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Highly Stereoselective Synthesis of Tricyclic Chromenoisoxazolidines by Intramolecular 1,3-Dipolar Cycloadditions

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The novel and simple synthesis of tricyclic chromenoisoxazolidine frameworks by using Baylis–Hillman derivatives through in situ formation of nitrones followed by an intramolecular [3+2] dipolar cycloaddition reaction sequence is described. The new [3+2] cycloaddition reaction leads to a novel class of angularly substituted fused tricyclic chromenoisoxazolidines, creating two rings and three contiguous stereocenters, one of them being a tetrasubstituted carbon center. Fused tricyclic compounds were obtained in a highly stereoselective fashion with high yields.

Introduction

The synthesis of complex heterocyclic compounds is very challenging and attractive in the field of organic chemistry.[1] Heterocycles are an important class of compounds not only due to their natural abundance but also because of their chemical and biological significances.[2] Usually, the synthesis of complex organic molecules involves a multistep reaction sequence. Among the wide variety of heterocycles, isoxazolidines are one of the most important and useful classes of compounds, which are widespread in nature. 1,3-Dipolar cycloaddition[1e,3] of an alkene with nitrone is one of the most reliable strategies for the construction of the important isoxazolidine moiety. In fact, isoxazolidine derivatives can be obtained through in situ formation of a nitrone followed by a 1,3-dipolar cycloaddition reaction sequence. For example, Oppolzer and co-workers reported the synthesis of benzopyran derivatives by intramolecular cycloaddition involving in situ nitrone preparation followed by the [3+2] cycloaddition reaction.[3f] Interestingly, the isoxazolidine products obtained from the nitrone cycloaddition can be easily modified into important amino alcohol building blocks through reductive cleavage of the N–O bond.[4]

There has been a flurry of activity in the synthesis of benzopyran and isoxazolidine derivatives due to their proven biological activity and medicinal utility. For example, benzopyran derivatives possess antiplatelet,[5a] antipsychotic, and antidepressant activities.[5b] Some of the benzopyran derivatives also have anti-HIV activity.[5c–5f] Similarly, isoxazolidine derivatives possess antifungal,[6a] anti-inflammatory,[6b] antimycobacterial,[6c] and cytotoxic activity,[6d] and they also act as DNA intercalators.[6e] Benzopyran and isoxazolidine derivatives are widespread in nature and are integral parts of many natural products such as broussoflavan A,[7a] clusiacyclol A,[7b] and pyrinodemin A.[7c]

The Baylis–Hillman reaction is one of the most important reactions in the field of organic synthesis.[8] In fact, Baylis–Hillman adducts and their derivatives are useful intermediates for the synthesis of many natural products and biologically active molecules.[8a–8c,9] To the best of our knowledge, Baylis–Hillman derivatives have not been utilized for the synthesis of angularly substituted fused tricyclic chromenoisoxazolidine derivatives through nitrone formation followed by intramolecular nitrone cycloaddition. We envisaged that Baylis–Hillman derivatives will be suitable substrates for the synthesis of complex angularly substituted chromenoisoxazolidine compounds by intramolecular 1,3-dipolar cycloaddition.

In continuation of our interest in Baylis–Hillman chemistry,[10] herein we report the first novel protocol for the synthesis of angularly substituted fused tricyclic chromenoisoxazolidine frameworks by using Baylis–Hillman derivatives through in situ formation of nitrone followed by an intramolecular [3+2] dipolar cycloaddition reaction sequence.

Results and Discussion

To execute our idea, first we selected methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates, bromide derivatives of Baylis–Hillman adducts (from benzaldehyde and methylacrylate), and salicylaldehyde to generate required precursor **1** to obtain desired tricyclic derivatives **4** through tandem nitrone formation followed by an intramolecular 1,3-dipolar cycloaddition reaction according to the retrosynthetic strategy shown in Scheme 1.

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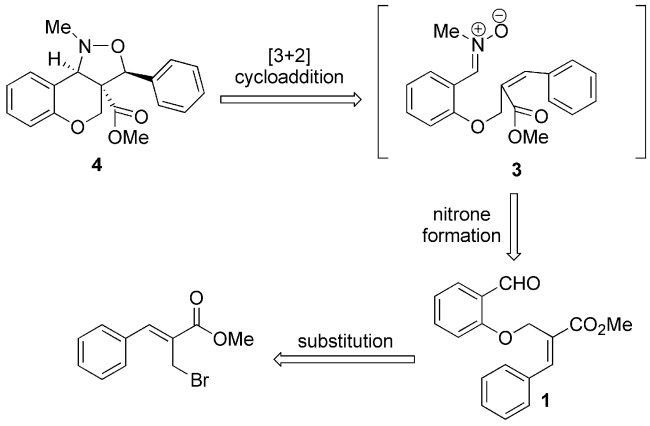


Scheme 1. Retrosynthetic strategy for the synthesis of tricyclic frameworks with angular substitution.

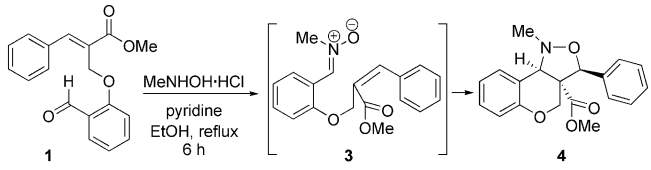
To prepare **4**, we first treated *N*-methylhydroxylamine hydrochloride and Baylis–Hillman derivative **1a**[10b] with triethylamine (3 equiv.) as the base in methanol, which provided desired tricyclic product **4a** in 22% yield (Table 1, Entry 1). Similarly, the reaction carried out in ethanol and acetonitrile led to desired isoxazolidine product **4a** in 29 and 25% yield, respectively (Table 1, Entries 2 and 3). To improve the yield of the reaction, we investigated various conditions (Table 1, Entries 4–9). Interestingly, we could obtain desired product **4a** in 71% yield when we carried out the reaction with pyridine (3 equiv.) in methanol as the solvent. Surprisingly, we could further improve the yield to 91% (Table 1, Entry 10) when we simply changed the solvent from methanol to ethanol in the presence of pyridine as the base. It is worth mentioning that this is the first synthesis of complex angularly substituted chromenoisoxazolidine compounds through the in situ formation of nitrone followed by an intramolecular nitrone cycloaddition reaction. Utilization of the Baylis–Hillman derivatives for the formation of important tricyclic isoxazolidine derivatives is new in the field of Baylis–Hillman chemistry.

Encouraged by this result, we treated a variety of Baylis–Hillman derivatives **1b**–**j** with *N*-methylhydroxylamine hydrochloride, which successfully yielded desired derivatives **4b**–**j** in 72–85% yield (Table 2).

To check the generality of the reaction, we prepared various Baylis–Hillman derivatives **5a**–**j** derived from acrylonitrile[10b] and heated them at reflux with *N*-methylhydroxylamine hydrochloride and pyridine in ethanol for 6 h, which successfully provided desired cyano-substituted **7a**–**j** in 71–86% yield. The isolated yields of pure products **7a**–**j** are summarized in Table 3.

It is worth mentioning that the highly stereoselective nature of the reaction was clearly evidenced by ^{1}H NMR spectroscopy and X-ray crystal analyses. Comparison of the ^{1}H NMR spectra of the crude and recrystallized products showed them to be identical, which confirms the highly stereoselective nature of the reaction. Furthermore, the stereochemistry of compound **4a** was confirmed by X-ray crystallographic analysis (Figure 1). The crystal structure of compound **4a** shows that the phenyl group and the adjacent ester moiety adopt an *anti* orientation, which is presumably due to the initial *trans* geometry of the phenyl group and ester moiety present in the double bond at the vicinal positions of compound **1a**. Similarly, the relative stereochemistry of compound **7a** was confirmed by X-ray crystallographic analysis (Figure 2). The crystal structure of compound **7a** shows that the phenyl group and adjacent nitrile moiety adopt a *syn* orientation, which was presumably due to the initial *cis* geometry of the phenyl group and nitrile moiety present in the double bond at the vicinal positions of compound **5a**.

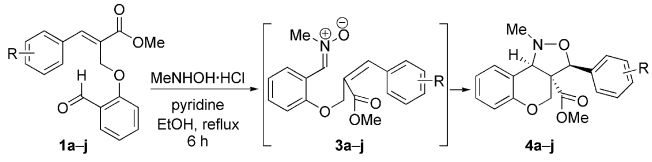
Table 1. Optimization of the formation of tricyclic compound **4** under various conditions.



Entry	Base[a]	Solvent[b]	Yield [%][c]
1	Et_3N	MeOH	22
2	Et_3N	EtOH	29
3	Et_3N	MeCN	25
4	NaOMe	toluene	18
5	NaOMe	MeOH	21
6	Na_2CO_3	MeCN	55
7	K_2CO_3	MeCN	58
8	pyridine	MeCN	60
9	pyridine	MeOH	71
10	pyridine	EtOH	91

[a] All reactions were carried out with 3 mmol of base. [b] All reactions were heated at reflux. [c] Isolated yield of the pure product after column chromatography.

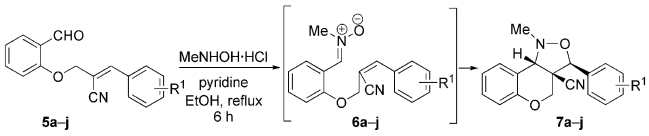
Table 2. Synthesis of tricyclic frameworks by using *N*-methylhydroxylamine hydrochloride with Baylis–Hillman derivatives **1a**–**j**.



Entry	Substrate	R	Product[a]	Yield [%][b,c]
1	**1a**	H	**4a**[d]	91
2	**1b**	3,4-CH=CH–CH=CH	**4b**	85
3	**1c**	2-Me	**4c**	72
4	**1d**	4-Me	**4d**	73
5	**1e**	4-*i*Pr	**4e**	72
6	**1f**	3,4-OCH_2O	**4f**	81
7	**1g**	3-Cl	**4g**	74
8	**1h**	4-Cl	**4h**	74
9	**1i**	3-Br	**4i**	80
10	**1j**	3-NO_2	**4j**	83

[a] All reactions were carried out on 1-mmol scale of *O*-alkylated compound **1a**–**j** with *N*-methylhydroxylamine hydrochloride (1.1 mmol) and pyridine (3 mmol) in ethanol as a solvent at reflux for 6 h. [b] Isolated yield of the pure product. [c] All compounds were fully characterized. [d] Structure was confirmed by single-crystal X-ray data.[11]

Table 3. Synthesis of tricyclic frameworks by using *N*-methylhydroxylamine hydrochloride with Baylis–Hillman derivatives **5a**–**j**.



Entry	Substrate	R^1	Product[a]	Yield [%][b,c]
1	**6a**	H	**7a**[d]	86
2	**6b**	3,4-CH=CH–CH=CH	**7b**	73
3	**6c**	2-Me	**7c**	80
4	**6d**	4-Me	**7d**	71
5	**6e**	4-Et	**7e**	72
6	**6f**	4-*i*Pr	**7f**	77
7	**6g**	3,4-$(MeO)_2$	**7g**	82
8	**6h**	3-Cl	**7h**	81
9	**6i**	2,4-Cl_2	**7i**	71
10	**6j**	3-Br	**7j**	72

[a] All reactions were carried out on 1-mmol scale of *O*-alkylated compound **5a**–**j** with *N*-methylhydroxylamine hydrochloride (1.1 mmol) and pyridine (3 mmol) in ethanol as a solvent at reflux for 6 h. [b] Isolated yield of the pure product. [c] All compounds were fully characterized. [d] Structure was confirmed by single-crystal X-ray data.[11]

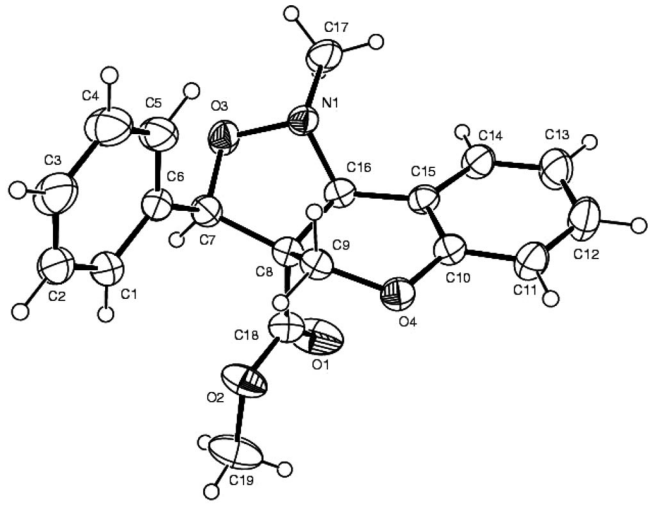


Figure 1. X-ray crystal structure of **4a**.

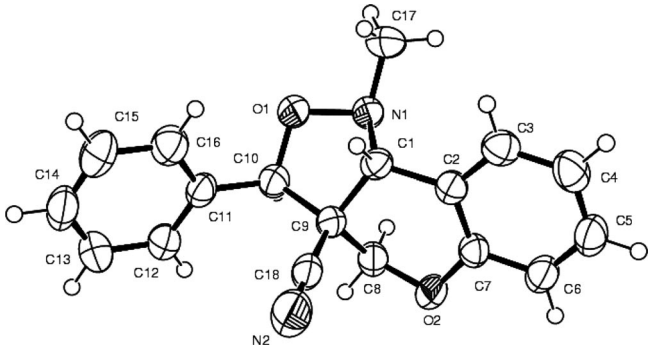


Figure 2. X-ray crystal structure of **7a**.

Conclusions

In conclusion, we have successfully developed a simple and novel protocol for the facile synthesis of complex angularly substituted tricyclic frameworks containing a chromenoisoxazolidine ring system by in situ formation of nitrone followed by intramolecular 1,3-dipolar nitrone cycloaddition by using Baylis–Hillman derivatives. The new [3+2] cycloaddition reaction leads to a novel class of angularly substituted fused tricyclic chromenoisoxazolidines, creating two rings and three contiguous stereocenters, one of them being a tetrasubstituted carbon center, in a unique fashion. Angularly substituted tricyclic compounds were obtained in a highly stereoselective fashion with high yields. This strategy also opens new opportunities for the preparation of libraries of a wide variety of chromenoisoxazolidines for biological screening.

Experimental Section

General Methods: Commercial reagents were used without further purification. Solvents were distilled prior to use. Column chromatography was performed on silica gel. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ as solvent and TMS as an internal standard.

General Procedure for the Synthesis of Compounds 4 or 7: A mixture of compound **1** or **6** (1 mmol), *N*-methylhydroxylamine hydrochloride (**2**; 1.1 mmol), pyridine (0.24 mL, 3 mmol), and ethanol (5 mL) were placed in a round-bottomed flask and heated at reflux for 6 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was diluted with water (10 mL) and dilute HCl (5 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine solution (10 mL) and concentrated. The crude product was purified by column chromatography to provide desired pure products **4** or **7** as colorless solids.

Methyl 3,3a,4,9b-Tetrahydro-1-methyl-3-phenyl-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carboxylate (4a): Yield: 288 mg (91%). White solid, m.p. 98–100 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1732, 1582, 1353 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.07 (s, 3 H, NCH_3), 3.79 (s, 3 H, CO_2CH_3), 3.87 (s, 2 H, OCH_2), 4.15 (s, 1 H, NC*H*Ar), 5.50 (s, 1 H, OC*H*Ar), 6.83–7.42 (m, 9 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.44, 52.91, 56.38, 66.19, 68.31, 81.71, 117.08, 117.38, 120.98, 126.38, 128.02, 128.23, 129.64, 130.79,136.35, 154.38, 171.83 ppm. MS: *m*/*z* = 326 [M + 1]$^+$. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.09, H 5.75, N 4.40.

Methyl 3,3a,4,9b-Tetrahydro-1-methyl-3-(naphthalen-3-yl)-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4b): Yield: 322 mg (85%). White solid; m.p. 150–152 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1732, 1585, 1395 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$, 25 °C): δ = 3.16 (s, 3 H, NCH_3), 3.70 (d, *J* = 11.7 Hz, 1 H, OCH*H*), 3.73 (s, 3 H, CO_2CH_3), 4.04 (d, *J* = 11.4 Hz, 1 H, OC*H*H), 4.36 (s, 1 H, NC*H*Ar), 6.37 (s, 1 H, OC*H*Ar), 6.83–7.91 (m, 11 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.85, 52.88, 56.51, 64.78, 69.87, 79.94, 117.14, 117.20, 120.90, 122.42, 125.16, 125.24, 125.69, 126.13, 128.79, 129.12, 129.79, 130.54, 130.76, 131.57, 133.58, 154.25, 171.98 ppm. MS: *m*/*z* = 376 [M + 1]$^+$. $C_{23}H_{21}NO_4$ (375.42): calcd. C 73.58, H 5.64, N 3.73; found C 73.49, H 5.56, N 3.82.

Methyl 3,3a,4,9b-Tetrahydro-1-methyl-3-*o*-tolyl-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carboxylate (4c): Yield: 244 mg (72%). White solid; m.p. 144–146 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1718, 1579, 1355 cm^{-1}. ^1H NMR: (300 MHz, $CDCl_3$, 25 °C): δ = 2.21 (s, 3 H, CH_3), 3.07 (s, 3 H, NCH_3), 3.76 (s, 3 H, CO_2CH_3), 3.86 (d, J = 11.7 Hz, 1 H, OCH*H*), 4.00 (d, J = 11.4 Hz, 1 H, OC*H*H), 4.19 (s, 1 H, NC*H*Ar), 5.74 (s, 1 H, OC*H*Ar), 6.86–7.63 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.96, 43.27, 52.86, 55.89, 65.19, 69.72, 80.05, 116.77, 117.17, 120.83, 125.87, 127.35, 127.99, 129.85, 130.43, 130.86, 134.67, 154.34, 171.90 ppm. MS: m/z = 340 $[M + 1]^+$. $C_{20}H_{21}NO_4$ (339.39): calcd. C 70.78, H 6.24, N 4.13; found C 70.82, H 6.13, N 4.21.

Methyl 3,3a,4,9b-Tetrahydro-1-methyl-3-*p*-tolyl-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carboxylate (4d): Yield: 248 mg (73%). White solid; m.p. 120–122 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1733, 1580, 1330 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3), 3.06 (s, 3 H, NCH_3), 3.79 (s, 3 H, CO_2CH_3), 3.88 (s, 2 H, OCH_2), 4.16 (s, 1 H, NC*H*Ar), 5.48 (s, 1 H, OC*H*Ar), 6.84–7.29 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.21, 43.57, 52.88, 56.46, 66.17, 68.34, 81.78, 117.09, 117.54, 120.98, 126.33, 128.94, 129.62, 130.80, 133.18, 137.72, 154.41, 171.84 ppm. MS: m/z = 340 $[M + 1]^+$. $C_{20}H_{21}NO_4$ (339.39): calcd. C 70.78, H 6.24, N 4.13; found C 70.79, H 6.20, N 4.19.

Methyl 3,3a,4,9b-Tetrahydro-3-(4-isopropylphenyl)-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4e): Yield: 265 mg (72%). White solid; m.p. 108–110 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1735, 1583, 1368 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25 (d, J = 6.9 Hz, 6 H, Me_2CH), 2.90 (sept., J = 6.9 Hz, 1 H, =CH–), 3.06 (s, 3 H, NCH_3), 3.79 (s, 3 H, CO_2CH_3), 3.89 (s, 2 H, OCH_2), 4.15 (s, 1 H, NC*H*Ar), 5.48 (s, 1 H, OC*H*Ar), 6.84–7.32 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.98, 24.03, 33.86, 43.59, 52.88, 56.50, 66.21, 68.35, 81.80, 117.08, 117.57, 120.98, 126.29, 126.38, 129.60, 130.79, 133.50, 148.74, 154.41, 171.86 ppm. MS: m/z = 368 $[M + 1]^+$. $C_{22}H_{25}NO_4$ (367.44): calcd. C 71.91, H 6.86, N 3.81; found C 71.72, H 6.71, N 3.48.

Methyl 3-(Benzo[*d*][1,3]dioxol-5-yl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4f): Yield: 299 mg (81%). White solid; m.p. 58–60 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1731, 1583, 1363 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.04 (s, 3 H, NCH_3), 3.78 (s, 3 H, CO_2CH_3), 3.93 (AB doublets, J = 11.4, 5.1 Hz, 2 H, OCH_2), 4.12 (s, 1 H, NC*H*Ar), 5.42 (s, 1 H, OC*H*Ar), 5.97 (s, 2 H, OCH_2O), 6.77–7.28 (m, 7 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.39, 52.91, 56.47, 66.11, 68.20, 81.56, 101.11, 107.08, 108.04, 117.08, 117.36, 119.83, 121.00, 129.66, 130.16, 130.80, 147.28, 147.64, 154.39, 171.80 ppm. MS: m/z = 370 $[M + 1]^+$. $C_{20}H_{19}NO_6$ (369.37): calcd. C 65.03, H 5.18, N 3.79; found C 65.11, H 5.20, N 3.82.

Methyl 3-(3-Chlorophenyl)-3,3a,4,9b-Tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4g): Yield: 272 mg (74%). White solid; m.p. 80–82 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1726, 1582, 1353 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.05 (s, 3 H, NCH_3), 3.80 (s, 3 H, CO_2CH_3), 3.83 (d, J = 11.1 Hz, 1 H, OCH*H*), 3.89 (d, J = 12.3, Hz, 1 H, OC*H*H), 4.10 (s, 1 H, NC*H*Ar), 5.45 (s, 1 H, OC*H*Ar), 6.85–7.45 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.15, 53.03, 56.17, 66.28, 68.09, 80.87, 117.01, 117.11, 121.09, 124.65, 126.58, 128.20, 129.54, 129.76, 130.82, 134.36, 138.85, 154.35, 171.72 ppm. MS: m/z = 361 $[M + 1]^+$. $C_{19}H_{18}ClNO_4$ (359.8): calcd. C 63.42, H 5.04, N 3.89; found C 63.31, H 5.10, N 3.92.

Methyl 3-(4-Chlorophenyl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4h): Yield: 272 mg (74%). White solid; m.p. 64–66 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1732, 1584, 1357 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.05 (s, 3 H, NCH_3), 3.79 (s, 3 H, CO_2CH_3), 3.84 (AB doublets, J = 11.1, 6.9, Hz, 2 H, OCH_2), 4.12 (s, 1 H, NC*H*Ar), 5.46 (s, 1 H, OC*H*Ar), 6.85–7.39 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.23, 52.96, 56.23, 66.28, 68.12, 80.97, 117.10, 117.17, 121.08, 127.90, 128.44, 129.74, 130.81, 133.77, 135.18, 154.36, 171.73 ppm. MS: m/z = 361 $[M + 1]^+$. $C_{19}H_{18}ClNO_4$ (359.8): calcd. C 63.42, H 5.04, N 3.89; found C 63.29, H 5.09, N 3.83.

Methyl 3-(3-Bromophenyl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4i): Yield: 326 mg (80%). White solid; m.p. 60–62 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1732, 1579, 1324 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.04 (s, 3 H, NCH_3), 3.77 (s, 3 H, CO_2CH_3), 3.86 (AB doublets, J = 11.1, 7.8 Hz, 2 H, OCH_2), 4.09 (s, 1 H, NC*H*Ar), 5.43 (s, 1 H, OC*H*Ar), 6.84–7.61 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.17, 53.04, 56.17, 66.31, 68.08, 80.77, 117.03, 117.11, 121.11, 122.55, 125.15, 129.47, 129.78, 129.84, 130.84, 131.14, 139.14, 154.35, 171.71 ppm. MS: m/z = 406 $[M + 2]^+$. $C_{19}H_{18}BrNO_4$ (404.25): calcd. C 56.45, H 4.49, N 3.46; found C 56.38, H 4.43, N 3.52.

Methyl 3,3a,4,9b-tetrahydro-1-methyl-3-(3-nitrophenyl)-1*H*-chromeno[4,3-*c*]isoxazole-3a-carboxylate (4j): Yield: 308 mg (83%). White solid; m.p. 118–120 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 1728, 1527, 1350 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$, 25 °C): δ = 3.08 (s, 3 H, NCH_3), 3.80 (s, 2 H, OCH_2), 3.83 (s, 3 H, CO_2CH_3), 4.13 (s, 1 H, NC*H*Ar), 5.55 (s, 1 H, OC*H*Ar), 6.85–8.33 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.00, 53.18, 56.10, 66.43, 67.86, 80.38, 116.85, 117.08, 121.25, 121.62, 123.02, 129.28, 129.85, 130.84, 132.63, 139.32, 148.27, 154.23, 171.56 ppm. MS: m/z = 371 $[M + 1]^+$. $C_{19}H_{18}N_2O_6$ (370.36): calcd. C 61.62, H 4.90, N 7.56; found C 61.58, H 4.80, N 7.62.

3,3a,4,9b-Tetrahydro-1-methyl-3-phenyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7a): Yield: 257 mg (86%). White solid; m.p. 128–130 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2230, 1527, 1310 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.02 (s, 3 H,NCH_3), 3.89 (s, 1 H, NC*H*Ar), 4.42 (AB doublets, J = 11.7, 4.2 Hz, 2 H, OCH_2), 4.89 (s, 1 H, OC*H*Ar), 7.03–7.51 (m, 9 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ 25 °C): δ = 42.45, 50.40, 67.06, 69.71, 82.53, 115.78, 117.44, 117.91, 122.11, 127.14, 128.92, 129.74, 130.66, 130.83, 134.99, 154.41 ppm. MS: m/z = 293 $[M + 1]^+$. $C_{18}H_{16}N_2O_2$ (292.33): calcd. C 73.95, H 5.52, N 9.58; found C 73.83, H 5.60, N 9.66.

3,3a,4,9b-Tetrahydro-1-methyl-3-(naphthalen-3-yl)-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carbonitrile (7b): Yield: 255 mg (73%). White solid; m.p. 196–198 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2231, 1584, 1395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.13 (s, 3 H, NCH_3), 3.42 (d, J = 11.4 Hz, 1 H, OCH*H*), 3.81 (d, J = 11.1 Hz, 1 H, OC*H*H), 4.04 (s, 1 H, NC*H*Ar), 6.42 (s, 1 H, OC*H*Ar), 6.89–8.19 (m, 11 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.43, 44.57, 64.71, 70.05, 79.39, 114.76, 117.59, 119.49, 121.65, 122.25, 124.79, 125.30, 126.19, 127.47, 129.11, 129.31, 130.18, 130.62, 131.02, 131.05, 133.52, 154.00 ppm. MS: m/z = 343 $[M + 1]^+$. $C_{22}H_{18}N_2O_2$ (342.39): calcd. C 77.17, H 5.30, N 8.18; found C 77.21, H 5.22, N 8.29.

3,3a,4,9b-Tetrahydro-1-methyl-3-*o*-tolyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7c): Yield: 247 mg (80%). White solid; m.p. 168–170 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2189, 1576, 1363 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.42 (s, 3H CH_3), 3.03 (s, 3 H, NCH_3), 3.85 (s, 1 H, NC*H*Ar), 4.54 (s, 2 H, OCH_2), 5.15 (s, 1 H, OC*H*Ar), 7.02–7.72 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.92, 42.21, 49.26, 66.92, 69.22, 78.62, 114.97, 117.13, 117.79, 121.93, 126.60, 126.77, 129.15,

130.76, 130.99, 131.16, 133.75, 135.26, 154.22 ppm. MS: *m*/*z* = 307 [M + 1]$^+$. $C_{19}H_{18}N_2O_2$ (306.36): calcd. C 74.49, H 5.92, N 9.14; found C 74.57, H 5.87, N 9.29.

3,3a,4,9b-Tetrahydro-1-methyl-3-*p*-tolyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7d): Yield: 220 mg (71%). White solid; m.p. 160–162 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2185, 1520, 1361 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ 25 °C): δ = 2.38 (s, 3 H, CH_3), 3.00 (s, 3 H, NCH_3), 3.88 (s, 1 H, NC*H*Ar), 4.41 (AB doublets, *J* = 10.8, 4.5 Hz, 2 H, OCH_2), 4.85 (s, 1 H, OC*H*Ar), 7.02–7.39 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.39, 42.46, 50.35, 67.05, 69.72, 82.50, 115.84, 117.60, 117.91, 122.09, 127.14, 129.62, 130.65, 130.87, 131.98, 139.64, 154.43 ppm. MS: *m*/*z* = 307 [M + 1]$^+$. $C_{19}H_{18}N_2O_2$ (306.36): calcd. C 74.49, H 5.92, N 9.14; found C 74.41, H 5.79, N 9.23.

3-(4-Ethylphenyl)-3,3a,4,9b-tetrahydro-1-methyl-*1H*-chromeno[4,3-*c*]-isoxazole-3a-carbonitrile (7e): Yield: 237 mg (72%). White solid; m.p. 150–152 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2238, 1580, 1341 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.68 (q, *J* = 16.2 Hz, 2 H, CH_2CH_3), 3.09 (s, 3 H, NCH_3), 3.89 (s, 1 H, NC*H*Ar), 4.41 (AB doublets, *J* = 11.4, 4.8, Hz, 2 H, OCH_2), 4.94 (s, 1 H, OC*H*Ar), 7.03–7.42 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.36, 28.68, 42.46, 50.33, 67.08, 69.80, 82.55, 115.89, 117.58, 117.91, 122.09, 127.28, 128.39, 130.63, 130.84, 132.10, 145.91, 154.44 ppm. MS: *m*/*z* = 321 [M + 1]$^+$. $C_{20}H_{20}N_2O_2$ (320.38): calcd. C 74.98, H 6.29, N 8.74; found C 74.89, H 6.20, N 8.86.

3,3a,4,9b-Tetrahydro-3-(4-isopropylphenyl)-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7f): Yield: 260 mg (77%). White solid; m.p. 136–138 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2214, 1580, 1361 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ 25 °C): δ = 1.26 (d, *J* = 6.9 Hz, 6 H, Me_2CH), 2.93 (sept., *J* = 6.9 Hz, 1 H, =CH–), 3.00 (s, 3 H, NCH_3), 3.89 (s, 1 H, NC*H*Ar), 4.41 (AB doublets, *J* = 11.1, 6.0, Hz, 2 H, OCH_2), 4.86 (s, 1 H, OC*H*Ar), 7.03–7.43 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.88, 23.98, 33.98, 42.49, 50.30, 67.11, 69.86, 82.55, 115.96, 117.61, 117.93, 122.13, 126.99, 127.41, 130.65, 130.87, 132.20, 150.52, 154.46 ppm. MS: *m*/*z* = 335 [M + 1]$^+$. $C_{21}H_{22}N_2O_2$ (334.41): calcd. C 75.42, H 6.63, N 8.38; found C 75.57, H 6.71, N 8.50.

3,3a,4,9b-Tetrahydro-3-(3,4-dimethoxyphenyl)-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7g): Yield: 295 mg (82%). White solid; m.p. 186–188 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2214, 1511, 1370 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.01 (s, 3 H, NCH_3), 3.89 (s, 1 H, NC*H*Ar), 3.90 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.39 (AB doublets, *J* = 11.1, 3.9, Hz, 2 H, OCH_2), 4.84 (s, 1 H, OC*H*Ar), 6.91–7.36 (m, 7 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.48, 50.41, 55.90, 56.05, 67.08, 69.86, 82.55, 110.25, 111.17, 115.96, 117.67, 117.91, 120.09, 122.13, 127.04, 130.64, 130.79, 149.25, 150.13, 154.44 ppm. MS: *m*/*z* = 353 [M + 1]$^+$. $C_{20}H_{20}N_2O_4$ (352.38): calcd. C 68.17, H 5.72, N 7.95; found C 68.23, H 5.68, N 8.09.

3-(3-Chlorophenyl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carbonitrile (7h): Yield: 265 mg (81%). White solid; m.p. 88–90 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2238, 1581, 1354 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.01 (s, 3 H, NCH_3), 3.86 (s, 1 H, NC*H*Ar), 4.42 (s, 2 H, OCH_2), 4.85 (s, 1 H, OC*H*Ar), 7.03–7.50 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.41, 50.31, 66.94, 69.51, 81.62, 115.49, 117.19, 117.93, 122.21, 125.29, 127.14, 129.87, 130.26, 130.78, 130.87, 134.91, 137.19, 154.33 ppm. MS: *m*/*z* = 327 [M + 1]$^+$. $C_{18}H_{15}ClN_2O_2$ (326.78): calcd. C 66.16, H 4.63, N 8.57; found C 66.23, H 4.68, N 8.69.

3-(2,4-Dichlorophenyl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-3a-carbonitrile (7i): Yield: 287 mg (71%). White solid; m.p. 164–166 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2234, 1584, 1392 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.03 (s, 3 H, NCH_3), 3.74 (s, 1 H, NC*H*Ar), 4.51 (d, *J* = 10.8 Hz, 1 H, OCH*H*), 4.74 (d, *J* = 12.0, Hz, 1 H, OC*H*H), 5.24 (s, 1 H, OC*H*Ar), 7.01–7.72 (m, 7 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.11, 49.08, 66.64, 69.24, 77.94, 114.35, 116.69, 117.84, 121.87, 127.77, 128.79, 129.72, 130.84, 131.00, 132.21, 133.24, 135.66, 154.23 ppm. MS: *m*/*z* = 362 [M + 1]$^+$. $C_{18}H_{14}Cl_2N_2O_2$ (361.22): calcd. C 59.85, H 3.91, N 7.76; found C 59.78, H 3.99, N 7.88.

3-(3-Bromophenyl)-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno-[4,3-*c*]isoxazole-3a-carbonitrile (7j): Yield: 273 mg (72%). White solid; m.p. 178–180 °C. Reaction time: 6 h. IR (neat): $\tilde{\nu}$ = 2234, 1576, 1356 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.01 (s, 3 H, NCH_3), 3.87 (s, 1 H, NC*H*Ar), 4.41 (s, 2 H, OCH_2), 4.84 (s, 1 H, OC*H*Ar), 7.03–7.65 (m, 8 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.43, 50.32, 66.93, 69.50, 81.54, 115.49, 117.20, 117.93, 122.22, 123.03, 125.79, 130.02, 130.51, 130.79, 130.89, 132.81, 137.43, 154.33 ppm. MS: *m*/*z* = 373 [M + 2]$^+$. $C_{18}H_{15}BrN_2O_2$ (371.23): calcd. C 58.24, H 4.07, N 7.55; found C 58.37, H 4.17, N 7.69.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of compounds **4a**–**j** and **7a**–**j**.

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[11] CCDC-748691 (for **4a**) and -748692 (for **7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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