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Novel synthesis of fused spiro piperidone-cyclopropanes from cyclopropyl amides and electron-deficient alkenes†

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We report here that a series of bridged *O,O*-ketal fused spiro piperidone-cyclopropane derivatives **3** can be constructed with excellent yields and good diastereoselectivity by the one-pot reaction of 1-acylcyclopropanecarboxamides **1** with electron-deficient alkene **2a** (EWG = CHO) *via* the domino process involving [4 + 2] annulation/intermolecular electrophilic addition/intramolecular cyclization. Furthermore, reactions of **1** with **2b**/**2c** (EWG = CN, COOMe), leading to spiro piperidone-cyclopropane derivatives **4** or **5** by base catalyst selection, were also presented.

Spiro-piperidine frameworks are embedded in a large quantity of natural products and bioactive molecules and have attracted increasing attention in recent years.[1] Numerous methods have been developed to fabricate spiro-piperidine bearing a five- or six-membered ring in the spiro system.[2] However, less reliable approaches are available for combining the three-membered carbocycle and spiro-piperidine motifs into one complex molecule until now. In fact, a survey of literature studies revealed that cyclopropane is a privileged structural unit and has become a "star" molecule in drug design and exhibits a broad spectrum of pharmacological and biological properties, such as antitumor,[3] anti-malarial,[4] anti-tuberculosis[5] and insecticidal activities.[6] Consequently, the incorporation of cyclopropane units into spiro-piperidine scaffolds may enhance the pharmacodynamic potential as well as structural diversity. Meanwhile, spiro piperidine-cyclopropane derivatives also prove to be useful synthetic intermediates for building molecular complexity owing to their strain energy and the tendency to release this strain through a ring-opening process, such as for the synthesis of 7-azaindolines and caprolactams.[7]

To the best of our knowledge, limited reports were disclosed on the synthesis of spiro piperidine-cyclopropane derivatives. In 1996, Goti and Brandi obtained 3-spirocyclopropane-4-pyridones successfully derived from nitrile oxides and bicyclopropylidene *via* the sequence of cycloaddition and thermal rearrangement processes.[8] In 2006, Kerr and co-workers reported a novel approach to spiropiperidine-2,4-diones through monoammonolysis of the diester moiety/DIBAL reduction/Horner–Emmons olefination followed by a base-induced ring formation.[7a] Furthermore, Padmavathi *et al.* constructed a core structure with tetra substituted 4-piperidone under ultrasound-assistance.[9] Afterward, Liu's group devised an alternative more straightforward way for the generation of spiropiperidine-2,4-diones through remote electronic effects, in which an aromatic substrate on the *N* atom is generally required.[10] Nevertheless, the majority of the developed methods may suffer from precursor availability, the limited substrate scope, harsh reaction conditions and tedious steps. In this regard, the development of facile and efficient synthetic methods toward highly functionalized spiro piperidine-cyclopropane from readily available starting materials under mild conditions is highly desirable.

1-Acylcyclopropanecarboxamides **1** bearing both *C*-electrophilic and *N*-nucleophilic centers showed fascinating reactivities in various types of reactions, especially in the synthesis of pyridin-2(1*H*)-ones,[11] isoquinolinedione,[12] furo[3,2-*c*]pyridinones[13] and furoquinoline derivatives.[14] Lately, we described the synthesis of polysubstituted pyrrolidones from 1-acylcyclopropanecarboxamides, alkynyl and PTSA in two steps.[15] In connection with these studies and motivated by our continuing interest in constructing a spiro piperidine-cyclopropane scaffold from **1**, we envisioned whether a polarized olefin, offering a C=C bond, would undergo a [4 + 2] cycloaddition with **1** at its potentially reactive sites under appropriate conditions to achieve the rapid synthesis of our target products. With this idea in mind, the reactions of substrates **1** with different polarized olefins **2** were investigated. As a result of the

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†Electronic supplementary information (ESI) available: CIF data for **3a** and **5d**, copies of ^{1}H, ^{13}CNMR spectra for compounds **3a–n**, **4a–h**, **5a–i** and noesy spectra of compound **4f**. CCDC 1948958 and 1948938. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00214g

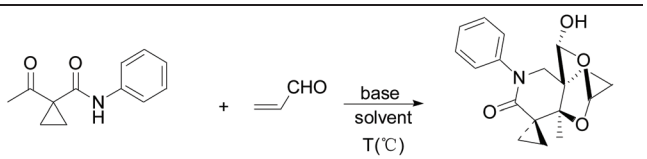
research, the one-pot cascade process that allows access to complicated spiro piperidone-cyclopropane derivatives is presented, which displays some significant advantages over traditional stepwise strategies by energy consumption, and increasing atom economy. Herein, we wish to communicate the results.

In the initial experiment, we selected 1-acetyl-*N*-phenylcyclopropanecarboxamide **1a** as one of the model compounds, which was easily prepared following the procedure described previously.[16] Our selection of acrolein **2a** as the second substrate was the introduction of a strong electron-withdrawing group into the alkene, in which one of the carbons in C=C is nucleophilic, and the other one electrophilic (cross polarization). To our surprise, a new bridged *O*,*O*-ketal fused spiro piperidone-cyclopropane **3a** with simultaneous formation of three new rings was isolated in 69% yield on treatment of **1a** with 2.0 equiv. **2a** in DABCO(1.0 equiv.)/CH_3CN at 60 °C for 10 h (Table 1, entry 1). Driven by the complexity of bridged *O*,*O*-ketals, coupled with their remarkable biological properties,[17] the one-pot entry to **3a** was then carefully explored.

As a result, it was found that when DABCO (1.5 equiv.) was used as the catalyst, the reaction gave **3a** in 93% yield at 60 °C with a reaction time of only 8 h (Table 1, entry 2). A further increase of the amount of DABCO (2.0 equiv.) afforded product **3a** in slightly reduced yield (Table 1, entry 3). By lowering the temperature to RT, the product **3a** was observed only in a trace amount even after prolonged stirring of the reaction mixture (Table 1, entry 4). Performing the reaction of **1a** and **2a** under otherwise identical conditions as in entry 2 but at 80 °C for 8 h led to **3a** in 38% yield (Table 1, entry 5). Screening of bases revealed that DABCO is superior to DBU, K_2CO_3, *t*-BuOK and NaOH (Table 1, entries 6–9). Among the solvents tested, CH_3CN seemed to be the best choice. For example, with DMF as the solvent, the yield of **3a** was fairly low (Table 1, entry 10). No desired **3a** could be detected when the reaction was carried out in EtOH or xylene (Table 1, entries 11 and 12).

With the optimized conditions in hand, the scope of the reaction was studied and the results are summarized in Table 2. It can be seen that the cascade reaction showed broad tolerance for various R^1, R^2 and R groups of substrates 1. Substrates **1a–g** containing phenyl (entry 1), electron-rich (entries 2–5) and electron-deficient aryl (entries 6–7) R^2 groups on the *N* atom reacted smoothly with **2a** to give bridged *O*,*O*-ketal fused spiro piperidone-cyclopropane **3a–g** in excellent yields. Similarly, a substrate with a Ph group at R^1 was also applicable, giving rise to the desired product **3h** in a promising 81% yield (entry 8). Disappointingly, the reaction of *N*-benzyl counterpart **1i** with **2a** failed to deliver the corresponding product **3i** (entry 9). In the same line, the substrate carrying a methyl group on the cyclopropane ring furnished **3j** in 89% yield (entry 10). Moreover, the reactions of substrates 1 bearing a vinyl group at R^1, such as styrene (**1k** and **1l**), cinnamon ethylene (**1m**) and 2-vinyl-furan (**1n**), were also reacted well, affording the corresponding products **3k–n** in good yields (entries 11–14). The structure of **3** was determined by means of ^{1}H-, ^{13}C-NMR, and mass spectral data, and further by the X-ray crystallographic data of **3a** (see Fig. 1). Also the structure of 3**j** was easily inferred from the compound **4f**, in which the relative configuration of spiro-piperidino-cyclopropane is not

Table 1 Optimization of the reaction conditions[a]

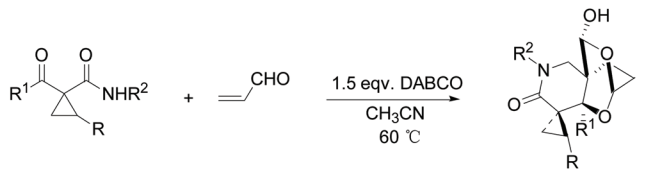


1a **2a** **3a**

Entry	Base (equiv.)	*T* (°C)	Solv.	*t* (h)	**3a** yield[b] (%)
1	DABCO (1.0 equiv.)	60	CH_3CN	10	69
2	DABCO (1.5 equiv.)	60	CH_3CN	8	93
3	DABCO (2.0 equiv.)	60	CH_3CN	8	90
4	DABCO (1.5 equiv.)	rt	CH_3CN	15	Trace
5	DABCO (1.5 equiv.)	80	CH_3CN	8	38
6	DBU (1.5 equiv.)	60	CH_3CN	8	44
7	K_2CO_3 (1.5 equiv.)	60	CH_3CN	10	16
8	*t*-BuOK (1.5 equiv.)	60	CH_3CN	4	—[c]
9	NaOH (1.5 equiv.)	60	CH_3CN	4	—[c]
10	DABCO (1.5 equiv.)	60	DMF	8	25
11	DABCO (1.5 equiv.)	60	EtOH	15	0
12	DABCO (1.5 equiv.)	60	Xylene	15	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), and solvent (5 mL). [b] Isolated yield. [c] A complex mixture.

Table 2 One-pot cascade leading to bridged *O*,*O*-ketal fused spiro piperidone-cyclopropane **3** from 1-acylcyclopropanecarboxamides **1** and acrolein **2a**[a]



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

Entry	11	R^1	R^2	R	*t* (h)	**3**[b] yield (%)
1	**1a**	Me	C_6H_5	H	8	93(**3a**)
2	**1b**	Me	4-MeC_6H_4	H	8	95(**3b**)
3	**1c**	Me	4-MeOC_6H_4	H	8	92(**3c**)
4[c]	**1d**	Me	2-MeC_6H_4	H	9	91(**3d**)
5[d]	**1e**	Me	2,4-$Me_2C_6H_3$	H	10	87(**3e**)
6	**1f**	Me	4-ClC_6H_4	H	8	88(**3f**)
7[e]	**1g**	Me	2-ClC_6H_4	H	8	85(**3g**)
8	**1h**	C_6H_5	C_6H_5	H	10	81(**3h**)
9	**1i**	Me	$CH_2C_6H_5$	H	12	0(**3i**)
10	**1j**	Me	4-MeOC_6H_4	Me	9	89(**3j**)
11	**1k**	PhCH=CH	C_6H_5	H	10	86(**3k**)
12[f]	**1l**	PhCH=CH	2-MeC_6H_4	H	10	79(**3l**)
13	**1m**	PhCH=CHCH=CH	C_6H_5	H	11	75(**3m**)
14	**1n**	furanCH=CH	C_6H_5	H	8	81(**3n**)

[a] All reactions were carried out in CH_3CN (5 mL) with **1** (1.0 mmol), **2a** (2.0 mmol), and DABCO (1.5 mmol) at 60 °C for 8–12 h. [b] Isolated yield. [c] dr = 1.4 : 1. [d] dr = 1.5 : 1. [e] dr = 1.1 : 1. [f] dr = 1.5 : 1.

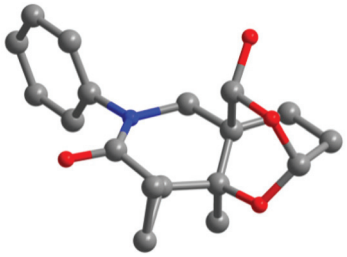


Fig. 1 ORTEP drawing of compound **3a**.

found to be altered. All of the reactions proceeded in a highly diastereoselective manner and only one diastereoisomer was obtained in most cases although the products contained four stereocenters at least. Notably, substrates **1** with a substituent located at the *ortho* position of the phenyl ring (**1d–e**, **1g** and **1l**) gave the corresponding products **3d–e**, **3g** and **3l** in 79–91% yields with different dr values, which may be attributed to the atropisomers caused by the steric hindrance and clearly detected from NMR spectroscopy.[18]

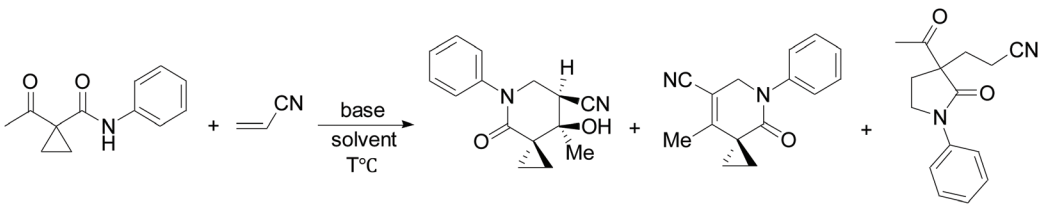
On the basis of the above experimental results, we reasoned that the spiro piperidone-cyclopropane could be prepared from **1** and other electron-deficient alkenes (*e.g.* acrylonitrile **2b** and methyl acrylate **2c**) *via* a [4 + 2] annulation in a single step under base conditions. Detailed examination of the reaction conditions indicated that 5-aza-spiro[2.5]octan-7-en-4-one **5a** could be obtained in 96% yield from **1a** (1.0 mmol) and **2b** (1.5 mmol) in the presence of *t*-BuOK (1.5 equiv.) at 60 °C for 8 h in EtOH (Table 3, entry 1). Interestingly, when DBU was utilized to replace *t*-BuOK with CH_3CN as the solvent for the reaction, 5-aza-spiro[2.5]octan-4-one **4a** was exclusively afforded in 89% yield (Table 3, entry 2). In addition, mediated by DABCO (1.5 equiv.), a ring-expanding product **6a** was formed in 98% yield after the reaction mixture was stirred in xylene for 10 h at 60 °C (entry 3), which is consistent with Liang's report.[19] From a synthetic point of view, the highly selective synthesis derived from the same starting materials by reaction condition selection is still a formidable challenge in organic synthesis,[20] and then the divergent method for the synthesis of **4** or **5** was probed.

To test the generality of this [4 + 2] approach, the reactions of **2b–c** with selected **1a–c**, **1h–j** and **1o** (R^1 = Me, R^2 = Ph, R = Me) were examined under identical conditions to those described in Table 3, entry 2. Fortunately, a new class of spiro piperidone-cyclopropane derivatives **4a–h** was prepared in good to high yields (Scheme 1). All of the structural assignments were unequivocally made on the basis of their ^{1}H and ^{13}C NMR spectra. And the identity of the relative configuration has been defined by NOESY analyses of **4f**, in which OH gave no correlation with proton (H①) adjacent to the CN group, but the Me (R^1) group has some correlation with proton (H①) and strong NOE cross peaks could be observed between OH and H②, thereby allowing to assign the methyl group (R^1), proton (H①), and methylene on the same face.

In the following work, under the optimized conditions (Table 3, entry 1), a range of reactions of **1a–e**, **1g–i** and **1p** (R^1 = Me, R^2 = Ph, R = Ph) with **2b** were carried out at 60 °C in 5 mL EtOH. Gratifyingly, all of them participated in this reaction successfully to generate the products **5a–i** in 87–98% yields. However, the reaction with **2c** gave none of the expected cyclization product **5j** but with a complex reaction system. One possible reason is that the strong base has an important effect on the ester group, leading to the decomposition of **5j**.

Taken together, the present results and related research,[7b,12,13,15] plausible mechanisms for the synthesis of **3**, **4** and **5** from 1-acylcyclopropanecarboxamides **1** and electron-deficient alkenes (**2a–c**) are proposed, as depicted in Scheme 2. The formation of **4** and **5** can be briefly described as an amide anion from substrate **1(A)** → *N*-nucleophilic addition → carbanion(**B**) → intramolecular *C*-nucleophilic addition to give cyclic products **4**, followed by dehydration to give **5**. It is worth noting that when acrolein **2a** was subjected to the above reaction sequences, compound **4** (R^3 = CHO) is formed and subsequent base-triggered dehydrogenation was performed to give a tertiary carbanion intermediate **C**, which

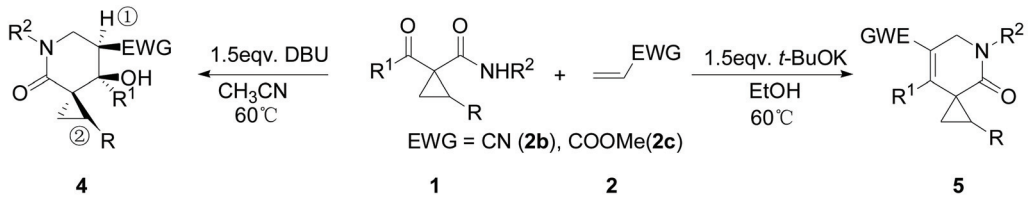
Table 3 Selective synthesis of **4a**[a] or **5a**[a] or **6a**[a] under basic conditions



1a **2b** **4a** **5a** **6a**

Entry	BASE (equiv.)	*T* (°C)	Solv.	Time (h)	**4a**[b] yield (%)	**5a**[b] yield (%)	**6a**[b] yield (%)
1	*t*-BuOK (1.5 equiv.)	60	EtOH	8	0	96	0
2	DBU (1.5 equiv.)	60	CH_3CN	10	89	0	0
3	DABCO (1.5 equiv.)	60	Xylene	10	0	0	98

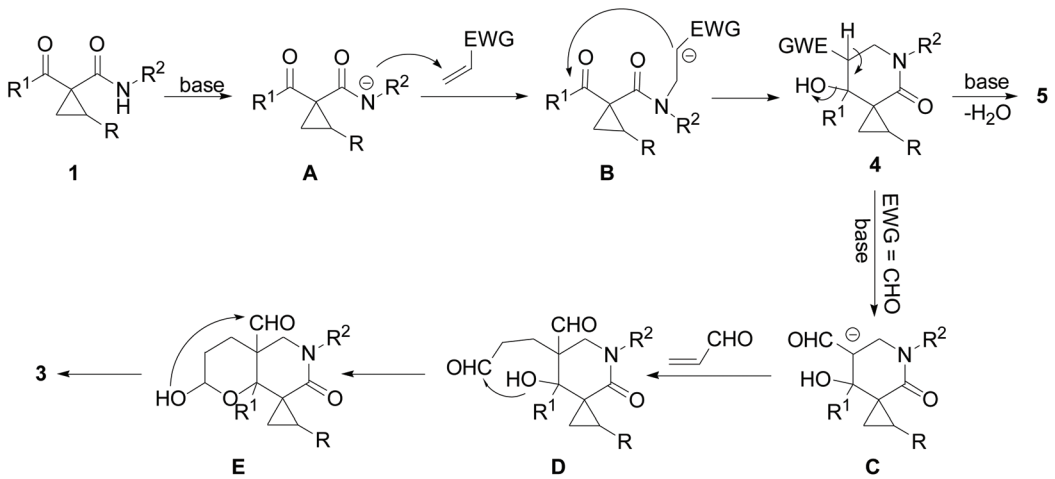
[a] The reactions were carried out in solvent (5 mL) with **1a** (1.0 mmol), **2a** (1.5 mmol), and base (1.5 mmol) at 60 °C. [b] Isolated yield.



4a(10 h, 89% yield): R^1 = Me, R^2 = C_6H_5, R = H, EWG = CN
4b(10 h, 83% yield): R^1 = Me, R^2 = 4-MeC_6H_4, R = H, EWG = CN
4c(10 h, 87% yield): R^1 = Me, R^2 = 4-MeOC_6H_4, R = H, EWG = CN
4d(12 h, 74% yield): R^1 = Ph, R^2 = C_6H_5, R = H, EWG = CN
4e(12 h, 81% yield): R^1 = Me, R^2 =$CH_2C_6H_5$, R = H, EWG = CN
4f(8.5 h, 76% yield): R^1 = Me, R^2 = 4-MeOC_6H_4, R = Me, EWG = CN
4g(9 h, 79% yield): R^1 = Me, R^2 = C_6H_5, R = Me, EWG = CN
4h(12 h, 80% yield): R^1 = Me, R^2 = C_6H_5, R = H, EWG = COOMe

5a(8 h, 96% yield): R^1 = Me, R^2 = C_6H_5, R = H, EWG = CN
5b(8 h, 94% yield): R^1 = Me, R^2 = 4-MeC_6H_4, R = H, EWG = CN
5c(8 h, 98% yield): R^1 = Me, R^2 = 4-MeOC_6H_4, R = H, EWG = CN
5d(10 h, 93% yield): R^1 = Me, R^2 = 2-MeC_6H_4, R = H, EWG = CN
5e(10 h, 89% yield): R^1 = Me, R^2 = 2,4-$Me_2C_6H_3$, R = H, EWG = CN
5f(7.5 h, 87% yield): R^1 = Me, R^2 = 2-ClC_6H_4, R = H, EWG = CN
5g(8 h,95% yield): R^1 = Ph, R^2 = C_6H_5, R = H, EWG = CN
5h(10 h, 93% yield): R^1 = Me, R^2 = $CH_2C_6H_5$, R = H, EWG = CN
5i(10 h, 88% yield): R^1 = Me, R^2 = C_6H_5, R = Ph, EWG = CN
5j(10~15 h, 0): R^1 = Me, R^2 = C_6H_5, R = H, EWG = COOMe

Scheme 1 Reaction scope of the base-induced [4 + 2] cycloaddition of **1** with electron-deficient alkene **2b**/**2c**.



Scheme 2 Proposed mechanistic pathway leading to the formation of complicated spiro piperidone-cyclopropanes **3**, **4** and **5**.

can be stabilized by the adjacent aldehyde group. Next, direct nucleophilic addition with another **2a** leads to the intermediate **D**. Eventually, the 6,6,6-bridged ring system **3** could be formed *via* two consecutive *O*-nucleophilic additions with an aldehyde group (**D** → **E** → **3**).[20d,21] In the cascade reactions, tandem C–N, C–O, and C–C bonds were established in one-pot with excellent yields.

In conclusion, we have developed a novel and efficient tactic for the atom economical synthesis of bridged *O*,*O*-ketal fused spiro pyridone-cyclopropane derivatives **3** and spiro piperidone-cyclopropanes **4** or **5** in good to excellent yields under mild reaction conditions by judicious selection of cyclopropanes and electron-deficient alkenes as precursors. The protocol also provides a complementary platform for the reactions of activated cyclopropanes with alkenes and the extension of the scope of the methodology is currently under investigation in our laboratory.

Experimental section

All reagents were commercial and were used without further purification. All products were purified by column chromatography over silica gel (200–300 mesh). Reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F254). Melting points were uncorrected. Unless noted, the ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ and the ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ with TMS as the internal standard. All coupling constants (J values) were reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF IIfocus spectrometer (ESI). The compound **3a** with dimension 0.18 × 0.17 × 0.16 mm^3 and **5d** with dimension 0.15 × 0.12 × 0.10 mm^3 were glued on a glass fiber. Data of **3a** were collected at 150 K using graphite-monochromated Cu Kα radiation (λ = 1.54184 Å) and the IP technique in the range of 5.424 < θ <

66.583. And data of **5d** were collected at 296 K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and the IP technique in the range of $3.52° < \theta < 25.01°$. Empirical absorption correction was applied. The structures were solved by direct methods and refined by the full-matrix least-squares method on F^2 using the SHELXL-2014 crystallographic software package. Anisotropic thermal parameters were used to refine all non-hydrogen atoms. Hydrogen atoms were located from difference Fourier maps.

General procedure for the synthesis of bridged *O*,*O*-ketal fused spiro piperidone-cyclopropane derivatives 3 (3a as an example)

To a 25 mL vial charged with **1a** (203 mg, 1.0 mmol), DABCO (168 mg, 1.5 mmol) and acrolein **2a** (0.13 mL, 2.0 mmol) was added CH_3CN (5 mL). Then the reaction mixture was allowed to stir at 60 °C for 8 h. After the substrate **1a** was consumed as indicated by TLC, the mixture was poured into water (20 mL), and then extracted with dichloromethane (3 × 15 mL), and the combined organic phase was washed with water (3 × 20 mL), dried over Na_2SO_4 and distilled under reduced pressure to give a crude product. The crude product was purified by column chromatography over silica gel using petroleum ether–acetone (4 : 1) as the eluent, affording **3a** in 93% yield.

3a: White solid; m.p. 155–157 °C; 93% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ:0.81 (t, J = 4.0 Hz, 1H), 0.83 (t, J = 4.0 Hz, 1H), 1.04–1.08 (m, 5H), 1.46–2.14 (m, 4H), 2.8 (s, 1H), 2.44–3.48 (s, 1H), 3.70–3.3.74 (s, 1H), 4.98 (s, 1H), 5.84 (s, 1H), 7.20 (t, J = 4.0 Hz, 2H), 7.25–7.36 (m, 1H), 7.37–7.39 (t, J = 4.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.6, 16.0, 16.9, 22.4, 26.6, 29.5, 37.5, 52.5, 72.5, 91.3, 91.4, 126.5, 127.0, 129.3, 142.7, 171.6. HRMS (ESI-TOF) calcd for $C_{18}H_{22}NO_4^+$([M + H]$^+$): 316.1543, found: 316.1556.

3b: White solid; m.p. 156–158 °C; 95% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.02 (t, J = 4.0 Hz, 1H), 1.06 (t, J = 4.0 Hz, 1H), 1.49–1.66 (m, 6H), 1.89–2.17 (m, 3H), 2.33 (s, 3H), 3.41 (d, J = 16.0 Hz, 1H), 3.70 (d, J = 12.0 Hz, 1H), 4.98 (s, 1H), 5.85 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.5, 16.0, 16.8, 21.0, 22.4, 26.6, 29.5, 37.5, 52.7, 72.5, 91.3, 91.4, 126.3, 129.8, 136.8, 140.2, 171.6. HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_4^+$([M + H]$^+$): 330.1700, found: 330.1709.

3c: White solid; m.p. 174–175 °C; 92% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.81 (q, J = 4.0 Hz, 1H), 1.04 (q, J = 4.0 Hz, 1H), 1.44–1.66 (m, 6 H), 1.88–2.17 (m, 3H), 3.43(d, J = 16.0 Hz, 1H), 3.69 (d, J = 12.0 Hz, 1H), 3.84 (s, 3H), 4.97 (s, 1H), 5.83 (s, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.6, 16.0, 16.8, 22.4, 26.7, 29.5, 37.5, 52.9, 55.5, 72.5, 91.3, 91.4, 114.5, 114.6, 127.7, 135.6, 158.3, 171.9. HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_5^+$([M + H]$^+$): 346.1649, found: 346.1643.

3d: White solid; m.p. 146–147 °C; 91% yield (9 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.81(t, J = 6.0 Hz, 1H), 1.05 (q, J = 5.5 Hz, 1H), 1.53–1.68 (m, 6H), 1.91–2.17 (m, 6H), 3.33–3.66 (m, 2H), 4.99 (s, 1H), 5.92 (d, J = 12.0 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 7.22 (t, J = 4.0 Hz, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.03, 8.63, 15.9, 16.0, 16.4, 16.6, 17.2, 17.7, 22.4, 22.6, 26.5, 29.3, 37.4, 37.6, 51.9, 52.0, 72.6 (2C), 91.4 (3C), 91.5, 126.7, 127.1, 127.4, 127.5, 127.8, 128.0, 130.9, 131.2, 135.4, 135.5, 141.2, 141.5, 170.8, 171.0. HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_4^+$([M + H]$^+$): 330.1700, found: 330.1710.

3e: White solid; m.p. 151–152 °C; 87% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.80 (q, J = 4.0 Hz, 1H), 1.03 (q, J = 5.0 Hz, 1H), 1.48–1.67 (m, 6H), 1.89–2.15 (m, 6H), 2.29 (s, 3H), 3.29–3.63 (m, 2H), 4.98 (s, 1H), 5.90 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.0, 8.6, 15.9, 16.0, 16.3, 16.5, 17.1, 17.6, 20.9, 21.0, 22.4, 22.6, 26.6, 29.3, 37.4, 37.6, 52.0, 52.1, 72.6, 72.6, 126.4, 127.2, 127.7, 128.1, 131.6, 131.9, 134.9, 135.0, 137.5, 137.7, 138.6, 138.9, 171.0. HRMS (ESI-TOF) calcd for $C_{20}H_{26}NO_4^+$([M + H]$^+$): 344.1856, found: 344.1862.

3f: White solid; m.p. 158–160 °C; 88% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.84 (q, J = 4.0 Hz, 1H), 1.02–1.07 (m, 1H), 1.45–1.68 (m, 6H), 1.90–2.17 (m, 3H), 3.44 (d, J = 12.0 Hz, 1H), 3.68 (d, J = 12.0 Hz, 1H), 4.98 (s, 1H), 5.83 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.7, 16.0, 17.1, 22.5, 26.6, 29.6, 37.5, 52.4, 72.4, 91.2, 91.4, 127.8, 129.3, 132.6, 141.2, 171.7. HRMS (ESI-TOF) calcd for $C_{18}H_{21}ClNO_4^+$([M + H]$^+$): 350.1154, found: 350.1151.

3g: White solid; m.p. 170–172 °C; 85% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.81(m, 1H), 1.10 (m, 1H), 1.50–1.70 (m, 6H), 1.90–2.18 (m, 3H), 3.34–3.62 (m, 2H), 4.99 (s, 1H), 5.87–6.01 (m, 1H), 7.15–7.19 (m, 1H), 7.23–7.32 (m, 2H), 7.43–7.47 (m, 1H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 8.2, 8.6, 16.0, 16.8, 22.5, 26.6, 29.3, 29.4, 37.5, 37.7, 51.4, 51.7, 72.5, 72.7, 76.7, 77.2, 77.3, 91.2, 91.3, 91.4, 91.5, 128.0, 128.3, 129.0, 129.1, 129.2, 129.8, 130.3, 130.5, 132.4, 132.5, 139.6, 139.9, 171.3, 171.5. HRMS (ESI-TOF) calcd for $C_{18}H_{21}ClNO_4^+$([M + H]$^+$): 350.1154, found: 350.1153.

3h: White solid; m.p. 160–162 °C; 81% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.44 (q, J = 4.0 Hz, 1H), 0.47–1.15(m, 1H), 1.26–1.33(m, 1H), 1.51–1.56 (m, 1H), 1.82–1.90 (m, 2H), 2.11–2.15 (m, 2H), 2.72 (s, 1H), 3.40 (d, J = 12.0 Hz, 1H), 3.63 (d, J = 12.0 Hz, 1H), 5.32 (s, 1H), 5.95 (s, 1H), 7.26–7.28 (m, 3H), 7.33–7.43 (m, 5H), 7.55–7.57 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 12.1, 15.6, 18.9, 26.7, 30.2, 38.2, 51.7, 78.4, 91.8, 91.9, 126.2, 126.9, 127.1, 127.8, 128.2, 129.2, 142.2, 142.8, 172.9. HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4^+$([M + H]$^+$): 378.1700, found: 378.1712.

3j: White solid; m.p. 178–180 °C; 89% yield (9 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.88 (q, J = 4.0 Hz, 1H), 1.17 (d, J = 8.0 Hz, 3H), 1.31 (q, J = 4.0 Hz, 1H), 1.46 (s, 3H), 1.61–1.68 (m, 1H), 1.90–2.15 (m, 4H), 3.37 (d, J = 12.0 Hz, 1H), 3.67 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H), 4.99 (s, 1H), 5.65 (s, 1H), 6.89 (q, J = 4.0 Hz, 2H), 7.06 (d, J = 4.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.4, 13.5, 16.1, 21.0, 22.0, 26.7, 34.5, 37.3, 53.1, 55.5, 73.4, 91.4, 91.7, 114.6, 127.7, 135.9, 158.3, 169.6. HRMS (ESI-TOF) calcd for $C_{20}H_{26}NO_5^+$([M + H]$^+$): 360.1806, found: 360.1811.

3k: White solid; m.p. 170–172 °C; 86% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.70 (q, J = 4.0 Hz, 1H), 1.16–1.20 (m, 1H), 1.52–1.71 (m, 3H), 1.99–2.10 (m, 3H), 3.56 (d, J = 12.0 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 5.19 (s, 1H), 5.91 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 6.83 (d, J = 16.0 Hz, 1H), 7.23–7.29 (m, 3H),

7.31–7.44 (m, 7H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 10.3, 16.4, 17.4, 26.7, 27.9, 38.2, 52.4, 75.8, 91.4, 91.9, 126.5, 126.7, 127.1, 128.1, 128.5, 128.8, 129.3, 130.8, 136.4, 142.8, 171.6. HRMS (ESI-TOF) calcd for $C_{25}H_{26}NO_4^+$([M + H]$^+$): 404.1856, found: 404.1861.

3l: White solid; m.p. 181–182 °C; 79% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.70–0.73 (m, 1H), 1.12–1.18 (m, 1H), 1.52–1.69 (m, 3H), 1.97–2.09 (m, 3H), 2.17–2.29 (m, 3H), 3.41–3.70 (m, 2H), 5.18 (s,1H), 5.96–5.98 (m, 1H), 6.45 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 7.06–7.11 (m, 1H), 7.21–7.30 (m, 8H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 9.63, 10.3, 16.3, 16.4, 16.9, 17.0, 17.3, 18.0, 18.4, 26.7, 27.6, 27.7, 38.1, 38.3, 51.8, 51.9, 75.8, 75.9, 91.5, 91.6, 91.8, 91.9, 126.6, 126.7, 127.2, 127.5, 127.6, 127.9, 128.0, 128.1, 128.4, 128.7, 128.8, 130.8, 130.9, 131.0, 131.3, 135.3, 135.5, 136.4, 141.2, 141.6, 170.9, 171.0. HRMS (ESI-TOF) calcd for $C_{26}H_{28}NO_4^+$([M + H]$^+$): 418.2013, found: 418.1998.

3m: White solid; m.p. 164–166 °C; 75% yield (11 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.69–0.70 (m, 1H), 1.14–1.19 (m, 1H), 1.51–1.67 (m, 3H), 1.96–2.09(m, 3H), 2.56 (s, 1H), 3.51 (d, J = 12.0 Hz, 1H), 3.73 (d, J = 12.0 Hz, 1H), 5.16 (s, 1H), 5.87 (s, 1H), 6.00 (d, J = 16.0 Hz, 1H), 6.63 (m, 2H), 6.89 (q, J = 9.0 Hz, 1H), 7.22–7.29 (m, 3H), 7.32–7.44(m, 7H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 10.2, 16.4, 17.3, 26.7, 27.9, 38.0, 52.3, 75.6, 91.3, 91.8, 126.4, 126.5, 127.1, 127.8, 128.7, 129.3, 131.2, 132.4, 133.7, 136.9, 142.7, 171.6. HRMS (ESI-TOF) calcd for $C_{27}H_{28}NO_4^+$([M + H]$^+$): 430.2013, found: 430.1996.

3n: White solid; m.p. 155–158 °C; 81% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.65–0.70 (m, 1H), 1.15–1.17 (m, 1H), 1.50–1.68 (m, 3H), 1.92–2.08 (m, 3H), 2.77 (s, 1H), 3.57 (d, J = 12 Hz, 1H), 3.73 (d, J = 12 Hz, 1H), 5.15 (s, 1H), 5.87 (s, 1H), 6.29–6.42 (m, 3H), 6.61 (d, J = 12.0 Hz, 1H), 7.23–7.29 (m, 3H), 7.37–7.41(m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 10.3, 16.4, 17.5, 26.7, 26.9, 38.1, 52.3, 75.6, 91.3, 91.9, 109.1, 111.5, 119.0, 126.6, 126.9, 127.1, 129.3, 142.3, 142.7, 152.1, 171.6. HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_5^+$([M + H]$^+$): 394.1649, found: 394.1652.

General procedure for the synthesis of 5-aza-spiro[2.5]octan-4-ones 4 (4a as an example)

DBU (0.225 mL, 1.5 mmol) was added to a stirring solution of 1-acetyl-1-carbamoyl cyclopropane **1a** (203 mg, 1.0 mmol) and acrylonitrile **2b** (0.1 mL, 1.5 mmol) in CH_3CN (5 mL). The resulting mixture was heated at 60 °C with constant stirring for 10 h. When **1a** disappeared as monitored by TLC, the reaction mixture was poured into a saturated NaCl solution (30 mL), extracted with chloroform (3 × 10 mL), dried over Na_2SO_4, and distilled under reduced pressure to give a crude product. The crude product was purified by column chromatography over silica gel using petroleum ether–acetone (3 : 1) as the eluent.

4a: White solid; m.p. 135–138 °C; 89% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.06–1.13 (m, 2H), 1.26–1.29 (m, 1H), 1.43 (s, 3H), 1.50–1.54 (m, 1H), 1.75–1.81 (s, 1H), 3.28 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 3.77 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 4.20–4.25 (m, 1H), 7.24 (q, J = 8.0 Hz, 2H), 7.30 (q, J = 4.0 Hz, 1H), 7.42(q, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 12.1, 14.5, 24.7, 30.7, 38.8, 48.2, 70.0, 117.2, 126.3, 127.5, 129.4, 142.1, 169.7. HRMS (ESI-TOF) calcd for $C_{15}H_{17}N_2O_2^+$([M + H]$^+$): 257.1285, found: 257.1283.

4b: White solid; m.p. 163–165 °C; 83% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.02–1.08 (m, 2H), 1.09–1.25 (m, 1H), 1.37 (s, 3H), 1.42–1.48 (m, 1H), 2.50 (s, 3H), 2.56 (s, 1H), 3.20 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 3.72 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 4.14 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.5, 14.2, 21.1, 23.5, 30.6, 38.3, 48.5, 69.9, 117.9, 126.3, 130.0, 137.4, 139.6, 170.3. HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2^+$([M + H]$^+$): 271.1441, found: 271.1447.

4c: White solid; m.p. 151–153 °C; 87% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.08 (t, J = 4.0 Hz, 2H), 124 (d, J = 4.0 Hz, 1H), 1.43 (s, 3H), 1.45 (m, 1H), 3.28 (t, J = 6.0 Hz, 1H), 3.74 (q, J = 6.5 Hz, 1H), 3.81 (s, 3H), 4.18 (q, J = 5.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 12.1, 14.2, 23.6, 30.6, 38.8, 48.5, 55.5, 69.9, 114.6, 114.7, 117.3, 127.5, 127.6, 135.0, 158.6, 170.0. HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_3^+$([M + H]$^+$): 287.1390, found: 287.1395.

4d: White solid; m.p. 164–166 °C; 74% yield (12 h); ^{1}HNMR (DMSO-d_6, 400 MHz) δ: 0.70–0.75 (m, 1H), 0.85 (t, J = 4.0 Hz, 1H), 1.05–1.10 (m, 1H), 1.32–1.39 (m, 1H), 3.27–3.30 (m, 1H), 3.78–3.91 (m, 1H), 3.99–4.16 (m, 1H), 6.39 (s, 1H), 7.11–7.16 (m, 2H), 7.20–7.29 (m, 1H), 7.38–7.41 (m, 3H), 7.41–7.47 (m, 2H), 7.49–7.57 (m, 2H); ^{13}CNMR (DMSO-d_6, 100 MHz) δ: 11.7, 13.6, 29.4, 38.2, 48.4, 72.5, 119.0, 126.3, 126.6, 126.8, 128.2, 128.3, 129.0, 142.0, 142.6, 170.1. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O_2^+$([M + H]$^+$): 319.1441, found: 319.1447.

4e: White solid; m.p. 113–115 °C; 81% yield (12 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.02–1.09 (m, 1H), 1.10–1.19 (m, 2H), 1.34 (d, J = 4.0 Hz, 3H), 1.52–1.56 (m, 1H), 1.57 (s, 1H), 3.12–3.32 (m, 1H), 3.32–3.67 (m, 1H), 3.68–3.71 (m, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.73 (d, J = 16.0 Hz, 1H), 7.22–7.36 (m, 5H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.8, 12.8, 23.4, 30.5, 38.1, 44.6, 50.5, 69.6, 117.7, 127.8, 128.0, 128.9, 136.2, 169.9. HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2^+$([M + H]$^+$): 271.1441, found: 271.1452.

4f: White solid; m.p. 148–150 °C; 76% yield (8.5 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.07 (q, J = 4.0 Hz, 1H), 1.14 (d, J = 8.0 Hz, 3H), 1.37 (q, J = 4.0 Hz, 1H), 1.55 (s, 3H), 1.62–1.71 (m, 1H), 2.00 (s, 1H), 3.36 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.92 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.7, 14.8, 18.6, 23.0, 36.9, 39.2, 49.2, 55.5, 69.4, 114.8, 117.5, 127.7, 134.7, 158.8, 168.3. HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_2O_3^+$([M + H]$^+$): 301.1547, found: 301.1551.

4g: White solid; m.p. 142–144 °C; 79% yield (9 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.10 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 1.16 (d, J = 4.0 Hz, 3H), 1.41 (t, J = 6.0 Hz, 1H), 1.58 (s, 3H), 1.65–1.73 (m, 1H), 1.82 (s, 1H), 3.40 (dd, J = 12 Hz, 4.0 Hz, 1H), 3.83 (t, J = 12.0 Hz, 1H), 3.97 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 6.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.7, 14.8, 18.7, 23.1, 36.9, 39.2, 48.9, 69.4, 117.4, 126.5, 127.6, 129.5, 141.9, 168.1. HRMS

(ESI-TOF) calcd for $C_{16}H_{19}N_2O_2^+$([M + H]$^+$): 271.1441, found: 271.1447.

4h: White solid; m.p. 157–159 °C; 80% yield (12 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.89–0.94 (m, 1H), 1.01–1.06 (m, 1H), 1.21–1.25 (m, 1H), 1.26–1.34 (m, 1H), 1.44 (s, 3H), 1.60 (s, 1H), 3.10 (t, J = 4.0 Hz, 1H), 3.79 (t, J = 4.0 Hz, 1H), 3.82 (s, 3H), 4.20 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 7.24–7.29 (m, 3H), 7.40 (t, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.5, 12.6, 25.5, 30.2, 48.4, 49.3, 52.6, 69.6, 126.6, 127.1, 129.3, 143.0, 170.8, 172.9. HRMS (ESI-TOF) calcd for $C_{16}H_{20}NO_4^+$([M + H]$^+$): 290.1387, found: 290.1391.

General procedure for the synthesis of 5-aza-spiro[2.5]octan-7-en-4-ones 5 (5a as an example)

To a solution of 1-acetyl-1-carbamoyl cyclopropane **1a** (203 mg, 1.0 mmol) and acrylonitrile **2b** (0.1 mL, 1.5 mmol) in EtOH (5 mL) at 60 °C was added $(CH_3)_3COK$ (168 mg, 1.5 mmol) in one portion. The reaction mixture was stirred for 8 h. After **1a** was consumed as indicated by TLC, the resulting mixture was poured into a saturated NaCl solution (30 mL) under stirring. Then the mixture was extracted with chloroform (3 × 10 mL) and dried over Na_2SO_4. Finally, the crude product was purified by flash chromatography (silica gel, petroleum ether–acetone 5 : 1) to give **5a** in 96% yield.

5a: White solid; m.p. 113–115 °C; 96% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.31 (q, J = 4.0 Hz, 2H), 1.77 (q, J = 4.0 Hz, 2H), 1.89 (t, J = 4.0 Hz, 3H), 4.47 (d, J = 4.0 Hz, 2H), 7.24 (t, J = 8.0 Hz, 2H), 7.31 (d, J = 4.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 17.2, 17.3, 27.2, 50.7, 101.4, 116.2, 126.1, 127.6, 129.5, 141.5, 152.7, 167.8. HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O^+$([M + H]$^+$): 239.1179, found: 239.1176.

5b: White solid; m.p. 117–120 °C; 94% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.30 (q, J = 4.0 Hz, 2H), 1.75 (q, J = 4.0 Hz, 2H), 1.87 (d, J = 4.0 Hz, 3H), 2.35 (s, 3H), 4.45 (d, J = 4.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 17.2, 21.1, 27.1, 50.8, 101.4, 116.2, 125.8, 130.0, 137.4, 138.9, 152.7, 167.8. HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O^+$([M + H]$^+$): 253.1335, found:253.1338.

5c: White solid; m.p. 102–105 °C; 98% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.30 (q, J = 4.0 Hz, 2H), 1.75 (q, J = 4.0 Hz, 2H), 1.87 (t, J = 4.0 Hz, 3H), 3.81 (s, 3H), 4.43 (s, 2H), 6.92 (q, J = 4.0 Hz, 2H), 7.16 (q, J = 4.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ:17.2, 27.1, 51.1, 55.5, 101.4, 114.7, 116.2, 127.3, 134.3, 152.7, 158.7, 167.9. HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O_2^+$([M + H]$^+$): 269.1285, found: 269.1279.

5d: White solid; m.p. 124–126 °C; 93% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.30 (q, J = 4.0 Hz, 2H), 1.76 (m, 2H), 1.89 (s, 3H), 2.19 (s, 3H), 4.24 (dd, J = 16.0, 4.0 Hz, 1H), 4.44 (dd, J = 16.0 Hz, 4.0 Hz, 1H), 7.12–7.15 (m, 1H), 7.24–7.28 (m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 16.9, 17.0, 17.2, 17.3, 26.8, 50.6, 101.3, 116.2, 126.9, 127.5, 128.4, 131.3, 135.4, 140.1, 152.8, 167.1. HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O^+$([M + H]$^+$): 253.1335, found: 253.1337.

5e: White solid; m.p. 121–123 °C; 89% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.28 (d, J = 4.0 Hz, 2H), 1.75 (q, J = 4.0 Hz, 2H), 1.88(s, 3H), 2.14 (s, 3H), 2.32 (s, 3H), 4.23 (dd, J = 16 Hz, 4.0 Hz, 1H), 4.41 (dd, J = 16.0 Hz, 4.0 Hz, 1H), 7.00–7.08 (m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 16.8, 16.9, 17.1, 17.2, 21.0, 26.8, 50.7, 101.3, 116.2, 126.6, 128.1, 132.0, 134.9, 137.5, 138.3, 152.8, 167.1. HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O^+$([M + H]$^+$): 267.1492, found: 267.1489.

5f: White solid; m.p. 145–147 °C; 87% yield (7.5 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.32 (m, 2H), 1.77 (m, 2H), 1.90 (t, J = 4.0 Hz, 3H), 4.30 (q, J = 16.0 Hz, 1H), 4.46 (q, J = 16.0 Hz, 1H), 7.27–7.35 (m, 3H), 7.48–7.51 (m, 1H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 16.8, 17.2, 17.4, 26.8, 50.0, 101.2, 116.1, 128.3, 129.4, 129.7, 130.6, 132.4, 138.6, 152.6, 167.6. HRMS (ESI-TOF) calcd for $C_{15}H_{14}ClN_2O^+$([M + H]$^+$): 273.0789, found: 273.0800.

5g: White solid; m.p. 154–156 °C; 95% yield (8 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.05 (d, J = 4.0 Hz, 2H), 1.76 (d, J = 4.0 Hz, 2H), 4.64 (s, 2H), 7.19 (d, J = 4.0 Hz, 2H), 7.34 (t, J = 6.0 Hz, 3H), 7.46 (t, J = 8.0 Hz, 5H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 17.4, 27.1, 51.2, 103.7, 115.7, 126.1, 127.6, 128.2, 128.8, 129.3, 129.5, 134.0, 141.5, 156.9, 168.0. HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_2O^+$([M + H]$^+$): 301.1335, found: 301.1340.

5h: White solid; m.p. 85–87 °C; 93% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.24 (q, J = 4.0 Hz, 2H), 1.75 (q, J = 4.0 Hz, 2H), 1.80 (s,3H), 4.01 (d, J = 4.0 Hz, 2H), 4.63 (s, 2H), 7.25–7.27 (m, 2H), 7.30–7.37(m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 16.9, 17.0, 26.5, 47.2, 50.3, 100.9, 116.3, 127.9, 128.3, 128.8, 135.8, 152.3, 167.6. HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O^+$([M + H]$^+$): 253.1335, found: 253.1341.

5i: White solid; m.p. 188–190 °C; 88% yield (10 h); ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.42 (s, 3H), 1.92 (q, J = 4.0 Hz, 1H), 2.50 (q, J = 4.0 Hz, 1H), 3.11 (t, J = 8.0 Hz, 1H), 4.32 (d, J = 16 Hz, 1H), 4.73 (dd, J = 16 Hz, 4.0 Hz, 1H), 7.23–7.36 (m, 8H), 7.44 (t, J = 8.0 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 18.2, 20.5, 35.1, 37.2, 50.0, 104.2, 116.3, 125.4, 127.3, 127.8, 128.9, 129.4, 129.5, 135.3, 141.6, 153.5, 168.3. HRMS (ESI-TOF) calcd for $C_{21}H_{19}N_2O^+$([M + H]$^+$): 315.1492, found: 315.1496.

Conflicts of interest

There are no conflicts to declare.

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