Selective hydrolysis of 1-cyanocyclopropane-1-carboxylates: concise preparation of 1-carbamoylcyclopropane-1-carboxylates

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An efficient and straightforward method has been developed for the preparation of 1-carbamoylcyclopropane-1-carboxylate derivatives *via* selective hydrolysis of 1-cyanocyclopropane-1-carboxylates by using hydroxylamine and sodium acetate system strategy. The structure of 1-carbamoylcyclopropane-1-carboxylate 2a was further confirmed by X-ray single crystal analysis.

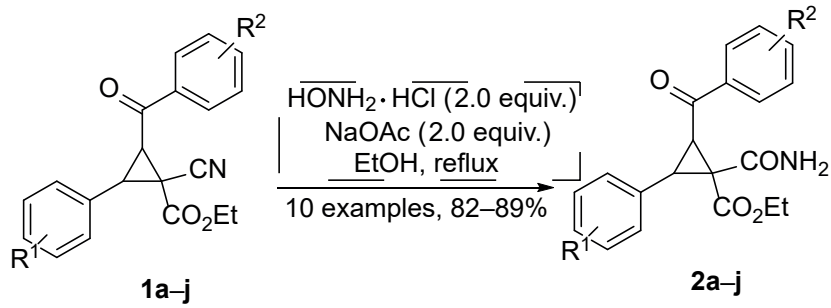
Keywords: cyclopropane, 1-cyanocyclopropane-1-carboxylate, 1-carbamoylcyclopropane-1-carboxylate, selective hydrolysis, neighbouring-group participation

Amides are important building blocks that are widely found in numerous natural products, as well as in a vast array of useful industrially important compounds.[1,2] Additionally, some amide derivatives are also used widely in applications in supramolecular and polymer chemistry.[3–6] Due to the important biological and pharmaceutical activities of these compounds containing amide cores, the construction of the amide bonds has become a topic of great interest among synthetic chemists, and as a consequence, many studies have been directed at increasing synthetic access to this structural subunit. Typical methods for the construction of amide cores deal with the approaches based on both the direct amidation of carboxylic acids[7] and controllable hydrolysis of nitriles. Recently improved protocol involved the condensation between a carboxylic acid and an amine promoted by alkylboronic acids or alkylphosphonic acid anhydride.[8–11] In addition to the conventional dehydrative amide synthesis,[7] there were also methods *via* oxidative amidation reactions employing alcohol or aldehyde precursors.[12] The use of nitrile-based starting materials for direct amidation has attracted significant attention. In a report on the Ritter reaction between alcohols and nitriles at room temperature in a solvent-free or low-solvent environment by using a Brønsted acid catalyst, a wide range of functionalised nitriles as well as secondary and tertiary alcohols were noted.[13] Selective hydrolysis of nitriles for the preparation of amides has also been described. Although this approach is very attractive, due to the use of stronger Brønsted acid catalysts such as trifluoroacetic acid and sulfuric acid[14,15] or alkaline reagents such as aqueous potassium carbonate and hydrogen peroxide,[16] high reaction temperatures are required and the substrate scope is limited in comparison with that of the direct amidation of carboxylic acids with amines.

Cyclopropanes with an amide moiety exhibit potent biological and pharmacological activity. Due to their high π character and intrinsic ring strain, they undergo a variety of ring-opening reactions under acidic and basic conditions.[17–19] It is quite evident that 1-carbamoylcyclopropane-1-carboxylates should not be prepared *via* selective hydrolysis of 1-cyanocyclopropane-1-carboxylates in the presence of conventional acidic and basic conditions. To avoid the ring opening of cyanocyclopropanes, we proposed that a controlled hydrolysis of 1-cyanocyclopropane-1-carboxylates could be carried out *via* neighbouring-group participation. In this communication, we report a novel selective hydrolysis of 1-cyanocyclopropane-1-carboxylates using hydroxylamine and sodium acetate. This protocol provides a simple and direct way to convert a nitrile group to an amide.

Results and discussion

We explored the selective hydrolysis reaction of ethyl 2-(4-bromobenzoyl)-1-cyano-3-(4-chlorobenzoyl) cyclopropane-1-carboxylate (**1a**) by using hydroxylamine and sodium acetate system. Our initial experiments focused on the appropriate amounts of hydroxylamine hydrochloride and sodium acetate. The reaction of **1a** (1.0 equiv.), hydroxylamine hydrochloride (1.0 equiv.) and sodium acetate (1.0 equiv.) was performed in ethanol under ambient conditions, as a result, the product **2a** was not isolated. However, while the resulting mixture was stirred under reflux for 18 h, this reaction afforded product **2a** in 63% yield. The further investigation found that the yield of product **2a** could be substantially increased by employing two equivalents of hydroxylamine hydrochloride and sodium acetate and heating the reaction mixture under refluxing for 18 h. Thus the product **2a** was now isolated in 87% yield. Further increase of the amount of hydroxylamine hydrochloride and sodium acetate had no significant beneficial effect on the hydrolysis reaction. Additionally, we studied the effect of solvent on the reaction. The reaction was carried out with different solvents such as THF, DMF and dioxane only gave the desired product **2a** in low yields, however ethanol gave good yields. Thus, we defined the reaction of the 1-cyanocyclopropanecarboxylate **1a** with hydroxylamine



1a–j **2a–j**

Scheme 1 Selective hydrolysis of 1-cyanocyclopropanecarboxylates.

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Table 1 Substrate scope of 1-cyanocyclopropanecarboxylates[a]

Entry	R^1	R^2	Product	Yield/%[b]
1	*p*-Br	*p*-Cl	**2a**	87
2	*p*-I	*p*-Br	**2b**	84
3	*p*-Cl	H	**2c**	83
4	*p*-Br	H	**2d**	86
5	*p*-COOMe	H	**2e**	85
6	*m*-Me	*p*-Cl	**2f**	89
7	*m*-Br	H	**2g**	88
8	*o*-I	*p*-Cl	**2h**	82
9	*o*-I	H	**2i**	86
10	3,4-OCH_2CH_2O	H	**2j**	87

[a]Reaction conditions: **1a–j** (2 mmol); hydroxylamine hydrochloride (278 mg, 4 mmol); and sodium acetate (328 g, 4 mmol); 95% EtOH (15 mL); reflux; 18 h.
[b]Isolated yields.

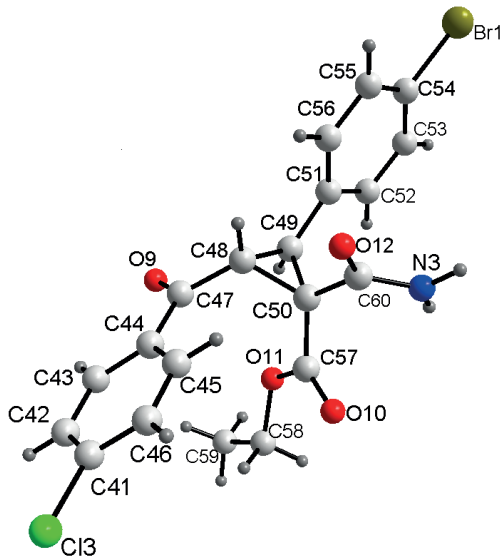


Fig. 1 Molecular structure of 1-carbamoylcyclopropane-1-carboxylate **2a**. Non-hydrogen atoms are shown at the 30% probability level.

hydrochloride (2 equiv.) and sodium acetate (2 equiv.) in ethanol under reflux for 18 h as the standard conditions. We explored the scope of this selective hydrolysis reaction with various 1-cyanocyclopropanecarboxylates (Scheme 1). To our satisfaction, the reaction took place easily to give a good yield and was applicable to a broad range of 1-cyanocyclopropane-1-carboxylates. The results were summarised in Table **1**. Both electron-rich and electron-deficient aromatic groups were similarly viable affording the products in good yields (82–89%). Substrates bearing chloro, bromo, iodo, methyl, and ethoxycarbonyl of the aryl displayed similar reactivity, but substrates bearing iodo at the 2-position of the aryl showed slightly lower activities to furnish the products in good yields.

All 1-carbamoylcyclopropane-1-carboxylates were analysed by their ^{1}H NMR, ^{13}C NMR and HRMS. Characteristic ^{1}H chemical shift of $CONH_2$ at δ *ca* 7.08 ppm (s), and 5.69 ppm (s), unequivocally indicated the exclusive chemical environment of amide protons. Two doublet peaks at δ *ca* 4.26 ppm (s), and 3.70 ppm (s) were assigned to C(2) and C(3) protons of cyclopropane. Unambiguous evidence for the structure and stereochemistry of **2a** was obtained from a single crystal X-ray analysis. ORTEP diagram of **2a** was shown in Fig. 1. The crystallographic data of **2a** are listed in Table 2. Crystallographic data for **2a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with the deposition number CCDC 1402516. The data

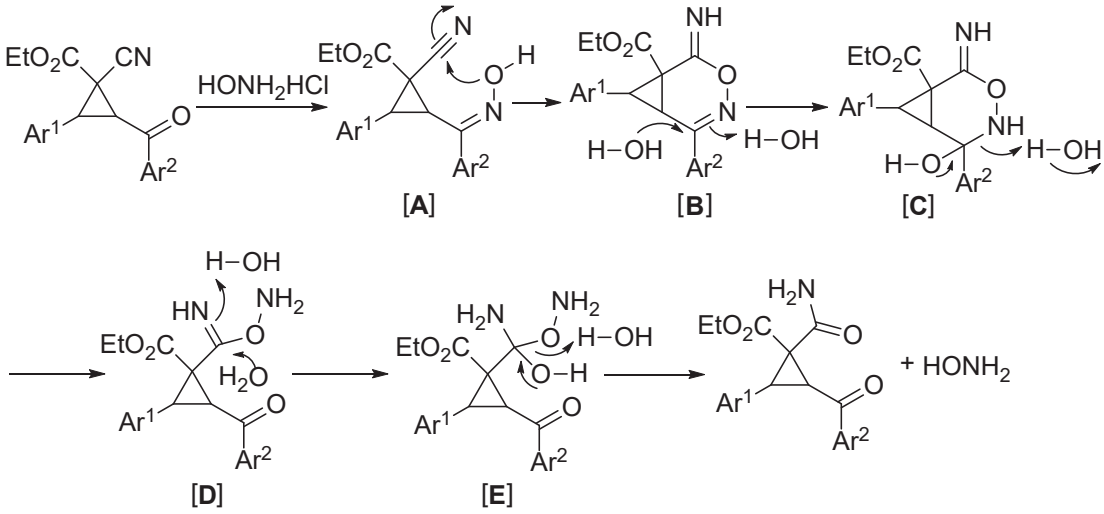
Table 2 Crystallographic data of **2a**

Entry	**2a**
Molecular formula	$C_{20}H_{17}BrClNO_4$
Formula weight	450.70
T/K	296(2)
Wavelength/nm	0.71073
Crystal system	Triclinic
Space group	Pbca
a/Å	17.340(5)
b/Å	24.663(6)
c/Å	9.304(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	3979(2)
Z	8
F(000)	1824
D_{calc}/mg m^{-3}	1.505
Absorption coefficient/mm^{-1}	2.225
θ range/°	2.35–27.71
Limiting indices	–22 < = h < = 22, –32 < = k < = 31, –12 < = l< =11
Reflections collected/unique	54035/4667, [R(int) = 0.0933]
Completeness to theta	99.6%
Data/restraints/parameters	4649/0/245
Refinement method	Full-matrix least-squares on F^2
Final *R* indices[*I*>2σ(*I*)]	R_1 = 0.0687, wR_2 = 0.1717
R indices (all data)	R_1 = 0.1365, wR_2 = 0.2008
Goodness-of-fit on F^2	1.040
Largest diff. peak and hole/(e.Å^{-3})	0.742 and –0.833

can be obtained free of charge from the CCDC *via* http://www.ccdc.cam.ac.uk/.

The mechanism proposed for the reaction is illustrated in Scheme 2. Firstly, in the presence of weak basic sodium acetate, the reaction of 1-cyanocyclopropane-1-carboxylates and hydroxylamine hydrochloride generated a stable intermediate 1-cyano-2-[(hydroxyimino)methyl]cyclopropane-1-carboxylate [**A**]. Then, the intramolecular nucleophilic addition of oxime [**A**] to cyano group formed the bicyclic 2-imino-3-oxa-4-azabicyclo[4.1.0]hept-4-ene-1-carboxylate intermediate [**B**]. Nucleophilic addition of water to the C=N of *O*-imino oxime afforded intermediate 5-hydroxy-2-imino-3-oxa-4-azabicyclo[4.1.0]heptane-1-carboxylate [**C**]. The opening ring of 6-imino-1,2-oxazinan-3-ol skeleton of intermediate [**C**] gave the intermediate 1-[(aminooxy)(imino)methyl]-2-aroyl-3-arylcyclopropane-1-carboxylate [**D**]. Then, the nucleophilic addition of water to the C=N of 1-[(aminooxy)(imino)methyl] cyclopropane-1-carboxylate formed the intermediate 1-amino-1-(aminooxy)-1-cyclopropylmethan-1-ol [**E**] again. Finally, removal of hydroxylamine mediated by sodium acetate produced the 1-carbamoylcyclopropane-1-carboxylates.

In conclusion, we have successfully developed a hydroxylamine-mediated selective hydrolysis of 1-cyanocyclo-propane-1-carboxylates. This reaction involved the sequential the nucleophilic addition reaction of 2-aroyl-3-aryl-1-cyanocyclo-propanecarboxylates with hydroxylamine to give the corresponding oximes, the formation of bicyclic 3-oxa-4-azabicyclo[4.1.0]heptanes *via* the intramolecular nucleophilic addition, ring opening of heterobicycles and removal of hydroxylamine. With this new and simple method, we can synthesise a series of 1-carbamoylcyclo-propane-1-carboxylates.



Scheme 2 Tentative reaction mechanism.

Experimental

All melting points were determined in a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded in a Nicolet FTIR 5DX spectrometer. The ^{1}H NMR (400 or 600 MHz) and ^{13}C NMR (100 or 150 MHz) spectra were recorded in a Bruker AV-400 or 600 spectrometer with TMS as internal reference in $CDCl_3$ or DMSO-d_6 solutions. The *J* values are given in hertz. High-resolution ESI mass spectra were obtained on a UHR-TOF maXis (ESI) mass spectrometer. X-ray crystallographic analysis was performed with a Smart Apex-II diffractometer. Flash chromatography was performed on silica gel (230–400 mesh) eluting with ethyl acetate–hexanes mixture. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

Synthesis of substituted 1-cyanopropane-1-carboxylates **1a**–**j**

The starting materials, 2-aroyl-3-aryl-1-cyanocyclopropane-1-carboxylates, were prepared *via* a modified method from the corresponding 1-(2-oxo-2-arylethyl)pyridin-1-ium salt and 2-cyano-3-arylacrylates in good yields under mild conditions according to the reported procedure.[20]

The synthesis of pyridinium salt was carried out by mixing substituted 2-bromo-1-phenylethan-1-one (2.2 mmol) and pyridine (10 mL) at about 100 °C under conventional heating for 0.5 h. The resulting precipitate was collected with filtration. The residue of the filtrate was washed by dichloromethane (10 mL) and then dried over air.

The substituted ethyl 2-cyano-3-phenylacrylate was obtained by the piperidine (2.0 mmol) promoted condensation of aromatic aldehydes (2.0 mmol) and ethyl cyanoacetate (2.0 mmol) in ethanol (10 mL) stirred at 0 °C for about 10 min. The resulting precipitate was collected with filtration. The residue of the filtrate was washed by water (10 mL) and then dried over air.

A mixture of pyridinium salt and substituted ethyl 2-cyano-3-phenylacrylate and triethylamine (0.2 g) in *N,N*-dimethylformamide (15 mL) was stirred at room temperature for 12 h, the reaction was completed by TLC analysis. The reaction mixture was extracted with ethyl acetate (3 × 10 mL) and dried using sodium sulfate anhydrous and then evaporated. The residue was recrystallised from ethanol to yield substituted 1-cyanocyclopropane-1-carboxylates **1a**–**j** in 58–72%.

Synthesis of substituted 1-carbamoylcyclopropane-1-carboxylates **2a**–**j**

The mixture of appropriate substituted 1-cyanopropane-1-carboxylates (2.0 mmol), hydroxylamine hydrochloride (278 mg, 4 mmol), and sodium acetate (328 g, 4 mmol) in the solution of 95% EtOH (15 mL) was stirred at room temperature. The resultant mixture was stirred under reflux for 18 h, and the completion of reaction was confirmed by TLC (hexanes/EtOAc, 2/1). Subsequently, the mixture was poured directly into ice-water (20 mL), and the crude product was obtained by filtering and then recrystallised from ethyl acetate and petroleum ether to the purified products **2a**–**f** in yields of 83–89%; afterwards the mixture was poured directly into ice-water (20 mL), the residue was extracted with dichloromethane (10 mL × 2). The organic phase was washed with water (10 mL) and brine (15 mL), and dried over anhydrate sodium sulfate. After removal of dichloromethane, the crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/3) and recrystallisation to give the desirable products **2g**–**j** of 82–88% in yields.

Ethyl 2-(4-bromophenyl)-1-carbamoyl-3-(4-chlorobenzoyl)cyclopropane-1-carboxylate (**2a**)

White solid, 87%; m.p. 247.8–248.2 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3447, 3315, 3185, 2984, 1722, 1670, 1599, 1488, 1442, 1399, 1281, 1216, 1133, 1092, 1010, 825, 778; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.07 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.28 (s, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 3.93–3.82 (m, 2H), 3.50 (d, *J* = 8.0 Hz, 1H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 197.2, 171.7, 169.8, 143.9, 140.0, 138.9, 136.1, 136.0, 135.4, 134.1, 125.8, 66.3, 51.8, 40.5, 38.3, 18.7; HRMS (ESI) for $C_{20}H_{17}BrClNNaO_4$ $[M + Na]^+$ calcd 471.9927; found: 471.9920.

Ethyl 2-(4-bromobenzoyl)-1-carbamoyl-3-(4-iodophenyl)cyclopropane-1-carboxylate (**2b**)

White solid, 84%; m.p. 244.3–244.7 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3474, 3326, 3178, 2989, 1724, 1673, 1584, 1481, 1391, 1273, 1115, 1005, 894, 820, 771; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.00 (s, 2H), 7.80 (s, 2H), 7.67 (s, 2H), 7.56 (s, 1H), 7.26 (s, 1H), 7.16 (s, 2H), 4.13 (s, 1H), 3.92-3.88 (m, 2H), 3.51 (s, 1H), 0.86 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm): 192.3, 166.5, 164.5, 136.8, 135.1, 134.0, 131.8, 131.0, 130.3, 127.9, 93.4, 61.1, 46.6, 35.2, 33.3, 13.5; HRMS (ESI) for $C_{20}H_{17}BrINNaO_4$ $[M + Na]^+$ calcd 563.9283; found: 563.9283.

Ethyl 2-benzoyl-1-carbamoyl-3-(4-chlorophenyl)cyclopropane-1-carboxylate (**2c**)

White solid, 83%; m.p. 210.1–211.0 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3441, 3302, 3187, 2981, 1722, 1670, 1603, 1494, 1448, 1404, 1280, 1135, 1091, 1056, 1013, 830, 749, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 7.6 Hz and 7.2 Hz, 1H), 7.47 (dd, *J* = 7.6 Hz and 7.2 Hz, 2H), 7.26–7.20 (m, 4H), 7.08 (s, 1H), 5.69 (s, 1H), 4.26 (d, *J* = 8.4 Hz, 1H), 4.02–3.93 (m, 2H), 3.70 (d, *J* = 8.4 Hz, 1H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.2, 168.7, 165.0, 136.4, 133.7, 131.8, 130.1, 128.8, 128.5, 62.3,

44.7, 36.7, 35.6, 13.3; HRMS (ESI) for $C_{20}H_{18}ClNNaO_4$ $[M + Na]^+$ calcd 394.0822; found: 394.0825.

Ethyl 2-benzoyl-3-(4-bromophenyl)-1-carbamoylcyclopropane-1-carboxylate (**2d**)

White solid, 86%; m.p. 217.3–217.9 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3438, 3327, 3186, 3048, 3004, 1718, 1669, 1589, 1427, 1377, 1263, 1221, 1136, 1016, 897, 825, 749; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (d, *J* = 8.4 Hz, 2H), 7.53 (dd, *J* = 7.6 Hz and 7.2 Hz, 1H), 7.42 (dd, *J* = 6.8 Hz and 6.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.99 (s, 1H), 5.45 (s, 1H), 4.21 (d, *J* = 8.0 Hz, 1H), 3.96–3.90 (m, 2H), 3.63 (d, *J* = 8.4 Hz, 1H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.1, 168.7, 164.9, 136.5, 133.6, 132.4, 131.4, 130.4, 128.8, 128.4, 121.9, 62.3, 44.8, 36.8, 35.6, 13.3; HRMS (ESI) for $C_{20}H_{18}BrNNaO_4$ $[M + Na]^+$ calcd 438.0317; found: 438.0314.

Methyl 4-(3-benzoyl-2-carbamoyl-2-(ethoxycarbonyl)cyclopropyl) benzoate (**2e**)

White solid, 85%; m.p. 158.4–159.1 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3440, 3314, 3187, 2989, 1722, 1674, 1607, 1441, 1279, 1184, 1112, 1017, 852, 766, 696; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.53 (dd, *J* = 7.8 Hz and 7.2 Hz, 1H), 7.42 (dd, *J* = 7.8 Hz and 7.2 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.95 (s, 1H), 5.54 (s, 1H), 4.26 (d, *J* = 7.8 Hz, 1H), 3.99–3.89 (m, 2H), 3.82 (s, 3H), 3.72 (d, *J* = 8.4 Hz, 1H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 192.6, 168.1, 166.2, 164.4, 138.2, 136.0, 133.2, 129.1, 128.3, 128.0, 61.9, 51.6, 44.5, 36.5, 35.2, 12.8; HRMS (ESI) for $C_{22}H_{21}NNaO_6$ $[M + Na]^+$ calcd 418.1267; found: 418.1266.

Ethyl 1-carbamoyl-2-(4-chlorobenzoyl)-3-(m-tolyl)cyclopropane-1-carboxylate (**2f**)

White solid, 89%; m.p. 171.7–172.5 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3449, 3342, 3287, 3059, 3017, 1719, 1676, 1592, 1441, 1403, 1285, 1214, 1133, 1018, 889, 826, 756; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.00 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.13 (dd, J = 7.8 Hz and 7.8 Hz, 1H), 7.02 (dd, J = 7.2 Hz and 7.2 Hz, 3H), 6.84 (s, 1H), 5.39 (s, 1H), 4.16 (d, J = 8.4 Hz, 1H), 4.00–3.91 (m, 2H), 3.64 (d, J = 8.4 Hz, 1H), 2.26 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.5, 168.6, 165.0, 140.1, 138.9, 136.2, 134.6, 130.0, 129.8, 129.7, 129.2, 127.9, 102.3, 62.2, 43.7, 37.3, 13.6; HRMS (ESI) for $C_{21}H_{20}ClNNaO_4$ $[M + Na]^+$ calcd 408.0979; found: 408.0980.

Ethyl 2-benzoyl-3-(3-bromophenyl)-1-carbamoylcyclopropane-1-carboxylate (**2g**)

White solid, 88%; m.p. 181.8–182.4 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3435, 3310, 3187, 3013, 1716, 1670, 1601, 1447, 1405, 1287, 1216, 1136, 1057, 1010, 852, 774, 690; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J* = 7.2 Hz, 2H), 7.58 (dd, *J* = 7.6 Hz and 7.2 Hz, 1H), 7.47 (dd, *J* = 7.6 Hz and 7.2 Hz, 2H), 7.45 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H), 7.02 (s, 1H), 5.70 (s, 1H), 4.25 (d, *J* = 8.4 Hz, 1H), 4.06–3.93 (m, 2H), 3.70 (d, *J* = 8.4 Hz, 1H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.1, 168.5, 164.9, 136.5, 135.7, 133.6, 131.9, 130.9, 129.7, 128.8, 128.5, 127.3, 122.2, 62.3, 44.8, 36.5, 33.5, 13.3; HRMS (ESI) for $C_{20}H_{18}BrNNaO_4$ $[M + Na]^+$ calcd 438.0317; found: 438.0315.

Ethyl 1-carbamoyl-2-(4-chlorobenzoyl)-3-(2-iodophenyl)cyclopropane-1-carboxylate (**2h**)

White solid, 82%; m.p. 191.5–191.9 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3431, 3328, 3189, 3059, 3001, 1714, 1666, 1596, 1431, 1397, 1283, 1216, 1135, 1013, 896, 824, 746; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 7.6 Hz and 7.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 7.6 Hz and 7.2 Hz, 1H), 5.74 (s, 1H), 4.32 (d, *J* = 8.8 Hz, 1H), 4.08–3.90 (m, 2H), 3.75 (d, *J* = 8.8 Hz, 1H), 0.99 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.5, 168.6, 165.0, 140.1, 138.9, 136.2, 134.6, 130.0, 129.8, 129.7, 129.2, 127.9, 102.3, 62.2, 43.7, 37.3, 13.6; HRMS (ESI) for $C_{20}H_{17}ClINNaO_4$ $[M + Na]^+$ calcd 519.9788; found: 519.9783.

Ethyl 2-benzoyl-1-carbamoyl-3-(2-iodophenyl)cyclopropane-1-carboxylate (**2i**)

White solid, 86%; m.p. 188.5–189.6 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3442, 3331, 3184, 3044, 3015, 1722, 1674, 1582, 1429, 1375, 1263, 1222 1133 1012, 898, 825, 746; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 7.8 Hz and 7.2 Hz, 2H), 7.41 (dd, *J* = 7.8 Hz and 7.2 Hz, 2H), 7.24 (dd, *J* = 7.8 Hz and 7.2 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.93 (dd, *J* = 7.2 Hz and 7.2 Hz, 1H), 5.61 (s, 1H), 4.31 (d, *J* = 9.0 Hz, 1H), 4.01–3.95 (m, 1H), 3.90–3.85 (m, 1H), 3.72 (d, *J* = 9.0 Hz, 1H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 191.6, 167.9, 164.2, 137.9, 135.5, 135.2, 132.6, 129.1, 128.6, 127.8, 127.4, 126.9, 101.3, 61.1, 42.8, 42.3, 36.6, 12.5; HRMS (ESI) for $C_{20}H_{18}INNaO_4$ $[M + Na]^+$ calcd 486.0178; found: 486.0183.

Ethyl 2-benzoyl-1-carbamoyl-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)cyclopro pane-1-carboxylate (**2j**)

White solid, 87%; m.p. 176.1–176.8 °C (EA/PE); IR (KBr, cm^{-1}): ν = 3442, 3335, 3217, 3043, 2989, 1730, 1672, 1599, 1428, 1389, 1284, 1215, 1132, 1012, 895, 821, 749; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 7.8 Hz, 2H), 7.51 (dd, *J* = 7.8 Hz and 7.2 Hz, 1H), 7.41 (dd, *J* = 7.8 Hz and 7.2 Hz, 2H), 6.92 (s, 1H), 6.74 (s, 1H), 6.70 (s, 2H), 5.56 (s, 1H), 4.15 (s, 5H), 3.96–3.89 (m, 2H), 3.58 (d, *J* = 8.4 Hz, 1H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 192.6, 167.8, 164.3, 142.2, 135.6, 132.5, 127.7, 127.5, 125.4, 120.7, 116.6, 116.1, 63.3, 63.2, 61.1, 44.1, 36.1, 34.7, 12.4; HRMS (ESI) for $C_{22}H_{21}NNaO_6$ $[M + Na]^+$ calcd 418.1267; found: 418.1265.

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