A New Convergent Synthesis of 4,4'-Bispyridyl-5,5'-Disubstituted-2,2-Bisoxazoles and -Bisthiazoles

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Received 28 May 2003; revised 26 June 2003

Abstract: A convergent strategy for the synthesis of 4,4'-bispyridyl-5,5'-disubstituted-2,2'-bisoxazoles and -bisthiazoles from diamides has been achieved.

Key words: heterocycles, amides, oxazoles, thiazoles, fluorine

In recent years oxazole and thiazole moieties have been of great interest in the field of organic synthesis as the core of complex biologically active molecules.1 As a part of our work related to the development of new antitumor agents, we became interested in the synthesis of 2,2'-bisoxazoles and -bisthiazoles, molecules structurally related to hemicolinium after quaternization of the pyridine nitrogen, which has a potent in vitro activity against HT-29 carcinoma cells.2 Thus, 5,5'-disubstituted-2,2'-bisoxazoles 1 and 2,2'-bisthiazoles 2, molecules structurally related to hemicolinium after quaternization of the pyridine nitrogen, have been extended to the preparation of polymers with a 2,2'-bisoxazole structure.10 In this paper, we wish to report our preliminary studies on the conversion of symmetrical diamides into 4,4'-bispyridyl-5,5'-disubstituted-2,2'-bisoxazoles 1 and -bisthiazoles 2 using a convergent strategy. We devised two synthetic pathways, described in Scheme 1.

Method A explores a synthetic strategy related to the one described by Braña et al. to obtain 5-alkyl-2-aryl-4-pyridoxazoles.11 Acylation of 4-aminomethylpyridine with different acylating agents, either carboxylic diacids in the presence of a condensation reagent or acid chlorides,12 lead to a series of N,N'-bis(4-pyridylmethylene)di-amides 4 with different spacers Z, both alkylic and aryllic. Then, when diamides 4 were treated with ethyl chloroformate and triethylamine in acetone, N,N'-bis(1-ethoxycarbonyl-1,4-dihydropyridylmethylene)diamides 5 were obtained as non-soluble products containing triethylammonium hydrochloride (a 1:5 relationship according to 1H NMR).13 Although free anhydrobases 5 could be purified and characterized,14 nucleophilic addition–cyclization was always accomplished by refluxing non-purified anhydrobases 5 with acetic anhydride using SnCl4 as catalyst. In this way, 5,5'-dimethyl-4,4'-bispyridyl-2,2'-bisox-

Reaction of 4,4'-bis(trifluoromethyl)-substituted hetero-1,3-dienes with tin(II) chloride provided 4,4'-bis(trifluoromethyl)-5,5'-difluor-2,2'-bisoxazoles and their corresponding thiazoles in low yields.8 A series of symmetrical 5,5'-bisoxazoles were synthesized by nucleophilic substitution of 5-fluoroxazoles with binucleophiles.9 This methodology has been extended to the preparation of polymers with a 2,2'-bisoxazole structure.12

Figure 1

Scheme 1.
azoles 1a–e were obtained in moderate to excellent yields (32–100%) (Table 1).

At this point our interest focussed on the preparation of 5,5'-bistrifluoromethyl- and 5,5'-bisperfluoroalkylbisoxazoles. It has been reported that perfluoroalkyl substituted derivatives sometimes exhibit advantageous chemical and physical properties compared to those of the corresponding alkyl compounds, as well as an ability to enhance biological activities.15 This behaviour has raised interest in the development of methodologies towards their synthesis. Nevertheless, the synthesis of 5-perfluoroalkylbisoxazoles scarcely appears in the literature. One example is the obtention of 5-trifluoromethylbisoxazoles when N-acyl-prolines and N-acyl-N-benzyl-α-amino acids were treated with trifluoroacetic anhydride.16

First, method A was applied by refluxing anhydrobases 5 with trifluoroacetic anhydride but, even increasing reaction times and/or reaction temperatures (different solvents were used), starting material was always recovered. A new synthetic strategy seemed to be required. Then, method B was devised and we obtained 5,5'-bistrifluoromethylbisoxazoles 1i–j, 5,5'-bispentafluoroethylbisoxazole 1k, and 5,5'-bisheptafluoropropylbisoxazole 1l in low to excellent yields (20–98%) by treating diamide 4a with the corresponding perfluoroalkyl anhydride and pyridine in anhyd toluene as solvent (Table 2).

As it has been previously mentioned, we were also interested in 2,2'-bisthiazoles as potential anticancer agents, and we planned to extend our methodology by reaction of thioamides with anhydrides (Scheme 1).

Thus, reaction of diamides 4 with Lawesson’s reagent (anisyldithiophosphine anhydride) in boiling tetrahydrofuran gave the corresponding dithioamides 6 in quantitative yields.17 When dithioamides 6 were reacted with fluorinated anhydrides in anhyd toluene in the presence of pyridine, 5,5'-bisthiazoles 2 were obtained in low to moderate yields (20–52%) (Table 3).

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Table 1  5,5'-Dimethylbisoxazoles 1a–e

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Z</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>1a</td>
<td>CH₃-C-CH₃</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>p-biphenyl</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>p-phenyl</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>CH₂CH₂</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>–</td>
<td>47</td>
</tr>
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</table>

Method A: Pyridine, (RCO)₂O, (R = CF₃, CF₃CF₂, CF₃CF₂CF₂); Method B: SnCl₄, (RCO)₂O, (R = CH₃)
To a stirred solution of the diamide 1 (1 mmol) in acetic anhydride (10 mL), kept under argon atmosphere, a solution of tin tetrachloride (0.6 mL, 1 M in CH₂Cl₂, 0.6 mmol) was added dropwise. The mixture was refluxed for 4 h and then the solvent was evaporated under reduced pressure. Cooled H₂O was added (3 mL) and when solid, the residue was filtered off and successively washed with aq NaHCO₃ (5%), H₂O and acetone. The obtained crude containing the 5,5'-dimethyl bisoxazole as main product and it was always used without a further purification.

Table 3 5,5'-Perfluoroalkyl Bisthiazoles 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Z</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>2a</td>
<td>CF₃</td>
<td>Me,C</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>CF₃</td>
<td>p-biphenylene</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>CF₃</td>
<td>p,p'-phenylenoxyphenylene</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>CF₃</td>
<td>p-phenyl</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>CF₃</td>
<td>p,p'-Ph(CF₃)₂Ph</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>CF₃CF₂</td>
<td>p-biphenylene</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>CF₃CF₂</td>
<td>p-phenyl</td>
<td>21</td>
</tr>
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</table>

In summary, in this work we have described a short and convergent new methodology to the synthesis of symmetric 5,5'-disubstituted bisoxazoles and bisthiazoles with a 2,2'-linkage but restricted to 4,4'-pyridyl substituents. Moreover, in a one-pot reaction the two heterocyclic rings are simultaneously constructed from easily available amides or anhydrides. Studies towards improving the accessibility of other substituents at position 5 of the heterocyclic ring are now under way.

The 1H and 13C NMR spectra were recorded on a Bruker AC 300 spectrometer with Me3Si as internal standard. IR spectra were taken on a Perkin–Elmer 1330 spectrometer. For purification of crude reaction mixtures by flash chromatography, Merck silica gel (230–240 mesh) was used as the stationary phase. Identification of products was made by analytical TLC (Merck Kieselgel 60F-254), UV light (λ = 254 mm). Reagents and solvents were handled by using standard syringe techniques. Lawesson reagent, CICO-Et, Et3N, pyridine, SnCl₄ and fluorinated anhydrides were obtained from Aldrich Chemical Co. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. Analyses indicated by the symbols of the element were within ±0.4% of theoretical values.

5,5'-Dimethyl Bisoxazoles 1a–e; Typical Procedure

To a stirred solution of the anhydride 5 (1 mmol) in acetic anhydride (10 mL), kept under argon atmosphere, a solution of tin tetrachloride (0.6 mL, 1 M in CH₂Cl₂, 0.6 mmol) was added dropwise. The mixture was refluxed for 4 h and then the solvent was evaporated.
added and the crude product was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed (brine) and dried (Na$_2$SO$_4$). The solvent was evaporated and purification was accomplished by flash column chromatography (silica gel; EtOAc–hexane, 9:1).

### 2,2'-Bis[5-trifluoromethyl-4-(4-pyridyl)oxazolyl]propane (1f)

IR (KBr): 3447, 2928, 2360, 1653, 1648, 1456 cm$^{-1}$.

H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 7.77 (d, 4 H, $J = 6.0$ Hz, Ph), 7.71 (d, 4 H, $J = 5.5$ Hz, Pyr), 7.21 (d, 4 H, $J = 4.8$ Hz, Ph).

13C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 119.3, 122.3, 122.4, 122.5, 122.6, 122.7, 122.8, 122.9, 124.7, 127.8, 127.9, 135.3, 136.7, 140.0, 143.1, 150.3, 161.7.

Anal. Calcd for C$_{30}$H$_{16}$F$_6$N$_4$O$_2$: C, 62.04; H, 2.78; N, 9.65.

### 4,4'-Bis[5-trifluoromethyl-4-(4-pyridyl)oxazolyl]biphenyl (1g)

IR (KBr): 3447, 2925, 2360, 1653, 1635, 1608, 1588, 1559, 1540, 1457, 1418 cm$^{-1}$.

H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 8.77 (s, 4 H, Pyr), 8.19 (d, 4 H, $J = 8.8$ Hz, Ph), 7.71 (d, 4 H, $J = 5.5$ Hz, Pyr), 7.21 (d, 4 H, $J = 8.8$ Hz, Ph).

13C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 112.1, 116.7, 120.2, 126.1, 136.0, 137.4, 142.8, 146.4, 146.6, 146.7, 165.8.

Anal. Calcd for C$_{60}$H$_{36}$O$_2$: C, 64.04; H, 2.78; N, 9.65.

### 4,4'-Bis[5-trifluoromethyl-4-(4-pyridyl)oxazolyl]oxybisphenyl (1h)

IR (KBr): 3435, 2925, 2360, 1653, 1635, 1608, 1588, 1559, 1540, 1457, 1418 cm$^{-1}$.

H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 8.77 (s, 4 H, Pyr), 8.19 (d, 4 H, $J = 8.8$ Hz, Ph), 7.71 (d, 4 H, $J = 5.5$ Hz, Pyr), 7.21 (d, 4 H, $J = 8.8$ Hz, Ph).

13C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 112.1, 116.7, 120.2, 126.1, 136.0, 137.4, 142.8, 146.4, 146.6, 146.7, 165.8.

Anal. Calcd for C$_{60}$H$_{36}$O$_2$: C, 64.04; H, 2.78; N, 9.65.

### 1,4-Bis[5-trifluoromethyl-4-(4-pyridyl)oxazolyl]benzene (1i)

IR (KBr): 3436, 1625, 1591, 1549, 1497, 1415 cm$^{-1}$.

H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.7 (d, 4 H, $J = 4.9$ Hz, Ph), 8.3 (s, 4 H, Ph), 8.8 (d, 4 H, $J = 4.9$ Hz, Pyr).

13C NMR (75 MHz, CDCl$_3$): $\delta$ = 119.3, 122.1, 122.4, 127.7, 128.4, 135.8, 136.8, 140.2, 140.3, 150.4, 169.9.

Anal. Calcd for C$_{26}$H$_{16}$F$_6$N$_4$: C, 54.30; H, 2.20; N, 7.67.

### 2,2'-Bis[5-trifluoromethyl-4-(4-pyridyl)oxazolyl]hexafluoropropane (1j)

IR (KBr): 3436, 1675, 1618, 1599, 1551, 1506, 1420 cm$^{-1}$.

H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 8.78 (d, 4 H, $J = 5.49$ Hz, Pyr), 8.26 (d, 4 H, $J = 8.52$ Hz, Ph), 7.70 (d, 4 H, $J = 5.49$ Hz, Ph), 7.64 (d, 4 H, $J = 8.55$ Hz, Ph).

13C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 120.9, 122.4, 126.2, 127.6, 130.8, 135.4, 135.8, 140.0, 150.6, 160.8.

Anal. Calcd for C$_{30}$H$_{16}$F$_6$N$_4$: C, 54.41; H, 2.21; N, 7.69. Found: C, 54.30; H, 2.20; N, 7.67.
1H NMR (300 MHz, DMSO-d6): δ = 7.66 (d, 4 H, J = 8.5 Hz, Ph), 7.71 (d, 4 H, J = 6.1 Hz, Pyr), 8.27 (d, 4 H, J = 8.5 Hz, Ph), 8.79 (d, 4 H, J = 6.1 Hz, Pyr).

13C NMR (75 MHz, DMSO-d6): δ = 47.8, 54.4, 116.9, 118.0, 120.4, 121.9, 122.0, 125.7, 127.1, 130.3, 134.9, 135.3, 139.5, 149.9, 150.0, 150.1, 160.3.

Anal. Calcd for C32H16F10N4S2: C, 54.09; H, 2.27; N, 7.88. Found: C, 54.02; H, 2.27; N, 7.88.

13C NMR (75 MHz, CDCl3): δ = 156.8, 150.2, 143.2, 142.5, 137.0, 134.5, 128.6, 128.5, 122.0, 118.0, 109.3.

IR (KBr): 3304, 2979, 2945, 2604, 2497, 1713, 1678, 1634, 1610, 1565, 1477, 1456 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 1.45 (s, 6 H, CH₃), 4.50 (d, 4 H, J = 5.5 Hz, CH₂), 7.77 (d, 2 H, J = 5.5 Hz, Pyr), 8.58 (t, 2 H, J = 5.5 Hz, NH). Anal. Calcd for C₂₃H₂₈N₄O₆: C, 60.52; H, 6.15; N, 12.22.

Acknowledgement

Support for this work from CAM (Comunidad Autónoma de Madrid. Grant 08.1/0045/298) is acknowledged. One of us (B.S.) thanks CAM for a post-doctoral grant.

References


(13) See experimental for typical procedure for the synthesis of anhydroses 5.

(14) See experimental for representative example of analytical data of compounds 5.


(17) See experimental for preparation of dithioamides 6, and representative example of analytical data.