Tetrahedron 65 (2009) 2430–2435

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new synthesis of benzo[*b*]thiophenes utilizing an interrupted Pummerer reaction

Kazuhiro Kobayashi *, Mai Horiuchi, Shuhei Fukamachi, Hisatoshi Konishi

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

ARTICLE INFO

Article history:
Received 8 January 2009
Received in revised form 20 January 2009
Accepted 20 January 2009
Available online 29 January 2009

Keywords:
Benzo[*b*]thiophenes
Interrupted Pummerer reaction
Sulfoxides
Acetic anhydride
Ring closure

ABSTRACT

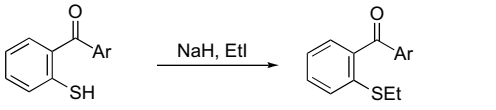
A convenient synthesis of 3-arylbenzo[*b*]thiophenes utilizing an interrupted Pummerer reaction of 2-(1-arylvinyl)phenyl ethyl sulfoxides is described. Thus, treatment of these sulfoxides, which were readily prepared from 2-sulfanylphenyl ketones or 2-fluoro-5-methoxybenzaldehyde, with acetic anhydride at 100 °C afforded 3-arylbenzo[*b*]thiophenes in reasonable yields.

1. Introduction

Literature survey has revealed that many molecules having the benzo[*b*]thiophene skeleton exhibit a wide variety of biological activities.[1] Therefore, many research groups[2] including us[3] have been developing a number of new methods for the preparation of benzo[*b*]thiophene derivatives. In this paper we wish to report a new and efficient method for the synthesis of benzo[*b*]thiophenes. We anticipated that reaction of 2-(1-arylvinyl)phenyl ethyl sulfoxides **5** with acetic anhydride would afford 3-arylbenzo[*b*]thiophenes **6**, via an interrupted Pummerer reaction,[4] because Bates et al. have reported that pyrrolo[2,1-*b*]benzothiazole is formed by treating alkyl 2-(pyrrol-1-yl)phenyl sulfoxides with trifluoroacetic anhydride.[4a] They have offered an interrupted Pummerer pathway for its formation.

2. Results and discussion

2-(1-Arylvinyl)phenyl sulfoxides **5** were readily prepared from aryl 2-ethylsulfanylphenyl ketones **2**, which were obtained by two different procedures starting with aryl 2-sulfanylphenyl ketones **1**[5] or commercially available 2-fluoro-5-methoxybenzaldehyde. In the first procedure, S-ethylation of **1** with iodoethane using sodium hydride as a base produced the corresponding 2-(ethylsulfanyl)phenyl ketones **2a**–**c** in good yields, as shown in Scheme 1. In the second procedure, aryl(2-fluoro-5-methoxyphenyl)methanones **3**, which were readily prepared from 2-fluoro-5-methoxybenzaldehyde via reaction with arylmagnesium bromide followed by the PCC oxidation in good yields (see Experimental section), were allowed to react with ethanethiol using sodium hydride as a base to give aryl 2-ethylsulfanyl-5-methoxyphenyl ketones **2d**–**i** in generally good yields, as shown in Scheme 2. A somewhat low yield was obtained with (2-fluoro-5-methoxyphenyl)(4-methoxyphenyl)methanone (**3g**). We reasoned that 4-methoxyphenyl substituent might lower the reactivity of **3g** toward sodium ethanethiolate.



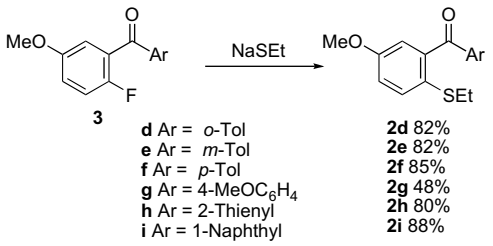
1a Ar = Ph
1b Ar = *p*-Tol
1c Ar = 4-ClC$_6$H$_4$

2a Ar = Ph 79%
2b Ar = *p*-Tol 78%
2c Ar = 4-ClC$_6$H$_4$ 81%

Scheme 1.

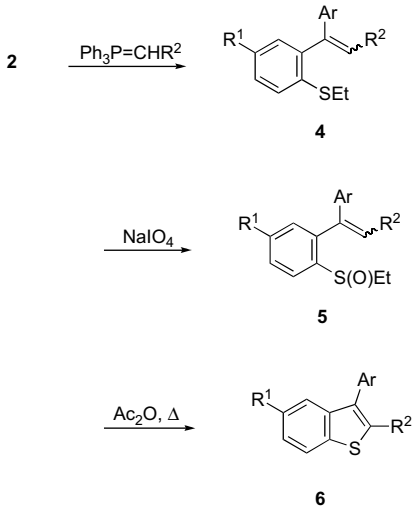
* Corresponding author. Tel./fax: +81 857 31 5263.
E-mail address: kkoba@chem.tottori-u.ac.jp (K. Kobayashi).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.01.084



Scheme 2.

We conducted the conversion of **2**, thus obtained, into 3-arylbenzo[*b*]thiophenes **6** as outlined in Scheme 3, and the results are summarized in Table 1. Thus, the reaction of compounds **2** with methylene- or ethylene-triphenylphosphorane gave 2-(ethylsulfanyl)styrene derivatives **4**, which was then oxidized with an equimolar amount of sodium metaperiodate to give 2-(1-arylvinyl)phenyl ethyl sulfoxides **5**. As can be seen from the Table, these conversions were carried out generally in good yields.

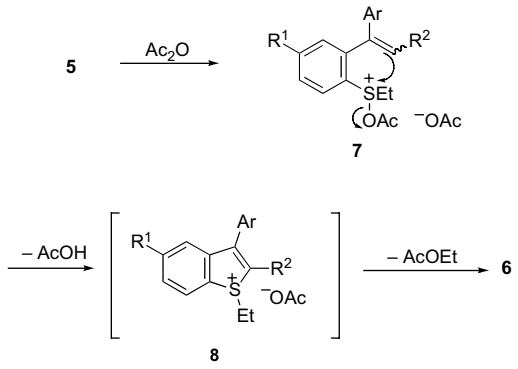


Scheme 3.

We were able to obtain 3-arylbenzo[*b*]thiophenes **6** by simply heating the sulfoxides **5** in acetic anhydride at 100 °C. We found that the reactions proceeded smoothly to give the desired products in good yields, when the α-substituents of **5** were phenyl, *p*-tolyl, 4-methoxyphenyl, 2-thienyl, or 1-naphthyl, and the β-substituent was hydrogen (entries 1, 2, 4–6, and 8–10). Poor yields were obtained, however, with ethyl (1-propenyl)phenyl sulfoxides **5c** and **5f–ii** (entries 3 and 7). Rather complicated mixtures of products were obtained, though no products arising from normal Pummerer reaction were isolated.

A limitation of the aforementioned method is that 3-alkylbenzo[*b*]thiophenes cannot be prepared. Thus, the treatment of ethyl 2-(1-methylethenyl)phenyl sulfoxide with acetic anhydride under conditions similar to those described above for the preparation of 3-arylbenzo[*b*]thiophenes **6** resulted in almost quantitative recovery of the starting sulfoxide; even the normal Pummerer product could not be formed, though we have no explanation of the reason for this.

A probable pathway leading to 3-arylbenzo[*b*]thiophenes **6** from 2-(1-arylethenyl)phenyl ethyl sulfoxides **5** is outlined in Scheme 4. This is parallel to that reported by Bates et al. for the formation of pyrrolo[2,1-*b*]benzothiazole from alkyl 2-(pyrrol-1-yl)phenyl sulfoxides.[4a] Thus, treatment of **5** with acetic anhydride generates an *S*-acetoxylated sulfonium ion intermediate **7**. The alkene π-electrons attack intramolecularly on the sulfur cation center with a loss of acetic acid to afford a benzothiophenium ion intermediate **8**. Ethyl acetate are eliminated from this intermediate to give rise to **6**. The lower yields in the reactions with ethyl (1-propenyl)phenyl sulfoxides **5c** and **5f–ii** thought to be due to unfavorable steric interaction between the methyl substituent and the ethyl group in the intermediate **8**.



Scheme 4.

In conclusion, the above-mentioned experiments have demonstrated that the treatment of 2-(1-arylethenyl)phenyl sulfoxides with acetic anhydride results in the formation of 3-arylbenzo[*b*]-thiophenes. As the present method starts with readily available materials and involves very simple manipulations, it may be of value in organic synthesis. Studies on the synthesis of sulfur-containing heterocycles utilizing this type of reaction are now under way in our laboratory.

Table 1
Preparation of benzo[*b*]thiophenes **6** from 2-(ethylsulfanyl)phenyl ketones **2**

Entry	**2**	R^2	**4** (Yield[a]/%)	**5** (Yield[a]/%)	**6** (Yield[a]/%)
1	**2a**	H	**4a** (73)	**5a** (74)	**6a** (77)
2	**2b**	H	**4b** (75)	**5b** (87)	**6b** (62)
3	**2c**	Me	**4c** (85)	**5c** (95)	**6c** (20)
4	**2d**	H	**4d** (59)	**5d** (96)	**6d** (67)
5	**2e**	H	**4e** (81)	**5e** (83)	**6e** (59)
6	**2f**	H	**4f–i** (81)	**5f–i** (93)	**6f–i** (75)
7	**2f**	Me	**4f–ii** (51)	**5f–ii** (78)	**6f–ii** (29)
8	**2g**	H	**4g** (75)	**5g** (81)	**6g** (86)
9	**2h**	H	**4h** (66)	**5h** (78)	**6h** (82)
10	**2i**	H	**4i** (76)	**5i** (92)	**6i** (78)

[a] Isolated yields.

3. Experimental

3.1. General

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.