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MICROWAVE PROMOTED DIELS-ALDER REACTION OF 1,2-DIHYDROPYRIDINE

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Abstract – The microwave-assisted Diels-Alder reaction between 1,2-dihydropyridine and activated dienophiles is reported. The conditions facilitate the production of the [2.2.2] scaffold in high yields with simple purification.

INTRODUCTION

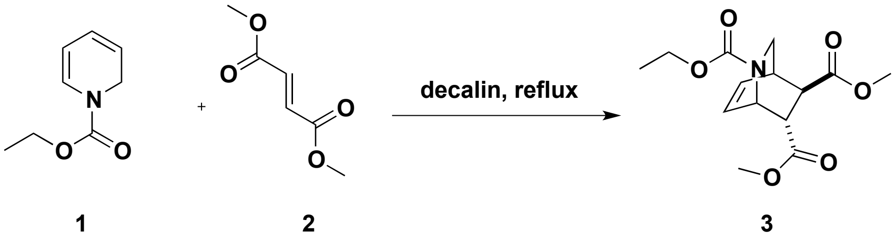
The [2.2.2] scaffold is reflected in biologically relevant natural products (i.e. – ibogaine, catharanthine)[1,2] and natural product mimics such as homoepibatidine.[1] The scaffold itself represents a promising starting point for future therapeutics due to its water solubility, constrained geometry, high percentage of sp^3 hybridized atoms, chiral centers and limited number of rotational bonds.[2-4] In addition, every heteroatom in the core scaffold can be easily substituted through a carefully designed synthetic protocol.[5]

Although Diels-Alder reactions to form the oxabicyclo[2.2.1]heptane and azabicyclo[2.2.1]heptane have been regularly utilized in the literature, examples of the analogous reaction to form the azabicyclo[2.2.2]octanes are relatively minimal. In fact, the first preparation of this scaffold reported through the Diels-Alder reaction was as a method of removing the 1,2-dihydropyridine "contaminant" from the desired 1,4-dihydropyridine.[6] The reaction was further developed by the Krow group through a series of papers over the next three decades detailing the reactivity and *endo*/*exo* selectivity for a number of different dienophiles as well as substituents on the 1,2-dihydropyridine.[1,5,7,8] Several reports have also detailed specialized conditions for the diastereoselective and enantioselective version of this reaction through the utilization of steric or chiral Lewis acid catalysis.[9-11] Asymmetric Diels-Alder reactions with 1,2-dihydropyridine and organocatalysts have recently been disclosed utilizing oxazolidines to synthesize oseltamivir or β-amino alcohols to produce isoquinuclidines.[12,13]

The use of microwave irradiation to accelerate reaction rates in organic synthesis has been applied to numerous reaction types over the past several years.[14] Often, use of microwave conditions can result in shortened reaction times, higher yields, higher purity, and altered product distributions.[14] The design of modern instruments enables quick reaction optimization through the use of sealed reaction vessels and elevated temperatures while protecting the safety of the investigator.[14] The rate differences are a matter of interest and debate, with recently published silicon carbide reactors suggesting that thermal effects are the sole component of the rate acceleration.[15] Recent reviews cover the effect of microwave irradiation on various cycloaddition reactions including the Diels-Alder reaction.[16,17]

RESULTS AND DISCUSSION

Our interest in the Diels-Alder reaction of 1,2-dihydropyridines was to produce multi-gram scale quantities of product for further chemical manipulation towards chemical probes of biological significance. Although a facile method for the production of these scaffolds, the limitations of the published method were quickly realized (Table 1). The use of a high-boiling solvent such as decalin is necessary for reasonable reaction rates, but exacerbates purification. The decalin solvent co-elutes with several of the desired products regardless of the size of column or gradient elution, requiring multiple columns for purification in several of the reactions. Secondly, decalin refluxes at ~185-190 °C with a flash point of 135 °C. Running these large-scale reflux reactions for 12 hours was not considered optimal from a safety standpoint. Thirdly, requiring multi-gram quantities of the products necessitated extremely large reactions due to the low yields. Lastly, the need to purify the 1,2-dihydropyridine under inert gas was timely and cumbersome at scale. Therefore, additional methods were sought.



Scheme 1. Diels-Alder Reaction with Published Conditions

Table 1. Diels-Alder Reaction with Published Conditions

Concentration (M)	Ratio of 1:2	Time (h)	Yield of 3 (%)[b]
1.0	1:1	10	14
1.0	X:1 [a]	10	51
2.0	X:1 [a]	10	46
0.5	X:1 [a]	10	50
1.0	X:1 [a]	7.5	47
1.0	X:1 [a]	5.0	62

10 mmol reaction scale (2), decalin, reflux 185-190 °C, product isomers inseparable

a – 4:1 ratio by mass utilizing unpurified mix containing 1,2- and 1,4-dihydropyridines, *b* – isolated yield

The activated dienophile dimethyl fumarate was utilized for the optimization of reactions due to the *endo*/*exo* products being inseparable, therefore simplifying the analysis (Scheme 1). The 1,2-dihydropyridine (DHP) was utilized due to its relatively easy synthesis combined with the expense of unsubstituted versus substituted pyridines. In addition, literature has indicated that steric influences can be substantial to both the rate as well as the *endo*/*exo* distribution.[5,18] The dimethyl fumarate ($R_f = 0.54$) was distinct on TLC from the DHP ($R_f = 0.70$) and product ($R_f = 0.27$) enabling simple reaction progress monitoring (R_f's determined in 25% EtOAc/Hexane). Despite attempts at reaction optimization (Table 1), sufficient yields at scale could not be achieved. It is not clear if this was a result of dihydropyridine decomposition or purification difficulties.

Table 2. Optimization of Microwave-Assisted Diels-Alder Reaction

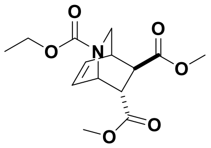
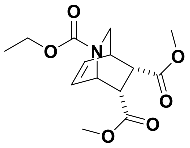
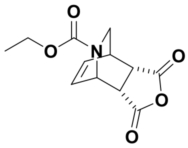
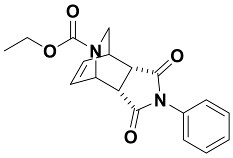
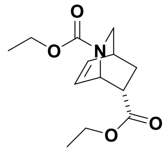
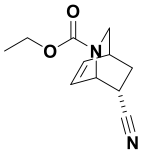
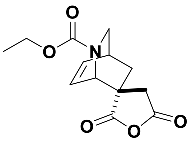
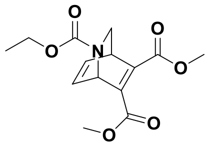
Entry	**Ratio**[a] **1:2**	**Solvent**	**Time (min)**	**Temperature (°C)**	**Yield**[c] **(%)**
1	1:1	MeCN	30	220	19
2	2:1	MeCN	30	220	38
3	3:1	MeCN	30	220	55
4	X:1[a]	MeCN	30	220	78
5	X:1[b]	MeCN	30	220	79
6	X:1[a]	toluene	30	220	75
7	X:1[a]	H_2O	120	200[d]	12
8	X:1[a]	$ClCH_2CH_2Cl$	30	220	33
9	X:1[a]	MeCN	15	220	67
10	X:1[a]	MeCN	20	220	61
11	X:1[a]	MeCN	25	220	67
12	X:1[a]	MeCN	45	220	68
13	X:1[a]	MeCN	60	220	71

2.5 mmol reaction scale (2), 1.0 M concentration, product isomers inseparable

a – 4:1 ratio by mass utilizing unpurified mix containing 1,2- and 1,4-dihydropyridines, *b* – 5:1 ratio by mass utilizing unpurified mix containing 1,2- and 1,4-dihydropyridines, *c* – isolated yield, *d* – excess pressure necessitated lowering of the reaction temperature; time was extended according to the Arrhenius equation.

As seen in Table 2, microwave conditions were discovered that provided increased yields, simple purification, and significantly shorter reaction times. The unpurified DHP mixture was attempted,[19] bypassing the silica gel purification under inert gas, but also complicating reaction monitoring with dienophiles of higher R_f (multiple spots on TLC from the DHP mixture). A balance between yield and conservation of starting material directed the use of a 4:1 ratio of dihydropyridine to dienophile (entries 1-5). Exploration of common solvents utilized in Diels-Alder chemistry revealed toluene and acetonitrile as comparable choices (entries 4, 6-8). The duration of heating found the highest yield at the initial 30 minutes (entries 9-14). Coupling the microwave conditions with utilization of the DHP mix afforded high yields progressing from simple pyridine to Diels-Alder product within a day.

Table 3. Scope of Microwave-Assisted Diels-Alder Reaction

Compound #	Dienophile	Product	Yield[a] (%)	*Endo*/*Exo* Ratio
3a	dimethyl fumarate		99	62:38[b]
3b	dimethyl maleate		81	77:23
3c	maleic anhydride		53	ND
3d	*N*-phenyl- maleimide		88	>95:5[c]
3e	ethyl acrylate		74	66:34
3f	acrylonitrile		70	53:47
3g	itaconic anhydride		NP	ND
3h	dimethyl acetylene- dicarboxylate		NP	ND

10 mmol reaction scale (2); *a* – isolated yield; *b* – ratio determined from ^{1}H NMR, *c* – Only endo product was detected by ^{1}H NMR analysis of crude or purified samples, NP – no product, ND – not determined

Next, the scope of the dienophile was investigated with regards to the electron-withdrawn activation of the dienophile according to normal demand Diels-Alder theory. As shown in Table 3, several dienophiles demonstrated good yields utilizing these conditions with *endo*/*exo* ratios within the expected range compared to previously reported studies.[5,7] The dimethyl fumarate yield increased to 99% upon scale-up, most likely due to limitations of stain sensitivity in the smaller scale reaction. Dimethyl maleate and acrylonitrile were submitted to extended conditions (100 minutes, 220 °C) in an effort to increase yields, yet results remained within experimental error (78% and 68% respectively). The maleic anhydride opened to provide the methanol adduct, significantly hindering elution from silica gel and resulting in a significantly lower yield. This product consisted of two isomers that co-eluted and appear to be the alternate anhydride ring opening products as opposed to the *endo*/*exo* products. The other cyclic dienophile, *N*-phenylmaleimide, provided predominantly *endo* product as expected, with no *exo* product being isolated or seen by ^{1}H NMR. Itaconic anhydride was attempted due to the predicted formation of a spirocyclic anhydride; however, the TLC contained greater than 12 distinct spots and purification efforts revealed no evidence of the desired products. Dimethyl acetylenedicarboxylate is another interesting dienophile that would afford further chemical manipulation of the core [2.2.2] scaffold, but also failed to provide the desired product. Spurred on by literature reports,[20] we attempted this reaction under various conditions (0 °C/4 hours, rt/7 days; 100 °C/10 minutes by microwave; and 220 °C/30 minutes by microwave), yet each reaction resulted in multiple spots on TLC and resultant purification yielding no evidence of product formation.

In conclusion, reported herein are the microwave conditions for a quick, efficient, and high-yielding Diels-Alder reaction between activated dienophiles and 1,2-dihydropyridine. This procedure does not require purified dihydropyridine and also requires considerably less purification efforts for the Diels-Alder product than previously reported conditions.[1,5] As evidenced in Table 3, the conditions are scalable to multi-gram quantities to support synthesis of natural product derivatives containing the azabicyclo[2.2.2]octane scaffold.

EXPERIMENTAL

All commercial reagents were used without further purification. Solvents were distilled before use: Acetonitrile was washed with potassium carbonate and distilled over calcium hydride; Toluene was distilled over sodium/benzophenone; Dichloroethane was distilled over calcium hydride. The 1,2-dihydropyridine was synthesized utilizing the method reported by Fowler.[6] Reactions were heated in a Biotage Initiator+ microwave with fixed hold time on to the temperature stated and for the duration indicated. This instrument utilizes sealed tubes and continually adjusts the wattage to maintain the set temperature. NMR data was acquired on a 300 MHz Bruker Avance and analyzed utilizing MestReNova software.

The *endo*/*exo* isomers were assigned based on the shift and COSY correlation of the bridgehead proton alpha to the bicyclic nitrogen (H_1/H_3). This proton has a characteristic peak near 5 ppm and correlates (^1H-^1H 2D COSY) to the vicinal proton (H_2/H_4) that is geminal to the newly incorporated functional group. The H_1 proton in the *endo* product is further downfield than the H_3 proton of the *exo* product. The COSY correlated H_2 proton (*endo*) demonstrates an upfield shift in the *exo* product (H_4 proton). These observations are consistent with previous reports.[5] Rotational or conformational isomers (rotamers) distinct on the NMR timescale were present in all samples and not resolved by a change in NMR solvent. These isomers result from restricted rotation of the carbamate protecting group and therefore are most distinct for the protons connected to this functional group.

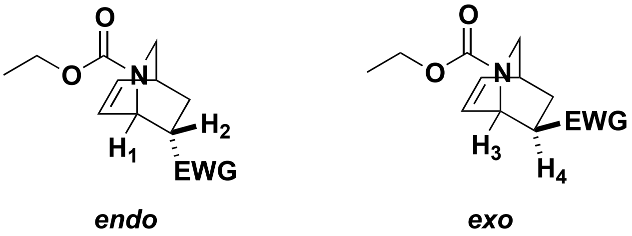


Figure 1. Assignment of *Endo*/*Exo*

General procedure for the preparation of azabicyclo[2.2.2]octenes 3a-3f

The 1,2-dihydropyridine was weighed into a 10-20 mL microwave vial and diluted with 10 mL of MeCN. The dienophile was then weighed and added to the reaction mixture. The vial was capped and heated by microwave to 220 °C for 30 min. After cooling, the reaction was evaporated under reduced pressure, then loaded onto a silica gel column in minimal CH_2Cl_2. Gradient elution with EtOAc/hexanes (Hex) provided the purified products.

2-Ethyl 5,6-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate 3a

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with dimethyl fumarate (1 eq, 10 mmol, 1.44 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 2.94 g of **3a** (99%) after purification on silica gel with a 0-30% EtOAc/Hex gradient. (Note: The assignment of *endo*/*exo* for this product is somewhat ambiguous since the dienophile is trans and symmetrical. Nevertheless, the assignment is consistent with the other products taking into account the orientation of the functional group vicinal to the H_1/H_3 proton as noted above.

***Endo* Product:** 1.3:1 mixture of rotamers (minor isomer in brackets) – Clear oil; R_f = 0.29 (30% EtOAc/Hex); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49-6.40 (1H, m), 6.37-6.28 (1H, m), [5.21-5.12 (0.43H, br s)], 5.09-4.95 (0.57H, m), 4.16-3.97 (2H, m), 3.70 (1.71H, s), [3.67 (1.29H, s)], 3.65-3.60 (3H, m), 3.58-3.52 (1H, m), 3.34-3.11 (2H, m), 3.03-2.76 (2H, m), [1.24 (1.29H, t, J = 7.1Hz)], 1.17 (1.71H, t, J = 7.1

Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.23, 172.58, [172.13], 155.57, [154.93], 132.91, 132.79, [132.48], 61.14, [52.45], 52.22 (2), [48.37], 48.11, 47.99, 46.22, [46.51], 42.45, [42.26], 33.09, [32.98], [14.66], 14.59. HRMS (ESI): 320.1095, calcd for $C_{14}H_{19}NO_6Na$ [M + Na]$^+$ 320.1110.

***Exo* Product:** 1.3:1 mixture of rotamers (minor isomer in brackets) – Clear oil; R$_f$ = 0.29 (30% EtOAc/Hex); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.50-6.38 (1H, m), 6.34-6.27 (1H, m), 5.08-5.02 (0.56H, d, J = 6.2), [4.99-4.95 (0.44H, d, J = 6.0)], 4.17-3.96 (2H, m), 3.66 (3H, s), 3.61 (3H, s), 3.38-3.15 (3H, m), 2.99-2.88 (2H, m), [1.18 (1.32H, t, J = 7.2 Hz)], 1.15 (1.68H, t, J = 7.1 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.78, [172.56], 172.02, 155.21, [154.73], [134.83], 134.59, 131.61 [131.28], [61.35], 61.24, [52.42], 52.35, [52.25], 52.23, [47.07], [46.69], 46.63, 46.51, [43.19], 42.81, [42.71], 42.50, 33.56, [33.39], [14.68], 14.62. HRMS (ESI): 320.1099, calcd for $C_{14}H_{19}NO_6Na$ [M + Na]$^+$ 320.1110.

2-Ethyl 5,6-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate 3b

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with dimethyl maleate (1 eq, 10 mmol, 1.44 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 2.41 g of **3b** (81%) after purification on silica gel with a 0-30% EtOAc/Hex gradient.

***Endo* Product:** 1.9:1 mixture of rotamers (minor isomer in brackets) – Yellow oil; R$_f$ = 0.29 (30% EtOAc/Hex); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.55-6.43 (1H, m), 6.41-6.29 (1H, m), [5.20 (0.34H, br s)], 5.14-4.98 (0.66H, m), 4.26-3.99 (3H, m), 3.72 (3H, d, J = 6.2 Hz), 3.65 (3H, br s), 3.42-3.14 (2H, m), 3.03-2.93 (2H, m), 1.34-1.14 (3H, m); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.29 [172.81], [172.63], 172.06, [156.47], 155.62, 132.95, 132.80, [132.52], [61.27], 61.18, 52.26 (2), [48.40], 48.15, 48.02, 46.55, [46.26], [42.53], 42.49, 33.12, [14.65], 14.62. HRMS (ESI): 320.1094, calcd for $C_{14}H_{19}NO_6Na$ [M + Na]$^+$ 320.1110.

***Exo* Product:** 1.08:1 mixture of rotamers (minor isomer in brackets) – Light yellow oil; R$_f$ = 0.21 (30% EtOAc/Hex); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.49-6.40 (2H, br s), [5.03 (0.48H, dd, J = 3.1, 3.8 Hz)], 4.89 (0.52H, d, J = 3.4 Hz), 4.14-4.01 (2H, m), 3.61-3.56 (6H, m), 3.47-3.34 (1H, m), 3.29-3.02 (2H, m), 2.97-2.88 (1H, m), 1.26-1.16 (3H, m); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.49, [172.40], [170.98], 170.83, 155.24, [154.83], 132.73, 131.12, [130.92], [61.40], 61.27, 51.83 (2), [48.49], 48.41, [47.18], 46.96, 46.84, 44.45, 33.63, 14.67. HRMS (ESI): 320.1095, calcd for $C_{14}H_{19}NO_6Na$ [M + Na]$^+$ 320.1110.

Ethyl 1,3-dioxo-1,3,3a,4,7,7a-hexahydro-4,7-(epiminomethano)isobenzofuran-9-carboxylate 3c

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with maleic anhydride (1 eq, 10 mmol, 0.98 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 1.34 g of **3c** (53%) after purification on silica gel with a 0-10% MeOH/EtOAc gradient.

***Endo* Product (major isomer):** 1.1:1 mixture of rotamers (minor isomer in brackets) – Yellow oil; R_f = 0.25 (100% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53-6.41 (2H, m), 5.11-5.03 (1H, m), 4.17-4.06 (2H, m), 3.60 (s, 3H), 3.52-3.37 (1H, m), 3.28 (1H, dd, *J* = 1.8, 4.2 Hz), 3.21-3.07 (2H, m), 3.00-2.91 (1H, m), 1.22 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.44 [176.58], 172.65 [172.60], 155.42 [155.48], 132.34 [132.47], 131.52 [131.22], 61.68, 51.80, 48.40, 46.99 [47.03], 46.91, 44.43, 33.83, 14.66. HRMS (ESI): 306.0980, calcd for $C_{13}H_{17}NO_6Na$ $[M + Na]^+$ 306.0954.

Isomeric Product (1.06-1 ratio of major isomer to minor): 1.2:1 mixture of rotamers (minor isomer in brackets) – Yellow oil; R_f = 0.25 (100% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53-6.41 (2H, m), 4.99-4.90 (1H, m), 4.17-4.06 (2H, m), 3.58 (s, 3H), 3.52-3.37 (1H, m), 3.32 (1H, dd, *J* = 1.9, 4.2 Hz), 3.21-3.07 (2H, m), 3.00-2.91 (1H, m), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.57 [174.80], 171.00 [171.20], 155.11, 132.94 [133.19], 130.99 [130.60], 61.53, 51.86, 48.65 [48.59], 47.36, 46.82 [46.72], 44.57 [44.61], 33.52 [33.44], 14.66. HRMS (ESI): 306.0988, calcd for $C_{13}H_{17}NO_6Na$ $[M + Na]^+$ 306.0954.

Ethyl 1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-(epiminomethano)isoindole-9-carboxylate 3d

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with *N*-phenylmaleimide (1 eq, 10 mmol, 1.73 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 2.87 g of **3d** (88%) after purification on silica gel with a 0-50% EtOAc/Hex gradient.

***Endo* Product:** 1.05:1 mixture of rotamers (minor isomer in brackets) – White solid; R_f = 0.10 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.35 (3H, m), 7.19-7.14 (2H, m), 6.57-6.40 (2H, m), 5.40 (0.51H, br s), [5.25 (0.49H, br s)], 4.24-4.12 (2H, m), 3.52-3.38 (2H, m), [3.43 (0.49H, d, *J* = 2.0 Hz)], 3.39 (0.51H, d, *J* = 2.1 Hz), 3.16-3.07 (2H, m), [1.32 (1.47H, t, *J* = 7.1 Hz)], 1.26 (1.53H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.71 [176.60], [174.98], 174.72, [155.32], 154.90, [132.70], 132.27, [131.92], 131.28, 129.19 (3), 128.86, 128.84, 61.78, [61.63], [46.43], 45.95, [45.81], 45.59, 45.53 [45.27], 40.84, [33.28], 33.06, 14.74. HRMS (ESI): 327.1328, calcd for $C_{18}H_{19}N_2O_4$ $[M + H]^+$ 327.1345; 349.1177, calcd for $C_{18}H_{18}N_2O_4Na$ $[M + Na]^+$ 349.1164.

2-Ethyl 6-methyl-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate 3e

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with ethyl acrylate (1 eq, 10 mmol, 1.00 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 1.87 g of **3e** (74%) after purification on silica gel with a 0-30% EtOAc/Hex gradient.

***Endo* Product:** 1.5:1 mixture of rotamers (minor isomer in brackets) – Clear oil; R_f = 0.47 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46-6.34 (2H, m), 5.13-5.08 (0.6H, m), [4.97-4.93 (0.4H, m)], 4.13-3.99 (4H, m), 3.20 (1H, dd, J = 2.2, 10.2 Hz), 3.03-2.94 (1H, m), 2.92-2.84 (1H, m), 2.80-2.73 (1H, m), 1.82-1.75 (2H, m), 1.22-1.14 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.63, [155.62], 155.40, 134.97, [134.92], 130.62, [130.28], 61.03, 60.64, [47.13], 47.01, [46.96], 46.54, [44.10], 43.83, 30.62, [30.38], [26.14], 25.92, 14.70, 14.14. HRMS (ESI): 276.1206, calcd for $C_{13}H_{19}NO_4Na$ $[M + Na]^+$ 276.1212.

***Exo* Product:** 1.4:1 mixture of rotamers (minor isomer in brackets) – Clear oil; R_f = 0.45 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.31-6.23 (2H, m), 4.99-4.97 (0.58H, m), [4.90-4.87 (0.42H, m)], 4.13-4.02 (4H, m), 3.30 (1H, dt, J = 2.0, 10.5 Hz), 2.92-2.84 (1H, m), 2.74-2.67 (1H, m), 2.51-2.42 (1H, m), 2.09-2.00 (1H, m), 1.56-1.43 (1H, m), 1.25-1.11 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ [173.38], 173.01, 155.10, [154.95], 135.23, [135.19], 132.20, [131.71], 61.14, 60.87, [48.23], 47.76, [47.40], 47.26, [44.49], 44.29, 30.21, [30.00], 25.06, [24.87], 14.64, 14.06. HRMS (ESI): 276.1203, calcd for $C_{13}H_{19}NO_4Na$ $[M + Na]^+$ 276.1212.

Ethyl 7-cyano-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate 3f

According to the general procedure, 1,2-dihydropyridine (4 eq, 40 mmol, 6.12 g) was reacted with acrylonitrile (1 eq, 10 mmol, 0.53 g) in MeCN (10 mL) at 220 °C for 30 min in the microwave to produce 1.45 g of **3f** (70%) after purification on silica gel with a 0-40% EtOAc/Hex gradient.

***Endo* Product:** 1.12:1 mixture of rotamers (minor isomer in brackets) – Yellow oil; R_f = 0.36 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.48-6.31 (2H, m), [5.02 (0.47H, d, J = 5.8 Hz)], 4.89 (0.53H, d, J = 6.1 Hz)], 4.20-3.99 (2H, m), [3.42 (0.47H, d, J = 2.0 Hz)], 3.38 (0.53H, d, J = 1.7 Hz), 3.01-2.94 (1H, m), 2.87-2.78 (1H, m), 2.59-2.50 (1H, m), 1.86-1.80 (2H, m), [1.23 (1.41H, t, J = 7.2 Hz)], 1.19 (1.59H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.62, [153.54], [136.30], 135.93, 130.28, [129.78], 120.64, [61.06], 60.98, [49.82], 49.29, [47.69], 47.39, 29.97, [29.75], [29.22], 29.04, 27.95, [14.72], 14.53. HRMS (ESI): 229.0976, calcd for $C_{11}H_{14}N_2O_2Na$ $[M + Na]^+$ 229.0953.

***Exo* Product:** 1.5:1 mixture of rotamers (minor isomer in brackets) – Yellow oil; R_f = 0.29 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.58-6.51 (1H, m), 6.48-6.39 (1H, m), 4.65 (0.6H, br s), [4.51 (0.4H, br s), 4.12-3.99 (2H, m), 3.19 (1H, d, J = 7.6 Hz), 3.09-3.03 (1H, m), 2.89-2.80 (2H, m), 2.01 (1H, t, J = 8.0 Hz), 1.59 (1H, dq, J = 2.4, 9.8 Hz), [1.20 (1.2H, t, J = 5.3 Hz)], 1.15 (1.8H, t, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.80, [155.11], [135.33], 135.01, 131.18, [130.63], 121.18, [121.00], [61.49], 61.41, 47.33, [47.16], 47.05, [46.62], 29.89, [29.73], 29.63, [29.48], 27.56, [27.21], 14.58. HRMS (ESI): 207.1140, calcd for $C_{11}H_{15}N_2O_2$ $[M + H]^+$ 207.1140; 229.0965, calcd for $C_{11}H_{14}N_2O_2Na$

$[M + Na]^+$ 229.0953.

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