Synthesis of Functionalized N-Vinyl Nitrogen-Containing Heterocycles

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Abstract: Microwave-assisted 1,3-dipolar cycloaddition of the azomethine ylide generated by ring opening of a N-vinylaziridine gave new N-vinyl derivatives of pyrrolidine, 3-pyrrrole, octahydropyrrolo[3,4-c]pyrrole and 1,2,4-triazolidine.

Key words: microwave-assisted 1,3-dipolar cycloaddition, Michael addition, allenes, N-vinyl heterocycles, aziridines, pyrrolidines, 3-pyrrolines, octahydropyrrolo[3,4-c]pyrroles, 1,2,4-triazolidines

The majority of biologically relevant molecules, namely drugs and natural products, contain nitrogen, justifying the continuous efforts by the scientific community to develop synthetic strategies for structures incorporating this heteroatom. Enamines are particularly interesting building blocks for introducing nitrogen-containing moieties in a synthetic sequence,1,2 and aziridines are valuable, strained small heterocycles of interest in preparative organic synthesis.3,4 In this context, we decided to focus on the synthesis of N-vinyl nitrogen-containing heterocyclic compounds.

Our main objective was to prepare N-vinylaziridines derived from amino esters and to explore their reactivity for the synthesis of other functionalized enamines. Allenoates undergo nucleophilic addition at the electrophilic α,β-carbon–carbon double bond giving Michael-type adducts which undergo migration of the carbon–carbon double bond to afford the more favorable enamine.5,6a Similarly, phosphorylated allenes have been used for the preparation of azaproline derivatives.6b Therefore, following our interest in the chemistry of electron-poor allenes and aziridines, we selected benzyl buta-2,3-dienoate (1) for the reaction with ethyl cis-3-phenylaziridine-2-carboxylate (2),8 in order to prepare a new N-vinylaziridine and to explore its reactivity for the preparation of five-membered ring heterocycles.

The synthesis of β-enamino ester 3 was very easily and efficiently achieved by carrying out the reaction of allene 2 with the aziridine 1 derived from α-amino ester in methanol at room temperature (Scheme 1). The target enamine 3 was obtained in 78% yield. The selective formation of Z-β-enamino esters in the reaction of allenoates with amines has been previously observed.6a In our case, however, we could conclude that the configuration of the enamine double bond was E, based on X-ray crystallographic determination of the structure of adduct 7, which was formed from enamine 3 (see below). Furthermore, in the NOESY spectrum of 3, the methyl protons show connectivity with the aromatic protons of the benzyl group which is in agreement with the assigned configuration.

Scheme 1

Aziridines undergo electrocyclic ring opening in a conrotatory manner upon thermolysis, giving azomethine ylides, which participate in 1,3-dipolar cycloadditions, an important and general route for the construction of five-membered heterocycles.9 Therefore, the reactivity of the N-vinylaziridine 3 as an azomethine ylide percursor was explored.

When the reaction of N-vinylaziridine 3 with dimethyl acetylenedicarboxylate was carried out in refluxing toluene for 6 hours, 3-pyrroline 5 was obtained in 40% yield. We observed that the same 1,3-dipolar cycloadduct was obtained in 75% yield and in a selective way under microwave irradiation at 150 °C for 10 minutes. In fact, the microwave methodology for the conrotatory ring opening of aziridine 3 leading to 1,3-dipole 4 and the subsequent cycloaddition proved to be more efficient than the conventional reaction conditions (Scheme 2). The success of this microwave-assisted 1,3-dipolar cycloaddition led us to further explore these reaction conditions.

The microwave irradiation of a solution of aziridine 3 and N-phenylmaleimide in toluene led to the synthesis of two octahydropyrrolo[3,4-c]pyrrole derivatives 6 (59%) and 7 (29%). Therefore, we could confirm that under microwave irradiation aziridine 3 undergoes ring opening in a conrotatory manner with a preference for the formation of the exo-adduct. It was established that compound 7 results from an endo approach of the dipole and dipolarophile,
whereas octahydropyrrolo[3,4-c]pyrrole 6 is the exo-adduct (Scheme 3).

The structure of ethyl endo-2-[(E)-4-(benzyloxy)-4-oxo-but-2-en-2-yl]-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (7) was determined by X-ray crystallography (Figure 1). There are four chirogenic centres, C1, C3, C3A and C6A, in the molecule. The molecule is comprised of two fused pyrrolidine rings with several substituents. The substituent at C1 is almost perpendicular to the C1–N2–C3–C3A–C6A mean plane; the C7–C1–N2–C3 torsion angle is –90.18(13)°. Across the ring there is a phenyl substituent, orientated towards the opposite face of the ring with a C17–C3–N2–C1 torsion angle of –136.69(11)°. The hydrogen atoms bonded to C3A and C6A are placed on the same face of the C1–N2–C3–C3A–C6A ring. When viewed along the double bond C24–C25, the molecule shows an eclipsed conformation with C23 and C26 almost superimposed.

The microwave-assisted 1,3-dipolar cycloaddition of the in situ generated azomethine ylide 4 in the presence of methyl vinyl ketone led to the regio- and diastereoselective synthesis of pyrrolidine 8 in 70% yield (Scheme 4).

1H and 13C NMR data for pyrrolidine 8 are collected in Table 1 (chemical shifts of the aromatic groups are not included). The assignment was supported by a DEPT spectrum and two-dimensional COSY, NOESY, HMQC and HMBC spectra (400 MHz). In the 13C NMR spectrum, one quaternary carbon was observed at 158.2 ppm, besides the three carbons of the carbonyl groups (C-14, C-6 and C-9) with chemical shifts at 168.2, 172.4 and 204.1 ppm, respectively. From the HMQC spectrum, it was established that the carbon with the chemical shift 28.9 ppm corresponds to a methylene group since it shows connectivity with two protons with different chemical shifts, 2.02 ppm.
and 2.80–2.90 ppm. In the COSY spectrum, the proton with chemical shift at 2.80–2.90 ppm correlates with the geminal proton but also with H-4 and H-2. Correlation of H-5 with H-4 was also observed. In the NOE spectrum, connectivity was observed between H-5 and H-4. In the HMBC spectrum, C-6 (172.4 ppm) shows connectivity with H-3 and H-7. On the other hand, carbon C-9 (204.1 ppm) shows connectivity with H-4, H-3 and H-10.

Table 1

<table>
<thead>
<tr>
<th>Position</th>
<th>1H NMR data δ (ppm)</th>
<th>13C NMR data δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.30 (t, J = 7.2 Hz, 3 H)</td>
<td>14.2 (CH3)</td>
</tr>
<tr>
<td>10</td>
<td>1.95 (s, 3 H)</td>
<td>30.5 (Me)</td>
</tr>
<tr>
<td>3</td>
<td>2.02 (dd, J = 13.6, 6 Hz, 1 H)</td>
<td>2.80–2.90 (m, 1 H)</td>
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<tr>
<td>12</td>
<td>2.29 (s, 3 H)</td>
<td>16.6 (Me)</td>
</tr>
<tr>
<td>4</td>
<td>3.75–3.80 (m, 1 H)</td>
<td>54.7 (CH)</td>
</tr>
<tr>
<td>7</td>
<td>4.16–4.32 (m, 2 H)</td>
<td>61.7 (CH2)</td>
</tr>
<tr>
<td>2</td>
<td>4.61 (br s, 1 H)</td>
<td>60.7 (CH)</td>
</tr>
<tr>
<td>13</td>
<td>4.61 (s, 1 H)</td>
<td>88.5 (CH)</td>
</tr>
<tr>
<td>15</td>
<td>4.97 (br d, J = 12.4 Hz, 1 H)</td>
<td>5.07 (d, J = 12.4 Hz, 1 H)</td>
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<tr>
<td>5</td>
<td>5.42 (br s, 1 H)</td>
<td>64.5 (CH)</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>158.2 (C)</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>168.2 (C)</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>172.4 (C)</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
<td>204.1 (C)</td>
</tr>
</tbody>
</table>

*Chemical shifts of the aromatic groups are not included.

Under microwave irradiation of aziridine 3, the dipole 4 can also be trapped by 1,3-dipolar cycloaddition with heterodipolarophiles. In fact, irradiation of aziridine 3 and diethyl diazene-1,2-dicarboxylate at 150 °C for 10 minutes afforded pentasubstituted 1,2,4-triazolidine 9 in 84% yield (Scheme 5).

A study on the thermal reaction of N-alkenylaziridines, prepared by palladium-catalyzed alkenylation of aziridines with alkenyl bromides, towards dimethyl acetylene-dicarboxylate has been reported; however, a 1:1 mixture of regioisomeric 2-pyrrolines was obtained via formal [3+2] cycloaddition. On the other hand, reaction between N-butyl- and N-aryiaziridines and activated acetylenes occurs with C–N bond cleavage of the aziridine ring instead of the C–C bond cleavage under photoinduced electron-transfer conditions. In conclusion, the stereoselective synthesis of N-vinyl nitrogen-containing heterocycles is reported. Michael addition of an aziridine derivative to benzyl buta-2,3-dienoate afforded the corresponding N-vinylaziridine. Using microwave methodology for the conrotatory ring opening of the aziridine in the presence of dipolarophiles, the synthesis of new 1,3-cycloadducts derived from amino esters, namely N-vinyl derivatives of pyrrolidine, 3-pyrroline, octahydropyrrolo[3,4-c]pyrrole and 1,2,4-triazolidine, was achieved.

1H NMR spectra were recorded on a Bruker Avance III instrument operating at 400 MHz. 13C NMR spectra were recorded on a Bruker Avance III instrument operating at 100 MHz. The solvent was CDCl3. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Mass spectra were recorded on a Bruker FTMS APEXIII instrument under electrospray ionization (ESI) or a HP 6890 Plus instrument under electron impact (EI). Crystallographic measurements were performed on a Bruker Smart APEX CCD diffractometer. Melting points were recorded on a Reichert hot stage apparatus and are uncorrected. Flash column chromatography was performed with Merck 9385 silica gel as the stationary phase.

**Ethyl cis-1-[[(E)-4-(Benzoxazoyl)-4-oxobut-2-en-2-yl]-3-phenylaziridine-2-carboxylate (3)**

Benzyl buta-2,3-dienoate 2 (261 mg, 1.5 mmol) was dissolved in anhyd MeOH (15 mL), which was followed by the dropwise addition of ethyl cis-3-phenylaziridine-2-carboxylate 4 (1:200 mg, 1 mmol). The reaction mixture was stirred for 48 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc–hexane, 1:4; then EtOAc–hexane, 1:3).

Yield: 288 mg (78%); oil.


**GC-MS (EI):** m/z (%): 365 (18) [M]+, 230 (58), 184 (26), 157 (27), 91 (100).

Microwave-Assisted 1,3-Dipolar Cycloaddition; General Procedure
A suspension of aziridine 3 (100 mg, 0.27 mmol) and a dipolarophile (0.40 mmol) in toluene (1 mL) was irradiated in the microwave reactor (CEM Focused Synthesis System, Discover S-Class) for 10 min with the temperature set to 150 °C. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc–hexane, 1:2).

2-Ethyl 3,4-Dimethyl 1-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-5-phenyl-2,5-dihydro-1H-pyrrrole-2,3,4-tricarboxylate (5)
Yield: 103 mg (75%); oil.
IR (film): 1454, 1583, 1693, 1743 cm⁻¹.
¹H NMR: δ = 1.26 (t, J = 7.2 Hz, 3 H), 2.23 (s, 3 H), 3.61 (s, 3 H), 3.82 (s, 3 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.73 (s, 1 H), 4.68 (d, J = 12.8 Hz, 1 H), 5.05 (d, J = 12.8 Hz, 1 H), 5.60 (br s, 1 H), 5.99 (br s, 1 H), 7.18–7.21 (m, 2 H, Ar-H), 7.26–7.31 (m, 8 H, Ar-H).
¹C NMR: δ = 14.1, 16.6, 52.4, 52.7, 62.4, 64.6, 69.5, 70.9, 70.9, 126.8, 127.6, 127.8, 128.3, 128.7, 129.1, 131.2, 137.3, 141.4, 161.9, 162.0, 167.8, 168.2.
LC-MS (ESI): m/z (%) = 508 (42) [M + H⁺], 464 (33), 400 (100), 399 (51).
HRMS (ESI): m/z [M + H⁺] calcld for C₂₈H₂₈NO₈: 508.19714; found: 508.19659.

Ethyl exo- and endo-2-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (6 and 7)
Workup of the reaction mixture by flash chromatography (EtOAc–hexane, 1:2; then EtOAc–hexane, 1:1) gave 6 (higher Rf), followed by 7.

Ethyl exo-2-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (6)
Yield: 85 mg (59%); oil.
IR (film): 1454, 1583, 1693, 1743 cm⁻¹.
¹H NMR: δ = 1.26 (t, J = 7.2 Hz, 3 H), 2.23 (s, 3 H), 3.61 (s, 3 H), 3.82 (s, 3 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.73 (s, 1 H), 4.68 (d, J = 12.8 Hz, 1 H), 5.05 (d, J = 12.8 Hz, 1 H), 5.60 (br s, 1 H), 5.99 (br s, 1 H), 7.18–7.21 (m, 2 H, Ar-H), 7.26–7.31 (m, 8 H, Ar-H).
¹C NMR: δ = 14.1, 16.6, 52.4, 52.7, 62.4, 64.6, 69.5, 70.9, 70.9, 126.8, 127.6, 127.8, 128.3, 128.7, 129.1, 131.2, 137.3, 141.4, 161.9, 162.0, 167.8, 168.2.
LC-MS (ESI): m/z (%) = 508 (42) [M + H⁺], 464 (33), 400 (100), 399 (51).
HRMS (ESI): m/z [M + H⁺] calcld for C₂₈H₂₈NO₈: 508.19714; found: 508.19659.

Triethyl 4-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-5-phenyl-1,2,4-triazolidine-1,2,3-tricarboxylate (9)
Yield: 123 mg (84%); oil.
IR (film): 1130, 1373, 1595, 1725, 1752 cm⁻¹.
¹H NMR: δ = 1.22–1.32 (m, 9 H), 2.37 (s, 3 H), 4.19–4.34 (m, 6 H), 4.66 (s, 1 H), 4.98 (d, J = 12.8 Hz, 1 H), 5.10 (d, J = 12.8 Hz, 1 H), 6.15 (br s, 1 H), 6.67 (br s, 1 H), 7.25–7.33 (m, 10 H, Ar-H).
¹C NMR: δ = 13.9, 14.0, 14.4, 16.7, 62.6, 63.5, 63.7, 64.9, 71.1, 74.2, 91.1, 126.0, 127.8, 128.0, 128.2, 128.4, 128.9, 129.1, 137.0, 137.1, 154.0, 156.4, 167.1, 167.6.
LC-MS (ESI): m/z (%) = 540 (18) [M + H⁺], 276 (100), 204 (24).
HRMS (ESI): m/z [M + H⁺] calcld for C₂₈H₂₈NO₈: 540.23459; found: 540.23404.

1,3-Dipolar Cycloaddition under Conventional Reaction Conditions; General Procedure
A soin of aziridine 3 (130 mg, 0.38 mmol) and a dipolarophile (0.57 mmol) in toluene (5 mL) was heated at reflux for 6–7 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc–hexane, 1:2).

2-Ethyl 3,4-Dimethyl 1-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-5-phenyl-2,5-dihydro-1H-pyrrrole-2,3,4-tricarboxylate (5)
Compound 5 was obtained in 40% yield by this procedure and was identified by comparison with the specimen previously prepared under microwave irradiation.

Ethyl 4-Acetyl-1-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-5-phenylpyrrrolidine-2-carboxylate (8)
Compound 8 was obtained in 30% yield by this procedure and was identified by comparison with the specimen previously prepared under microwave irradiation.

Crystal Data for Ethyl endo-2-[(E)-4-(Benzylxoy)-4-oxobut-2-en-2-yl]-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (7)
C₂₈H₂₈NO₈. M = 538.58, triclinic, P胸, with unit cell, a = 10.1175(2) Å, b = 10.9760(2) Å, c = 16.0279(3) Å, α = 105.902(1)°, β = 107.492(1)°, γ = 96.794(1)°. V = 1593.08(5) Å³. It contains two molecules/unit cell. Dθ = 1.123 g cm⁻³, Z = 2, μ = 0.078 mm⁻¹. R1 = 0.0495 and wR2 = 0.1581 for 8131
independent reflections. H atoms were placed at calculated positions and refined as riding on their parent atoms. The unit cell contains solvent-accessible voids of 265 Å³ each. A difference map revealed a series of electron-density peaks corresponding to EtOAc disordered over several positions. No multipart disorder model could be refined satisfactorily, so the residual electron density was removed using the SQUEEZE routine of PLATON.12

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