An Improved Method for the Preparation of 2,5-Disubstituted Thiophenes*

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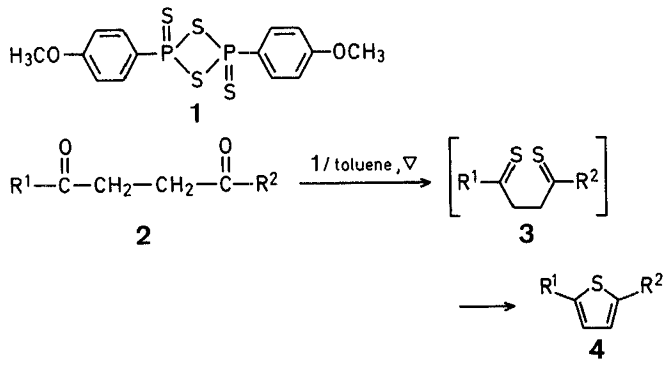
Some 2,5-disubstituted thiophenes were needed in substantial quantities as intermediates for syntheses of thiophene derivatives of medicinal interest. However, all reported methods[1-4] were found to be unsatisfactory for the preparation of these compounds on a large scale as they suffer from disadvantages such as operationally difficult reaction conditions, contamination of the desired product with difficultly separable isomers, and poor yields. Furthermore, even the classic synthesis[5] of thiophenes by the action of phosphorus(V) sulfide on 1,4-dicarbonyl compounds has been reported[6] to be generally unsatisfactory due to the formation of tarry products or unpredictable and often poor yields.

We have previously reported[7] the use of the cyclic trithiophosphonic anhydrosulfide **1** (2,4-bis[4-methoxyphenyl]-2,4-dithioxo-P^V,P^V-1,3,2,4-dithiadiphosphetane, "Lawesson reagent") for the conversion of lactams into thiolactams in nearly quantitative yields. We now report that the interaction of this reagent with 1,4-alkanediones **(2)** under mild conditions provides a convenient method for the synthesis of the desired thiophenes **(4)**.



The reaction presumably involves the formation of the 1,4-dithioxo compounds **3** as intermediates which undergo spontaneous *in situ* cyclization to give the thiophenes **4**. The structure of products **4** was confirmed by microanalyses, I.R., ^{1}H-N.M.R., and mass spectrometry.

The mild reaction conditions (heating of the components in boiling toluene for 1-2 h), the easy work-up, the high yields, and the purity of the products make the present synthesis a convenient general method for the preparation of 2,5-disubstituted thiophenes.

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were performed using a Hosli microcombustion apparatus MK 101. Mass spectra were recorded on a Varian MAT CH 7A mass spectrometer. I.R. spectra were taken on a Perkin-Elmer 577 spectrophotometer and the ^{1}H-N.M.R. spectra were recorded on a Varian A-90 (EM-390) spectrometer.

Table. 2,5-Disubstituted Thiophenes **(4)** from 1,4-Diketones **(2)**[a]

4	R^1	R^2	Yield[b] [%]	m.p. or b.p. [°C]	Molecular formula[c] or Lit. m.p. or b.p.	M.S. (70 eV) *m/e* (M^+)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	CH_3	CH_3	87[d]	b.p. 133°	b.p. 133-134°[8]	112	2.3 (s, 6H); 6.4 (s, 2H)
b	C_6H_5	CH_3	80	m.p. 49-51°	m.p. 49-51°[5]	174	2.5 (s, 3H); 6.7 (d, 1H, $J=3$ Hz); 7.05 (d, 1H, $J=3$ Hz); 7.2-7.7 (m, 5H)
c	4-H_3C—C_6H_4—	CH_3	86	m.p. 44-45°	m.p. 44.5-45°[14]	188	2.35 (s, 3H); 2.5 (s, 3H); 6.7 (d, 1H, $J=3$ Hz); 7.05 (d, 1H, $J=3$ Hz); 7.3 (AB q, 4H, $J=8$ Hz)
d	4-H_3CO—C_6H_4—	CH_3	90	m.p. 96-97°	$C_{12}H_{12}OS$ (204.2)	204	2.5 (s, 3H); 3.85 (s, 3H); 6.7 (d, 1H, $J=3$ Hz); 6.95 (d, 1H, $J=3$ Hz); 7.2 (AB q, 4H, $J=8$ Hz)
e	4-Br—C_6H_4—	CH_3	98	m.p. 127-128°	$C_{11}H_9BrS$ (253.2)	252, 254	2.50 (s, 3H); 6.76 (d, 1H, $J=3$ Hz); 7.1 (d, 1H, $J=3$ Hz); 7.43 (s, 4H)
f	C_6H_5	C_6H_5	80	m.p. 153°	m.p. 152-153°[9]	236	7.1-7.7 (m, 12H)
g	4-H_3C—C_6H_4—	4-H_3C—C_6H_4—	70	m.p. 171°	m.p. 171°[12]	264	2.4 (s, 6H); 7.27 (s, 2H); 7.4 (AB q, 8H, $J=8$ Hz)
h	C_6H_5	4-H_3CO—C_6H_4—	62	m.p. 163-164°	m.p. 164-165.5°[15]	266	3.8 (s, 3H); 6.8-7.8 (m, 11H)

[a] Compounds **2** were prepared according to Ref.[8-13].

[b] Yield of pure isolated product based on **2**.

[c] The microanalyses of the new compounds were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.30.

[d] A mixture of reagent **1** (36 mmol) and the diketone **2a** (30 mmol) is heated at 140 °C for 1 h in the absence of solvent and the resultant product **4a** is directly distilled from the reaction mixture.

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2,5-Disubstituted Thiophenes (4); General Procedure:
A stirred mixture of Lawesson reagent (**1**; 36 mmol) and the diketone **2** (30 mmol) is heated under reflux in toluene (150 ml). The progress of the reaction is monitored by T.L.C. (silica gel, hexane/benzene). After all the diketone has been consumed, the mixture is cooled to room temperature and filtered through a 25 × 5 cm column filled with silica gel using hexane/ether (1/1) as eluent. The solvent is evaporated to give the pure product **4**.

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