyl-3-(thiophen-2-yl)-1*H*-pyrazole (**4f**)**:** Pale yellow soild; mp 69-70 ºC; IR (neat, ν): 3234, 3083, 2954, 2921, 2853, 1571, 1459, 1420, 1269, 1219, 1136, 1018, 922, 838, 788, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.58 (s, 1H), 7.25 (dd, J_1 = 3.5 Hz, J_2 = 1.0 Hz, 1H), 7.15 (dd, J_1 = 5.3 Hz, J_2 = 1.3 Hz, 1H), 6.97 (dd, J_1 = 5.0 Hz, J_2 = 3.5 Hz, 1H), 6.19 (s, 1H), 2.49 (t, *J* = 8.0 Hz, 2H), 1.54 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.26-1.16 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 145.8, 136.7, 127.4, 124.1, 123.6, 100.7, 31.4, 28.8, 25.9, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{12}H_{17}N_2S$ $[M+H]^+$ 221.1107, found 221.1102.

3-Ethyl-5-pentyl-1*H*-pyrazole (**4g**)**:** Colorless oil; IR (neat, ν): 3190, 3132, 3099, 3026, 2927, 2862, 1578, 1461, 1345, 1149, 1006, 961, 801 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 5.86 (s, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.63 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.36-1.30 (m, 4H), 1.24 (t, *J* = 7.8 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 149.1, 101.4, 31.6, 29.1, 27.0, 22.4, 20.3, 14.0, 13.6; HRMS (ESI): *m/z* calcd. for $C_{10}H_{19}N_2$ $[M+H]^+$ 167.1543, found 167.1514.

5-Hexyl-3-phenyl-1*H*-pyrazole (**4h**)**:** White soild; mp 70-71 ºC; IR (neat, ν): 3240, 3042, 2921, 2856, 1572, 1455, 1368, 1320, 1264, 1137, 1069, 1022, 958, 760, 684 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.63 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.34-1.30 (m, 2H), 1.29-1.23 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 148.0, 132.6, 128.7, 127.8, 125.7, 101.0, 31.6, 29.2, 29.0, 26.4, 22.6, 14.1; HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}N_2$ $[M+H]^+$ 229.1699, found 229.1702.

5-Cyclohexyl-3-phenyl-1*H*-pyrazole (**4i**)**:** White soild; mp 69-70 ºC; IR (neat, ν): 3168, 3068, 2924, 2850, 1575, 1455, 1360, 1266, 1156, 1075, 1031, 857, 755, 686 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.33 (s, 1H), 2.59 (tt, J_1 = 11.6 Hz, J_2 = 3.5 Hz, 1H), 1.96 (dd, J_1 = 13.1 Hz, J_2 = 1.8 Hz, 2H), 1.77-1.71 (m, 2H), 1.69-1.63 (m, 1H), 1.40 (ddd, J_1 = 24.5 Hz, J_2 = 12.3 Hz, J_3 = 2.7 Hz, 2H), 1.30-1.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 149.9, 132.9, 128.6, 127.7, 125.7, 99.2, 35.8, 32.9, 26.1, 25.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1543, found 227.1526.

5-(4-Chlorobutyl)-3-phenyl-1*H*-pyrazole (**4j**)**:** Pale yellow soild; mp 69-70 ºC; IR (neat, ν): 3230, 2922, 2855, 1642, 1568, 1435, 1304, 1261, 1108, 1072, 1014, 958, 799, 764, 686, 636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 3.55-3.46 (m, 2H), 2.73-2.60 (m, 2H), 1.86-1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 147.9, 131.9, 128.8, 128.1, 125.8, 101.3, 44.6, 31.9, 26.4, 25.8; HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}ClN_2$ $[M+H]^+$ 235.0997, found 235.0994.

Methyl 4-(3-phenyl-1*H*-pyrazol-5-yl)butanoate (**4k**)**:** Pale yellow oil; IR (neat, ν): 3320, 3193, 3099, 3011, 2949, 2864, 1728, 1574, 1440, 1363, 1201, 1148, 1071, 1020, 963, 808, 766, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.36 (s, 1H), 3.65 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.98 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 149.4, 147.3, 132.3, 128.7, 127.9, 125.7, 101.3, 51.6, 33.2, 25.8, 24.5; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1285, found 245.1281.

Preparation of 1-acyl-pyrazole 7 and 3-pentyl-5-phenyl-1*H*-pyrazole 8

To a solution of 1-acyl-5-hydroxypyrazoline **3a** (0.3 mmol, 1.0 equiv., 100.8 mg) in dry THF (3.0 mL) was added $BF_3{\cdot}Et_2O$ (20 mol%) and then stirred at 40 ºC for 5.5 h. THF was removed under reduced

pressure and the residue was purified by SiO_2-column chromatography (petroleum ether / EtOAc =10/1) to afford the corresponding 1-acyl-pyrazole **7**.

(3-Pentyl-5-phenyl-1*H*-pyrazol-1-yl)(phenyl)methanone (7): Yellow solid; mp 94-95 °C; IR (neat, ν): 3061, 2926, 2859, 1705, 1568, 1497, 1449, 1332, 1175, 1075, 998, 902, 819, 759, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.43-7.40 (m, 2H), 7.39-7.34 (m, 3H), 6.37 (s, 1H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.70 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.40-1.34 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 156.6, 147.9, 133.1, 132.7, 131.8, 131.1, 128.6, 128.4, 128.2, 128.1, 111.0, 31.6, 28.7, 28.3, 22.5, 14.1; HRMS (ESI): *m/z* calcd. for $C_{21}H_{23}N_2O$ $[M+H]^+$ 319.1805, found 319.1793.

To a solution of 1-acyl-5-hydroxypyrazoline **3a** (0.3 mmol, 1.0 equiv., 100.8 mg) in dry THF (3.0 mL) was added $BF_3 \cdot Et_2O$ (40 mol%) and then stirred at 25 °C for 48 h. THF was removed under reduced pressure and the residue was purified by SiO_2-column chromatography (petroleum ether / EtOAc = 6/1) to afford the corresponding 3,5-disubstituted pyrazole **8**. The characterization data of 3-Pentyl-5-phenyl-1*H*-pyrazole **8** was identical to the reported compound in patent.[21]

3-Pentyl-5-phenyl-1*H*-pyrazole (8): pale yellow solid; mp 76-77 °C; IR (neat, ν): 3233, 3065, 2953, 2922, 2857, 1682, 1573, 1454, 1289, 1182, 1133, 1069, 1027, 954, 762, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.37 (s, 1H), 2.64 (t, *J* = 7.8 Hz, 2H), 1.67 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.36-1.30 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 147.8, 132.9, 128.7, 128.0, 125.7, 101.2, 31.4, 28.9, 26.4, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1543, found 215.1542.

AUTHOR CONTRIBUTIONS

†H. Wu and R. Hou contributed equally.

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