Diels–Alder Reaction of Methoxythiophenes: A New One-Pot Synthesis of Dimethyl Phthalates

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A series of dimethyl phthalates have been prepared from methoxythiophenes and dimethyl acetylenedicarboxylate (DMAD) in xylene. When the reaction is carried out in acetic acid, thienylfumarates are obtained.

The thermal reaction of a thiophene, acting as a 4π component, with a dienophile in a suprafacial manner is an orbital symmetry-allowed process. There is, however, a certain unfavorable Diels–Alder equilibrium that has been explained[1] by the fact that stabilization of the antisymmetric π MO of the butadiene moiety in the thiophene by the antisymmetric 3d AO of the sulphur is no longer possible in the products.

Examples of this type of (4 + 2) cycloaddition have been restricted to reactions of thiophene itself and alkyl- and arylthiophenes with dienophiles having a reactive triple bond such as dicyanoacetylene[2] and dimethyl acetylenedicarboxylate (DMAD).[3] In the first case, reactions were carried out in closed vessels at high temperatures and in the second one, more drastic reaction conditions were used and only GC yields of dimethyl phthalates were given. In both cases, the final compounds were formed by sulfur extrusion of the initial (4 + 2) adducts. On the other hand, there are only a few examples of thiophene derivatives adding in a (4 + 2)-cycloaddition mode to strong dienophiles containing a double bond: maleic anhydride,[4] hexachlorocyclopentadiene,[5] tetrachlorothiophene 1,1-dioxide,[6] *O*-silylated oximes,[7] *o*-quinone monoimides,[8] or arsaalkenes.[9] Thiophenes are inactive towards diverse double bond dienophiles in the reaction catalyzed by cation exchange clay minerals.[10]

In this paper we describe the results of the Diels–Alder type reactions of 2- and 3-methoxythiophenes **1**, both unsubstituted and substituted with additional electron releasing groups (Me, Ph, SMe, OMe) with dimethyl acetylenedicarboxylate at atmospheric pressure in xylene or acetic acid as solvents (Scheme).

When the reaction is carried out in xylene at reflux, compounds **3** are obtained, this reaction represents a new

Table 1. Synthesis of Dimethyl Phthalates **3**

Product[a]	Reflux time (h)	Yield (%)	mp (°C) (Hexane/EtOAc)	IR (Nujol) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
3a[b]	96[c]	17		–	–
3b[b]	48	16	oil	–	–
3c[b]	48	28		–	–
3d	48	35	oil	1730, 1710	2.40 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 7.08 (s, 1H, H3), 7.43 (s, 1H, H6).
3e	48	26	oil	1740, 1720	3.80 (s, 3H, OCH_3), 3.94 (s, 6H, $2CO_2CH_3$), 7.18 (s, 1H, H3), 7.30–7.60 (m, 5H, phenyl), 7.75 (s, 1H, H6).
3f[b]	24	48		–	–
3g	4	75	oil	1740, 1700	2.30 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 7.29 (d, 1H, *J* = 10 Hz, H5), 7.70 (s, 1H, *J* = 10 Hz, H6).
3h[b]	24	56	oil	–	–
3i	8	62	82–83	1740, 1710	2.39 (s, 3H, SCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 6.95 (d, 1H, *J* = 2.0 Hz, H4), 7.20 (d, 1H, *J* = 2.0 Hz, H6).
3j[b]	1.5	68		–	–
3k	24	58	86–87	1720 (br)	2.17 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.86 (s, 6H, $2CO_2CH_3$), 7.29 (s, 1H_{arom}).
3l	3	68	74–76	1730, 1710	2.30 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 3.97 (s, 6H, $2CO_2CH_3$), 7.53 (s, 1H_{arom}).
3m[b]	2	55		–	–
3n	2	58	115–117	1720 (br)	3.26 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 3.86 (s, 3H, CO_2CH_3), 7.36 (s, 6H_{arom}).
3o	5	51	86–88	1720 (br)	3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 6H, $2CO_2CH_3$), 7.33 (s, 1H_{arom}).

[a] Satisfactory microanalyses obtained: C ± 0.22, H ± 0.07, S ± 0.20, Cl ± 0.19.

[b] These compounds are described in the literature: **3a**,[12,13] mp 76–78 °C; **3b**,[13] oil; **3c**,[13] mp 69 °C; **3f**,[13,14] mp 68.0–68.5 °C; **3h**,[13] oil; **3j**,[15] mp 99 °C; **3m**,[16] mp 68–69 °C. Their physical and spectroscopic data are in agreement with literature.

[c] The following solvent systems were used as eluents for purification of the products by flash chromatography on silica gel: **3a–c**, **e**, **h**, **i** (hexane/EtOAc, 5 : 1); **3d** (hexane/EtOAc, 3 : 1), **3f**, **g**, **j–o** (hexane/EtOAc, 5 : 2).

one-pot synthesis of dimethyl phthalates. The reaction possibly occurs through a bicyclic intermediate **2**, which leads to compounds **3** by sulfur extrusion in agreement with references.[2,3] This reaction takes a different course than that of 3-pyrrolidinothiophenes with dimethyl acetylenedicarboxylate in polar solvents, which is a (2 + 2) cycloaddition.[11]

The yields of dimethyl phthalates are related to the nature and position of the substituents in thiophene. When there is only a methoxy group on the thiophene nucleus (**1a, b**) the yields are low, but the presence of other electron releasing groups increase the reactivity (shorter reflux time and better yields) in the expected order, OMe > SMe ≥ Ph ≈ Me (Table 1).

For the 3-methoxy derivatives, substitution at the 5-position (**1h–j**) is more efficient than substitution at the 4-position (**1c–e**) as shown by doubling of yields in nearly half the reaction time from **1h–j** in relation to **1c–e**. The introduction of other substituents (Me or Ph) (**1k–n**) in the 4-position of the 3,5-derivatives does not produce remarkable variations on the reaction rate or in the yields, but if the substituent is a chlorine atom (**1o**) the reactivity decreases.

Nevertheless, the most reactive compound in the series is the 2-methoxy-3-methylthiophene (**1g**) (1 h, 75 % yield), while its isomer 3-methoxy-2-methylthiophene (**1f**) has a rather lower reactivity (24 h, 48 % yield). All these data allow the important influence of the 2- and 5-positions of the thiophene nucleus closer to the sulfur atom to be established.

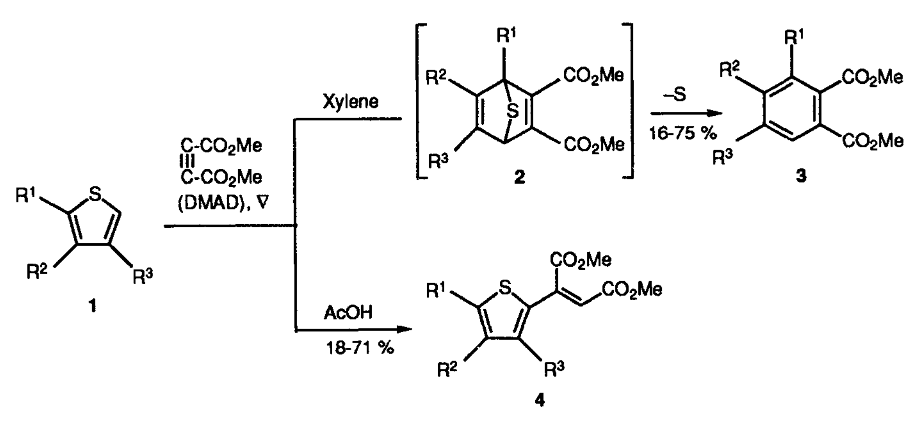
When the reaction is carried out in acetic acid it takes a different course and the isolated products are the thienylfumarates **4** (Table 2) corresponding to a Michael addition of the 2-position of the thiophene to the triple bond of dimethyl acetylenedicarboxylate. Yields of compounds **4** are very similar to that observed for compounds **3** but reaction times are rather lower. The structures of **4** were assigned on the basis of the spectroscopic data, specially the ^{1}H NMR data of the derivatives with the 3-position unsubstituted **1a, 1b** and **1g** (R^3 = H). These compounds show a singlet corresponding to the H-3, instead of the doublet expected for compounds **2**.

Melting points were measured on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-435 IR spectrophotometer and ^{1}H NMR on a Bruker AM (200 MHz) spectrometer. All the reagents used were of commercial grade and used as received. TLC plates and silica gel (230–240 mesh) were from E. Merck, Darmstadt. Microanalyses were done on a Perkin-Elmer 240 analyzer.

The starting compounds **1** were prepared according to the literature: **1a**,[17] **1b**,[18] **1c–e**,[19] **1f**,[20] **1g**,[21] **1h, i**,[22] **1j**,[23] **1k, l**,[22] **1m, n**,[24] and **1o**.[23]

Dimethyl Phthalates 3; General Procedure:
DMAD (3.0 g, 0.021 mol) was added to a solution of the corresponding methoxythiophene **1** (0.007 mol) in xylene (15 mL) and the mixture was refluxed for the time shown in Table 1. After cooling the solvent was removed in vacuo and the residue was purified by column flash chromatography on silica gel using mixtures of EtOAc and hexane as eluents (Table 1).

Thienyl Fumarates 4; General Procedure:
DMAD (3.0 g, 0.021 mol) was added to a solution of the corresponding methoxythiophene **1** (0.007 mol) in HOAc (15 mL) and



1-4	R¹	R²	R³	1-4	R¹	R²	R³
a	OMe	H	H	**i**	SMe	H	OMe
b	H	OMe	H	**j**	OMe	H	OMe
c	H	OMe	Me	**k**	Me	Me	OMe
d	H	OMe	SMe	**l**	SMe	Me	OMe
e	H	OMe	Ph	**m**	OMe	Me	OMe
f	Me	OMe	H	**n**	OMe	Ph	OMe
g	OMe	Me	H	**o**	OMe	Cl	OMe
h	Me	H	OMe				

Scheme

Table 2. Synthesis of Thienyl Fumarates **4**

Product[a]	Reflux time (h)	Yield (%)	mp (°C) (Hexane/EtOAc)	IR (Film/Nujol) $\nu_{C=O}$ (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	8	28	58–60	1735, 1705	3.70 (s, 3H, OCH_3), 3.86 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 5.90 (s, 1H, CH=C), 6.13 (d, 1H, J = 3.0, H-4 thiophene), 6.83 (d, 1H, J = 3.0, H-3 thiophene)
4b	6	18	oil	1720	3.67 (s, 3H, OCH_3), 3.73 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 6.76 (s, 1H, CH=C), 6.79 (d, 1H, J = 5.0, H-4 thiophene), 7.31 (d, 1H, J = 5.0, H-5 thiophene)
4c	7	37	oil	1720	2.07 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.63 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 6.83 (s, 1H, CH=C), 6.90 (s, 1H, H-5 thiophene)
4e	7	23	112–113	1735–1710	3.33 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 6.23 (s, 1H, CH=C), 7.20–7.66 (m, 6H_{arom})
4g	0.2	69	97–98	1735–1700	1.98 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.90 (s, 6H, 2CO_2CH_3), 5.90 (s, 1H, CH=C), 6.76 (s, 1H, H-3 thiophene)
4h	4	52	oil	1730	2.24 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.91 (s, 3H, CO_2CH_3), 6.18 (s, 1H, CH=C), 6.74 (s, 1H, H-4 thiophene)
4i	2	53	81–82	1730–1705	2.50 (s, 3H, SCH_3), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 6.13 (s, 1H, CH=C), 6.70 (s, 1H, H-4 thiophene)
4j	0.25	71	110–112	1740, 1700	3.67 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.83 (s, 6H, 2CO_2CH_3), 5.87 (s, 1H, CH=C), 6.02 (s, 1H, H-4 thiophene)
4k	8	65	oil	1720	1.95 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 6.70 (s, 1H, CH=C)
4l	1.5	41	oil	1730, 1710	2.07 (s, 3H, CH_3), 2.37 (s, 3H, SCH_3), 3.60 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 6.80 (s, 1H, CH=C)
4m	2	58	96–97	1740, 1710	1.97 (s, 3H, CH_3), 3.70 (s, 6H, 2OCH_3), 3.90 (s, 6H, 2CO_2CH_3), 5.87 (s, 1H, CH=C)
4n	2	57	104–106	1735, 1710	3.30 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.88 (s, 6H, 2CO_2CH_3), 5.95 (s, 1H, CH=C), 7.24–7.70 (m, 5H, C_6H_5)
4o	2	39	oil	1720	3.65 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 5.90 (s, 1H, CH=C)

[a] Satisfactory microanalyses obtained: C ± 0.30; H ± 0.07; S ± 0.32; Cl ± 0.28.

the mixture was refluxed for the time shown in Table 2. After cooling, the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel, using as eluent a mixture of EtOAc and hexane (5:1) as eluent (Table 2).

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