A New Synthesis of N-Alkyl 4-Methyl-1,4-dihydropyridines Utilizing sec-Aminodienyl Esters with Crotonaldehyde

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Received October 27, 2000; accepted January 9, 2001

The reactions of sec-aminodienyl esters 3 with crotonaldehyde (4) afforded N-alkyl 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines 5, providing a new azaelectrocyclization reaction.

Key words  aminodienyl ester; primary amine; crotonaldehyde; 1,4-dihydropyridine; azaelectrocyclization reaction

We are interested in the reactivities of the sec-aminodienyl esters 3. The enaminic, dienic, and electronic “push pull” character of these molecules can lead to interesting cyclodisch and azaelectrocyclization reactions, as well as nitrode enamines and aminoacrylates synths.1–4) Previously,1) we reported the cycloaddition reactions of methyl 5-(N,N-dimethylamino)-2,4-pentadienoate (tert-aminodienyl ester 1) with α,β-unsaturated carbonyl compounds and quinones gave aromatic compounds.5–8) We also determined that the reactions of methyl 5-(N-alkylamino)-2,4-pentadienones (sec-aminodienyl esters 3) with acetaldehyde provided 2,3-dihydro-6H-1,3-oxazines, and the reactions of 3 in the presence of propargylaldehyde diethylacetate afforded self-condensation products, 1,4-dihydropyridines, as an unexpected reaction.1,6) Although several reactions using related aminodienyl esters have been reported, their utility and basic reactivity have not been well documented.9–12)

Dihydropyridine derivatives are important for developing drugs and are relatively difficult to be synthesized. At this time, we firstly synthesized designed 1,4-dihydropyridine derivatives utilizing sec-aminodienyl esters 3 with crotonaldehyde (4), which produced the expected reaction. This reaction is a new synthetic method for obtaining 1,4-dihydropyridine derivatives, which is interesting in terms of organic chemistry research and also regarding the biological activity of drugs (hypotensive, anti-inflammatory and mutagenic effects).5–7) The sec-aminodienyl esters 3 were prepared by reactions of the tert-aminodienyl ester 1 with primary amines 2. The reactions of 3 with crotonaldehyde (4) afforded N-alkyl 3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridines 5, providing a new azaelectrocyclization reaction.

The methyl 5-(N-alkylamino)-2,4-pentadienoate derivatives listed in Table 1, sec-aminodienyl esters 3a–f, were selected for investigation (Chart 1). The sec-aminodienyl esters 3 were prepared by the reaction of the tert-aminodienyl ester 1 with the corresponding primary amines, namely, 3,4,5-trimethoxybenzylamine (2a), 4-chlorobenzylamine (2b), 2-(4-chlorophenyl)ethylamine (2c), 2-(2-chlorophenyl)ethylamine (2d), 2-(4-bromophenyl)ethylamine (2e), and 2,4-difluorobenzylamine (2f), respectively, under reflux in tetrahydrofuran (THF) (Table 1).

Previous syntheses of 1,4-dihydropyridines have been reported,6–7) but synthetic methods using the related aminodienyl esters have barely been studied. On the basis of our earlier report on the formation of the product 2,3-dihydro-6H-1,3-oxazines1) by the reaction of sec-aminodienyl esters with acetaldehyde, we attempted to prepare the product 1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethenyl]-4-methyl-1,4-dihydropyridine (5a) by azaelectrocyclization reaction of the sec-aminodienyl ester 3a with crotonaldehyde (4). As expected, the product 5a was obtained in 53% yield by refluxing 3a with crotonaldehyde (4) in xylene.

The structure of 5a was proposed on the basis of the following spectroscopic analyses. The molecular formula of 5a was found to be C20H22N2O5. The 1H-NMR spectrum of 5a showed the presence of aromatic protons at δ 6.40 (2H, s), ethylene protons at δ 4.29 (2H, s), and three methoxy protons at δ 3.84 (3H, s) and 3.85 (6H, s) due to a 3,4,5-trimethoxybenzyl group, methoxy protons at δ 3.72 (3H, s), two olefinic protons at δ 5.62 (1H, d, J=15.3 Hz) and 7.25 (1H, d, J=15.3 Hz) due to (methoxycarbonyl)ethyl group, methoxy protons at δ 3.40 (3H, s) and 3.85 (6H, s) due to 3-(methoxycarbonyl)ethyl group, methoxy protons at δ 3.72 (3H, s), and three methoxy protons at δ 3.84 (3H, s). The IR spectrum of 5a indicated absorption bands at 1720 cm⁻¹ (methoxycarbonyl) and 3400 cm⁻¹ (methoxyl group). The UV spectrum of 5a showed absorption bands at 1720 cm⁻¹ (methoxycarbonyl) and 3400 cm⁻¹ (methoxyl group). The UV spectrum of 5a showed absorption bands at 1720 cm⁻¹ (methoxycarbonyl) and 3400 cm⁻¹ (methoxyl group).
<table>
<thead>
<tr>
<th>Starting amine</th>
<th>R</th>
<th>Reaction time (h)</th>
<th>Reaction product</th>
<th>Yield (%)</th>
<th>Appearance [solvent, mp (°C)]</th>
<th>$^1$H-NMR, δ (ppm)</th>
<th>IR (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td></td>
<td>90</td>
<td>3a</td>
<td>62</td>
<td>Light yellow oil</td>
<td>3.70 (3H, s, –Me), 3.84 (3H, s, –Me), 3.85 (3H, s, –Me), 3.86 (3H, s, –Me), 4.17 (2H, d, $J=5.0$ Hz, methylene H), 5.37 (1H, dd, $J=13.1$, 11.2 Hz, olefinic H), 5.50 (1H, d, $J=14.9$ Hz, olefinic H), 6.50 (2H, s, aromatic H), 6.80 (1H, dd, $J=13.1$, 7.5 Hz, olefinic H), 7.34 (1H, dd, $J=14.9$, 11.2 Hz, olefinic H), [CDCl$_3$]</td>
<td>3370, 1730, 1700, 1695, 1680, 1640, (neat)</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>92</td>
<td>3b</td>
<td>72</td>
<td>Light yellow plates (ether–hexane, 83—84)</td>
<td>3.69 (3H, s, –Me), 4.22 (2H, d, $J=5.5$ Hz, methylene H), 5.31 (1H, dd, $J=13.1$, 11.6 Hz, olefinic H), 5.48 (1H, d, $J=15.0$ Hz, olefinic H), 6.78 (1H, dd, $J=13.1$, 7.6 Hz, olefinic H), 7.22 (2H, d, $J=8.6$ Hz, aromatic H), 7.31 (1H, dd, $J=15.0$, 11.6 Hz, olefinic H), 7.32 (2H, d, $J=8.6$ Hz, aromatic H), [CDCl$_3$], [KBr]</td>
<td>3330, 1730, 1690, 1680, 1630, 1605, (KBr)</td>
</tr>
<tr>
<td>2c</td>
<td></td>
<td>76</td>
<td>3c</td>
<td>63</td>
<td>Light yellow oil</td>
<td>2.84 (2H, t, $J=7.0$ Hz, methylene H), 3.32 (2H, q, $J=7.0$ Hz, methylene H), 3.69 (3H, s, –Me), 5.32 (1H, dd, $J=13.1$, 11.6 Hz, olefinic H), 5.49 (1H, d, $J=15.0$ Hz, olefinic H), 6.67 (1H, dd, $J=13.1$, 7.6 Hz, olefinic H), 7.12 (2H, d, $J=8.5$ Hz, aromatic H), 7.29 (2H, d, $J=8.5$ Hz, aromatic H), 7.31 (1H, dd, $J=15.0$, 11.6 Hz, olefinic H), [CDCl$_3$], [KBr]</td>
<td>3350, 1720, 1695, 1685, 1640, 1610, (neat)</td>
</tr>
<tr>
<td>2d</td>
<td></td>
<td>72</td>
<td>3d</td>
<td>84</td>
<td>Light yellow oil</td>
<td>3.00 (2H, t, $J=7.0$ Hz, methylene H), 3.35 (2H, q, $J=7.0$ Hz, methylene H), 3.68 (3H, s, –Me), 5.34 (1H, dd, $J=13.1$, 11.6 Hz, olefinic H), 5.47 (1H, d, $J=14.7$ Hz, olefinic H), 6.68 (1H, dd, $J=13.1$, 7.9 Hz, olefinic H), 7.23—7.17 (3H, m, aromatic H), 7.32 (1H, dd, $J=14.7$, 11.6 Hz, olefinic H), 7.38—7.36 (1H, m, aromatic H), [CDCl$_3$], [KBr]</td>
<td>3350, 1730, 1690, 1620, 1595, 1540, (neat)</td>
</tr>
<tr>
<td>2e</td>
<td></td>
<td>71</td>
<td>3e</td>
<td>61</td>
<td>Light yellow oil</td>
<td>2.81 (2H, t, $J=6.6$ Hz, methylene H), 3.31 (2H, q, $J=6.6$ Hz, methylene H), 3.69 (3H, s, –Me), 5.30 (1H, dd, $J=13.2$, 11.4 Hz, olefinic H), 5.48 (1H, d, $J=14.7$ Hz, olefinic H), 6.66 (1H, dd, $J=13.2$, 7.7 Hz, olefinic H), 7.05 (2H, d, $J=8.4$ Hz, aromatic H), 7.31 (1H, dd, $J=14.7$, 11.4 Hz, olefinic H), 7.44 (2H, d, $J=8.4$ Hz, aromatic H), [CDCl$_3$], [KBr]</td>
<td>3350, 1730, 1700, 1695, 1685, 1640, (neat)</td>
</tr>
<tr>
<td>2f</td>
<td></td>
<td>86</td>
<td>3f</td>
<td>69</td>
<td>Light yellow plates (ether–hexane, 89—91)</td>
<td>3.68 (3H, s, –Me), 4.25 (2H, d, $J=5.3$ Hz, methylene H), 5.32 (1H, dd, $J=13.0$, 11.4 Hz, olefinic H), 5.48 (1H, d, $J=14.7$ Hz, olefinic H), 7.45—6.63 (5H, m, aromatic H and olefinic H), [CDCl$_3$], [KBr]</td>
<td>3330, 1720, 1690, 1650, 1620, 1595, (KBr)</td>
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</tbody>
</table>

a) All reactions were run in refluxing THF.
Table 2. The Reactions of sec-Aminodienyl Esters 3 with Crotonaldehyde (4)\(^a\)

<table>
<thead>
<tr>
<th>Starting material</th>
<th>R</th>
<th>Reaction product</th>
<th>Yield (%)</th>
<th>(^1)H-NMR, (\delta) (ppm)</th>
<th>IR (cm(^{-1}))</th>
<th>Formula, HR-MS m/z Caled (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td></td>
<td>5a</td>
<td>53</td>
<td>1.13 (3H, (d, J=6.4) Hz, –Me), 3.40 (1H, (q, J=6.4) Hz, methine H), 3.72 (3H, s, –Me), 3.84 (3H, s, –Me), 3.85 (6H, s, –Me), 4.29 (2H, s, methylene H), 4.84 (1H, (dd, J=7.9, 4.9) Hz, olefinic H), 5.62 (1H, (dd, J=7.9, 1.5) Hz, olefinic H), 6.35 (1H, (d, J=0.9) Hz, olefinic H), 6.40 (2H, s, aromatic H), 7.25 (1H, (d, J=15.3) Hz, olefinic H), [CDCl(_3)]</td>
<td>1720, 1690, 1720, 1690, 1610, 1590, (359.1702)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>5b</td>
<td>53</td>
<td>1.11 (3H, (d, J=6.7) Hz, –Me), 3.38 (1H, (q, J=6.7) Hz, methine H), 3.72 (3H, s, –Me), 4.31 (2H, s, methylene H), 4.82 (1H, (dd, J=7.6, 4.9) Hz, olefinic H), 5.62 (1H, (d, J=15.3) Hz, olefinic H), 5.78 (1H, (dd, J=7.6, 1.2) Hz, olefinic H), 6.32 (1H, (d, J=0.9) Hz, olefinic H), 7.14 (2H, (d, J=8.2) Hz, aromatic H), 7.23 (1H, (d, J=15.3) Hz, olefinic H), 7.33 (2H, (d, J=8.5) Hz, aromatic H), [CDCl(_3)]</td>
<td>1720, 1700, 1690, 1700, 1605, 1580, (303.1056)</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td></td>
<td>5c</td>
<td>40</td>
<td>1.06 (3H, (d, J=6.7) Hz, –Me), 2.80 (2H, t, (J=7.0) Hz, methylene H), 3.35 (2H, t, (J=7.0) Hz, methylene H), 3.35 (1H, (q, J=6.7) Hz, methine H), 3.71 (3H, s, –Me), 4.75 (1H, (dd, J=7.9, 4.9) Hz, olefinic H), 5.57 (1H, (d, J=15.3) Hz, olefinic H), 5.68 (1H, (dd, J=7.9, 1.5) Hz, olefinic H), 6.13 (1H, (d, J=0.9) Hz, olefinic H), 7.09 (2H, (d, J=8.2) Hz, aromatic H), 7.17 (1H, (d, J=15.3) Hz, olefinic H), 7.27 (2H, (d, J=8.2) Hz, aromatic H), [CDCl(_3)]</td>
<td>1720, 1690, 1720, 1690, 1605, 1580, (317.1180)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td></td>
<td>5d</td>
<td>41</td>
<td>1.06 (3H, (d, J=6.4) Hz, –Me), 2.97 (2H, t, (J=7.0) Hz, methylene H), 3.34 (1H, (q, J=6.4) Hz, methine H), 3.40 (2H, t, (J=7.0) Hz, methylene H), 3.71 (3H, s, –Me), 4.75 (1H, (dd, J=7.9, 4.9) Hz, olefinic H), 5.56 (1H, (d, J=15.3) Hz, olefinic H), 5.74 (1H, (dd, J=7.9, 1.5) Hz, olefinic H), 6.14 (1H, (d, J=1.2) Hz, olefinic H), 7.17 (1H, (d, J=15.3) Hz, olefinic H), 7.26—7.16 (3H, m, aromatic H), 7.38—7.36 (1H, m, aromatic H), [CDCl(_3)]</td>
<td>1715, 1695, 1720, 1690, 1605, 1580, (317.1165)</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>5e</td>
<td>42</td>
<td>1.06 (3H, (d, J=6.7) Hz, –Me), 2.78 (2H, t, (J=7.0) Hz, methylene H), 3.34 (1H, (q, J=6.7) Hz, methine H), 3.34 (1H, (q, J=6.7) Hz, methine H), 3.71 (3H, s, –Me), 4.75 (1H, (dd, J=7.9, 4.9) Hz, olefinic H), 5.57 (1H, (d, J=15.3) Hz, olefinic H), 5.68 (1H, (dd, J=7.9, 1.5) Hz, olefinic H), 6.13 (1H, (d, J=0.9) Hz, olefinic H), 7.03 (2H, (d, J=8.5) Hz, aromatic H), 7.17 (1H, (d, J=15.3) Hz, olefinic H), 7.42 (2H, (d, J=8.5) Hz, aromatic H), [CDCl(_3)]</td>
<td>1720, 1690, 1720, 1690, 1610, 1580, (361.0752)</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td></td>
<td>5f</td>
<td>49</td>
<td>1.10 (3H, (d, J=6.7) Hz, –Me), 3.36 (1H, (q, J=6.7) Hz, methine H), 3.72 (3H, s, –Me), 4.34 (2H, s, methylene H), 4.82 (1H, (dd, J=7.9, 4.9) Hz, olefinic H), 5.61 (1H, (d, J=15.3) Hz, olefinic H), 5.82 (1H, (dd, J=7.9, 1.5) Hz, olefinic H), 6.34 (1H, (d, J=0.9) Hz, olefinic H), 6.90—6.82 (2H, m, aromatic H), 7.19 (1H, (d, J=8.6) Hz, aromatic H), 7.23 (1H, (d, J=15.3) Hz, olefinic H), [CDCl(_3)]</td>
<td>1720, 1695, 1720, 1685, 1670, (305.1200)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All reactions were run in refluxing xylene for 2 h.
1.13 (3H) and the olefinic proton of a (methoxycarbonyl)-ethenyl group at δ 5.62 (1H), and a cross-peak between the methylene protons of a trimethoxybenzyl group at δ 4.29 (2H) and the 6-olefinic proton at δ 5.83 (1H). Therefore, it may be deduced that 5a is a 4-methyl-1,4-dihydopyridine.

Regarding sec-dienylamine chemistry, we investigated the reactions of nitrodienes with acetaldehyde gave 1,2-dihydopyridine derivatives, and the reactions of aminodienyl esters with crotonaldehyde in affording 1,4-dihydopyridine derivatives. These results have shown that their azaelectrocyclization reactions depend on the nature of the electron-withdrawing group at the terminal position of the sec-dienylamines, which result in changes in the reactive carbon site in the transition state. Their behavior suggests that we could make either 1,2- or 1,4-dihydopyridine derivatives as reaction products depending on the choice of sec-dienylamines. Namely, reagent treatment of sec-dienylamines which have a nitro group would provide 1,2-dihydopyridines, and reagent treatment of sec-dienylamines having a methoxycarbonyl group would yield 1,4-dihydopyridines.

1,4-Dihydopyridine compounds are a product of certain drugs. Drug derivatives containing halogen atoms (ex. Br, Cl, F) have often been known to show strong biological activity. Therefore, we synthesized 1,4-dihydopyridine derivatives having halogenated groups. In a similar manner, several other substituted 3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridines, 5b—f, listed in Table 2, were prepared from the corresponding 3b—f (Chart 1, Table 2).

The 6π-azaelectrocyclization reactions of sec-aaminodienyl esters 3 with crotonaldehyde (4) may be explained as follows. Initially, the condensation reaction of 3 with crotonaldehyde (4) may generate the intermediate 6, followed by intramolecular ring closure with dehydridation, which could lead to 4-methyl-1,4-dihydropyridines 5, as shown in Chart 2.

These results provide a new method of synthesizing N-alkyl 3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridines 5 utilizing sec-aaminodienyl esters 3 with crotonaldehyde (4).

**Experimental**

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-200 spectrometer, and 1H- and 13C-NMR spectra with a JEOL JNM-EX 90 or JEOL JNM-e500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded with a JEOL JMS-D 300 spectrometer. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. NH-DOM 102 (basic 100 Å type silica gel, Fuji Siyusia Chemical, Ltd.) was used for column chromatography and thin layer chromatography (TLC). All runs were carried out under an argon atmosphere.

**General Procedure for Reactions of tert-Aminodienyl Ester 1 with Primary Amines 2** A solution of the tert-aminodienyl ester 1 (233 mg, 1.5 mmol) and an amine 2 (0.5 mmol) in THF (4 ml) was refluxed for an appropriate period until the disappearance of the amine (checked by TLC). The reaction mixture was concentrated under a vacuum, then the residue was subjected to NH silica gel column chromatography with appropriate solvents. The isolated yield of 3 is based on 2. The reaction conditions and properties of the prepared compounds 3 are shown in Table 1.

Methyl 5-[3-(4-chloromethoxy)phenethyl]amino]-2,4-pentadienone (3a) was synthesized by the previously reported method.16


Methyl 5-[2-(4-Chlorophenylethyl)amino]-2,4-pentadienone (3c): Amine 2c: 78 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product 3c: 84 mg. High-resolution EI-MS m/z: Calcd for C14H16BrNO2 (M+): 265.0867. Found: 265.0677.


Methyl 5-[2-(4-Bromophenylethyl)amino]-2,4-pentadienone (3e): Amine 2e: 100 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product 3e: 95 mg. High-resolution EI-MS m/z: Calcd for C14H16BrNO2 (M+): 309.0360. Found: 309.0357.

Methyl 5-[2-(4-Difluorobenzenyl)amino]-2,4-pentadienone (3f): Amine 2f: 72 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product 3f: 87 mg. High-resolution EI-MS m/z: Calcd for C14H16F2NO2 (M+): 253.0915. Found: 253.0942.

General Procedure for Reactions of sec-Aminodienyl Esters 3 with Crotonaldehyde (4) A solution of sec-aaminodienyl esters 3 (0.6035 mmol) and crotonaldehyde (10.0 µl, 0.1207 mmol) in xylene (3 ml) was refluxed for 20 h. The reaction mixture was subjected to NH silica gel column chromatography with appropriate solvents. The properties of the prepared compound 5 are shown in Table 2.

1-[(3,4,5-Trifluorobenzyl)amino]-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5a): Substrate 3a: 185 mg. Solvent for chromatography: 40% ethyl acetate in hexane. Product 5a: 23 mg. 13C-NMR (125 MHz, CDCl3): δ: 23.4, 27.3, 51.1, 56.1, 57.5, 57.5, 60.9, 103.7, 103.7, 107.3, 108.6, 112.6, 127.6, 133.0, 137.5, 138.9, 146.2, 153.6, 153.6, 168.8.

1-(4-Chlorobenzyl)-1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5b): Substrate 3b: 152 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product 5b: 20 mg.

1-(4-Chlorobenzyl)-1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5c): Substrate 3c: 160 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product 5c: 15 mg.

1-(4-Chlorobenzyl)-1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5d): Substrate 3d: 160 mg. Solvent for chromatography: 25% ethyl acetate in hexane. Product 5d: 16 mg.

1-(4-Bromophenyl)-1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5e): Substrate 3e: 187 mg. Solvent for chromatography: 25% ethyl acetate in hexane. Product 5e: 18 mg.

1-(2,4-Difluorobenzyl)-1-(3,4,5-trimethoxybenzyl)-3-[2-(methoxycarbonyl)ethylidene]-4-methyl-1,4-dihydopyridine (5f): Substrate 3f: 153 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product 5f: 18 mg.

**Acknowledgements**

The author is grateful to Mr. T. Nakagomi, Y. Yamaura, and Miss R. Yanagisawa for assisting in part of this study.

**References**
