S₅Ar REACTIONS OF METHYL AND ETHYL 2-NITRO-5-FLUOROBENZOATES IN THE SYNTHESIS OF PYRRO[2,1-c][1,4]BENZODIAZEPINE PRECURSORS

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Abstract: The title reaction was investigated as part of an effective synthesis of pyrrolo[2,1-c][1,4]-benzodiazepines possessing a long alkylamino unit at position 7.

There is growing interest in pyrrolo[2,1-c][1,4]benzodiazepine (PBD) ring systems as synthetic targets and as potential anticancer agents. The PBDs are a class of antitumor antibiotics produced by various actinomycetes which include anthramycin, tomaymycin, neothramycin and DC-81. These compounds can recognize and bind to preferred sequences of double helical DNA and have potential as therapeutic agents in the treatment of certain genetic disorders including some cancers. They appear to exert their biological activity by reacting covalently in the minor groove of DNA to form an aminal linkage between the electrophilic carbinolamine present at the C-11 position and the N2 of guanine. The preferred bonding sequence involves a 5'-PuGPu motif.

Reversible Interactions

Covalent Interactions (PBD)

Scheme 1

In the last few years, various strategies have been proposed for the synthesis of these antibiotics and have met with varying degrees of success while exhibiting significant limitations. In order to alter the DNA-recognition ability and selectivity of PBDs (Scheme 1), it was considered desirable to introduce polyaminoalkyl groups as side-chains at the positions 7 and 9 of the A ring of PBD which is known to interact with DNA reversibly. Our strategy for this purpose is shown as Scheme 2. In this connection, we describe below S₅Ar (nucleophilic aromatic substitution) reaction of alkyl 2-nitro-5-fluorobenzoates.
The straight-chain polyaminoalkanes \(10a-e\) were chosen for the ready availability as side-chains interacting with DNA electrostatically. The amino part of 1,2-diaminoethane \(7a\) or 1,3-diaminopropane \((7b)\) was \(p\)-toluenesulfonylated, metallized, and treated with 2-chloroethanol or 3-chloropropanol, and the diols \(9a-d\) were thereby obtained. Then the diols \(9a-d\) were selectively monobenzylated with dilute benzyl bromide in THF in the presence of sodium hydride, producing the corresponding monobenzylalcohols \(10a-e\) (Scheme 3).

First, the effectiveness of the \(S^1_Ar\) reaction of the esters \(13\), which were obtained by the nitration of 3-fluorobenzoic acid \(11\), followed by esterification, was investigated as a method of introduction of the side-chain. For example, the reaction of the ester \(13b\) with the alcohol \(10a\) readily took place in THF on treating with sodium hydride, giving the product \(14ab\) in 59% yield. Thus, the \(S^1_Ar\) reaction is effective as a method of side-chain introduction (Scheme 4). The use of the alcohol \(10a\) \((n=0, m=1)\), in which the number of methylene groups between the oxygen and the nitrogen atoms is two, gave the \(S^1_Ar\) products \(14aa\) and \(14ab\) almost selectively in both cases of the esters \(13a\) and \(13b\), whereas in the case of \(10b\) \((n=0, m=2)\) in which the methylene-chain is three, the transesterification took place preferentially to give \(15bb\). However, in the cases of \(10c\) \((n=1, m=1)\) and \(10d\) \((n=1, m=2)\), derivatives of
1,3-propanediamine, the $S^\text{Ar}$ products were obtained almost exclusively regardless of the length of methylene-chain between the oxygen and the nitrogen atoms (Table 1). The reason for the difference among these reactions is not clear at present.

Further studies toward the synthesis of conjugated PBD are in progress and will be reported in due course.

**Table 1. $S^\text{Ar}$ and transesterification reactions of 13**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Benzoate</th>
<th>14 (%)</th>
<th>15 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a ($n = 0, m = 1$)</td>
<td>13a</td>
<td>35(14aa)</td>
<td>trace</td>
</tr>
<tr>
<td>a ($n = 0, m = 1$)</td>
<td>13b</td>
<td>59(14ab)</td>
<td>0</td>
</tr>
<tr>
<td>b ($n = 0, m = 2$)</td>
<td>13b</td>
<td>6(14bb)</td>
<td>39(15bb)</td>
</tr>
<tr>
<td>c ($n = 1, m = 1$)</td>
<td>13b</td>
<td>72(14cb)</td>
<td>trace</td>
</tr>
<tr>
<td>d ($n = 1, m = 2$)</td>
<td>13b</td>
<td>65(14db)</td>
<td>---</td>
</tr>
<tr>
<td>e ($n = 1, m = 2$)</td>
<td>13a</td>
<td>45(14ea)</td>
<td>---</td>
</tr>
</tbody>
</table>

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**EXPERIMENTAL**

Experimental details are same as described before.  

1,2-Bis(tosylamino)ethane 8a. To a solution of 1,2-diaminoethane (6.0 g, 0.10 mol) in pyridine (130 ml) was added p-toluenesulfonyl chloride (384 g, 0.20 mol) in small portions over a period of 30 min at 0 °C. The mixture was stirred at 60 °C for 6 h. Then water was added and the precipitate was collected, recrystallized from acetone to afford 8a (27.6 g, 72 %) as colorless needles. mp 164-165 °C (acetone); $^1$H NMR (270 MHz, CDCl$_3$) δ: 2.43 (6H, s), 3.04-3.08 (4H, m), 5.05 (2H, br. s), 7.25-7.74 (8H, m); $^{13}$C NMR (67.8 MHz, CDCl$_3$) δ: 21.5 (q), 43.0 (t), 127.1 (d), 129.8 (d), 136.4 (s), 143.8 (s); IR umax (film): 3286, 1156, 663, 550 cm$^{-1}$. Anal. Calcd for C$_{16}$H$_{20}$O$_2$N$_2$S$_2$: C, 52.16; H, 5.48; N, 7.61. Found: C, 52.33; H, 5.52; N, 7.59.
1,3-Bis(toylamino)propane 8b was prepared in a similar manner in 59% yield as colorless needles; mp 141.0-142.0 °C (ethyl acetate-hexane); 1H NMR (270 MHz, CDCl3) δ: 1.58-1.72 (2H, m), 2.41 (6H, s), 2.99 (4H, q, J = 6.5 Hz), 5.12 (2H, t, J = 6.5 Hz), 7.29 (4H, d, J = 8.1 Hz), 7.72 (4H, d, J = 8.1 Hz); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 29.7, 39.8, 127.0, 129.8, 136.7, 143.5; IR umax (nujol): 3248, 1354, 1341, 1158, 717, 549, 516 cm⁻¹; Anal. Calcd for C17H22O4N3S2: C, 53.39; H, 6.66; N, 5.85. Found: C, 53.39; H, 6.66; N, 5.85.

N,N'-Bisotosyl-1,2-bis(2-hydroxyethylamino)ethane 9a. A General Procedure

To a solution of 8a (13.2 g, 34 mmol) in DMF (80 ml) was added potassium carbonate (23.4 g, 170 mmol), and the mixture was refluxed for 30 min. Then to the mixture was added a solution of 2-chloroethanol (11.6 g, 74.4%) as colorless needles; mp 155-156 °C (ethanol); 1H NMR (270 MHz, CDCl3) δ: 2.44 (6H, s), 2.86 (2H, t, J = 5.0 Hz), 3.41 (4H, s), 3.81 (4H, t, J = 5.0 Hz), 7.31-7.74 (8H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 30.4, 53.1, 61.1, 127.4, 129.9, 135.0, 143.8; IR umax (film): 3354, 1341, 1154, 1086, 811, 566, 548 cm⁻¹; Anal. Calcd for C22H24O6N3S2: C, 55.32; H, 6.66; N, 5.78. Found: C, 54.53; H, 6.60; N, 5.52.

N,N'-Bisotosyl-1,2-bis(3-hydroxypropylamino)ethane 9b was prepared in a similar manner in 59% yield as colorless oil; 1H NMR (270 MHz, CDCl3) δ: 1.70-1.96 (6H, m), 2.43 (6H, s), 5.78 (2H, t, J = 5.4 Hz), 7.24-7.72 (8H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 29.7, 33.4, 46.9, 49.4, 75, 89, 127.2, 129.8, 135.4, 143.6; IR umax (film): 3354, 1341, 1154, 1086, 811, 566, 548 cm⁻¹; Anal. Calcd for C22H24O6N3S2: C, 55.32; H, 6.66; N, 5.78. Found: C, 54.53; H, 6.60; N, 5.52.

N,N'-Bisotosyl-1,2-bis(3-hydroxypropylamino)propane 9c was prepared in a similar manner in 84% yield as colorless oil; 1H NMR (270 MHz, CDCl3) δ: 1.34-3.28 (8H, m), 3.77 (4H, q, J = 5.4 Hz), 7.30-7.72 (8H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 28.9, 52.0, 61.6, 127.2, 129.8, 135.4, 143.6; IR umax (neat): 3450, 1322, 1149 cm⁻¹.

N,N'-Bisotosyl-1,2-bis(2-hydroxyethylamino)propane 9d was prepared in a similar manner in 66% yield as colorless oil; 1H NMR (270 MHz, CDCl3) δ: 1.70-1.96 (6H, m), 2.43 (6H, s), 2.52 (2H, br. s, D2O exchangeable), 3.15 (4H, t, J = 7.4 Hz), 3.21 (4H, t, J = 6.8 Hz), 3.72 (4H, q, J = 5.5 Hz), 7.27-7.70 (8H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 28.9, 31.7, 46.1, 47.5, 59.0, 127.1, 129.8, 135.7, 143.6; IR umax (neat): 3370, 1327, 1148 cm⁻¹.

N,N'-Bisotosyl-1-(2-benzoxoethylamino)-2(2-hydroxyethylamino)ethane 10a. A General Procedure

To a solution of the diol 9a (912 mg, 2.0 mmol) in THF (20 ml) was added 50% sodium hydride (96 mg, 2.0 mmol), and the suspension was refluxed for 30 min. To the mixture was added a solution of benzyl bromide (0.29 mg, 2.4 mmol) in THF (10 ml) at the same temperature, and the mixture refluxed over night. Then water (10 ml) was added to the mixture, and the organic layer was extracted with ethyl acetate (10 ml, 3 times). The combined organic layer was washed with brine (10 ml), and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was further purified by column chromatography on silica gel (30 g) with ethyl acetate and hexane (1:1, v/v) to afford monobenzyl alcohol 10a (792 mg, 72.5% yield) as colorless needles; mp 106-107 °C (Ethyl acetate-Hexane); 1H NMR (270 MHz, CDCl3) δ: 2.19 (1H, br s, -OH), 2.43 (6H, s), 3.13 (2H, t, J = 5.1 Hz), 3.32-3.40 (2H, m), 3.38 (4H, s), 3.63 (4H, J = 5.1 Hz), 4.46 (2H, s), 7.24-7.72 (13H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 49.6, 49.7, 49.9, 52.7, 61.2, 69.4, 73.2, 127.2, 127.3, 127.8, 127.9, 128.4, 129.8, 129.9, 135.4, 135.7, 143.5, 143.6; IR umax (film): 3528, 1340, 1158, 1089, 718, 549 cm⁻¹; Anal. Calcd for C27H49O6N3S2: C, 59.32; H, 6.27; N, 5.12. Found: C, 59.10; H, 6.33; N, 5.07.

N,N'-Bisotosyl-1-(3-benzoxoethylamino)-2(3-hydroxypropylamino)ethane 10b was prepared in a similar manner in 55% yield as colorless needles; mp 111-112 °C (Ethyl acetate-Hexane); 1H NMR (270 MHz, CDCl3) δ: 1.72-1.93 (4H, m), 2.28 (1H, br s), 2.42 (6H, s), 3.18-3.29 (6H, m), 3.50 (2H, t, J = 6.0 Hz), 3.66-3.74 (2H, m), 4.47 (2H, s), 7.25-7.72 (8H, m); 13C NMR (67.8 MHz, CDCl3) δ: 21.5, 29.0, 31.3, 46.8, 47.4, 48.8, 49.1, 58.8, 67.1, 72.9, 127.1, 127.2, 127.6, 127.7, 128.4, 129.8, 129.9, 135.4, 135.6, 138.2, 143.6, 143.7; IR umax (film): 3543, 1341, 1158, 1090, 726, 549 cm⁻¹; Anal. Calcd for C29H40O6N3S2: C, 60.60; H, 6.66; N, 4.87. Found: C, 60.32; H, 6.67; N, 4.86.
N, N'-Blstosyl-1-(2-benzyloxyethylamino)-3(2-hydroxyethylamino)propane 10c was prepared in a similar manner in 50 % yield as a colorless oil; 1H NMR (270 MHz, CDCl3) δ: 1.71-1.92 (6H, m), 2.39 (3H, s), 2.37 (3H, s), 2.62 (1H, br.s), 3.24 (2H, t, J = 5.4 Hz), 3.30-3.58 (6H, m), 3.76 (2H, t, J = 5.4 Hz), 129.2 (Jc,F = 8.5 Hz), 144.3, 164.2 (Jc,F = 258.8 Hz), 168.6; νmax (film): 1715, 1590, 1528, 1438, 1348 cm⁻¹; MS (m/z) : 185 (M⁺), 152, 94; HRMS 185.0125 (M⁺, 185.0124 calcd for C₁₀H₁₇O₅F). Anal. Calcd for C₁₀H₁₇O₅F: C, 61.20; H, 6.85; N, 4.76. Found: C, 61.11; H, 6.82; N, 4.62.

N, N'-Blstosyl-1-(2-benzyloxyethylamino)-2(2-hydroxyethylamino)ethane 10e was prepared in a similar manner in 50 % yield as a colorless oil; 1H NMR (270 MHz, CDCl₃) δ: 1.37 (3H, t, J = 7.3 Hz), 4.41 (2H, q, J = 7.3 Hz), 7.26-7.42 (2H, m), 7.97-8.05 (1H, m); 13C NMR (67.8 MHz, CDCl₃) δ: 13.7, 62.9, 116.9 (JC,F = 25.6 Hz), 113.1 (JC,F = 24.3 Hz), 126.8 (JC,F = 9.7 Hz), 131.1 (JC,F = 8.7 Hz), 143.8, 164.3, 164.4 (JC,F = 258.3 Hz); νmax (film): 1737, 1591, 1537, 1350, 1289, 1215, 1089 cm⁻¹; MS (m/z) : 213 (M⁺), 185, 168 (100%), 152, 94; HRMS 213.0121 (M⁺, 213.0121 calcd for C₁₂H₁₇O₅N₂F).

General Procedure for the S₂Ar Reaction of 13 with 10. A typical example for 14aa. To a solution of the benzyl ether 10a (745 mg, 1.36 mmol) in THF (20 ml) was added sodium hydride (131 mg, 4.09 mmol) in 5 ml of THF. The mixture was allowed to stir for 30 min at room temperature. After addition of water (10 ml), the organic layer was extracted with ethyl acetate (15 ml, 3 times). The combined organic layer was washed with brine (10 ml), dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was further purified by column chromatography on silica gel (30 g) with ethyl acetate/hexane (1:3) as eluent. The product was recrystallized from ethyl acetate/hexane to afford the product in 81 % yield as colorless needles; mp 97-98 °C (ethanol); 1H NMR (270 MHz, CDCl₃) δ: 1.93 (2H, quint, J = 7.0 Hz), 2.41 (3H, s), 2.42 (3H, s), 2.51 (1H, t, J = 5.9 Hz, D2O exchangeable), 3.07-3.16 (4H, m), 3.34 (2H, t, J = 5.4 Hz), 3.62 (2H, t, J = 5.4 Hz), 3.67 (2H, q, J = 5.4 Hz), 4.45 (2H, s), 7.22-7.70 (13H, m); 13C NMR (67.8 MHz, CDCl₃) δ: 21.5, 28.4, 47.4, 48.2, 48.5, 51.9, 61.5, 69.5, 73.2, 127.1, 127.2, 127.7, 128.4, 129.7, 129.8, 135.5, 136.2, 137.7, 143.3, 143.5; IR νmax (neat): 3485, 3300, 1152 cm⁻¹; Anal. Calcd for C₁₀H₁₇O₆N₂S₂F: C, 59.58; H, 6.47; N, 5.00. Found: C, 59.83; H, 6.51; N, 4.85.
SnAr Reactions of methyl and ethyl 2-nitro-5-fluorobenzoates in the synthesis of pyrro[2,1-c][1,4]benzodiazepine precursors

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REFERENCES AND NOTES


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