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Thermal [3+2] cycloaddition reaction of azomethine imines with allenoates for dinitrogen-fused heterocycles

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ABSTRACT

The thermal [3+2] cycloaddition reactions of two classes of azomethine imines with allenoates have been investigated. The reactions are operationally simple and proceed smoothly under mild reaction conditions to provide a variety of dinitrogen-fused heterocycles in moderate to excellent yields.

1. Introduction

1,3-Dipolar cycloaddition reaction has emerged as one of the most powerful tools for the construction of a variety of heterocycles from simpler starting materials.[1] Various 1,3-dipoles such as nitrone, azomethine ylide, azomethine imine, nitrile oxide, carbonyl ylide, azide, nitrile imine, carbonyl oxide, diazoalkane, and diazoacetate have been used for all kinds of target heterocycles.[1] Among these 1,3-dipoles, azomethine imine is a highly attractive one due to its salient features such as easy preparation, stability, and the potential application of the corresponding cycloadduct.[2] It has been employed as efficient 1,3-dipole in various thermal, metal-catalyzed, and organocatalytic cycloadditions.[2,3] Various dipolarophiles such as alkenes and alkynes could undergo [3+2] cycloaddition with azomethine imines to furnish the useful heterocycles.[2,3] Although the allenes have similar reaction mode as alkenes and alkynes and have been extensively studied in the cycloaddition reactions with numerous 1,3-dipoles,[4] the cycloaddition of allenoates with azomethines has been overlooked for so many years. Most recently, we reported first phosphine-catalyzed [3+2], [3+3], [4+3], and [3+2+3] annulation reactions of allenoates with azomethine imines, providing generally applicable routes toward dinitrogen-fused heterocycles, such as tetrahydropyrazolo-pyrazolone, -pyridazinone, -diazepinone, and -diazocinone,[5] which are key units in or building blocks of many pharmaceuticals, agrochemicals, biologically active compounds, and other useful chemicals.[6] In the study of the phosphine-catalyzed cycloadditions, when the reaction temperature was higher than room temperature, the thermal cycloaddition product was often observed and isolated as side-product. It prompted us to investigate thermal cycloaddition reaction of azomethine imines with allenoates in detail. Herein, we describe first thermal [3+2] cycloaddition of azomethine imines with allenoates to furnish functionalized dinitrogen-fused heterocycles (Scheme 1).

2. Results and discussion

The two classes of azomethine imines, *C,N*-cyclic azomethine imines **1** and *N,N′*-cyclic azomethine imines **2**, were investigated in our research and prepared according to the reported procedure.[3j,m,n,cc,7] We first tried the reaction of *C,N*-cyclic azomethine imine **1a** with the allenoate **2a** in dichloromethane at room temperature. The reaction was sluggish to give the corresponding annulation product as a diastereomeric mixture of **4aa** and **4′aa** in 40% yield, which couldn't be separated by silica gel chromatography (Table 1, entry 1).[8] Using the NMR spectroscopy and X-ray crystallography[9] (Fig. 1), the structures of **4aa** and **4′aa** were established to be [3+2] cycloaddition products, and the product **4aa** was the major

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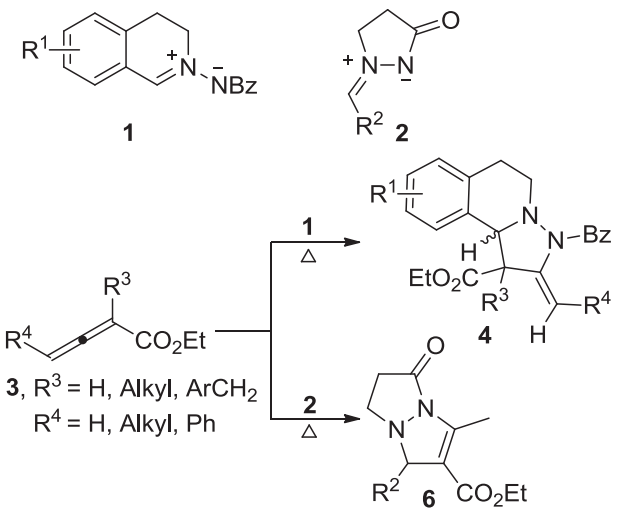
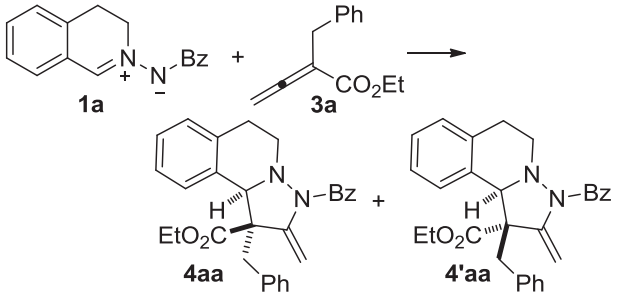


Scheme 1. The thermal [3+2] cycloaddition of azomethine imines with allenoates.

Table 1
The thermal cycloaddition of α-benzyl allenoate **3a** with *C*,*N*-cyclic azomethine imines **1a**[a]



Entry	Temp (°C)	Solvent	Product[b]	Yield[c] (%)
1	25	CH_2Cl_2	**4aa**+**4′aa**	44
2	40	CH_2Cl_2	**4aa**+**4′aa**	65
3	80	$ClCH_2CH_2Cl$	**4aa**+**4′aa**	66
4	80	*i*-PrOH	**4aa**+**4′aa**	86[d]
5	80	Toluene	**4aa**+**4′aa**	79
6	80	DMF	**4aa**+**4′aa**	42

[a] Allenoate (1.2 equiv) was used. The reaction time was 48 h.
[b] The **4aa**/**4′aa** ratios were not determined, except the case in entry 4.
[c] Isolated yields.
[d] The **4aa**/**4′aa** ratio was 90:10, based on integration of signals in the ^{1}H NMR spectrum.

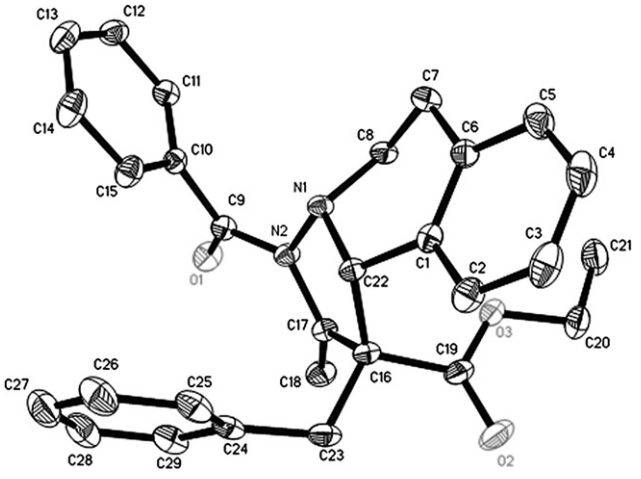
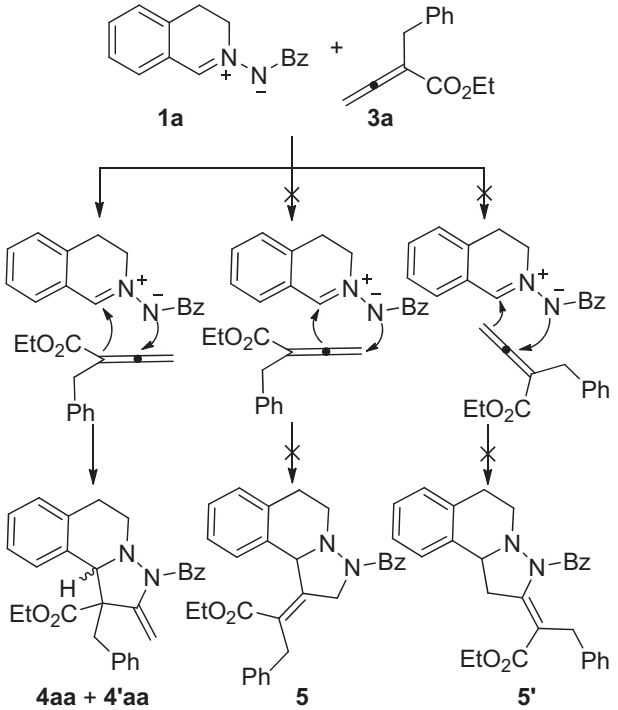


Fig. 1. The X-ray structure of **4aa**.

isomer. Considering the efficiency of thermal cycloaddition reaction depends on the reaction temperature, the temperature was increased to 40 °C from room temperature, and accordingly the yield was improved to 65% (entry 2). Next, the reactions were performed at 80 °C in several high boiling solvents such as 1,2-dichloroethane, isopropanol, toluene, and *N*,*N*-dimethylformamide. In these cases, a significant solvent effect was observed. The isopropanol proved to be the optimal solvent to give 86% yield (entry 4). In contrast, 1,2-dichloroethane and toluene afford 66% and 79% yields, respectively, and *N*,*N*-dimethylformamide only provided poor 42% yield (entries 3, 5, 6).

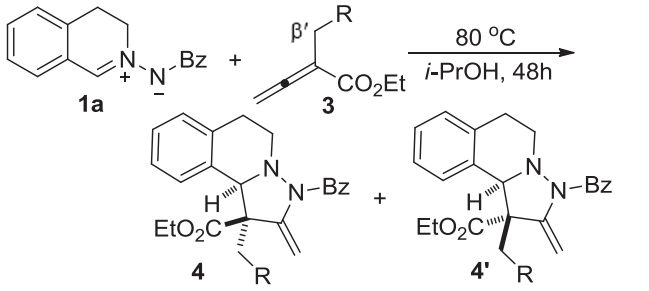
Allenes bear quite useful 1,2-propadiene system. Both C=C bonds are active positions for dipolar attack, which can proceed with two opposite orientations, especially, allenes possessing electron-withdrawing substituents are very active to undergo dipolar cycloaddition. Therefore, the cycloaddition reaction of azomethine imine **1a** with the allenoate **2a** might follow three possible reaction pathways (Scheme 2). However, the cycloaddition product **5** and **5′** hadn't been observed. The cycloaddition reaction of azomethine imine with allenoate was highly regioselective to afford the 2-*exo* methylene isomer as sole regioisomer, which possessed two chiral carbons and was isolated as the diastereomeric mixture (**4aa** and **4′aa**). It is quite interesting that a quaternary carbon center was incorporated into the molecular skeleton of the products **4aa** and **4′aa**.



Scheme 2. The possible reaction pathways of thermal [3+2] cycloaddition of azomethine imines with allenoates.

Under the optimal reaction conditions (in isopropanol at 80 °C), the reactions of a range of distinctly substituted allenoates **3** with the azomethine imine **1a** were carried out for 48 h, giving the derivatives of ethyl 3-benzoyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]*iso*quinoline-1-carboxylate **4** and **4′** as a mixture of diastereomers in moderate to excellent yields with high diastereoselectivity (Table 2). Although the R in allenoate is far away from the reacted double bond, it still exerted certain influence on the course of the reaction. A variety of β′-aryl-substituted allenoates underwent the cycloaddition reaction smoothly, providing the corresponding product in good to excellent yields (entries 1–9).

Table 2
The thermal cycloaddition of α-substituted allenoate **3** with *C*,*N*-cyclic azomethine imine **1a**[a]



Entry	R	Product	Yield[b] (%)	Ratio (**4**/**4′**)[c]
1	Ph (**3a**)	**4aa**+**4′aa**	86	90:10
2	3-ClC_6H_4 (**3b**)	**4ab**+**4′ab**	85	89:11
3	4-ClC_6H_4 (**3c**)	**4ac**+**4′ac**	80	90:10
4	2-BrC_6H_4 (**3d**)	**4ad**+**4′ad**	62	81:19
5	3-BrC_6H_4 (**3e**)	**4ae**+**4′ae**	83	87:13
6	4-BrC_6H_4 (**3f**)	**4af**+**4′af**	93	87:13
7	2-MeC_6H_4 (**3g**)	**4ag**+**4′ag**	84	83:17
8	3-MeC_6H_4 (**3h**)	**4ah**+**4′ah**	87	86:14
9	4-MeC_6H_4 (**3i**)	**4ai**+**4′ai**	91	86:14
10	Vinyl (**3j**)	**4aj**+**4′aj**	48	88:12
11	Styryl (**3k**)	**4ak**+**4′ak**	67	83:17
12	CO_2Et (**3l**)	**4al**+**4′al**	76	88:12
13	H (**3m**)	**4am**+**4′am**	49	88:12
14	Et (**3n**)	**4an**+**4′an**	52	92:8

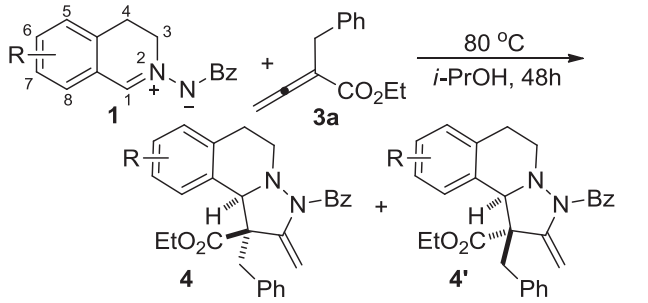
[a] Allenoate (1.2 equiv) was used.
[b] Isolated yields.
[c] Based on integration of signals in the ^{1}H NMR spectrum.

Allenoates featuring aryl groups with electron-withdrawing worked very well as those substrates with electron-donating substituents under otherwise identical conditions. The reaction of β′-styryl- and β′-ethoxycarbonyl-substituted allenoates gave slightly lower yields of the cycloaddition products (entries 11 and 12). In comparison, the reactions of β′-vinyl-, β′-hydrogen-, and β′-ethyl-substituted allenoates were relative sluggish, affording their corresponding products in moderate yields (entries 10, 13, and 14). In all cases, the diastereoselectivities ranged in narrow scope from 81:19 to 92:8. The diastereomeric mixture couldn't be separated by flash silica gel column. In particular, by recrystallizing the mixture in methanol and dichloromethane, the product **4ak** could be obtained as a single diastereomer.

The reactions of several azomethine imines **1** bearing different substituents on the benzene ring with α-benzyl allenoate **3a** also worked efficiently in isopropanol at 80 °C to provide the corresponding [3+2] cycloaddition products in high yields and with uniformly high diastereoselectivities (Table 3, entries 1–5). It seems the substituents on the benzene ring of the azomethine imines **1** didn't essentially influence the reaction process and diastereoselectivity. Electron-donating alkyl substituted imines provided similar yields as those with electron-withdrawing group did (entries 4 and 5 vs entries 1–3).

Besides α-substituted allenoates, γ-substituted allenoates **3o**–**3s** had been studied in the cycloaddition reaction too. Compared with the former, the reactions of γ-substituted allenoates with azomethine imine **1a** were lethargic, affording the corresponding product in moderate to good yield (Table 4). The γ-alkyl-substituted allenoates underwent the reaction to give fair yields of the cycloaddition products (entries 1–3), but the bulky *tert*-butyl resulted in the low 41% yield (entry 4). The reaction of γ-phenyl-substituted allenoate only afforded poor yield of the corresponding product (entry 5). Although a single diastereoisomer **4** was isolated on the basis of NMR and 2D NMR data, it couldn't be excluded that other diastereomer or regiomer hadn't been generated. When the

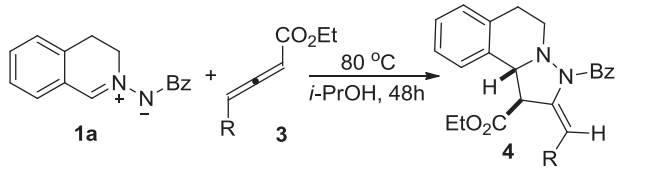
Table 3
The thermal cycloaddition of α-benzyl allenoate **3a** with *C*,*N*-cyclic azomethine imines **1**[a]



Entry	R	Product	Yield[b] (%)	Ratio (**4**/**4′**)[c]
1	7-Cl (**1b**)	**4ba**+**4′ba**	78	85:15
2	7-Br (**1c**)	**4ca**+**4′ca**	77	85:15
3	6-Br (**1d**)	**4da**+**4′da**	80	85:15
4	5-Me (**1e**)	**4ea**+**4′ea**	77	85:15
5	7-Me (**1f**)	**4fa**+**4′fa**	89	85:15

[a] Allenoate (1.2 equiv) was used.
[b] Isolated yields.
[c] Based on integration of signals in the ^{1}H NMR spectrum.

Table 4
The thermal cycloaddition of γ-substituted allenoates **3** with *C*,*N*-cyclic azomethine imine **1a**[a]



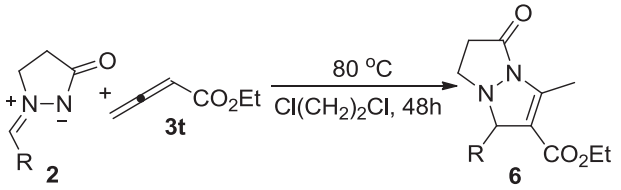
Entry	R	Product	Yield[b] (%)
1	Me (**3o**)	**4ao**	71
2	Et (**3p**)	**4ap**	60
3	*i*-Pr (**3q**)	**4aq**	65
4	*t*-Bu (**3r**)	**4ar**	41
5	Ph (**3s**)	**4as**	35

[a] Allenoate (1.2 equiv) was used.
[b] Isolated yields.

reaction was monitored using TLC, several spots could be observed, but the amount of some products was too small to be isolated.

After the completion of the investigation on the reaction of *C*,*N*-cyclic azomethine imines **1** with allenoates, the reaction of *N*,*N*′-cyclic azomethine imines **2** with allenoates was examined. Compared with the imine **1**, the imine **2** is not very active. Those α-substituted allenoates and γ-substituted allenoates gave complex mixture in the cycloaddition reactions with **2** and most of imines couldn't completely convert even at 110 °C. Only ethyl 2,3-butadienoate (**3t**) could carry out the cycloaddition reaction in 1,2-dichloroethane at 80 °C to give the derivatives of ethyl 3-methyl-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-*a*]pyrazole-2-carboxylate in good to excellent yields (Table 5). The structure of **6** was determined to be a [3+2] cycloaddition product by NMR spectra and the X-ray crystallography[9] (Fig. 2). Interestingly, a remarkable electronic effect related to the stability of [3+2] cycloaddition product was observed. The products from the annulation reaction of aromatic azomethine imines **2** bearing strong electron-withdrawing groups (**2a**–**2c**) were very stable and could be stored at room temperature for a couple of weeks. The phenyl imine and those aromatic imines containing weak electron-withdrawing or electron-donating groups also carried out the annulation reaction with high conversion, but the corresponding products were not very stable and decomposed easily in the solution in 24 h.

Table 5
The thermal cycloaddition of allenoate **3t** with *N*,*N*′-cyclic azomethine imines **2**[a]



Entry	R	Product	Yield[b] (%)
1	2-$NO_2C_6H_4$ (**2a**)	**6at**	73
2	3-$NO_2C_6H_4$ (**2b**)	**6bt**	77
3	4-$NO_2C_6H_4$ (**2c**)	**6ct**	82
4	2-ClC_6H_4 (**2d**)	**6dt**	90
5	2-BrC_6H_4 (**2e**)	**6et**	92

[a] Allenoate (1.2 equiv) was used.
[b] Isolated yield.

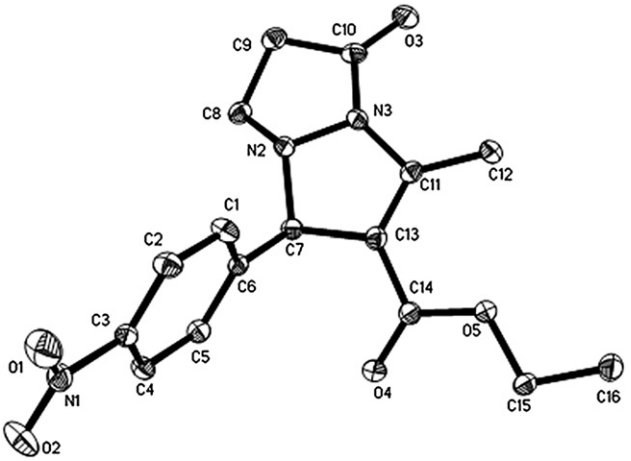


Fig. 2. The X-ray structure of **6ct**.

3. Conclusions

In summary, the thermal [3+2] cycloaddition reactions of two classes of azomethine imines with allenoates have been explored. To the best of our knowledge, this is first time to employ allenoate as dipolarophile in thermal 1,3-dipolar cycloaddition of azomethine imines. The reactions are operationally simple and work efficiently to afford a broad range of dinitrogen-fused heterocycles in moderate to excellent yield.

4. Experimental

4.1. General

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Reactions were monitored through thin-layer chromatography (TLC) on silica gel-precoated glass plates. Chromatograms were visualized by fluorescence quenching under UV light at 254 nm. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (200–300 mesh). Infrared spectra were recorded using a Bruker Optics TENSOR 27 instrument. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker-300 spectrometer. Accurate mass measurements were performed using an Agilent instrument with the ESI-MS technique. X-ray crystallographic data were collected using a Bruker SMART CCD-based diffractometer equipped with a low-temperature apparatus operated at 100 K.

4.2. General procedure for the [3+2] annulations products of azomethine imines and allenoates

A solution of azomethine imine **1** or **2** (0.125 mmol) and the allenoate (0.15 mmol) in 5 mL of solvent (isopropanol for the imine **1**, 1,2-dichloroethane for the imine **2**) was stirred at 80 °C for 48 h and then concentrated. The residue was purified through flash column chromatography (EtOAc/hexane) to afford the corresponding cycloaddition product.

4.3. Characterization data for the [3+2] annulation products 4 and 6

Although some annulation products (**4** and **4′** in Tables 1–3) were the diastereomeric mixture, which couldn't be separated by the flash silica gel column, the NMR signals of the product **4** could be clearly read and picked out from the NMR spectra of the diastereomeric mixture. For the products in Tables 1–3, the IR data and HRMS data were collected by using the diastereomeric mixture of **4** and **4′**.

*4.3.1. Ethyl 3-benzoyl-1-benzyl-2-methylene-1,2,3,5,6,10b-hexahydro-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4aa**).* Yield 86%, a foam-like white solid. IR (neat) ν_{max} 508, 634, 666, 702, 738, 760, 784, 863, 908, 949, 1011, 1046, 1077, 1106, 1200, 1231, 1283, 1340, 1383, 1446, 1454, 1495, 1580, 1602, 1636, 1663, 1728, 2893, 2981, 3027, 3062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.00 (m, 14H), 6.15 (s, 1H), 5.06 (d, J=1.1 Hz, 1H), 4.84 (s, 1H), 3.83–3.44 (m, 5H), 2.78–2.48 (m, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.3, 145.9, 135.8, 135.4, 133.7, 132.6, 131.0, 130.0, 128.5, 128.2, 127.8, 127.4, 127.2, 127.1, 126.0, 125.7, 100.5, 64.9, 61.6, 61.2, 48.5, 44.8, 28.6, 13.3; HRMS (EI) calcd for $C_{29}H_{29}N_2O_3^+$ $[M+H]^+$ 453.2173, found 453.2172.

*4.3.2. Ethyl 3-benzoyl-1-(3-chlorobenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ab**).* Yield 85%, a foam-like white solid. IR (neat) ν_{max} 636, 667, 702, 738, 761, 788, 866, 908, 949, 1012, 1046, 1080, 1104, 1200, 1232, 1283, 1339, 1382, 1428, 1446, 1476, 1495, 1573, 1598, 1663, 1728, 2898, 2989, 3027, 3063 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–6.95 (m, 13H), 6.14 (s, 1H), 5.02 (d, J=1.2 Hz, 1H), 4.78 (s, 1H), 3.81–3.42 (m, 5H), 2.84–2.36 (m, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.2, 145.5, 137.9, 135.1, 134.2, 133.7, 132.2, 131.0, 130.1, 129.7, 129.1, 128.3, 127.8, 127.6, 127.5, 127.3, 127.2, 126.1, 125.7, 101.0, 64.8, 62.2, 61.3, 48.5, 44.4, 28.6, 13.3; HRMS (EI) calcd for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$ 487.1783, found 487.1783.

*4.3.3. Ethyl 3-benzoyl-1-(4-chlorobenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ac**).* Yield 80%, a foam-like white solid. IR (neat) ν_{max} 479, 515, 597, 635, 666, 701, 738, 762, 787, 832, 864, 908, 928, 950, 1015, 1045, 1078, 1096, 1200, 1232, 1283, 1339, 1382, 1446, 1493, 1579, 1600, 1635, 1662, 1728, 2902, 2934, 2980, 3028, 3062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.02 (m, 13H), 6.14 (s, 1H), 5.01 (d, J=1.2 Hz, 1H), 4.75 (s, 1H), 3.83–3.66 (m, 2H), 3.66–3.45 (m, 3H), 2.79–2.55 (m, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.4, 145.5, 135.1, 134.3, 133.7, 133.5, 132.3, 132.2, 130.2, 128.6, 128.5, 128.3, 127.7, 127.52, 127.48, 127.36, 127.2, 126.0, 125.7, 101.0, 64.8, 62.1, 61.3, 48.5, 44.1, 28.6, 13.3; HRMS (EI) calcd for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$ 487.1783, found 487.1783.

*4.3.4. Ethyl 3-benzoyl-1-(2-bromobenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ad**).* Yield

62%, a foam-like white solid. IR (neat) ν_{max} 516, 584, 635, 666, 701, 737, 759, 783, 865, 908, 928, 950, 1030, 1043, 1078, 1105, 1178, 1231, 1266, 1283, 1313, 1336, 1382, 1446, 1471, 1496,1579, 1601, 1635, 1662, 1728, 2900, 2938, 2981, 3060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, J=7.8, 1.5 Hz, 1H), 7.61 (dd, J=8.0, 1.2 Hz, 1H), 7.55–7.27 (m, 3H), 7.25–7.08 (m, 6H), 7.08–6.99 (m, 2H), 6.15 (s, 1H), 5.07 (s, 1H), 4.84 (s, 1H), 4.17 (d, J=14.4 Hz, 1H), 3.80–3.59 (m, 2H), 3.56–3.27 (m, 2H), 3.12–2.44 (m, 3H), 0.73 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.0, 145.9, 135.3, 135.0, 133.7, 132.8, 132.7, 132.4, 130.1, 129.0, 128.3, 128.0, 127.9, 127.7, 127.5, 127.2, 127.1, 126.9, 126.4, 126.0, 100.8, 65.5, 61.9, 61.3, 48.8, 42.9, 28.7, 13.2; HRMS (EI) calcd for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$ 531.1278, found 531.1271.

*4.3.5. Ethyl 3-benzoyl-1-(3-bromobenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ae**).* Yield 83%, a foam-like white solid. IR (neat) ν_{max} 636, 667, 701, 738, 761, 788, 865, 908, 949, 1012, 1046, 1075, 1105, 1200, 1232, 1283, 1339, 1382, 1426, 1446, 1475, 1495, 1567, 1600, 1637, 1663, 1728, 2892, 2981, 3061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.44–7.00 (m, 12H), 6.14 (s, 1H), 5.02 (s, 1H), 4.78 (s, 1H), 3.83–3.41 (m, 5H), 2.82–2.33 (m, 3H), 0.77 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.2, 145.4, 138.2, 135.1, 133.9, 133.7, 132.2, 130.5, 130.1, 130.0, 129.6, 128.3, 127.8, 127.3, 127.2, 126.1, 125.7, 122.4, 101.0, 64.8, 62.2, 61.4, 48.5, 44.3, 28.6, 13.3; HRMS (EI) calcd for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$ 531.1278, found 531.1278.

*4.3.6. Ethyl 3-benzoyl-1-(4-bromobenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4af**).* Yield 93%, a foam-like white solid. IR (neat) ν_{max} 513, 596, 626, 667, 702, 738, 762, 787, 811, 829, 862, 908, 950, 1012, 1044, 1108, 1201, 1231, 1283, 1339, 1383, 1446, 1489, 1579, 1601, 1634, 1661, 1728, 2898, 2981, 3027, 3062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.08 (m, 12H), 7.03 (d, J=5.7 Hz, 1H), 6.12 (s, 1H), 5.00 (d, J=1.2 Hz, 1H), 4.73 (s, 1H), 3.78–3.43 (m, 5H), 2.86–2.43 (m, 3H), 0.75 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.4, 145.5, 135.2, 134.8, 133.7, 132.7, 132.2, 131.5, 130.2, 128.3, 127.7, 127.4, 127.2, 126.0, 125.7, 121.6, 101.0, 64.8, 62.1, 61.3, 48.5, 44.2, 28.6, 13.3; HRMS (EI) calcd for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$ 531.1278, found 531.1271.

*4.3.7. Ethyl 3-benzoyl-1-(2-methylbenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ag**).* Yield 84%, a foam-like white solid. IR (neat) ν_{max} 514.8, 593.8, 636, 666, 701, 738, 784, 866, 908, 951, 1010, 1059, 1077, 1112, 1208, 1230, 1283, 1383, 1446, 1493, 1579, 1602, 1635, 1662, 1728, 2901, 2980, 3026, 3060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J=7.4, 1.5 Hz, 1H), 7.61–6.99 (m, 12H), 6.09 (d, J=0.8 Hz, 1H), 4.95 (d, J=1.2 Hz, 1H), 4.70 (s, 1H), 3.84–3.35 (m, 5H), 2.78–2.56 (m, 3H), 2.48 (d, J=6.3 Hz, 3H), 0.72 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.2, 145.7, 137.6, 135.3, 134.3, 133.8, 132.8, 130.7, 130.6, 130.0, 128.30, 128.26, 127.9, 127.3, 127.2, 127.0, 126.3, 126.0, 125.7, 100.9, 65.4, 62.8, 61.2, 48.6, 40.6, 28.8, 21.0, 13.2; HRMS (EI) calcd for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329.

*4.3.8. Ethyl 3-benzoyl-1-(3-methylbenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ah**).* Yield 87%, a foam-like white solid. IR (neat) ν_{max} 525, 604, 636, 666, 702, 737, 762, 788, 861, 908, 927, 950, 1011, 1046, 1077, 1105, 1178, 1203, 1231, 1266, 1283, 1340, 1383, 1446, 1494, 1580, 1603, 1635, 1663, 1728, 2954, 2980, 3027, 3058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–6.95 (m, 13H), 6.13 (s, 1H), 5.07 (d, J=1.1 Hz, 1H), 4.83 (s, 1H), 3.80–3.66 (m, 2H), 3.56 (dd, J=25.9, 14.0 Hz, 3H), 2.78–2.43 (m, 3H), 2.23 (s, 3H), 0.75 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.2, 146.0, 138.2, 135.7, 135.4, 133.6, 132.6, 131.4, 129.8, 128.31, 128.25, 128.15, 128.1, 128.0, 127.6, 127.4, 127.2, 127.0, 126.0, 125.6, 100.3, 64.8, 61.4, 61.2, 48.5, 44.6, 28.6, 21.2, 13.3; HRMS (EI) calcd for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329.

*4.3.9. Ethyl 3-benzoyl-1-(4-methylbenzyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ai**).* Yield 91%, a foam-like white solid. IR (neat) ν_{max} 494, 521, 598, 633, 667, 701, 737, 762, 787, 817, 864, 908, 950, 1012, 1045, 1077, 1106, 1200, 1231, 1283, 1340, 1383, 1446, 1495, 1515, 1580, 1601, 1634, 1663, 1728, 2953, 2980, 3026, 3057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–6.96 (m, 13H), 6.13 (s, 1H), 5.04 (d, J=1.2 Hz, 1H), 4.83 (s, 1H), 3.80–3.64 (m, 2H), 3.63–3.42 (m, 3H), 2.79–2.46 (m, 3H), 2.23 (s, 3H), 0.75 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 167.4, 146.0, 137.0, 135.4, 133.6, 132.6, 130.8, 129.9, 129.1, 128.2, 127.8, 127.2, 127.0, 126.0, 125.7, 100.3, 64.9, 61.4, 61.2, 48.5, 44.4, 28.6, 20.9, 13.3; HRMS (EI) calcd for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329.

*4.3.10. Ethyl 1-allyl-3-benzoyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4aj**).* Yield 48%, a foam-like white solid. IR (neat) ν_{max} 666, 701, 740, 762, 788, 861, 909, 941, 1027, 1098, 1187, 1232, 1284, 1382, 1447, 1495, 1579, 1601, 1662, 1731, 2901, 2982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 − 7.68 (m, 2H), 7.49 − 7.32 (m, 3H), 7.22 − 7.10 (m, 3H), 7.12 − 7.01 (m, 1H), 6.08 (s, 1H), 5.99 − 5.82 (m, 1H), 5.40 (s, 1H), 5.32 (d, J = 11.5 Hz, 1H), 4.93 (d, J = 1.2 Hz, 1H), 4.80 (s, 1H), 3.78 − 3.53 (m, 3H), 3.14 − 2.71 (m, 4H), 2.65 − 2.53 (m, 1H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.4, 145.3, 135.4, 133.6, 133.0, 132.0, 130.4, 128.4, 128.2, 127.5, 127.2, 126.2, 125.8, 120.8, 99.9, 63.6, 63.2, 61.1, 48.3, 43.9, 28.6, 13.3; HRMS (EI) calcd for $C_{25}H_{27}N_2O_3^+$ $[M+H]^+$ 403.2016, found 403.2023.

*4.3.11. Ethyl 3-benzoyl-1-cinnamyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ak**).* Yield 67%, a foam-like white solid. IR (neat) ν_{max} 637, 667, 699, 739, 762, 788, 861, 925, 1015, 1047, 1104, 1179, 1211, 1230, 1284, 1339, 1365, 1382, 1446, 1495, 1579, 1601, 1638, 1661, 1728, 2898, 2980, 3027, 3066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.54 (m, 1H), 7.44–7.01 (m, 13H), 6.69 (d, J=16.1 Hz, 1H), 6.39–6.21 (m, 1H), 6.07 (s, 1H), 5.01 (d, J=1.1 Hz, 1H), 4.83 (s, 1H), 3.80–3.55 (m, 3H), 3.32–3.03 (m, 2H), 2.95–2.85 (m, 1H), 2.85–2.69 (m, 1H), 2.65–2.52 (m, 1H), 0.78 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.9, 145.5, 136.7, 135.9, 135.4, 133.6, 132.1, 130.2, 128.6, 128.2, 128.1, 127.6, 127.5, 127.3, 126.3, 126.2, 125.9, 124.4, 100.5, 64.0, 63.7, 61.2, 48.3, 43.5, 28.6, 13.4; HRMS (EI) calcd for $C_{31}H_{31}N_2O_3^+$ $[M+H]^+$ 479.2329, found 479.2334.

*4.3.12. Ethyl 3-benzoyl-1-(2-ethoxy-2-oxoethyl)-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4al**).* Yield 76%, a foam-like white solid. IR (neat) ν_{max} 506, 598, 635, 667, 696, 717, 739, 784, 862, 907, 950, 976, 1013, 1028, 1047, 1084, 1105, 1231, 1283, 1338, 1381, 1447, 1495, 1578, 1600, 1662, 1727, 2900, 2981, 3027, 3059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.74 (m, 2H), 7.43–7.28 (m, 3H), 7.19–7.11 (m, 3H), 7.05 (dd, J=7.5, 4.7 Hz, 1H), 6.06 (s, 1H), 5.13 (s, 1H), 5.07 (d, J=1.3 Hz, 1H), 4.25–4.04 (m, 2H), 3.77–3.52 (m, 3H), 3.29 (dd, J=48.0, 16.4 Hz, 2H), 3.01–2.67 (m, 2H), 2.58 (dd, J=16.1, 2.4 Hz, 1H), 1.23 (t, J=7.1 Hz, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.9, 167.7, 145.1, 135.6, 133.6, 131.3, 130.2, 128.5, 128.34, 128.26, 127.52, 127.48, 127.4, 126.6, 125.7, 100.8, 64.8, 61.8, 61.4, 60.9, 48.0, 43.3, 28.5, 14.1, 13.3. HRMS (EI) calcd for $C_{26}H_{29}N_2O_5^+$ $[M+H]^+$ 449.2071, found 449.2070.

*4.3.13. Ethyl 3-benzoyl-1-methyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4am**).* Yield 49%, a foam-like white solid. IR (neat) ν_{max} 668, 701, 739, 764, 788, 862,

908, 954, 1020, 1115, 1179, 1211, 1234, 1283, 1337, 1382, 1446, 1496, 1578, 1601, 1634, 1660, 1728, 2892, 2982, 3027, 3062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92–7.74 (m, 2H), 7.49–7.30 (m, 3H), 7.24–7.02 (m, 4H), 6.05 (s, 1H), 4.86 (d, J=1.2 Hz, 1H), 4.56 (s, 1H), 3.78–3.51 (m, 3H), 2.90–2.70 (m, 2H), 2.64–2.51 (m, 1H), 1.88 (s, 3H), 0.77 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 167.5, 148.3, 135.4, 133.5, 131.6, 130.5, 128.5, 128.3, 127.5, 127.4, 126.3, 125.9, 98.4, 68.5, 61.1, 60.6, 47.7, 28.65, 28.60, 13.4; HRMS (EI) calcd for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$ 377.1860, found 377.1860.

*4.3.14. Ethyl 3-benzoyl-2-methylene-1-propyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4an**).* Yield 52%, a foam-like white solid. IR (neat) ν_{max} 667, 701, 737, 763, 788, 859, 907, 938, 1039, 1112, 1178, 1211,1229, 1282, 1382, 1447, 1494, 1579, 1601, 1660, 1727, 2874, 2961, 3028, 3062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J=8.2, 1.3 Hz, 2H), 7.47–7.30 (m, 3H), 7.22–7.11 (m, 3H), 7.13–7.00 (m, 1H), 6.02 (s, 1H), 4.87 (d, J=0.9 Hz, 1H), 4.71 (s, 1H), 3.72–3.48 (m, 3H), 2.99–2.72 (m, 2H), 2.70–2.54 (m, 1H), 2.23–2.12 (m, 2H), 1.78–1.45 (m, 2H), 1.05 (t, J=7.2 Hz, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 167.2, 145.5, 135.4, 133.5, 132.0, 130.4, 128.4, 128.2, 127.5, 127.2, 126.5, 125.8, 100.1, 64.5, 64.4, 60.9, 48.1, 41.5, 28.6, 17.2, 14.6, 13.3; HRMS (EI) calcd for $C_{25}H_{29}N_2O_3^+$ $[M+H]^+$ 405.2173, found 405.2173.

*4.3.15. trans-(E)-Ethyl 3-benzoyl-2-ethylidene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ao**).* Yield 71%, a foam-like white solid. IR (neat) ν_{max} 730, 1095, 1231, 1346, 1456, 1641, 1662, 1702, 1733, 1811, 2875, 2936 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–7.69 (m, 2H), 7.43–7.27 (m, 3H), 7.24–7.10 (m, 3H), 7.09–6.99 (m, 1H), 6.72 (qd, J=7.2, 2.3 Hz, 1H), 4.90 (d, J=9.3 Hz, 1H), 4.44–4.30 (m, 1H), 3.88–3.58 (m, 3H), 2.95–2.67 (m, 2H), 2.65–2.49 (m, 1H), 1.72 (dd, J=7.2, 1.4 Hz, 3H), 0.90 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 170.7, 167.9, 136.1, 136.0, 134.0, 130.6, 130.0, 128.3, 128.2, 127.43, 127.38, 125.6, 112.6, 61.8, 60.9, 54.1, 47.9, 28.6, 14.5, 13.7; HRMS (EI) calcd for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$ 377.1860, found 377.1860.

*4.3.16. trans-(E)-Ethyl 3-benzoyl-2-propylidene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ap**).* Yield 60%, a foam-like white solid. IR (neat) ν_{max} 620, 633, 664, 698, 761, 787, 858, 918, 961, 990, 1032, 1068, 1097, 1121, 1174, 1232, 1273, 1338, 1368, 1392, 1446, 1456, 1494, 1578, 1601, 1641, 1662, 1733, 2875, 2935, 2965, 3027, 3059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, J=8.3, 6.7 Hz, 2H), 7.44–7.26 (m, 3H), 7.22–7.10 (m, 3H), 7.10–7.00 (m, 1H), 6.66 (td, J=7.7, 2.1 Hz, 1H), 4.90 (d, J=9.3 Hz, 1H), 4.37 (dd, J=9.3, 1.1 Hz, 1H), 3.85–3.58 (m, 3H), 2.94–2.66 (m, 2H), 2.57 (dd, J=16.3, 1.7 Hz, 1H), 2.19–1.91 (m, 2H), 1.05 (t, J=7.5 Hz, 3H), 0.89 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.8, 136.1, 134.6, 134.0, 130.6, 130.0, 128.24, 128.20, 127.41, 127.36, 125.6, 119.5, 61.7, 60.9, 54.1, 47.8, 28.6, 23.1, 13.8, 13.6; HRMS (EI) calcd for $C_{24}H_{27}N_2O_3^+$ $[M+H]^+$ 391.2016, found 391.2017.

*4.3.17. trans-(E)-Ethyl 3-benzoyl-2-(2-methylpropylidene)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4aq**).* Yield 65%, a foam-like white solid. IR (neat) ν_{max} 662, 697, 744, 761, 787, 864, 918, 990, 1030, 1069, 1109, 1174, 1272, 1338, 1366, 1391, 1446, 1577, 1642, 1662, 1735, 2870, 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.71 (m, 2H), 7.44–7.27 (m, 3H), 7.23–7.09 (m, 3H), 7.09–6.96 (m, 1H), 6.54 (dd, J=10.6, 1.9 Hz, 1H), 4.92 (d, J=9.3 Hz, 1H), 4.47–4.29 (m, 1H), 3.90–3.58 (m, 3H), 2.93–2.64 (m, 2H), 2.64–2.46 (m, 1H), 2.35–2.12 (m, 1H), 1.10 (d, J=6.5 Hz, 3H), 0.98 (d, J=6.6 Hz, 3H), 0.88 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 167.7, 136.2, 134.0, 133.1, 130.7, 130.0, 128.3, 128.24, 128.19, 127.40, 127.36, 125.6, 124.7, 61.6, 60.9, 54.0, 47.8, 30.2, 28.6, 23.2, 22.4, 13.6; HRMS (EI) calcd for $C_{25}H_{29}N_2O_3^+$ $[M+H]^+$ 405.2173, found 405.2179.

*4.3.18. trans-(E)-Ethyl 3-benzoyl-2-(2,2-dimethylpropylidene)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ar**).* Yield 41%, a foam-like white solid. IR (neat) ν_{max} 662, 676, 697, 742, 761, 849, 869, 935, 986, 1029, 1086, 1124, 1174, 1211, 1244, 1274, 1336, 1364, 1386, 1427, 1446, 1476, 1579, 1657, 1706, 1733, 2904, 2958, 3027, 3061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.61 (m, 2H), 7.41–7.27 (m, 3H), 7.25–7.09 (m, 3H), 7.09–6.96 (m, 1H), 6.84 (d, J=2.0 Hz, 1H), 4.80 (d, J=9.1 Hz, 1H), 4.45 (dd, J=9.1, 2.1 Hz, 1H), 3.82–3.63 (m, 2H), 3.56 (dq, J=10.8, 7.1 Hz, 1H), 2.89 (ddd, J=10.3, 5.6, 1.7 Hz, 1H), 2.73 (ddd, J=17.7, 12.3, 5.7 Hz, 1H), 2.56 (dd, J=16.5, 2.0 Hz, 1H), 1.14 (s, 9H), 0.85 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 169.0, 136.9, 134.0, 132.0, 130.4, 129.7, 129.05, 129.03, 128.2, 127.8, 127.43, 127.39, 125.3, 62.7, 60.8, 53.1, 47.1, 33.1, 30.3, 28.5, 13.5; HRMS (EI) calcd for $C_{26}H_{31}N_2O_3^+$ $[M+H]^+$ 419.2329, found 419.2334.

*4.3.19. trans-(E)-Ethyl 3-benzoyl-2-benzylidene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4as**).* Yield 35%, a foam-like white solid. IR (neat) ν_{max} 667, 696, 750, 764, 1019, 1179, 1261, 1276, 1364, 1390, 1494, 1661, 1730, 1811, 3006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.75 (m, 3H), 7.46–7.12 (m, 11H), 7.08–7.00 (m, 1H), 4.99 (d, J=9.4 Hz, 1H), 4.75 (dd, J=9.4, 2.3 Hz, 1H), 3.76–3.58 (m, 1H), 3.56–3.32 (m, 2H), 2.99–2.90 (m, 1H), 2.86–2.69 (m, 1H), 2.59 (d, J=15.2 Hz, 1H), 0.73 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 168.1, 136.5, 136.2, 135.9, 133.9, 130.3, 128.5, 128.32, 128.28, 128.24, 127.51, 127.46, 126.7, 125.5, 118.5, 62.4, 60.6, 54.5, 48.0, 28.5, 13.4; HRMS (EI) calcd for $C_{28}H_{27}N_2O_3^+$ $[M+H]^+$ 439.2016, found 439.2016.

*4.3.20. Ethyl 3-benzoyl-1-benzyl-9-chloro-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ba**).* Yield 78%, a foam-like white solid. IR (neat) ν_{max} 510, 635, 666, 702, 736, 760, 787, 816, 866, 908, 929, 946, 1011, 1045, 1097, 1132, 1198, 1228, 1274, 1296, 1332, 1379, 1414, 1446, 1489, 1578, 1601, 1637, 1665, 1729, 2901, 2980, 3027, 3060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H), 7.37–7.07 (m, 10H), 6.97 (d, J=8.1 Hz, 1H), 6.15 (s, 1H), 5.09 (d, J=1.3 Hz, 1H), 4.77 (s, 1H), 3.91–3.75 (m, 2H), 3.67–3.43 (m, 3H), 2.73–2.35 (m, 3H), 0.87 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.3, 145.6, 135.5, 135.2, 134.4, 132.3, 131.7, 131.0, 130.0, 129.5, 128.6, 127.7, 127.6, 127.3, 127.2, 125.7, 100.9, 64.8, 61.4, 48.3, 44.7, 28.2, 13.4; HRMS (EI) calcd for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$ 487.1783, found 487.1783.

*4.3.21. Ethyl 3-benzoyl-1-benzyl-9-bromo-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ca**).* Yield 77%, a foam-like white solid. IR (neat) ν_{max} 510, 621, 645, 667, 702, 736, 760, 785, 813, 845, 865, 908, 927, 945, 1045, 1078, 1108, 1133, 1198, 1228, 1274, 1294, 1331, 1378, 1409, 1446, 1487, 1578, 1600, 1637, 1665, 1728, 2899, 2980, 3027, 3060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.07 (m, 12H), 6.90 (d, J=8.2 Hz, 1H), 6.14 (s, 1H), 5.08 (d, J=1.3 Hz, 1H), 4.76 (d, J=4.4 Hz, 1H), 3.94–3.70 (m, 2H), 3.68–3.41 (m, 3H), 2.73 (ddd, J=9.8, 4.9, 2.3 Hz, 1H), 2.65–2.42 (m, 2H), 0.87 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.3, 145.6, 135.5, 135.2, 134.8, 132.8, 131.0, 130.1, 130.0, 129.8, 128.65, 128.57, 127.7, 127.6, 127.3, 119.5, 100.9, 64.9, 61.45, 61.38, 48.2, 44.7, 28.2, 13.4; HRMS (EI) calcd for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$ 531.1278, found 531.1271.

*4.3.22. Ethyl 3-benzoyl-1-benzyl-8-bromo-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4da**).* Yield 80%, a foam-like white solid. IR (neat) ν_{max} 665, 702, 734, 761, 786, 806, 865, 908, 946, 1013, 1046, 1077, 1111, 1200, 1230, 1278, 1327, 1382, 1446, 1488, 1600, 1664, 1728, 2981, 3028, 3060 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 7.49–6.96 (m, 13H), 6.14 (s, 1H), 5.07 (d, J=1.3 Hz, 1H), 4.76 (s, 1H), 3.88–3.39 (m, 5H), 2.79–2.42 (m, 3H), 0.84 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 167.3, 145.6, 136.1, 135.6, 135.3, 131.7, 131.0, 130.9, 130.1, 129.1, 128.6, 128.3, 127.7, 127.6, 127.3, 120.9, 100.7, 64.8, 61.43, 61.37, 48.1, 44.7, 28.5, 13.4; HRMS (EI) calcd for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$ 531.1278, found 531.1278.

*4.3.23. Ethyl 3-benzoyl-1-benzyl-7-methyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4ea**).* Yield 77%, a foam-like white solid. IR (neat) ν_{max} 512, 619, 653, 667, 702, 735, 767, 787, 864, 909, 928, 973, 1028, 1049, 1078, 1120, 1222, 1236, 1268, 1298, 1336, 1366, 1386, 1446, 1475, 1495, 1580, 1601, 1636, 1662, 1728, 2980, 3028, 3060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–6.98 (m, 13H), 6.18 (s, 1H), 5.09 (d, J=1.1 Hz, 1H), 4.83 (s, 1H), 3.85–3.45 (m, 5H), 2.79 (ddd, J=9.9, 5.7, 1.8 Hz, 1H), 2.62–2.30 (m, 2H), 2.15 (s, 3H), 0.76 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.3, 145.9, 135.82, 135.75, 135.4, 132.4, 132.2, 131.0, 129.9, 128.43, 128.38, 128.33, 127.8, 127.4, 127.2, 125.8, 123.5, 100.7, 64.8, 61.8, 61.2, 48.4, 44.9, 25.9, 19.3, 13.3; HRMS (EI) calcd for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329.

*4.3.24. Ethyl 3-benzoyl-1-benzyl-9-methyl-2-methylene-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4fa**).* Yield 89%, a foam-like white solid. IR (neat) ν_{max} 511, 644, 666, 702, 736, 762,786, 799, 811, 865, 909, 929, 959, 1011, 1046, 1078, 1108, 1161, 1223, 1242, 1281, 1300, 1335, 1380, 1446, 1495, 1508, 1580, 1602, 1636, 1663, 1728, 2935, 2980, 3026, 3059 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.40 (m, 2H), 7.36–7.09 (m, 8H), 7.01–6.88 (m, 3H), 6.14 (s, 1H), 5.06 (d, J=1.1 Hz, 1H), 4.81 (s, 1H), 3.81–3.70 (m, 2H), 3.60 (d, J=2.9 Hz, 2H), 3.56–3.43 (m, 1H), 2.79–2.44 (m, 3H), 2.33 (s, 3H), 0.77 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.3, 146.0, 135.8, 135.5, 135.3, 132.4, 131.0, 130.6, 129.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.4, 127.2, 126.1, 100.4, 64.8, 61.6, 61.2, 48.6, 44.8, 28.2, 21.1, 13.3; HRMS (EI) calcd for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329.

*4.3.25. Ethyl 3-methyl-1-(2-nitrophenyl)-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (**6at**).* Yield 73%, a foam-like yellow solid. IR (neat) ν_{max} 675, 678, 685, 693, 717, 733, 757, 786, 838, 913, 1019, 1063, 1079, 1102, 1136, 1170, 1207, 1229, 1323, 1385, 1527, 1623, 1690, 1723, 2980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J=8.1, 1.0 Hz, 1H), 7.72–7.58 (m, 2H), 7.44 (ddd, J=8.1, 7.2, 1.6 Hz, 1H), 5.73 (d, J=1.3 Hz, 1H), 4.05–3.81 (m, 2H), 3.57 (ddd, J=8.9, 7.9, 2.6 Hz, 1H), 3.28 (ddd, J=11.7, 9.0, 7.5 Hz, 1H), 3.00–2.70 (m, 2H), 2.67 (d, J=1.4 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 163.8, 150.2, 145.0, 135.1, 132.8, 130.4, 128.6, 123.6, 112.1, 67.0, 59.9, 52.1, 36.4, 13.7, 11.2.; HRMS (EI) calcd for $C_{16}H_{17}N_3O_5^+$ $[M]^+$ 331.1163, found 331.1174.

*4.3.26. Ethyl 3-methyl-1-(3-nitrophenyl)-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (**6bt**).* Yield 77%, a foam-like yellow solid. IR (neat) ν_{max} 678, 683, 690, 696, 705, 721, 743, 751, 765, 785, 810, 829, 843, 907, 933, 1020, 1164, 1117, 1171, 1210, 1230, 1326, 1348, 1362, 1385, 1529, 1618, 1689, 1724, 2983 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.37–8.32 (m, 1H), 8.20 (ddd, J=8.2, 2.3, 1.1 Hz, 1H), 7.90–7.79 (m, 1H), 7.59 (t, J=7.9 Hz, 1H), 5.19 (d, J=1.3 Hz, 1H), 4.14–3.89 (m, 2H), 3.48 (td, J=8.0, 1.7 Hz, 1H), 3.20–2.87 (m, 2H), 2.75 (ddd, J=16.3, 6.9, 1.7 Hz, 1H), 2.67 (d, J=1.3 Hz, 3H), 1.09 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 165.4, 164.0, 148.2, 144.4, 143.0, 134.7, 128.9, 123.4, 122.7, 111.8, 73.2, 59.8, 51.8, 36.2, 13.7, 11.0; HRMS (EI) calcd for $C_{16}H_{17}N_3O_5^+$ $[M]^+$ 331.1163, found 331.1172.

*4.3.27. Ethyl 3-methyl-1-(4-nitrophenyl)-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (**6ct**).* Yield 82%, a foam-like yellow solid. IR (neat) ν_{max} 681, 688, 701, 757, 786, 833, 848, 1015, 1063, 1102, 1170, 1209, 1229, 1345, 1362, 1385, 1520, 1619, 1690, 1722, 2927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.7 Hz, 2H), 5.12 (d, J=1.0 Hz, 1H), 4.02 (qq, J=10.9, 7.1 Hz, 2H), 3.49–3.37 (m, 1H), 3.00 (dddd, J=19.9, 16.3, 12.1, 7.6 Hz, 2H), 2.74 (ddd, J=13.1, 7.8, 5.7 Hz, 1H), 2.66 (d, J=1.1 Hz, 3H), 1.08 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.1, 147.7, 147.5, 144.4, 129.3, 123.4, 112.0, 73.3, 60.1, 51.8, 36.3, 14.0, 11.3; HRMS (EI) calcd for $C_{16}H_{17}N_3O_5^+$ $[M]^+$ 331.1163, found 331.1163.

*4.3.28. Ethyl 1-(2-chlorophenyl)-3-methyl-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (**6dt**).* Yield 90%, a foam-like white solid. IR (neat) ν_{max} 675, 681, 686, 711, 719, 728, 743, 763, 788, 841, 914, 949, 1019, 1040, 1064, 1104, 1144, 1171, 1208, 1230, 1324, 1363, 1385, 1443, 1475, 1488, 1548, 1573, 1626, 1708, 2982 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.45–7.14 (m, 4H), 5.68 (d, J=1.3 Hz, 1H), 4.10–3.85 (m, 2H), 3.37–3.23 (m, 1H), 3.15 (ddd, J=10.1, 8.7, 7.8 Hz, 1H), 2.87–2.66 (m, 2H), 2.64 (d, J=1.4 Hz, 3H), 1.01 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 165.5, 164.1, 144.6, 137.1, 134.1, 129.7, 129.3, 129.0, 127.0, 111.9, 68.4, 59.7, 51.2, 36.5, 13.6, 11.0; HRMS (EI) calcd for $C_{16}H_{17}ClN_2O_3^+$ $[M]^+$ 320.0922, found 320.0921.

*4.3.29. Ethyl 1-(2-bromophenyl)-3-methyl-5-oxo-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (**6et**).* Yield 92%, a foam-like white solid. IR (neat) ν_{max} 676, 681, 688, 737, 762, 788, 801, 820, 1023, 1064, 1103, 1171, 1208, 1230, 1323, 1363, 1386, 1441, 1487, 1627, 1708, 2977 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.57 (dd, J=8.0, 1.2 Hz, 1H), 7.42–7.28 (m, 2H), 7.23–6.99 (m, 1H), 5.68 (d, J=1.2 Hz, 1H), 4.12–3.80 (m, 2H), 3.36–3.25 (m, 1H), 3.18 (ddd, J=10.0, 8.7, 7.9 Hz, 1H), 2.87–2.66 (m, 2H), 2.63 (d, J=1.4 Hz, 3H), 1.00 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 165.5, 164.1, 144.6, 138.7, 132.6, 130.0, 129.4, 127.6, 124.5, 112.2, 70.9, 59.7, 51.1, 36.5, 13.6, 11.0; HRMS (EI) calcd for $C_{16}H_{17}BrN_2O_3^+$ $[M]^+$ 364.0417, found 364.0411.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.029.

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9. Crystallographic data for **4aa** and **6ct** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 847231 and 804943. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.