A Novel Synthesis of Precursors to 3-Thienylmalonic Acid

Peter W. Raynolds

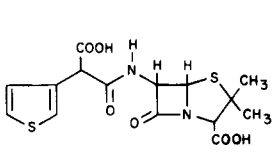
Research Laboratories, Eastman Chemicals Division, Eastman Kodak Company,
Kingsport, Tennessee 37662

Received October 11, 1983

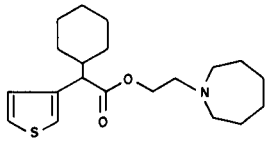
Methyl 2-cyano-2-(3-thienyl)acetate can be prepared in 95% yield by treating methyl 2-cyano-2-(3-tetrahydrothienylidene)acetate with sulfuryl chloride, followed by dehydrohalogenation with pyridine. The product can be hydrolyzed to 3-thienylmalonic acid, a pharmaceutical intermediate.

J. Heterocyclic Chem., **21**, 1231 (1984).

Thiophene-3-malonic acid, **1**, is an important intermediate in the production of the semisynthetic β-lactam antibiotic ticarcillin, **2** [1] and the diester **8b** can be used to prepare cetiedil, **3**, a peripheral vasodilator [2]. Although **1a** can be prepared from 3-methylthiophene, [3] the length of the reaction route and the high cost of the starting material have led to numerous attempts to develop a less costly, practical synthesis of 3-substituted thiophenes of this type [4]. We are reporting a novel method of preparing **8** in high yield from simple, acyclic precursors by a new and potentially general route.

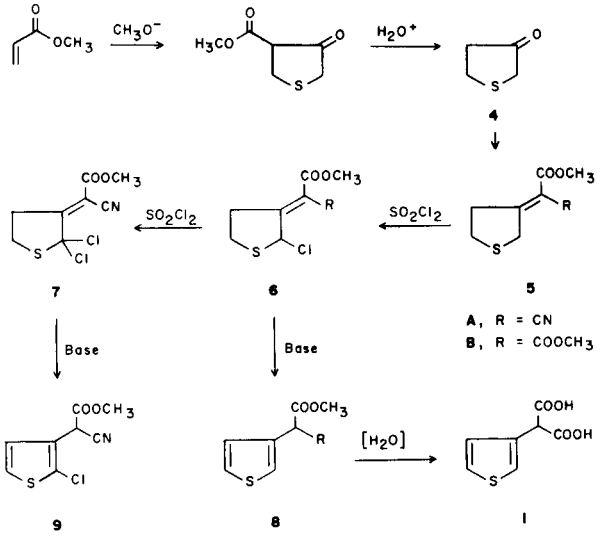


2



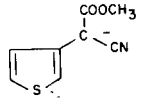
3

Known methods were used to prepare 3-ketotetrahydrothiophene, **4**, from methyl thioglycolate and methyl acrylate [5]. Although malonic esters failed to condense with the relatively unreactive carbonyl under normal Knoevenagel reaction conditions, the method of Lehnert [6] (titanium tetrachloride-pyridine) gave 92% of **5b**. More practical was the synthesis of **5a** from **4** and methyl cyanoacetate [7].



7 6 5 9 8 1

Substituted dihydrothiophenes have been dehydrogenated with disulfides [8,9] quinone reagents [8,10] and halogenating agents, [11] as well as by other methods [11,4a]. It has been observed that in many of these procedures large quantities of noxious by-products are generated, a product is obtained that is difficult to purify, or a relatively expensive oxidizing agent is required [11]. Treatment of **5a** with sulfur gave the Gewald reaction [7] and only a few percent of an unidentified thiophene was produced when **5a** was refluxed with palladium on charcoal in cyclododecene. Monochlorination (1 equivalent of sulfuryl chloride, methylene chloride, 5°, 10 minutes) and dichlorination (3 equivalents of sulfuryl chloride, methylene chloride, 25°, 3 hours) of **5a** gave **6a** and **7**, in quantitative yield as oils that decomposed when heated to above 50°. Attempts to aromatize **6a** with strong bases such as sodium methoxide or triethylamine led to the formation of tars containing little or no **8a**. It was realized that under strongly basic conditions **8a** exists in the ionized form, **10**, which could react with **6a**. The two methods shown below were devised to avoid contact of **10** with **6a**.

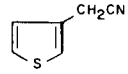


10

Pyridine was found to be a strong enough base to dehydrohalogenate **6a**, without deprotonating **8a**. When the reactions to chlorinate **5a** and to dehydrochlorinate the resultant product with pyridine were conducted in the same reactor under dilute (5 g **5a**/100 ml of dichloromethane) conditions, a 95% yield of analytically pure **8a** was obtained after aqueous workup and bulb to bulb distillation [12]. Hydrolysis of **8a** then affords **1** [1]. The yield decreased to 80% when the concentration of **5a** was raised fourfold, reflecting the bimolecular nature of the decomposition step. Similar results were obtained in the conversion of **5b** to **8b**. Chlorothiophene **9** was obtained from **7**.

Another approach to increasing the yield in the dehydrohalogenation step involves the extraction of **10** from the reaction medium. Although the yield of **8a** is very low when **6a** in dichloromethane is treated with triethylamine,

it increases dramatically when water is added to the mixture. As the triethylammonium salt of **10** is formed, it is extracted into the aqueous layer where **8a** may be recovered by acidification. A disadvantage of this approach is that the reaction conditions must be carefully controlled to keep **8** from hydrolyzing rapidly to **11**.



II

EXPERIMENTAL

A solution of 5.00 g (27.3 mmoles) of **5a** in 100 ml of methylene chloride was cooled to 5° under nitrogen, and 3.70 g (27.4 mmoles) of sulfuryl chloride in 5 ml of methylene chloride was added all at once. After 15 minutes at 5°, the solution was purged with a vigorous stream of nitrogen for 5 minutes. Pyridine (4.0 g, 50 mmoles) was added, and the solution was brought to 25° with a water bath. After 30 minutes, the reaction was quenched with 30 ml of 1 *M* sulfuric acid and 70 ml of water. The organic phase was washed with a 5% solution of sodium bicarbonate and water and then dried by passing through a cone of anhydrous calcium sulfate. Solvent was removed to yield an orange oil that was homogeneous by thin layer chromatography and gas liquid chromatography. Bulb to bulb distillation (120°/0.5 torr) yielded 4.67 g (95%) of **8a** as an analytically pure, pale yellow oil, bp 108-110°/0.5 torr (lit [13] 107-109°/0.95 torr); ir (film): 4.42 (w), 5.73 (s), 6.98 (m), 8.00 (s), 9.86 (m), 12.95 (s) μm; nmr (deuteriochloroform): δ 7.6-7.4 (m, 2H), 7.3-7.1 (d × d, J = 2, 5 Hz, 1H), 5.00 (s, 1H), 3.90 (s, 3H); uv: max 234 nm; ^{13}C nmr (deuteriochloroform): δ 165.0, 129.1, 127.5, 126.6, 124.7, 115.5, 53.9, 38.9.

Anal. Calcd. for $C_8H_7NO_2S$: C, 53.02; H, 3.89; N, 7.73; S, 17.70. Found: C, 53.28; H, 3.83; N, 7.79; S, 17.47.

REFERENCES AND NOTES

[1] U. K. Patent 1,125,557; *Chem. Abstr.*, **70**, 4105f (1969).

[2a] French Demande 2,260,575; *Chem. Abstr.*, **84**, 89988h (1976); [b] German Offen. 2,523,208; *Chem. Abstr.*, **84**, 89991d (1976).

[3] E. Campaigne and R. L. Patrick, *J. Am. Chem. Soc.*, **77**, 5425 (1955).

[4a] German Offen 2,163,523; *Chem. Abstr.*, **78**, 29613y (1973); [b] R. J. Gillespie and A. E. A. Porter *J. Chem. Soc., Perkin Trans. I*, 2624 (1979); [c] Japan Kokai 76,149,267; *Chem. Abstr.*, **87**, 68134y (1977); [d] Y. L. Gol'dfarb, A. P. Yakubov and L. I. Belen'kii, *Khim. Geterotsikl. Soedin.*, 1044 (1979); *Chem. Abstr.*, **91**, 193081n (1979); [e] U. K. Patent Appl 2,008,570; *Chem. Abstr.*, **92**, 76274n (1980); [f] J. P. Clayton, A. W. Guest, A. W. Taylor and R. Ramage, *J. Chem. Soc., Chem. Commun.*, 500 (1979); [g] German Offen. 2,854,197; *Chem. Abstr.*, **93**, 186150x (1980); [h] U. K. Patent Appl 2,009,158; *Chem. Abstr.*, **92**, 215266b (1980); [i] German Offen. 2,157, 540; *Chem. Abstr.*, **77**, 61798c (1972).

[5a] R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946); [b] O. Hromatka, D. Binder and K. Eichinger, *Monatsh. Chem.*, **104**, 1520 (1973); [c] H. Wynberg, A. Logothetis and O. VerPloeg, *J. Am. Chem. Soc.*, **79**, 1972 (1957).

[6] W. Lehnert, *Tetrahedron*, **29**, 635 (1973).

[7] K. Gewald and J. Schael, *J. Prakt. Chem.*, **315**, 39 (1973).

[8] B. D. Tilak, H. S. Desai and S. S. Gupte, *Tetrahedron Letters*, 1609 (1964).

[9] F. A. Buiter, J. H. S. Weiland and H. Wynberg, *Rec. Trav. Chim.*, **83**, 1160 (1964).

[10] J. M. McIntosh and H. Khalil, *Can. J. Chem.*, **53**, 209 (1975).

[11] P. A. Rossy, W. Hoffmann, N. Müller, *J. Org. Chem.*, **45**, 617 (1980).

[12] U. S. Patent 4,307,239; *Chem. Abstr.*, **96**, 142690f (1982).

[13] U. S. Patent 3,427,302; *Chem. Abstr.*, **70**, 68356w (1968).