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Synthesis of Heterocyclic [3.3.3]Propellanes via a Sequential Four-Component Reaction

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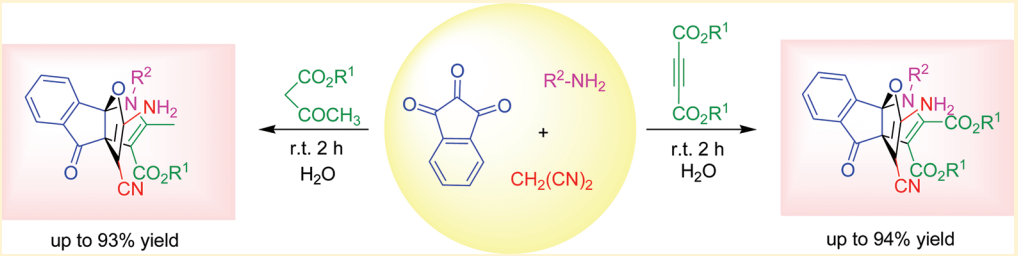
Supporting Information



ABSTRACT: A highly chemoselective heteroannulation protocol for the synthesis of unreported polysubstituted heterocyclic [3.3.3]propellanes has been developed by sequential four-component reaction of ninhydrin, malononitrile, primary amines, and dialkyl acetylenedicarboxylates under mild conditions in water. To the best of our knowledge, there are no previous reports for the synthesis of these classes of heterocyclic [3.3.3]propellanes. The merit of this sequential Knoevenagel condensation/enamine formation/Michael addition/cyclization sequence is highlighted by its high atom-economy, excellent yields, the use of water as reaction media, and the efficiency of production without the use of any activator or metal promoters. This synthesis serves as a nice addition to group-assistant-purification (GAP) chemistry in which purification via chromatography and recrystallization can be avoided, and the pure products were obtained simply by washing the crude products with 95% ethanol.

INTRODUCTION

Propellanes are annulated tricyclic systems exhibiting a Y-shaped bridgehead−bridgehead central bond (Figure 1).[1] They

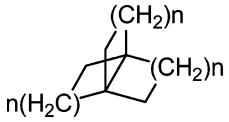


Figure 1. General structure of propellanes.

can be found as scaffolds of non-naturally and naturally occurring products having many applications, including bioactive medicinal compounds[2] or polymers.[3] The first propellanes were synthesized in the 1930s during investigations into the Diels−Alder reaction.[4−9] However, the first "propellane by design" was synthesized much later, in 1965.[10,11] The term propellane was proposed in 1966 by Ginsburg's group[12] because of the characteristic propeller shape of these molecules. Since their discovery in 1965,[13] these polycyclic structures have received attention by many research groups[14] due to their extended use and challenging architecture. Some modern synthetic approaches to form carbocyclic or heterocyclic propellanes include [4 + 2]cycloadditions,[15] palladium[16] or manganese[17] catalysis, and nucleophilic substitutions of 1,1,2,2-tetrasubstituted alkenes.[18]

The propellane moiety is a part of many natural products, such as batrachotoxin (**A**), a steroidal alkaloid skin neurotoxin from the South American frog *Phyllobates terribilis*,[19] hasubanan alkaloids[20] (**B**), and merrilactone A (**C**), with therapeutic potential in the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Figure 2).[21] Total synthesis of many different propellane-containing natural products have recently been reviewed.[14]

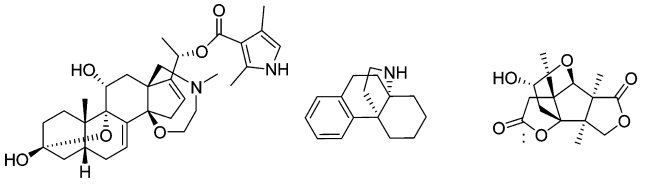


Figure 2. Biologically active propellane-based natural products.

The conventional multistep methods for the preparation of complex molecules involve a large number of synthetic operations, including extraction and purification processes for each individual step, that lead to synthetic inefficiency and the

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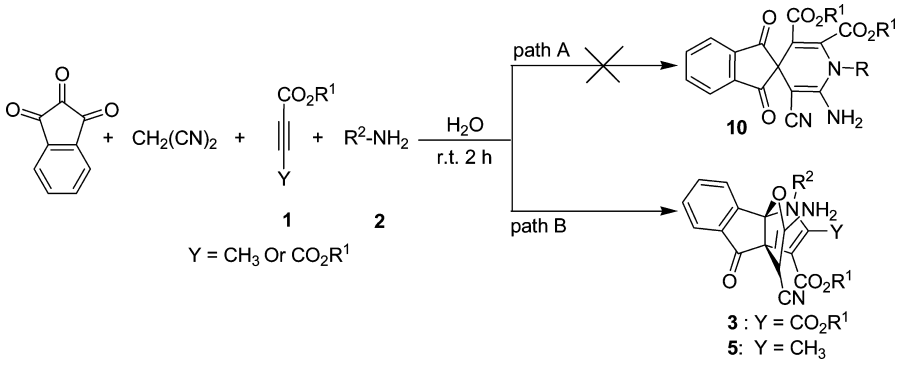
Scheme 1. Synthetic Scheme for the Generation of 3 and 5



generation of large amounts of waste. Multicomponent reactions (MCRs) allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of workups, extraction and purification processes, and hence minimized waste generation rendering the transformations green. One aspect of multicomponent reactions that has received relatively little attention is their development in aqueous environments.[22] In this regard, water is nature's reaction medium and constitutes a nonflammable, nonhazardous, nontoxic, uniquely redox-stable, inexpensive solvent that has the additional advantage of being a nonexhaustible resource that is almost freely available, even in the least-developed countries.[23] For these reasons, the development of synthetically useful multicomponent reactions using water as the green reaction medium has gained considerable interest.

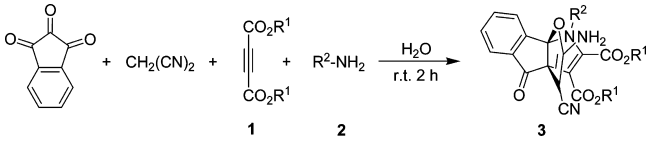
Our research goal during the past few years has been the synthesis of a library of pharmacologically relevant fused polyheterocyclic systems employing enamines and dienamines.[24] The chemistry of enamines has numerous attractive features that have made them important building blocks in current organic trends.[25] Over the decades, they have been used for the synthesis of a wide variety of heterocyclic compounds, natural products,[26] and precursors of chiral amines upon asymmetric transformations.[27]

RESULTS AND DISCUSSION

Inspired by these results and with given our interest and experience in the area of one-pot-multicomponent reactions, we became attracted to how Knoevenagel adduct generated in situ from ninhydrin and malononitrile could be trapped by enamine to give a heterocycle product. For this purpose, we investigated the reaction of ninhydrin, malononitrile, dialkyl acetylenedicarboxylate **1**, and primary amine **2** in water at room temperature. Quite surprisingly, instead of the anticipated spiropyridine product **10** (Scheme 1), we observed an unexpected process leading to heterocyclic propellane **3** in excellent yields (Table 1). To the best of our knowledge, no analogous products have been reported in the literature yet.

Initially, we explored the reaction of ninhydrin with malononitrile at room temperature in the presence of triethylamine (0.1 mmol) that afforded the expected Knoevenagel adduct intermediate. Next, the sequential one-pot addition of dialkyl acetylenedicarboxylate **1** and primary amine **2** successfully gave the aza[3.3.3]propellane derivatives **3** in 83−94% yields (Table 1). Several solvent and basic catalysts were examined to set up a standard reaction condition, and

Table 1. One-Pot, Four-Component Synthesis of Aza[3.3.3]propellane Derivatives 3a−j[a]



entry	R^1	R^2	products **3**	yield (%)[b]
1	Me	*n*-ethyl	**3a**	90
2	Me	*n*-propyl	**3b**	93
3	Et	*n*-propyl	**3c**	91
4	Me	*i*-butyl	**3d**	84
5	Et	*i*-butyl	**3e**	87
6	Me	*n*-butyl	**3f**	94
7	Et	*n*-butyl	**3g**	90
8	Me	*p*-methylbenzyl	**3h**	83
9	Me	*p*-methoxybenzyl	**3i**	88
10	Et	*p*-methoxybenzyl	**3j**	85

[a]Reactions were performed at 1 mmol scale of substrates in H_2O (4 mL) at room temperature. Reaction time was typically 2 h (see the Supporting Information). [b]Isolated yield.

experimental results showed that the reaction proceeded with excellent yields when water and triethylamine were utilized as the solvent and base.

In view of the success of the above reaction and having established the optimal conditions, we explored the scope of this promising reaction by varying the structure of the primary amine **2** and dialkyl acetylenedicarboxylate **1** component (Table 1). The reaction proceeded very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed.

Being inspired by the above results, it was thought worthwhile to replace the dialkyl acethylenedicarboxylate with alkyl acetoacetate in order to get some newly substituted aza[3.3.3]propellane. For this aim, we have examined the reaction of ninhydrin, malononitrile, alkyl acetoacetate **4**, and primary amine **2** under the same previous reaction conditions. Fortunately, the desired reaction took place successfully to afford a series of aza[3.3.3]propellane derivatives **5** in excellent yields. The results are shown in Table 2.

The structures all of the products **3a−j** and **5a−d** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra (see the Supporting Information) and unambiguously confirmed by X-ray crystal structure analysis of **3b** and **5c** (see the Supporting Information).[28]

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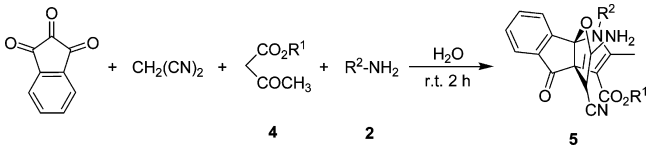
Table 2. One-Pot, Four-Component Synthesis of Aza[3.3.3]propellane Derivatives 5a–d[a]



entry	R^1	R^2	products 3	yield (%)[b]
1	Me	*n*-propyl	**5a**	93
2	Et	*n*-propyl	**5b**	90
3	Me	*n*-butyl	**5c**	88
4	Et	*n*-butyl	**5d**	90

[a]Reactions were performed at 1 mmol scale of substrates in H_2O (4 mL) at room temperature. Reaction time was typically 2 h (see the Supporting Information). [b]Isolated yield.

We have believed that the reaction mechanism is a special case, and on the basis of the results obtained above, a plausible reaction scenario for this one-pot four-component reaction is outlined in Scheme 2. It is conceivable that initially the ninhydrin undergoes triethylamine promoted Knoevenagel condensation with malononitrile to give adduct **6**, which acts as Michael acceptor. Next, the formation of enamine **7** occurs through condensation of amine **2** with acethylene compound **1** or alkyl acetoacetate **4**. Then, the enamine **7** attacks to Knoevenagel adduct **6** in a Michael-type addition to produce an open chain intermediate **8**, which transformed to intermediate **9** through the migration of the hydrogen atom. At this stage, considering the previous articles, we would normally expect that **9** undergoes *N*-cyclization via attack to the C≡N triple bond and tautomerization to give the desired spiropyridines **10** (path A). But considering IR, ^1H and ^{13}C NMR spectra, and X-ray diffraction, this product was not created, and another considerable event occurs. In fact, in this stage, chemoselective nucleophilic addition of amino group to C=O bond afforded intermediate **11**. Then, *O*-cyclization and the tautomerization of imino group to amino group of could lead to aza[3.3.3]-propellanes **3** and **5** (path B).

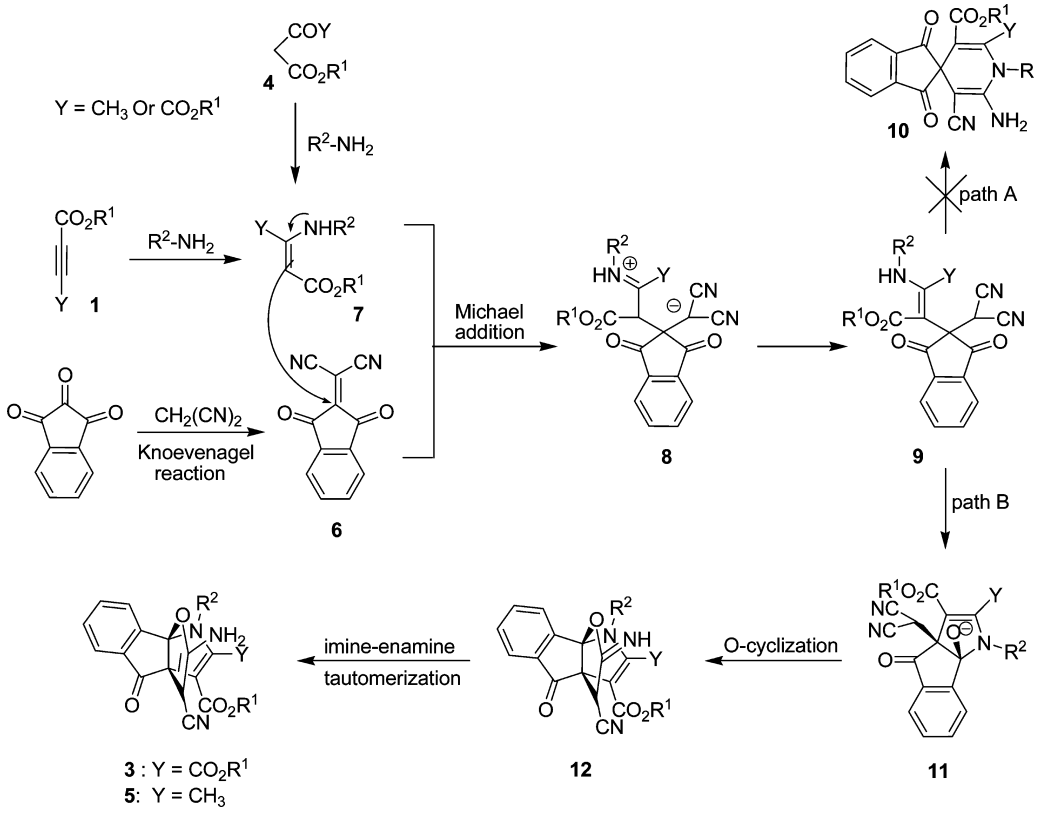
■ CONCLUSIONS

We have discovered a novel and convenient four-component synthesis of efficient assembly of heterocyclic [3.3.3]-propellanes, through sequential Knoevenagel/Michael/intramolecular cyclization sequences in water. This class of compounds is not only prepared by a multicomponent reaction for the first time, but also to our knowledge, there is no other efficient method for their synthesis. This reaction includes some important aspects like simple operation under mild conditions, easy accessibility of reactants and workup procedure, absence of transition metal catalysts, high atom economy, and the use of water as a green reaction medium. Further investigations in this area are currently under way and will be reported in due course.

■ EXPERIMENTAL SECTION

General Procedure for the Synthesis of Dialkyl-8c-amino-8b-cyano-8-oxo-3-alkyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate 3a–j. To a solution of ninhydrin (1 mmol) and malononitrile (1 mmol) in water (4 mL) was added triethylamine (0.1 mmol), and the solution was stirred for 1 h at room temperature. Then, dialkyl acetylenedicarboxylate **1** (1 mmol) and primary amine **2** (1 mmol) were added at once and dropwise over 15 min, respectively. Upon completion (50–60 min) as monitored by

Scheme 2. Mechanistic Rationalization for the Formation of 3 and 5



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TLC, the reaction mixture was filtered to give the crude product, which was further washed by 95% ethanol to give pure product **3a−j**.

Dimethyl-8c-amino-8b-cyano-8-oxo-3-ethyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3a). White crystals: 0.35 g, 90% yield; mp 177−179 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.13 (t, J = 7.2 Hz, 3H), 3.46−3.59 (m, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 7.63 (s, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.91−7.98 (m, 2H), 8.11 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 15.8, 50.6, 53.3, 53.3, 56.0, 68.0, 100.2, 109.4, 117.0, 125.0, 125.2, 131.8, 136.0, 136.7, 143.1, 150.4, 161.6, 162.9, 167.2, 194.0; IR (KBr) ν 3376, 3321, 2197, 1725, 1652, 1593, 1441, 1344 cm^{-1}; MS m/z 396, (M^+ + 1), 377, 366, 352, 320, 305, 291, 261, 249, 233, 205, 179, 151, 102, 76, 59. Anal. Calcd for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63. Found: C, 60.68; H, 4.24; N, 10.59.

Dimethyl-8c-amino-8b-cyano-8-oxo-3-propyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3b). White crystals: 0.38 g, 93% yield; mp 180−182 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.84 (br, 3H), 1.51−1.60 (m, 2H), 3.24−3.44 (m, 2H), 3.63 (s, 3H), 3.81 (s, 3H), 7.55 (s, 2H), 7.76−8.02 (m, 4H); ^{13}C NMR (125 MHz, DMSO) δ 11.2, 23.5, 45.9, 51.0, 53.7, 68.5, 100.7, 110.0, 117.4, 125.5, 125.6, 132.2, 136.5, 137.0, 143.4, 151.0, 162.0, 163.3, 167.7, 194.4; IR (KBr) ν 3350, 3310, 2202, 1721, 1650, 1592, 1437, 1336 cm^{-1}; MS m/z 409 (M^+), 366, 334, 317, 292, 260, 232, 205, 192, 129, 91, 59. Anal. Calcd for $C_{21}H_{19}N_3O_6$: 61.61; H, 4.68; N, 10.26. Found: C, 61.52; H, 4.59; N, 10.30. Crystal data for **3b** $C_{21}H_{19}N_3O_6$ (CCDC 846789): M_W = 409.39, monoclinic, space group $P21/n$, a = 9.9784(5) Å, b = 13.6537(7) Å, c = 14.6285(7) Å, α = 90.00, β = 104.214(5), γ = 90.00, V = 1932.00(17) Å^3, Z = 4, D_c = 1.407 mg/m^3, $F(000)$ = 856, crystal dimension 0.43 × 0.39 × 0.35 mm, radiation, MoKα (λ = 0.71073 Å), 2.83 ≤ 2θ ≤ 25.10, intensity data were collected at 295(2) K, and employing $\omega/2\theta$ scanning technique, in the range of −11≤ h ≤ 11, −15≤ k ≤ 16, −16≤ l ≤ 17; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2686 observed reflections with R(into) = 0.0528 by a full-matrix least-squares technique converged to R = 0.0371 and Raw = 0.0961 [I > 2σ(I)].

Diethyl-8c-amino-8b-cyano-8-oxo-3-propyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3c). White crystals: 0.039, 91% yield; mp 182−184 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.84 (t, J = 6.6 Hz, 3H), 1.24 (s, 6H), 1.50−1.62 (m, 2H), 3.20−3.31 (m, 1H), 3.41−3.48 (m, 1H), 4.08 (m, 2H), 4.28 (m, 2H), 7.57 (s, 2H), 7.77 (t, J = 6.8 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.95 (t, J = 7.1 Hz, 1H), 8.04 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 11.2, 14.0, 14.5, 23.5, 45.8, 59.8, 62.8, 62.9, 100.0, 110.0, 117.5, 125.6, 125.7, 132.3, 136.5, 137.0, 143.4, 148.1, 150.9, 161.5, 162.8, 167.8, 194.4; IR (KBr) ν 3386, 3325, 2198, 1728, 1655, 1594, 1436, 1379 cm^{-1}; MS m/z 437 (M^+), 422, 394, 348, 320, 261, 234, 205, 178, 151, 130, 102, 56. Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.61. Found: C, 63.08; H, 5.25; N, 9.56.

Dimethyl-8c-amino-8b-cyano-3-isobutyl-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3d). White crystals: 0.35 g, 84% yield; mp 182−184 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.83 (s, 3H), 0.92 (s, 3H), 2.03 (br, 1H), 2.82−2.90 (m, 1H), 3.31 (br, 1H), 3.62 (s, 3H), 3.80 (s, 3H), 7.57 (s, 2H), 7.77−7.96 (m, 4H); ^{13}C NMR (125 MHz, DMSO) δ 19. 8, 20.0, 28.4, 51.0, 51.8, 53.7, 68.5, 100.5, 110.3, 117.4, 125.7, 125.8, 132.3, 132.7, 136.5. 137.0, 142.9, 152.0, 162.0, 163.4, 167.7, 194.6; IR (KBr) ν 3384, 3310, 2154, 1720, 1644, 1588, 1432, 1328 cm^{-1}; MS m/z 423 (M^+), 394, 380, 348, 292, 261, 234, 205, 164, 130, 57. Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.38; H, 4.95; N, 9.90.

Diethyl-8c-amino-8b-cyano-3-isobutyl-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3e). White crystals: 0.39 g, 87% yield; mp 186−188 °C; ^{1}H NMR (400 MHz, DMSO) δ 0.86 (t, J = 6.4 Hz, 3H), 0.95 (t, J = 6.8 Hz, 3H), 1.26 (dd, J = 13.2 Hz, J = 6.8 Hz, 6H), 2.05−2.09 (m, 1H), 2.86−2.92 (m, 1H), 3.37−3.39 (m, 1H), 4.06−4.15 (m, 2H), 4.24−4.27 (m, 2H), 7.59 (s, 2H), 7.80 (t, J = 7.2 Hz, 1H), 7.93−8.0 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 13.5, 14.1, 19.4, 19.6, 27.9, 51.3, 53.2, 59.4, 62.4, 68.1, 100.0, 109.9, 117.2, 125.3, 125.3, 131.8, 136.1, 136.6, 142.3, 150.7, 161.1, 162.4, 167.3, 194.1; IR (KBr) ν 3337, 3256, 2196, 1732, 1658, 1590, 1437, 1374 cm^{-1}; MS m/z 451 (M^+), 436, 408, 362, 334, 278, 261, 234, 205, 151, 97, 57. Anal. Calcd for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.78; H, 5.52; N, 9.33.

Dimethyl-8c-amino-3-butyl-8b-cyano-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3f). White crystals: 0.39 g, 94% yield; mp 178−180 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.85 (t, J = 7.1 Hz, 3H), 1.22−1.30 (m, 2H), 1.45−1.49 (m, 1H), 1.57−1.61 (m, 1H), 3.25−3.31 (m, 1H), 3.44−3.48 (m, 1H), 3.62 (s, 3H), 3.81 (s, 3H), 7.58 (s, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.96 (t, J = 7.3 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 13.9, 19.5, 32.3, 44.1, 51.0, 53.7, 68.0, 100.7, 110.0, 117.4, 125.5, 125.7, 132.3, 136.5, 137.1, 143.3, 151.0, 162.0, 163.3, 167.7, 194.5; IR (KBr) ν 3441, 3338, 2191, 1727, 1642, 1588, 1441, 1355 cm^{-1}; MS m/z 423 (M^+), 394, 380, 348, 321, 292, 260, 234, 205, 178, 97, 57. Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.37; H, 5.08; N, 9.87.

Diethyl-8c-amino-3-butyl-8b-cyano-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3g). White crystals: 0.40 g, 90% yield; mp 182−184 °C; ^{1}H NMR (400 MHz, DMSO) δ 0.89 (t, J = 6.4 Hz, 3H), 1.24−1.33 (m, 8H), 1.46.1.52 (m, 1H), 1.58−1.63 (m, 1H), 3.26−3.32 (m, 1H), 3.45−3.52 (m, 1H), 4.06−4.14 (m, 2H), 4.27−4.28 (m, 2H), 7.60 (s, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.92−7.99 (m, 2H), 8.05 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 13.5, 13.6, 14.1, 19.1, 31.9, 43.6, 53.3, 59.4, 62.5, 68.1, 100.2, 109.6, 117.1, 125.1, 125.2, 131.8, 136.1, 136.6, 142.9, 150.5, 161.1, 162.4, 167.3, 193.9; IR (KBr) ν 3430, 3183, 2202, 1721, 1650, 1592, 1437, 1336 cm^{-1}; MS m/z 451 (M^+), 436, 408, 345, 317, 290, 261, 234, 189, 151, 97, 57. Anal. Calcd for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.81; H, 5.61; N, 9.33.

Dimethyl-8c-amino-8b-cyano-3-(4-methylbenzyl)-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3h). White crystals: 0.37 g, 83% yield; mp 188−190 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.25 (s, 3H), 3.44 (s, 3H), 3.67 (s, 3H), 4.67 (d, J = 16.4 Hz, 1H), 4.81 (d, J = 16.8 Hz, 1H), 6.96 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.67 (s, 2H), 7.76 (t, J = 7.2 Hz, 1H), 7.88 (t, J = 7.2 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 20.6, 50.6, 52.8, 53.4, 56.0, 68.0, 101.3, 109.4, 117.0, 125.2, 125.19, 127.4, 128.9, 131.8, 133.1, 136.0, 136.6, 136.8, 143.4, 149.7, 161.2, 162. 8, 167.2, 194.0; IR (KBr) ν 3554, 3360, 2190, 1710, 1659, 1596, 1438, 1334 cm^{-1}; MS m/z 453, 428, 397, 364, 337, 292, 250, 205, 179, 135, 105, 77, 51. Anal. Calcd for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91 Found C, 66.18; H, 4.46; N, 8.98.

Dimethyl-8c-amino-8b-cyano-3-(4-methoxylbenzyl)-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3i). White crystals: 0.42 g, 88% yield; mp 188−190 °C; ^{1}H NMR (400 MHz, DMSO) δ 0. 3.45 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 4.64 (d, J = 16.4 Hz, 1H), 4.79 (d, J = 16.4 Hz, 1H),), 6.86 (d, J = 8.4 Hz, 2H), 6.10 (d, J = 8.8 Hz, 2H), 7.67 (s, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.89−7.95 (m, 2H), 8.08 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 46.6, 50.6, 52.8, 53.5, 55.1, 67.9, 101.2, 109.3, 113.8, 117.0, 125.1, 127.8, 129.0, 131.9, 134.2, 136.0, 136.7, 143.4, 149.6, 158.7, 161.2, 162.8, 167.2, 194.0; IR (KBr) ν 3430, 3321, 2193, 1731, 1647, 1592, 1438, 1333 cm^{-1}; MS m/z 487 (M^+), 458, 444, 380, 309, 292, 234, 205, 151, 121, 91, 77, 59. Anal. Calcd for $C_{26}H_{21}N_3O_7$: C, 64.06; H, 4.34; N, 8.62 Found C, 63.99; H, 4.37; N, 8.64.

Diethyl-8c-amino-8b-cyano-3-(4-methoxylbenzyl)-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1,2-dicarboxylate (3j). White crystals: 0.43 g, 85% yield; mp 186−188 °C; ^{1}H NMR (400 MHz, DMSO) δ 0.92 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 3.71(s, 3H), 3.87 (q, J = 7.2 Hz, 2H), 4.07−4.11 (m, 2H), 4.65 (d, J = 16.4 Hz, 1H), 4.80 (d, J = 16.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.67 (s, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 8.09 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 13.1, 14.1, 46.5, 53.6, 56.0, 59.4, 62.1, 68.0, 101.3, 109.4, 113.7, 117.1, 125.1, 125.2, 128.0, 128.9, 131.8, 136.0, 136.6, 143.5, 149.6, 158.8, 160.8, 162.2, 167.3, 193.9; IR (KBr) ν 3421, 3324, 2202, 17236, 1648, 1596, 1436, 1327 cm^{-1}; MS m/z 516 (M^+ + 1), 472, 427, 380, 323, 261, 234, 205, 137, 121, 91, 77, 57. Anal.

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Calcd for $C_{28}H_{25}N_3O_7$: C, 65.24; H, 4.89; N, 8.15 Found C, 65.27; H, 5.85; N, 8.17.

General Procedure for the Synthesis of Alkyl-8c-amino-8b-cyano-2-alkyl-8-oxo-3-alkyl-3*H*,8*H*-8d-oxa-3-azapentaleno-[3a,6a-*a*]indene-1,2-dicarboxylate 5a−d. To a solution of ninhydrin (1 mmol) and malononitrile (1 mmol) in water (4 mL) was added triethylamine (0.1 mmol), and the solution was stirred for 1 h at room temperature. Then, alkyl acetoacetate **4** (1 mmol) and primary amine **2** (1 mmol) were added at once and dropwise over 15 min, respectively. Upon completion (50−60 min) as monitored by TLC, the reaction mixture was filtered to give the crude product, which was further washed by 95% ethanol to give pure product **5a−d**.

Methyl-8c-amino-8b-cyano-2-methyl-8-oxo-3-propyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1-carboxylate (5a). White crystals: 0.33 g, 93% yield; mp 177−179 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.92 (br, 3H), 1.52 (br, 1H), 1.72 (br, 1H), 2.23 (s, 3H), 3.29 (s, 3H), 3.55 (br, 1H), 3.69 (br,1H) 7.65 (s, 2H), 7.81−8.48 (m, 4H); ^{13}C NMR (125 MHz, DMSO) δ 11.6, 13.4, 22.8, 43.9, 50.5, 58.0, 65.0, 96.5, 113.0, 113.4, 124.1, 125.1, 131.3, 134.7, 136.7, 149.1, 159.0, 160.9, 164.8, 195.1; IR (KBr) ν 3310, 3228, 2136, 1722, 1624, 1541, 1440, 1369 cm^{-1}; MS m/z 365 (M^+), 350, 322, 290, 247, 208, 180, 152, 126, 96, 76. Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.70; H, 5.21; N, 11.56.

Ethyl-8c-amino-8b-cyano-2-methyl-8-oxo-3-propyl-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1-carboxylate (5b). White crystals: 0.34 g, 90% yield; mp 190−192 °C; ^{1}H NMR (400 MHz, DMSO) δ 0.89 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 6.8 Hz, 3H), 1.41−1.50 (m, 1H), 1.60−1.68 (m, 1H), 2.27 (s, 3H), 3.47 (t, J = 8.0 Hz, 2H), 4.04−4.18 (m, 2H), 7.35 (s, 2H), 7.73 (t, J = 7.2 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.92 (t, J = 7.2 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 10.9, 11.9, 14.4, 23.2, 43.7, 54.5, 58.2, 67.9, 98.0, 108.9, 118.0, 124.9, 125.0, 131.3, 136.0, 136.3, 143.6, 159.6, 164.8, 167.3, 195.0; IR (KBr) ν 3409, 3335, 2188, 1717, 1642, 1594, 1430, 1325 cm^{-1}; MS m/z 379 (M^+), 304, 248, 194, 125, 111, 97, 83, 69, 57. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.05; N, 11.08. Found: C, 66.39; H, 5.5.10; N, 11.12.

Methyl-8c-amino-3-butyl-8b-cyano-2-methyl-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1-carboxylate (5c). White crystals: 0.33 g, 88% yield; mp 180 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.89 (t, J = 7.0 Hz, 3H), 1.29−1.43 (m, 3H), 1.57−1.62 (m, 1H), 2.25 (s, 3H), 3.34 (s, 3H), 3.48 (t, J = 7.0 Hz 1H), 3.61 (br, 1H), 7.32 (s, 2H), 7.72 (t, J = 7.3 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.91 (t, J = 7.3 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 11.9, 13.6, 19.4, 31.9, 41.4, 49.4, 54.5, 68.0, 97.7, 108.9, 117.8, 124.9, 125.0, 131.3, 136.0, 136.2, 143.6, 159.7, 165.2, 167.2, 195.1; IR (KBr) ν 3409, 3328, 2187, 1717, 1642, 1590, 1429, 1332 cm^{-1}; MS m/z 379 (M^+), 351, 337, 256, 211, 149, 125, 111, 97, 84, 71, 57. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.05; N, 11.08. Found: C, 66.40; H, 5.07; N, 11.09. Crystal data for **5c** $C_{21}H_{19}N_3O_4$ (CCDC 864461): M_W = 377.39, triclinic, space group $P\bar{1}$, a = 9.6045(5) Å, b = 17.1080(7) Å, c = 11.7885(5) Å, α = 90.00, β = 97.614(4), γ = 90.00, V = 1919.93(15) Å^3, Z = 4, D_c = 1.306 mg/m^3, $F(000)$ = 792, crystal dimension 0.32 × 0.26 × 0.20 mm, radiation, MoKα (λ = 0.71073 Å), 2.95 ≤ 2θ ≤ 25.10, intensity data were collected at 293(2) K, and employing $\omega/2\theta$ scanning technique, in the range of −10≤ h ≤ 11, −20≤ k ≤ 19, −11≤ l ≤ 14; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2485 observed reflections with R(into) = 0.1026 by a full-matrix least-squares technique converged to R = 0.0784 and Raw = 0.2240 [$I > 2\sigma(I)$].

Ethyl-8c-amino-3-butyl-8b-cyano-2-methyl-8-oxo-3*H*,8*H*-8d-oxa-3-azapentaleno[3a,6a-*a*]indene-1-carboxylate (5d). White crystals: 0.35 g, 90% yield; mp 194−196 °C; ^{1}H NMR (500 MHz, DMSO) δ 0.91 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 6.8 Hz, 3H), 1.32−1.39 (m, 1H), 1.39−1.45 (m, 2H), 1.58−1.65 (m, 1H), 2.27 (s, 3H), 3.50 (t, J = 7.6 Hz, 2H), 4.03−4.10 (m, 1H), 4.14−417 (m, 1H), 7.35 (s, 2H), 7.74 (t, J = 7.2 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.92 (t, J = 7.2 Hz, 1H), 8.01 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 11.9, 13.6, 14.37, 19.40, 31.9, 41.9, 56.0, 67.9, 98.0, 109.0, 118.0, 124.9, 125.0, 131.3, 136.0, 136.3, 143.6, 159.6, 164.8, 167.2, 195.0; IR (KBr) ν 3382, 3317, 2189, 1724, 1638, 1594, 1424, 1324 cm^{-1}; MS m/z 393 (M^+), 350, 322, 304, 248, 235, 164, 125, 111, 97, 83, 69, 57. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.22; H, 6.85; N, 10.66.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, copies of ^{1}H and ^{13}C NMR spectra of products, crystallographic data, and ORTEP/X-ray structure for **3a** and **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(28) Complete crystallographic data for compounds **3b** and **5c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 846789 and 864461. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax: 0044 1223 336 033. E-mail: deposit@ccdc.cam.ac.uk.