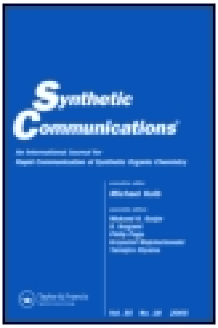

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3-Alkyl or Aryl Thiophenes from Malonaldehyde Derivatives

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3-ALKYL OR ARYL THIOPHENES FROM MALONALDEHYDE DERIVATIVES

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A synthesis of 3-alkyl or aryl thiophenes is described starting from malonaldehydes.

Thiophenes derivatives have always been of great interest to the synthetic chemist . We describe herein an easy access to thiophenes from substituted malonaldehydes derivatives. Different methods of synthesis of substituted thiophenes have been described using ring construction or substitution and coupling reactions[1]. The method described here allows the preparation of 3-aryl or-alkyl substituted thiophenes.

In the synthesis,(scheme 1), malonaldehyde derivatives $\underline{1}$ are condensed with an alkyl thioglycolate (2-mole-equivalents) in presence of a catalytic amount of an acid.

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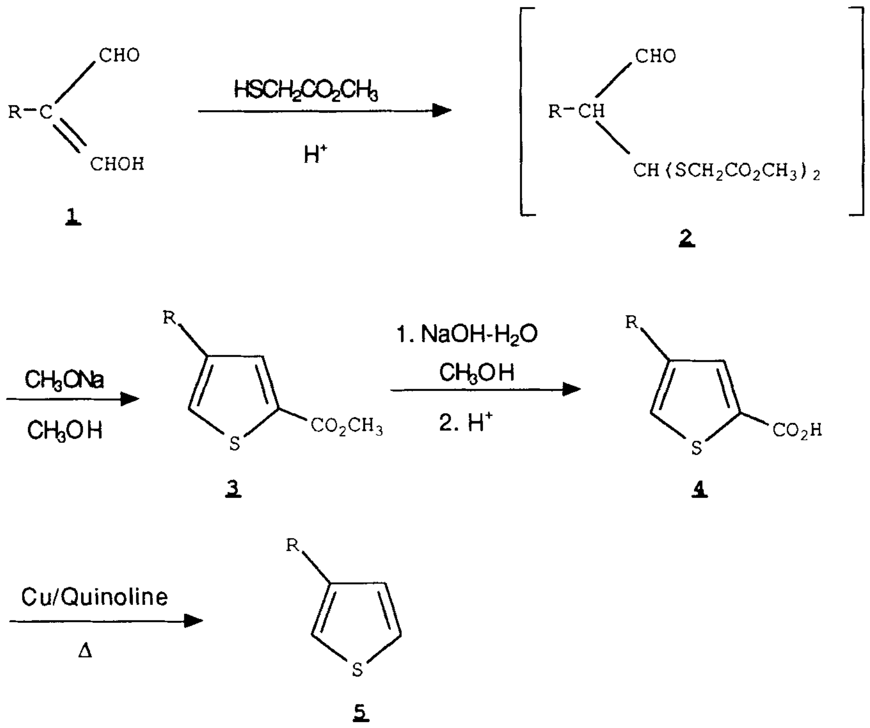
Scheme 1



1 - 5	a	b	c	d
R	nC_4H_9-	$C_6H_5CH_2-$	C_6H_5-	$pCH_3O\ C_6H_4-$

The reaction goes through the dithioketal 2, generally not isolated, which is cyclised by using an excess (3 times molar) of sodium methoxide in methanol.

Ester 3 is isolated and purified. Its hydrolysis yields the acid 4 which is easily decarboxylated by refluxing in quinoline in presence of copper bronze.

The 3-alkyl or aryl thiophenes 5 are purified by distillation or recry/stallization.

The structures of all compounds were confirmed by microanalysis and spectroscopic data (Table). The malonaldehydes present particular NMR data which were discussed elsewhere[3].

EXPERIMENTAL

Substituted malonaldehydes 1

Preparation of compounds 1a and 1b was made according to ARNOLD and SORM[4]. 1c and 1d were prepared according to JUTZ[5], the iminium-perchlorate were hydrolysed by refluxing in sodium hydroxide solution (25%).

Synthesis of carbomethoxy thiophenes 3

A mixture of malonaldehyde 1 (0,05 mole) and methylthioglycolate (0,1 mole, 10,6g) are heated to 100°. One drop of concentrated HCl is then added (temperature rises to 120-130°) and heating is maintained 15 minutes. After cooling to room temperature, the crude dithioketal 2 is added to a stirred solution of sodium (0,15 at.g. 3,6g) in methanol (50 ml). Stiring is maintained for 30 minutes. Excess of methanol is distilled off under reduced pressure and the residue taken in 500 ml of water. The thiophenes 3 are extracted with ether or separated by filtration.
Purification occurs through distillation or recristallization (methanol-water).

Preparation of 3-substituted thiophenes 5

The esters 3 were hydrolysed by refluxing with sodium hydroxide in aqueous methanol. Dilution with water, acidification by 50 % HCl and filtration yields the acids 4. For decarboxylation of 4 : a solution of the acid 4 in quinoline (5 ml quinoline for 1 g acid) with copper bronze (0,1g for 1g of acid) is refluxed for 1 h. After cooling to room temperature, the solution is poured into 50% HCl and stirred for one hour.

TABLE: Malonaldehydes and thiophenes prepared

Product	R	Yield %	mp(°C) bp(°C)/Torr	H^1NMR δppm/TMS ($CDCl_3$)
1a	nC_4H_9-	50	58 (54-55)[4]	0.9(d 3H) 1.35(m 4H) 2.2(t 2H) 8.2(s 2H) 10.5(m 1H)
1b	$C_6H_5CH_2$-	60	140 (136-137)[4]	3.55(s 2H) 7.2(s 5Harom) 8.2(s 2H) 9.85(m 1H)
1c	C_6H_5-	72	92 (92-93)[5]	7.35(s 5H) 8.63(s 2H) 13(m 1H)
1d	$pOMeC_6H_4$-	65	130	3.8(s 3H) 6.85(d 2H) 7.40(d 2H) 8.35(s 2H) 10.25(m 1H)
3a	nC_4H_9-	40	118/2.5	0.8(d 2H) 1.35(m 4H) 2.5(t 2H) 3.7(s 3H) 6.9(d 1H) 7.4(s 1H)
3b	$C_6H_5CH_2$-	51	55	3.75(s 3H) 3.88(s 2H) 7.1(m 6H) 7.5(d 1H)
3c	C_6H_5-	63	94.5	3.8(s 3H) 7.2-7.4(m 4H+1H) 7.95(d 1H)
3d	$pOMeC_6H_4$-	72	102	3.8(s 3H) 3.9(s 3H) 6.9(d 2H) 7.5(d 1H) 7.5(d1H)7.95(d 1H)

TABLE: continued

Product	R	Yield %	mp(°C) bp(°C)/Torr	H^1NMR δppm/TMS ($CDCl_3$)
4a	nC_4H_9-	90	90	0.9(d 2H) 1.40(m 4H) 2.5(t 2H) 7.1(s 1H) 7.6(s 1H) 12.8(s 1H)
4b	$C_6H_5CH_2$-	95	98 (105)^6	3.9(s 2H) 7.2(m 6H) 7.7(s 1H) 12.4(s 1H)
4c	C_6H_5-	93	167	7.27-7.5(m 6H) 8.1(d 1H) 11.1(s 1H)
4d	$pOMeC_6H_4$-	96	193	3.85(s 2H) 6.75(m 2H) 7.3-7.6(m 3H) 8.05(d 1H) 11(s 1H
5a	nC_4H_9-	70	85/15 (177)^7	0.8(d 2H) 1.35(m 4H) 7.05(m 1H) 7.1(m 6H)
5b	$C_6H_5CH_2$-	85	174/14 (109/2.3)^6	3.85(s 2H) 6.7(m 2H) 7.1(s 6H) 7.5(d 1H)
5c	C_6H_5-	88	89 (91-92)^8	7.1-7.6(m 8H)
5d	$pOMeC_6H_4$-	85	127	3.8(s 3H) 6.7(d2H,J=8.7Hz) 7.2(s 2H) 7.27(s 1H) 7.4(d 2H,J=8.7Hz)

Methylene chloride is added and the two layers system filtered with filter aid (celite) under vaccum. The filter is rinsed with methylene chloride. The organic layer is then separated, washed with water, dried with sodium sulfate and concentrated. The compounds 5 are purified by distillation or recristallization (petroleum ether).

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