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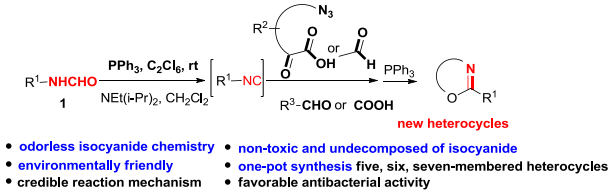
Odorless Isocyanide Chemistry：One-Pot Synthesis of Heterocycles *via* Passerini and the Post-Modification Tandem Reaction Based on *In-situ* Capture of Isocyanides

Na Liu,[‡,†] Fei Chao,[‡,†] Ming-Guo Liu,[§,†] Nian-Yu Huang,[§] Kun Zou,[§] Long Wang,*[,‡]

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

[§]Hubei Key Laboratory of Natural Products Research and Development, College of Biology and Pharmacy, China Three Gorges University, Yichang, Hubei 443002, China.

Email: wanglongchem@ctgu.edu.cn

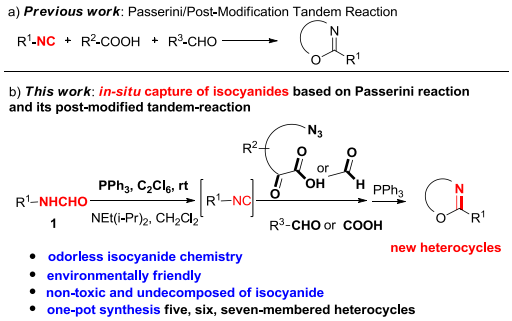


This paper reports the tandem-reaction strategy of Passerini/Staudinger/aza-Wittig reaction based on the in-situ capture of isocyanides. According to this strategy, isocyanides are synthesized in situ, which immediately work as the substrate for Passerini reaction and post-modified tandem reaction in one-pot. In addition, two types new compounds of 5-oxo-3,5-dihydrobenzo[*e*][1,4] oxazepines and 6-oxo-5,6-dihydro-2*H*-1,4-oxazines were synthesized using the tandem-reaction strategy which undergos five-step transformations in one-pot.

Key words: isocyanides, *in-situ* capture, tandem-reaction, heterocycles

Multicomponent reaction has attracted more and more attention in recent years thanks to the good reaction efficiency and atom economy.[1] The Passerini reaction is an isocyanide-based multicomponent reaction, and has turned into one of the hot spots of multicomponent reaction research in recent years thanks to the possibility of protecting or preserving the functional group in a certain component before post-modified reaction.[2] Many important organic reactions, such as Aldol reaction, Heck reaction, S_NAr reaction, Wittig reaction and aza-Wittig reaction are used in series for the post-modified reaction of isocyanide-based multicomponent reaction (IMCR) to synthesize a variety of heterocycles(Scheme 1a).[3] In recent years, our team and other researchers have used this tandem-reaction strategy to achieve a series of research findings in respect of the synthesis of heterocycles.[4] However, there are several extremely severe problems with isocyanide-based reactions: 1) The poor environmental friendliness of isocyanides (strong foul odor). 2) Poor stability of isocyanides. 3) Isocyanides are highly toxic. The said drawbacks of isocyanides demand prompt solution because they severely hinder the progress of the isocyanide chemistry.

Scheme 1. Synthesis of new heterocycles via the *in-situ* capture of isocyanides based Passerini reaction and its post-modified tandem-reaction strategy.



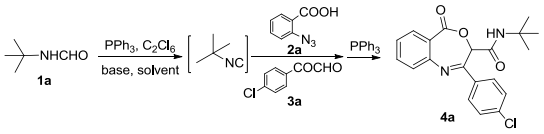
In-situ capture of isocyanides in reaction is an effective solution to this problem. According to this method, isocyanides are obtained through *in-situ* synthesis of precursor and are then immediately used which avoid the storage, separation and purification of isocyanides, thereby avoiding isocyanides exposure-induced strong foul odor, isocyanides decomposition and other problems, which significantly makes up for the drawbacks of the isocyanide chemistry(Scheme 1b).[5] In recent years, breakthroughs have been achieved in reaction based on the *in-situ* capture of isocyanides. In 2005, Parsons et al. reported the multicomponent reaction realized with isocyanides prepared in situ from epoxides.[5a] In 2009, Kaim et al. reported the Ugi reaction realized using isocyanides prepared in situ from benzyl chloride and silver cyanide.[5b-5d] In 2013, Kim et al. reported the first odorless Passerini reaction realized through the integrated microfluidic system.[5e] In 2015, Dömling et al. also realized the multicomponent reaction based on the *in-situ* capture of isocyanides.[5f] To the best of our knowledge, however, no post-modified tandem reaction of *in-situ* capture of isocyanides based Passerini reaction has been reported so far.

Heterocycles are widely distributed in nature and account for one third of the known organic compounds. Among them, 5-oxo-3,5-dihydrobenzo[*e*][1,4]oxazepines are very important and common nitrogen-containing heterocycles that exhibit favorable biological activities in respect of diminishing inflammation, killing bacteria and resisting cancer, etc. Additionally, these compounds are basic skeletons for many natural products and biological active compounds.[6] Thus, their synthesis has received certain attention.[7] Based on our previous studies,[8] we developed a tandem-reaction strategy based on the *in-situ* capture of isocyanides of the Passerini reaction and post-modified reactions and a series of 5-oxo-3,5-dihydrobenzo[*e*][1,4]oxazepines, 6-oxo-5,6-dihydro-2*H*-1,4-oxazines and oxazoles were synthesized using the tandem-reaction.

First of all, the reaction conditions were explored by using amide **1a**, o-azidobenzoic acid **2a** and 4-chlorophenylglyoxal **3a** as model substrates. Firstly, target compound **4a** was obtained with a yield of 16% at room temperature by using dichloromethane and potassium carbonate as solvent and base, respectively. The bases were then screened (Table 1). Base had a great effect on reaction; inorganic bases offered poor reaction effect, while organic bases performed better. When triethylamine was used as the base, target compound **4a** was obtained with yield up to 51%. Further optimization of the base indicated that the yield was 66% when diisopropylethylamine was used as the base. Afterward, the solvent was optimized, and it

was found that the yield decreased when the solvent was changed to acetonitrile and DMF. The reaction temperature was further screened and room temperature was found to be the most suitable temperature for the reaction. However, when C_2Cl_6 was substituted to I_2, no target compound **4a** was obtained.[9]

Table 1. Optimization of the reaction conditions.[a,b,c]

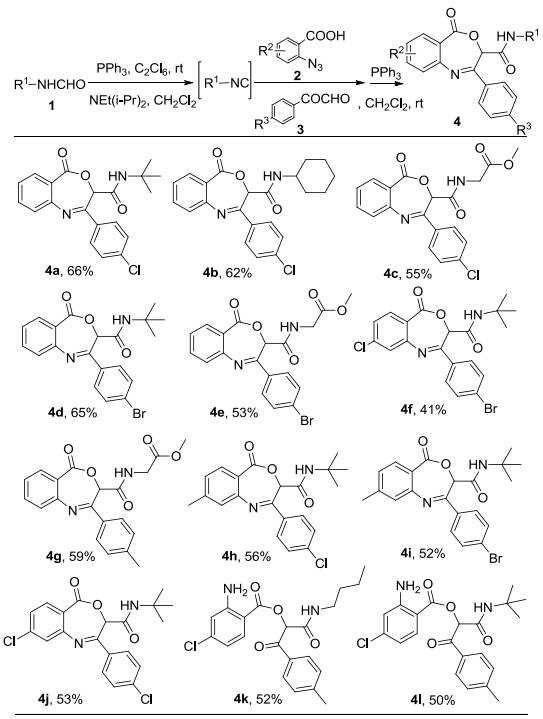


Entry	Solvent	Base	*T*	**4a**[%][b]
1	CH_2Cl_2	K_2CO_3	rt	16
2	CH_2Cl_2	Cs_2CO_3	rt	0
3	CH_2Cl_2	Na_2CO_3	rt	0
4	CH_2Cl_2	NEt_3	rt	51
5	CH_2Cl_2	NEt(*i*-Pr)$_2$	rt	66
6	CH_2Cl_2	DBU	rt	36
7	CH_2Cl_2	DABCO	rt	51
8	CH_3CN	NEt(*i*-Pr)$_2$	rt	36
9	DMF	NEt(*i*-Pr)$_2$	rt	18
10	CH_2Cl_2	NEt(*i*-Pr)$_2$	0	52
11	CH_2Cl_2	NEt(*i*-Pr)$_2$	60	20
12	CH_2Cl_2	NEt(*i*-Pr)$_2$	rt	0[c]

[a] *Condotions:* 1) **1a** (1 mmol), PPh_3 (1.1 mmol), C_2Cl_6 (1.1 mmol), solvent (10 ml), base (2.2 mmol), air, **2a** (1.1 mmol), **3a** (1.1 mmol) and then PPh_3 (1.2 mmol). [b] 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 (Scheme 2). Aliphatic isocyanides offered satisfactory reaction because 5-oxo-3,5-dihydrobenzo[*e*][1,4] oxazepines were obtained with yields of approximately 60%. However, the hythrolyzates of **4k** and **4l** were obtained when R^2 is electron-withdrawing substituent and R^3 is electron-donating substituent while 5-oxo-3,5-dihydrobenzo[*e*][1,4] oxazepines can not be obtained. Additionally, 2.22g of **4a** was synthesized at a yield of 60% when the reaction was amplified to 10 mmol.

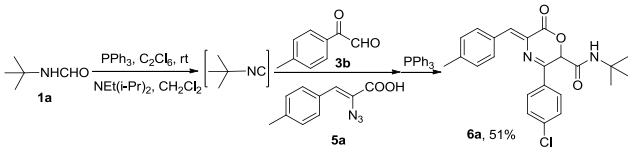
Scheme 2. Preparation of 5-oxo-3,5-dihydrobenzo [*e*][1,4]oxazepines **4** by the tandem reaction.[a]



[a] Yields based on **1**.

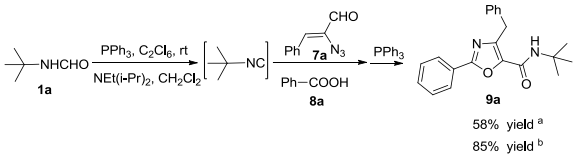
6-oxo-5,6-dihydro-2*H*-1,4-oxazines are also a very important category of heterocycles.[10] We employed the tandem-reaction strategy of *in-situ* capture of isocyanides based Passerini reaction, Staudinger reaction and intramolecular aza-Wittig reaction for the synthesis of 6-oxo-5,6-dihydro-2*H*-1,4-oxazines (Scheme 3). Meanwhile, the compound of **6a** was synthesized in one-pot and needs very mild reaction conditions.

Scheme 3. Preparation of 6-oxo-5,6-dihydro-2*H*-1,4-oxazine **6a** by the tandem reaction.



Oxazoles are also a very important category of compounds that exhibit favorable biological activities in terms of anti-inflammatory, antifungal, anticancer, etc.[11] Added to this, oxazoles are basic skeletons of many natural products and biologically active compounds.[12] Therefore, oxazoles were also synthesized using the tandem-reaction strategy which based on the *in-situ* capture of isocyanides (Scheme 4). The yield of synthetic compound **9a** is 58%, which undergoes five-step transformations in one-pot. And the yield of 58% means the total yield of the five-steps transformations, which was based on amide **1a**, while the yield of 70% was based on azidocinnamaldehyde **7a** in the literature.[4d] In addition, we had much higher yields of 85% if the yields are also based on azidocinnamaldehyde **7a**, which are much higher than that reported in literature of 70%. Meanwhile, the compound was synthesized in one-pot and needs very mild reaction conditions, which provided an efficient and simple method to synthesis of oxazole derivative with: 1) five steps in 58% yield (one-pot) vs four steps in 85% yield stepwise. 2) simplicity of operator; 3) strong anti-interference ability.

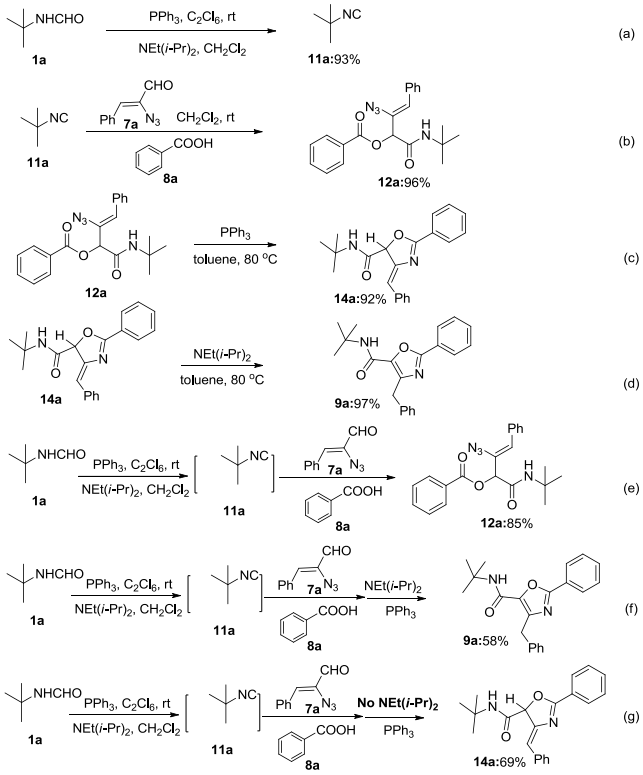
Scheme 4. Preparation of Oxazoles **9** by the tandem reaction.



[a] The total yield of the five-steps transformations and the yield was based on **1a**. [b] Based on **7a**.

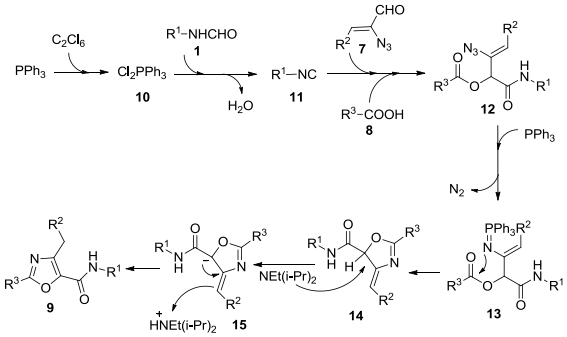
Added to this, in order to make further understanding of this tandem reaction, we probed into the reaction mechanism through condition control experiments. Amide **1a** was used to obtain the isocyanide **11a** at a yield of 93% under the action of PPh_3, C_2Cl_6 and NEt(*i*-Pr)$_2$. The Passerini reaction between isocyanide **11a**, α-azidocinnamaldehyde **7a** and acid **8a** in CH_2Cl_2 at room temperature obtained intermediate **12a** at a yield of 96%. Intermediate **12a** was converted into cyclic intermediate **14a** at yield of 92% through Staudinger reaction with PPh_3. Under the action of NEt(*i*-Pr)$_2$, intermediate **14a** generated oxazoles **9a** at a yield of 97%. α-azidocinnamaldehyde **7a** and acid **8a** captured *in-situ* prepared isocyanide **11a** in CH_2Cl_2 at room temperature, and obtained intermediate **12a** at a yield of 85%. Under the action of PPh_3 and NEt(*i*-Pr)$_2$, the target compound **9c** was obtained at a yield of 58% through Passerini/Staudinger/aza-Wittig/Aromatization tandem reaction through *in-situ* prepared isocyanide **11a** captured byα-azidocinnamaldehyde **7a** and acid **8a**. However, no target compound was obtained when no additional NEt(*i*-Pr)$_2$ was added during the reaction, although cyclic intermediate **14a** was obtained at a yield of 69%.

Scheme 5. Control experiments and mechanism investigation.



Based on the result of condition control experiment, we proposed a possible reaction mechanism (Scheme 6). First, triphenylphosphine reacted with hexachloroethane to produce phosphine salt **10**; A molecule of water was removed by **10** from amide **1** to get isocyanide **11** in situ; azidocinnamaldehyde **7** and carboxylic acid **8** captured isocyanide **11** prepared in situ, and produced intermediate **12** through Passerini reaction; The Staudinger reaction between intermediate **12** and triphenylphosphine released a molecule of nitrogen and produced phosphine imine **13**; Phosphine imine **13** generated cyclization product **14** through intramolecular aza-Wittig reaction; The 1,3-H shift of compound **14** under the action of base produced oxazoles **9**.

Scheme 6. The proposed possible mechanism.



At the same time, we tested the bactericidal activity of some of the synthesized compounds. The bactericidal activities of some of the compounds against five important fungi, i.e., Fusarium graminearum, Magnaporthe oryzae, Penicillium digitatum, Penicillium italicum and Rhizoctonia solani by using Triadmefon and Diniconazle as positive control agents (Table 2). Test result showed that some of compounds, for example, **9a**, exhibited an inhibition ratio of up to 70% against Rhizoctonia solani, which was higher than the inhibition ratio of control agent Triadmefon. According to the summary of inhibition ratio and structure-activity relationship of compound, the antibacterial activity is higher when the substituent contains chlorine (e.g., **4c**).

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

Compd.	Inhibition rate /(%)				
	P. digitatum	P. italicum	F. graminearum	M. oryzae	R. solani
4c	41	38	15	23	35
4e	26	25	0	21	27
4g	43	37	25	27	37
9a	62	50	38	57	70
triadmefon	65	63	45	56	67
diniconazle	100	99	91	97	99

In summary, this paper reports the tandem-reaction strategy of Passerini/Staudinger/aza-Wittig reaction based on the *in-situ* capture of isocyanides. Two types new compounds of 5-oxo-3,5-dihydrobenzo[*e*][1,4] oxazepines and 6-oxo-5,6-dihydro-2*H*-1,4-oxazines was synthesized in one-pot for the first time. Additionally, a relatively credible reaction mechanism was proposed through a series of condition control experiments. The strategy described in this article is the isocyanides was synthesized in situ and immediately used for Passerini reaction and its post-modified tandem reaction. Moreover, this

avoids the separation, purification and storage of isocyanides, and solves the problems such as isocyanides exposure (isocyanides are toxic and strongly fetid) induced environmentally unfriendliness and isocyanides decomposition, having remarkably improved the drawbacks of the isocyanide chemistry.

EXPERIMENTAL SECTION

General Methods and Materials.

All the obtained products were characterized ^{1}H NMR spectra and ^{13}C NMR spectra (400 or 600 MHz). ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury 400 or 600 spectrometer and referenced to $CDCl_3$ (7.26 ppm for 1H, and 77.0 ppm for ^{13}C) with tetramethylsilane as internal standard (0 ppm). 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); High resolution mass spectra (HRMS) were recorded on LTQ-FTUHRA mass spectrometer. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm; Unless otherwise stated, all the reagents were purchased from commercial sources and used without further purification.

Typical procedure for the synthesis of 4. A mixture of PPh_3 (288 mg, 1.1 mmol) and C_2Cl_6 (257 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 1 h. Subsequently, NEt(*i*-Pr)$_2$ (284 mg, 2.2 mmol) and **1** (1 mmol) were added. The mixture was stirred for 2 h and then **2** (1.1 mmol) and **3** (1.1 mmol) were added and stirred for another 1-24 h. After the reaction was completed, PPh_3 (314 mg, 1.2 mmol) was added and stirred at room temperature for another 1-6 h. After removing the solvent under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (15:1, v/v) as eluent to give **4**.

N-(tert-butyl)-2-(4-chlorophenyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4a)****:* (White solid, 0.24 g, 66% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.98 (d, J = 7.6 Hz, 1H), 7.85 - 7.65 (m, 3H), 7.50 - 7.35 (m, 4H), 6.76 (s, 1H), 5.18 (s, 1H), 1.36 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.7, 165.1, 163.8, 145.9, 137.2, 134.2, 133.0, 131.9, 128.9, 128.6, 127.3, 127.2, 121.4, 71.8, 52.2, 28.4 ; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{19}ClN_2O_3Na$ 393.0976; found 393.0983.

2-(4-chlorophenyl)-N-cyclohexyl-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4b)****:* (White solid, 0.25 g, 62% yield); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.98 (d, J = 6.0Hz, 1H), 7.82 - 7.65 (m, 3H), 7.52 - 7.33 (m, 4H), 6.91 (s,1H), 5.24 (s, 1H), 3.79 (s, 1H), 1.96 - 1.15 (m, 10H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.7, 164.9, 163.7, 145.9, 137.2, 134.2, 131.9, 131.1, 131.0, 128.8, 128.7, 127.3, 121.3, 71.9, 48.5, 32.6, 25.2, 24.8; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}ClN_2O_3$ 397.1313; found 397.1323.

methyl(2-(4-chlorophenyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carbonyl)glycinate ***(4c)****:* (White solid, 0.21 g, 55% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.99 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.71 (t, J = 7.2 Hz, 1H), 7.54 (s, 1H), 7.51-7.37 (m, 4H), 5.37 (s, 1H), 4.37-3.89 (m, 2H), 3.78 (s, 3H);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 169.3, 166.4, 165.5, 164.3, 145.9, 137.5, 134.3, 133.9, 132.1, 131.5, 129.2, 128.9, 127.4, 121.3, 72.0, 52.5, 40.6; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}ClN_2O_5$ 387.0742; found 387.0743.

2-(4-bromophenyl)-N-(tert-butyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4d)****:* (White solid, 0.27 g, 65% yield); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.97 (d, *J* = 7.2 Hz, 1H), 7.69 (s, 3H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.77 (s, 1H), 5.16 (s, 1H), 1.38 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.6, 165.2, 163.7, 145.9, 134.2, 131.8, 131.5, 131.1, 129.1, 127.3, 127.2, 121.4, 71.7, 52.1, 28.4; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}BrN_2O_3$ 415.0652; found 415.0657.

methyl(2-(4-bromophenyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carbonyl)glycinate ***(4e)****:* (White solid, 0.23 g, 53% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.98 (d, *J* = 6.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 3H), 7.58 (d, *J* = 7.2 Hz, 3H), 7.50-7.36 (m, 2H), 5.37 (s, 1H), 4.30-3.90 (m, 2H), 3.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 169.3, 166.4, 165.5, 164.5, 145.9, 137.3, 134.3, 133.3, 132.1, 131.9, 129.3, 127.4, 125.9, 121.3, 71.9, 52.5, 40.6; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}BrN_2O_5$ 431.0237; found 431.0234.

2-(4-bromophenyl)-N-(tert-butyl)-8-chloro-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4f)****:* (White solid, 0.18 g, 41% yield) , ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.92 (d, *J* = 8.4 Hz, 1H), 7.75-7.62 (m, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 6.72 (s, 1H), 5.17 (s, 1H), 1.37 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.4, 165.9, 163.4, 146.9, 140.5, 133.2, 131.7, 129.2, 127.6, 127.2, 126.3, 119.9, 71.8, 52.3, 28.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}ClBrN_2O_3$ 449.0262; found 449.0270.

methyl(2-(4-bromophenyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carbonyl)glycinate ***(4g)****:* (White solid, 0.22 g, 59% yield)； ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.98 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.60 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0Hz, 2H), 5.37 (s, 1H), 4.25-3.92 (m, 2H), 3.77 (s, 3H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 169.3, 166.8, 165.7, 165.2, 146.3, 141.7, 134.2, 131.9, 129.4, 127.7, 127.3, 126.9, 121.3, 72.3, 52.5, 40.7, 21.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}N_2O_5$ 367.1288; found 367.1291.

N-(tert-butyl)-2-(4-chlorophenyl)-8-methyl-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4h)****:* (White solid, 0.21 g, 56% yield)； ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 5.16 (s, 1H), 2.47 (s, 3H), 1.35 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.8, 165.0, 163.9, 145.9, 145.5, 137.2, 132.0, 129.0, 128.6, 128.4, 127.7, 118.8, 72.0, 52.2, 28.5, 21.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}ClN_2O_3$ 385.1313; found 385.1306.

2-(4-bromophenyl)-N-(tert-butyl)-8-methyl-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4i)****:* (White solid, 0.22 g, 52% yield)； ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.88 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 5.17 (s, 1H), 2.47 (s, 3H), 1.35 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.8, 165.1, 163.9, 145.9, 145.5,

132.0, 131.6, 129.1, 128.4, 127.7, 125.6, 118.8, 71.9, 52.2, 28.5, 21.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}BrN_2O_3$ 429.0808; found 429.0817.

N-(tert-butyl)-8-chloro-2-(4-chlorophenyl)-5-oxo-3,5-dihydrobenzo[e][1,4]oxazepine-3-carboxamide ***(4j)****:* (White solid, 0.21 g, 53% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.92 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 6.4 Hz, 2H), 7.48 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 6.72 (s, 1H), 5.18 (s, 1H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.2, 165.9, 163.5, 147.0, 140.6, 137.8, 133.3, 129.1, 128.8, 127.5, 127.3, 120.0, 71.9, 52.3, 28.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}Cl_2N_2O_3$ 405.0767; found 405.0775.

1-(butylamino)-1,3-dioxo-3-(p-tolyl)propan-2-yl 2-amino-4-chlorobenzoate ***(4k)****:* (White solid, 0.21 g, 52% yield); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.08 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 6.65 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.48(t, J = 5.4 Hz, 1H), 6.45 (s, 1H), 5.80 (s, 2H), 3.37-3.23 (m, 2H), 2.41 (s, 3H), 1.54-1.46 (m, 2H), 1.37-1.27 (m, 2H), 0.88(t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ (ppm) 191.5 165.3, 163.8, 151.7, 145.4, 141.0, 132.4, 131.7, 129.7, 129.4, 116.8, 116.1, 107.2, 76.3, 39.4, 31.3, 27.8, 19.9, 13.6; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}ClN_2O_4$ 403.1419; found 403.1422.

1-(tert-butylamino)-1,3-dioxo-3-(p-tolyl)propan-2-yl 2-amino-4-chlorobenzoate ***(4l)****:* (White solid, 0.20 g, 50% yield); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.07 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 6.65 (s, 1H), 6.63 (d, J = 9.0 Hz, 1H), 6.34(s, 1H), 6.22 (s, 1H), 5.80 (s, 2H), 2.41 (s, 3H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ (ppm) 191.9 165.2, 163.0, 151.7, 145.2, 141.0, 132.2, 131.9, 129.7, 129.4, 116.8, 116.1, 107.3, 76.4, 51.9, 28.5, 21.8; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}ClN_2O_4$ 403.1419; found 403.1423.

Typical procedure for the synthesis of 6a: A mixture of PPh_3 (288 mg, 1.1 mmol) and C_2Cl_6 (257 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 1 h. Subsequently, NEt(*i*-Pr)$_2$ (284 mg, 2.2 mmol) and **1a** (101 mg, 1 mmol) were added. The mixture was stirred for 2 h and then **3b** (163 mg,1.1 mmol) and **5a** (223 mg, 1.1 mmol) were added and stirred for another 6 h. After the reaction was completed, the solvent of CH_2Cl_2 was changed to toluene (5 mL), then PPh_3 (314 mg, 1.2 mmol) was added and stirred at room temperature for another 3 h. After removing the solvent under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (15:1, v/v) as eluent to give **6a**.

(Z)-N-(tert-butyl)-3-(4-chlorophenyl)-5-(4-methylbenzylidene)-6-oxo-5,6-dihydro-2H-1,4-oxazine-2-carboxamide ***(6a)****:* (White solid, 0.21 g, 51% yield); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.10 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.35-7.21 (m, 3H), 6.27 (s, 1H), 6.05 (s, 1H), 2.50 (s, 3H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ (ppm) 163.9, 161.3, 157.5, 139.3, 138.0, 133.4, 132.7, 132.6, 132.2, 130.4, 130.3, 129.3, 129.0, 128.2, 125.9, 76.2, 52.5, 28.4, 20.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}ClN_2O_3$ 411.1470; found 411.1479.

Typical procedure for the synthesis of 9a: A mixture of PPh_3 (288 mg, 1.1 mmol) and C_2Cl_6 (257 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under air condition for 1 h. Subsequently, NEt(*i*-

Pr)$_2$ (284 mg, 2.2 mmol) and **1a** (101 mg, 1 mmol) were added. The mixture was stirred for 2 h and then **7a** (190 mg,1.1 mmol) and **8a** (134 mg, 1.1 mmol) were added and stirred for another 24 h. After the reaction was completed, the solvent of CH_2Cl_2 was changed to toluene (5 mL), PPh_3 (314 mg, 1.2 mmol) was added and stirred at 80 ^oC for 3 h and then NEt(*i*-Pr)$_2$ (13 mg, 0.1 mmol) was added and stirred for another 1 h. After removing the solvent under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (15:1, v/v) as eluent to give **9a**.

*4-benzyl-N-(tert-butyl)-2-phenyloxazole-5-carboxamide (**9a**)*： (White solid, 0.19 g, 58% yield). Mp: 143−145 ℃, lit[4d] 145−146 ℃; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.03 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.8 Hz, 5H), 7.28 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 6.08 (s, 1H), 4.34 (s, 2H), 1.50 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ (ppm) 159.8, 157.6, 145.5, 139.4, 138.6, 131.1, 129.0, 128.7, 128.3, 126.9, 126.5, 126.3, 51.7, 32.8, 29.0.

*2-isocyano-2-methylpropane (**11a**):* (light brown liquid, 93% yield), lit[13] light yellow liquid, 82% yield, b.p.: 90-92 ℃/750 mm Hg; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.45 (t, J = 2.0 Hz, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 152.3, 54.1, 30.7.

Typical procedure for the synthesis of 12a: A mixture of isocyanide **11a** (83 mg, 1.0 mmol), α-azidocinnamaldehyde **7a** (190 mg,1.1 mmol) and acid **8a** (134 mg, 1.1 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 under reduced pressure, the resulting crude was purified by column chromatography with petroleum ether/ethyl acetate (10:1, v/v) as eluent to give **12a**.

*(Z)-3-azido-1-(tert-butylamino)-1-oxo-4-phenylbut-3-en-2-yl benzoate (**12a**):* (White solid, 0.36 g, 96% yield); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.12 (d, J = 7.2 Hz, 2H), 7.70-7.60 (m, 3H), 7.52 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 6.11 (s, 1H), 6.09 (s, 1H), 6.08 (s, 1H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 164.9, 164.4, 134.0, 133.6, 129.9, 129.4, 129.3, 128.8, 128.6, 128.2, 128.1, 121.9, 76.7, 52.1, 28.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_4O_3$ 379.1765; found 379.1769.

Typical procedure for the synthesis of 14a: A mixture of **12a** (189 mg, 0.5 mmol) and PPh_3 (144 mg, 0.55 mmol) in toluene (5 mL) was stirred at 80 ^oC for 3 h. After the reaction was completed, 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 **14a**.

*(Z)-4-benzylidene-N-(tert-butyl)-2-phenyl-4,5-dihydrooxazole-5-carboxamide (**14a**):* (White solid, 0.15 g, 92% yield); ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.12 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.42-7.29 (m, 4H), 6.15 (s, 1H), 6.06 (s, 1H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ (ppm) 165.1, 164.3, 135.5, 134.2, 133.8, 129.8, 129.3, 129.0, 128.8, 128.7, 128.1, 118.3, 78.8, 51.9, 28.6; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_2$ 335.1754; found 335.1757.

Fungicidal Activities Assays

The bactericidal activities on 100 mg/L of some of the compounds against five important fungi, i.e., Fusarium graminearum, Magnaporthe oryzae, Penicillium digitatum, Penicillium italicum and Rhizoctonia solani by using Triadmefon and Diniconazle as positive control agents. First, the agar were autoclaved. The tested compounds were dissolved in 0.2 mL of DMSO and added aseptically to molten agar which has cooled to approximately 40−50 ℃. The concentration of solvent never exceeded 0.1 mg/L. The 5 mm in diameter inocula which was removed from the margins of actively growing colonies of mycelium, placed in the centers of the above plates. The mixed medium without sample was used as the blank control. Three replicates were done for each compound, and the control plates were sealed with parafilm and incubated at 26 ℃ in darkness and measured after 48 h. Inhibition percent (%) = (hyphal diameter in the control − hyphal diameter in the treatment)/hyphal diameter in the control.

ASSOCIATED CONTENT

* **Supporting Information**

NMR spectra and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

E-mail: wanglongchem@ctgu.edu.cn

Author Contributions

† These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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Reference:

1. For some examples, see: (a) Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. Metal-Mediated Post-Ugi Transformations for the Construction of Diverse Heterocyclic Scaffolds. *Chem. Soc. Rev*. **2015**, *44*, 1836-1860. (b) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev*. **2006**, *106*, 17-89.
2. For some examples, see: (a) Soyler, Z.; Onwukamike, K. N.; Grelier, S.; Grau, E.; Cramail, H.; Meier, M. A. R. Sustainable Succinylation of Cellulose in a CO_2-Based Switchable Solvent and Subsequent Passerini 3-CR and Ugi 4-CR Modification. *Green Chem.* **2018**, *20*, 214-224. (b) Shen, Y. Y.; Huang,

B.; Zeng, L. W.; Cui, S. L. Single Reactant Replacement Approach of Passerini Reaction: One-Pot Synthesis of β-Acyloxyamides and Phthalides. *Org. Lett*. **2017**, *19*, 4616-4619. (c) Chandgude, A. L.; Dömling, A. Unconventional Passerini Reaction toward α-Aminoxy-amides. *Org. Lett*. **2016**, *18*, 6396-6399. (d) Moni, L.; Banfi, L.; Basso, A.; Martino, E.; Riva, R. Diastereoselective Passerini Reaction of Biobased Chiral Aldehydes: Divergent Synthesis of Various Polyfunctionalized Heterocycles. *Org. Lett*. **2016**, *18*, 1638-1641. (e) Chandgude, A. L.; Dömling, A. An Efficient Passerini Tetrazole Reaction (PT-3CR). *Green Chem.* **2016**, *18*, 3718-3721. (f) Ramozzi, R.; Morokuma, K. Revisiting the Passerini Reaction Mechanism: Existence of the Nitrilium, Organocatalysis of Its Formation, and Solvent Effect. *J. Org. Chem*. **2015**, *80*, 5652-5657. (g) Lyu, L. Y.; Xie, H.; Mu, H. X.; He, Q. J.; Bian, Z. X.; Wang, J. $AlCl_3$-Catalyzed *O*-Alkylative Passerini Reaction of Isocyanides, Cinnamaldehydes and Various Aliphatic Alcohols for Accessing α-Alkoxy-β,γ-enamides. *Org. Chem. Front.* **2015**, *2*, 815-818.

3. (a) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. P. To Each His Own: Isonitriles for All Flavors. Functionalized Isocyanides as Valuable Tools in Organic Synthesis. *Chem. Soc. Rev*. **2017**, *46*, 1295-1357. (b) Moni, L.; Banfi, L.; Riva, R.; Basso, A. External-Oxidant-Based Multicomponent Reactions. *Synthesis* **2016**, *48*, 4050-4059. (c) Alvim, H. G. O.; da Silva Júnior, E. N.; Neto, B. A. D. What do We Know About Multicomponent Reactions? Mechanisms and Trends for the Biginelli, Hantzsch, Mannich, Passerini and Ugi MCRs. *RSC Adv*. **2014**, *4*, 54282-54299. (d) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. Palladium-Catalyzed Migratory Insertion of Isocyanides: An Emerging Platform in Cross-Coupling Chemistry. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084-7097. (e) Heravi, M. M.; Nazari, N. Isocyanide-based Cascade Reactions in the Synthesis of Aza-heterocycles: A Marriage of Convenience. *Curr. Org. Chem.* **2017**, *21*, 1440-1529. (f) Sadjadi, S.; Heravi, M. M.; Nazari, N. Isocyanide-based multicomponent reactions in the synthesis of heterocycles. *RSC Adv*. **2016**, *6*, 53203-53272.

4. (a) Ren, Z. L.; Sun, M.; Guan, Z. R.; Ding, M. W. New Efficient Synthesis of 1,2,4-Trisubstituted Furans by a Sequential Passerini/Wittig/Isomerization Reaction Starting from Baylis–Hillman β-Bromo Aldehydes. *Synlett* **2018**, *29*, 106-110. (b) Spallarossa, M.; Banfi, L.; Basso, A.; Moni, L.; Riva, R. Access to Polycyclic Alkaloid-Like Structures by Coupling the Passerini and Ugi Reactions with Two Sequential Metal-Catalyzed Cyclizations. *Adv. Synth. Catal.* **2016**, *358*, 2940-2948. (c) Ma, G. H.; Jiang, B.; Tu, X. J.; Ning, Y. ; Tu, S. J. Li, G. G. Synthesis of Isocoumarins with Different Substituted Patterns via Passerini–Aldol Sequence. *Org. Lett*. **2014**, *16*, 4504-4507. (d) Wang, L.; Ren, Z. L.; Chen, M.; Ding, M. W. One-Pot Synthesis of 2,4,5-Trisubstituted Oxazoles via a Tandem Passerini Three-Component Coupling/Staudinger/Aza-Wittig/Isomerization Reaction. *Synlett* **2014**, *25*, 721-723.

5. (a) Fédou, N. M.; Parsons, P. J.; Viseux, E. M. E.; Whittle, A. J. Multicomponent Cascade Reactions: Sequential [1+4] and [2+3] Cycloadditions for the Generation of Heterocyclic Ring Systems. *Org. Lett*. **2005**, *7*, 3179-3182. (b) El Kaim, L.; Grimaud, L.; Schiltz, A. "Isocyanide-free" Ugi Reactions. *Org. Biomol. Chem.* **2009**, *7*, 3024-3026. (c) El Kaim, L.; Grimaud, L.; Schiltz, A. One-Pot Synthesis of

Oxazoles Using Isocyanide Surrogates. *Tetrahedron Lett.* **2009**, *50*, 5235-5237. (d) El Kaim, L.; Grimaud, L.; Schiltz, A. Isocyanide-Based Multicomponent Reaction 'without' Isocyanides. *Synlett* **2009**, *9*, 1401-1404. (e) Sharma, S.; Maurya, R. A.; Min, K. I.; Jeong, G. Y.; Kim, D. P. Odorless Isocyanide Chemistry: An Integrated Microfluidic System for a Multistep Reaction Sequence. *Angew. Chem. Int. Ed.* **2013**, *52*, 7564-7568. (f) Neochoritis, C. G.; Stotani, S.; Mishra, B.; Dömling, A. Efficient Isocyanide-less Isocyanide-Based Multicomponent Reactions. *Org. Lett*. **2015**, *17*, 2002-2005.

6. (a) Mor, S.; Nagoria, S.; Sindhu, S.; Khatri, M.; Sidhu, G.; Singh, V. Synthesis of Indane-Based 1,5-Benzothiazepines Derived from 3-Phenyl-2,3-dihydro-1*H*-inden-1-one and Antimicrobial Studies Thereof. *J. Heterocyclic. Chem.* **2017,** *54*, 3282-3293. (b) Doyle, K.; Lonn, H.; Kack, H.; Van de Poel, A.; Swallow, S.; Gardiner, P.; Connolly, S.; Root, J.; Wikell, C.; Dahl, G.; Stenvall, K.; Johannesson, P. Discovery of Second Generation Reversible Covalent DPP1 Inhibitors Leading to an Oxazepane Amidoacetonitrile Based Clinical Candidate (AZD7986). *J. Med. Chem.* **2016**, *59*, 9457-9472.
7. (a) Zora, M.; Dikmen, E.; Kelgokmen, Y. One-Pot Synthesis of Iodine-Substituted 1,4-Oxazepines. *Tetrahedron Lett.* **2018**, *59*, 823-827. (b) Yadav, V. D.; Srivastava, K.; Tripathi, R.; Batra, S. Synthesis of β-Carboline-Fused 1,4-Oxazepines and Their Assessment as Antiplasmodial Agents. *Tetrahedron* **2017**, *73*, 5680-5689. (c) Shen, J. H.; Xue, L. L.; Lin, X.; Cheng, G. L.; Cui, X. L. The Base-Promoted Synthesis of Multisubstituted Benzo[*b*][1,4]oxazepines. *Chem. Commun.* **2016**, *52*, 3292-3295. (d) Hu, F. D.; Liu, H. H.; Jia, J.; Ma, C. Transition-Metal-Free Synthesis of Indole-Fused Dibenzo[*b*,*f*][1,4]oxazepines *via* Smiles Rearrangement. *Org. Biomol. Chem.* **2016**, *14*, 11076-11079.
8. (a) Wang, L.; Ren, Z. L.; Ding, M. W. Synthesis of 2,3-Dihydro-1*H*-2-benzazepin-1-ones and 3*H*-2-Benzoxepin-1-ones by Isocyanide-Based Multicomponent Reaction/Wittig Sequence Starting from Phosphonium Salt Precursors. *J. Org. Chem.* **2015**, *80*. 641-646. (b) Wang, L.; Guan, Z. R.; Ding, M. W. One-Pot Synthesis of 1*H*-Isochromenes and 1,2-Dihydroisoquinolines by a Sequential Isocyanide-Based Multicomponent/Wittig Reaction. *Org. Biomol. Chem.* **2016**, 14, 2413-2420. (c) Xie, Y. B.; Ye, S. P.; Chen, W. F.; Hu, Y. L.; Li, D. J.; Wang, L. Brønsted-Acid-Catalyzed Multicomponent One-Pot Reaction: Efficient Synthesis of Polysubstituted 1,2-Dihydropyridines. *Asian. J. Org. Chem.* **2017**, *6*, 746-750. (d) Wang, L.; Xie, Y. B.; Huang, N. Y.; Yan, J. Y.; Hu, W. M.; Liu, M. G.; Ding, M. W. Catalytic aza-Wittig Reaction of Acid Anhydride for the Synthesis of 4*H*-Benzo[*d*][1,3]oxazin-4-ones and 4-Benzylidene-2-aryloxazol-5(4*H*)-ones. *ACS Catal.* **2016**, *6*, 4010-4016. (e) Wang, L.; Xie, Y. B.; Huang, N. Y.; Zhang, N. N.; Li, D. J.; Hu, Y. L.; Liu, M. G.; Li, D. S. Disulfide-Directed C–H Hydroxylation for Synthesis of Sulfonyl Diphenyl Sulfides and 2-(Phenylthio)phenols with Oxygen as Oxidant. *Adv. Synth. Catal.* 2017, **359**, 779-785.
9. Wang, X.; Wang, Q. G.; Luo, Q. L. Synthesis of Isonitriles from N-Substituted Formamides Using Triphenylphosphine and Iodine. *Synthesis* **2015**, *47*, 49-54.
10. Kalepu, J.; Katukojvala, S. Dienamine Activation of Diazoenals: Application to the Direct Synthesis of Functionalized 1,4-Oxazines. *Angew. Chem. Int. Ed.* **2016**, *55*, 7831-7835.
11. Ryan, N. J.; Lo, J. H. Delamanid: First Global Approval. *Drugs.* **2014**, *74*. 1041-1045.

12. (a) Ibrar, A.; Khan, I.; Abbas, N.; Farooq, U.; Khan, A. Transition-Metal-Free Synthesis of Oxazoles: Valuable Structural Fragments in Drug Discovery. *RSC Adv.* **2016**, *6*, 93016-93047. (b) Hernandez, D.; Riego, E.; Albericio, F.; Alvarez, M. Synthesis of Natural Product Derivatives Containing 2,4-Concatenated Oxazoles. *Eur. J. Org. Chem.* **2008**, 3389-3396.
13. Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. Isonitrile Syntheses. *Angew. Chem., Int. Ed.* **1965**, *4*, 472-484.