A facile synthesis of β-amino carbonyl compounds through an aza-Michael addition reaction under solvent-free conditions

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General Method

All compounds were fully characterized by spectroscopic techniques. The NMR spectra were recorded on a Bruker-Avance 400 MHz spectrometer (\(^1\)H: 400 MHz, \(^{13}\)C: 100 MHz) with tetramethylsilane (TMS) as the internal standard (δ 0.0 ppm), chemical shifts (δ) are expressed in ppm, and J values are given in Hz. Deuterated CDCl\(_3\) was used as a solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using neutral alumina. The melting points were determined on an XT-4A melting point apparatus and are uncorrected. HRMS was performed on an Agilent LC-MSD TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on neutral alumina.

Preparation of diethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate 1.

Diethyl acetylenedicarboxylate 12 mmol and furan 60 mmol were placed in a sealed tube, which was heated at 100 °C for 20 hours. The reaction mixture was distilled under vacuum. The endoxide was obtained as a light yellow oil.
A schlenk was charged with 1 (0.4 mmol, 95.3 mg), amine 2 (0.8 mmol), and the solution was stirred for 1 minute to 6 days at room temperature until the 1 was completely consumed. The mixture was purified by flash column chromatography. The desired compounds (3a–3j) were formed from 1 in yields: 54-97%.

A Schlenk was charged with diethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate 1 (0.4 mmol, 95.3 mg), amine 2 (0.8 mmol), and the solution was stirred for 1 minute to 6 days at 90 °C until 1 was completely consumed. The mixture was purified by flash column chromatography. The desired compounds 4 were formed from 1 in yields 42-77%.

Synthesis of β-amino carbonyl compounds 3h and 4a
The β-amino carbonyl compound 4a was prepared during the formation of β-amino carbonyl compound 3h. According to experimental results (scheme 1), 4a and 5 can be obtained directly with 42% yield from oxabornene 1 and aniline 2a under room temperature without reagent and catalyst. Also, compound 4a and 5 were obtained from thermal degradation of 3h at 90 °C, identified by spectroscopy.

![Scheme 1. Synthesis of β-amino carbonyl compounds 3h and 4a](image)
Diethyl 2-(phenylamino)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (3h):

Yield 62%; White solid; mp: 107-108 °C; IR (KBr) ($\nu$ max, cm$^{-1}$) 3385, 2974, 2331, 1735, 1604, 1511, 1449, 1377, 1321, 1254, 1062, 1011, 859, 749, 689, 551 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.26-7.16 (2H, m), 6.84-6.80 (4H, m), 6.47-6.46 (1H, dd, $J$ = 5.8, 1.9 Hz), 5.15-5.14 (1H, m), 5.06-5.05 (1H, m), 4.41 (1H, s), 4.20-4.09 (4H, m), 3.19 (1H, d, $J$ = 4.4 Hz), 1.30 (3H, t, $J$ = 7.2 Hz), 1.15 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 169.8, 144.9, 138.3, 132.3, 129.1, 119.5, 115.8, 86.5, 80.6, 72.4, 61.9, 61.2, 58.2, 14.1, 14.0. HRMS (TOF ES$^+$): m/z calcd for C$_{18}$H$_{22}$NO$_5$ [(M+H)$^+$], 332.1492; found, 332.1483.

Diethyl 2-(phenylamino)maleate (4a):

Yield 77%; Yellow oil; IR (KBr) ($\nu$ max, cm$^{-1}$) 3279, 2984, 2344, 1735, 1668, 1607, 1498, 1382, 1274, 1208, 1137, 1039, 861, 755, 693, 553 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.68 (1H, s), 7.30-7.25 (2H, m), 7.11-7.07 (1H, m), 6.92 (2H, d, $J$ = 7.7 Hz), 5.38 (1H, s), 4.22-4.13 (4H, m), 1.30 (3H, t, $J$ = 7.1 Hz), 1.09 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.7, 164.5, 148.5, 140.5, 129.2, 124.3, 121.1, 93.9, 62.2, 60.1, 14.5, 13.7. HRMS (TOF ES$^+$): m/z calcd for C$_{14}$H$_{17}$NO$_4$Na$^+$ [(M+Na)$^+$], 286.1050; found, 286.1055.
$^1$H and $^{13}$C NMR Spectra of Compounds 3a-3k, 4a-4f

Figure 1 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3a

Figure 2 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3a
Figure 3 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3b

Figure 4 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3b
Figure 5 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3c

Figure 6 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3c
**Figure 7** $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3d

**Figure 8** $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3d
Figure 9 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3e

Figure 10 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3e
**Figure 11** $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3f

**Figure 12** $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3f
Figure 13 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3g

Figure 14 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3g
**Figure 15** $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3h

**Figure 16** $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3h
**Figure 17** $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 3i

**Figure 18** $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 3i
Figure 19 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4a

Figure 20 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4a
Figure 21 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4b

Figure 22 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4b
Figure 23 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4c

Figure 24 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4c
Figure 25 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4d

Figure 26 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4d
Figure 27 $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4e

Figure 28 $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4e
**Figure 29** $^1$H NMR (400 MHz, CDCl$_3$) spectra of compound 4f

**Figure 30** $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of compound 4f
References