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Highly regioselective and practical synthesis of 1-acyl-5-hydroxypyrazolines and 1-acyl pyrazoles from 1,2-allenic ketones and hydrazides

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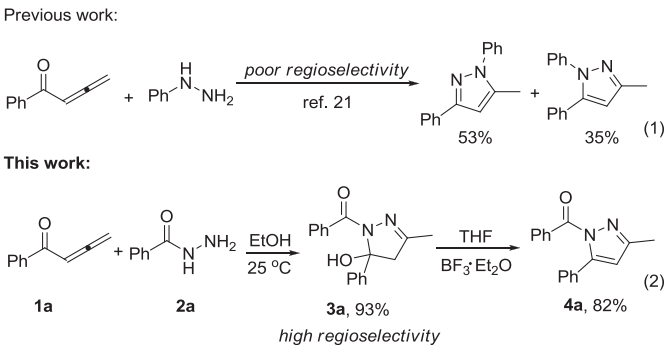
ABSTRACT

A mild and highly regioselective synthesis of 1-acyl-5-hydroxypyrazolines has been achieved through the condensation of 1,2-allenic ketones with hydrazides in the absence of any catalyst. Moreover, the obtained 1-acyl-5-hydroxypyrazolines can be easily transformed into 1-acyl pyrazoles under the promotion of $BF_3 \cdot Et_2O$. It was also found that 1-acyl pyrazoles can be produced directly from allenic ketones and hydrazides through a one-pot procedure.

1. Introduction

Pyrazoline and pyrazole derivatives have been extensively studied for decades since many of them are versatile synthetic blocks, frequent structural skeleton of natural products, or potential drug molecules.[1] In particular, 5-hydroxypyrazolines have been reported to possess anti-inflammatory,[2] antimicrobial,[3] antimalarial,[4] anti-PDE_3,[5] analgesic,[6] and hypolipidemic[7] activities. So far, the most frequently used methods for the construction of 5-hydroxypyrazolines involve the cyclocondensation of hydrazides with β-diketones,[3a,8] α,β-acetylenic ketones,[9] chalcone dibromides,[3b,7] or 3-alkoxy-2-en-1-ones.[2a,4,10] While these synthetic methods are generally effective, they still suffer from low yields, poor regioselectivity, harsh reaction conditions, or difficult-to-obtain starting materials. On the other hand, 1-acyl pyrazoles exhibit potent antifungal,[11] anti-inflammatory,[12] antimicrobial,[13] and anticonvulsant[14] activities, and appear promising as potential cytotoxic,[15] and antitumor[16] agents, and inhibitors of human neutrophil elastase.[17] Typical synthetic methods for 1-acyl pyrazoles mostly involve the acylation of 1*H*-pyrazoles[18] and the condensation of hydrazides with 1,3-diketones[19a] or α,β-unsaturated ketones.[19b,c] However, these known methods have several disadvantages, such as high reaction temperature, poor regioselectivity, use of expensive reagents, and/or catalysts, and limited substrate scope. Therefore, the development of a more practical, efficient, and regioselective access to 5-hydroxypyrazolines and 1-acyl pyrazoles remains an attractive task for organic chemists.

1,2-Allenic ketones, which are versatile synthetic intermediates, can be widely used for many organic transformations.[20] Recently, we have reported an efficient synthetic route to 3,5-disubstituted pyrazoles through the cyclocondensation of 1,2-allenic ketones with hydrazine hydrate.[21] When phenyl substituted hydrazine was used, the cyclocondensation reaction showed poor regioselectivity (Scheme 1, eq. 1), which was plausibly attributed to the inherent similar nucleophilicity of the two nitrogen atoms in phenyl hydrazine. Based on the above results, we envisioned that if one of the nitrogen atoms in hydrazine was attached with a strong electron-withdrawing



Scheme 1.

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substituent, such as a benzoyl group, the nucleophilicity of this nitrogen atom should be reduced more substantially than the another one. As a result, the regioselectivity of the condensation between substituted hydrazines and allenic ketones may be improved accordingly.

To check the feasibility of this tentative idea, allenic ketone **1a** was treated with benzohydrazide **2a** in ethanol in the absence of any catalyst. We were pleased to find that the cyclocondensation reaction of **1a** and **2a** proceeded smoothly and in a highly regioselective manner to afford pyrazoline **3a** in high yield. Furthermore, upon treatment with $BF_3\cdot Et_2O$, **3a** could be smoothly transformed into pyrazole **4a** (Scheme 1, eq. 2). In this paper, we would like to report the details of our research work in this aspect.

2. Results and discussion

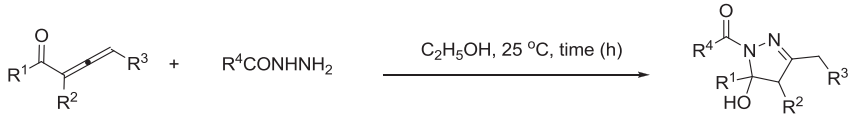
Initially, we chose 1,2-allenic ketone **1a** and benzohydrazide **2a** as model substrates. After the mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol) in ethanol[21] being stirred at 25 °C for 1 h, 5-hydroxypyrazoline **3a** was obtained exclusively in a yield of 93% (Scheme 1, eq. 2). Considering the easy nature and high efficiency of the above process, no further optimization of the reaction conditions was tried. Next, the scope of allenic ketones was examined by using benzohydrazide **2a** as nucleophile. When 1-aryl substituted allenic ketones with different substituents on the aromatic ring were employed as substrates, the desired pyrazolines **3a**–**3d**[22] were formed in 89–93% yields (Table 1,entries 1–4). 1-Benzyl substituted allenic ketone also reacted very well with **2a** to generate **3e** (Table 1, entry 5). In addition, the reaction of 1-alkyl-4-aryl or 1,4-diaryl substituted allenic ketones with **2a** proceeded smoothly to provide **3f**–**3i** in 61–83% yields (Table 1, entries 6–9). We also investigated the scope of hydrazides. With *p*-methylbenzohydrazide or *p*-chlorobenzo-hydrazide, **3j**–**3l** were obtained in 70–79% yields (Table 1, entries 10–12). In addition, acetohydrazide showed good reactivity and regioselectivity to give 1-acetyl-5-hydroxypyrazolines **3m**–**3o** in moderate to good yields (Table 1, entries 13–15). We noticed that 1-acetyl-5-hydroxypyrazolines have been previously synthesized through the reaction of acetohydrazide with alkynones.[9a] However, with that procedure, higher temperature, longer reaction period (6–24 h), and excess amounts of acetohydrazide were required. Moreover, to further expand the scope of allenic ketones, we also studied the cyclocondensation of 2-substituted allenic ketone with benzohydrazide. This cyclocondensation proceeded smoothly under the optimized conditions, to afford two diastereoisomers of pyrazoline **3p** with a ratio of 2:1 in 70% total yield (Table 1, entry 16).

With 1-acyl-5-hydroxypyrazolines **3** in hand, we were then interested in their dehydration to give the corresponding 1-acyl pyrazoles **4**. Literature searching revealed that although the dehydration of 1-acyl-5-hydroxypyrazolines has been extensively studied, mild and efficient methods without using strong acidic conditions and thus avoiding deacylation are still highly desirable.[9c,23,24] Recently, $BF_3\cdot Et_2O$ has emerged as a mild catalyst for the dehydration of secondary and/or tertiary alcohols.[25] This promoted us to try the dehydration of **3a** under the catalysis of $BF_3\cdot Et_2O$. When **3a** was treated with $BF_3\cdot Et_2O$ in THF at 25 °C for 12 h, the corresponding pyrazole **4a** was obtained in 82% yield (Table 2, entry 1). With CH_3CN or ethanol as the medium, the dehydration of **3a** also proceeded smoothly to provide **4a** in 72% or 71% yield (Table 2, entries 2–3). However, when it was run in DCM, the reaction was less efficient and some unknown by-products were generated (Table 2, entry 4).

Based on the above results, THF was used as the solvent for subsequent substrate scope studies. The representative examples are summarized in Table 3. It showed that 1-acyl-5-hydroxypyrazolines **3** with various substitution patterns underwent the dehydration process smoothly to give the corresponding pyrazoles **4** in good yields under the promotion of $BF_3\cdot Et_2O$ (Table 3, entries 1–9).

As a further aspect, it has been well demonstrated that the combination of two or more synthetic steps in one-pot not only saves time and energy, but also reduces the use of solvents in the isolation and purification of intermediates. Therefore, the feasibility of one-pot synthesis of 1-acyl pyrazoles **4** directly from allenic ketones **1** and hydrazides **2** was studied. For this purpose, **1a** and **2a** were used as model substrates and two operation methods were tried (Scheme 2). Encouragingly, our following studies showed that **4a** could be obtained in a yield of 75% directly from **1a** and **2a** by using Method A (Scheme 2). On the other hand, with Method B, two

Table 1
Synthesis of 1-acyl-5-hydroxypyrazolines **3**[a]

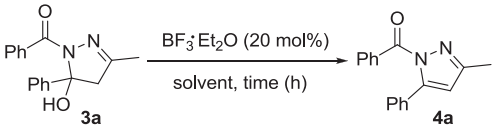


1 2 3

Entry	R^1	R^2	R^3	R^4	Time (h)	Product	Yield[b] (%)
1	C_6H_5	H	H	C_6H_5	1	**3a**	93
2	*o*-FC_6H_4	H	H	C_6H_5	1	**3b**	91
3	*o*-ClC_6H_4	H	H	C_6H_5	1	**3c**	90
4	*o*-BrC_6H_4	H	H	C_6H_5	1	**3d**	89[c]
5	$C_6H_5CH_2$	H	H	C_6H_5	1	**3e**	82
6	CH_3	H	C_6H_5	C_6H_5	1	**3f**	80
7	CH_3	H	*p*-FC_6H_4	C_6H_5	1	**3g**	83
8	CH_3	H	*p*-$CH_3OC_6H_4$	C_6H_5	1	**3h**	61
9	C_6H_5	H	C_6H_5	C_6H_5	1	**3i**	71
10	C_6H_5	H	H	*p*-$CH_3C_6H_4$	1	**3j**	79
11	C_6H_5	H	H	*p*-ClC_6H_4	1	**3k**	70
12	*o*-ClC_6H_4	H	H	*p*-ClC_6H_4	1	**3l**	78
13	C_6H_5	H	H	CH_3	1	**3m**	60
14	*o*-ClC_6H_4	H	H	CH_3	1	**3n**	83
15	*p*-ClC_6H_4	H	H	CH_3	1	**3o**	61
16	C_6H_5	CH_3	H	C_6H_5	10	**3p**	70[d]

[a] All reactions were carried out using 0.5 mmol of allenic ketone, 0.5 mmol of hydrazide in ethanol (5 mL) at 25 °C.
[b] Isolated yields.
[c] X-ray crystal structure of compound **3d** is available in Supplementary data.
[d] Total isolated yield of two diastereoisomers of pyrazoline **3p**.

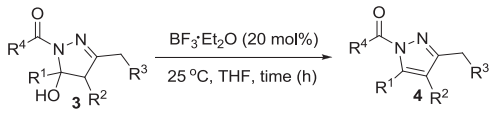
Table 2
Optimization studies for the dehydration of compound **3a**[a]

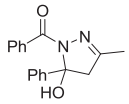
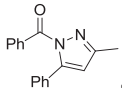
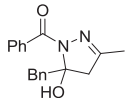
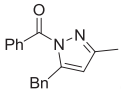
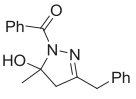
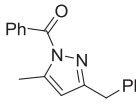
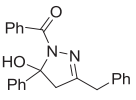
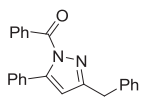
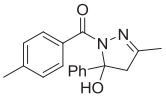
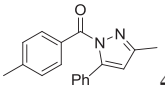
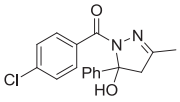
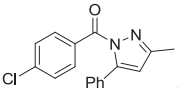
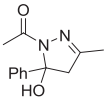
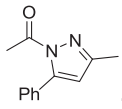
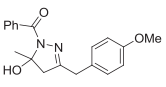
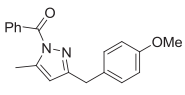
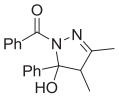
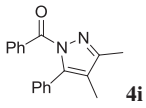


Entry	Solvent	Time (h)	Yield[b] (%)
1	**THF**	**12**	**82**
2	CH_3CN	1	72
3	EtOH	8	71
4	DCM	2	52

[a] All reactions were run at 25 °C on 0.5 mmol scale.
[b] Isolated yields.

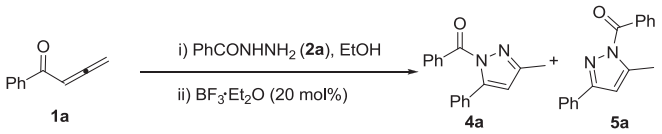
Table 3
Synthesis of pyrazoles **4** via the dehydration of pyrazolines **3**[a]



Entry	Substrate	Product	Time (h)	Yield[b] (%)
1		 **4a**	12	82
2		 **4b**	5	70
3		 **4c**	8	78
4		 **4d**	24	69
5		 **4e**	12	70
6		 **4f**	12	66
7		 **4g**	12	75
8		 **4h**	3	82
9		 **4i**	5	81

[a] All reactions were conducted in dry THF on 0.3–0.5 mmol scale using 20 mol % $BF_3 \cdot Et_2O$ as catalyst.
[b] Isolated yields.

regioisomers **4a** and **5a** were formed in 31% and 22% yields, respectively. The poor regioselectivity observed with Method B might result from the much enhanced electrophilicity and thus reduced selectivity of **1a** toward the two nitrogen atoms in **2a** by coordinating with $BF_3 \cdot Et_2O$.



Method A: **1a** and **2a** were stirred at 25 °C for 1 h in EtOH; And then $BF_3 \cdot Et_2O$ was added into the reaction mixture and the resulting mixture was stirred for another 8 h.	75%	*not observed*
Method B: **1a**, **2a** and $BF_3 \cdot Et_2O$ were mixed in EtOH and then stirred at 25 °C for 8 h.	31%	22%

Scheme 2. Optimization studies for one-pot synthesis of **4a**.

The generality of this one-pot synthesis of 1-acyl pyrazoles was then investigated. A variety of allenic ketones and hydrazides were found to be well compatible with the one-pot procedure to provide the corresponding pyrazoles **4** in moderate to good yields (Table 4, entries 1–11). It was also found that the dehydration rate of intermediates **3** strongly depended on the electronic effect of R^1. When R^1 is an electron-donating substituent, much shorter reaction period is required to complete the dehydration process (Table 4, entries 9 vs 10–11). This observation might be explained by the stabilization effect of the electron-donating group on the proposed cationic intermediate involved in the dehydration process.

3. Conclusion

In summary, we have developed a highly regioselective protocol for the synthesis of 1-acyl-5-hydroxypyrazolines and 1-acyl pyrazoles. Catalyst-free cyclocondensation of allenic ketones with hydrazides affords 1-acyl-5-hydroxypyrazolines in good to excellent yields with high regioselectivity under extremely mild reaction conditions. The thus formed 1-acyl-5-hydroxypyrazolines can be further converted into 1-acyl pyrazoles via $BF_3 \cdot Et_2O$-catalyzed dehydration. In addition, 1-acyl pyrazoles can also be obtained directly from allenic ketones and hydrazides through a one-pot procedure. Compared with literature methods, advantages of the present protocol include high regioselectivity, good yields, mild reaction conditions, and simple operation process.

4. Experimental section

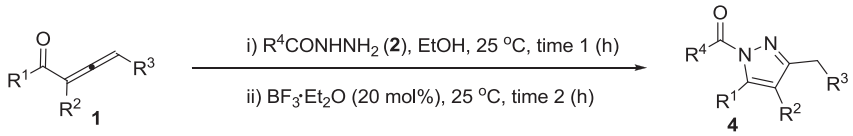
4.1. General

THF was distilled from sodium/benzophenone. DCM and CH_3CN were distilled from CaH_2. Unless noted, all commercial reagents were used without further purification. 1,2-Allenic ketones were prepared from commercially available reagents according to literature procedures.[26] ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm).

4.2. General procedure for the preparation of 1-acyl-5-hydroxypyrazolines 3 from 1,2-allenic ketones 1 and hydrazides 2

To a solution of 1,2-allenic ketone **1** (0.5 mmol) in EtOH (5 mL) was added hydrazide **2** (0.5 mmol) and then stirred at 25 °C until

Table 4
One-pot synthesis of pyrazoles **4** starting from allenic ketones **1** and hydrazides **2**[a]



Entry	R^1	R^2	R^3	R^4	Time 1 (h)	Time 2 (h)	Product	Yield[b] (%)
1	C_6H_5	H	H	C_6H_5	1	8	**4a**	75
2	$C_6H_5CH_2$	H	H	C_6H_5	1	3	**4b**	64
3	CH_3	H	C_6H_5	C_6H_5	1	2	**4c**	81
4	C_6H_5	H	H	*p*-$CH_3C_6H_4$	1	12	**4e**	60
5	C_6H_5	H	H	*p*-ClC_6H_4	1	12	**4f**	60
6	C_6H_5	H	H	CH_3	1	12	**4g**	50
7	CH_3	H	*p*-$CH_3OC_6H_4$	C_6H_5	1	3	**4h**	47
8	C_6H_5	CH_3	H	C_6H_5	10	5	**4i**	52
9	*p*-NCC_6H_4	H	H	C_6H_5	1	24	**4j**	53
10	*p*-$CH_3OC_6H_4$	H	H	C_6H_5	1	3	**4k**	75
11	3,4-$(CH_3O)_2C_6H_3$	H	H	C_6H_5	1	4	**4l**	66

[a] Allenic ketones **1** (0.5 mmol) and hydrazide **2** (0.5 mmol) were stirred at 25 °C for the time 1 in EtOH, and then $BF_3{\cdot}Et_2O$ (0.1 mmol) was added into the reaction mixture and the resulting mixture was stirred for the time 2.
[b] Isolated yields.

allenic ketone **1** was consumed completely. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica-gel to afford the corresponding 1-acyl-5-hydroxypyrazoline **3**.

*4.2.1. Pyrazoline **3a**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=8:1–5:1) afforded **3a** as yellow solid in 93% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (s, 3H), 2.90 (d, *J*=18.4 Hz, 1H), 3.20 (d, *J*=18.4 Hz, 1H), 5.38 (s, 1H), 7.18–7.22 (m, 1H), 7.28–7.34 (m, 4H), 7.38–7.41 (m, 3H), 7.85 (d, *J*=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 53.6, 94.5, 123.9, 127.7, 127.9, 128.6, 129.9, 131.5, 133.7, 143.6, 154.9, 168.1. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$: 281.1290, found: 281.1288.

*4.2.2. Pyrazoline **3b**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=8:1–5:1) afforded **3b** as yellow solid in 91% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 3.20 (d, *J*=18.8 Hz, 1H), 3.26 (d, *J*=18.8 Hz, 1H), 5.73 (s, 1H), 7.02–7.07 (m, 1H), 7.18–7.21 (m, 1H), 7.28–7.33 (m, 1H), 7.39–7.49 (m, 3H), 7.76–7.80 (m, 1H), 7.90 (d, *J*=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 52.3, 91.3, 116.1 (d, *J*=22.1 Hz, 1C), 123.9 (d, *J*=3.8 Hz, 1C), 127.5 (d, *J*=2.3 Hz, 1C), 127.7, 130.0, 130.1, 130.2, 131.6, 133.6, 155.1, 159.4 (d, *J*=245.4 Hz, 1C), 168.3. HRMS (ESI) calcd for $C_{17}H_{16}FN_2O_2$ $[M+H]^+$: 299.1196, found: 299.1192.

*4.2.3. Pyrazoline **3c**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–4:1) afforded **3c** as white solid in 90% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3H), 3.14 (d, *J*=19.2 Hz, 1H), 3.33 (d, *J*=18.4 Hz, 1H), 5.58 (s, 1H), 7.26 (t, *J*=7.2 Hz, 1H), 7.33–7.43 (m, 4H), 7.48 (t, *J*=7.2 Hz, 1H), 7.91 (d, *J*=7.2 Hz, 2H), 7.96 (d, *J*=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 51.4, 92.4, 126.8, 127.7, 128.1, 129.5, 130.3, 131.06, 131.09, 131.6, 133.5, 139.4, 155.3, 168.2. HRMS (ESI) calcd for $C_{17}H_{16}ClN_2O_2$ $[M+H]^+$: 315.0900, found: 315.0902.

*4.2.4. Pyrazoline **3d**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–4:1) afforded **3d** as white solid in 89% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14 (s, 3H), 3.12 (d, *J*=18.0 Hz, 1H), 3.36 (d, *J*=18.4 Hz, 1H), 5.60 (s, 1H), 7.15–7.19 (m. 1H), 7.37–7.44 (m, 3H), 7.49 (t, *J*=7.2 Hz, 1H), 7.60 (d, *J*=8.4 Hz, 1H), 7.95–7.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 51.4, 93.1, 120.0, 127.4, 127.7, 128.4, 129.7, 130.4, 131.7, 133.4, 134.7, 140.6, 155.5, 168.3. HRMS (ESI) calcd for $C_{17}H_{16}BrN_2O_2$ $[M+H]^+$: 359.0395, found: 359.0393.

*4.2.5. Pyrazoline **3e**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–4:1) afforded **3e** as colorless oil in 82% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (s, 3H), 2.88 (d, *J*=18.0 Hz, 1H), 3.03 (d, *J*=18.4 Hz, 1H), 3.42 (d, *J*=14.0 Hz, 1H), 3.81 (d, *J*=14.0 Hz, 1H), 5.58 (s, 1H), 7.28–7.33 (m, 5H), 7.41–7.51 (m, 3H), 7.85 (d, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 44.1, 47.7, 95.2, 127.1, 127.8, 128.5, 129.8, 130.2, 131.3, 134.4, 135.8, 155.7, 169.1. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1441.

*4.2.6. Pyrazoline **3f**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=5:1–4:1) afforded **3f** as colorless oil in 80% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (s, 3H), 2.72 (d, *J*=18.4 Hz, 1H), 2.97 (d, *J*=18.0 Hz, 1H), 3.65 (d, *J*=15.2 Hz, 1H), 3.71 (d, *J*=14.8 Hz, 1H), 5.03 (brs, 1H), 7.22–7.36 (m, 5H), 7.42–7.52 (m, 3H), 7.92 (d, *J*=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 37.0, 48.7, 92.9, 127.2, 127.7, 128.86, 128.91, 130.0, 131.3, 134.3, 135.7, 157.4, 168.7. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1446.

*4.2.7. Pyrazoline **3g**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=4:1–3:1) afforded **3g** as colorless oil in 83% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (s, 3H), 2.70 (d, *J*=19.2 Hz, 1H), 2.95 (d, *J*=18.4 Hz, 1H), 3.58–3.66 (m, 2H), 5.18 (brs, 1H), 7.01 (t, *J*=8.0 Hz, 2H), 7.15–7.19 (m, 2H), 7.39–7.49 (m, 3H), 7.90 (d, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 36.1, 48.7, 92.9, 115.7 (d, *J*=21.4 Hz, 2C), 127.7, 130.0, 130.4 (d, *J*=8.4 Hz, 2C), 131.3, 131.4 (d, *J*=3.0 Hz, 1C), 134.2, 157.1, 162.0 (d, *J*=243.9 Hz, 1C), 168.7. HRMS (ESI) calcd for $C_{18}H_{18}FN_2O_2$ $[M+H]^+$: 313.1352, found: 313.1355.

*4.2.8. Pyrazoline **3h**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=5:1–4:1) afforded **3h** as colorless oil in 61% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 3H), 2.70 (d, *J*=18.4 Hz, 1H), 2.95 (d, *J*=18.4 Hz, 1H), 3.58 (d, *J*=14.8 Hz, 1H), 3.64 (d, *J*=15.2 Hz, 1H), 3.79 (s, 3H), 6.85–6.89 (m, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 7.41–7.51 (m, 3H), 7.90–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 36.1, 48.6, 55.3, 92.9, 114.3, 127.6, 127.7,

129.8, 130.0, 131.3, 134.2, 157.8, 158.7, 168.7. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$: 325.1552, found: 325.1551.

*4.2.9. Pyrazoline **3i**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–4:1) afforded **3i** as yellow oil in 71% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.92 (d, J=18.0 Hz, 1H), 3.24 (d, J=18.8 Hz, 1H), 3.77 (s, 2H), 5.48 (s, 1H), 7.26–7.40 (m, 8H), 7.47–7.57 (m, 5H), 8.05 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.9, 51.4, 94.7, 124.0, 127.2, 127.9, 128.0, 128.7, 128.8, 129.0, 130.2, 131.7, 133.7, 135.5, 143.6, 157.2, 168.3. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$: 357.1603, found: 357.1603.

*4.2.10. Pyrazoline **3j**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–5:1) afforded **3j** as yellow solid in 79% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.41 (s, 3H), 2.99 (d, J=18.4 Hz, 1H), 3.30 (d, J=18.4 Hz, 1H), 5.56 (s, 1H), 7.25 (d, J=7.2 Hz, 2H), 7.31–7.32 (m, 1H), 7.38 (t, J=7.2 Hz, 2H), 7.52 (d, J=7.2 Hz, 2H), 7.90 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 21.6, 53.6, 94.5, 124.1, 128.0, 128.5, 128.7, 130.2, 130.9, 142.1, 143.9, 154.9, 168.2. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1443.

*4.2.11. Pyrazoline **3k**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–5:1) afforded **3k** as yellow solid in 70% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 3.00 (d, J=19.2 Hz, 1H), 3.30 (d, J=18.0 Hz, 1H), 5.40 (s, 1H), 7.31–7.41 (m, 5H), 7.47 (d, J=7.2 Hz, 2H), 7.92 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 53.6, 94.6, 123.9, 128.07, 128.12, 128.7, 131.6, 132.0, 137.7, 143.5, 155.5, 166.9. HRMS (ESI) calcd for $C_{17}H_{16}ClN_2O_2$ $[M+H]^+$: 315.0900, found: 315.0910.

*4.2.12. Pyrazoline **3l**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=6:1–5:1) afforded **3l** as yellow solid in 78% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3H), 3.13 (d, J=18.4 Hz, 1H), 3.32 (d, J=18.4 Hz, 1H), 5.55 (brs, 1H), 7.24–7.38 (m, 5H), 7.86 (d, J=8.4 Hz, 2H), 7.94 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 51.4, 92.4, 126.8, 128.0, 128.1, 129.6, 131.0, 131.1, 131.77, 131.82, 137.8, 139.1, 155.7, 166.9. HRMS (ESI) calcd for $C_{17}H_{15}Cl_2N_2O_2$ $[M+H]^+$: 349.0511, found: 349.0509.

*4.2.13. Pyrazoline **3m**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=4:1–3:1) afforded **3m** as white solid in 60% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (s, 3H), 2.31 (s, 3H), 2.91 (d, J=19.2 Hz, 1H), 3.27 (d, J=18.0 Hz, 1H), 5.13 (s, 1H), 7.26–7.30 (m, 1H), 7.35–7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 22.2, 54.2, 93.4, 123.8, 128.0, 128.7, 143.8, 154.2, 170.3. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$: 219.1134, found: 219.1135.

*4.2.14. Pyrazoline **3n**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=5:1–4:1) afforded **3n** as white solid in 83% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3H), 2.26 (s, 3H), 3.11 (d, J=18.8 Hz, 1H), 3.17 (d, J=18.8 Hz, 1H), 5.15 (s, 1H), 7.21–7.30 (m, 2H), 7.34 (d, J=7.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 21.9, 52.1, 91.2, 126.7, 127.6, 129.3, 130.9, 131.0, 139.5, 154.6, 170.2. HRMS (ESI) calcd for $C_{12}H_{14}ClN_2O_2$ $[M+H]^+$: 253.0744, found: 253.0750.

*4.2.15. Pyrazoline **3o**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=5:1–4:1) afforded **3o** as white solid in 61% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (s, 3H), 2.30 (s, 3H), 2.87 (d, J=18.0 Hz, 1H), 3.25 (d, J=18.0 Hz, 1H), 5.15 (s, 1H), 7.26–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 22.2, 54.1, 92.9, 125.4, 128.8, 133.8, 142.4, 154.2, 170.4. HRMS (ESI) calcd for $C_{12}H_{14}ClN_2O_2$ $[M+H]^+$: 253.0744, found: 253.0741.

*4.2.16. Pyrazoline **3p**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=10:1–6:1) afforded two diastereoisomers of pyrazoline **3p** as colorless oil in 70% total yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72 (d, J=7.6 Hz, 1H), 1.30 (d, J=7.6 Hz, 2H), 2.03 (s, 3H), 3.02 (q, J=7.6 Hz, 0.66H), 3.34 (q, J=7.6 Hz, 0.33H), 5.33 (brs, 0.6H), 5.49 (brs, 0.3H), 7.30–7.33 (m, 1H), 7.37–7.54 (m, 7H), 7.97–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.9, 13.3, 14.2, 14.5, 54.8, 56.3, 94.3, 97.5, 123.9, 127.8, 127.9, 128.2, 128.5, 128.7, 130.0, 130.1, 131.5, 131.6, 133.8, 133.9, 139.9, 144.5, 159.1, 159.7, 168.1, 168.9. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1450.

4.3. General procedure for the preparation of 1-acyl pyrazoles 4 via the dehydration of pyrazolines 3

To a solution of 1-acyl-5-hydroxypyrazoline **3** (0.3–0.5 mmol) in dry THF (3–5 mL) was added $BF_3\cdot Et_2O$ (20 mol %) and then stirred at 25 °C for the time indicated in Table 3. THF was removed under reduced pressure and the residue was purified by chromatography on silica-gel to afford the corresponding 1-acyl pyrazole **4.**

*4.3.1. Pyrazole **4a**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4a** as white solid in 82% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 6.38 (s, 1H), 7.39–7.51 (m, 7H), 7.60 (t, J=8.0 Hz, 1H), 8.04 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 112.1, 128.1, 128.3, 128.4, 128.6, 130.9, 131.7, 132.7, 133.1, 148.1, 152.1, 167.4. HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1184, found: 263.1175.

*4.3.2. Pyrazole **4b**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4b** as colorless oil in 70% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3H), 4.42 (s, 2H), 5.85 (s, 1H), 7.23–7.35 (m, 5H), 7.45 (t, J=8.0 Hz, 2H), 7.55 (t, J=7.2 Hz, 1H), 7.98 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 34.4, 111.6, 126.7, 127.9, 128.6, 129.1, 131.4, 132.5, 133.3, 138.0, 148.8, 152.1, 168.4. HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341, found: 277.1336.

*4.3.3. Pyrazole **4c**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4c** as colorless oil in 78% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 4.00 (s, 2H), 6.04 (s, 1H), 7.26–7.38 (m, 5H), 7.52 (t, J=7.2 Hz, 2H), 7.60–7.63 (m, 1H), 8.09 (d, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 34.9, 110.4, 126.6, 127.9, 128.6, 128.9, 131.6, 132.6, 133.3, 138.7, 145.4, 155.2, 168.5. HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341, found: 277.1340.

*4.3.4. Pyrazole **4d**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4d** as colorless oil in 69% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (s, 2H), 6.33 (s, 1H), 7.28–7.29 (m, 1H), 7.35–7.44 (m, 9H), 7.53 (t, J=8.0 Hz, 2H), 7.65 (t, J=7.6 Hz, 1H), 8.12 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.9, 111.3, 126.7, 128.16, 128.24, 128.4, 128.7, 129.0, 130.8, 131.8, 132.5, 133.3, 138.6, 148.3, 155.3, 167.5. HRMS (ESI) calcd for $C_{23}H_{19}N_2O$ $[M+H]^+$: 339.1497, found: 339.1505.

*4.3.5. Pyrazole **4e**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4e** as colorless oil in 70% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 2.36 (s, 3H), 6.29 (s, 1H), 7.21 (d, J=8.4 Hz, 2H), 7.30–7.37 (m, 5H), 7.89 (d, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 21.8, 111.8, 128.2, 128.3, 128.5, 128.9, 129.8, 131.0, 131.9, 144.1, 148.0, 151.9, 167.4. HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341, found: 277.1345.

*4.3.6. Pyrazole **4f**.* Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4f** as colorless oil in 66% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 6.37 (s,

1H), 7.39–7.47 (m, 7H), 7.99–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 112.3, 128.2, 128.35, 128.40, 128.7, 130.7, 131.0, 133.1, 139.5, 148.1, 152.4, 166.3. HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O$ $[M+H]^+$: 297.0795, found: 297.0781.

4.3.7. Pyrazole ***4g***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4g** as colorless oil in 75% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.70 (s, 3H), 6.21 (s, 1H), 7.39 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 23.8, 112.9, 127.8, 128.6, 128.9, 131.3, 146.6, 152.0, 170.2. HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$: 201.1028, found: 201.1025.

4.3.8. Pyrazole ***4h***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4h** as colorless oil in 82% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.62 (s, 3H), 3.80 (s, 3H), 3.90 (s, 2H), 6.00 (s, 1H), 6.86–6.89 (m, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.47–7.51 (m, 2H), 7.57–7.61 (m, 1H), 8.04–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 33.9, 55.2, 110.2, 114.0, 127.9, 129.8, 130.8, 131.5, 132.5, 133.3, 145.3, 155.6, 158.3, 168.5. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 307.1447, found: 307.1445.

4.3.9. Pyrazole ***4i***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=20:1–15:1) afforded **4i** as colorless oil in 81% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 3H), 2.32 (s, 3H), 7.36–7.49 (m, 7H), 7.56–7.60 (m, 1H), 8.03 (d, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.2, 12.4, 119.2, 128.0, 128.21, 128.24, 129.1, 131.3, 131.5, 132.7, 133.1, 143.4, 152.5, 167.1. HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341, found: 277.1338.

4.4. General procedure for the one-pot synthesis of 1-acyl pyrazoles 4 from 1,2-allenic ketones 1 (Scheme 2, Method A)

To a solution of 1,2-allenic ketone **1** (0.5 mmol) in EtOH (5 mL) was added hydrazide **2** (0.5 mmol) and then stirred at 25 °C until allenic ketone **1** was consumed completely. Next, $BF_3\cdot Et_2O$ (0.1 mmol) was added into the resulting mixture and stirred at the same temperature for the time 2 indicated in Table 4. And then the solvent was removed under reduced pressure and the residue was purified by chromatography on silica-gel to afford the corresponding 1-acyl pyrazole **4**.

The characterization data of **4a**–**4c** and **4e**–**4i** obtained via the one-pot procedure is the same as the one obtained through the direct dehydration reaction of pyrazolines **3**.

4.4.1. Pyrazole ***4j***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=10:1–6:1) afforded **4j** as white solid in 53% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 6.44 (s, 1H), 7.46–7.54 (m, 4H), 7.60–7.68 (m, 3H), 8.03–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 112.1, 113.1, 118.6, 128.2, 129.1, 131.7, 132.0, 133.5, 135.5, 146.0, 152.5, 167.2. HRMS (ESI) calcd for $C_{18}H_{14}N_3O$ $[M+H]^+$: 288.1137, found: 288.1140.

4.4.2. Pyrazole ***4k***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **4k** as white solid in 75% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 3.79 (s, 3H), 6.30 (s, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.45 (t, J=7.2 Hz, 2H), 7.56 (t, J=7.2 Hz, 1H), 8.02 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 55.3, 111.6, 113.7, 123.2, 128.1, 129.7, 131.7, 132.8, 133.1, 147.9, 152.1, 159.9, 167.6. HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$: 293.1290, found: 293.1289.

4.4.3. Pyrazole ***4l***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=10:1–6:1) afforded **4l** as white solid in 66% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.33 (s, 1H), 6.85 (d, J=7.6 Hz, 1H), 6.94–6.98 (m, 2H), 7.45 (t, J=7.6 Hz, 2H), 7.56 (t, J=6.8 Hz, 1H), 8.01 (d, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 55.85, 55.91, 110.7, 111.6, 111.7, 121.2, 123.4, 128.1, 131.6, 132.7, 133.1, 147.9, 148.5, 149.4, 152.1, 167.5. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1396, found: 323.1405.

4.5. Preparation of pyrazoles 4a and 5a by using Method B (Scheme 2)

To a solution of 1,2-allenic ketone **1a** (0.5 mmol) in EtOH (5 mL) were added hydrazide **2a** (0.5 mmol) and $BF_3\cdot Et_2O$ (0.1 mmol) and then stirred at 25 °C for 8 h. When the reaction was completed, the solvent was removed under reduced pressure and the crude products were purified by chromatography on silica-gel to afford pyrazoles **4a** and **5a** in 31% and 22% yields, respectively.

The characterization data of **4a** obtained via this procedure is the same as the one obtained through the direct dehydration of pyrazolines **3a**.

4.5.1. Pyrazole ***5a***. Column chromatography on silica-gel (petroleum ether/ethyl acetate=15:1–10:1) afforded **5a** as colorless oil in 22% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (s, 3H), 6.60 (s, 1H), 7.37–7.43 (m, 3H), 7.50 (t, J=7.6 Hz, 2H), 7.61 (t, J=8.0 Hz, 1H), 7.82 (d, J=7.2 Hz, 2H), 8.12 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 108.0, 126.3, 127.8, 128.7, 129.0, 131.7, 132.0, 132.6, 133.1, 145.8, 153.4, 168.6. HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1184, found: 263.1188.

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Supplementary data

The X-ray crystal structure of **3d** and the copies of ^{1}H NMR and ^{13}C NMR spectra of **3a**–**3p**, **4a**–**4l**, and **5a**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.07.046.

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