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A Passerini/Michael pathway towards butyrolactones

Shuanglong Jia,^[a] Laurent El Kaïm^{*[a]}

Dedication ((optional))

Abstract: The Passerini adducts of aromatic aldehydes may act as nucleophiles in Michael additions with acrylonitrile. The reaction proceeds together with hydrolysis of the ester. The resulting γ -hydroxynitrile may be cyclized under acidic conditions to afford a three-steps synthesis of γ -butyrolactones from isocyanides.

Introduction

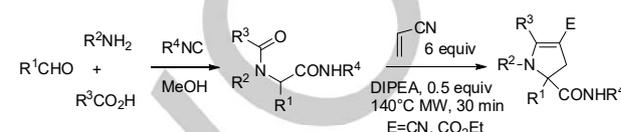
Isocyanide based multicomponent reactions (IMCRs) are now well established as efficient tools for the preparation of libraries of heterocycles.^[1] These syntheses are usually performed via two-step procedures using first an Ugi reaction as the IMCR affording the highest diversity and functional tolerance. The heterocyclic core is then obtained in a second cyclization step involving additional functionalities proper selected in the starting materials. We recently started a program to evaluate the potential of intermolecular reactions of Ugi adducts as a way to expand the diversity and scope of heterocycles accessible by these two-step procedures. In this direction, the peptidyl position of Ugi adducts was selected due to the ability to tune its acidity by proper selection of the aldehyde partner together with the challenge of performing intermolecular reactions at a relative hindered position.^[2] Among the various solutions explored, we discovered while attempting to performed Michael additions with Ugi adducts as nucleophiles a [3+2] type cycloaddition of the latter with acrylonitrile leading to pyrrole derivatives (Scheme 1).^{[2]h)} Gratified by this coupling but still failing to observe any Michael addition with Ugi adducts, we decided to explore the behavior of Passerini adducts in similar reactions.^[3] We now wish to report a successful Passerini/Michael addition tandem with acrylonitrile and its application to new γ -butyrolactone preparation.

Results and Discussion

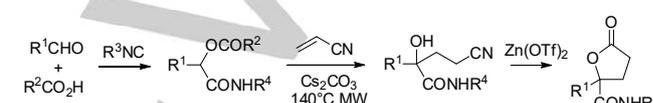
Our work as well as reports by others on cyclizations involving the peptidyl position of Ugi adducts showed the importance of selecting aromatic aldehydes for successful selective deprotonation/alkylation strategies.^[2] Thus, Passerini adduct **1a** was prepared in quantitative yield letting stoichiometric amount of *p*-chlorobenzaldehyde, cyclohexylisocyanide and acetic acid to react for two days under solvent free conditions.^[4] At the

onset of the study, acrylonitrile was chosen as Michael acceptor due to its higher efficiency as electrophile in our previous study on Ugi adducts.^{[2]h)}

Pyrrole synthesis while attempting Micheal additions on Ugi adducts:

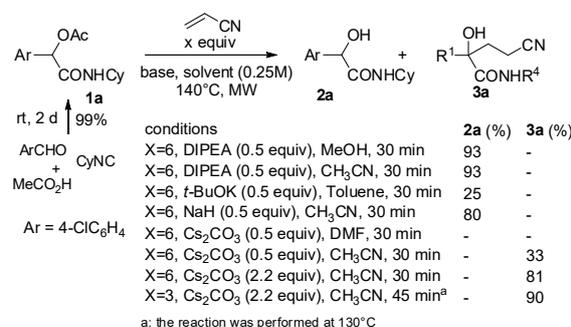


This work: γ -butyrolactones through Passerini/Michael tandem



Scheme 1. Addition of acrylonitrile on Ugi and Passerini adducts

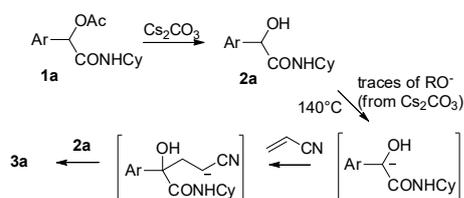
When **1a** was reacted under standard Michael addition reaction (various amount of DBU, acetonitrile or THF at rt or reflux conditions) we could not observe any reaction apart from partial hydrolysis of the acetate. Microwave conditions were then selected. When **1a** was heated in methanol at 140°C in the presence of diisopropylamine (0.5 equiv) and large excess of acrylonitrile (6 equiv), nearly quantitative yield of alcohol **2a** was obtained after 30 min heating (Scheme 2). Replacing methanol by acetonitrile didn't change a behavior consistent with the relatively sensitive ester moieties of Passerini adducts as already observed in our recent conversion of Passerini adducts of cinnamaldehyde into α -ketoamides.^[5] The nature of the base and solvent were then varied working at the same temperature until we gratifyingly observed a modest 33% isolated yield of expected **3a** when cesium carbonate was selected as base in acetonitrile. Raising the amount of base to two equivalents led us to a nice 81% isolated yield whereas lowering the temperature to 130°C and the excess of acrylonitrile gave us the best yield after 45 min of reaction (Scheme 2). These conditions were selected for the rest of the study.



Scheme 2. Optimized conditions for the formation of Michael adduct **3a**.

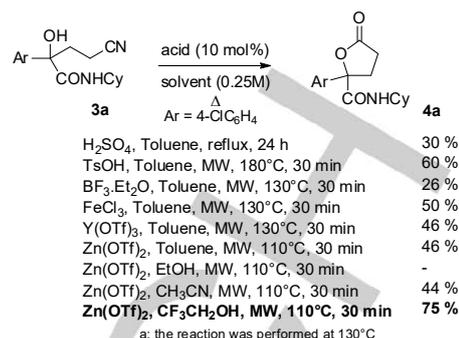
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The formation of **3a** most probably involves an initial saponification followed by a Michael addition of the resulting hydroxy derivative **2a**. The presence of the aryl group in the hydroxyl **2a** allows a selective CH deprotonation induced by Cs₂CO₃ (probably triggered by trace of water) followed by Michael addition (Scheme 3). The closest Michael additions reported in the literature involve the base triggered addition of acrylates or acrylonitrile to benzoin derivatives.^[6] Easy enolate formation of the latter allows these Michael additions to proceed under mere treatment with DBU at room temperature. Such precedents, easy formation of **2a** when **1a** was treated at lower temperature and ability to convert isolated **2a** into **3a** in 89% isolated yield under our optimized conditions bring further elements in support for the proposed timing of the process.



Scheme 3. Probable mechanism for conversion of **1a** into **3a**.

Even though the formation of alcohol **3a** with loss of the acetate moiety was not a good point in terms of diversity, it offers an interesting opportunity for the preparation of butyrolactones through cyclization of the alcohol onto the nitrile group. Butyrolactones and their unsaturated butenolides analogues are important scaffolds^[7] appearing in many natural products and associated with important biological activities such as anticancer,^[8] antibiotic^[9] or anti-inflammatory activities.^[10] Butyrolactone synthesis from 4-hydroxynitriles is well documented,^[11] occurring under both acidic and basic conditions. In most cases the imidate intermediate is not observed leading directly to the butyrolactone. Considering the literature on those cyclizations together with the rather harsh basic conditions selected for our Michael addition, the lack of cyclised products was rather a surprise in our case. Thus, the ability of **3a** to cyclize was directly tested under acidic conditions. The few trials performed confirmed the relative stability of **3a**, nevertheless we could observe the expected butyrolactone **4a** in a good 75% isolated yield heating the alcohol under microwave conditions in trifluoroethanol as solvent and in the presence of a catalytic amount of zinc triflate (Scheme 4).



Scheme 4. Cyclization of **3a** to butyrolactone **4a**.

The scope of this two-step butyrolactone synthesis was then evaluated on a set of different Passerini adducts prepared from acetic acid under solvent less conditions. The results are displayed in Table 1.

Table 1. scope of γ -butyrolactone synthesis

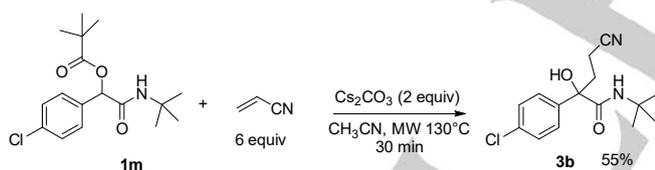
Entry	R ¹	R ²	1 (yield) ^[a]	3 (yield) ^[a]	4 (yield) ^[a]
1	4-ClC ₆ H ₄	<i>t</i> -Bu	1b (98%)	3b (90%)	4b (62%)
2	4-ClC ₆ H ₄		1c (80%)	3c (95%)	4c (92%)
3	4-ClC ₆ H ₄		1d (84%)	3d (79%)	4d (86%)
4	4-FC ₆ H ₄	Cy	1e (90%)	3e (95%) ^[b]	4e (87%)
5	4-NO ₂ C ₆ H ₄	Cy	1f (99%)	3f (39%)	4f (83%)
6	Ph	Cy	1g (82%)	3g (73%)	4g (72%)
7	2-pyridyl	Cy	1h (82%)	3h (66%)	4h (50%)
8	2-furyl	Cy	1i (78%)	3i (99%)	4i (20%)
9	Stryryl	Cy	1j (77%)	3j (61%)	4j (0%)
10	4-MeOC ₆ H ₄	Cy	1k (72%)	3k (0%)	
11	isobutyl	Cy	1l (88%)	3l (0%)	

[a] Isolated yields after column chromatography on silica gel. [b] 110°C was used....

On the three steps of the overall procedure, the first Passerini step has the wider scope and gives high yields for most aldehydes and isocyanides tested. The synthetic sequence is limited to aromatic aldehydes in agreement with the need of a relatively acidic position for the Michael step to proceed. Indeed, when Passerini adduct **1l** (Table 1, entry 11) obtained in 88% isolated yield from isovaleraldehyde was treated with acrylonitrile under our optimized conditions for the Michael addition step, we could not isolate any addition product and

only observed a saponification of the ester giving the corresponding hydroxyamide in 96% isolated yield. This further supports our mechanistic proposition of scheme 3 as for the latter the OH group is now probably deprotonated faster preventing the required carbanion formation for Michael addition. The Passerini adduct of 4-methoxybenzaldehyde behaves similarly probably due to more difficult deprotonation at the α -position. In the opposite direction, the use of 4-nitrobenzaldehyde lead to quantitative formation of Passerini adduct **1f** (Table 1, entry 5) but the resulting anion is probably too stabilized to give an efficient coupling with acrylonitrile affording **3f** only in a moderate 39% isolated yield. The furyl derivative **1i** gave us our best yield in the Michael addition step (Table 1, entry 8), which was a bit surprising in light of the electronrich nature of the ring and the failure of the 4-methoxyaryl group to participate in the sequence. Finally, in the case of cinnamaldehyde derived Passerini adduct **1j**, we were delighted to observe the formation of Michael addition product **3j** in moderate yield (Table 1, entry 9) as such conditions were close to the one we proposed for the conversion of the same Passerini adducts into α -ketoamides. Nevertheless, the resulting nitrile **3j** failed to cyclise in trifluoroethanol with $\text{Zn}(\text{OTf})_2$ as catalyst.

To progress further on the mechanism of the reaction and determine whether the Michael addition step could be observed before the saponification of the ester, we prepared a Passerini analogue of **1b** using pivalic instead of acetic acid. When the pivalate **1m** was treated under microwave conditions with 6 equiv of acrylonitrile in acetonitrile, we couldn't indeed isolate any Michael adduct without loss of the pivalate moiety and **3b** was again obtained in a low 55% yield (Scheme 5). Lowering the amount of base to 1 equiv afforded **3b** in lower yields supporting further the mechanistic propositions of scheme 3.



Scheme 5. Michael addition of pivalate ester **1m**.

The Passerini/Michael/Cyclization sequence was next attempted using different Michael acceptors. Starting from Passerini adduct **1a**, we could not form any addition product using methyl acrylate as Michael acceptor. DMF or acetonitrile as solvent and raising the temperature up to 140°C led either to decomposition or sole isolation of alcohol **2a**. The same results were observed with methyl vinyl ketone.

Conclusions

We have settled a two-step sequence for the preparation of γ -butyrolactones from Passerini adducts of aromatic and

heteroaromatic aldehydes. This strategy significantly expands the scope of the butyrolactones syntheses from benzoin derivatives with microwave conditions allowing to counterbalance the poorer electron-withdrawing group effect of the amide moiety. Further work is under progress to raise the diversity of the synthesis by performing the reaction on a larger array of Michael acceptors.

Experimental Section

General Considerations

NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. ^1H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference (CDCl_3 δ 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or overlap of nonequivalent resonances), coupling constants, integration. ^{13}C NMR spectra were recorded at 100 MHz and residual solvent peaks were used as an internal reference (CHCl_3 δ 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH_3 , CH_2 , CH , Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence (λ_{max} = 254 nm or 360 nm) and by staining with *p*-anisaldehyde, potassium permanganate or vanillin TLC stain solutions, followed by heating. Flash chromatography employed VWR (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen or argon in oven-dried or flame dried glassware, and at ambient room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried with a MBRAUN Solvent Purification System SPS-800. Petroleum ether refers to the 40–60 °C boiling fraction. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR Spectrometer. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra were recorded on an Agilent 1100 series LC-MS (with a 6310 ion trap) under electrospray ionization (ESI). For compounds containing bromine, the mass of 79Br was used. Monowave 300 produced by Anton Paar was used for the microwave conditions.

Synthesis of **1a** to **1l**

General procedure A:

In a round bottom flask under Argon was added the aldehyde (10 mmol, 1 equiv), glacial acetic acid (0.60 g, 0.57 ml, 10 mmol) and the isocyanide (10 mmol, 1 equiv). The mixture was stirred at room temperature for two days during which times it slowly solidifies. The pure Passerini adducts **1a–1l** were then obtained by column chromatography on silica gel when the crude were not pure enough.

1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl acetate (**1a**): Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol) gave **1a** in quantitative yield (3.07 g, 9.9 mmol, 99%). Aspect: white solid, m.p. 160.1–161.2 °C (after washing with an $\text{Et}_2\text{O}/\text{PE}$ = 5/5 mixture). Rf: 0.44 (EA:PE = 3:7). ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.31 (m, 4H), 6.04–5.99 (m, 2H), 3.77 (tdt, J = 12.2, 8.1, 3.9 Hz, 1H), 2.18 (s, 6H), 1.91–1.88 (m, 2H), 1.71–1.59 (m, 3H), 1.40–1.30 (m, 2H), 1.21–1.09 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.1, 166.9, 135.0, 134.5, 129.0, 128.9, 74.9, 48.4, 33.1, 33.0, 25.5, 24.9, 21.2. HRMS: calculated for $\text{C}_{16}\text{H}_{20}\text{ClNO}_3$:

309.1132, found: 309.1133. IR (thin film): 3689, 3432, 2937, 2858, 1747, 1681, 1598, 1520, 1492, 1452, 1373, 1222, 1094, 1045, 1016 cm^{-1} .

2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl acetate (**1b**): Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and *t*-butyl isocyanide (0.83 g, 1.13 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et₂O = 50:50) to afford **1b** (2.78 g, 9.8 mmol, 98%). Aspect: white solid, m.p. 127.1-127.9 °C. Rf: 0.35 (Et₂O:PE = 5:5). ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.31 (m, 4H), 5.95 (s, 1H), 5.90 (s, 1H), 2.17 (s, 3H), 1.35 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 169.1, 167.0, 134.9, 134.6, 129.0, 128.9, 75.0, 51.8, 28.8, 21.2. HRMS: calculated for C₁₄H₁₈ClNO₃: 283.0975, found: 283.0987. IR (thin film): 3433, 2971, 1748, 1685, 1521, 1492, 1456, 1369, 1218, 1093, 1037, 1016 cm^{-1} .

1-(4-chlorophenyl)-2-((4-methoxybenzyl)amino)-2-oxoethyl acetate (**1c**): Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and 1-(isocyanomethyl)-4-methoxybenzene (1.47 g, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **1c** (2.78 g, 8.0 mmol, 80%). Aspect: white solid, m.p. 97.1-98.2 °C. Rf: 0.32 (EA:PE=3:7). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.28 (m, 4H), 7.11-7.08 (m, 2H), 6.87-6.79 (m, 3H), 6.00 (s, 1H), 4.31 (qd, *J* = 14.7, 5.8 Hz, 2H), 3.76 (s, 3H), 2.11 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.3, 168.0, 159.1, 134.9, 134.2, 129.7, 129.0, 128.9, 128.8, 114.1, 74.8, 55.2, 42.8, 20.9. HRMS: calculated for C₁₈H₁₈ClNO₄: 347.0924, not found, fragment: 287.0708(-HOAc). IR (thin film): 3295, 3072, 2935, 2836, 1742, 1657, 1612, 1512, 1490, 1463, 1438, 1369, 1300, 1222, 1175, 1090, 1033, 1015 cm^{-1} .

1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethylacetate (**1d**): Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and 4-(2-isocianoethyl)-1,2-dimethoxybenzene (1.91 g, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 80:20) to afford **1d** (3.29 g, 8.4 mmol, 84%). Aspect: white solid, m.p. 104.8-105.7 °C Rf: 0.43 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 4H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.67-6.63 (m, 2H), 6.17 (s, 1H), 5.98 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.55-3.49 (m, 2H), 2.80-2.71 (m, 2H), 2.10 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.1, 167.9, 149.2, 147.9, 135.0, 134.1, 130.9, 129.0, 128.8, 120.8, 112.0, 111.3, 74.8, 56.0, 56.0, 40.6, 35.1, 21.0. HRMS: calculated for C₂₀H₂₂ClNO₅: 391.1187, found: 391.1187. IR (thin film): 3319, 2936, 2835, 1743, 1661, 1592, 1514, 1491, 1464, 1418, 1370, 1261, 1228, 1156, 1141, 1090, 1027, 1016 cm^{-1} .

2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl acetate (**1e**): Following general procedure A with *para*-fluorobenzaldehyde (1.24 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et₂O = 50:50) to afford **1e** (2.64 g, 9.0 mmol, 90%). Aspect: white solid, m.p. 170.8-171.9 °C. Rf: 0.22 (Et₂O:PE = 5:5). ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.38 (m, 2H), 7.06-7.02 (m, 2H), 6.01 (s, 2H), 3.83-3.75 (m, 1H), 2.17 (s, 3H), 1.91 (bs, 2H), 1.72-1.60 (m, 3H), 1.44-1.28 (m, 2H), 1.25-1.07 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.2, 167.2, 163.1 (*J* = 246 Hz), 131.9, 129.5, 115.9, 115.7, 74.9, 48.4, 33.1, 25.5, 24.9, 21.2. HRMS: calculated for C₁₆H₂₀FNO₃: 293.1427, found: 293.1420. IR (thin film): 3296, 2932, 2855, 1747, 1657, 1538, 1510, 1371, 1223, 1159, 1045 cm^{-1} .

2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate (**1f**): Following general procedure A with *para*-nitrobenzaldehyde (1.51 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), gave **1f** in quantitative yield (3.17 g, 99%). Aspect: white solid, m.p. 144.8-145.3 °C (after washing the solid with an Et₂O:PE = 5/5 mixture). Rf: 0.31 (EA:PE = 3:7). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 6.14-6.10 (m, 2H), 3.81-3.72 (m, 1H), 2.23 (s, 3H), 1.93-1.87 (m,

2H), 1.73-1.61 (m, 3H), 1.42-1.29 (m, 2H), 1.22-1.12 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.8, 166.1, 148.2, 142.9, 128.2, 124.0, 74.5, 48.6, 33.1, 33.0, 25.5, 24.9, 21.1. HRMS: calculated for C₁₆H₂₀N₂O₅: 320.1372, not found, fragment: 195.0534. IR (thin film): 3692, 3433, 2938, 2858, 1751, 1682, 1608, 1524, 1452, 1373, 1350, 1217, 1049 cm^{-1} .

2-(cyclohexylamino)-2-oxo-1-phenylethyl acetate (**1g**): Following general procedure A with benzaldehyde (1.06 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 70:30) to afford **1g** (1.65 g, 8.2 mmol, 82%). Aspect: white solid m.p. 133.9-140.5 °C. Rf: 0.46 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.40 (m, 2H), 7.38-7.33 (m, 3H), 6.03-6.01 (m, 2H), 3.83-3.73 (m, 1H), 2.17 (s, 3H), 1.91-1.87 (m, 2H), 1.71-1.58 (m, 3H), 1.40-1.29 (m, 2H), 1.21-1.08 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.3, 167.3, 135.9, 129.0, 128.8, 127.5, 75.6, 48.3, 33.0, 25.5, 24.8, 21.2. HRMS: calculated for C₁₆H₂₁NO₃: 275.1521, found: 275.1530. IR (thin film): 3294, 3066, 2930, 2854, 1739, 1650, 1536, 1495, 1451, 1370, 1223, 1189, 1096, 1042, 1030 cm^{-1} .

2-(cyclohexylamino)-2-oxo-1-(pyridin-2-yl)ethyl acetate (**1h**): Following general procedure A with picolinaldehyde (1.07 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 60:40) to afford **1h** (2.27 g, 8.2 mmol, 82%). Aspect: white solid, m.p. 95.2-96.3 °C. Rf: 0.38 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 8.52-8.51 (m, 1H), 7.70-7.66 (m, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.23-7.20 (m, 1H), 6.72 (d, *J* = 6.4 Hz, 1H), 6.05 (s, 1H), 3.74-3.66 (m, 1H), 2.20 (s, 3H), 1.87-1.52 (m, 5H), 1.32-1.04 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 169.4, 166.0, 155.1, 149.1, 137.2, 123.5, 122.2, 75.7, 48.4, 32.7, 25.5, 24.7, 21.0. HRMS: calculated for C₁₅H₂₀N₂O₃: 276.1474, found: 276.1471. IR (thin film): 3690, 3429, 3062, 3019, 2937, 2858, 1746, 1681, 1594, 1575, 1525, 1473, 1452, 1438, 1373, 1256, 1228, 1152, 1112, 1047 cm^{-1} .

2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl acetate (**1i**): Following general procedure A with furan-2-carbaldehyde (0.96 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **1i** (2.07 g, 7.8 mmol, 78%). Aspect: white solid, m.p. 131.8-132.6 °C. Rf: 0.44 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.14-6.11 (m, 2H), 3.84-3.75 (m, 1H), 2.13 (s, 3H), 1.94-1.86 (m, 2H), 1.71-1.56 (m, 3H), 1.39-1.28 (m, 2H), 1.23-1.09 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.1, 165.0, 148.3, 143.5, 111.2, 110.7, 68.8, 48.4, 32.9, 32.8, 25.5, 24.8, 20.9. HRMS: calculated for C₁₄H₁₉NO₄: 265.1314, found: 265.1312. IR (thin film): 3296, 2932, 2855, 1749, 1659, 1536, 1451, 1370, 1222, 1151, 1097, 1032, 1014 cm^{-1} .

(E)-1-(cyclohexylamino)-1-oxo-4-phenylbut-3-en-2-yl acetate (**1j**): Following general procedure A with cinnamaldehyde (1.32 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA=70:30) to afford **1j** (2.71 g, 9.0 mmol, 90%). Aspect: white solid m.p. 141.8-142.6 °C. Rf: 0.49 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.35-7.27 (m, 3H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 16.0, 6.9 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.72 (d, *J* = 6.9 Hz, 1H), 3.86-3.77 (m, 1H), 2.22 (s, 3H), 1.96-1.93 (m, 2H), 1.74-1.62 (m, 3H), 1.43-1.33 (m, 2H), 1.23-1.16 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.4, 167.2, 135.8, 134.9, 128.8, 128.5, 127.0, 122.8, 74.6, 48.4, 33.1, 25.6, 24.9, 21.3. HRMS: calculated for C₁₈H₂₃NO₃: 301.1678, found: 301.1678. IR (thin film): 3288, 2931, 2854, 1743, 1659, 1546, 1449, 1371, 1230, 1031 cm^{-1} .

2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl acetate (**1k**): Following general procedure A with *para*-methoxybenzaldehyde (1.36 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the

mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **1k** (2.20 g, 7.2 mmol, 72%). Aspect: white solid, m.p. 162.5–163.4 °C. Rf: 0.33 (EA:PE=4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.32 (m, 2H), 6.88–6.86 (m, 2H), 6.03–5.98 (m, 2H), 3.85–3.78 (m, 4H), 2.14 (s, 3H), 1.89–1.86 (m, 2H), 1.70–1.59 (m, 3H), 1.38–1.29 (m, 2H), 1.19–1.11 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.4, 167.6, 160.1, 129.1, 128.0, 114.2, 75.2, 55.4, 48.3, 33.0, 33.0, 25.5, 24.8, 21.2. HRMS: calculated for C₁₇H₂₃NO₄: 305.1627, found: 305.1623. IR (thin film): 3299, 2931, 2854, 1742, 1650, 1611, 1535, 1512, 1450, 1370, 1227, 1176, 1031 cm⁻¹

1-(cyclohexylamino)-4-methyl-1-oxopentan-2-yl acetate (**1l**): Following general procedure A with isovaleraldehyde (0.86 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et₂O = 50:50) to afford **1l** (2.25 g, 8.8 mmol, 88%). Aspect: white solid, m.p. 87.2–88.6 °C. Rf: 0.32 (Et₂O:PE = 5:5). ¹H NMR (400 MHz, CDCl₃) δ 5.86 (s, 1H), 5.12–5.09 (m, 1H), 3.77–3.69 (m, 1H), 2.11 (s, 3H), 1.92–1.86 (m, 2H), 1.71–1.56 (m, 6H), 1.37–1.28 (m, 2H), 1.15–1.11 (m, 3H), 0.98–0.88 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 169.3, 73.0, 47.9, 40.8, 33.0, 25.5, 24.8, 24.6, 23.2, 21.9, 21.1. HRMS: calculated for C₁₄H₂₅NO₃: 255.1834, found: 255.1837. IR (thin film): 3288, 2930, 2855, 1744, 1648, 1536, 1450, 1370, 1224, 1063, 1028 cm⁻¹

Synthesis of 3a to 3j

General procedure B:

To a dried microwave tube was added Passerini adduct **1** (0.375 mmol, 1 equiv), acetonitrile (1.5 ml) followed by acrylonitrile (60 mg, 1.125 mmol, 3 equiv), and Cs₂CO₃ (269 mg, 0.825 mmol, 2.2 equiv). The tube was filled with Ar before heating under microwave condition to 130 °C for 45 min. After completion, the solvent was removed under reduced pressure and the crude mixture purified by column chromatography on silica gel to afford the desired **3a–3j**.

2-(4-chlorophenyl)-4-cyano-N-cyclohexyl-2-hydroxybutanamide (**3a**): Following general procedure B with 1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl acetate **1a** (116 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **3a** (108 mg, 0.338 mmol, 90%). Aspect: colorless oil. Rf: 0.31 (EA:PE = 3:7). ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.43 (m, 2H), 7.35–7.32 (m, 2H), 6.51 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 1H), 3.68–3.59 (m, 1H), 2.66–2.59 (m, 1H), 2.45–2.27 (m, 3H), 1.85–1.58 (m, 5H), 1.37–1.25 (m, 2H), 1.18–1.02 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 139.7, 134.5, 129.0, 126.7, 119.8, 77.5, 48.8, 35.1, 33.0, 32.8, 25.5, 24.8, 24.8, 12.3. HRMS: calculated for C₁₇H₂₁ClN₂O₂: 320.1292, found: 320.1284. IR (thin film): 3591, 3417, 2937, 2858, 1671, 1598, 1519, 1491, 1452, 1401, 1350, 1253, 1206, 1096, 1014 cm⁻¹.

N-(tert-butyl)-2-(4-chlorophenyl)-4-cyano-2-hydroxybutanamide (**3b**): Following general procedure B with 2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl acetate **1b** (111 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et₂O = 50:50) to afford **3b** (99 mg, 0.338 mmol, 90%). Aspect: colorless oil. Rf: 0.44 (Et₂O:PE=6:4). ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.41 (m, 2H), 7.37–7.33 (m, 2H), 6.34 (s, 1H), 3.56 (s, 1H), 2.67–2.53 (m, 1H), 2.49–2.23 (m, 3H), 1.29 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 139.8, 134.6, 129.1, 126.7, 119.8, 77.6, 51.8, 35.1, 28.6, 12.3. HRMS: calculated for C₁₅H₁₉ClN₂O₂: 294.1135, found: 294.1139. IR (thin film): 3691, 3590, 2971, 2935, 2260, 1678, 1598, 1519, 1491, 1457, 1394, 1368, 1268, 1223, 1096, 1014 cm⁻¹.

2-(4-chlorophenyl)-4-cyano-2-hydroxy-N-(4-methoxybenzyl)butanamide (**3c**): Following general procedure B with 1-(4-chlorophenyl)-2-((4-methoxybenzyl)amino)-2-oxoethyl acetate **1c** (130 mg, 0.375 mmol) the

mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **3c** (128 mg, 0.356 mmol, 95%). Aspect: yellow oil. Rf: 0.49 (EA:PE = 5:5). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.07–7.02 (m, 3H), 6.81–6.79 (m, 2H), 4.24 (qd, *J* = 14.6, 5.8 Hz, 2H), 4.16 (s, 1H), 3.77 (s, 3H), 2.64–2.54 (m, 1H), 2.35–2.23 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.5, 159.1, 139.6, 134.3, 129.4, 128.8, 128.7, 126.7, 119.7, 114.2, 77.5, 55.3, 43.0, 34.7, 12.0. HRMS: calculated for C₁₉H₁₉ClN₂O₃: 358.1084, found: 358.1093. IR (thin film): 3690, 3590, 3426, 3007, 2937, 2839, 1676, 1613, 1514, 1491, 1465, 1303, 1251, 1176, 1096, 1035, 1014 cm⁻¹.

2-(4-chlorophenyl)-4-cyano-N-(3,4-dimethoxyphenethyl)-2-hydroxybutanamide (**3d**): Following general procedure B with 1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl acetate **1d** (147 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 80:20) to afford **3d** (119 mg, 0.296 mmol, 79%). Aspect: colourless oil. Rf: 0.48 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.35 (m, 2H), 7.33–7.29 (m, 2H), 6.73–6.70 (m, 1H), 6.61 (d, *J* = 1.9 Hz, 1H), 6.58–6.48 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.75 (s, 1H), 3.51–3.41 (m, 2H), 2.70–2.64 (m, 2H), 2.59–2.47 (m, 1H), 2.32–2.22 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.1, 149.1, 147.9, 139.4, 134.5, 130.7, 129.0, 126.7, 120.8, 119.7, 111.8, 111.4, 77.6, 56.0, 56.0, 40.8, 35.1, 35.0, 12.1. HRMS: calculated for C₂₁H₂₃ClN₂O₄: 402.1346, found: 402.1348. IR (thin film): 3691, 3593, 3427, 2938, 1676, 1594, 1516, 1491, 1262, 1238, 1158, 1142, 1028, 1014 cm⁻¹.

4-cyano-N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxybutanamide (**3e**): Following general procedure B with 2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl acetate **1e** (110 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et₂O = 30:70) to afford **3e** (108 mg, 0.356 mmol, 95%). Aspect: yellow oil. Rf: 44 (Et₂O:PE = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.47 (m, 2H), 7.06–7.02 (m, 2H), 6.57 (d, *J* = 7.5 Hz, 1H), 3.89 (s, 1H), 3.64 (bs, 1H), 2.63–2.60 (m, 1H), 2.43–2.30 (m, 3H), 1.85–1.66 (m, 5H), 1.334–1.06 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 171.4, 162.7 (*J* = 246 Hz), 137.0, 127.1, 119.9, 115.8, 77.48, 48.7, 35.1, 33.0, 32.8, 25.5, 24.8, 12.3. HRMS: calculated for C₁₇H₂₁FN₂O₂: 304.1587, found: 304.1583. IR (thin film): 3345, 2932, 2855, 1646, 1602, 1525, 1506, 1451, 1225, 1161, 1092 cm⁻¹.

4-cyano-N-cyclohexyl-2-hydroxy-2-(4-nitrophenyl)butanamide (**3f**): Following general procedure B with 2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate **1f** (120 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **3f** (48 mg, 0.146 mmol, 39%). Aspect: yellow oil. Rf: 0.53 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 4.38 (s, 1H), 3.67–3.58 (m, 1H), 2.77–2.68 (m, 1H), 2.42–2.31 (m, 3H), 1.87–1.82 (m, 2H), 1.73–1.57 (m, 3H), 1.37–1.01 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 170.4, 148.4, 147.8, 126.4, 123.8, 119.6, 77.9, 48.9, 35.2, 33.0, 32.7, 25.4, 24.8, 24.7, 12.3. HRMS: calculated for C₁₇H₂₁N₃O₄: 331.1532, not found, fragment: 248.0671. IR (thin film): 3691, 3589, 3417, 2937, 2858, 1674, 1606, 1524, 1452, 1350 cm⁻¹.

4-cyano-N-cyclohexyl-2-hydroxy-2-phenylbutanamide (**3g**): Following general procedure B with 2-(cyclohexylamino)-2-oxo-1-phenylethyl acetate **1g** (103 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **3g** (78 mg, 0.274 mmol, 73%). Aspect: white solid, m.p. 107.3–108.6 °C. Rf: 0.50 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.46 (m, 2H), 7.39–7.32 (m, 3H), 6.48 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 1H), 3.68–3.61 (m, 1H), 2.64–2.59 (m, 1H), 2.44–2.28 (m, 3H), 1.84–1.75 (m, 2H), 1.67–1.56 (m, 3H), 1.35–1.25 (m, 2H), 1.18–1.06 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 141.1, 129.0, 128.5, 125.2, 119.9, 77.8, 48.7, 35.1, 33.0, 32.8, 25.5, 24.8, 12.3. HRMS: calculated for C₁₇H₂₂N₂O₂: 286.1681, found:

286.1681. IR (thin film): 3349, 2932, 2855, 1646, 1524, 1448, 1350, 1316, 1253, 1207, 1152, 1076 cm⁻¹.

4-cyano-N-cyclohexyl-2-hydroxy-2-(pyridin-2-yl)butanamide (**3h**):

Following general procedure B with 2-(cyclohexylamino)-2-oxo-1-(pyridin-2-yl)ethyl acetate **1h** (104 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 70:30) to afford **3h** (71 mg, 0.248 mmol, 66%). Aspect: light brown coloured oil. Rf: 0.51 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 8.50-8.48 (m, 1H), 7.91-7.88 (m, 1H), 7.79-7.75 (m, 1H), 7.32-7.29 (m, 2H), 6.33 (s, 1H), 3.71-3.61 (m, 1H), 2.58-2.51 (m, 1H), 2.38-2.23 (m, 3H), 1.88-1.85 (m, 1H), 1.76-1.55 (m, 5H), 1.40-1.25 (m, 2H), 1.22-1.06 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 157.4, 147.2, 138.0, 123.7, 121.4, 119.5, 76.6, 48.6, 36.7, 33.0, 32.8, 25.5, 24.8, 12.2. HRMS: calculated for C₁₆H₂₁N₃O₂: 287.1634, not found, fragment: 161.0707. IR (thin film): 3405, 3287, 2937, 2858, 1670, 1593, 1573, 1517, 1468, 1452, 1437, 1395, 1350, 1253, 1214, 1154, 1137, 1094, 1052 cm⁻¹.

4-cyano-N-cyclohexyl-2-(furan-2-yl)-2-hydroxybutanamide (**3i**): Following general procedure B with 2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl acetate **1i** (99 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 70:30) to afford **3i** (102 mg, 0.371 mmol, 99%). Aspect: white solid, m.p. 104.8-105.8 °C. Rf: 0.38 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.41-6.32 (m, 3H), 4.16 (s, 1H), 3.77-3.69 (m, 1H), 2.39-2.37 (m, 4H), 1.92-1.81 (m, 2H), 1.72-1.59 (m, 3H), 1.38-1.30 (m, 2H), 1.24-1.08 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.8, 152.8, 142.9, 119.4, 111.2, 108.1, 74.0, 49.2, 34.7, 32.9, 32.8, 25.5, 24.7, 24.7, 12.0. HRMS: calculated for C₁₅H₂₀N₂O₃: 276.1474, found: 276.1473. IR (thin film): 3691, 3594, 3418, 2937, 2858, 1675, 1602, 1525, 1452, 1375, 1350, 1317, 1253, 1221, 1150, 1128, 1066, 1006 cm⁻¹.

(E)-2-(2-cyanoethyl)-N-cyclohexyl-2-hydroxy-4-phenylbut-3-enamide (**3j**): Following general procedure B with (E)-1-(cyclohexylamino)-1-oxo-4-phenylbut-3-en-2-yl acetate **1j** (113 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA=70:30) to afford **3j** (78 mg, 0.251 mmol, 67%). Aspect: yellow oil. Rf: 0.33 (EA:PE = 3:7). ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.31 (m, 5H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 3.82-3.75 (m, 1H), 3.27 (s, 1H), 2.57-2.38 (m, 3H), 2.22-2.14 (m, 1H), 1.97-1.87 (m, 2H), 1.81-1.65 (m, 3H), 1.45-1.36 (m, 2H), 1.28-1.16 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 135.7, 130.8, 129.7, 128.9, 128.5, 126.9, 119.9, 48.8, 35.2, 33.2, 33.0, 25.5, 24.9, 12.1. HRMS: calculated for C₁₉H₂₄N₂O₂: 312.1838, not found, fragment (-C₆H₁₁CONH): 186.0914. IR (thin film): 3387, 2932, 2855, 1642, 1525, 1449 cm⁻¹.

Synthesis of 4a to 4i

General procedure C:

To a dried microwave tube was added **3** (0.375 mmol, 1 equiv), Zn(OTf)₂ (14 mg, 10 mol%) and 2,2,2-trifluoroethanol (1.5 ml). The tube was filled with Ar before heating under microwave condition to 110 °C for 30 min. After completion, the solvent was removed under reduced pressure and crude mixture purified by column chromatography to afford **4a-4i**.

2-(4-chlorophenyl)-N-cyclohexyl-5-oxotetrahydrofuran-2-carboxamide (**4a**): Following general procedure C with 2-(4-chlorophenyl)-4-cyano-N-cyclohexyl-2-hydroxybutanamide **3a** (120 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 90:10) to afford **4a** (90 mg, 0.281 mmol, 75%). Aspect: white solid, m.p. 113.2-113.7 °C. Rf: 0.47 (EA:PE = 3:7). ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.29 (d, *J* = 7.4 Hz, 1H), 3.70-3.63 (m, 1H), 3.11-3.04 (m, 1H), 2.65-2.43 (m, 3H), 1.90-1.88 (m, 1H), 1.71-1.57 (m, 4H), 1.37-1.00 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 169.1, 137.5, 134.8, 128.9, 126.2, 87.5, 48.9, 33.6, 33.0, 32.7,

28.3, 25.4, 24.9, 24.8. HRMS: calculated for C₁₇H₂₀ClNO₃: 321.1132, not found, fragment: 295.0970. IR (thin film): 3422, 2937, 2858, 1788, 1677, 1598, 1521, 1490, 1452, 1403, 1351, 1286, 1255, 1222, 1186, 1173, 1156, 1095, 1061, 1015 cm⁻¹.

N-(tert-butyl)-2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-carboxamide (**4b**): Following general procedure C with N-(tert-butyl)-2-(4-chlorophenyl)-4-cyano-2-hydroxybutanamide **3b** (111 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:Et₂O = 80:20) to afford **4b** (69 mg, 0.233 mmol, 62%). Aspect: white solid, m.p. 94.2-95.7 °C. Rf: 0.48 (Et₂O:PE=5:5). ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.46 (m, 2H), 7.35-7.33 (m, 2H), 6.19 (s, 1H), 3.09-3.02 (m, 1H), 2.65-2.39 (m, 3H), 1.29 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 169.1, 137.6, 134.7, 128.9, 126.1, 87.7, 51.9, 33.6, 28.6, 28.3. HRMS: calculated for C₁₅H₁₈ClNO₃: 295.0975, found: 295.0980. IR (thin film): 3691, 3423, 2972, 2260, 1787, 1683, 1599, 1520, 1491, 1458, 1395, 1368, 1279, 1219, 1187, 1173, 1095, 1065, 1040 cm⁻¹.

2-(4-chlorophenyl)-N-(4-methoxybenzyl)-5-oxotetrahydrofuran-2-carboxamide (**4c**): Following general procedure C with 2-(4-chlorophenyl)-4-cyano-2-hydroxy-N-(4-methoxybenzyl)butanamide **3c** (135 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 80:20) to afford **4c** (124 mg, 0.345 mmol, 92%). Aspect: white solid, m.p. 162.5-163.1 °C. Rf: 0.42 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.48 (m, 2H), 7.37-7.33 (m, 2H), 7.08-7.05 (m, 2H), 6.83-6.79 (m, 2H), 6.74 (s, 1H), 4.37-4.27 (m, 2H), 3.77 (s, 3H), 3.15-3.08 (m, 1H), 2.65-2.45 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.8, 169.9, 159.3, 137.3, 134.9, 129.2, 129.1, 129.0, 126.2, 114.3, 87.5, 55.4, 43.3, 33.7, 28.2. HRMS: calculated for C₁₉H₁₈ClNO₄: 359.0924, found: 359.0913. IR (thin film): 3691, 3431, 2958, 2937, 2839, 1789, 1682, 1613, 1514, 1491, 1442, 1303, 1250, 1224, 1176, 1113, 1094, 1065, 1036 cm⁻¹.

2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-5-oxotetrahydrofuran-2-carboxamide (**4d**): Following general procedure C with 2-(4-chlorophenyl)-4-cyano-N-(3,4-dimethoxyphenethyl)-2-hydroxybutanamide **3d** (151 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 70:30) to afford **4d** (130 mg, 0.323 mmol, 86%). Aspect: white solid, m.p. 101.1-102.4 °C. Rf: 0.50 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.54 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.44 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.52-3.42 (m, 2H), 3.09-3.02 (m, 1H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.49 (t, *J* = 7.9 Hz, 2H), 2.43-2.36 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 174.8, 167.0, 149.1, 147.8, 137.4, 134.8, 130.6, 128.9, 126.1, 120.8, 111.8, 111.3, 87.6, 56.0, 55.9, 40.8, 35.1, 33.5, 28.1. HRMS: calculated for C₂₁H₂₂ClNO₅: 403.1187, found: 403.1190. IR (thin film): 3691, 3606, 3432, 3009, 2938, 2839, 1788, 1683, 1599, 1516, 1491, 1466, 1263, 1237, 1158, 1142, 1095, 1028 cm⁻¹.

N-cyclohexyl-2-(4-fluorophenyl)-5-oxotetrahydrofuran-2-carboxamide (**4e**): Following general procedure C with 4-cyano-N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxybutanamide **3e** (114 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:Et₂O = 50:50) to afford **4e** (99 mg, 0.326 mmol, 87%). Aspect: colourless oil. Rf: 0.58 (Et₂O:PE = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.51 (m, 2H), 7.08-7.03 (m, 2H), 6.29 (d, *J* = 7.8 Hz, 1H), 3.67 (tdt, *J* = 12.1, 8.1, 3.9 Hz, 1H), 3.10-3.03 (m, 1H), 2.65-2.45 (m, 3H), 1.91-1.88 (m, 1H), 1.74-1.56 (m, 4H), 1.38-0.99 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 175.1, 169.3, 162.9(d, *J* = 246 Hz), 134.8, 134.8, 126.7, 126.7, 115.8, 115.6, 87.6, 48.8, 33.7, 33.1, 32.7, 28.3, 25.4, 24.9, 24.8. HRMS: calculated for C₁₇H₂₀FNO₃: 305.1427, found: 305.1426. IR (thin film): 3348, 2931, 2855, 1784, 1666, 1603, 1506, 1451, 1225, 1182, 1152, 1106, 1060 cm⁻¹.

N-cyclohexyl-2-(4-nitrophenyl)-5-oxotetrahydrofuran-2-carboxamide (**4f**): Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-(4-nitrophenyl)butanamide **3f** (124 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 90:10) to afford **4f** (103 mg, 0.311 mmol, 83%). Aspect: white solid, m.p. 151.2–152.1 °C. Rf: 0.56 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 8.24–8.21 (m, 2H), 7.79–7.75 (m, 2H), 6.36 (d, *J* = 8.1 Hz, 1H), 3.71–3.62 (m, 1H), 3.21–3.14 (m, 1H), 2.69–2.44 (m, 3H), 1.92–1.88 (m, 1H), 1.72–1.56 (m, 4H), 1.35–1.02 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 174.4, 168.3, 148.1, 145.8, 125.9, 123.9, 87.2, 49.1, 33.8, 33.0, 32.6, 28.1, 25.4, 24.9, 24.8. HRMS: calculated for C₁₇H₂₀N₂O₅: 332.1372, not found, fragment: 206.0449. IR (thin film): 3691, 3421, 2938, 2858, 1803, 1680, 1606, 1525, 1494, 1453, 1352, 1184, 1170, 1155, 1062 cm⁻¹.

N-cyclohexyl-5-oxo-2-phenyltetrahydrofuran-2-carboxamide (**4g**): Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-phenylbutanamide **3g** (107 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 80:20) to afford **4g** (78 mg, 0.27 mmol, 72%). Aspect: light brown oil. Rf: 0.46 (EA:PE = 3:7). ¹H NMR (400 MHz, CDCl₃) δ 7.55–7.52 (m, 2H), 7.39–7.33 (m, 3H), 6.28 (d, *J* = 7.8 Hz, 1H), 3.71–3.64 (m, 1H), 3.11–3.06 (m, 1H), 2.63–2.50 (m, 3H), 1.92–1.88 (m, 1H), 1.74–1.56 (m, 4H), 1.35–1.02 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 175.3, 169.4, 139.0, 128.8, 128.7, 124.7, 88.1, 48.8, 33.5, 33.1, 32.7, 28.4, 25.5, 24.9, 24.8. HRMS: calculated for C₁₇H₂₁NO₃: 287.1521, found: 287.1522. IR (thin film): 3349, 2931, 2854, 1783, 1666, 1518, 1449, 1224, 1183, 1153, 1109, 1085, 1054 cm⁻¹.

N-cyclohexyl-5-oxo-2-(pyridin-2-yl)tetrahydrofuran-2-carboxamide (**4h**): Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-(pyridin-2-yl)butanamide **3h** (108 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 50:50) to afford **4h** (54 mg, 0.188 mmol, 50%). Aspect: white solid, m.p. 109.9–110.5 °C. Rf: 0.34 (EA:PE = 5:5). ¹H NMR (400 MHz, CDCl₃) δ 8.62–8.60 (m, 1H), 7.74–7.69 (m, 1H), 7.52–7.50 (m, 1H), 7.29–7.26 (m, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 3.82–3.73 (m, 1H), 3.01–2.94 (m, 1H), 2.85–2.63 (m, 3H), 1.89–1.85 (m, 2H), 1.71–1.57 (m, 3H), 1.39–1.28 (m, 2H), 1.20–1.11 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.9, 168.6, 157.3, 149.5, 137.3, 123.8, 120.6, 88.0, 48.6, 32.9, 31.9, 28.7, 25.5, 24.8. HRMS: calculated for C₁₆H₂₀N₂O₃: 288.1474, found: 288.1476. IR (thin film): 3691, 3606, 3421, 2937, 2858, 1786, 1677, 1589, 1524, 1470, 1452, 1435, 1226, 1181, 1157, 1109, 1066 cm⁻¹.

N-cyclohexyl-2-(furan-2-yl)-5-oxotetrahydrofuran-2-carboxamide (**4i**): Following general procedure C with 4-cyano-N-cyclohexyl-2-(furan-2-yl)-2-hydroxybutanamide **3i** (104 mg, 0.375 mmol), the mixture was purified by column chromatography on silica gel (eluent:PE:Et₂O = 80:20) to afford **4i** (21 mg, 0.075 mmol, 20%). Aspect: yellow oil. Rf: 0.42 (EA:PE = 4:6). ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.39 (m, 1H), 6.47–6.35 (m, 3H), 3.81 (tdd, *J* = 12.1, 8.2, 4.0 Hz, 1H), 2.87–2.74 (m, 3H), 2.68–2.55 (m, 1H), 1.97–1.89 (m, 2H), 1.76–1.61 (m, 3H), 1.42–1.32 (m, 2H), 1.24–1.16 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.2, 167.4, 150.5, 143.8, 110.8, 109.5, 83.7, 48.9, 33.0, 32.9, 30.2, 28.6, 25.5, 24.9, 24.9. HRMS: calculated for C₁₅H₁₉NO₄: 277.1314, found: 277.1310. IR (thin film): 3361, 2931, 2855, 1757, 1710, 1663, 1529, 1451, 1347, 1259, 1185, 1154, 1098, 1067, 1009 cm⁻¹.

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Keywords: Passerini • Michael addition • butyrolactone • multicomponent reaction • acrylonitrile

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Multicomponent reaction*

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