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Domino Vilsmeier–Haack/ring closure sequences: a facile synthesis of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes

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ABSTRACT

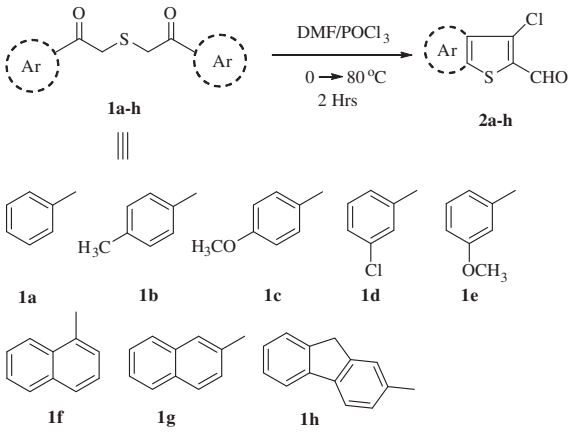
Vilsmeier's reagent treatment of substituted diphenacyl sulfides or diphenacyl disulfides has led to the formation of a series of benzfused 3-chlorothiophene-2-carbaldehydes by a Domino Vilsmeier–Haack reaction/ring closure sequence, opening a new route for the synthesis of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes and their benzfused analogues. A plausible mechanism has been proposed.

Vilsmeier–Haack reaction has emerged as a popular tool for the formylation and acylation of aromatic rings and construction of heterocycles.[1] This reaction, when carried out on active methylene compounds, leads mainly to the formation of β-halo-carboxaldehyde derivatives, which are useful precursors in the construction of different heterocyclic compounds by numerous transformations[2] and thus the Vilsmeier–Haack procedure facilitates an easy entry into various nitrogen- and oxygen-based heterocycles.[3]

Benzo[*b*]thiophene nucleus has attracted much attention as it is present in various natural products.[4] The benzo[*b*]thiophene skeleton was found to be present in several drug candidates.[5,6] Sertaconazole[7] was recently approved as a topical anti-fungal agent and zileuton[8] is used for the chronic treatment of asthma. Mobam[9] represents a potent insecticide which inhibits the enzyme acetyl cholinesterase. Many benzo[*b*]thiophene derivatives are well known to exhibit a broad range of interesting biological activities, including anti-inflammatory,[10] antidepressive,[11] antipsychotic,[12] antiviral,[13] antiallergic,[14] herpes virus inhibitors,[15] prostaglandin or dopamine receptor antagonists[16] and tubulin polymerization inhibitors.[17] Thioindigo and its derivatives are benzothiophene containing dyestuffs.[18]

3-Chlorobenzo[*b*]thiophene-2-carbaldehyde can be synthesized by one-pot intramolecular cyclization of 2-[(carboxymethyl) sulfanyl]benzoic acid under Vilsmeier–Haack condition[19] and by a two-step reduction/oxidation of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid.[20] Many other synthetic protocols for construction of benzo[*b*]thiophene derivatives[21–28] have been reported in the literature.

This Letter describes the synthesis of 3-chlorobenzo [*b*] thiophene-2-carbaldehyde and their derivatives from 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanones by a domino Vilsmeier–Haack reaction/ring closure sequence (Scheme 1). The synthesised 3-chlorobenzo[*b*]thiophene-2-carbaldehydes can be used to generate pyridylbenzo[*b*]thiophene-2-carboxamide **4** and subsequently benzo[*b*]thieno[2,3-*c*]naphthyridin-2-one **5**, which act as antitumour agents (Scheme 2).[29]



Scheme 1. Synthesis of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes **2a–h**.

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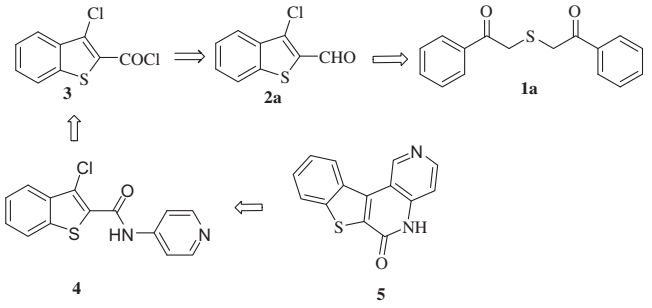


Scheme 2. Retrosynthetic route for the antitumor agent **5**.

Initially, 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanones **1a**–**h** were treated with Vilsmeier reagent at 0 °C for 10 min. The mixture quickly became viscous, but no products could be detected by TLC. When the resulting mixture was heated at 80 °C for 2 h, the reaction proceeded smoothly.[30] The products, 2,3-disubstituted benzo[*b*]thiophenes **2a**–**h** were purified by column chromatography (Scheme 1, Fig. 1). In the case of *m*-chloro and *m*-methoxy substituted aryl systems, a mixture of products, **2d**′, **2d**″ and **2e**′, **2e**″, respectively, were obtained (Fig. 1). However, the reaction seems to be regiospecific with **1g** and **1h**. In **1g**, the 1 position of naphthyl, and not 3 position, is involved in thiopohene ring formation. In **1h** also, it is found that angular cyclisation is preferred over linear cyclisation. No singlet appeared in the aryl region of the ^{1}H NMR spectrum of **2h**, differentiating the compound from its regio isomer.

The structures of benzo[*b*]thiophenes, **2** were established by ^{1}H, ^{13}C and 2D NMR spectral data as illustrated for a representative example, **2e**″. In the ^{1}H NMR spectrum of **2e**″(Fig. 2),[31] the OCH_3 protons appear as a three hydrogen singlet at 3.93 ppm and the aldehyde proton as a one hydrogen singlet at 10.31 ppm, the respective carbons appearing at 55.6 and 183.3 ppm. The doublet at 7.35 ppm with a *meta* coupling of 2.4 Hz is assigned to H-4, which is having a C,H-COSY correlation with the signal at 103.9 ppm assignable to C-4. This hydrogen has HMBC contours with carbon signals at 120.9, 129.9, 132.9 and 158.5 ppm ascribable to C-6, C-3, C-7a and C-5, respectively (Fig. 2). The doublet of doublet at 7.22 ppm (J = 9.0, 2.4 Hz) is assigned to H-6 and is having C,H-COSY correlation with the signal at 120.9 ppm. It has HMBC contours with carbon signals at 103.9, 132.9 and 158.5 ppm due to C-4, C-7a and C-5, respectively. The doublet at 7.72 ppm (J = 9.0 Hz) is assigned to H-7, which gives C,H-COSY

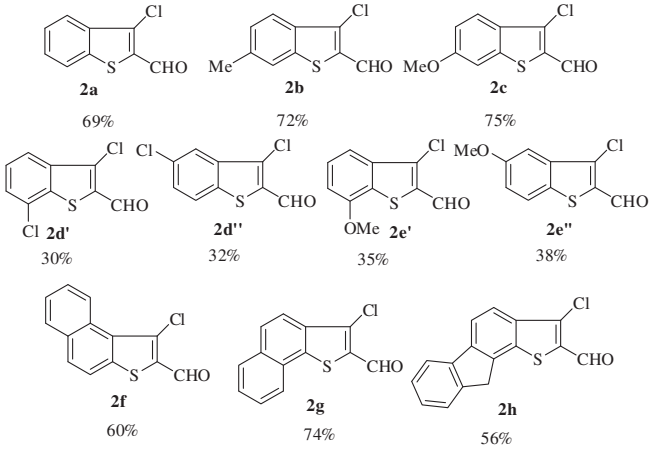


Fig. 1. Structures and yields of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes **2a**–**h**.

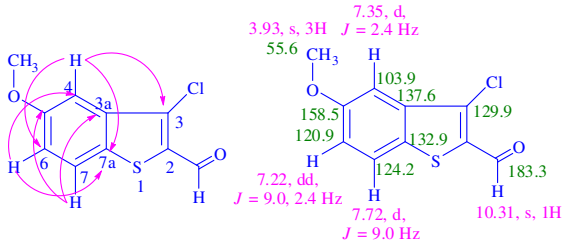


Fig. 2. Selected HMBCs and ^{1}H, ^{13}C NMR chemical shifts in **2e**″.

correlation with C-7 at 124.2 ppm and HMBC contours with C-3a at 137.6 and C-5 at 158.5 ppm. **2e**′, which is the isomeric product of **2e**″, can be distinguished unambiguously from the latter from its proton NMR spectrum. The structures of the benzo[*b*]thiophenes **2a**–**h** were further confirmed by a single crystal X-ray crystallographic study of **2g** (Fig. 3).[32]

The scope and generality of this methodology has been illustrated by carrying out the reaction with 1,5-diketones having α-,β-naphthyl and 9H-fluorene rings (Scheme 1, **1f**–**h**). Benzfused benzothiophene systems, 1-chloronaphtho[2,1-*b*]thiophene-2-carbaldehyde, 3-chloronaphtho[1,2-*b*]thiophene-2-carbaldehyde and 3-chloro-10*H*-fluoreno[1,2-*b*]thiophene-2-carbaldehyde have been obtained in good yields (Fig. 1).

A plausible mechanistic pathway for the formation of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes **2a**–**h** can be explained by an initial Vilsmeier–Haack reaction of 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanones (Scheme 3) to give functionalized chloromethyleneiminium salt intermediate **6.** Though an electrophilic attack by sulfur in the *ortho* position of the aryl ring[33] or a concerted six electron ring closure[34] could be advanced as the possible routes to the ring closure, the route shown in Scheme 3 may be credible, in which sulfide intermediate **9** is proposed. The subsequent cleavage of group X assisted by phosphorous oxychloride can lead to the observed product. The recovery of 3-chloro-3-phenyl-2-propenal from the reaction mixture, which may be obtained by the reaction of acetophenone on Vilsmeier–Haack reagent, supports the proposed mechanism. The fact that 2-naphthyl substituted system undergoes ring closure exclusively in the 1-naphthyl position and also the 2-naphthyl system undergoes reaction in a facile manner compared to 1-naphthyl system can be explained by the relative stability of the cations **11**, **12** and **13** (Fig. 4) expected in the proposed transformations.

2-Mercapto-1-phenylethanone **14** on reaction with the Vilsmeier–Haack reagent (Scheme 4, Table 1) following the above procedure yielded the same benzo[*b*]thiophenes **2**. As the dimer of 2-mercapto-1-phenylethanone **14**, 2,2′-disulfanediylbis(1-phenylethanone) **15** under similar reaction conditions provides the same product, it is proposed that the dimerisation occurs initially in the case of 2-mercapto-1-phenylethanone and the remaining

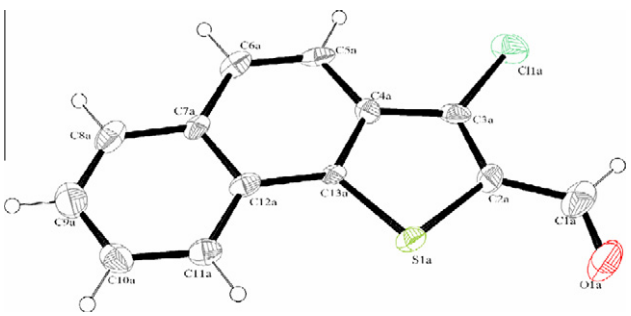
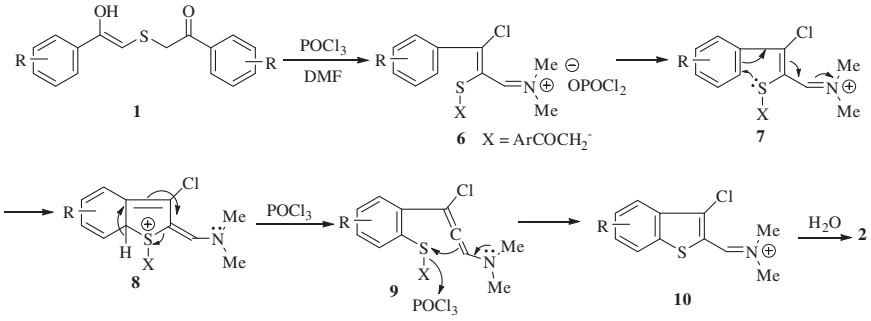


Fig. 3. ORTEP diagram of **2g**.



Scheme 3. Plausible mechanism for formation of 3-chloro benzo[*b*] thiophene-2-carbaldehydes **2**.

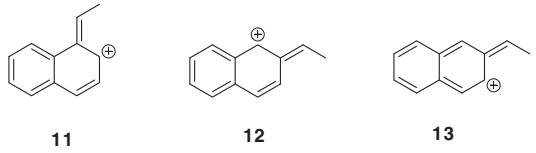
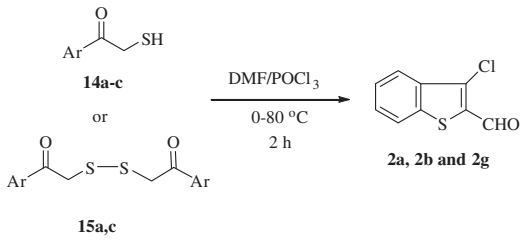


Fig. 4. Structures of cations from **1e** and **1f**.



Scheme 4. Synthesis of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes from 2,2′-disulfanediylbis(1-phenylethanone).

Table 1
Synthesis of **2a**, **2b** and **2g**

Entry	Ar	Compound	Yield from 14[a] (%)	Yield from 15[a] (%)
a	C_6H_5	**2a**	43	69
b	4-MeC_6H_4	**2b**	40	—[b]
c	2-Naphthyl	**2g**	45	72

[a] Yield after purification by column.
[b] Reaction not performed.

pathway is expected to be the same as explained above for 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanones **1**. It must be added that $ArCOCH_2SAr$ does not undergo this reaction yielding benzothiophene.

In conclusion, the use of the Vilsmeier–Haack conditions has permitted us to develop a fast method for the construction of benzo[*b*]thiophene derivatives. This methodology opens a new route to the synthesis of 3-chlorobenzo[*b*]thiophene-2-carbaldehydes, 1-chloronaphtho[2,1-*b*]thiophene-2-carbaldehyde, 3-chloronaphtho[1,2-*b*]thiophene-2-carbaldehyde and 3-chloro-10*H*-fluoreno[1,2-*b*]thiophene-2-carbaldehyde via the domino Vilsmeier–Haack reaction/intramolecular cyclization sequences.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.046.

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30. *Typical procedure for synthesis of* **2a–h**: 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanone (0.1 mol) was dissolved in dry DMF (7 ml) and the solution was cooled to 0 °C. To this cold solution $POCl_3$ (0.5 mol) was added drop wise and allowed stirring for 10 min. The temperature was increased to 80 °C and after completion of reaction (monitored by TLC) the mixture was poured into ice cold sodium acetate (0.2 mol) solution and the solid was filtered out and purified by column chromatography using ethyl acetate/petroleum ether mixture (3:1 v/v) to to yield pure **2a–h.**
31. *3-Chloro-5-methoxybenzo[b]thiophene-2-carbaldehyde* (**2e**′′). Isolated as colorless solid; yield: 38%, mp 140–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.93 (s, 3H, OCH_3), 7.22 (dd, 1H, *J* = 9.0, 2.4 Hz, Ar–H), 7.35 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.72 (d, 1H, *J* = 9.0 Hz, Ar–H), 10.31 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 55.7, 104.0, 121.0, 124.2, 130.0, 132.9, 136.1, 137.6, 158.5, 183.3. Anal. Calcd for $C_{10}H_7ClO_2S$: C, 52.99; H, 3.11%. Found C, 52.94; H, 3.05.
32. Crystallographic data (excluding structure factors) for compound **2g** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 817499. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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