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Formal [4+1] Annulation of α-Arylhydrazonoketones and Dimethylsulfoxonium Methylide: One-pot Synthesis of Substituted Pyrazoles and Dihydropyrazoles

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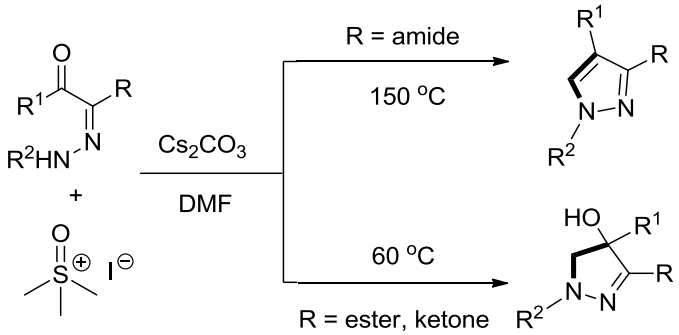
Abstract



A formal [4+1] annulation of readily available α-arylhydrazonoketones and trimethylsulfoxonium iodide in the presence of cesium carbonate is described involving a sequential Corey-Chaykovsky reaction and intramolecular nucleophilic cyclization process. Substituted pyrazoles were obtained

exclusively from the reactions of *α*-arylhydrazono-*β*-oxo-amides and trimethylsulfoxonium iodide in moderate to good yields, whereas the reactions of *α*-arylhydrazono-*β*-oxo-ketone/*α*-arylhydrazono-*β*-oxo-ester afforded the corresponding dihydropyrazoles in good yields.

Introduction

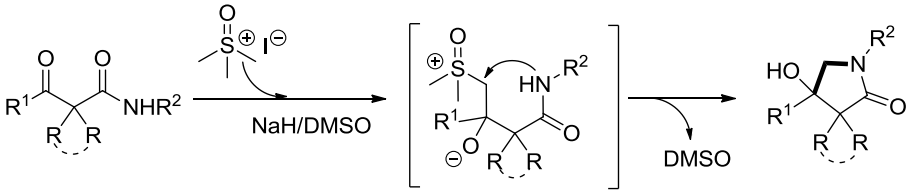
Over the past decades, pyrazole chemistry has attracted considerable interest of research for their broad range of properties. [1,2] Pyrazole is a key unit found in a number of natural products and other small molecules along with important bioactivities, such as cyclooxygenase-2 (Cox-2) inhibitors, HIV-1 reverse transcriptase inhibitors, and protein kinase inhibitors.[3] In addition, some functionalized pyrazoles have been used in supramolecular and polymer chemistry, in the food industry, as cosmetic colorings, UV stabilizers, and ligands for the transition metal-catalyzed reactions.[4-6] The conventional approaches have been well-established for the preparation of such aza-heterocycles, involving either the modification of the pre-constructed pyrazole ring by their cross-coupling reactions with electrophiles to create C-N and C-C bonds,[7-9] or the construction of the pyrazole skeleton from appropriately substituted acyclic precursors. The latter becomes more attractive for its general applicability to achieve more flexible substitution, which include the condensation of hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents,[10,11] cycloaddition of electron-rich diazo compounds,[12] nitrile imines[13] or sydnones with alkynes or alkenes,[14] metal-catalyzed intramolecular nitrogen addition to alkynes.[15] In our previous work, we developed efficient synthesis of pyrazoles,[16] pyrazolin-5-ones[17] and pyrazolin-5-one *N*-oxides[18] from enaminones and 1-carbamoyl-1-oximyl cyclopropanes, respectively.

On the other hand, dimethylsulfoxonium methylide (DSM), *i.e.* Corey–Chaykovsky reagent,[19] have been widely used as a methylene-transfer reagent in organic conversion to three-membered ring compounds, such as epoxides, aziridines and cyclopropanes.[20-23] Most recently, we investigated the reaction of *α*,*α*-dialkyl *β*-oxo amides and trimethylsulfoxonium iodide in the presence of NaH, and

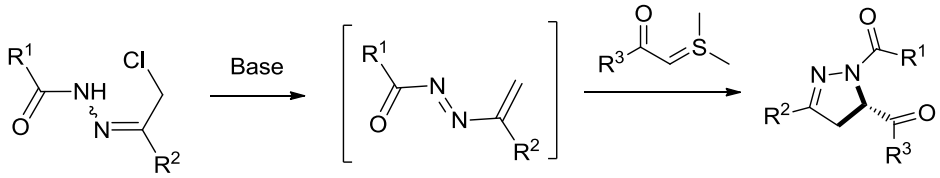
achieved efficient synthesis of γ-lactams *via* tandem Corey–Chaykovsky reaction and intramolecular lactamization (Scheme 1a),[24] and Chen and co-workers developed an unprecedented strategy to access dihydropyrazoles by a formal [4+1] cycloadditions of in-situ-derived azoalkenes and sulfur ylides (Scheme 1b).[25] Encouraged by these results and in continuation with our research interest in the synthesis of highly valuable heterocycles, we are interested to investigate the reaction of 3-oxo-2-arylhydrazonobutanamides with trimethylsulfoxonium iodide in the presence of Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF). As a result of these studies, we developed a facile one-pot synthesis of substituted pyrazoles and dihydropyrazoles from α-arylhydrazonoketones with varied substituted groups (Scheme 1c). Herein, we wish to report our experimental results and present a proposed mechanism involved in the formal [4+1] annulation reaction.

Scheme 1. [4+1] Annulation Reactions.

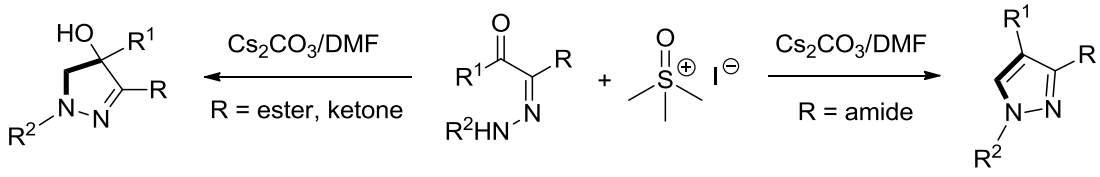
(a) Previous work: Formal [4+1] Annulation of β-Oxo Amides and Sulfur Ylide.



(b) Previous work: Formal [4+1] Cycloaddition of Azoalkenes and Sulfur Ylides.



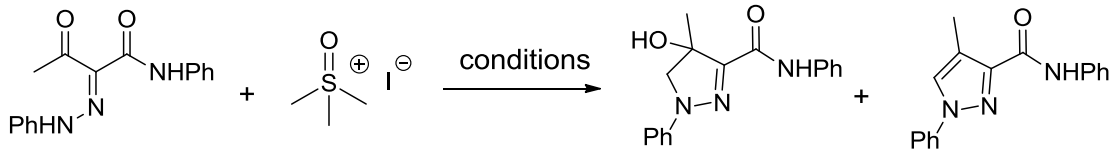
(c) This work: Formal [4+1] Annulation of α-Arylhydrazonoketones and Sulfur Ylide.



Results and Discussion

The substrates, *α*-arylhydrazonoketones **1**, were prepared from commercially available 1,3-dicarbonyl compounds and diazonium chloride salt in the presence of sodium acetate according to a reported procedure.[26] We then selected 3-oxo-*N*-phenyl-2-(2-phenylhydrazono)butanamide **1a** as a model compound to examine its reaction behavior. Thus, the reaction of **1a** and trimethylsulfoxonium iodide **2** (1.2 equiv.) in the presence of Cs_2CO_3 (1.5 equiv.) in DMF was first attempted at room temperature. As indicated by TLC results, the reaction yielded a yellow solid along with the recovery of some starting material after work-up and purification of the resulting mixture by column chromatography. The product was characterized as 4-hydroxy-4-methyl-*N*,1-diphenyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide **3a** on the basis of its spectral and analytical data (Table 1, entry 1). It was noted that when the load amount of Cs_2CO_3 was increased to 3.0 equivalents, there was still quite a lot of starting material remaining intact although the yield of **3a** was slightly increased (Table 1, entry 2). Very interestingly, when the reaction temperature was increased to 60 ℃, another product was obtained along with **3a**, which was characterized as 4-methyl-*N*, 1-diphenyl-1*H*-pyrazole-3-carboxamide **4a** (Table 1, entry 3). Obviously, 1*H*-pyrazole **4a** was derived from 4,5-dihydro-1*H*-pyrazole **3a** upon a dehydration process.

Table 1. Reaction of *α*-Arylhydrazono-*β*-oxo-amide 1a and Trimethylsulfoxonium Iodide 2 under Different Conditions.[a]



1a **2** **3a** **4a**

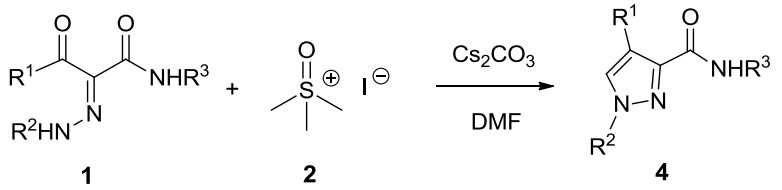
Entry	Base (equiv)	Solvent	Temp. (^oC)	Time (h)	Yield [b] (%)	
					3a	**4a**
1	Cs_2CO_3(1.5)	DMF	rt	26.0	28(64)	0

2	Cs_2CO_3(3.0)	DMF	rt	26.0	37(60)	0
3	Cs_2CO_3(3.0)	DMF	60	26.0	35(15)	30
4	Cs_2CO_3(3.0)	DMF	100	23.0	0	81
5	Cs_2CO_3(3.0)	DMF	130	12.5	0	84
6	**Cs_2CO_3(3.0)**	**DMF**	**150**	**5.0**	**0**	**87**
7	Cs_2CO_3(1.5)	DMF	150	7.0	0	82
8	NaH(3.0)	DMF	150	13.0	0	45
9	NaOH(3.0)	DMF	150	14.0	0	43
10	DBU(3.0)	DMF	150	8.0	0	80
11	Cs_2CO_3(3.0)	DMSO	150	5.0	0	83
12	Cs_2CO_3(3.0)	xylene	reflux	15.0	0	72
13	Cs_2CO_3(3.0)	DCE[c]	reflux	24.0	16	58

[a] Reagents and conditions: (1) **1a** (1.0 mmol), **2** (1.2 mmol), solvent (4.0 mL); entries 1-3 and 13: under air; entries 4-12: under N_2. [b] Isolated yield (data in parentheses for the recovery of **1a**). [c] DCE =1,2-Dichloroethane.

The optimization of the reaction conditions, including the reaction temperature, solvent and base, was then investigated as shown in Table 1. The experiments revealed that the reaction temperature had significant influence on the reaction. At 100 ℃ under nitrogen, the reaction could be completed and exclusively afforded pyrazole **4a** in 81% yield (Table 1, entry 4), and further increase of temperature could even reduce the reaction time to 5.0 h (Table 1, entries 5 and 6). Reducing the loading of Cs_2CO_3 would result in slightly low yield of **4a** (Table 1, entry 7). Other inorganic and organic bases, such as NaH, NaOH and DBU, were also examined, but either lower yield of **4a** was obtained or prolonged reaction time was required (Table 1, entry 8-10). It should be mentioned that the nature of the solvent played a crucial role during the cyclization process, and the further dehydration reaction was favoured to proceed at higher reaction temperature (entries 11-13).

Table 2. Synthesis of Pyrazoles 4 from *α*-Arylhydrazono-*β*-oxo-amides 1 and Trimethylsulfoxonium Iodide 2.[a]



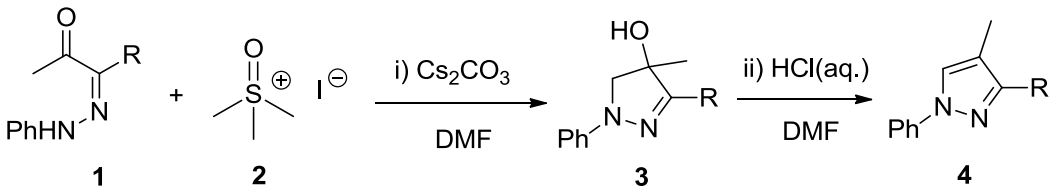
Entry	1	R^1	R^2	R^3	Time(h)	4	Yield(%)[b]
1	**1a**	Me	C_6H_5	C_6H_5	5.0	**4a**	87
2	**1b**	Me	2-$MeOC_6H_4$	C_6H_5	4.0	**4b**	78
3	**1c**	Me	3-MeC_6H_4	C_6H_5	6.0	**4c**	89
4	**1d**	Me	3-ClC_6H_4	C_6H_5	11.0	**4d**	81
5	**1e**	Me	4-ClC_6H_4	C_6H_5	5.0	**4e**	83
6	**1f**	Me	4-$MeOC_6H_4$	C_6H_5	5.0	**4f**	90
7	**1g**	Me	C_6H_5	2-MeC_6H_4	6.0	**4g**	84
8	**1h**	Me	C_6H_5	2-ClC_6H_4	5.0	**4h**	75
9	**1i**	Me	C_6H_5	3-MeC_6H_4	6.0	**4i**	80
10	**1j**	Me	C_6H_5	Me	10.0	**4j**	72
11	**1k**	Pr	C_6H_5	C_6H_5	3.0	**4k**	71
12	**1l**	CF_3	C_6H_5	C_6H_5	9.0	**4l**	64
13	**1m**	C_6H_5	C_6H_5	C_6H_5	6.0	**4m**	70

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.2 mmol), Cs_2CO_3 (3.0 mmol), DMF (4.0 mL), 150 ℃, N_2. [b] Isolated yields.

Under the optimal conditions as for **4a** in entry 6 (Table 1), a range of reactions of *α*-arylhydrazono-*β*-oxo-amides **1** and trimethylsulfoxonium iodide **2** were carried out, and some of the results are summarized in Table 2. It was found that the reactions of **1b–i** bearing varied aryl groups

R^2 and R^3 could proceed smoothly to afford the corresponding 1*H*-pyrazole **4b-i** in good to high yields (Table 2, entries 2–9). In the case of the reaction of **1j** bearing an alkyl group R^3 could undergo formal [4+1] annulation reaction to furnish the corresponding 1*H*-pyrazole **4j** in good yield (Table 2, entry 10). The versatility of this 1*H*-pyrazole synthesis was further evaluated by performing substrate **1k-1m** bearing varied alkyl and aryl group R^1 with **2** under the identical conditions (Table 2, entries 11-13). It should be noted that the structure of **4e** was further confirmed by X-ray single crystal analysis (See Supporting Information) and its spectral and analytical data. In contrast to our previous work,[24] the preferential formation of pyrazole ring in the present work over a γ-lactam ring implies that the cyclization occurs in a chemoselective manner.

Table 3. Expansion of the Scope of the Formal [4+1] Annulation. [a]



Entry	**1**	R	**3**	Yield(%)[b]	**4**	Yield(%)[c]
1	**1n**	COOEt	**3n**	84	**4n**	89
2	**1o**	COMe	**3o**	88	**4o**	93
3	**1p**	COPh	**3p**	80	**4p**	87

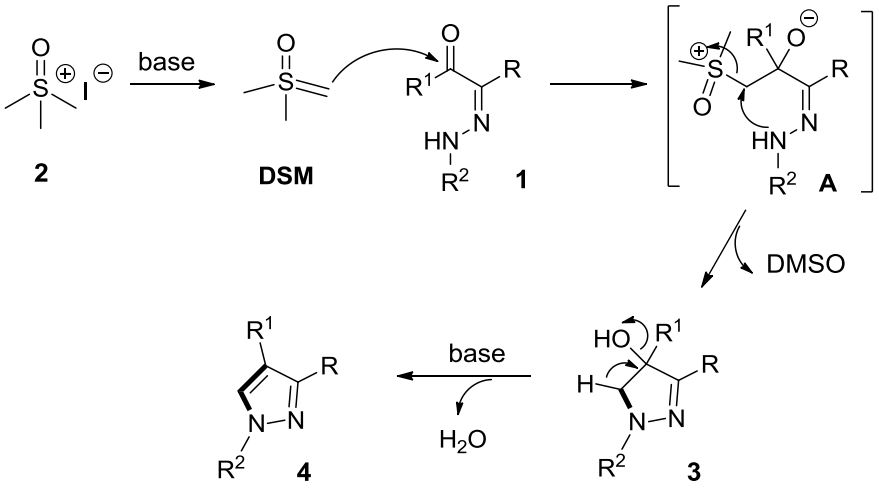
[a] Reagents and conditions: i) **1** (1.0 mmol), **2** (1.2 mmol), Cs_2CO_3 (3.0 mmol), DMF (4.0 mL), 60 ^oC, 1.0-2.0 h. ii) concentrated HCl (aq., 0.2 mL), DMF (4.0 mL), rt, 0.5 h. [b] Isolated yields for **3**; [c] Isolated yields for **4**.

To further expand the scope of the cyclization protocol, we investigated the reaction of α-arylhydrazono-β-oxo-ester **1n** in the same fashion (Table 3). As indicated by TLC results, the reaction of **1n** and sulfur ylide **2** could proceed smoothly at 60 ℃ to furnish a product, which was characterized as dihydropyrazole **3n**. However, further increasing of reaction temperature to 100 ℃,

for example, would lead to the formation of a complex mixture, which might be attributed to the decomposition of **3n**. Then, a separate experiment was performed by treatment of **3n** with concentrated aqueous HCl (2.4 equiv.) in DMF at room temperature. The reaction was completed within half an hour and furnished a product, which was characterized as ethyl 4-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate **4n**.[27] Similarly, dihydropyrazoles **3o** and **3p and** pyrazoles **4o and 4p** were synthesized in high yields, respectively (Table 3).[28] It should be mentioned that one-pot two-step synthesis of **4n-p** from **1n-p** was achieved by acidification of the reaction system after **1n-p** was completely converted into **3n-p**.

On the basis of the above experimental results together with some reported literature, a mechanism for the formal [4+1] annulation of readily available *α*-arylhydrazonoketones and trimethylsulfoxonium iodide was proposed as depicted in Scheme 2. In the presence of Cs_2CO_3, trimethylsulfoxonium iodide **2** is converted into sulfur ylide, *i.e.* Corey–Chaykovsky reagent DSM.[24] The attack of the *in-situ* generated sulfur ylide on the carbonyl group of **1** forms intermediate **A**, which is followed by an intramolecular chemoselective aza-cyclization to afford 4,5-dihydro-1*H*-pyrazole **3** with the elimination of DMSO,[19,24] and further to gives rise to 1*H*-pyrazole **4** through a dehydration process.

Scheme 2. Plausible Mechanism for the Formal [4+1] Annulation of *α*-Arylhydrazonoketones 1 and Trimethylsulfoxonium Iodide 2.



Conclusions

In summary, a facile and efficient synthesis of substituted pyrazoles and dihydropyrazoles from *α*-arylhydrazonoketones and trimethylsulfoxonium iodide in the presence of cesium carbonate is developed, which involves *via* a Corey–Chaykovsky reaction and intramolecular nucleophilic cyclization reaction sequence. The ready availability of substrates, simplicity of execution, and synthetic potential of the products make this novel protocol very attractive. Further work on the utilization and extension of the scope of the methodology is currently under investigation in our laboratory.

Experimental Section

General Experimental

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 ^{o}C at 300 MHz (400 MHz or 600 MHz) and 100 MHz (or 150 MHz), respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400-4000 cm^{-1}. High resolution mass spectra were recorded on a mass spectrometer. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. Melting points were uncorrected.

Synthesis and analytical data of compounds 3 and 4

Procedure A for the synthesis of 4,5-dihydro-1*H*-pyrazoles 3a: The Corey–Chaykovsky reagent was prepared by adding Cs_2CO_3 (3.0 mmol) in one portion into a solution of trimethylsulfoxonium iodide **2** (1.2 mmol) in DMF (4.0 mL) under stirring for 15 min at room temperature. To the above Corey–Chaykovsky reagent was added **1a** (1.0 mmol), which was stirred for 26.0 h at room temperature. After the reaction was completed, the resulting mixture was poured into saturated aqueous NaCl (100 mL), which was extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and

evaporated in vacuo. The crude product was purified by flash silica gel chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **3a** as a yellow solid (109 mg, 37%).

4-Hydroxy-4-methyl-N,1-diphenyl-4,5-dihydro-1H-pyrazole-3-carboxamide ***(3a).*** Yellow solid, m.p. 142-143 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 3.44 (s, 1H), 3.90 (d, J = 11.7 Hz, 1H), 4.09 (d, J = 11.7 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.12-7.19 (m, 3H), 7.33-7.40 (m, 4H), 7.62 (d, J = 8.1, 2H), 8.32 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 25.2, 62.0, 79.1, 112.7, 118.7, 120.7, 123.4, 128.1, 128.3, 136.3, 141.7, 143.5, 159.2; **IR** (KBr): ν = 3394, 3384, 3058, 2925, 1646, 1596, 1537, 1498 cm^{-1}; **HRMS** (ESI-TOF) calcd for M = $C_{17}H_{17}N_3O_2$ $[M+Na]^+$, 318.1213; found, 318.1218.

Ethyl 4-hydroxy-4-methyl-1-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylate ***(3l).*** Prepared according to the general procedure A using **1l** (1.0 mmol) as substrate. To the Corey–Chaykovsky reagent was added **1l,** which was stirred for 2.0 h at 60 ℃. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **3l** as a light yellow solid (208 mg, 84%). Light yellow solid, m.p. 154-156 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H), 1.75 (s, 3H), 2.99 (s, 1H), 3.87 (d, J = 12.0 Hz, 1H), 4.09 (d, J = 12.0 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 6.99 (t, J = 7.2 Hz, 1H), 7.17-7.21 (m, 2H), 7.29-7.35 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 13.3, 24.9, 60.1, 61.7, 78.8, 113.1, 121.0, 128.2, 140.7, 141.4, 161.7; **IR** (KBr): ν = 3471, 3005, 2982, 2932, 1682, 1523, 1504, 1494 cm^{-1}; **HRMS** (ESI-TOF) calcd for M = $C_{13}H_{16}N_2O_3$ $[M+Na]^+$, 271.1053; found, 271.1057.

1-(4-hydroxy-4-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)ethanone ***(3m).*** Prepared according to the general procedure A using **1m** (1.0 mmol) as substrate. To the Corey–Chaykovsky reagent was added **1m**, which was stirred for 1.5 h at 60 ℃. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **3m** as a yellow solid (192 mg, 88%). Yellow solid, m.p. 75-77 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.74 (s, 3H), 2.49 (s, 3H), 3.18 (s, 1H), 3.86 (d, J = 12.0 Hz, 1H), 4.08 (d, J = 12.0 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 7.18-7.22 (m, 2H), 7.32-7.38 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 24.8, 25.2, 62.3, 78.6, 113.2, 121.4, 128.3, 141.2,

148.2, 193.8; **IR** (KBr): ν = 3491, 2971, 1647, 1595, 1498 cm^{-1}; **HRMS** (ESI-TOF) calcd for M = $C_{12}H_{14}N_2O_2$ $[M+Na]^+$, 241.0947; found, 241.0952.

(4-hydroxy-4-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)(phenyl)methanone ***(3p).*** Prepared according to the general procedure A using **1p** (1.0 mmol) as substrate. To the Corey−Chaykovsky reagent was added **1p**, which was stirred for 2.0 h at 60 ℃. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **3p** as a yellow solid (224 mg, 80%). Yellow solid, m.p. 104-105 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 3.78 (s, 1H), 3.91 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 12.0 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.36 (t, J = 8.1 Hz, 2H), 7.50 (t, J = 7.2 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 8.21 (d, J = 7.5 Hz, 2H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 9.2, 118.3, 122.1, 126.1(2), 127.0, 128.5, 129.7, 131.4, 137.0, 138.7, 147.8, 188.3; **IR** (KBr): ν = 3483, 2932, 1600, 1504, 1353, 1288, 1177, 1149 cm^{-1}; **HRMS** (ESI-TOF) calcd for M = $C_{17}H_{16}N_2O_2$ $[M+Na]^+$, 303.1104; found, 303.1097.

Procedure B for the synthesis of 1*H*-pyrazoles 4a: The Corey−Chaykovsky reagent was prepared by adding Cs_2CO_3 (3.0 mmol) in one portion into a solution of trimethylsulfoxonium iodide **2** (1.2 mmol) in DMF (4.0 mL) under stirring for 15 min at room temperature. To the above Corey−Chaykovsky reagent was added **1a** (1.0 mmol), which was heated to reflux and stirred for 5.0 h under N_2. After the reaction was completed, the resulting mixture was poured into saturated aqueous NaCl (100 mL), which was extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by flash silica gel chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4a** as a white solid (240 mg, 87%).

4-Methyl-N,1-diphenyl-1H-pyrazole-3-carboxamide ***(4a).*** White solid, m.p. 157-159 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.47 (d, J = 0.6 Hz, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.33-7.39 (m, 3H), 7.47-7.53 (m, 2H), 7.70-7.73 (m, 4H), 7.76 (d, J = 0.6 Hz, 1H), 8.86 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.7, 118.3, 118.7, 120.4, 122.9, 126.2, 127.2, 128.0, 128.5, 137.0, 138.5, 143.5, 159.7; **IR**

(KBr): ν = 3391, 3097, 3053, 1671, 1595, 1521, 1503 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{17}H_{15}N_3O$ $[M+H]^+$, 278.1288; found, 278.1285.

1-(2-Methoxyphenyl)-4-methyl-N-phenyl-1H-pyrazole-3-carboxamide ***(4b).*** Prepared according to the general procedure B using **1b** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **4b** as a yellow oil (239 mg, 78%). Yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.47 (d, J = 0.6 Hz, 3H), 3.92 (s, 3H), 7.07-7.13 (m, 3H), 7.33-7.40 (m, 3H), 7.68-7.73 (m, 3H), 7.83 (d, J = 0.6 Hz, 1H), 8.85 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.6, 54.9, 111.3, 118.6, 118.8, 120.1, 122.8, 124.3, 127.9(2), 128.0, 132.1, 137.1, 142.7, 150.6, 159.9; **IR** (KBr): ν = 3382, 3054, 2927, 1678, 1595, 1528, 1502 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{18}H_{17}N_3O_2$ $[M+Na]^+$, 330.1213; found, 330.1214.

4-Methyl-N-phenyl-1-(m-tolyl)-1H-pyrazole-3-carboxamide ***(4c).*** Prepared according to the general procedure B using **1c** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4c** as a yellow solid (259 mg, 89%). Yellow solid, m.p. 139-141 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.46 (s, 6H), 7.09-7.18 (m, 2H), 7.34-7.39 (m, 3H), 7.48-7.55 (m, 2H), 7.71-7.75 (m, 3H), 8.85 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.7, 20.5, 115.5, 118.7, 119.1, 120.2, 122.9, 127.0, 127.2, 127.9, 128.3, 137.0, 138.5, 138.7, 143.4, 159.8; **IR** (KBr): ν = 3373, 3140, 2972, 1682, 1592, 1530 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{18}H_{17}N_3O$ $[M+H]^+$, 292.1444; found, 292.1441.

1-(3-Chlorophenyl)-4-methyl-N-phenyl-1H-pyrazole-3-carboxamide ***(4d).*** Prepared according to the general procedure B using **1d** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4d** as a yellow solid (252 mg, 81%). Yellow solid, m.p. 159-161 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.46 (d, J = 0.9 Hz, 3H), 7.13 (t, J = 7.5 Hz, 1H), 7.30-7.45 (m, 4H), 7.56-7.60 (m, 1H), 7.70-7.74 (m, 2H), 7.75 (d, J = 0.9 Hz, 1H), 7.78 (t, 1H), 8.81 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.7, 116.0, 118.6, 118.7, 120.8, 123.0, 126.1, 127.1, 128.0, 129.6, 134.4, 136.8, 139.4, 144.0, 159.4; **IR** (KBr): ν = 3371, 3098, 3053, 1679,

1594, 1531 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{17}H_{14}ClN_3O$ $[M+H]^+$, 312.0898; found, 312.0894.

1-(4-Chlorophenyl)-4-methyl-N-phenyl-1H-pyrazole-3-carboxamide ***(4e).*** Prepared according to the general procedure B using **1e** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4e** as a yellow solid (258 mg, 83%). Yellow solid, m.p. 160-162 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.46 (d, J = 0.6 Hz, 3H), 7.13 (t, J = 7.2 Hz, 1H), 7.37-7.39 (m, 2H), 7.47 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 9.0 Hz, 2H), 7.69-7.72 (m, 2H), 7.73 (d, J = 0.6 Hz, 1H), 8.80 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.6, 118.7, 119.4, 120.7, 123.0, 127.1, 128.0, 128.6, 131.7, 136.8, 137.0, 143.8, 159.5; **IR** (KBr): ν = 3384, 3093, 3045, 1671, 1591, 1520, 1497 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{17}H_{14}ClN_3O$ $[M+H]^+$, 312.0898; found, 312.0893.

1-(4-Methoxyphenyl)-4-methyl-N-phenyl-1H-pyrazole-3-carboxamide ***(4f).*** Prepared according to the general procedure B using **1f** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **4f** as a yellow solid (276 mg, 90%). Yellow solid, m.p. 158-161 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.46 (d, J = 0.9 Hz, 3H), 3.87 (s, 3H), 7.00 (d, J = 9.0 Hz, 2H), 7.12 (t, J = 7.2 Hz, 1H), 7.34-7.39 (m, 2H), 7.61 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 0.9 Hz, 1H), 7.69-7.73 (m, 2H), 8.84 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.6, 54.6, 113.6, 118.6, 120.0(2), 122.8, 127.3, 127.9, 132.2, 137.0, 143.0, 157.8, 159.8; **IR** (KBr): ν = 3311, 3129, 2955, 1659, 1597, 1538, 1514 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{18}H_{17}N_3O_2$ $[M+H]^+$, 308.1394; found, 308.1390.

4-Methyl-1-phenyl-N-(o-tolyl)-1H-pyrazole-3-carboxamide ***(4g).*** Prepared according to the general procedure B using **1g** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4g** as a white solid (244 mg, 84%). White solid, m.p. 99-100 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.47 (d, J = 0.6 Hz, 3H), 7.07 (t, J =7.5 Hz, 1H), 7.21-7.28 (m, 4H), 7.35 (t, J =7.5 Hz, 1H), 7.47-7.52 (m, 2H), 7.69-7.23

(m, 2H), 7.78 (d, *J* = 0.6 Hz, 1H), 8.18 (d, 1H), 8.87 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.6, 16.7, 118.1, 120.3, 120.7, 123.3, 125.8, 126.1, 126.9, 127.0, 128.5, 129.3, 135.0, 138.5, 143.8, 159.6; **IR** (KBr): ν = 3399, 3085, 3053, 2974, 1683, 1587, 1533, 1503 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{18}H_{17}N_3O$ $[M+H]^+$, 292.1444; found, 292.1440.

N-(2-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide ***(4h).*** Prepared according to the general procedure B using **1h** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4h** as a white solid (233 mg, 75%). White solid, m.p. 135-136 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.47 (d, *J* = 0.9 Hz, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.28-7.43 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.72-7.75 (m, 2H), 7.79 (d, *J* = 0.9 Hz, 1H), 8.57-8.61 (m, 1H), 9.58 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.6, 118.0, 120.0, 120.4, 121.9, 123.1, 126.1, 126.6, 126.9, 128.1, 128.5, 133.9, 138.4, 143.3, 159.7; **IR** (KBr): ν = 3374, 3050, 2926, 1692, 1591, 1533, 1520 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{17}H_{14}ClN_3O$ $[M+H]^+$, 312.0898; found, 312.0906.

4-Methyl-1-phenyl-N-(m-tolyl)-1H-pyrazole-3-carboxamide ***(4i).*** Prepared according to the general procedure B using **1i** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4i** as a yellow solid (232 mg, 80%). Yellow solid, m.p. 96-99 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.47 (d, *J* = 0.9 Hz, 3H), 6.84 (d, *J* = 7.5 Hz, 1H), 7.21-7.27 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.45-7.52 (m, 3H), 7.63 (s, 1H), 7.69-7.73 (m, 2H), 7.76 (d, *J* = 0.9 Hz, 1H), 8.83 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.7, 20.5, 115.7, 118.3, 119.3, 120.3, 123.7, 126.2, 127.1, 127.8, 128.5, 136.9, 137.9, 138.5, 143.6, 159.7; **IR** (KBr): ν = 3314, 2960, 2919, 1669, 1591, 1539, 1532, 1501 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{18}H_{17}N_3O$ $[M+H]$+ 292.1444 found 292.1441.

N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide ***(4j).*** Prepared according to the general procedure B using **1j** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **4j** as a white solid (155 mg,

72%). White solid, m.p. 100-102 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.42 (d, J = 0.9 Hz, 3H), 2.99 (d, J = 5.1 Hz, 3H), 7.01 (s, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.42-7.48 (m, 2H), 7.63-7.68 (m, 2H), 7.71 (d, J = 0.9 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.5, 24.5, 118.1, 119.6, 125.9, 126.6, 128.4, 138.6, 143.7, 162.5; **IR** (KBr): v = 3345, 3058, 2927, 1644, 1598, 1544, 1504 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{12}H_{13}N_3O$ $[M+Na]^+$, 238.0951; found, 238.0948.

N,1-diphenyl-4-propyl-1H-pyrazole-3-carboxamide ***(4k).*** Prepared according to the general procedure B using **1k** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give **4k** as a white solid (216 mg, 71%). White solid, m.p. 95-97 ℃; **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.03 (t, J = 7.8 Hz, 3H), 1.72-1.76 (m, 2H), 2.92 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.34-7.38 (m, 3H), 7.50 (t, J = 7.2 Hz, 2H), 7.70-7.73 (m, 4H), 7.77 (s, 1H), 8.88 (s, 1H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 13.0, 22.4, 25.3, 118.4, 118.7, 122.9, 125.6, 126.2, 126.5, 128.0, 128.5, 137.0, 138.6, 143.1, 159.6; **IR** (KBr): v = 3389, 2966, 2938, 2878, 1686, 1603, 1532, 1504, 760 cm^{-1}; **HRMS** (ESI-TOF) calcd for M =$C_{19}H_{19}N_3O$ $[M+H]^+$, 306.1601; found, 306.1596.

N,1-diphenyl-4-(trifluoromethyl)-1H-pyrazole-3-carboxamide ***(4l).*** Prepared according to the general procedure B using **1l** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give **4l** as a yellow solid (211 mg, 64%). Yellow solid, m.p. 122-124 ℃; **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.15 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 7.8 Hz, 4H), 8.25 (s, 1H), 8.76 (s, 1H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 114.8 (q, $^2J_{CF}$ = 30), 118.8, 119.1, 120.6 (q, $^1J_{CF}$ = 270), 123.5, 127.7, 128.0, 128.9, 129.0, 136.3, 137.5, 143.2, 156.2; **IR** (KBr): v = 3383, 3122, 1700, 1603, 1544, 1441, 760 cm^{-1}; **HRMS** (ESI-TOF) calcd for M =$C_{17}H_{12}F_3N_3O$ $[M+H]^+$, 332.1005; found, 332.0997.

N,1,4-triphenyl-1H-pyrazole-3-carboxamide ***(4m).*** Prepared according to the general procedure B using **1m** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel,

petroleum ether/ethyl acetate = 6:1) to give **4m** as a light yellow solid (237 mg, 70%). Light yellow solid, m.p. 149-150 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.12 (t, 1H), 7.32-7.45 (m , 6H), 7.55 (t, 2H), 7.67-7.71 (m, 4H), 7.79 (d, 2H), 8.03 (s, 1H), 8.92 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ118.6, 118.9, 123.0, 125.7, 126.6, 127.1, 127.2, 127.9, 128.4, 128.6, 130.1, 136.9, 138.2, 142.3, 158.7; **IR** (KBr): v = 3320, 3305, 1671, 1602, 1534, 1506, 761, 700 cm^{-1}; **HRMS** (ESI-TOF) calcd for M =$C_{22}H_{17}N_3O$ $[M+Na]^+$, 362.1264; found, 362.1241.

Procedure C for the synthesis of 4n: To a 50 mL round-bottomed flask was added **3n** (1.0 mmol), DMF (4 mL) and concentrated HCl (0.2 mL). Then the mixture was stirred at room temperature for 1.0 h. After the reaction was completed, the resulting mixture was poured into saturated aqueous NaCl (100 mL), which was extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give **4n** as a white solid (204 mg, 89%).

Ethyl 4-methyl-1-phenyl-1H-pyrazole-3-carboxylate ***(4n).*** White solid, m.p. 72-74 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.43 (t, J = 7.2 Hz, 3H), 2.37 (d, J = 0.9 Hz, 3H), 4.44 (q, J = 7.2 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.43-7.48 (m, 2H), 7.69-7.73 (m, 2H), 7.74 (d, J = 0.9 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.9, 13.4, 59.7, 118.8, 121.2, 126.2, 126.6, 128.4, 138.6, 141.7, 162.0; **IR** (KBr): v = 3134, 3077, 2981, 1714, 1595, 1506, 1366, 1278, 1241 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{13}H_{14}N_2O_2$ $[M+Na]^+$, 253.0947; found, 253.0943.

1-(4-Methyl-1-phenyl-1H-pyrazol-3-yl)ethanone ***(4o).*** Prepared according to the general procedure C using **3o** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give **4o** as a white solid (186 mg, 93%). White solid, m.p. 65-68 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.37 (d, J = 0.6 Hz, 3H), 2.66 (s, 3H), 7.34 (t, J = 7.2 Hz, 1H), 7.45-7.50 (m, 2H), 7.70-7.74 (m, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.9, 26.1, 118.4, 120.2, 126.1, 126.6, 128.5, 138.8, 148.4, 194.6; **IR** (KBr): v = 3133, 3095, 3059,

2956, 1667, 1504 cm^{-1}; **HRMS** (MALDI-TOF) calcd for M = $C_{12}H_{12}N_2O$ $[M+Na]^+$, 223.0842; found, 223.0844.

(4-methyl-1-phenyl-1H-pyrazol-3-yl)(phenyl)methanone ***(4p).*** Prepared according to the general procedure C using **3p** (1.0 mmol) as substrate. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **4p** as a light yellow solid (227 mg, 87%). Light yellow solid, m.p. 93-96 ℃; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.33 (t, J = 7.5 Hz, 1H), 7.45-7.52 (m, 4H), 7.59 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.82 (s, 1H), 8.30 (d, J = 7.2 Hz, 2H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 25.2, 61.5, 79.9, 113.4, 121.5, 127.1, 128.4, 129.1, 131.6, 136.1, 141.2, 147.6, 187.0; **IR** (KBr): ν = 3145, 3105, 1652, 1603, 1512, 1370, 1277 cm^{-1}; **HRMS** (ESI-TOF) calcd for M = $C_{17}H_{14}N_2O$ $[M+Na]^+$, 285.0998; found, 285.0996.

Associated Content

Supporting Information

The supporting Information is available free of charge on the ACS Publication website at DOI:10.1021/acs.joc.XXXXXXXX.

^{1}H and ^{13}C NMR spectra of products **3** and **4** (PDF). X-ray crystallographic data (CIF file) of **4e**.

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Note

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