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Graphical Abstract

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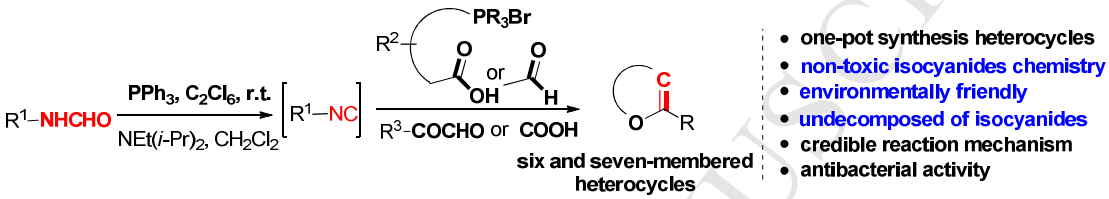
Key laboratory of inorganic nonmetallic crystalline and energy conversion materials, College of Materials and Chemical Engineering, China Three Gorges University, Yichang, Hubei 443002, China.



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Tandem Reaction Strategy of the Passerini/Wittig Reaction Based on the *in Situ* Capture of Isocyanides: One-Pot Synthesis of Heterocycles

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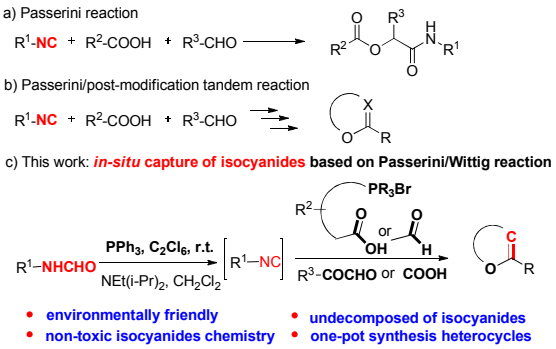
Abstract—This paper reports the tandem reaction strategy of the Passerini/Wittig reaction based on the *in situ* capture of isocyanides. According to this strategy, plenty of isocyanides have been synthesized, which is immediately used for the tandem reaction of Passerini/Wittig reaction in one pot. Compared to the previous work, this strategy avoids the separation, purification, and storage of isocyanides, which prominently solves the problems of isocyanide-based multicomponent reaction such as: (a) The environmentally unfriendly (strong foul odor), (a) the labile of Isocyanides, (c) high toxicity of isocyanides. In the meantime, in order to expand the application scope of our strategy, 1*H*-isochromenes and 3*H*-2-benzoxepin-1-ones have also been synthesized, which undergoes four-step transformations in one-pot. In addition, a relatively credible reaction mechanism has also been proposed, based on a series of control experiments. Furthermore, preliminary testing was performed on biological activity of some obtained compounds; These results showed that the synthesized compounds exhibited certain activity over P. digitatum and P. italicum.

Keywords: Isocyanides; in situ capture; tandem reaction; heterocycles

1. Introduction

In recent years, people have attached increasing importance to isocyanide-based reactions,[1] and a series of original symbolic achievements have been reported in succession.[2] Isocyanide-based multicomponent reactions have got extensive concern in the field of organic synthesis due to its high reaction efficiency, wide range of substrates, and the avoidance of intermediate separation losses and tedious processes.[3] The Passerini reaction is a one pot three-component reaction for preparation of α-acyloxy acidamide involving aldehyde and ketone, carboxylic acid and isocyanide(Scheme 1a). Lots of diverse compounds in complex structures are synthesized directly and efficiently from simple and readily available materials through advance protection or reservation of functional group on a certain component and the linkage with postmodification reaction(Scheme 1b).[4] This tandem reaction which based on the Passerini reaction and its postmodification reaction has, which exhibits a series of excellent achievements in succession.[5] However, this cascade reactions is barely used in production practices at present, because: 1) The environmentally unfriendly (strong foul odor), 2) the labile of Isocyanides, and 3) high toxicity of isocyanides.



Scheme 1. The tandem reaction strategy of Passerini/Wittig reaction based on the in situ capture of isocyanides.

In recent, a new strategy, via based on the in situ capture of isocyanides, has been reported in succession. According to this strategy, the in situ generation of isocyanides from its precursor could solve some problems such as separation, purification, the smell of exposure, decomposition.This may dramatically overcome the drawbacks of isocyanide chemistry.[6] For example, Parsons et al. reported multicomponent cascade reaction based on the in situ capture of isocyanides in 2005. This strategy was developed to prepare isocyanides in situ through the ring opening of epoxide.[6a] In 2009, Kaim et al. reported the Ugi reaction based on the in situ capture of isocyanides. This strategy prepared isocyanides *in situ* from benzyl chloride, silver cyanide and potassium cyanide.[6b-6d] In 2013, Kim et

al. reported an integrated microfluid-based Passerini reaction.[6e] According to this strategy, isocyanides were produced in situ within an integrated microfluidic system. In 2015, Domling et al. reported the attainment of a multicomponent reaction based on the in situ capture of isocyanides with formamide, ketone, aldehyde and other oxygenated compounds as precursors.[6f]

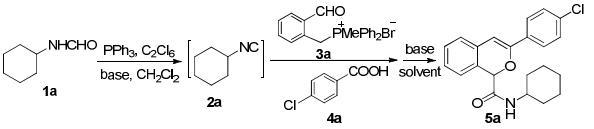
The Wittig reaction is an all-important reaction for preparation of carbon-carbon double bonds by the reaction of phosphorus ylide and reactive carbonyl. This reaction is characterized by simplicity of operation, mild conditions, fewer side reactions, and high yield, etc.[7] The Wittig reaction can be used to prepare five-member, six-member, seven-member and macrocyclic heterocyclic compounds.[8] The tandem reactions of isocyanide-based multicomponent reaction and the Wittig reaction has been extensively used for organic synthesis, pharmaceutical synthesis, etc.[9]

Isochromenes are very important category of compounds that exhibit favorable biological activities. Additionally, isochromenes are basic skeletons for some natural products, sensors and biological active compounds. Thus, their synthesis methods have received certain attention.[10] To the best of our knowledge, however, no tandem reaction of in situ capture of isocyanides based Passerini/Wittig reaction has been reported so far. Based on our previous studies,[11] we developed a tandem reaction strategy based on the in situ capture of isocyanides of the Passerini/Wittig reaction and a series of 1*H*-Isochromene and 3*H*-2-benzoxepin-1-ones were synthesized by using the tandem-reaction.

2. Results and Discussion

According to the literatures, we found that amide **1a** was easily prepared from cyclohexanone and formamide with high yield.[6f] Therefore, amide **1a**, phosphonium salts **3a** and parachlorobenzoic acid **4a** were used as model substrates to explore the reaction conditions.First, target compound **5a** was not obtained at 60 ^{o}C by using THF and NaOH as the solvent and base, respectively. To our surprise, target compound **5a** was obtained with a yield of 13% only needed to change the base from NaOH to $K_2CO_3$to K_2CO_3. Further optimization of the base showed that the yield was 23% when the base was diisopropylethylamine. Afterward, the solvent was optimized, and it was found that the yield was 51% when the solvent was changed to toluene. However, the reaction could not be carried out when the solvent was changed from THF to methanol. The reaction temperature was further screened and it was found that increasing the temperature was beneficial to the reaction. Therefore, 110 ^{o}C was found to be the most suitable temperature for the reaction. It is also important to note that the reaction cannot occur without base. However, when C_2Cl_6 was substituted by I_2, no target compound **4a** was obtained.[12]

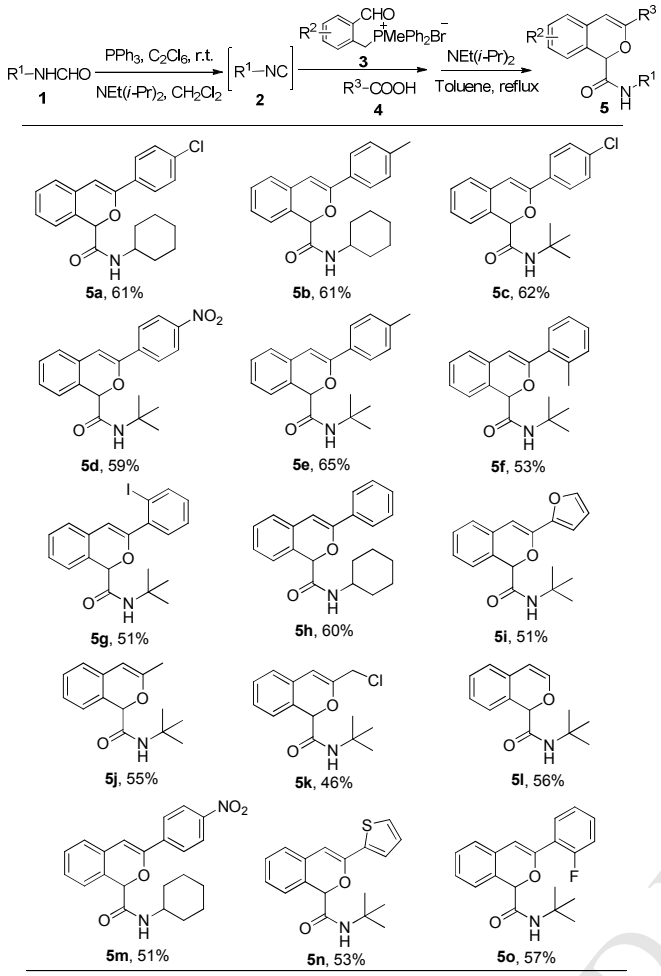
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Base	T[^{o}C]	**5a**[%][b]
1	THF	NaOH	60	NR
2	THF	K_2CO_3	60	13
3	THF	NEt_3	60	16
4	THF	NEt(*i*-Pr)$_2$	60	23
5	THF	DABCO	60	11
6	MeOH	NEt(*i*-Pr)$_2$	60	NR
7	Toluene	NEt(*i*-Pr)$_2$	60	51
8	CH_2Cl_2	NEt(*i*-Pr)$_2$	60	12
9	Toluene	NEt(*i*-Pr)$_2$	110	61
10	Toluene	NEt(*i*-Pr)$_2$	r.t.	trace
11	Toluene	--	110	NR
12	Toluene	NEt(*i*-Pr)$_2$	110	NR[c]

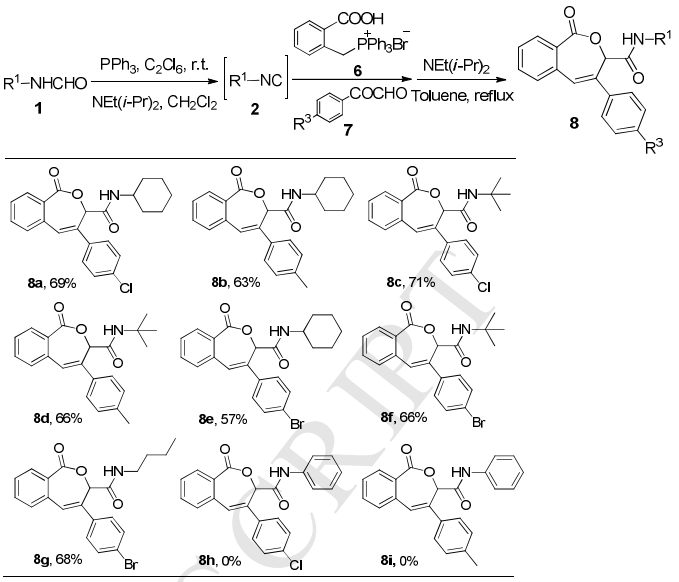
[a] *Conditions:* **1a** (1 mmol), PPh_3 (1.5 mmol), C_2Cl_6 (1.5 mmol), CH_2Cl_2 (10 ml), base (3.0 mmol), air, **3a** (1.1 mmol), **4a** (1.1 mmol) and then solvent (10 ml), base (1.1mmol). [b] Yields based on **1a**. [c] C_2Cl_6 was replaced with I_2.

The reaction substrate was expanded under the optimal reaction conditions. It was found that the reaction exhibited good universality for various substrates while the electronic effects and steric effects of substrate functional groups did not significantly affect the reaction(Scheme 2). Various substituted phenyl carboxylic acids and aromatic heterocyclic carboxylic acids can be transformed into target compounds with good yields. Meanwhile, target compounds can also be obtained with relatively moderate yields for aliphatic carboxylic acids, such as formic acid and acetic acid. The yield of 46-65% is the total yield of the four-steps transformations, which was count on amide **1**, while the yield of 68-89% was based on phosphonium salt **3** in the literature,[11a] which was very different from this manuscript.



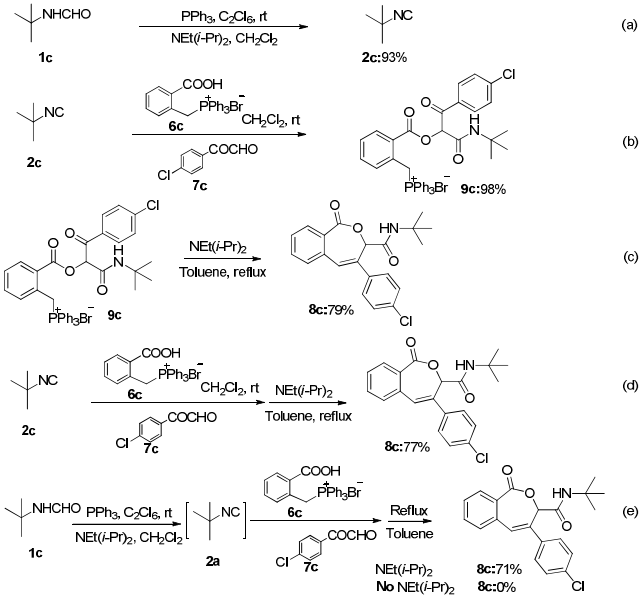
Scheme 2. Preparation of 1*H*-isochromenes **5** by the tandem reaction. [a] Condotions: **1** (1 mmol), PPh_3 (1.5 mmol), C_2Cl_6 (1.5 mmol), CH_2Cl_2 (10 ml), NEt(*i*-Pr)$_2$ (3.0 mmol), air, r.t., **3** (1.1 mmol), **4** (1.1 mmol) and then toluene (10 ml), NEt(*i*-Pr)$_2$ (1.2 mmol), 110 ^oC. [b] Yields based on **1**.

Meanwhile, in order to further expand the application scope of our strategy, we also synthesized the known 3*H*-2-Benzoxepin-1-ones by using this strategy. 3*H*-2-Benzoxepin-1-ones are also an important category of heterocycles which serves as the basic skeleton of some important bioactive molecules and sensors.[13] Therefore, a series of 3*H*-2-benzoxepin-1-ones were synthesized using the "one-pot" method based on the tandem-reaction strategy of Passerini/Wittig reaction based on the *in-situ* capture of isocyanides(Scheme 3). It was found that the reaction exhibited good universality for substrate: Various substrate were favorably converted into products even when N-primary-alkylformamide such as N-*n*-butylformamide was used as substrate. The yield of 57-71% also is the total yield of the four-steps transformations, which is based on amide **1**. However, no target compound **8h** and **8i** were obtained when N-phenylformamide was used as substrate.



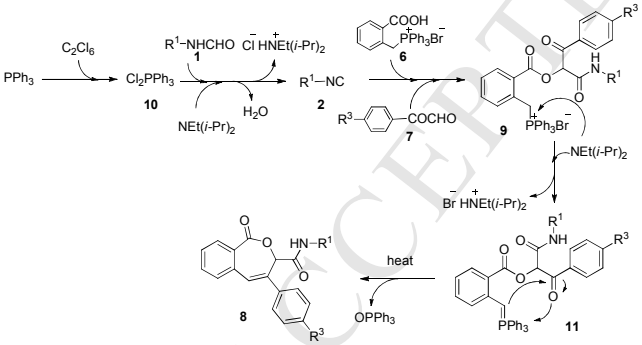
Scheme 3. Preparation of 3*H*- 2-benzoxepin-1-ones **8** by the tandem reaction.

After expanding the reaction substrate, we probed into the reaction mechanism by condition control experiments. The isocyanide **2c** was obtained from amide **1c** with the yield of 93% under the action of C_2Cl_6, PPh_3 and NEt(*i*-Pr)$_2$ (Scheme 4a). The Passerini reaction between isocyanide **2c**, phosphonium salts **6c** and 4-chlorophenylglyoxal **7c** in CH_2Cl_2 at room temperature afforded intermediate **9c** with the yield of 98% (Scheme 4b). Under the action of NEt(*i*-Pr)$_2$, intermediate **9c** generated target compound **8c** with 79% yield (Scheme 4c). The isocyanide **2c** reacted with phosphonium salt **6c** and 4-chlorophenylglyoxal **7c** in CH_2Cl_2 at room temperature, providing target compound **8c** at a yield of 77% (Scheme 4d). However, it should be noted that no target compound was obtained when no additional NEt(*i*-Pr)$_2$ was added into the last step of the tandem reaction (Scheme 4e).



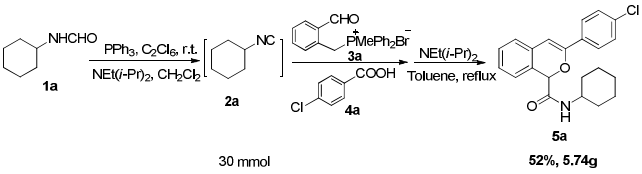
Scheme 4. Control experiments and mechanism investigation.

On the base of the results of the controlled experiment, we proposed a possible reaction mechanism(Scheme 5). First, hexachloroethane reacted with triphenylphosphine to produced phosphonium salt **10**; then phosphonium salt **10** removed H_2O from amide **1** to get isocyanide **2** *in situ*; Phosphonium salt **6** and phenylglyoxal **7** captured isocyanide **2** produced intermediate **9** through Passerini reaction; A molecule of HBr was removed by NEt(*i*-Pr)$_2$ from intermediate **9** to get phosphine ylide **11**; Phosphine ylide **11** generated the target compound **8** through intramolecular Wittig reaction in the heating condition.



Scheme 5. The proposed possible mechanism.

In addition, we conducted a scale-up test to determine the applicability of this strategy we developed. 5.74g of **5a** was synthesized with high yield through this tandem reaction (Scheme 6).



Scheme 6. The synthesis of 3-(4-chlorophenyl)-N-cyclohexyl-1H-isochromene-1-carboxamide in large scale.

At the same time, we also tested the bactericidal activity of some synthetic compounds against Fusarium graminearum, Magnaporthe oryzae, Penicillium digitatum, Penicillium italicum, and Rhizoctonia solani with triadmefon as the positive control (Table 2). The test showed that the compounds had antibacterial activity against P. digitatum and P. italicum. The compound **8c** exhibited an inhibition ratio of ≤ 81% against P. digitatum, ≤ 79% against P. italicum, which was close to the inhibition ratio of positive control agent Triadmefon. According to the summary of the inhibition ratio and the structure-activity relationship of the compound, the antibacterial activity is higher when the substituent contains chlorine and nitro substituent groups, such as **5d** and **8c**.

Table 2. Fungicidal activities of compounds against five kinds of fungus.

Compd.	Inhibition rate /(%)				
	P. digitatum	P. italicum	F. graminearum	M. oryzae	R. solani
5a	45	37	11	26	21
5b	21	22	0	0	0
5c	56	45	15	0	27
5d	63	61	20	36	55
5g	35	29	0	0	14
5j	0	15	0	0	0
5k	38	35	0	0	15
8a	33	26	0	0	21
8b	21	0	0	11	17
8c	81	79	42	48	66
8e	35	28	0	19	21
8f	42	33	13	11	55
triadmefon	95	91	55	72	81

3.Conclusion

In summary, a novel tandem reaction strategy of the Passerini/Wittig reaction based on the *in situ* capture of isocyanides has been reported and two types of compounds have been synthesized by using the strategy. This strategy avoids the separation, purification, and storage of isocyanides, which prominently solves the problems of isocyanide-based multicomponent reaction such as: 1) The environmentally unfriendly (strong foul odor), 2) the labile of Isocyanides, 3) high toxicity of isocyanides. A series of 1*H*-isochromenes and 3*H*-2-benzoxepin-1-ones are synthesized by using the one-pot process. Meanwhile, preliminary testing was performed on biological activity of some compounds; the test showed that the synthesized compounds exhibited certain activity against P. digitatum and P. italicum. Furthermore, we proposed a possible

mechanism of the present reaction through verification based on a series of experiments under controlled conditions.

4. Experimental

4.1 General

All the obtained products were characterized ^{1}H NMR spectra and ^{13}C NMR spectra (400 MHz or 600 MHz). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m);

*4.2 Typical procedure for the synthesis of **5***

*4.2.1 3-(4-chlorophenyl)-N-cyclohexyl-1H-isochromene-1-carboxamide (**5a**)*

A mixture of PPh_3 (378 mg,1.5 mmol) and C_2Cl_6 (355 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 1 h. Subsequently, NEt(*i*-Pr)$_2$ (387 mg, 3 mmol) and **1a** (127 mg, 1 mmol) were added. The mixture was stirred for 2 h and then **3a** (439 mg, 1.1 mmol) and **4a** (172 mg, 1.1 mmol) were added and stirred for another 12 h. After the reaction was completed, the solvent of CH_2Cl_2 (10 mL) was changed to toluene (10 mL) and NEt(*i*-Pr)$_2$ (142 mg, 1.1 mmol) was added and stirred at 110 ^{0}C for another 2 h. After removing the solvent under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (10:1, v/v) as eluent to give **5a**. White solid, yield 65%, mp 194–196 °C, lit[11a] 196–197 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.66 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.39 (t, *J* = 8.4 Hz, 3H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 7.11 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.48 (s, 1H, =CH), 6.30 (d, *J* = 7.2Hz, 1H, NH), 5.59 (s, 1H, CH), 3.85 (d, *J* = 7.8 Hz, 1H, CH), 1.93 (d, *J* = 9.6 Hz, 1H, 0.5 CH_2), 1.80 (t, *J* = 9.6 Hz, 1H, 0.5 CH_2), 1.64 (d, *J* = 9.6 Hz, 1H, 0.5 CH_2), 1.57 (t, *J* =9.6 Hz, 2H, CH_2), 1.40-1.27 (m, 2H, CH_2), 1.23-1.11 (m, 2H, CH_2), 1.09-1.01 (m, 1H, 0.5 CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.5, 150.1, 134.9, 131.9, 130.0, 128.9, 128.7, 127.4, 126.4, 125.9, 125.1, 124.2, 102.4, 77.9, 47.8, 32.7, 25.3, 24.5.

*4.2.2 N-cyclohexyl-3-(p-tolyl)-1H-isochromene-1-carboxamide (**5b**).* White solid, yield 61%, mp 167–169 °C, lit[11a] 168–169 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.63 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.41 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.28-7.20 (m, 4H, Ar-H), 7.10 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.46 (s, 1H, =CH), 6.41 (d, *J* = 7.2Hz, 1H, NH), 5.59 (s, 1H, CH), 3.85 (s, 1H, CH), 2.40 (s, 3H, CH_3), 1.95 (d, *J* = 9.0 Hz, 1H, 0.5 CH_2), 1.81 (d, *J* = 7.2 Hz, 1H, 0.5 CH_2), 1.65-1.57 (m, 3H, CH_2, 0.5 CH_2), 1.38-1.28 (m, 2H, CH_2), 1.20-1.11 (m, 2H, CH_2), 1.07-1.03 (m, 1H, 0.5 CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.9, 151.2, 139.4, 130.7, 130.5, 129.3, 128.7, 127.0, 126.4, 125.0, 124.7, 123.9, 101.2, 77.8, 47.9, 32.7, 25.4, 24.5, 21.4.

*4.2.3 N-(tert-butyl)-3-(4-chlorophenyl)-1H-isochromene-1-carboxamide (**5c**).* White solid, yield 62%, mp 124–125 °C, lit[11a] 126–127 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.66 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.39 (t, *J* = 7.8 Hz, 3H, Ar-H), 7.30-7.23 (m, 2H, Ar-H), 7.10 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.48 (s, 1H, =CH), 6.28 (s, 1H, NH), 5.49 (s, 1H, CH), 1.33 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 149.9, 134.9, 132.0, 129.9, 128.8, 128.7, 127.4, 126.6, 125.9, 125.1, 124.2, 124.0, 101.5, 77.9, 51.3, 28.6.

*4.2.4 N-(tert-butyl)-3-(4-nitrophenyl)-1H-isochromene-1-carboxamide (**5d**).* White solid, yield 59%, mp 166–167 °C, lit[11a] 167–168 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.26 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.89 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.42 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.39-7.28 (m, 2H, Ar-H), 7.18 (d, *J* = 6.6 Hz, 1H, Ar-H), 6.70 (s, 1H, =CH), 6.23 (s, 1H, NH), 5.55 (s, 1H, CH), 1.36 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.3, 148.7, 147.5, 139.5, 129.3, 129.0, 128.4, 126.9, 125.1, 125.0, 124.9, 124.8, 123.9, 123.8, 105.7, 77.9, 51.4, 28.6.

*4.2.5 N-(tert-butyl)-3-(p-tolyl)-1H-isochromene-1-carboxamide (**5e**).* White solid, yield 65%, mp 84–86 °C, lit[11a] 86–87 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.62 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.39 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.27-7.19 (m, 4H, Ar-H), 7.08 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.45 (s, 1H, =CH), 6.39 (s, 1H, NH), 5.48 (s, 1H, CH), 2.37 (s, 3H, CH_3), 1.32 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 168.0, 151.0, 139.2, 130.7, 130.3, 129.2, 128.6, 126.8, 126.5, 125.2, 124.5, 123.9, 101.3, 77.8, 51.2, 28.6, 21.3.

*4.2.6 N-(tert-butyl)-3-(o-tolyl)-1H-isochromene-1-carboxamide (**5f**).* Light yellow oil, yield 53%, lit[11a] light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.45 (t, *J* = 5.4 Hz, 2H, Ar-H), 7.33-7.21 (m, 5H, Ar-H), 7.10 (d, *J* = 5.4 Hz, 1H, Ar-H), 6.34 (s, 1H, =CH), 6.12 (s, 1H, NH), 5.48 (s, 1H, CH), 2.50 (s, 3H, CH_3), 1.36 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 153.5, 136.7, 134.5, 130.9, 130.7, 128.9, 128.8, 128.6, 127.2, 126.3, 125.8, 124.6, 123.9, 106.3, 77.9, 51.3, 28.7, 20.9.

*4.2.7 N-(tert-butyl)-3-(2-iodophenyl)-1H-isochromene-1-carboxamide (**5g**).* White solid, yield 51%, mp 74–76 °C, lit[11a] 73–75 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.94 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.52 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.47 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.31-7.26 (m, 2H, Ar-H), 7.13-7.07 (m, 2H, Ar-H), 6.47 (s, 1H, =CH), 6.17 (s, 1H, NH), 5.64 (s, 1H, CH), 1.41 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.1, 153.6, 140.1, 139.7, 130.5, 130.4, 130.3, 128.6, 128.5, 128.1, 127.7, 126.4, 124.1, 123.9, 106.6, 96.2, 78.0, 51.3, 28.5.

*4.2.8 N-cyclohexyl-3-phenyl-1H-isochromene-1-carboxamide (**5h**).* White solid, yield 60%, mp 144–145 °C, lit[11a] 144–146 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.45-7.35 (m, 4H, Ar-H), 7.29-7.21 (m, 2H, Ar-H), 7.10 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.50 (s, 1H, =CH), 6.40 (d, *J* = 7.2 Hz, 1H, NH), 5.60 (s, 1H, CH), 3.86 (s, *J* = 8.4 Hz, 1H,H, CH), 1.96-1.78 (m, 2H, CH_2), 1.66-1.51 (m, 3H, 1.5 CH_2), 1.39-1.11 (m, 5H, 2.5 CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 151.0,

133.4, 130.3, 129.1, 128.7, 128.6, 127.1, 126.4, 125.0, 124.7, 124.1, 101.0, 77.8, 47.8, 32.7, 25.3, 24.4.

*4.2.9 N-(tert-butyl)-3-(furan-2-yl)-1H-isochromene-1-carboxamide (**5i**).* White solid, yield 51%, mp 96–97 °C, lit[11a] 98–99 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.49–7.05 (m, 5H, Ar–H), 6.63–6.46 (m, 2H, Ar–H), 6.45 (s, 1H, NH), 6.42 (s, 1H,=CH), 5.46 (s, 1H, CH), 1.33 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 148.6, 143.3, 143.1, 129.3, 128.7, 127.1, 126.7, 125.9, 124.1, 111.5, 108.0, 101.3, 77.5, 51.3, 28.5.

*4.2.10 N-(tert-butyl)-3-methyl-1H-isochromene-1-carboxamide (**5j**).* Light yellow oil, yield 55%, lit[11a] light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.32 (d, J = 7.2 Hz, 1H, Ar-H), 7.21 (t, J = 7.2 Hz, 1H, Ar-H), 7.16 (d, J = 7.2 Hz, 1H, Ar-H), 6.92 (d, J = 7.2 Hz, 1H, Ar-H), 6.29 (s, 1H, NH), 5.70 (s, 1H, =CH), 5.32 (s, 1H, CH), 1.99 (s, 3H, CH_3), 1.39 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 168.1, 151.9, 130.4, 128.6, 126.3, 125.4, 124.9, 122.6, 102.7, 77.7, 51.2, 28.6, 19.6.

*4.2.11 N-(tert-butyl)-3-(chloromethyl)-1H-isochromene-1-carboxamide (**5k**).* White solid, yield 46%, mp 122–124 °C, lit[11a] 124–125 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.36 (d, J = 6.0 Hz, 1H, Ar-H), 7.26-7.18 (m, 2H, Ar-H), 7.00-6.92 (m, 1H, Ar-H), 6.86 (s, 1H, NH), 5.91 (s, 1H, =CH), 5.53 (s, 1H, CH), 4.29-4.10 (m, 2H, CH_2), 1.37 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.9, 147.8, 128.7, 128.0, 127.8, 126.9, 126.0, 124.1, 105.0, 77.6, 51.8, 44.3 28.7.

*4.2.12 N-(tert-butyl)-1H-isochromene-1-carboxamide (**5l**).* White solid, yield 56%, mp 55–56 °C, lit[11a] 58–60 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.36 (d, J = 7.2 Hz, 1H, Ar-H), 7.23-7.17 (m, 2H, Ar-H), 6.96 (d, J = 7.2 Hz, 1H, Ar-H), 6.57 (d, J = 6.0 Hz, 1H, =CH), 6.31 (s, 1H, NH), 5.86 (d, J = 6.6 Hz, 1H, =CH)), 5.34 (s, 1H, CH), 1.38 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 143.0, 128.8, 128.6, 127.2, 126.5, 125.0, 123.3, 106.6, 77.3, 51.2, 28.7.

*4.2.13 N-cyclohexyl-3-(4-nitrophenyl)-1H-isochromene-1-carboxamide (**5m**).* White solid, yield 51%, mp 205–207 °C, lit[11a] 207–208 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.30 (q, J = 8.4 Hz, 2H, Ar-H), 7.91 (q, J = 8.4 Hz, 2H, Ar-H), 7.52-7.40 (m, 1H, Ar-H), 7.38-7.28 (m, 2H, Ar-H), 7.24-7.16 (m, 1H, Ar-H), 6.71 (t, J = 7.2 Hz, 1H, =C-H), 6.24 (d, J = 9.6 Hz, 1H, NH), 5.67 (t, J = 7.2 Hz, 1H, CH), 3.88 (d, J = 10.2 Hz, 1H, CH), 2.04-1.06 (m, 10H, $5CH_2$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.2, 148.9, 147.6, 139.5, 129.4, 129.0, 128.5, 126.7, 125.2, 125.0, 124.8, 123.9, 105.7, 77.9, 48.1, 32.8, 25.3, 24.5.

*4.2.14 N-(tert-butyl)-3-(thiophen-2-yl)-1H-isochromene-1-carboxamide (**5n**).* White solid, yield 53%, mp 105–108 °C, lit[11a] 107–108 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.42-7.03 (m, 7H, Ar-H), 6.46 (s, 1H, NH), 6.38 (s, 1H, =CH), 5.50 (s, 1H, CH), 1.35 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 146.5, 137.8, 129.7, 128.7, 127.9, 126.9, 126.4, 126.1, 125.7, 124.3, 123.8, 101.2, 77.8, 51.4, 28.6.

*4.2.15 N-(tert-butyl)-3-(2-fluorophenyl)-1H-isochromene-1-carboxamide (**5o**).* White solid, yield 57%, mp 88–89 °C, lit[11a] 87–88 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.72 (t, J = 7.2 Hz, 1H, Ar-H), 7.41 (d, J = 7.2 Hz, 1H, Ar-H), 7.36-7.18 (m, 4H, Ar-H), 7.12 (d, J = 7.2 Hz, 2H, Ar-H), 6.64 (s, 1H, =CH), 6.46 (s, 1H, NH), 5.51 (s, 1H, CH), 1.35 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.8, 160.9, 159.3, 146.3, 130.2, 129.9, 128.7, 127.9, 127.5, 126.6, 125.2, 124.5, 124.4, 121.9, 116.3, 107.4, 77.7, 51.3, 28.6.

*4.3 Typical procedure for the synthesis of **8***

*4.3.1 4-(4-chlorophenyl)-N-cyclohexyl-1-oxo-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8a**).*
A mixture of PPh_3 (378 mg,1.5 mmol) and C_2Cl_6 (355 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 1 h. Subsequently, NEt(i-Pr)$_2$ (387 mg, 3 mmol) and **1a** (127 mg, 1 mmol) were added. The mixture was stirred for 2 h and then **6a** (525 mg, 1.1 mmol) and **7a** (185 mg, 1.1 mmol) were added and stirred for another 12 h. After the reaction was completed, the solvent of CH_2Cl_2 (10 mL) was changed to toluene (10 mL) and NEt(i-Pr)$_2$ (142 mg, 1.1 mmol) was added and stirred at 110 ^{o}C for another 3 h. After removing the solvent under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (10:1, v/v) as eluent to give **8a**. White solid, yield 69%, mp 206–207 °C, lit[11b] 209–212 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.92 (d, J = 7.8 Hz, 1H, Ar-H), 7.58 (t, J = 7.2 Hz, 1H, Ar-H), 7.45-7.38 (m, 2H, Ar-H), 7.34 (d, J = 8.4 Hz, 1H, Ar-H), 7.29 (d, J = 8.4 Hz, 2H, Ar-H), 7.24 (d, J = 7.8 Hz, 2H, Ar-H), 6.08 (s, 1H, CH), 5.62 (d, J = 7.2 Hz, 1H, NH), 3.78-3.66 (m, 1H, CH), 1.88-1.60 (m, 5H, $2.5CH_2$), 1.45-0.82 (m, 5H, $2.5CH_2$); ^{13}CNMR ($CDCl_3$, 150 MHz) δ (ppm) 168.5, 164.8, 139.4, 135.7, 134.3, 134.0, 132.9, 132.6, 132.3, 131.1, 129.8, 129.5, 128.6, 128.4, 127.4, 127.3, 74.5, 48.6, 32.7, 25.2, 24.7.

*4.3.2 N-cyclohexyl-1-oxo-4-(p-tolyl)-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8b**).* White solid, yield 63%, mp 125–127 °C, lit[11b] 128–130 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.97 (d, J = 7.8 Hz, 1H, Ar-H), 7.58 (d, J = 7.8 Hz, 2H, Ar-H), 7.48-7.40 (m, 2H, Ar-H), 7.28 (d, J = 8.4 Hz, 2H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 6.04 (s, 1H, CH), 5.39 (d, J = 6.0 Hz, 1H, NH), 3.67 (d, J = 9.0 Hz, 1H, CH), 2.31 (s, 3H, CH_3), 1.96-1.77 (m, 2H, CH_2), 1.54 (d, J = 6.6 Hz, 3H, $1.5CH_2$), 1.22-0.93 (m, 5H, $2.5CH_2$); ^{13}CNMR ($CDCl_3$, 150 MHz) δ (ppm) 168.8, 164.4, 139.6, 138.2, 136.9, 133.4, 132.6, 132.4, 132.3, 131.3, 129.9, 129.4, 129.3, 125.8, 75.0, 48.5, 32.3, 25.3, 24.6, 21.0.

*4.3.3 N-(tert-butyl)-4-(4-chlorophenyl)-1-oxo-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8c**).* White solid, yield 71%, mp 160–162 °C, lit[11b] 163–164 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.96 (d, J = 7.8 Hz, 1H, Ar-H),

7.58 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.48-7.42 (m, 2H, Ar-H), 7.38 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.33 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.02 (s, 1H, CH), 5.38 (s, 1H, NH), 1.22 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) *δ* (ppm) 168.4, 165.1, 140.2, 135.2, 134.3, 133.9, 133.0, 132.5, 132.2, 130.9, 129.7, 129.3, 128.4, 127.4, 74.5, 51.7, 28.3.

*4.3.4 N-(tert-butyl)-1-oxo-4-(p-tolyl)-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8d**).* White solid, yield 66%, mp 136–137 °C, lit[11b] 136–138 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) *δ* (ppm) 7.98 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.62-7.54 (m, 2H, Ar-H), 7.49-7.40 (m, 2H, Ar-H), 7.29 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.16 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.99 (s, 1H, CH), 5.25 (s, 1H, NH), 2.33 (s, 3H, CH_3), 1.14 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) *δ* (ppm) 168.8, 164.4, 140.4, 138.2, 136.7, 133.5, 133.3, 132.7, 132.4, 132.3, 131.2, 129.9, 129.4, 129.3, 125.8, 75.0, 51.6, 28.2, 21.0.

*4.3.5 4-(4-bromophenyl)-N-cyclohexyl-1-oxo-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8e**).* White solid, yield 57%, mp 220–223 °C, lit[11b] 222–224 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) *δ* (ppm) 7.93 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.55 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.45-7.38 (m, 4H, Ar-H), 7.35 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.23 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.06 (s, 1H, CH), 5.57 (d, *J* = 7.2 Hz, 1H, NH), 3.71 (d, *J* = 8.4 Hz, 1H, CH), 1.86 (d, *J* = 9.0 Hz, 1H, $0.5CH_2$), 1.75-1.55 (m, 4H, $2CH_2$), 1.39-1.26 (m, 2H, CH_2), 1.19-1.04 (m, 2H, CH_2), 0.98-0.86 (m, 1H, $0.5CH_2$); ^{13}CNMR ($CDCl_3$, 150 MHz) *δ* (ppm) 168.5, 164.8, 139.4, 135.9, 134.8, 132.9, 132.6, 132.3, 131.5, 131.1, 129.8, 129.5, 127.6, 122.2, 74.5, 48.8, 32.6, 25.3, 24.7.

*4.3.6 4-(4-bromophenyl)-N-(tert-butyl)-1-oxo-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8f**).* White solid, yield 66%, mp 146–148 °C, lit[11b] 149–151 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) *δ* (ppm) 7.94 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.46-7.39 (m, 4H, Ar-H), 7.35 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.25 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.00 (s, 1H, CH), 5.48 (s, 1H, NH), 1.23 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) *δ* (ppm) 168.5, 165.0, 140.1, 135.5, 134.9, 133.0, 132.6, 132.3, 131.5, 131.0, 129.7, 129.5, 127.6, 122.2, 74.5, 51.8, 28.3.

*4.3.7 4-(4-bromophenyl)-N-butyl-1-oxo-1,3-dihydrobenzo[c]oxepine-3-carboxamide (**8g**).* White solid, yield 68%, mp 175–176 °C, lit[11b] 176–178 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) *δ* (ppm) 8.04 (d, J = 7.8 Hz, 1H, Ar-H), 7.64 (t, J = 7.2 Hz, 1H, Ar-H), 7.55-7.45 (m, 3H, Ar-H), 7.41 (d, J = 7.8 Hz, 1H, Ar-H), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 7.00 (s, 1H, =CH), 6.90 (s, 1H, NH), 5.31 (s, 1H, CH), 3.40-3.30 (m, 2H, CH_2), 1.50-1.35 (m, 2H, CH_2), 1.33-1.16 (m, 2H, CH_2), 0.90 (d, J = 7.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 167.9, 165.7, 141.5, 136.6, 135.0, 134.1, 132.9, 132.4, 131.5, 129.6, 129.5, 128.9, 128.7, 122.5, 75.4, 39.0, 31.3, 19.9, 13.6.

*4.4 Typical procedure for the synthesis of **9c***

*4.3.1 (2-(((1-(tert-butylamino)-3-(4-chlorophenyl)-1,3-dioxopropan-2-yl)oxy)carbonyl)benzyl) triphenylphosphonium bromide (**9c**).*

A mixture of isocyanide **2c** (125 mg, 1.5 mmol), phosphonium salts **6c** (477 mg, 1.0 mmol) and 4-chlorophenylglyoxal **7c** (218 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 24 h. After the reaction was completed, the solvent was removed under reduced pressure, the resulting crude was washed with petroleum ether/diethyl ether (2:1, v/v) to give **8a**. Light yellow solid, yield 98%, mp 175–178 °C, lit[11b] 178–179 °C; ^{1}H NMR (DMSO, 600 MHz) *δ* (ppm) 8.36 (s, 1H, N-H), 8.02 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.95 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.87 (t, *J* = 7.2 Hz, 3H, Ar-H), 7.77-7.53 (m, 15H, Ar-H), 7.34-7.06 (m, 2H, Ar-H), 6.27 (s, 1H, CH), 5.66-5.43 (m, 2H, CH_2), 1.22 (s, 9H, $3CH_3$); ^{13}CNMR (DMSO, 100 MHz) *δ* (ppm) 189.6, 164.7, 162.1, 139.0, 135.0, 133.9, 133.8, 133.5, 132.3, 132.2, 132.1, 131.8, 130.5, 130.1, 130.0, 129.8, 129.7, 129.2, 129.1, 128.9, 128.8, 128.1, 125.2, 117.8, 116.9, 77.6, 51.1, 28.0, 26.8, 26.3.

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