A New Entry to Benzo[4,5]furo[3,2-*b*]pyridines via *N*-(Benzofuran-3-yl)iminophosphorane

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Dedicated to the memory of Professor Antonio Mario Tamburro.

Abstract: Mild thermal reaction of enones with *N*-(benzofuran-3-yl)iminophosphorane, newly prepared by Staudinger reaction of 3-azidobenzofuran with triphenylphosphine, provides a synthetic entry to virtually unknown benzo[4,5]furo[3,2-*b*]pyridines via a tandem aza-Wittig–electrocyclization process.

Key words: iminophosphoranes, azides, aza-Wittig, electrocyclization, benzofuropyridines

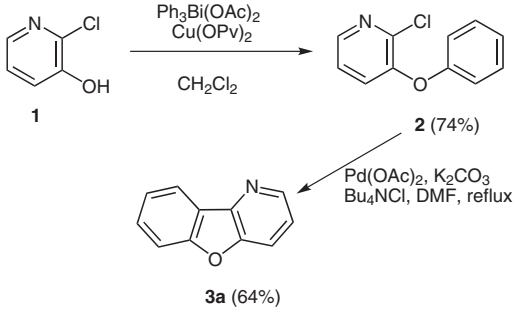
Small heterocyclic molecules play an important role in modern pharmaceutical and medicinal chemistry.[1] In particular, benzo[4,5]furopyridines, isosteric of both carbolines and dibenzofuran, often display important biological and pharmacological activities.[2,3]

Benzo[4,5]furo[*c*]pyridines and their tetrahydro derivatives are long-known compounds available through various reported methods.[4] In contrast, the benzo[4,5]furo[*b*]pyridine congeners remain little known. Indeed, only scant examples of benzo[4,5]furo[2,3-*b*]pyridines were present in the literature[4b,5c,d] until two very recent papers described the preparation of a variety of those tricyclic compounds through the unusual use of in situ generated 2-aminobenzofuran as the crucial intermediate.[5a,b,6]

As for the possible benzo[4,5]furo[3,2-*b*]pyridine family, surprisingly the parent compound **3a** seems to represent the only documented member. In fact, the parent benzofuropyridine **3a** was recently produced in fairly good yield through 'intramolecular Heck cyclization' of chlorophenoxypyridine **2** achieved by not trivial phenylation of commercially available chloropyridinol **1** with triphenylbismuth(V) diacetate and Cu(II) pivaloate (Scheme 1).[4b,7]

Unfortunately, this interesting, though rather expensive, organometallic method would be poorly practicable for attaining desired substitution of the pyridine moiety owing to often (very) difficult access to 2-chloro-3-pyridinol bearing further substituent(s) on the heteroaromatic ring.

In the past thirty years iminophosphoranes, first prepared at the beginning of the last century by Staudinger by reacting phenyl azides with triphenylphosphine, have become a powerful tool in synthetic methods for the construction of nitrogen-containing heterocycles.[8a]



Scheme 1 Synthesis of parent benzo[4,5]furo[3,2-*b*]pyridine

In particular, the aza-Wittig reaction of suitable iminophosphoranes with α,β-unsaturated carbonyl compounds, followed by 6π-electrocyclization of the resultant azahexatrienes, has found extensive application in the synthesis of simple and *c*-fused pyridines[8a–c,9] as well as, but to a much lesser extent, of the *b*-fused ones.[8d]

Our long interest in the chemistry of nitrogen-containing heteroaromatic systems recently led us to discover that iminophosphoranes arising from 2-azido- and 3-azidobenzothiophene are conveniently employed in the aza-Wittig-electrocyclization strategy for the synthesis of benzothieno[3,2-*b*]pyridines and benzothieno[2,3-*b*]pyridines.[10] More recently, we also found that such a strategy can successfully be extended to iminophosphoranes prepared from 2-azido-1-methylindole for the construction of a variety of pyrido[2,3-*b*]indoles (α-carbolines).[11]

In this paper we report our preliminary results from attempted use of analogous methodology for the preparation of parent benzofuro[3,2-*b*]pyridine **3a** and additional mono- and disubstituted congeners **3b–f** shown in Scheme 4.

The appealing use of *N*-(benzofuranyl)iminophosphoranes in the synthesis of benzofuro[*b*]pyridines is unprecedented. Indeed, iminophosphoranes derived from 3-azido- or 2-azido-benzofuran remain to date totally unknown, despite the fact that straightforward methods affording both azido precursors have long been available.[12,13] Particularly, 3-azidobenzofuran (**4**) was

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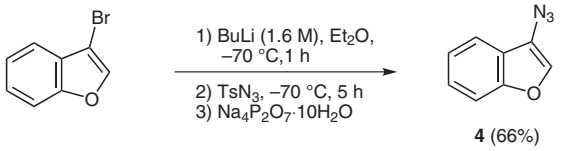
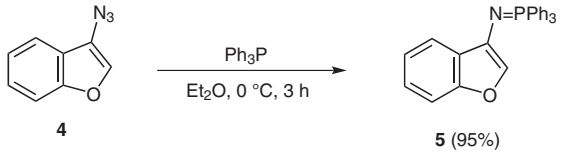
newly prepared in very good yield as early as 1978 through a peculiar method entailing smooth addition of iodine azide to benzofuran, followed by treatment of resulting *cis*/*trans*-2,3-diazido-2,3-dihydrobenzofuran adducts with ethanolic potassium hydroxide.[13]

Since (parent) 2- and 3-azides, including 2-azidobenzofuran,[12] arising from electron-rich five-membered heteroarenes are usually prepared by means of 'azido-group transfer' reaction of tosyl azide with the lithiated heteroarene,[8d,14] at the outset of the present work we became interested in proving that the azido-transfer method could conceivably be applied to the additional synthesis of azide **4**. It was actually found that standard lithiation of 3-bromobenzofuran with BuLi at –70 °C, followed by usual reaction with tosyl azide and final hydrolysis with aqueous sodium pyrophosphate, led to rewarding isolation of **4** in 66% yield after chromatographic purification on Florisil column (Scheme 2). The obtained azide **4** was an oily compound whose physical and IR and NMR spectral data were consistent with those previously reported.[13,15] In order to avoid dangerous use of explosive iodine azide we presently chose to adopt the azido-transfer method even though the original protocol was found to afford a still better yield of **4**.



Scheme 2 Synthesis of 3-azidobenzofuran

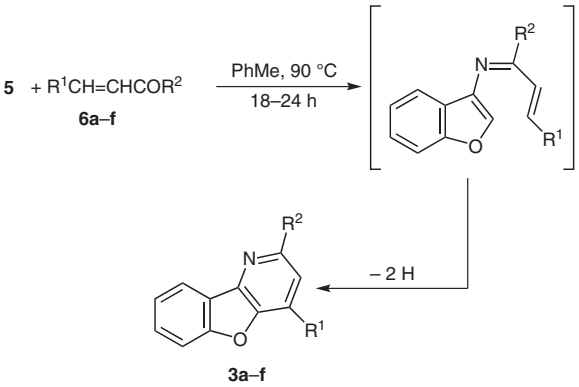
Staudinger reaction of azide **4** with triphenylphosphine in diethyl ether at 0 °C furnished an excellent yield of the desired iminotriphenylphosphorane **5** which was isolated as a stable, yellow, oily compound (Scheme 3).[16]



Scheme 3 Synthesis of (benzofuran-3-yl)iminotriphenylphosphorane

The new iminophosphorane **5** was then reacted in toluene solution at 90 °C with equimolar amounts of various α,β-unsaturated aldehydes and ketones, including acrylaldehyde (**6a**), *trans*-crotonaldehyde (**6b**), *trans*-cinnamaldehyde (**6c**), but-2-enone (**6d**), methyl *trans*-4-oxo-2-pentenoate (**6e**), and methyl *trans*-4-(4-methylphenyl)-4-oxo-2-butenoate (**6f**). The enones **6a**–**e** were commercial compounds, whereas the oxobutenoate **6f** was produced by conventional esterification of the commercially available acid (Scheme 4).

After suitably prolonged reaction time (18–24 h) every crude mixture was evaporated under reduced pressure and then directly subjected to chromatographic purification.



a $R^1 = R^2 = H$ **b** $R^1 = Me$, $R^2 = H$
c $R^1 = Ph$, $R^2 = H$ **d** $R^1 = H$, $R^2 = Me$
e $R^1 = COOMe$, $R^2 = Me$ **f** $R^1 = COOMe$, $R^2 = 4\text{-}MeC_6H_4$

Scheme 4 Synthesis of benzofuro[3,2-*b*]pyridines

Table 1 Benzofuropyridines **3a**–**f**[17] Prepared from Iminophosphorane **5** and Enones **6a**–**f**

Entry	Enone **6**	Yield of benzofuropyridine **3** (%)
1	**6a** $R^1 = R^2 = H$	**3a** 34
2	**6b** $R^1 = Me$, $R^2 = H$	**3b** 20
3	**6c** $R^1 = Ph$, $R^2 = H$	**3c** 21
4	**6d** $R^1 = H$, $R^2 = Me$	**3d** 28
5	**6e** $R^1 = COOMe$, $R^2 = Me$	**3e** 80
6	**6f** $R^1 = COOMe$, $R^2 = 4\text{-}MeC_6H_4$	**3f** 85

As can be seen from Table 1 (entries 1–3) and Scheme 4, with the aldehydes **6a**–**c** iminophosphorane **5** actually furnished the corresponding unsubstituted benzofuropyridine **3a** as well as the 4-Me- and 4-Ph-substituted ones **3b**,**c** but only in modest, though still practicable, yields (20–34%). These rather disappointing findings were somewhat unexpected since previous reactions of our benzothienyl and indolyl iminophosphoranes with the same aldehydes were generally found to afford markedly better yields of *b*-fused pyridine products.[10,11] However, with the 4-oxo-2-pentenoate **6e** and 4-oxo-2-butenoate **6f** very good yields of the desired 2,4-disubstituted pyridines **3e**–**f** could be fortunately achieved (Table 1, entries 5, 6, and Scheme 4). Such observations strictly supported original chemical evidence that tandem aza-Wittig electrocyclization reactions of heteroaryl iminophosphoranes are significantly encouraged by the use of enones bearing electron-withdrawing methoxycarbonyl substituent on the β-ethylenic carbon.[10,11] Interestingly, simple but-2-enone **6d** also gave a useful yield of the respective 2-methylpyridine **3d** (Table 1, entry 4, and Scheme 4). This fact is noteworthy in light of the relative inertness previously

displayed by that ketone with both 2- and 3-(benzothienyl)iminotriphenylphosphoranes.[10a,b]

It is worth noting that with the enones **6b–f** the outcoming benzofuropyridines **3b–f** were always produced as single regioisomeric compounds.[10a] Evidently, the iminophosphorane **5** could initially form formal aza-Wittig azahexa-1,3,5-triene intermediates. These intermediates then underwent thermal electrocyclization eventually leading to the isolated pyridines **3** after further dehydrogenation of the cyclized dihydropyridines (Scheme 4). In this respect, the (benzofuran-3-yl)iminotriphenylphosphorane (**5**) was consistent with the benzothienyl and indolyl counterparts which similarly furnished only aza-Wittig electrocyclization pyridines in their reactions with enones.[10a,11,18]

However, the rather peculiar outcome of the iminophosphorane **5** reactions with aldehydes **6a–c** remains unclear at this stage. It is possible that in such cases ensuing hexatriene intermediates were notably prevented from undergoing usual electrocyclization reaction owing to special occurrence of inappropriate geometrical isomers.

In conclusion, we have shown that the fairly mild thermal reaction of simple enones with *N*-(benzofuran-3-yl)iminotriphenylphosphorane (**5**) can offer a synthetic entry to virtually unknown benzo[4,5]furo[3,2-*b*]pyridines, which should be especially rewarding when using enones 'activated' by a suitable carbonyl substituent attached to the β-ethylenic carbon.

Even though pyridine products should predictably arise to an extent highly dependent upon structural and electronic features of the starting enones, the present protocol could, however, find wide synthetic interest owing to prompt availability of iminophosphorane and enone precursors, fair flexibility for substituent introduction, and very simple practical use.

Studies are in progress to fully discover the actual synthetic potential of our protocol through the use of other (benzofuran-3-yl)iminophosphoranes *P*-phenyl/methyl-substituted.[19]

Acknowledgment

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(15) **Synthesis of 3-Azidobenzofuran (4) via Azido-Group-Transfer Reaction**
To a solution of 3-bromobenzofuran (1.07 mmol) in dry Et_2O (6 mL) *n*-BuLi (1.6 M in hexane, 1.07 mmol) was added at –70 °C under a stream of nitrogen. After 1 h, tosyl azide (1.07 mmol in 4 mL of dry Et_2O) was added dropwise, and the mixture was stirred for 5 h at –70 °C. The resulting yellow mixture was slowly led to r.t. and then treated with an aq solution of sodium pyrophosphate (5 mL, 1.07 mmol). After stirring for 30 min, the eventual reaction mixture was extracted with Et_2O and then with EtOAc; the collected organic layers were dried over Na_2SO_4 and finally evaporated in vacuo. Column chromatography of the crude on a Florisil column using PE as eluant isolated the title azide (0.71 mmol, 66%) as yellow thick oil. Physical and IR and NMR spectral data were fully consistent with those originally reported.

(16) **Synthesis of Triphenyliminophosphorane 5**
3-Azidobenzofuran (**4**, 1 mmol) in dry Et_2O (3 mL) was slowly added to a solution of Ph_3P (1 mmol) in dry Et_2O (3 mL) at 0 °C under a stream of nitrogen. The mixture was stirred at 0 °C for 3 h and then at r.t. for an additional 1 h. Removal of the solvent in vacuo afforded the title iminophosphorane as yellow thick oil in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.70 (m, 16 H), 7.20 (t, *J* = 10.5 Hz, 2 H), 7.03 (d, *J* = 9.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 132.78, 132.71, 132.59, 132.51, 131.99, 131.75, 128.77, 128.67, 128.53, 128.44, 123.57, 121.18, 120.05, 119.84, 110.88, 110.67.

(17) **Synthesis of Benzofuropyridines 3a–f: Typical Procedure**
A mixture of iminotriphenylphosphorane **5** (1 mmol) and methyl *trans*-4-oxo-2-pentenoate (**6e**, 1 mmol) in dry toluene (5 mL) was stirred at 90 °C for ca. 20 h under a stream of nitrogen. After cooling, the solvent was removed in vacuo, and the resultant crude was purified on a silica gel column by progressive elution with PE–EtOAc mixtures to give the benzofuropyridine **3e** in 80% yield as a dark-yellow thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.0 Hz, 1 H), 7.76 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.0 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 4.10 (s, 3 H), 2.81 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 164.3, 156.2, 153.6, 133.5, 130.2, 126.2, 124.2, 121.7, 118.6, 114.1, 113.2, 52.7, 29.7. MS (EI): *m/z* = 241 [M]. The parent benzofuropyridine **3a** had spectral data consistent with those previously reported.[4b] The hitherto unknown benzofuropyridines **3b–d**,**f** were identified on the basis of ^{1}H NMR, ^{13}C NMR, and MS spectral data.

(18) Reactions of enones with (benzothien-3-yl)iminophosphoranes bearing methyl substituent(s) on phosphorus were shown to form *b*-fused pyridines due to aza-Wittig electrocyclization along with those due to opposite regiochemistry, see ref. 10b,c.

(19) Replacement of phenyl with electron-donating methyl group(s) on phosphorus could enhance the reactivity of previous (benzothien-2-yl)- and, especially, (benzothien-3-yl)imino-phosphoranes with enones, see ref. 10b,c.