Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 7515–7520

TETRAHEDRON

Smiles rearrangement for the synthesis of 5-amino-substituted [1]benzothieno[2,3-*b*]pyridine

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Received 11 April 2003; revised 3 July 2003; accepted 25 July 2003

Abstract—The Smiles rearrangement was successfully applied to 4-hydroxybenzo[*b*]thiophene furnishing a facile entry to the 4-amino derivative. The rearrangement was extended to 5-methoxy-4-methoxycarbonyl[1]benzothieno[2,3-*b*]pyridine obtained via aza-Wittig/electrocyclization reaction of novel *N*-(4-methoxybenzothiophen-2-yl)iminomethyldiphenylphosphorane with methyl *trans*-4-oxo-2-pentenoate. The preparation of a novel 5-amino-4-methoxycarbonyl[1]benzothieno[2,3-*b*]pyridine, which is of interest as a potential secondary peptide structure mimic, was successfully achieved.

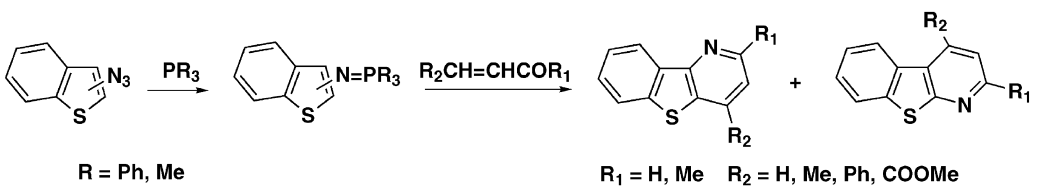
1. Introduction

The direct conversion of phenols into anilines represents an intriguing organic reaction and there are few reports in the literature concerning this subject.[1] An interesting solution for this conversion is the Smiles rearrangement of 2-aryloxy-2-methylpropanamides, normally performed in dioxane in the presence of a base.[2]

This procedure is usually applicable to aromatic compounds bearing electron-withdrawing substituents. For aromatic substrates deactivated to nucleophilic substitution, the alternative use of a 10:1 mixture of *N*,*N*-dimethylformamide and *N*,*N*′-dimethyl-*N*,*N*′-propylen-urea [DMPU; 1,3-dimethyltetrahydropyrimidin-2-(1*H*)-one] has been recommended.[3] To the best of our knowledge such Smiles rearrangement has never been applied to heteroaromatic compounds, except in the case of 4-hydroxybenzo(*b*)thiophene.[2] However, in a recent study, the conversion of phenols to ethers via aryloxy-2-methylpropanoic acids has been replaced by a simpler procedure which has not yet been applied to a benzothiophene substrate.[3,4] In the present study we became interested in applying this new procedure to model 4-hydroxybenzo(*b*)thiophene and then to a particularly hindered 5-methoxy-substituted(1)benzothieno(2,3-*b*)pyridine.

Benzothienopyridines represent a class of interesting tricyclic compounds with reported pharmacological activity such as antiallergic,[5] antibacterial,[6] or as anxioselective agents[7] without undesired side-effects typical of classical benzodiazepines such as diazepam. We have recently reported a new methodology[8–10] to furnish [1]benzothieno[2,3-*b*]pyridines, as well as [1]benzothieno[3,2-*b*]-pyridines in acceptable yields, using the aza-Wittig/electrocyclization reaction of *N*-2-(and *N*-3)-benzothienyliminophosphoranes with α,β-unsaturated aldehydes and ketones (Scheme 1).

Here we report our successful preparation of a novel 5-amino-4-methoxycarbonyl-substituted [1]benzothieno[2,3-*b*]pyridine derivative by means of the Smiles rearrangement of the corresponding 5-methoxy derivative which in turn became available by the tandem aza Wittig/electrocyclization reaction



Scheme 1.

Keywords: Smiles rearrangement; heterocyclic rings; aza Wittig reaction; aminobenzothienopyridine.
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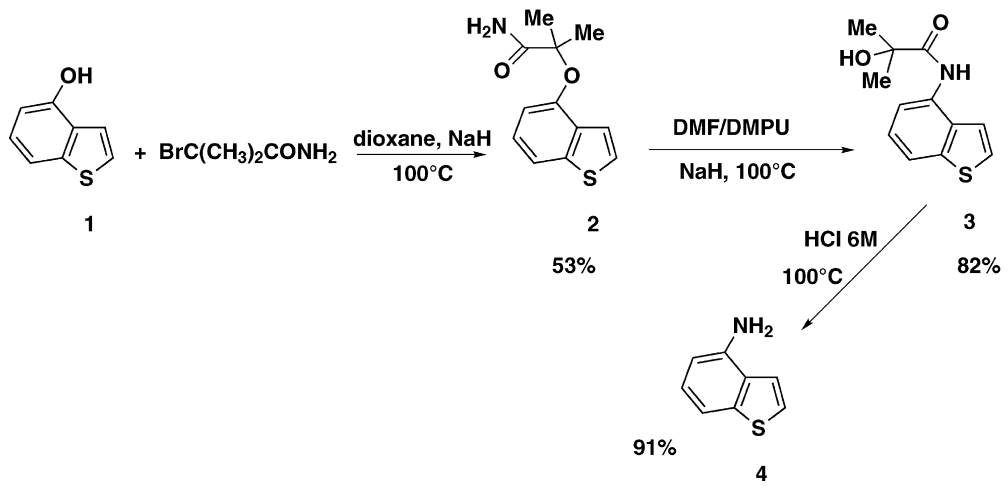
doi:10.1016/S0040-4020(03)01177-3



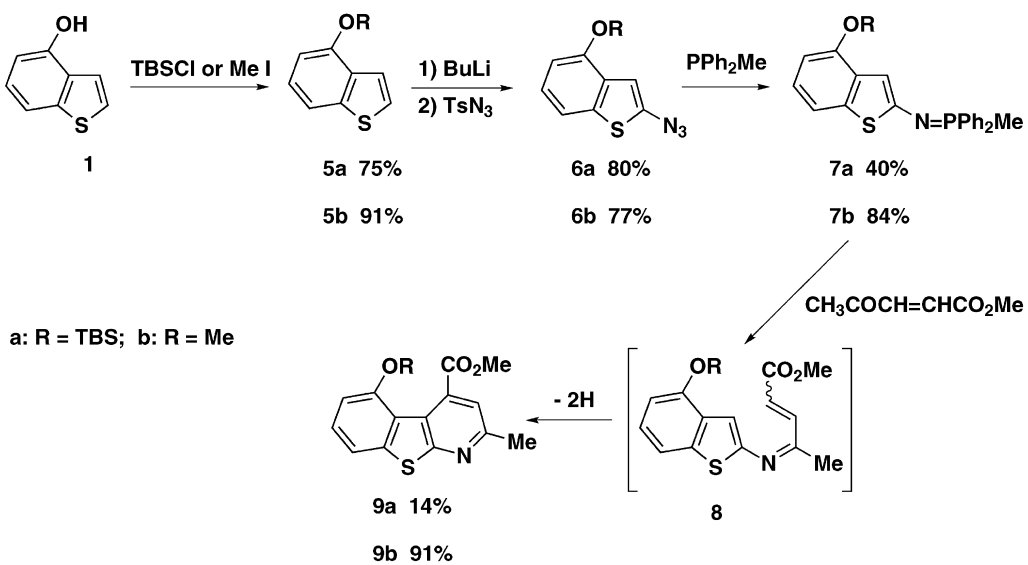
Scheme 2.

of *N*-(4-methoxybenzothiophen-2-yl)iminomethyldiphenylphosphorane with methyl *trans*-4-oxo-2-pentenoate. This kind of aminobenzothienopyridine appears of particular interest since, in principle, it might behave like a turn of a secondary peptide structure due to the presence of both methoxycarbonyl and amino substituents in the appropriate 4- and 5-positions.[11] Furthermore, [1]benzothieno[2,3-*b*]pyridines bearing a substituent in the benzene moiety have only been prepared in low yields or in a multistep sequence.[6,12]

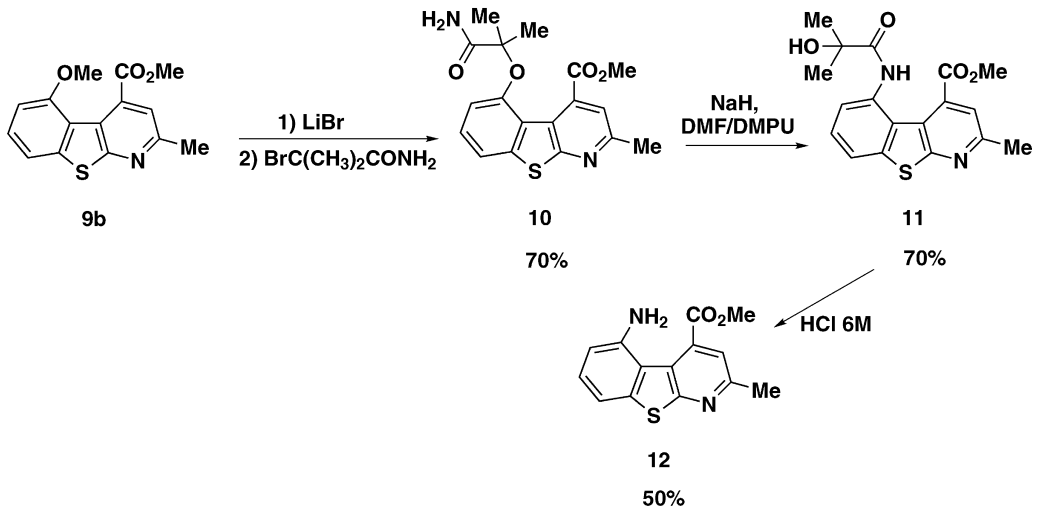
2. Results and discussion

Available 4-hydroxybenzo[*b*]thiophene **1**[13] can be considered a suitable heteroaromatic substrate for the use of the 'Smiles rearrangement' methodology, recently reported for non-activated aromatic rings. In the Smiles rearrangement the preliminary conversion of phenol into 2-aryloxy-2-methylpropanamide is of primary importance: such a conversion can be efficiently achieved by treatment with sodium hydride in hexamethylphosphoric triamide for 1 h.[2] A similar conversion has originally been applied also to the compound **1**, but the reported protocol has presently been changed in the light of a subsequent work.[3] We could in fact obtain directly 2-(benzo(*b*)thiophen-4-yloxy)-2-methylpropanamide in 53% yield upon refluxing the sodium salt of the compound **1** and 2-bromo-2-methylpropanamide in dry 1,4-dioxane for 4 h (Scheme 2). The derived propanamide **2** was subsequently submitted to the Smiles rearrangement by treatment with sodium hydride in a refluxing 10:1 mixture of DMF/DMPU for 2 h. The resultant *N*-(benzo(*b*)thiophen-4-yl)-2-hydroxy-2-methylpropanamide **3** was eventually converted into 4-aminobenzothiophene **4** in 91% yield upon treatment with 6 M HCl for 2 h at 100°C. The facile conversion of the compound **1** into 4-aminobenzo[*b*]thiophene **4** in 40% overall yield led us to extend the above procedure to an interesting tricyclic compound such as the 5-hydroxy[1]benzothieno[2,3-*b*]pyridine **9**, R=H (Scheme 3), which might have been transformed eventually into the target 5-amino-4-methoxycarbonyl-2-methyl[1]benzothieno[2,3-*b*]pyridine **12** (Scheme 4).

According to our previous protocol, we initially planned to convert the phenol **1** into the iminophosphorane **7**, R=H and



Scheme 3.



Scheme 4.

thence to prepare the 5-hydroxybenzothienopyridine **9**, R=H by subsequent aza-Wittig/electrocyclization reaction with methyl *trans*-4-oxo-2-pentenoate.[10] However, our initial efforts to directly prepare azide **6**, R=H via azidation of **1** with tosyl azide[10,14] only resulted in fragmentation of the resultant triazene salt to intractable material. This result led us to examine the alternative use of the *O*-silyl protected azide **6a**, which could be obtained in good yield (80%) by azidation of the silyloxybenzothiophene **5a**. Subsequent Staudinger reaction of **6a** with methyldiphenylphosphine[10] readily furnished the corresponding phosphorane **7a**.

Reaction of phosphorane **7a** with methyl *trans*-4-oxo-2-pentenoate gave only a poor yield (14%) of the desired benzothienopyridine **9a** (Scheme 3). Presumably, in this case, the electrocyclization process of the aza-Wittig imine **8a** was strongly limited by the presence of the bulky silyloxy substituent in the *peri* position. However, the analogous methoxy-substituted phosphorane **7b**, which was easily available from methoxybenzothiophene **5b**, following the same procedure, was found to react smoothly with methyl *trans*-4-oxo-2-pentenoate, in chloroform at 50°C, to give directly the fused pyridine **9b** in 91% yield via electrocyclization of the imine **8b** (Scheme 3).

This readily prepared 5-methoxy-substituted benzothienopyridine **9b** was then demethylated with lithium bromide (Scheme 4) and directly treated with 2-bromo-2-methylpropanamide following the same procedure as employed for 4-hydroxybenzothiophene **1**, to obtain the propanamide **10** in 70% yield. Compound **10** was then subjected to the Smiles rearrangement by treatment with sodium hydride in a 10:1 mixture of DMF/DMPU at 100°C for 2 h. The rearranged amide **11**, obtained in 70% yield, was finally converted to the target 5-amino-4-methoxycarbonylbenzothienopyridine **12** in acceptable yield (50%) upon hydrolysis in 6 M HCl at 100°C for 2 h (Scheme 4).

Unfortunately, probably due to competing hydrolysis of the carbomethoxy group, the resultant yield of the target compound **12** could not exceed 50% even when other hydrolytic conditions were attempted.

3. Conclusions

In this paper, we have reported the first preparation of 4-aminobenzo(*b*)thiophene in only three steps by using a modified procedure of the Smiles rearrangement. Furthermore, we have shown that such Smiles rearrangement, coupled with the aza Wittig/electrocyclization reaction, can provide a useful entry to novel 5-amino-substituted [1]benzothieno[2,3-*b*]pyridines such as the aminobenzothienopyridine **12**. This tricyclic compound **12** is of special interest due to the concomitant presence of carbomethoxy and amino group in the 4 and 5 positions, respectively.

4. Experimental

4.1. General

Column chromatography was carried out on Merck silica gel (0.063–0.200 mm particle size) by progressive elution with petroleum ether/ethyl acetate mixtures. ^{1}H and ^{13}C NMR spectra were normally carried out in $CDCl_3$ solutions on a Bruker AM 300 MHz. IR spectra were carried out on a Perkin–Elmer 883. Mass spectra were obtained with a Hewlett–Packard 5971 mass-selective detector on a Hewlett–Packard 5890 gas chromatograph (OV-1 capillary column between 70–250°C (20°C min^{-1}).

Dichloromethane, chloroform and carbon tetrachloride were dried with anhydrous $CaCl_2$; diethyl ether and 1,4-dioxane were dried using sodium/benzophenone. Dry dimethylformamide was commercially available. 4-Hydroxybenzothiophene **1** was prepared according to the literature.[13] 2-Bromo-2-methylpropanamide was synthesised as recently reported[3] and used in Smiles rearrangement as reported in the same paper to obtain the suitable 2-aryloxy-2-methylpropanamide.

4.1.1. 2-(1-Benzothiophen-4-yloxy)-2-methylpropanamide 2. 4-Hydroxybenzothiophene **1** (100 mg, 0.67 mmol) was stirred in dry 1,4-dioxane (6 ml) with sodium hydride (40 mg, 1.33 mmol) for 3 h at 30°C in a nitrogen

atmosphere. Then, 2-bromo-2-methylpropanamide was added and the reaction mixture was kept at 100°C and stirred for 4 h.

After cooling, the sodium bromide was filtered and the organic solution was diluted with ethyl acetate and washed first with 2 M NaOH and then with water and brine. After solvent removal the crude product was chromatographed on silica gel, using petroleum ether/ethyl acetate 1:1 as eluant, to give the title compound as a white solid (83 mg, 53%). Elemental analysis and melting point was in accordance to reported data,[2] while spectroscopic data were as follows. δ_H (300 MHz, $CDCl_3$): 7.57–7.53 (m, 1H); 7.47–7.43 (m, 1H), 7.37–7.33 (m, 1H); 7.25–7.20 (m, 1H); 6.87–6.83 (m, 1H); 6.77 (bs, 1H); 5.57 (bs, 1H); 1.65 (s, 6H); δ_C (75 MHz): 178.5, 148.4, 139.4, 139.3, 128.0, 122.2, 114.6, 111.8, 67.3, 23.0. ν_{max}/cm^{-1} 3520, 3420 (NH_2); 1690 (CO)

4.1.2. *N*-(1-Benzothiophen-4-yl)-2-hydroxy-2-methylpropanamide 3. To a solution of the compound **2** (141 mg, 0.60 mmol) in a mixture of *N*,*N*-dimethylformamide (DMF)/1,3-dimethyltetrahydropyrimidin-2-(1*H*)-one (DMPU) 10:1 was added sodium hydride (44 mg, 2 mmol) and the reaction mixture was kept at 100°C for 2 h. After this time, the temperature was cooled to 25°C and the solution was poured into 50 ml of water and extracted with an equal amount of ethyl acetate. Then the organic layer was washed with 50 ml of water for four times, dried over sodium sulphate and after removal of solvent the crude product was purified on silica gel using petroleum ether/ethyl acetate 1:1 as eluant furnishing *N*-(1-benzothiophen-4-yl)-2-hydroxy-2-methylpropanamide **3** (116 mg) in 82% yield. Elemental analysis and melting point was in accord with reported data,[2] while spectroscopic data was as follows. δ_H (300 MHz, $CDCl_3$): 9.17 (bs, 1H); 8.03–7.99 (m, 1H); 7.64–7.60 (m, 1H); 7.32–7.28 (m, 1H); 7.24–7.20 (m, 2H) 3.18 (bs, 1H); 1.58 (s, 6H); δ_C (75 MHz): 174.2, 140.7, 132.0, 131.7, 126.3, 125.0, 119.0, 116.3, 74.5, 28.1. ν_{max}/cm^{-1}: 3450 (NH), 3250 (OH), 1670 (CO).

4.1.3. 4-Aminobenzo[*b*]thiophene 4. 70 mg (0.3 mmol) of *N*-aryloxy compound **3** was refluxed in 6 M HCl for two hours, then the reaction mixture was cooled to 25°C and treated with NaOH solution until neutrality. The aqueous solution was extracted with diethyl ether, dried over sodium sulphate and after solvent removal the crude was purified on silica gel using petroleum ether/ethyl acetate 9:1 as eluant to give the title compound (41 mg, 91%) as a white solid. Mp 50°C (lit.[15] 50–51°C). Spectroscopic data was as follows. δ_H (300 MHz, $CDCl_3$): 7.46–7.42 (m, 1H), 7.40–7.36 (m, 1H), 7.18–7.13 (m, 2H), 6.66–6.62 (m, 1H), 4.08 (bs, 2H); δ_C (75 MHz):141.3, 129.1, 128.5, 125.3, 124.0, 119.5, 113.2, 109.1. ν_{max}/cm^{-1}: 3440, 3340 (NH_2), *m*/*z*: 149 (M^+).

4.1.4. 4-(*tert*-Butyldimethylsilyloxy)benzo[*b*]thiophene 5a. 4-Hydroxybenzothiophene **1** (512 mg, 3.05 mmol) was dissolved in 10 ml of dry dichloromethane and to this solution were added *tert*-butyldimethylsilylchloride (4.58 mmol), imidazole (9.15 mmol) and a catalytic amount of 4-dimethylaminopyridine. The resulting mixture was stirred in inert atmosphere for 3 h at room temperature, then was filtered and washed with saturated ammonium chloride solution and twice with water. After solvent removal the crude product was chromatographed on silica gel, using petroleum ether/ethyl acetate 95:5 as eluant, to give **5a** as a thick oil (604 mg, 75%). (Found: C, 63.59; H, 7.59; S, 12.15%. $C_{14}H_{20}OSSi$ requires: C, 63.58; H, 7.62; S, 12.12%), δ_H (300 MHz, $CDCl_3$): 7.72–7.67 (m, 2H), 7.53–7.37 (m, 2H), 6.99–6.93 (m, 1H), 1.35 (s, 9H), 0.50 (s, 6H); δ_C (75 MHz): 150.7, 141.5, 133.5, 125.3, 124.3, 121.0, 115.7, 113.1, 25.7, 18.5, −0.4. *m*/*z*: 264 (M^+), 207 (100).

4.1.5. 4-Methoxybenzo(*b*)thiophene 5b. A solution of 4-hydroxybenzothiophene **1** (131 mg, 0.87 mmol) in 10 ml of anhydrous 1,4-dioxane was treated with sodium hydride (2.5 mmol) at 30°C for ca. 2 h. After this time methyl iodide (1.04 mmol) was added to the resultant mixture and then stirred at 50°C in inert atmosphere for 25 h: filtration and solvent removal gave an oily residue.

Chromatography on silica gel, using petroleum ether/ethyl acetate 9:1 as eluant, furnished the title compound **5b** as a thick red oil (130 mg, 91%). (Found: C, 65.85; H, 4.88; S, 19.56%. C_9H_8OS requires C, 65.83; H, 4.91; S, 19.52%); δ_H (300 MHz, $CDCl_3$): 7.65–7.5 (m, 2H); 7.45–7.38 (m, 2H); 6.84–6.80 (m, 1H); 3.99 (s, 3H); δ_C (75 MHz): 155.0, 141.2, 130.5, 125.3, 124.6, 120.5, 115.0, 104.1, 55.9. *m*/*z*: 164 (M^+), 149 (100).

4.1.6. [(2-Azido-1-benzothiophen4-yl)oxy]-(*tert*-butyl)dimethylsilane 6a. Compound **5a** (300 mg, 1.14 mmol) in 6 ml of dry diethyl ether was treated, in inert atmosphere, with *n*-butyllithium 1.6 M in hexane (1.25 mmol) and refluxed for 1 h. Then the reaction mixture was cooled to −70°C and, slowly, tosyl azide (476 mg, 1.3 mmol) in 3 ml of dry diethyl ether was added. After 5 h at this temperature the obtained triazene salt was filtered on buckner, washed with dry diethyl ether and then treated at 0°C with an aqueous solution of sodium pyrophosphate decahydrate (556 mg, 1.25 mmol, in 5 ml of water). After 15 min of stirring at this temperature the suspension was filtered on buckner and extracted twice with diethyl ether and then with ethyl acetate until the organic phase appeared colourless.

Then, after solvent removal, the crude product was purified by chromatography on florisil (eluant petroleum ether/ethyl acetate 8:2) giving the title compound (279 mg, 80%) as a thick yellow oil (Found: C, 55.07; H, 6.21; N, 13.78; S, 10.44%. $C_{14}H_{19}N_3OSSi$ requires C, 55.05; H, 6.27; N, 13.76; S, 10.50%); ν_{max}/cm^{-1} 2110 (N_3); δ_H (300 MHz, $CDCl_3$): 7.50–7.40 (m, 1H), 7.19–7.11 (m, 1H), 6.89 (s, 1H), 6.72–6.68 (m, 1H), 1.07 (s, 9H), 0.27 (s, 6H); δ_C (75 MHz): 142.7, 125.3, 124.5, 121.0, 115.6, 115.0, 113.6, 108.3, 25.8, 15.9, −0.53.

4.1.7. 2-Azido-4-methoxy-1-benzothiophene 6b. Compound **5b** (130 mg, 0.8 mmol) in 4 ml of dry diethyl ether was treated, in inert atmosphere, with *n*-butyllithium 1.6 M in hexane (0.9 mmol) and refluxed for 1 h. Then the reaction mixture was cooled to −70°C and tosyl azide (170 mg, 0.9 mmol) in 4 ml of dry diethyl ether was added dropwise. After 5 h at this temperature, the obtained triazene salt was filtered on buckner, washed with dry diethyl ether and then treated at 0°C with an aqueous solution of sodium pyrophosphate decahydrate (413 mg, 0.9 mmol, in 4 ml of

water). After 15 min of stirring at this temperature the suspension was filtered on buckner and extracted twice with diethyl ether and then with ethyl acetate until the organic phase appeared colourless.

Then, after solvent removal, the crude product was purified by chromatography on florisil (eluant petroleum ether/ethyl acetate 8:2) giving the title compound (126 mg, 77%) as a thick yellow oil. Found: C, 52.65; H, 3.47; N, 20.45; S, 15.63%. $C_9H_7N_3OS$ requires: C, 52.67; H, 3.44; N, 20.47; S, 15.62%; ν_{max}/cm^{-1} 2113 (N_3); δ_H (300 MHz, $CDCl_3$): 7.35–7.20 (m, 2H); 7.05 (s, 1H); 6.80–6.75 (m, 1H); 3.95 (s, 3H); δ_C (75 MHz): 152.7, 139.5, 138.2, 125.3, 124.6, 117.1, 115.7, 110.3, 50.5.

4.1.8. [(4-[*tert*-Butyl(dimethyl)silyl]oxy-1-benzothiophen-2-yl) imino](methyl)diphenylphosphorane 7a. This was prepared from the azide **6a** (140 mg, 0.46 mmol) and methyldiphenylphosphine (92 mg, 0.46 mmol) following a procedure recently reported[10] for unsubstituted benzothiophene. Chromatography with petroleum ether/ethyl acetate 70:30 as eluant gave the title compound (88 mg, 40%) as a brown powder, mp 90–92°C (diethyl ether). (Found: C, 67.66; H, 6.79; N, 2.99; S, 6.73%. $C_{27}H_{32}NOPSSi$ requires C, 67.89; H, 6.75; N, 2.93; S, 6.71%); δ_H (300 MHz, $CDCl_3$): 7.83–7.77 (m, 5H), 7.58–7.37 (m, 5H), 7.11–7.06 (m, 1H), 6.87–6.77 (m, 1H), 6.52–6.49 (m, 1H), 6.02 (s, 1H), 2.25–2.20 (d, 3H, J_{PH}=12.8 Hz); 0.95 (s, 9H), 0.1 (s, 6H); δ_C (75 MHz): 168.3, 151.7, 147.5, 135.8, 134.7, 134.0, 132.2, 131.2, 130.8, 129.5, 129.0, 128.8, 120.9, 116.1, 113.2, 101.9, 25.7, 18.3, 14.5, 13.8, −0.42.

4.1.9. [(4-methoxy-1-benzothiophen-2-yl)imino](methyl)diphenylphosphorane 7b. This was prepared from the azide **6b** (126 mg, 0.62 mmol) and methyldiphenylphosphine (124 mg, 0.62 mmol) following a procedure recently reported[10] for unsubstituted benzothiophene. Chromatography with petroleum ether/ethyl acetate 70:30 as eluant gave the title compound (196 mg, 84%) as a red oil (Found: C, 70.04; H, 5.36; N, 3.69; S, 8.50%. $C_{22}H_{20}NOPS$ requires C, 70.01; H, 5.34; N, 3.71; S, 8.49%); δ_H (300 MHz, $CDCl_3$): 7.62–7.50 (m, 5H), 7.43–7.32 (m, 5H), 6.98–6.90 (m, 1H), 6.87–6.80 (m, 1H), 6.53–6.48 (m, 1H), 6.08 (s, 1H), 3.70 (s, 3H), 2.25–2.20 (d, 3H, J_{PH}=12.8 Hz); δ_C (75 MHz): 157.0, 152.3, 140.2, 135.3, 133.0, 132.5, 132.0, 131.7, 131.4, 130.0 129.5, 128.2, 125.8, 121.0, 114.3, 101.5, 55.5, 15.5.

4.1.10. Synthesis of the (1)benzothieno[2,3-*b*]pyridines 9a,b. A solution of the appropriate iminophosphorane **7a**,**b** (0.12 mmol) in 3 ml of dry chloroform was treated with 15 mg (0.12 mmol) of methyl *trans* 4-oxo-2-pentenoate and then stirred in inert atmosphere for 34 h at 45°C. After removal of the solvent, the crude product was chromatographed on silica gel, using petroleum ether/ethyl acetate 70:30 as eluant.

Methyl 5-[*tert-butyl*(*dimethyl*)*silyl*]*oxy*-2-*methyl*(1)*benzothieno*[2,3-*b*]*pyridine*-4-*carboxylate* **9a**. This was obtained as a thick oil (7 mg, 14%). (Found: C, 62.00; H, 6.53; N, 3.58; S, 8.24%. $C_{20}H_{25}NO_3SSi$ requires: C, 61.98; H, 6.50; N, 3.61; S, 8.27%); δ_H (300 MHz, $CDCl_3$): 7.50–7.25 (m, 3H), 7.00–6.95 (m, 1H), 3.90 (s, 3H), 2.72 (s, 3H), 0.81 (s, 9H), 0.15 (s, 6H); δ_C (75 MHz): 169.5, 154.2, 151.9, 150.5, 149.5, 141.5, 131.7, 128.4, 117.7, 117.0, 116.2, 53.9, 29.8, 26.2, 25.7, 19.8, 18.5, −0.4. *m/z*: 287 (M^+).

Methyl 5-*methoxy*-2-*methyl*(1)*benzothieno*[2,3-*b*]*pyridine*-4-*carboxylate* **9b**. This was obtained as a thick oil (31 mg, 91%). (Found: C, 62.72; H, 4.58; N, 4.85; S, 11.13%. $C_{15}H_{13}NO_3S$ requires C, 62.70; H, 4.56; N, 4.87; S, 11.16%); δ_H (300 MHz, $CDCl_3$): 7.75–7.70 (m, 1H), 7.57–7.50 (m, 1H), 7.47–7.40 (m, 1H), 6.95–6.90 (m, 1H), 3.98 (s, 6H), 2.72 (s, 3H); δ_C (75 MHz): 169.4, 167.8, 156.8, 139.4, 138.2, 132.5, 131.2, 129.1, 128.8, 118.2, 115.6, 106.6, 55.9, 30.3. *m/z*: 287 (M^+).

4.1.11. Methyl 5-(2-amino-1,1-dimethyl-2-oxoethoxy)-2-methyl(1)benzothieno[2,3-*b*]pyridine-4-carboxylate 10. The benzothienopyridine **9b** (31 mg, 0.11 mmol) was treated with lithium bromide (31 mg, 0.36 mmol) in 5 ml of dioxane at room temperature for 19 h. The resulting mixture was then directly treated with 2-bromo-2-methylpropanamide (18 mg, 0.11 mmol) according to a known procedure.[3] Chromatography gave the title compound as a thick oil (28 mg, 70%). (Found: C, 60.30; H, 5.03; N, 7.85; S, 8.97%. $C_{18}H_{18}N_2O_4S$ requires: C, 60.32; H, 5.06; N, 7.82; S, 8.95%). δ_H (300 MHz, $CDCl_3$): 7.48 (s, 1H), 7.46–7.42 (m, 1H), 7.24–7.22 (m, 1H), 6.92–6.90 (m, 1H), 6.58 (bs, 1H), 5.72 (bs, 1H), 3.98 (s, 3H), 2.72 (s, 3H), 1.55 (s, 6H); δ_C (75 MHz): 175.2, 169.2, 165.4, 156.4, 149.6, 139.8, 139.0, 138.1, 131.3, 128.0, 124.5, 118.0, 114.3, 106.2, 66.0, 55.5, 24.2, 22.4. *m/z*: 358 (M^+).

4.1.12. Methyl 5-[(2-hydroxy-2-methylpropanoyl)-amino]-2-methyl(1)benzothieno[2,3-*b*]pyridine-4-carboxylate 11. This was obtained as a thick oil (19 mg, 70%) from the above compound **10** (27.6 mg, 0.078 mmol) according to a known procedure.[3] (Found: C, 60.34; H, 5.05; N, 7.84; S, 8.97%. $C_{18}H_{18}N_2O_4S$ requires: C, 60.32; H, 5.06; N, 7.82; S, 8.95%); δ_H (300 MHz, $CDCl_3$): 7.48 (s, 1H), 7.45 (s, 1H) 7.30–7.25 (m, 2H), 6.98–6.92 (m, 1H), 3.97 (s, 3H), 2.73 (s, 3H), 1.8 (s, 1H), 1.30 (s, 6H); δ_C (75 MHz): 175.2, 169.2, 162.21, 156.7, 149.6, 139.8, 139.0, 138.1, 131.0, 128.7, 118.2, 115.6, 105.7, 68.3, 55.8, 29.9, 24.4. *m/z*: 358 (M^+).

4.1.13. Methyl 5-amino-2-methyl(1)benzothieno[2,3-*b*]pyridine-4-carboxylate 12. Compound **11** (19 mg, 0.054 mmol) was dissolved in 6 M HCl (3 ml) and the resulting mixture was stirred at 100°C for 2 h. After cooling to 25°C the mixture was slowly treated with a solution of 20% NaOH until neutrality, then extracted twice with ethyl acetate and dried over sodium sulphate. Removal of the solvent gave the compound **12** as a thick oil (7 mg, 50%). (Found: C, 61.78; H, 4.42; N, 10.32; S, 11.79%. $C_{14}H_{12}N_2O_2S$ requires: C, 61.75; H, 4.44; N, 10.29; S, 11.77%. δ_H(300 MHz, $CDCl_3$): 7.77 (m, 1H), 7.52 (m, 1H), 7.46 (s, 1H), 7.0 (m, 1H), 6.64 (s, 2H), 3.97 (s, 3H), 2.72 (s, 3H); δ_C (75 MHz): 170.2, 161.1, 152.0, 144.0, 139.3, 137.7, 127.1, 126.1, 123.2, 119.7, 121.3, 113.8, 52, 24.3.

Acknowledgements

The authors gratefully acknowledge Università di Bologna

and MIUR (Ministry of Instruction, University and Research—Rome) for financial support (Project FIRB RBNE017F8N).

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