JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02894 • Publication Date (Web): 04 Jan 2018

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Diversity-oriented synthesis of heterocycles: $Al(OTf)_3$ - promoted cascade cyclization and ionic hydrogenation

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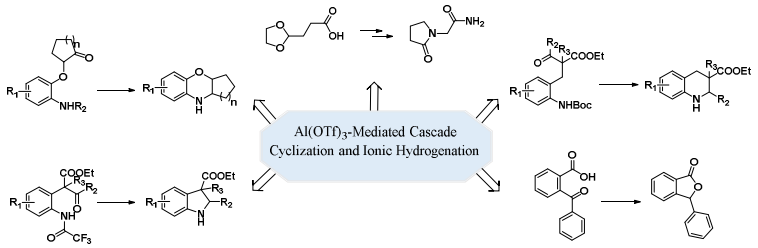
Supporting Information Placeholder



ABSTRACT: An efficient and facile method has been developed for diversity-oriented synthesis of heterocycles. Hexahydrophenoxazines, tetrahydroquinolines, indolines, hexahydrocarbazoles and lactones were conducted via $Al(OTf)_3$ promoted cascade cyclization and ionic hydrogenation. Furthermore, this protocol was utilized to smoothly prepare piracetam and its key intermediate as well.

INTRODUCTION

Substituted heterocycles are critical scaffolds that have received considerable attention due to their wide existence in a myriad of natural products,[1] pharmaceutical agents[2] and diverse functional materials in organic chemistry.[3] These compounds include hexahydrocarbazoles, tetrahydroquinolines, indolines, pyrrolidones and other related heterocycles, represented by Levofloxacin,[4] (+)-cuspareine,[5] (±)-strychnine[6] and piracetam[7] (Figure 1), which are of great interest for possessing numerous biologic activities and extensive applications, such as anti-tumor, anti-parasitic, immunoprotective, anti-depression, diuresis and anti-inflammatory drugs.

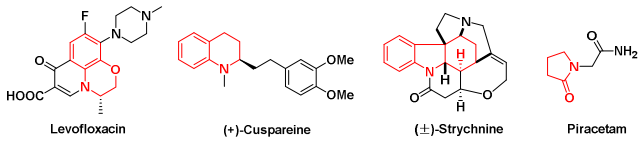
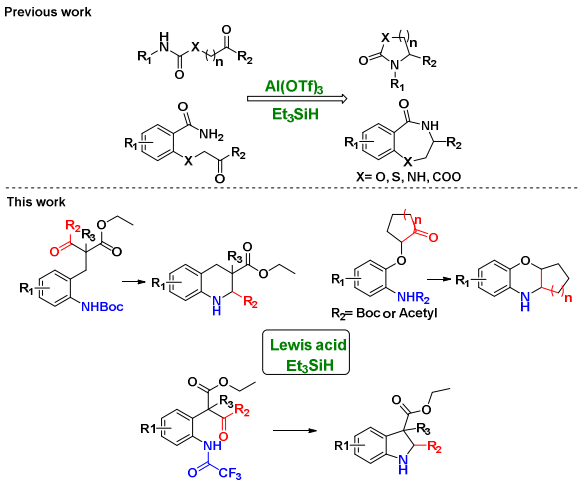


Figure 1. Various heterocycles in natural products and pharmaceutical agents.

During the past decade, a great deal of effort has been devoted to studies on new synthetic methodologies to access the above heterocyclic compounds,[8] which to date has experienced enormous and impressive progress.[9] However, there are few reports involved diversity-oriented synthesis (DOS) of heterocycles.[10] DOS is considered as an efficient method to achieve structural diversity along with structural complexity, which is of great significance in both chemical and pharmaceutical fields. Hence, the discovery of novel and diversity-oriented synthetic approaches remains a challenging task, calling for more efficient protocols for the production of heterocycles.

Nowadays, ionic hydrogenation is becoming more frequently used as a powerful tool in the reduction of various unsaturated functional groups.[11] Recently, our group has disclosed a facile $Al(OTf)_3$-mediated cascade cyclization and ionic hydrogenation strategy that provide efficient access to a broad range of *N*-heterocycles in good yields, including pyrrolidinones, piperidones, isoindolinones, oxazolidinone, dihydro-1,4-benzoxazepinones and dihydro-1,4-benzoxazines.[12] By developing this method into a general DOS approach for the preparation of heterocycles, on the basis of forward-synthetic analysis, we anticipate that in situ syntheses of diverse heterocycles could be achieved under specifically optimized reaction conditions. Herein, we described the elaborate methodology where substrates underwent an $Al(OTf)_3/Et_3SiH$-promoted cascade deprotection, cyclization and ionic hydrogenation, which enabled the assembly of hexahydrophenoxazines, hexahydrocarbazoles, tetrahydroquinolines, octahydroacridines, indolines and other related heterocycles (Scheme 1).

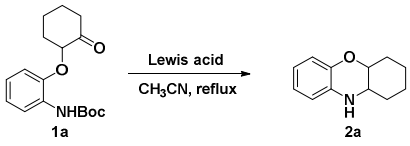
Scheme 1. Strategies for the construction of heterocycles.



RESULTS AND DISCUSSION

Initially, our studies were focused on the cascade method by using substrate **1a** as a model substrate, with $Al(OTf)_3$ as the catalyst and exploiting the appropriate reaction condition to deliver compound **2a**. We postulated that **1a** would undergo cleavage of the *t*-butyloxycarbonyl group, followed by intramolecular cyclization and ultimately the key ionic hydrogenation step to afford corresponding product. To our delight, the desired product was produced in 92% with the utilization of $Al(OTf)_3$ (Table 1, entry 1). Subsequently, Lewis acids were then screened to determine their catalytic activity. As shown in Table 1, the yield varied based on the selection of catalyst, including CF_3COOH, $AlCl_3$, $TiCl_4$ and $SnCl_4$ (Table 1, entry 2-5). None of these catalysts exhibited a better performance than $Al(OTf)_3$, little desired product was produced when utilizing

Table 1. Optimization of the reaction conditions



entry[a]	acid	equivalent (1a: acid: silane)	time (h)	Yield[b,c] (%)
1	$Al(OTf)_3$	1:2:2	1	92
2	CF_3COOH	1:2:2	4	trace
3	$AlCl_3$	1:2:2	1	71
4	$TiCl_4$	1:2:2	4	75
5	$SnCl_4$	1:2:2	1	25
6	$Al(OTf)_3$	1:1:2	1	90
7	$Al(OTf)_3$	1:0.5:2	1	92
8	$Al(OTf)_3$	1:0.5:1	3	63

[a] The reaction was performed using 1a, Lewis acid, and Et_3SiH in CH_3CN at reflux. [b] Diastereomeric ratio was determined by NMR analysis of the crude reaction mixture and indicated a ratio of ~3:1 in all cases. [c] Isolated yield.

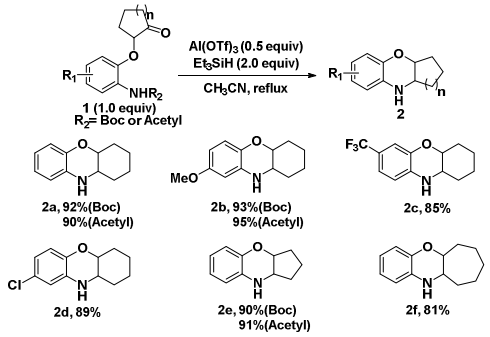


Figure 2. Synthesis of 3,4-dihydro-1,4-benzoxazine (**2**).

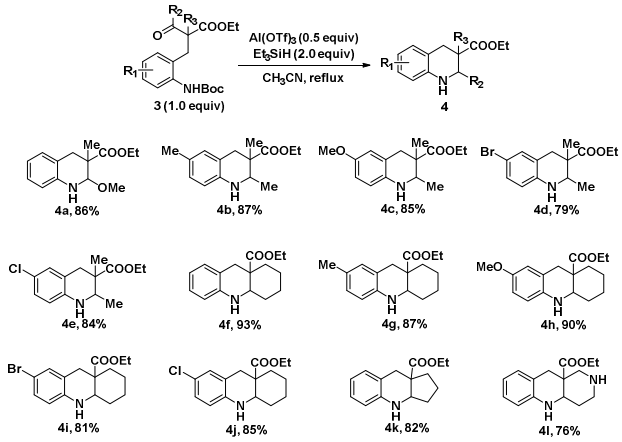


Figure 3. Synthesis of 1,2,3,4-tetrahydroquinolines (**4**).

CF_3COOH as the catalyst (Table 1, entry 2). To improve the applicability of the reaction, other parameters such as the ratio of acid to reductant and reaction time were optimized. Notably, when the proportion of $Al(OTf)_3$ was appropriately decreased (Table 1, entry 6-7), good to excellent yields were maintained, which confirmed the efficiency of $Al(OTf)_3$ as an auxiliary. In contrast, apparent reduction of the conversion was observed when the loading of Et_3SiH was decreased to 1.0 equiv, albeit with an extended reaction time (Table 1, entry 8). After careful optimization, it turned out that by refluxing 1a (1.0 equiv) in the presence of $Al(OTf)_3$ (0.5 equiv)/Et_3SiH (2.0 equiv) for 1h in CH_3CN, the reaction resulted in an excellent isolated yield of **2a**.

With the optimized reaction conditions in hand, we sought to further demonstrate the synthetic utility of this method for the production of 3,4-dihydro-1,4-benzoxazine, which is of great significance as a privileged skeleton with widespread use in biological and pharmacological agents (Figure 2).[13] As expected, this cascade reaction protocol proved efficient and provided the desired products in satisfactory yields (81–92%). In addition, when expanding the ring from a six-membered ring to a five- membered (**2e**) and seven-membered ring (**2f**), the cascade route still worked well, providing good yields of isolated products. The construction of **2f** exhibited lower yield than other 3,4-dihydro-1,4- benzoxazines, we assumed that this can be attributed to steric hindrance. It was noted that substrates with electron-donating groups (**2b**), electron-withdrawing groups (**2c**), as well as halides (**2d**), proceeded the facile reaction smoothly. Typically, substrate **1c** which has a trifluoromethyl functionality on its arene ring, afforded the corresponding product **2c** in 84% yield. In addition, changing

N-protective group from the *t*-butyloxycarbonyl moiety to an acetyl moiety (**2a, 2b,**

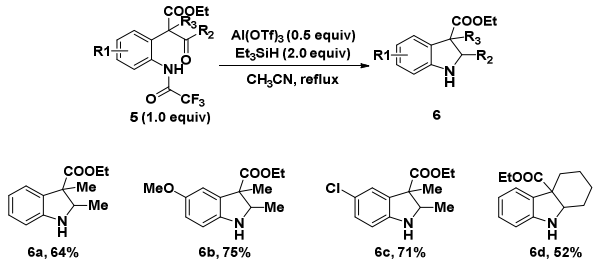


Figure 4. Synthesis of 2,3-dihydroindoles (**6**).

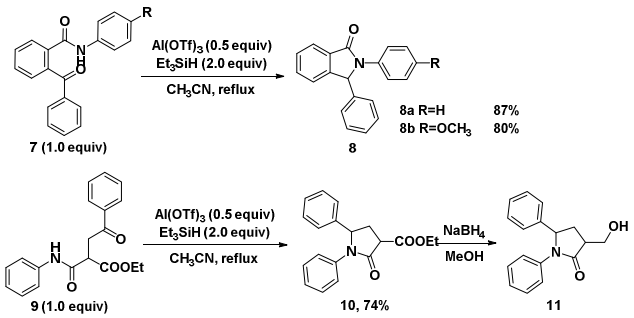


Figure 5. Synthesis of 2,3-diphenylisoindolin-1-ones (**8**) and methyl 2-oxo-1,5-diphenylpy-rrolidine-3-carboxylate (**10**).

2e) had little influence on the reaction.

Subsequently, the preparation of 1,2,3,4-tetrahydroquinoline was also attempted to prove the versatility of this catalytic system intensively (Figure 3). Similar to the formation of 3,4-dihydro-1,4-benzoxazine, a plausible cascade pathway was deducted via deprotection, cyclization and ionic hydrogenation. Gratifyingly, various functional groups on the aromatic ring were well tolerated, regardless of the electronic nature and steric hindrance of ring system. Substrates containing either an electron-rich or halogen substituent, such as methoxy, chloro and bromo, gave satisfactory yields (**4c-4e, 4h-4j**). It was noteworthy that high performances were observed when tetrahydroquinoline was fused with another six-membered aliphatic ring to give tricyclic architectures (**4f-4j**), which was suitable for five-membered ring as well (**4k**). Furthermore, it was found that compound **4l**, which has a nitrogen atom in its six-membered ring, could be obtained in moderate yield.

Meanwhile, it is well acknowledged that indolines serve as core structures in a large numbers of pharmaceuticals and dyestuffs.[13] Encouraged by the above results, our research was then extended to the generation of 2,3-dihydroindoles using trifluoroacetyl group protected substrates (Figure 4).[14] Due to high tolerance and compatibility of function groups, this strategy can be applied to compounds possessing either electron-donating or halogen substituents (**6a-6c**), further proving its efficiency and practicability. During this exploration, a fused tricyclic scaffold identified as a hexahydrocarbazole was isolated in 52% yield. This core is present in varieties of bioactive natural products and known as a key intermediate in the synthesis of novel antibiotics.[15]

Next, we turned our attention to the preparation of isoindolinones, pyrrolidin-2-one and other crucial motifs in pharmaceutical chemistry,[16] employing several *N*-aryl amides as substrates. There was no doubt that the reaction occurred rapidly as predictable, with corresponding products separated in moderate to good yields (Figure 5). Notably, methyl 2-oxo-1,5-diphenyl-pyrrolidine-3-carboxylate (**10**) can be readily reduced to 3-(hydroxymethyl)-1,5-diphenylpyrrolidin-2-one (**11**), and the expo-

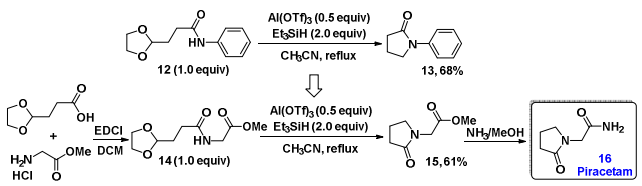


Figure 6. Synthesis of 1-phenylpyrrolidin-2-one (**13**) and Piracetam (**16**).

Figure 7. Synthesis of 3-phenylisobenzofuran-1(3H)-one (**18**).

sure of hydroxy group would facilitate further modification.

Importantly, it should be noted that all the aforementioned substrates had certain common characters, namely a keto group and an amide group, which were believed to enforce the $Al(OTf)_3$-catalyzed cyclization. Therefore, it remained to be addressed that whether the aldehyde or acetal group could still condense with the amide group to trigger the cascade reaction. To investigate the reactivity in depth, compound **12**, which was equipped with an acetal instead of a keto group, was designed and synthesized. To our satisfactory, **12** participated in the cascade reaction successfully, producing 1-phenylpyrrolidin-2-one (**13**) in acceptable yield (Figure 6). Inspired by this finding, more attention was paid on its utilization for the construction of piracetam, an approved medication for the treatment of dementia, depression, anxiety and other neurological and mental diseases.[17] As shown in Figure 6, 3-(1,3-dioxolan-2-yl) propanoic acid was selected as the starting material, and it proceeded through acylation, ionic hydrogenation and ammonolysis, to afford piracetam(**16**) in a total yield of 52%. Notably, this methodology provided a good platform to prepare piracetam and its vital intermediate **15** in an efficient and non-toxic pathway, ease of the use of ethyl chloroacetate, which is currently thought to be genotoxic.[18]

So far, we have described an efficient synthetic methodology for C-N bond formation based on $Al(OTf)_3$-mediated cascade deprotection, cyclization and ionic hydrogenation pathway. Apart from that application, this approach might also be allowed to construct lactones (Figure 7). Consequently, the feasibility of 2-benzoylbenzoic acid was examined. Satisfyingly, under the same conditions, the desired 3-phenylisobenzofuran-1(3H)-one (**18**) was synthesized smoothly in 91% yield, amplifying the substrate scope and highlighting broad applicability and utility.

CONCLUSIONS

In conclusion, an efficient and versatile $Al(OTf)_3$-catalyzed cascade deprotection, cyclization and ionic hydrogenation method has been developed for the delivery of diverse heterocycles in good to excellent yields, including hexahydrophenoxazines, tetrahydroquinolines, indoline, hexahydrocarbazoles and pyrrolidones. In particular, this strategy can be employed as a key step towards the formation of piracetam, offer-

ing an alternative and non-toxic route to the traditional methods. Interestingly, except for the construction of C-N bond, the assemble of lactone can be achieved efficiently as well. Generally, readily available starting materials, mild conditions, extensive functional groups tolerance and high efficiency make this diversity-oriented synthetic protocol promising and attractive for organic synthesis. Further investigation on regioselectivity and detailed applications are currently underway.

EXPERIMENTAL SECTION

General Information. Melting points were determined on Yanaco MP-*J*3 microscope melting point apparatus. NMR spectra were recorded on Mercury-400, Mercury-500 and Mercury-600 spectrometer. Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale) and all coupling constant (*J*) values are given in Hz. ESI-HRMS data were measured on Thermo Exactive Orbitrap plus spectrometer. Flash column chromatography was performed on Biotage Isolera one. All the solvents and chemicals were obtained from commercial sources and used without further purification.

General Procedure for Synthesis of heterocycles (2a−f, 4a-l, 6a−d, 8, 10, 13, 15, 18). To a solution of corresponding substrate (1.0 mmol) in CH_3CN (5 mL) were added Et_3SiH (2.0 mmol) and $Al(OTf)_3$ (0.5 mmol) at room temperature. The reaction mixture was heated at reflux for the corresponding time and then concentrated under vacuum. The residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography to afford the desired product.

General Procedure for Synthesis of 3-(hydroxymethyl)-1,5-diphenylpyrrolidin-2-one (11). To a solution of **10** (100.0 mg, 0.3 mmol) in MeOH was added $NaBH_4$ (51.1 mg, 1.4 mmol) portionwise. The reaction mixture was stirred at room temperature for 5 h and then concentrated. The residue was diluted with EtOAc, washed with 1 N HCl, saturated aq $NaHCO_3$, and brine, and then dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 20:1) to afford the desired product (76.0 mg, 84% yield) as a white solid. mp: 98-101 °C. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.31 – 7.27 (m, 4H), 7.24-7.18 (m, 4H), 7.17 – 7.13 (m, 1H), 7.05 (tt, *J* = 7.4, 1.2 Hz, 1H), 5.33 (dd, *J* = 8.8, 7.5 Hz, 1H), 4.05 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.82 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.95-2.89 (m, 1H), 2.77-2.69 (m, 1H), 2.12-2.04 (m, 1H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 175.9, 141.5, 137.8, 128.4, 128.2, 127.5, 127.1, 125.5, 124.3, 62.4, 60.5, 45.4, 32.3. HRMS (ESI): m/z calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$ 268.1332, found 268.1327.

General Procedure for Synthesis of methyl (3-(1,3-dioxolan-2-yl) propanoyl) glycinate (14). To a solution of 3-(1,3-dioxolan-2-yl) propanoic acid (1.0g, 6.8mmol) in CH_2Cl_2 was added EDCI (1.6g, 8.2mmol) and TEA (1.9g, 18.5mmol). After the reaction mixture was stirred at room temperature for 0.5 h, methyl glycinate was added and continued stirring for 5h. The mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 20:1) to afford the desired product (1.3g, 90% yield) as a white solid. mp: 42-44 °C. ^{1}H NMR (500 MHz, Chloroform-d) δ 6.27 (s, 1H), 4.94 (s, 1H), 4.07 – 4.02 (m, 2H), 3.97-3.86 (m, 4H), 3.75 (s, 3H), 2.39 (t, J = 6.5 Hz, 2H), 2.10 – 1.98 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.7, 170.7, 103.3, 65.1, 52.5, 41.4, 30.2, 29.1. HRMS (ESI): m/z calcd for $C_9H_{16}NO_5$ $[M + H]^+$ 218.1023, found 218.1022.

General Procedure for Synthesis of 2-(2-oxopyrrolidin-1-yl) acetamide (16, Piracetam). To a sealed tube was added **15** (100mg, 0.64mmol) and NH_3(1ml, 7N in MeOH), then the mixture was heated to 60℃ for 4h and concentrated. The residue was purified by silica gel flash column chromatography to afford the desired product (84.1 mg, 93% yield) as a white solid. mp: 145-147 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H), 7.07 (s, 1H), 3.74 (s, 2H), 3.37 – 3.34 (m, 2H), 2.24 – 2.20 (m, 2H), 1.97 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.0, 170.3, 47.9, 45.4, 30.6, 18.0. HRMS (ESI): m/z calcd for $C_6H_{10}N_2O_2Na$ $[M + Na]^+$ 165.0634, found 165.0634.

2,3,4,4a,10,10a-hexahydro-1H-phenoxazine ***(2a)***. Light brown solid. Yield: 92% (Boc, 174 mg); mp: 74-75 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.82 – 6.73 (m, 2H), 6.69 – 6.56 (m, 2H), 4.26-4.24 (m, 1H), 3.53 (s, 1H), 3.40 – 3.36 (m, 1H), 2.20 – 1.76 (m, 2H), 1.74 – 1.61 (m, 3H), 1.49 – 1.25 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 143.0, 132.3, 121.0, 118.3, 116.5, 115.0, 72.7, 54.2, 31.3, 29.4, 24.2, 21.1. HRMS (ESI): m/z calcd for $C_{12}H_{16}NO$ $[M + H]^+$ 190.1226, found 190.1224.

8-methoxy-2,3,4,4a,10,10a-hexahydro-1H-phenoxazine ***(2b)***. Brown wax. Yield: 93% (Boc, 204 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.72-6.68 (m, 1H), 6.24 – 6.15 (m, 2H), 4.19-4.16 (m, 1H), 3.71 (s, 3H), 3.64 (s, 1H), 3.36-3.32 (m, 1H), 2.18 – 1.72 (m, 2H), 1.70-1.58 (m, 3H), 1.49 – 1.22 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 154.3, 137.1, 132.8, 116.6, 103.0, 100.8, 72.4, 55.5, 54.3, 30.4, 29.4, 24.2, 21.0. HRMS (ESI): m/z calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1332, found 220.1330.

7-(trifluoromethyl)-2,3,4,4a,10,10a-hexahydro-1H-phenoxazine ***(2c)***. Light yellow solid. Yield: 85% (219 mg); mp: 91-94 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.92 – 6.85 (m, 1H), 6.85 – 6.78 (m, 2H), 4.28-4.25 (m, 1H), 3.41 – 3.38 (m, 1H), 2.98 (td, *J* = 7.9, 4.2 Hz, 0H), 2.21 – 1.75 (m, 2H), 1.72-1.62 (m, 3H), 1.49 – 1.30 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 145.4, 132.6, 124.5 (q, *J* =271.8 Hz), 123.2 (q, *J* =31.7 Hz), 116.4, 115.3 (q, *J* =3.9 Hz), 111.5 (q, *J* =3.8 Hz), 78.3, 53.9, 30.2, 29.3, 24.1, 21.0. HRMS (ESI): m/z calcd for $C_{13}H_{15}F_3NO$ $[M + H]^+$ 258.1100, found 258.1096.

8-chloro-2,3,4,4a,10,10a-hexahydro-1H-phenoxazine ***(2d)***. White solid. Yield: 89% (199 mg); mp: 75-77 °C. ^{1}H NMR (400 MHz, Chloroform-d) (*major diastereomer*) δ 6.70-6.67 (m, 1H), 6.60 – 6.53 (m, 2H), 4.22-4.19 (m, 1H), 3.78 (s, 1H), 3.38-3.34 (m, 1H), 2.18 – 1.75 (m, 2H), 1.70 – 1.59 (m, 3H), 1.47 – 1.27 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-d) (*major diastereomer*) δ 141.5, 133.5, 125.6, 117.6, 117.3, 114.3, 72.7, 49.6, 30.2, 29.4, 24.2, 20.9. HRMS (ESI): m/z calcd for $C_{12}H_{15}ClNO$ $[M + H]^+$ 224.0837, found 224.0838.

1,2,3,3a,9,9a-hexahydrobenzo[b]cyclopenta[e] [1,4] oxazine ***(2e)***. Yellow oil. Yield: 90% (Boc, 158mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.84 – 6.77 (m, 2H), 6.65 (td, *J* = 7.6, 1.3 Hz, 2H), 6.30 (dd, *J* = 8.0, 1.6 Hz, 2H), 4.24 – 4.21 (m, 1H), 3.72 (s, 1H), 3.67 – 3.62 (m, 1H), 2.01 – 1.85 (m, 4H), 1.72-1.60 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 142.7, 132.2, 121.4, 117.9, 116.8, 114.6, 76.1, 54.7, 30.2,

29.8, 20.1. HRMS (ESI): m/z calcd for $C_{11}H_{14}NO$ $[M + H]^+$ 176.1070, found 176.1066.

5a,6,7,8,9,10,10a,11-octahydrobenzo[b]cyclohepta[e][1,4]-oxazine ***(2f)***. White solid. Yield: 81% (165 mg); mp: 80-81 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.81 – 6.72 (m, 2H), 6.68 – 6.55 (m, 2H), 4.32-4.28 (m, 1H), 3.47 (dt, *J* = 8.8, 3.0 Hz, 1H), 1.92 – 1.44 (m, 10H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 143.2, 132.9, 121.0, 118.1, 116.3, 114.5, 76.2, 53.4, 31.4, 30.6, 27.9, 23.0, 21.4. HRMS (ESI): m/z calcd for $C_{13}H_{18}NO$ $[M + H]^+$ 204.1383, found 204.1380.

Ethyl 2,3-dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate ***(4a)***. Yellow oil. Yield: 86% (201 mg). ^{1}H NMR (400 MHz, Chloroform-d) (*major diastereomer*) δ 7.06 – 6.97 (m, 2H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.70 (q, *J* = 6.5 Hz, 1H), 3.55 (s, 1H), 3.27 (d, *J* = 15.6 Hz, 1H), 2.61 (d, *J* = 16.0 Hz, 1H), 1.29 – 1.24 (m, 3H), 1.14-1.11 (m, 3H), 1.11 – 1.09 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-d) (*major diastereomer*) δ 176.4, 142.8, 129.5, 126.8, 119.1, 117.3, 113.7, 60.7, 51.4, 43.3, 38.1, 17.0, 15.1, 14.2. HRMS (ESI): m/z calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1489, found 234.1489.

Ethyl 2,3,6-trimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate ***(4b)***. Pale yellow oil. Yield: 87% (215 mg). ^{1}H NMR (400 MHz, Chloroform-d) (*major diastereomer*) δ 6.84-6.79 (m, 2H), 6.46-6.42 (m, 1H), 4.20-4.14 (m, 2H), 3.65 (q, *J* = 6.4 Hz, 1H), 3.60 (s, 1H), 3.23 (d, *J* = 16.0 Hz, 1H), 2.55 (d, *J* = 16.0 Hz, 1H), 2.21 (s, 3H), 1.28 – 1.23 (m, 4H), 1.11 – 1.09 (m, 3H), 1.08 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) (*major diastereomer*) δ 176.5, 140.4, 130.0, 127.5, 126.5, 119.3, 114.0, 60.6, 51.6, 43.4, 38.1, 20.5, 16.9, 15.1, 14.2. HRMS (ESI): m/z calcd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1645, found 248.1643.

Ethyl 6-methoxy-2,3-dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate ***(4c)***. Yellow oil. Yield: 85% (224 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.62 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.49-6.47 (m, 1H), 4.20-4.13 (m, 2H), 3.72 (s, 3H), 3.61 (q, *J* = 6.4 Hz, 1H), 3.27 (d, *J* = 16.0 Hz, 1H), 2.56 (d, *J* = 16.0Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.10-1.08 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 176.4, 152.0, 136.7, 120.7, 115.3, 114.6, 113.1, 60.6, 55.7, 51.8, 43.5, 38.2, 16.8, 15.1, 14.2. HRMS (ESI): m/z calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$ 264.1594, found 264.1597.

Ethyl 6-bromo-2,3-dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate ***(4d)***. Green oil. Yield: 79% (247 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 7.11-7.04 (m, 2H), 6.38-6.35(m, 1H), 4.19-4.13 (m, 2H), 3.75 (s, 1H), 3.66 (q, *J* = 6.5 Hz, 1H), 3.42 (q, *J* = 6.9 Hz, 0H), 3.20 (d, *J* = 16.0 Hz, 1H), 2.54 (d, *J* = 16.0 Hz, 1H), 1.26 – 1.23 (m, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 176.0, 141.8, 131.8, 129.5, 121.2, 115.2, 108.6, 60.8, 51.4, 43.0, 37.5, 16.8, 15.5, 14.2. HRMS (ESI): m/z calcd for $C_{14}H_{19}BrNO_2$ $[M + H]^+$ 312.0594, found 312.0598.

Ethyl 6-chloro-2,3-dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate ***(4e)***. Green oil. Yield: 84% (225 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.98 – 6.91 (m, 2H), 6.43 – 6.39 (m, 1H), 4.20-4.13 (m, 2H), 3.80 (s, 1H), 3.66 (q, *J* = 6.5 Hz, 1H), 3.20 (d, *J* = 16.4 Hz, 1H), 2.54 (s, 1H), 1.25(t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 176.0, 141.3, 129.0, 126.7, 121.6, 120.7, 114.8, 60.8, 51.5, 43.0, 37.5, 16.8, 15.5, 14.2. HRMS (ESI): m/z calcd for $C_{14}H_{19}ClNO_2$ $[M + H]^+$ 268.1099, found 268.1100.

Ethyl 5,7,8,9,10,10a-hexahydroacridine-8a(6H)-carboxylate ***(4f)***. Pale yellow wax. Yield: 93% (241 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.95 (m, 2H), 6.60 (td, *J* = 7.4, 1.1 Hz, 1H), 6.48 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (dd, *J* = 6.8, 3.2 Hz, 1H), 3.71 (s, 1H), 3.02 – 2.79 (m, 2H), 1.84 – 1.40 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.2, 142.6, 129.3, 126.9, 118.0, 116.5, 113.3, 60.5, 51.1, 44.1, 34.2, 30.0, 29.8, 22.2, 21.2, 14.2. HRMS (ESI): m/z calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1645, found 260.1644.

Ethyl 2-methyl-5,7,8,9,10,10a-hexahydroacridine-8a(6H)-carboxylate ***(4g)***. Reddish-brown oil. Yield: 87% (238 mg). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.81 – 6.79 (m, 2H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.79 – 3.78 (m, 1H), 3.49 (s, 1H), 3.00-2.76 (m, 2H), 2.22 (s, 3H), 1.84 – 1.43 (m, 8H), 1.25 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.2, 140.2, 129.8, 127.5, 125.7, 118.0, 113.5, 60.5, 51.2, 44.3, 34.0, 30.1, 29.7, 22.1, 21.3, 20.5, 14.2. HRMS (ESI): m/z calcd for $C_{17}H_{24}NO_2$ $[M + H]^+$ 274.1802, found 274.1800

Ethyl 2-methoxy-5,7,8,9,10,10a-hexahydroacridine-8a(6H)-carboxylate ***(4h)***. Brown oil. Yield: 90% (260 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.60 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.44-6.42 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.28 (s, 1H), 3.00-2.78 (m, 2H), 1.84–1.36 (m, 8H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.2, 151.5, 136.6, 119.3, 114.7, 114.5, 113.2, 60.5, 55.8, 51.5, 44.4, 33.7, 30.4, 29.6, 22.0, 21.6, 14.1. HRMS (ESI): m/z calcd for $C_{17}H_{24}NO_3$ $[M + H]^+$ 290.1751, found 290.1752

Ethyl 2-bromo-5,7,8,9,10,10a-hexahydroacridine-8a(6H)-carboxylate ***(4i)***. Brown solid. Yield: 81% (274 mg); mp: 80-81 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 7.05 – 7.01 (m, 2H), 6.32 (d, *J* = 8.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.75 (dd, *J* = 7.2, 3.4 Hz, 1H), 3.70 (s, 1H), 2.95 – 2.75 (m, 2H), 1.83 – 1.36 (m, 8H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 175.8, 141.6, 131.6, 129.6, 120.1, 114.8, 107.8, 60.7, 51.3, 43.8, 33.2, 30.3, 29.8, 21.9, 21.5, 14.1. HRMS (ESI): m/z calcd for $C_{16}H_{21}BrNO_2$ $[M + H]^+$ 338.0750, found 338.0756.

Ethyl 2-chloro-5,7,8,9,10,10a-hexahydroacridine-8a(6H)-carboxylate ***(4j)***. Brown oil. Yield: 85% (250 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 6.91 – 6.88 (m, 2H), 6.36 (d, *J* = 8.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.75 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.68 (s, 1H), 2.95 – 2.75 (m, 2H), 1.85 – 1.35 (m, 8H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) (*major diastereomer*) δ 175.8, 141.2, 128.8, 126.7, 120.7, 119.6, 114.4, 60.7, 51.4, 43.9, 33.2, 30.3, 29.8, 21.9, 21.6, 14.1. HRMS (ESI): m/z calcd for $C_{16}H_{21}ClNO_2$ $[M + H]^+$ 294.1255, found 294.1256.

Ethyl 1,2,3,3a,4,9-hexahydro-9aH-cyclopenta[b]quinoline-9a-carboxylate ***(4k)***. Orange oil. Yield: 82% (201 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03-6.99 (m, 2H), 6.66 – 6.62 (m, 1H), 6.53-6.51 (m, 1H), 4.12-4.07 (m, 3H), 3.84 (s, 1H), 3.12-2.66 (m, 2H), 2.18 – 2.00 (m, 2H), 1.81 – 1.53 (m, 4H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.1, 143.6, 128.8, 127.1, 120.1, 117.2, 113.6, 60.7, 58.3, 51.0, 35.0, 34.3, 33.2, 21.0, 14.0. HRMS (ESI): m/z calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ 246.1489, found 246.1489.

Ethyl 2,3,4,4a,5,10-hexahydrobenzo[b] [1,6] naphthyridine-10a(1H)-carboxylate ***(4l)***. Pale brown wax. Yield: 76% (198 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 – 6.92 (m, 2H), 6.60 (t, J = 7.4 Hz, 1H), 6.50 (d, J = 8.0 Hz 1H), 4.25-4.13 (m, 2H), 3.90-3.88 (m, 1H), 3.82 (s, 1H), 3.33 (m, 1H), 3.12-3.02 (m, 3H), 2.85 – 2.76 (m, 3H), 1.85 – 1.79 (m, 1H), 1.63 – 1.56 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 175.1 142.3, 129.2, 127.0, 117.5, 117.0 113.6, 60.9, 49.8, 49.0, 44.3, 41.6, 30.6, 29.7, 14.1. HRMS (ESI): m/z calcd for $C_{15}H_{21}N_2O_2$ [M + H]$^+$ 261.1598, found 261.1599

Ethyl 2,3-dimethylindoline-3-carboxylate ***(6a)***. Orange oil. Yield: 64% (140 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29-7.26 (m, 1H), 7.07 (td, J = 7.6, 1.2 Hz, 1H), 6.76 (td, J = 7.5, 1.1 Hz, 1H), 6.65-6.63 (m, 1H), 4.34 (q, J = 6.5 Hz, 1H), 4.23 (qd, J = 7.1, 1.4 Hz, 2H), 3.62 (s, 1H), 1.35 (s, 3H), 1.32 – 1.27 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.6, 149.2, 132.8, 128.2, 124.2, 119.1, 109.7, 61.0, 60.3, 54.3, 18.9, 15.6, 14.2. HRMS (ESI): m/z calcd for $C_{13}H_{18}NO_2$ [M + H]$^+$ 220.1332, found 220.1329.

Ethyl 5-methoxy-2,3-dimethylindoline-3-carboxylate ***(6b)***. Yellowish-brown wax. Yield: 75% (187 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 (d, J = 2.4 Hz, 1H), 6.66 – 6.57 (m, 2H), 4.30 (q, J = 6.4 Hz, 1H), 4.26 – 4.18 (m, 2H), 3.74 (s, 3H), 1.33 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.27 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.4, 153.8, 143.0, 134.6, 113.5, 110.8 110.6, 61.0, 60.8, 55.9, 54.7, 18.7, 15.6, 14.2. HRMS (ESI): m/z calcd for $C_{14}H_{20}NO_3$ [M + H]$^+$ 250.1438, found 250.1433

*Ethyl 5-chloro-2,3-dimethylindoline-3-carboxylat*e ***(6c)***. Brown oil. Yield: 71% (180 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 8.2, 2.2 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 4.32 (q, J = 6.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.55 (s, 1H), 1.33 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.0, 147.6, 134.4, 128.1, 124.5, 123.6, 110.5, 61.2, 60.7, 54.3, 18.9, 15.6, 14.2. HRMS (ESI): m/z calcd for $C_{13}H_{17}ClNO_2$ [M + H]$^+$ 254.0942, found 254.0940.

Ethyl 1,2,3,4,9,9a-hexahydro-4aH-carbazole-4a-carboxylate ***(6d)***. Pale yellow solid. Yield: 52% (128 mg); mp: 52-53 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.27 (m, 1H), 7.08 (td, J = 7.7, 1.3 Hz, 1H), 6.76 (td, J = 7.5, 1.1 Hz, 1H), 6.71 – 6.69 (m, 1H), 4.28 – 4.21 (m, 3H), 3.55 (s, 1H), 2.22-2.18 (m, 1H), 1.88 – 1.75 (m, 2H), 1.66 – 1.47 (m, 4H), 1.32 (t, J = 7.2 Hz, 3H), 1.28 – 1.19 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.8, 149.3, 133.0, 128.0, 123.2, 118.9, 110.3, 60.9, 60.8, 54.0, 32.6, 27.2, 21.8, 20.4, 14.3. HRMS (ESI): m/z calcd for $C_{15}H_{20}NO_2$ [M + H]$^+$ 246.1489, found 246.1490.

2,3-diphenylisoindolin-1-one ***(8a)***. White solid. Yield: 87% (248 mg); mp: 195-198 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.96 (m, 1H), 7.62 – 7.59 (m, 2H), 7.54 – 7.47 (m, 2H), 7.32 – 7.26 (m, 4H), 7.25 – 7.19 (m, 4H), 7.09 (tt, J = 7.4, 1.1 Hz, 1H), 6.09 (s, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.9, 145.6, 137.6, 137.6, 132.4, 131.1, 129.1, 128.8, 128.5, 128.3, 126.9, 124.9, 124.1, 123.0, 122.5, 65.6. HRMS (ESI): m/z calcd for $C_{20}H_{16}NO$ [M + H]$^+$ 286.1226, found 286.1223.

2-(4-methoxyphenyl)-3-phenylisoindolin-1-one ***(8b)***. Offwhite solid. Yield: 80% (252 mg); mp: 196-198 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.94 (m, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.41 (m, 2H), 7.30 – 7.26 (m, 1H), 7.26 – 7.21 (m, 3H), 7.19 – 7.16 (m, 2H), 6.85 – 6.81 (m, 2H), 6.00 (s, 1H), 3.75 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.8, 157.0, 145.6, 137.6, 132.2, 131.3, 130.5, 129.0, 128.5, 128.3, 127.1, 124.7, 124.0, 123.0, 114.1, 66.2, 55.3. HRMS (ESI): m/z calcd for $C_{21}H_{18}NO_2$ [M + H]$^+$ 316.1332, found 316.1325.

Methyl 2-oxo-1,5-diphenylpyrrolidine-3-carboxylate ***(10)***. White solid. Yield: 74% (218 mg); mp: 112-114 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) (*major diastereomer*) δ 7.44 – 7.41 (m, 1H), 7.34 – 7.30 (m, 2H), 7.28-.7.26 (m, 2H), 7.26 – 7.18 (m, 4H), 7.10 – 7.04 (m, 1H), 5.40-5.36 (m, 1H), 3.82 (s, 2H), 3.81 – 3.79 (m, 1H), 3.05-2.98 (m, 1H), 2.27-2.21 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) (*major diastereomer*) δ 170.3, 169.8, 140.6, 137.9, 129.3, 129.0, 128.2, 126.1, 125.6, 122.3, 62.6, 53.1, 48.6, 33.4. HRMS (ESI): m/z calcd for $C_{18}H_{18}NO_3$ [M + H]$^+$ 296.1281, found 296.1273.

1-phenylpyrrolidin-2-one ***(13)***. Purple solid. Yield: 68% (110 mg); mp: 59-60 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.59 (m, 2H), 7.39 – 7.34 (m, 2H), 7.16 – 7.12 (m, 1H), 3.86 (t, J = 7.0 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 2.19 – 2.12 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.2, 139.4, 128.8, 124.4, 119.9, 48.8, 32.7, 18.0. HRMS (ESI): m/z calcd for $C_{10}H_{12}NO$ [M + H]$^+$ 162.0913, found 162.0908.

Methyl 2-(2-oxopyrrolidin-1-yl) acetate ***(15)***. Pale yellow oil. Yield: 61% (96 mg). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.14 (s, 2H), 3.81 (s, 3H), 3.56 (t, J = 6.8 Hz, 2H), 2.50 (t, J = 8.0 Hz, 2H), 2.16 (quint, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 175.6, 169.2, 52.2, 47.7, 43.9, 30.2, 17.9. HRMS (ESI): m/z calcd for $C_7H_{12}NO_3$ [M + H]$^+$ 158.0812, found 158.0811.

3-phenylisobenzofuran-1(3H)-one ***(18)***. White solid. Yield: 91% (191 mg); mp: 107-110 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.96 (m, 1H), 7.65 (td, J = 7.5, 0.9 Hz, 1H), 7.58-7.54 (m, 1H), 7.40 – 7.36 (m, 3H), 7.34 (dt, J = 7.8, 0.9 Hz, 1H), 7.29 – 7.27 (m, 2H), 6.41 (s, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.5, 149.7, 136.4, 134.3, 129.3, 129.3, 129.0, 127.0, 125.6, 125.6, 122.8, 82.7. HRMS (ESI): m/z calcd for $C_{14}H_{11}O_2$ [M + H]$^+$ 211.0754, found 211.0747.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and ^{13}C NMR spectra for all reaction products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for financial support from the National Natural Science Foundation of China (No. 81473096, No. 81602949) and CAMS Collaborative Innovation Project (No. 2017-I2M-3-011)

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