COMMUNICATION

New entry to benzo[*b*]thieno[2,3-*b*]- and benzo[*b*]thieno-[3,2-*b*]-pyridines using 2- and 3-azidobenzo[*b*]thiophene as the nitrogen precursors

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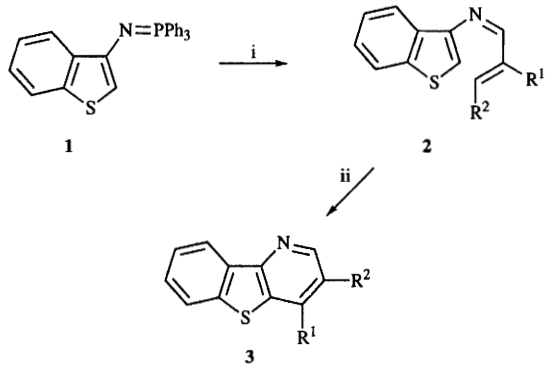
***N*-(3-Benzo[*b*]thienyl)- and *N*-(2-benzo[*b*]thienyl)-imino-triphenylphosphorane—prepared from the corresponding azidobenzo[*b*]thiophenes—react with α,β-unsaturated aldehydes under mild conditions to give directly benzo-[*b*]thieno[3,2-*b*]- and benzo[*b*]thieno[2,3-*b*]-pyridines through electrocyclization (and eventual dehydrogenation) of the initial aza Wittig imine products.**

In recent years the use of iminophosphoranes, normally available from azides or primary amines, has become a powerful tool in organic syntheses, especially directed towards the construction of nitrogen-containing heterocycles.[1] In particular, the aza Wittig reaction of iminophosphoranes derived from β-aryl (heteroaryl) vinyl azides with α,β-unsaturated aldehydes followed by 6π-electrocyclization of the intermediate 3-azahexa-1,3,5-trienes has found recent application in the construction of simple pyridines.[2] Moreover, a modification of this strategy using saturated aldehydes or various heterocumulenes has been widely applied for the *c*-fusion of a pyridine ring onto both aromatic[3] and heteroaromatic systems, including furan,[4] thiophene,[4] indole,[5] pyrazole[6] and pyridine[7] rings. Such a so-called tandem aza Wittig–electrocyclization strategy has, however, found a limited application in the synthesis of *b*-fused pyridines. In fact, *b*-fused pyridines (including a number of quinoline,[8] α-carboline,[9] pyrazolo[5,4-*b*]pyridine[10] and pyrido[2,3-*d*]pyrimidine[11] derivatives) have invariably been prepared from heterocumulenes and those iminophosphoranes produced from azides (or amines) bearing a vinylic *ortho*-substituent, which are not normally readily accessible. An important extension of this methodology in the construction of *b*-fused pyridines could involve the use of α,β-unsaturated carbonyl compounds and iminophosphoranes having (*ortho*-unsubstituted) five-membered heteroaryl *N*-substituents.

However, these iminophosphorane derivatives are to date virtually unexplored, despite the fact that an easy method for their preparation now exists from readily available azido precursors[12] rather than scarcely accessible and/or unstable amine precursors. Our long interest in the investigation of the chemical reactivity and synthetic application of azido-thiophenes[12,13] and -benzo[*b*]thiophenes[12,13] led us to undertake a study of the reaction of *N*-(3-benzo[*b*]thienyl)- and *N*-(2-benzo[*b*]thienyl)-iminophosphoranes with unsaturated aldehydes and ketones as a potential route to benzo[*b*]thieno[3,2-*b*]- and benzo[*b*]thieno[2,3-*b*]-pyridines, for which compounds the few reported synthetic methods are rather difficult and/or give (very) low yields.[14–16] Benzothienopyridines are of pharmacological interest arising from their isosterism with indolopyridines.[14b] Moreover, these tricyclic systems are also of interest as heterocyclic models related to acridines and phenanthridines[14b] and as annelated NADH models.[15]

We now report preliminary results from our study.

Iminotriphenylphosphoranes **1** and **4** were easily obtained in high yield by reacting 3-azido- and 2-azido-benzo[*b*]thiophene with triphenylphosphine following the classical Staudinger method. Treatment of the phosphorane **1** with a three-fold excess of acrylaldehyde, in toluene at 70 °C, directly furnished parent benzo[*b*]thieno[3,2-*b*]pyridine **3a**,†[14a] which was isolated in 70% yield after chromatographic separation (Scheme 1). Evidently, the phosphorane **1** smoothly reacted with the



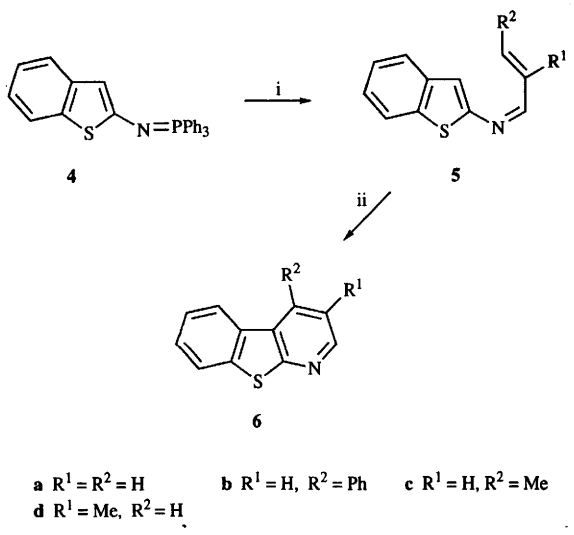
a $R^1 = R^2 = H$ **b** $R^1 = H$, $R^2 = Ph$ **c** $R^1 = H$, $R^2 = Me$
d $R^1 = Me$, $R^2 = H$

Scheme 1 *Reagents and conditions:* i, $+R^2CH{=}CR^1CHO$, PhMe, 70 °C; ii, $-2H$

above aldehyde to give the formal azahexa-1,3,5-triene intermediate **2a**. This intermediate **2a** then underwent thermal electrocyclization eventually leading to the isolated pyridine **3a** after further dehydrogenation of the cyclized dihydropyridine[1,2] (Scheme 1). Comparable findings were obtained from analogous thermal reactions of the iminophosphorane **1** with *trans*-cinnamaldehyde, *trans*-crotonaldehyde and methacrylaldehyde, which afforded the desired benzo[*b*]thieno[3,2-*b*]pyridines **3b**,† **3c**†[16a] and **3d**† in 40–50% yields.

Like the phosphorane **1**, its positional isomer **4** reacted with the same aldehyde compounds to eventually furnish the desired benzo[*b*]thieno[2,3-*b*]pyridines **6a**,†[14b] **6b**,† **6c**†[16c] and **6d**† in 40–50% isolated yields (Scheme 2). However, the initial aza

† The benzothienopyridines **3a–d** and **6a–d** prepared herein were generally identified on the basis of ^1H and ^{13}C NMR and mass spectral data.



a $R^1 = R^2 = H$ b $R^1 = H$, $R^2 = Ph$ c $R^1 = H$, $R^2 = Me$
d $R^1 = Me$, $R^2 = H$

Scheme 2 *Reagents and conditions:* i, $+R^2CH{=}CR^1CHO$, PhMe, 70 °C; ii, $-2H$, heat, *hv*

Wittig reactions of this latter phosphorane **4** generally proceeded somewhat more slowly and, additionally, the ensuing products **5** normally proved to be less prone to thermal ring closure. Indeed, total cyclization of the intermediates **5** was usually only achieved upon further irradiation with a high pressure mercury vapour lamp. Subsequent efforts to enlarge the scope of our procedure by using but-3-en-2-one as the carbonyl substrate were unrewarding, since both iminophosphoranes **1** and **4** were essentially unreactive towards this ketone even in boiling toluene. It is hoped that future employment of *P*-alkyl analogues of the phosphoranes **1** and **4** (which we expect to be more reactive [1a]) will be profitable.

In conclusion, we have uncovered a new, simple protocol for the preparation of benzothieno[*b*]pyridines which in principle should be of wide utility for performing *b*-fusion of a pyridine ring onto five-membered heteroarenes using the α- and β-azido derivatives as the nitrogen precursors.

Experimental

N-(3-Benzo[*b*]thienyl)iminotriphenylphosphorane 1

A solution of 3-azidobenzo[*b*]thiophene [17] (1.65 mmol) in 13 cm^3 of dry dichloromethane was added dropwise at 0 °C to a solution of triphenylphosphine (1.65 mmol) in the same solvent (10 cm^3). The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for a further 15 h. Removal of the solvent and subsequent silica gel chromatography of the crude product, using an 80:20 mixture of hexane–ethyl acetate as eluent, gave the *title iminophosphorane* **1** (1.42 mmol, 86%), as orange plates, mp 163–164 °C (Found: C, 76.2; H, 4.7; N, 3.4; S, 7.9. $C_{26}H_{20}NPS$ requires C, 76.45; H, 4.7; N, 3.45; S, 7.85%); δ_H(300 MHz, $CDCl_3$) 5.65 (1 H, s) and 7.3–8.2 (19 H, complex m).

N-(2-Benzo[*b*]thienyl)iminotriphenylphosphorane 4

Treatment of 2-azidobenzo[*b*]thiophene [18] (1.85 mmol) with triphenylphosphine (1.85 mmol) as described above for the 3-azido isomer gave, after chromatographic purification, the *title iminophosphorane* **4** (1.72 mmol, 93%), as a yellowish solid, mp 80–81 °C (Found: C, 76.3; H, 4.7; N, 3.5; S, 7.8%); δ_H(300 MHz $CDCl_3$): 6.0 (1 H, s), 6.9–7.3 (3 H, m) and 7.4–7.85 (16 H, m).

Benzo[*b*]thieno[3,2-*b*]pyridine 3a

A mixture of the iminophosphorane **1** (0.2 mmol) and acrylaldehyde (0.6 mmol) in dry toluene (6 cm^3) was stirred at 70 °C for 24 h. After cooling, the solvent was removed under reduced pressure and the residual material chromatographed on a silica gel column, eluting with an 80:20 mixture of hexane–ethyl acetate, to give the title compound **3a** (0.14 mmol, 70%), mp 80–81 °C (lit., [14a] 81–82 °C); δ_H(300 MHz, $CDCl_3$) 7.38–7.44 (1 H, m), 7.5–7.6 (2 H, m), 7.82–7.92 (1 H, m), 8.2 (1 H, d, *J* 8), 8.48–8.52 (1 H, m) and 8.73 (1 H, d, *J* 8); δ_C(75 MHz, $CDCl_3$) 120.8, 122.8, 122.9, 125.2, 128.5, 131.2, 134, 137.5, 141.2, 145.1 and 146; *m/z* 185 (M^+).

Benzo[*b*]thieno[2,3-*b*]pyridine 6a

A mixture of the iminophosphorane **4** (0.25 mmol and acrylaldehyde (0.75 mmol) in dry toluene (7 cm^3) was stirred at 70 °C for 24 h, after which it was treated with additional acrylaldehyde (0.5 mmol) and stirred at 70 °C for a further 12 h. The excess solvent was removed and the residue was dissolved in 5 cm^3 of chloroform and then irradiated in a Pyrex tube for 1 h with a high pressure mercury vapour lamp. Column chromatography of the crude prouct gave the title compound **6a** (0.16 mmol, 65%), mp 73–75 °C (lit., [14b] 73–74 °C); δ_H(300 MHz, $CDCl_3$) 7.39–7.45 (1 H, m), 7.5–7.55 (2 H, m), 7.88–7.93 (1 H, m), 8.14–8.18 (1 H, m), 8.4 (1 H, d, *J* 6) and 8.66 (1 H, d, *J* 6); δ_C(75 MHz, $CDCl_3$) 119, 122, 123, *128*, *129.1*, *130.2*, *136*, 137, 144.9 and 148; *m/z* 185 (M^+).

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