

Cascade synthesis of new tetracyclic heteroaromatic thieno[2,3-*b*]pyridine-containing ring systems

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Received (in Montpellier, France) 24th August 2009, Accepted 6th October 2009

First published as an Advance Article on the web 22nd October 2009

DOI: 10.1039/b9nj00528e

Flash vacuum pyrolysis of appropriate stabilised ylides, prepared in a few steps from 2-(methylthio)nicotinic acid, give products containing previously unknown naphtho-, phenanthro-, benzothieno- and benzofuro-fused thieno[2,3-*b*]pyridine ring systems.

We have previously shown that the thermal extrusion of triphenylphosphine oxide from suitably substituted stabilised ylides, the so-called intramolecular Wittig reaction, may be accompanied by the loss of a methyl radical and cyclisation if the substituent at one end of the initially formed alkyne is a benzene ring bearing an *ortho*-methoxy or methylthio group, leading to benzofurans and benzothiophenes.¹ By having a suitable group at the other end of the intermediate alkyne, a cascade reaction can result, leading to tetracyclic products.² We have recently extended this approach to *ortho*-aminophenyl ylides to produce tetracyclic ring-fused carbazoles,³ but all of the studies to date have relied on an *ortho*-disubstituted benzene ring as the basis for cyclisation. We now report that this approach is also successful with a 2,3-disubstituted pyridine as the cyclisation centre, providing convenient access to six different tetra- and pentacyclic fused ring thieno[2,3-*c*]pyridine heterocyclic systems, five of them being previously unknown. Ring-fused thieno[2,3-*c*]pyridine derivatives have been reported to have a range of medicinal applications as anti-inflammatory agents,^{4,5} GABA-A modulators with anxiolytic activity,⁶ GABA-B allosteric enhancers for the treatment of CNS disorders⁷ and agents to enhance erythropoiesis in the treatment of kidney failure.⁸

In order to test the cyclisation process, we first prepared model ylides **3** and **4** by the conversion of commercially available 2-(methylthio)nicotinic acid (**1**) into acid chloride **2** with thionyl chloride, followed by the addition of **2** to 2 equiv. of a non-stabilised phosphonium ylide in THF to give the products in excellent yield (Scheme 1).

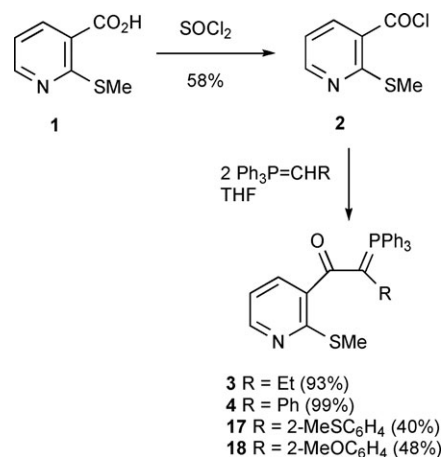
When these were subjected to flash vacuum pyrolysis (FVP) in a conventional flow system at 10^{-1} – 10^{-2} Torr, complete reaction occurred at a furnace temperature of 850 °C and the products had the expected thieno[2,3-*b*]pyridine structure (Scheme 2). The formation of vinyl compound **5** from **3** by a mechanism involving intramolecular abstraction of a hydrogen atom and the formation of phenyl compound **6** from **4** by intermolecular hydrogen atom abstraction are entirely consistent with the behaviour of benzene-based analogues.¹ The fact that

processes of this type proceed by a mechanism involving the loss of a methyl radical to give a stabilised (thio)phenoxy radical, which then cyclises onto the triple bond, has been established by previous mechanistic studies, including deuterium labelling.^{1,9}

For greater synthetic flexibility, the incorporation of an ylide functionality immediately adjacent to the pyridine ring is advantageous. Therefore, we prepared stable phosphonium salt **7** from **1** by a sequence of esterification, reduction, bromination and quaternisation with triphenylphosphine (Scheme 3). This was then readily converted into ylides **8–11**, which are suitable for investigating cascade cyclisation, by treatment with butyllithium followed by 0.5 equiv. of the appropriate arylpropenoyl chloride.

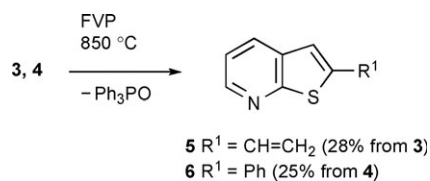
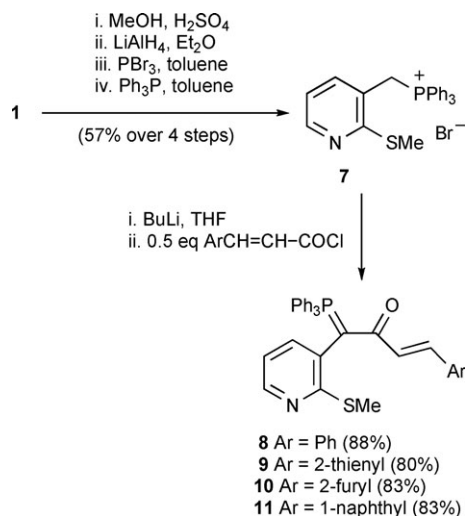
Upon FVP at 850 °C, ylides **8–10** underwent the desired conversion, and after chromatographic purification and recrystallisation, the previously unknown tetracyclic products naphtho[1',2':4,5]thieno[2,3-*b*]pyridine (**12**), benzothieno[4',5,5':4]-thieno[2,3-*b*]pyridine (**13**) and benzofuro[4',5,5':4]thieno[2,3-*b*]pyridine (**14**) were isolated in moderate yield (Scheme 4). Pyrolysis of naphthyl ylide **11** at 800 °C similarly afforded phenanthro[1',2':4,5]thieno[2,3-*b*]pyridine (**15**) in a somewhat lower yield. All four compounds are previously unknown and represent the first examples of their respective ring systems, with the sole exception of **13**, where a single previous example, functionalised compound **16**, has been described.¹⁰

In previous work, we were able to obtain tetracyclic products with a different arrangement of fused rings by designing ylides that would give an intermediate alkyne with an *ortho*-methoxyphenyl or methylthiophenyl group at each end.²

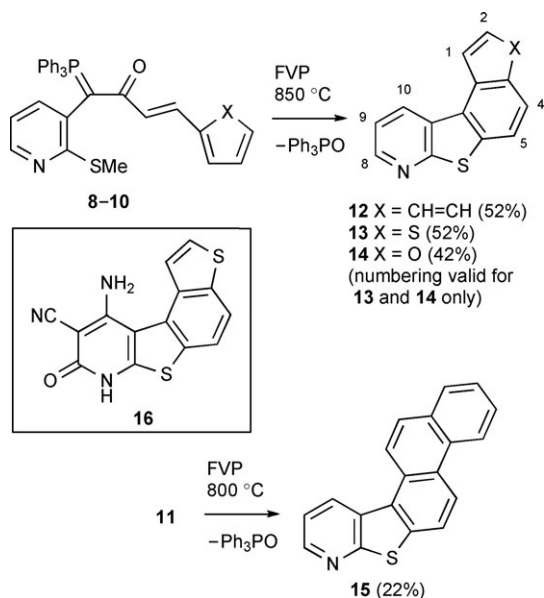


Scheme 1 The formation of ylides using acid chloride **2**.

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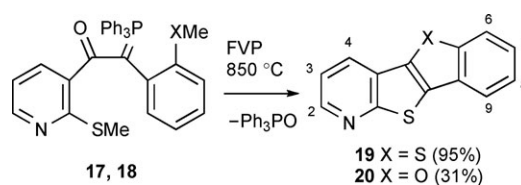
Scheme 2 Pyrolytic formation of simple thieno[2,3-*b*]pyridines.

Scheme 3 Formation of ylides using salt 7.



Scheme 4 The pyrolytic formation of fused-ring thienopyridines.

This approach was also successful in the pyridine series, and ylides **17** and **18**, prepared in moderate yield by acylation of the appropriate ylides with **2** (Scheme 1), were pyrolysed at 850 °C to give two further new tetracyclic heteroaromatic compounds, both being the first representatives of new ring systems. Thus (Scheme 5), **17** gave an excellent yield of benzothieno[2',3':4,5]thieno[2,3-*b*]pyridine (**19**) after chromatography and recrystallisation, while **18** similarly gave a lower yield of benzofuro[2',3':4,5]thieno[2,3-*b*]pyridine (**20**).



Scheme 5 The formation of a different arrangement of rings.

It is worth noting that, as far as we are aware, compounds **14** and **20** are the first to contain benzene, pyridine, thiophene and furan rings fused together in any arrangement.

We thank the EPSRC for a studentship (A.N.G.).

Experimental

Preparation of ylide 9

A suspension of phosphonium salt **7** (5 g, 10 mmol) in dry THF (40 cm³) was stirred under N₂ while a solution of butyllithium in hexanes (4.16 cm³, 2.5 M, 10 mmol) was added. The resulting deep red solution was stirred for a further 2 h before a solution of 3-(2-thienyl)propenoyl chloride (0.90 g, 5 mmol) in dry THF (10 cm³) was added. After stirring for a further 18 h, the mixture was added to water (100 cm³) and extracted with ethyl acetate (3 × 150 cm³). The combined extracts were washed with water (100 cm³), dried and evaporated to give an orange solid. This was dissolved in ethyl acetate (250 cm³), the hot solution filtered and the solid obtained on evaporation recrystallised from ethyl acetate to give the product (2.13 g, 80%) as yellow crystals. Mp 248–249 °C (found: C, 71.5; H, 4.5; N, 2.6; C₃₂H₂₆NOPS₂ requires C, 71.5; H, 4.9; N, 2.6%); $\nu_{\text{max}}/\text{cm}^{-1}$: 1618, 1504, 1201, 1104, 973, 841, 750, 717 and 693; δ_{H} (300 MHz, CDCl₃): 8.19 (1 H, d, $J = 5$ Hz, 6 H), 7.80–7.52 (7 H, m, vinyl-H and Ph), 7.52–7.28 (9 H, m, Ph), 7.12 (2 H, m, Ar-H), 7.01 (1 H, d, $J = 2$ Hz, Ar-H), 6.89 (1 H, t, $J = 2$ Hz, Ar-H), 6.67 (1 H, dd, $J = 4$ and 3 Hz, Ar-H), 6.40 (1 H, d, $J = 15$ Hz, vinyl-H) and 2.32 (3 H, s, SMe); δ_{C} (75 MHz, CDCl₃): 180.2 (d, $J = 5$ Hz, CO), 165.7 (C-2 of Pyr), 147.4 (C-6 of Pyr), 142.5 (C-1 of thienyl), 142.3 (d, $J = 3$ Hz, C-4 of Pyr), 134.0 (6C, d, $J = 10$ Hz, C-2 of Ph), 132.0 (3C, d, $J = 3$ Hz, C-4 of Ph), 131.4 (d, $J = 12$ Hz, C-3 of Pyr), 128.6 (6C, d, $J = 12$ Hz, C-3 of Ph), 128.2 (2C, thienyl), 127.2 (C=C), 126.6 (3C, d, $J = 90$ Hz, C-1 of Ph), 125.6 (d, $J = 10$ Hz, C=C), 125.6 (thienyl), 118.1 (C-5 of Pyr), 69.2 (d, $J = 111$ Hz, P=C) and 13.8 (SMe); δ_{P} (121 MHz, CDCl₃): +16.7; m/z = 535 (M^+ , 16%), 520 (11), 488 (100), 277 (14), 262 (65), 183 (45), 160 (35), 132 (35) and 91 (27).

Pyrolysis of ylide 9

Using the equipment described previously,¹¹ FVP of the title compound (0.60 g) at 825 °C and $3\text{--}5 \times 10^{-2}$ Torr gave a brown oily solid at the furnace exit. Column chromatography of this material using diethyl ether–hexane (1 : 3) as the eluent gave a pale brown solid, which was distilled at 195 °C/0.2 Torr, and the resulting material was recrystallised (EtOH) to give the product, benzothieno[4',5',5':4]thieno[2,3-*b*]pyridine (**13**) (0.14 g, 52%), as a pale brown solid. Mp 180.5–182 °C (found: C, 65.0; H, 2.6; N, 5.75; C₁₃H₇NS₂ requires C, 64.7;

H, 2.6; N, 5.8%); $\nu_{\max}/\text{cm}^{-1}$: 1549, 1398, 1211, 1163, 1109, 859, 791, 745 and 692; δ_{H} (300 MHz, CDCl_3): 8.69 (2 H, m, 8,10-H), 8.09 (1 H, d, $J = 6$ Hz, 1-H), 8.02 (1 H, d, $J = 8$ Hz, 5-H), 7.84 (1 H, d, $J = 8$ Hz, 4-H), 7.77 (1 H, d, $J = 6$ Hz, 2-H) and 7.48 (1 H, dd, $J = 8$ and 6 Hz, 9-H); δ_{C} (75 Mz, CDCl_3): 162.1, 147.6, 138.1, 135.4, 135.0, 130.9, 129.8, 128.8, 127.0, 122.2, 121.0, 119.7 and 119.3; $m/z = 241$ (M^+ , 100%), 209 (7), 196 (20), 170 (15), 152 (5), 120 (17) and 107 (25).

Pyrolysis of ylide 10

FVP of the title compound (1.0 g) at 850 °C and $1-2 \times 10^{-2}$ Torr gave a brown oily solid at the furnace exit. Column chromatography of this material using diethyl ether–hexane (1:9) as the eluent gave a pale brown waxy solid, which was recrystallised (EtOH) to give the product, benzofuro-[4',5,5':4]thieno[2,3-*b*]pyridine (**14**) (0.18 g, 42%), as a pale brown solid. Mp 144.5–146 °C (found: C, 69.6; H, 3.2; N, 6.2; $\text{C}_{13}\text{H}_7\text{NOS}$ requires C, 69.3; H, 3.1; N, 6.2%); $\nu_{\max}/\text{cm}^{-1}$: 1551, 1425, 1249, 1215, 1174, 1151, 1054, 913, 802, 782 and 748; δ_{H} (300 MHz, CDCl_3): 8.69 (1 H, d, $J = 5$ Hz, 8-H), 8.55 (1 H, d, $J = 7$ Hz, 10-H), 7.88 (1 H, d, $J = 2$ Hz, 2-H), 7.80 (1 H, d, $J = 8$ Hz, 5-H), 7.72 (1 H, d, $J = 8$ Hz, 4-H), 7.48 (1 H, dd, $J = 7$ and 5 Hz, 9-H) and 7.35 (1 H, d, $J = 2$ Hz, 1-H); δ_{C} (75 Mz, CDCl_3): 162.8, 153.7, 147.8, 146.2, 133.1, 130.3, 129.8, 125.5, 122.7, 119.6, 118.8, 112.0 and 104.8; $m/z = 225$ (M^+ , 100%), 196 (29), 170 (13), 153 (18), 126 (10), 113 (27), 99 (32) and 85 (26).

Pyrolysis of ylide 17

FVP of the title compound (1.2 g) at 850 °C and $8-9 \times 10^{-2}$ Torr gave a light brown solid at the furnace exit. Column chromatography of this material using diethyl ether–hexane (1:1) as eluent gave a beige solid, which was recrystallised (EtOH) to give the product, benzothieno[2',3':4,5]thieno[2,3-*b*]pyridine (**19**) (0.50 g, 95%), as beige crystals. Mp 184–187 °C (found: C, 65.2; H, 2.6; N, 5.6; $\text{C}_{13}\text{H}_7\text{NS}_2$ requires C, 64.7; H, 2.9; N, 5.8%) (HRMS: found M^+ (241.0023); $\text{C}_{13}\text{H}_7\text{NS}_2$ requires $M = 241.0020$); $\nu_{\max}/\text{cm}^{-1}$: 1547, 1344, 1325, 1304, 1257, 1103, 1063, 1019, 948, 793, 741 and 723; δ_{H} (300 MHz, CDCl_3): 8.57 (1 H, d, $J = 5$ Hz, 2-H), 8.12 (1 H, d, $J = 8$ Hz, 4-H), 7.98–7.86 (2 H, m, 6,9-H) and 7.55–7.32 (3 H, m); δ_{C}

(75 Mz, CDCl_3): 164.0, 146.8, 142.0, 133.4, 133.1, 130.1, 128.9, 128.0, 125.9, 125.3, 124.1, 122.3 and 119.9; $m/z = 241$ (M^+ , 100%), 209 (9), 196 (5), 183 (7) and 121 (6).

Pyrolysis of ylide 18

FVP of the title compound (1.0 g) at 850 °C and $8-9 \times 10^{-2}$ Torr gave a deep brown oil at the furnace exit. Column chromatography of this material using diethyl ether–hexane (1:3) as eluent gave a brown oil that solidified with time. The solid was recrystallised from ethanol to give the product, benzofuro[2',3':4,5]thieno[2,3-*b*]pyridine (**20**) (0.13 g, 31%), as pale brown leaves. Mp 151–153 °C (found: C, 69.8; H, 2.8; N, 6.2; $\text{C}_{13}\text{H}_7\text{NOS}$ requires C, 69.3; H, 3.1; N, 6.2%) (HRMS: found M^+ (225.0254); $\text{C}_{13}\text{H}_7\text{NOS}$ requires $M = 225.0248$); $\nu_{\max}/\text{cm}^{-1}$: 1553, 1436, 1402, 1368, 1364, 1302, 1190, 1131, 1108, 1063, 803 and 747; δ_{H} (300 MHz, CDCl_3): 8.51 (1 H, d, $J = 6$ Hz, 2-H), 8.12 (1 H, d, $J = 7$ Hz, 4-H), 7.67 (1 H, d, $J = 7$ Hz, 9-H), 7.58 (1 H, d, $J = 7$ Hz, 6-H) and 7.42–7.24 (3 H, m); δ_{C} (75 Mz, CDCl_3): 163.2, 158.3, 149.4, 146.4, 127.0, 125.7, 123.8, 123.7, 120.1, 120.1, 119.9, 118.2 and 112.6; $m/z = 225$ (M^+ , 100%), 196 (9), 135 (8) and 113 (5).

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