A Convenient Synthesis of Ethyl 2-(4-Nitrophenyl)-3,4-disubstituted and *c*-Fused Thiophene-5-carboxylates

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Received January 25, 1991

A convenient one step synthesis of the hitherto unknown ethyl 2-(4-nitrophenyl)-3,4-disubstituted and *c*-fused thiophene-5-carboxylates was achieved by the condensation of ethyl 4-nitrobenzylthioacetate with a variety of 1,2-dicarbonyl compounds using sodium ethoxide in refluxing ethanol.

J. Heterocyclic Chem., **28**, 1455 (1991).

Substituted thiophene derivatives find considerable interest in the fields of biologically active compounds [1], fluorescent compounds [2] and dyestuffs [3].

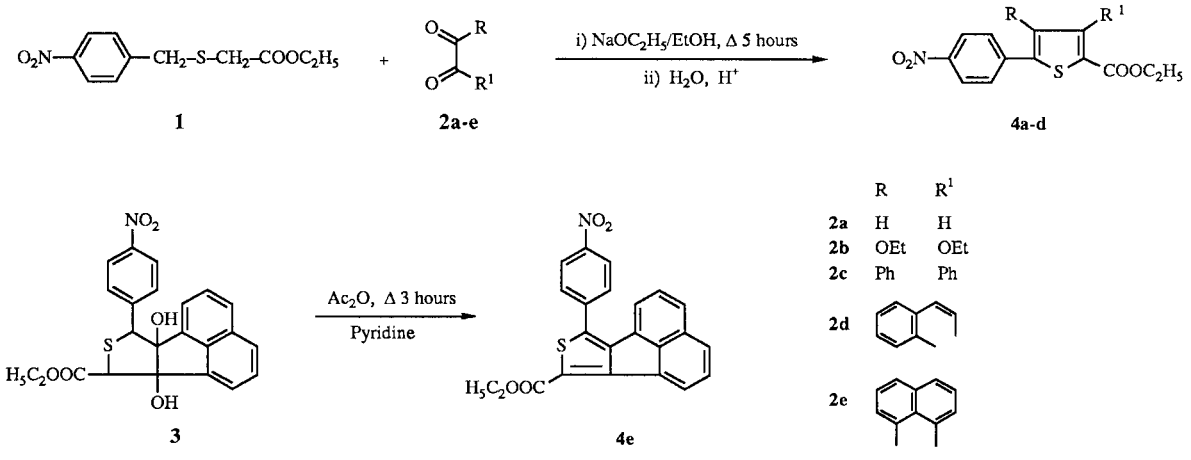
Amongst synthetic approaches described for substituted thiophenes in the literature, important methods are Gewald's Synthesis [4], Hinsberg's Synthesis [5], a method comprising of condensation of mercaptoacetic acid or its ester with suitable three carbon atom chain systems [6] and a method involving condensation of α-thioacetaldehyde or the respective ketone with acetylenic esters [7].

We wish to report in this note the synthesis of ethyl 2-(4-nitrophenyl)-3,4-disubstituted and *c*-fused thiophene-5-carboxylates **4a-e** by a convenient method. Although some symmetrical 3,4-disubstituted-2,5-dicarbethoxythiophenes have been described earlier involving condensation of α,α-dicarbethoxydimethyl sulphide with 1,2-dicarbonyl compounds using Hinsberg's synthesis [5], the unsymmerical ethyl 2-aryl-3,4-disubstituted and *c*-fused thiophene-5-carboxylates are hitherto unknown. This is probably because of the inaccessibility of a suitable unsymmetrical α,α-disubstituted (*viz.*, α-aryl-α-carbethoxy)dimethyl sulphide derivative required in the Hinsberg's synthesis of such thiophene compounds.

In connection with our study of the novel structures of arylazothiophene dyes, we have devised the following approach in synthesising a variety of 2-(4-nitrophenyl)-3,4-disubstituted and *c*-fused thiophene-5-carboxylates **4a-e**.

The key compound α-aryl-α-carbethoxydimethyl sulphide used in the present approach was ethyl 4-nitrobenzylthioacetate **1**. 4-Nitrobenzyl bromide was condensed with ethyl thioacetate to obtain **1** following the procedure described in literature [8]. Various 1,2-dicarbonyl compounds such as glyoxal **2a**, diethyl oxalate **2b**, benzil **2c**, 1,2-naphthoquinone **2d** and 1,2-acenaphthylenedione **2e** were condensed with **1**. Variations in the experimental conditions were followed using solid potassium hydroxide in ethanol, sodium ethoxide in ethanol, piperidine in ethanol and piperidine in dimethylformamide at reflux temperatures. The best yields of the compounds **4a-d** and **3** were obtained by following condensation of **1** with **2a-e** using sodium ethoxide in refluxing ethanol. In the case of the condensation of **1** with 1,2-acenaphthylenedione **2e**, the intermediate ethyl 9-(4-nitrophenyl)-6b,7,9,9e-tetrahydro-6b,9a-dihydroxyacenaphtho[1,2-*c*]thiophene-7-carboxylate **3** which resulted underwent dehydration to ethyl 9-(4-nitrophenyl)acenaphtho[1,2-*c*]thiophene-7-carboxylate

Scheme 1



4e by the treatment with catalytic pyridine in refluxing acetic anhydride.

The scope of the present synthesis is broad depending upon the availability of the suitable α-aryl-α-carbethoxydimethyl sulphides which can be condensed with several 1,2-dicarbonyl compounds to result in ethyl 2-aryl-3,4-disubstituted and *c*-fused-thiophene-5-carboxylates.

EXPERIMENTAL

All melting points are uncorrected and are in °C. The infrared spectra were recorded on a Perkin-Elmer Model 397 spectrophotometer in Nujol mulls. The ^{1}H nmr spectra were recorded on Varian-60 MHz instrument EM-360-L using TMS as the internal standard and the chemical shifts are given in δ (ppm). Mass spectra were recorded on a Varian Mat-311 instrument (70 eV).

Ethyl 2-(4-Nitrophenyl)thiophene-5-carboxylate (**4a**).

To a solution prepared by addition of 0.46 g (0.02 mole) of sodium in 100 ml of absolute ethanol was slowly added 5.10 g (0.02 mole) of ethyl 4-nitrobenzylthioacetate **1** with stirring at 5°. The reaction mixture was stirred for an additional 15 minutes and then 2.90 ml (0.02 mole) of glyoxal (40%) was added. The mixture was then refluxed for about 4-6 hours until the reaction was complete (monitored by tlc). The resultant mixture was allowed to cool to room temperature and added to an ice-water mixture. The solution was then neutralised with dilute hydrochloric acid (10%). The separated solid was filtered, washed with water and recrystallised from a dimethylformamide-ethanol (1:1) mixture which yielded 2.10 g (76%) of **4a** as a light brown crystalline solid, mp 227°; ir (nujol): (neat) 1710 cm^{-1}; ms: m/z 277 (M$^+$).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 3.97; N, 5.05; S, 11.55. Found: C, 56.36; H, 3.95; N, 5.01; S, 11.49.

Ethyl 2-(4-Nitrophenyl)-3,4-dihydroxythiophene-5-carboxylate (**4b**).

The same procedure as described for **4a** was used except diethyl oxalate **2b** was used in place of **2a**, which yielded ethyl 2-(4-nitrophenyl)-3,4-dihydroxythiophene-5-carboxylate **4b**, and was recrystallised from dimethylformamide to yield 2.13 g (69%) of **4b**, mp 280°; ir (nujol): (neat) 1700, 3280-3450 cm^{-1}; ms: m/z 309 (M$^+$).

Anal. Calcd. for $C_{13}H_{11}NO_6S$: C, 50.48; H, 3.55; N, 4.53; S, 10.35. Found: C, 50.56; H, 3.48; N, 4.50; S, 10.31.

Ethyl 2-(4-Nitrophenyl)-3,4-diphenylthiophene-5-carboxylate (**4c**).

The same procedure as described for **4a** was used except benzil **2c** was used in place of **2a**, which yielded ethyl 2-(4-nitrophenyl)-3,4-diphenylthiophene-5-carboxylate **4c** and was recrystallised from dimethylformamide to yield 3.38 g (79%) of **4c**, mp >360°; ir (nujol): (neat) 1710 cm^{-1}; ^{1}H nmr (deuteriochloroform-trifluoroacetic acid): δ 1.3 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.1-7.9 (m, 12H, aromatics H-2′, H-6′, H-8′, H-10′, H-11′, H-12′, H-14′, H-15′, H-16′, H-17′, H-18′), 8.2 (d, 2H, H-3′, H-5′).

Anal. Calcd. for $C_{25}H_{19}NO_4S$: C, 69.93; H, 4.42; N, 3.26; S, 7.45. Found: C, 69.98; H, 4.40; N, 3.21; S, 7.40.

Ethyl 2-(4-Nitrophenyl)naphtho[1,2-*c*]thiophene-5-carboxylate (**4d**).

The same procedure as described for **4a** was used except 1,2-naphthoquinone **2d** was used in place of **2a**, which yielded ethyl 3-(4-nitrophenyl)naphtho[1,2-*c*]thiophene-1-carboxylate **4d**, and was recrystallised from a dimethylformamide-ethanol (1:1) mixture to yield 2.41 g (64%) of **4d**, mp >360°; ir (nujol): (neat) 1720 cm^{-1}; ^{1}H nmr (deuteriochloroform-trifluoroacetic acid): δ 1.2 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.2-7.6 (m, 8H, aromatics, H-2′, H-6′, H-7′, H-8′, H-9′, H-10′, H-11′, H-12′), 8.0 (d, 2H, H-3′, H-5′); ms: m/z 377 (M$^+$).

Anal. Calcd. for $C_{21}H_{15}NO_4S$: C, 66.84; H, 3.97; N, 3.71; S, 8.48. Found: C, 66.90; H, 4.01; N, 3.66; S, 8.42.

Ethyl 9-(4-Nitrophenyl)-6b, 7,9,9a-tetrahydro-6b,9a-dihydroxyacenaphtho[1,2-*c*]thiophene-7-carboxylate (**3**).

The same procedure as described for **4a** was used except 1,2-acenaphthylenedione **2e** was used in place of **2a**, which yielded ethyl 9-(4-nitrophenyl)-6b,7,9,9a-tetrahydro-6b,9a-dihydroxyacenaphtho[1,2-*c*]thiophene-7-carboxylate **3**, and recrystallised from dimethylformamide to yield 2.97 g (66%) of **3**, mp 198°; ir (nujol): 1710, 3450 cm^{-1}; ms: m/z 437 (M$^+$).

Anal. Calcd. for $C_{23}H_{19}NO_6S$: C, 63.15; H, 4.34; N, 3.20; S, 7.32. Found: C, 63.09; H, 4.30; N, 3.16; S, 7.30.

Ethyl 9-(4-Nitrophenyl)acenaphtho[1,2-*c*]thiophene-7-carboxylate (**4e**).

To a solution of 20 ml of acetic unhydride containing a catalytic amount 0.5 ml of pyridine and 4.37 g (0.01 mole) of ethyl 9-(4-nitrophenyl)-6b,7,9,9a-tetrahydro-6b,9a-dihydroxyacenaphtho[1,2-*c*]thiophene-7-carboxylate **3** was added. The solution was then heated to reflux and the reflux temperature was maintained for about 3 hours until the reaction was complete (monitored by tlc). The resultant mixture was then cooled to room temperature and added to an ice-water mixture with vigorous stirring. The separated solid was filtered, washed well with cold water and dried. Recrystallisation from dimethylformamide yielded 2.64 g (66%) of **4e** as a light brown crystalline solid, mp 251°; ir (nujol): 1710 cm^{-1}, absence of broad peak at 3450 cm^{-1}; ^{1}H nmr (deuteriochloroform-trifluoroacetic acid): δ 1.3 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 7.1-7.8 (m, 8H, aromatics, H-2′, H-6′, H-8′, H-9′, H-10′, H-14′, H-15′, H-16′); 8.0 (d, 2H, H-3′, H-5′); ms: m/z 401 (M$^+$).

Anal. Calcd. for $C_{23}H_{15}NO_4S$: C, 68.82; H, 3.74; N, 3.49; S, 7.98. Found: C, 68.89; H, 3.79; N, 3.46; S, 7.95.

REFERENCES AND NOTES

[1] V. I. Shevdov and O. A. Satanova, *Khim. Farm Zh.*, **12**, 53 (1978); *Chem. Abstr.*, **90**, 87343 (1979); F. J. Tinney and W. A. Cetenko, *J. Med. Chem.*, **24**, 878 (1981); M. S. Manhas, S. D. Sharma and S. G. Amin, *J. Med. Chem.*, **15**, 106 (1972); M. B. Devani, C. J. Shishoo, U. S. Pathak, S. H. Parikh, G. F. Shah and A. C. Padhya, *J. Pharm. Sci.*, **65**, 660 (1976); J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979).

[2] A. E. Siegrist, Ciba Geigy A. G., German Offen, 2,148,512 (1972); *Chem. Abstr.*, **77**, 63355 (1972); H. Schlaepfer, Ciba Geigy A. G., German Offen, 2,355,116 (1974); *Chem. Abstr.*, **81**, 171366 (1974); G. Beck and D. Guenther, Hoechst A. G., German Offen 2,212,694 (1974), *Chem. Abstr.*, **80**, 72087 (1974); R. Bamberger, Bayer A. G., French Demande 2,010,602 (1971); *Chem. Abstr.*, **74**, 4703 (1971); M. P. Schmidt and G. A. Hagenbocker, *Ber.*, **54**, 2191 (1921); R. W. Sabnis and D. W. Rangnekar, *J. Heterocyclic Chem.*, **27**, 417 (1990).

[3] D. W. Rangnekar and R. W. Sabnis, *Dyes Pigm.*, **10**, 295 (1989); D. W. Rangnekar and R. W. Sabnis, *J. Chem. Tech. Biotechnol.*, **47**, 39 (1990).

[4] K. Gewald, E. Shinke and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).

[5] H. Wynberg and H. J. Kooreman, *J. Am. Chem. Soc.*, **87**, 1739

(1965).

[6] C. M. Beaton, N. B. Chapman, K. Clarke and J. M. Willis, *J. Chem. Soc., Perkin Trans. I*, 2355 (1976); S. Hauptmann, M. Weissenfels, M. Scholz, E. M. Werner, H. J. Koenler and J. Weisflog, *Tetrahedron Letters*, 1317 (1968); Farbwerke Hoechst A. G., British Patent 91,78,54 (1963); *Chem. Abstr.*, **59**, 3895 (1963); S. Hauptmann and F. M. Werner, *J. Prakt. Chem.*, **314**, 499 (1972); B. D. Tilak, H. S. Desai and S. S. Gupte, *Tetrahedron Letters*, 1609 (1964); H. Hartmann, J. Liebscher and A. Meissner, German Patent 91,671 (1972); *Chem. Abstr.*, **78**, 58235 (1973); J. Liebscher and H. Hartmann, J. Prakt. Chem., **318**, 731 (1976); H. Fiesselmann, Forbwerke Hoechst A. G., German Patent 1,088,507 (1958); *Chem. Abstr.*, **56**, 457 (1962); H. Fiesselmann and H. Habbicht, Farbwerk Hoechst A. G., German Patent 1,092,929 (1960); *Chem. Abstr.*, **57**, 5894 (1962).

[7] M. Derenberg and P. Hodge, *Tetrahedron Letters*, 3825 (1971); F. Bohlmann and E. Bresinsky, *Chem, Ber.*, **97**, 2109 (1964).

[8] M. E. Wain, E. M. Acton, B. R. Baker and L. Goodman, *J. Org. Chem.*, **27**, 2905 (1962).