EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000496

Link to VoR: https://doi.org/10.1002/ejoc.202000496

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FULL PAPER

Iodine-Catalyzed Ring Opening of 1,1-Diacylcyclopropanes for Synthesis of Fully Substituted Pyrazole Derivatives

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Abstract: An iodine-catalyzed [3+2] cycloaddition/ring opening reaction of 1,1-diacylcyclopropanes with sulfonyl hydrazides has been reported. In the presence of 20 mol % iodine, a range of structurally diverse fully substituted pyrazoles with a hydroxy functional group are obtained in moderate to excellent yields with extremely high regioselectivity.

Introduction

Pyrazole is an extensively utilized moiety, particularly in the field of medicinal chemistry, both as a pendant functional group and as a core template in a wide variety of therapeutic areas.[1] At present, many pyrrole skeleton-containing compounds have been developed as marketed drugs or clinical research.[2] Among a group of pyrazole derivatives, pyrazolol is a very special class, because it not only can be oxidized into aldehydes or carboxylic acids, but also be further modified into various alkoxypyrazoles.[3] For example (Figure 1), BKI 1708 (I), as a synaptic kinase inhibitor, can be used for the treatment of cryptosporidiosis.[4] Lonazolac (II), as a nonsteroidal anti-inflammatory drug (NSAID), it can be used to relieve pain caused by joints and spine, such as arthritis and ankylosing spondylitis.[5] In addition, 3-alkoxypyrazoles (III) can be used as an inhibitor of human dihydroorotate dehydrogenase (DHODH) and shows activity against measles virus.[6]

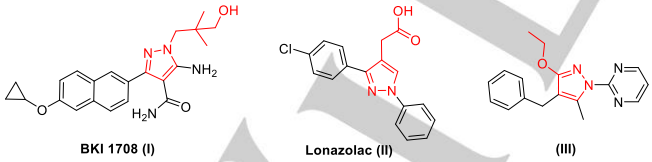


Figure 1. Some inhibitors and drug active molecules.

During the course of a medicinal chemistry campaign, much attention has been paid to the synthesis of substituted fully substituted pyrazole derivatives.[7] On the other hand, the synthesis of fully substituted pyrazole derivatives with a hydroxy functional group via a highly efficient and convergent method endured some challenges. The construction of alcohol motifs has received intensive attention owing to the fact that these compounds are versatile precursors of various functionalities and moieties in organic synthesis.[8] The traditional method used preformed organometallic reagents to couple with various carbonyl compounds.[9] However, little has been published on synthesis of fully substituted pyrazole derivatives with a hydroxy functional group in one step.[7g]

As a mild oxidant and mild Lewis acid property, iodine is widely used in organic synthesis.[10] Recently, Chang's group has realized iodine-mediated synthesis of pyrazole derivatives using α,β-unsaturated aldehydes or ketones and hydrazine under metal-free conditions in the form of oxidative C-N bond formation.[11] Encouraged by this method, in this context, we envisioned that sulfonyl hydrazides reacted with 1,1-diacylcyclopropanes via cycloaddition to afford pyrazole ring, which then undergo ring opening reaction to give fully substituted pyrazole derivatives with a hydroxy functional group.

Results and Discussion

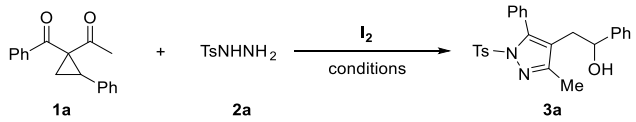
We initiated our investigation with the cyclization of cyclopropyl ketone **1a** and *p*-toluenesulfonyl hydrazide **2a** in the presence of iodine (Table 1). First, we selected dichloromethane as solvent, disappointingly, no desired product was obtained at room temperature. Then raising the reaction temperature to 70 ℃, the target product was observed in 60% yield. Encouraged by this result, various solvents were examined, and a 64% yield was achieved when using acetonitrile as solvent. Moreover, replacing iodine with other catalysts, such as *N*-iodosuccinimide (NIS), sodium iodide, ammonium iodide, etc., gave much lower yields. Finally, screening additives revealed that the additives have great impact on the reaction. The highest yield, 81%, was obtained when ammonium iodide was used as additive. Thus, the optimal reaction conditions were 1 equiv. of **1a**, 2 equiv. of **2a**, 0.2 equiv. of I_2, and 2 equiv. of NH_4I in CH_3CN at 70 ℃. It is worth noting that when ammonium iodide and iodine were added, the solution showed a colorless state, so we speculated that the presence of iodide ions can form iodine triple negative ions with iodine, thereby improving the reaction yield.

With the optimal reaction conditions secured, a series of 1,1-diacylcyclopropanes were investigated for this reaction (Table 2). First, a range of cyclopropylketones bearing various aromatic ketones (R_2 = aryl) proved to work well in this reaction, in moderate to good yields (54-88%) with extremely high regioselectivity. Notably, the reaction tolerated a variety of functional groups, such as alkoxy, fluoro, chloro, bromo, iodo. Methyl substituted cyclopropylketones (R_2 = Me) gave **3r** with a lower yield (48%). However, when both substitutions of the

cyclopropane were benzoyl, no product (**3s**) was found under the standard conditions. The extra substituent (R^1) on the cyclopropyl ketones also have a great influence on the yield. When a series of aryl-, vinyl-, or alkyl-substituted cyclopropyl ketones (**1a-1r**) were treated, the desired products (**3a-3r**) were obtained in moderate to good yields. When the substituent (R^1 = H, Me), the desired products (**3t-3v**) were obtained in moderate to good yields.

Subsequently, the scope of sulfonyl hydrazides was tested (Table 3). A range of aryl sulfonyl hydrazides that have electron-donating and electron-withdrawing groups gave the desired products in moderate to good yields (**4a-4l**). In addition, alkyl sulfonyl hydrazides proved to be suitable reaction partners, giving products (**4m-4q**) with similar efficiency. In addition to a variety of sulfonyl hydrazides, simple aliphatic hydrazides, phenyl hydrazines and hydrazine hydrate can also react under our standard condition to obtain the corresponding products (**4r-4t**).

Table 1. Optimization on Reaction Conditions.[a]



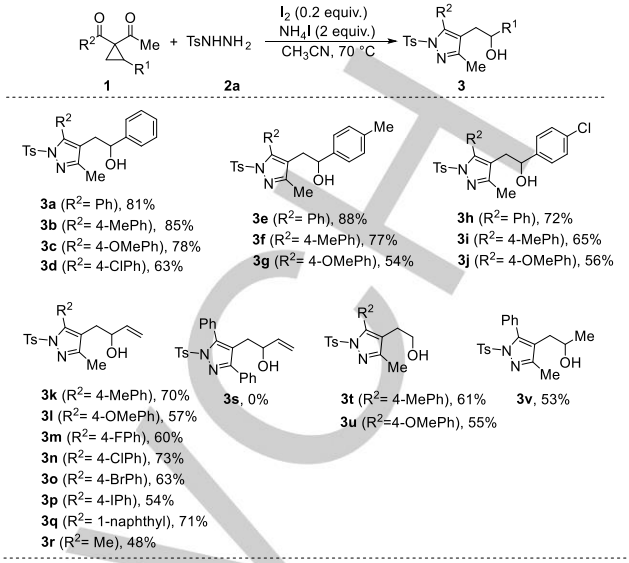
1a **2a** **3a**

Entry	Catalyst (equiv.)	Temp. (℃)	Solvent	Yield[b] (%)
1	I_2 (0.2)	70	CH_2Cl_2	60
2	I_2 (0.2)	70	$CHCl_3$	48
3	I_2 (0.2)	70	EtOAc	43
4	I_2 (0.2)	70	Toluene	41
5	I_2 (0.2)	70	CH_3NO_2	46
6	I_2 (0.2)	70	CH_3CN	64
7	I_2 (0.2)	70	DMSO	trace
8	I_2 (0.2)	70	DMF	trace
9	I_2 (0.2)	70	Dioxane	33
10	I_2 (0.2)	70	THF	40
11	I_2 (0.2)	80	CH_3CN	59
12	I_2 (0.2)	90	CH_3CN	trace
13[c]	I_2 (0.2)	70	CH_3CN	30
14[d]	I_2 (0.2)	70	CH_3CN	59
15	I_2 (0.3)	70	CH_3CN	54
16	I_2 (0.4)	70	CH_3CN	56
17	NBS (0.2)	70	CH_3CN	42
18	NIS (0.2)	70	CH_3CN	58
19	NH_4I (2.0)	70	CH_3CN	35
20	NaI (2.0)	70	CH_3CN	62
21[e]	I_2 (0.2)	70	CH_3CN	trace
22[f]	I_2 (0.2)	70	CH_3CN	53
23[g]	I_2 (0.2)	70	CH_3CN	77
24[h]	I_2 (0.2)	70	CH_3CN	81
25[i]	I_2 (0.2)	70	CH_3CN	trace
26[j]	I_2 (0.2)	70	CH_3CN	35
27[k]	I_2 (0.2)	60	CH_3CN	56

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), I_2 (0.02 mmol), solvent (1.0 mL), under air in a sealed tube at 70 ℃ (oil bath) for 16 h. [b] Isolated yield based on **1a**. [c] **1a** (0.12 mmol), **2a** (0.1 mmol). [d] **1a** (0.1 mmol),**2a** (0.3 mmol). [e] TBHP (2 equiv.) as additive. [f] KI (2 equiv.) as additive. [g] NaI (2 equiv.) as additive. [h] NH_4I (2 equiv.) as additive. [i] TsOH (1 equiv.) as additive. [j] Et_3N (1 equiv) as additive. [k] NH_4I (2 equiv.) as additive.

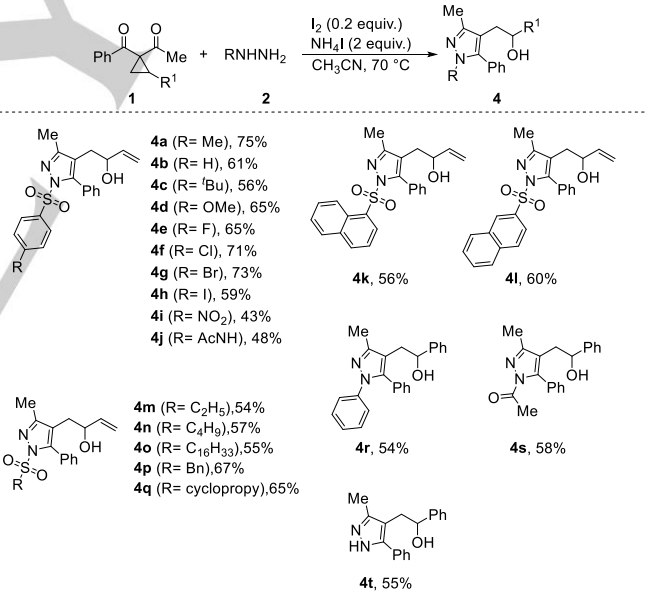
To gain insight into the reaction mechanism, a series of control experiments with possible intermediates was performed (Scheme 1). Compound **5a** was easily obtained under the standard conditions. Treatment of **5a** with sulfonyl hydrazides gave the product **3a** in 74% yield, which substantially demonstrates that the reaction went through a sulfonylhydrazone intermediate (Scheme 1, eq 1). Moreover, the addition of the free radical inhibitor 2,6-di-*tert*-butyl-*p*-cresol (BHT) to the reaction

Table 2. Scope of 1,1-diacylcyclopropanes.[a]



[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), I_2 (0.02 mmol), NH_4I (0.2 mmol), solvent (1.0 mL), under air in a sealed tube at 70 ℃ (oil bath) for 16 h. [b] Isolated yield based on **1**.

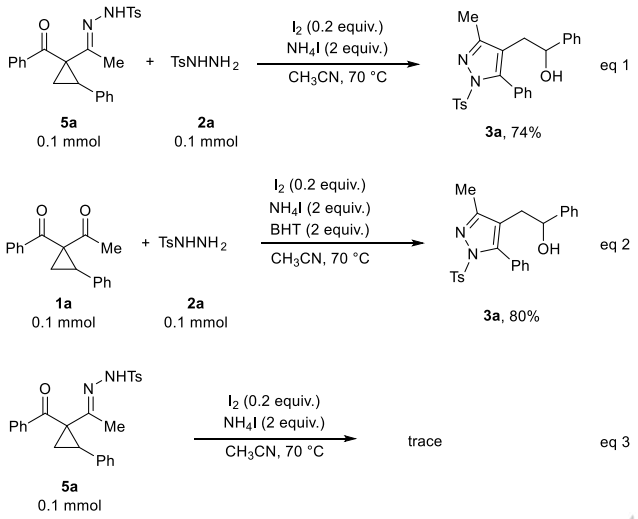
Table 3. Scope of sulfonyl hydrazides.[a]



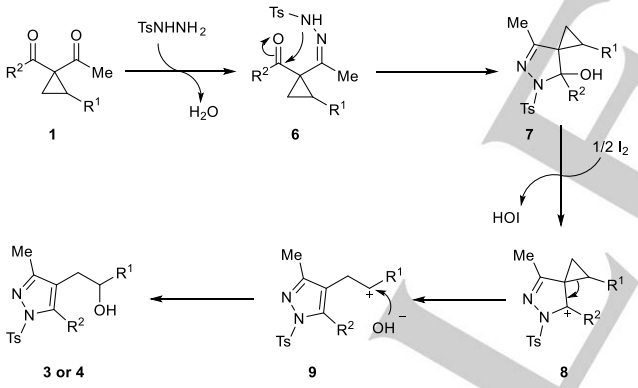
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), I_2 (0.02 mmol), NH_4I (0.2 mmol), solvent (1.0 mL), under air in a sealed tube at 70 ℃ (oil bath) for 16 h. [b] Isolated yield based on **2**.

mixture of diacylcyclopropane and sulfonyl hydrazide had no effect on the reaction efficiency, indicating that the reaction process might not involve radical intermediates (Scheme 1, eq 2). Furthermore, we also used Intermediate **5a** alone to react under standard conditions and found that the target product could not be obtained. Combined with our previous screening experiments, without adding any catalyst, only adding 2 equiv of sulfonyl hydrazide can not get the target product (Scheme 1,eq 3). Therefore, we exclude the catalysis of sulfonyl hydrazide.

According to the results of the above control experiments, a proposed pathway is illustrated (Scheme 2). Initially, diacylcyclopropane **1** reacts with sulfonyl hydrazide to give sulfonylhydrazone **6**, which undergoes intramolecular condensation to offer **7.** Then intermediate **7** reacts with iodine to afford intermediate **8** and at the same time iodine is converted into hypoiodic acid[12-13]. Due to the ring tension, **8** undergoes ring opening to give **9,** which is attacked by the previously removed hydroxyl anion to give the desired product **3 or 4**.

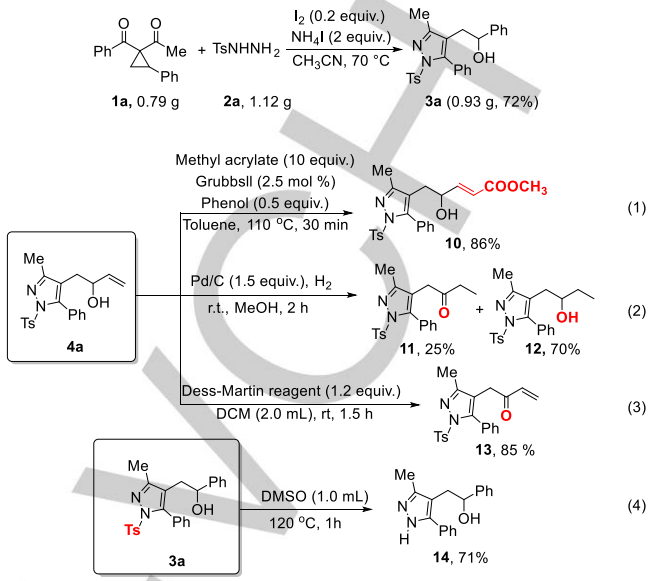


Scheme 1. Control experiments.



Scheme 2. Proposed mechanism.

To demonstrate the practicality of this protocol, a gram-scale reaction proceeded smoothly without apparent yield loss (Scheme 3). In the end, to indicate the synthetic utility of reaction, we undertook a series of reactions using the representative product **4a**. The vinyl-bearing product **4a** can form a vinyl α-addition product **10** in 86% yield under the action of 2-generation Grubbs catalyst. At the same time, the double bond can be selectively reduced by H_2 and Pd/C, obtaining a double bond reduction product **12** in 70% yield, while **4a** can undergo intramolecular enol-type interconversion and isomerization to carbonyl compound **11**. In addition, it can also be selectively oxidized to ketone by Dess-Martin oxidant to obtain oxidation product **13** in 85% yield. Moreover, at high temperature, the group *p*-toluenesulfonyl can be easily removed, affording the compound **14** in 71% yield (Scheme 3).



Scheme 3. Gram scale and synthetic transformations.

Conclusion

In conclusion, we have developed a highly effective strategy to achieve iodine-catalyzed [3+2] cycloaddition of diacylcyclopropanes with sulfonyl hydrazide. This reaction tolerates a broad range of cyclopropyl ketones and sulfonyl hydrazides to afford useful and densely functionalized pyrazole derivatives with an hydroxy functional group. The easy handle process, high synthetic value of resulting products, and intriguing mechanism of the titled process render it not only conceptually novel, but also synthetically useful.

Experimental Section

General Procedure for Synthesis of 3 or 4: To a solution of sulfonyl hydrazide **2** (0.2 mmol) in CH_3CN (1.0 mL) was added NH_4I (28.98 mg, 0.2 mmol), diacylcyclopropane **1** (0.1 mmol) and I_2 (5.08 mg, 0.02 mmol). The resulting mixture was stirred at 70 ℃ (oil bath) under air for 16 h, cooled to room temperature, and purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (10/1 to 5/1) to give mainly desired product **3** or **4**. **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 6.5, 2.9 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.29 (d, J = 8.2 Hz, 2H), 7.19 – 7.07 (m, 3H), 7.02 – 6.93 (m, 2H), 4.55 (t, J = 6.8 Hz, 1H), 2.95 (dd, J = 14.4, 6.9 Hz, 1H), 2.77 (dd, J = 14.4, 6.7 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 3H), 2.13 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 155.4, 145.2, 143.2, 142.3, 135.4, 132.5, 129.9, 128.7, 128.5, 128.4, 128.3, 127.8, 127.7, 125.6, 116.8, 74.0, 33.7, 21.7, 11.2; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_3S^+$ $(M+H)^+$ 433.1580, found 433.1579.

Synthesis of 10: To a solution of **4a** (38.25 mg, 0.1 mmol) in toluene (1.0 mL) was added methyl acrylate (86.09 mg, 1.0 mmol), phenol (4.70 mg, 0.05 mmol) and Grubbs2nd catalyst (2.12 mg, 0.0025 mmol). The resulting mixture was stirred at 110 ℃ (oil bath) under air for 30 min, cooled to room temperature, and purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (8:1) to give **10** in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.42 – 7.36 (m, 3H), 7.32 (d, J = 8.3 Hz, 2H), 6.79 – 6.73 (dd, J = 15.6, 4.8 Hz, 1H), 5.93 – 5.82 (dd, J = 15.6, 1.6 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.71 (s, 3H), 2.82 – 2.65 (m, 2H), 2.52 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 155.2, 148.7, 145.5, 142.4, 135.0, 132.1, 130.0, 128.9, 128.6, 128.4, 127.8, 120.3, 116.0, 70.7, 51.7, 31.0, 21.8, 11.9; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_5S^+$ $(M+H)^+$ 441.1479, found 441.1480.

Synthesis of 11 and 12: To a solution of **4a** (38.25 mg, 0.1 mmol) and Pd/C (15.96 mg) in MeOH (1.0 mL) was stirred at room temperature under 1.0 atm hydrogen atmosphere. After being stirred for 2 h, the mixture was filtrated through a pad of Celite and the filtration was concentrated in vacuo, the residue was purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (10:1) to give **11** and **12** in 25% and 70% yield.**11**:^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 2H), 7.46 – 7.36 (m, 5H), 7.34 (d, J = 7.8 Hz, 2H), 3.53 (s, 2H), 2.47 (s, 3H), 2.42 (s, 3H), 2.36 (q, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 155.3, 145.4, 142.3, 135.2, 132.0, 130.0, 128.8, 128. 6, 128.4, 127.9, 114.0, 37. 8, 35.4, 21.7, 11.8, 7.8; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_3S^+$ $(M+H)^+$ 383.1424, found 383.1426; **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 2H), 7.64 – 7.54 (m, 2H), 7.44 – 7.36 (m, 3H), 7.32 (d, J = 8.2 Hz, 2H), 3.57 – 3.39 (m, 1H), 2.71 – 2.57 (m, 2H), 2.54 (s, 3H), 2.42 (s, 3H), 1.44 – 1.35 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 145.3, 141.9, 135.3, 132.5, 129.9, 128.7, 128.5, 128.4, 127.9, 117.5, 73.0, 31.3, 29.8, 21.7, 11.8, 9.8; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_3S^+$ $(M+H)^+$ 385.1580, found 385.1582.

Synthesis of 13: To a solution of **4a** (38.25 mg, 0.1 mmol) in CH_2Cl_2 (2.0 mL) was added Dess-Martin reagent (50.90 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 1.5 h, and purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (10:1) to give **13** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.44 – 7.35 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 6.42 – 6.12 (m, 2H), 5.81 (dd, J = 10.1, 1.4 Hz, 1H), 3.71 (s, 2H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 155.4, 145. 5, 142.6, 135.2, 135.1, 131.9, 130.0, 129.4, 128.8, 128.6, 128.4, 127.8, 113.5, 35.5, 21.7, 11.8; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_3S^+$ $(M+H)^+$ 381.1267, found 381.1269.

Synthesis of 14: To a solution of **3a** (43.25 mg, 0.1 mmol) in DMSO (1.0 mL). The resulting mixture was stirred at 120 ℃ for 1 h, cooled to room temperature, and purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (3:1) to give **14** in 71% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.2 Hz, 2H), 7.21 – 7.14 (m, 3H), 4.58 (t, J = 6.8 Hz, 1H), 2.91 (dd, J = 14.3, 7.2 Hz, 1H), 2.71 (dd, J = 14.3, 6.6 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 132.3, 128.7, 128.3, 128.0, 127.9, 127.5, 125.8, 111.4, 74.3, 33.9, 10.7; HRMS (ESI) calcd for $C_{18}H_{19}N_2O^+$ $(M+H)^+$ 279.1492, found 279.1496.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grant Nos. 21102179 and 21572271), Qing Lan Project of Jiangsu Province, and the "Double First-Class" University project (CPU2018GY35, CPU2018GF02) and Postgraduate Scientific Research Innovation Projects of Jiangsu Province (KYCX19_0624).

Keywords: Iodine catalysis • Cycloaddition • Ring opening • Pyrazole derivatives

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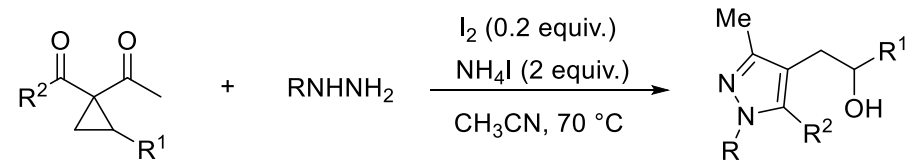
Entry for the Table of Contents



R^1 = aryl, alkyl, vinyl, H

R^2 = aryl, alkyl R = aryl, alkyl,H

41 examples
up to 88% yield

Heterocycles Synthesis: Iodine-catalyzed ring opening of 1,1-diacylcyclopropanes for synthesis of fully substituted pyrazole derivatives have been reported. This reaction tolerates a broad range of cyclopropyl ketones and sulfonyl hydrazides to afford useful and densely functionalized pyrazole derivatives with an hydroxy functional group.