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Reactivity of Thienyl Phosphonyl Carbinols in Acidic Medium: Synthesis of Aryl- and Alkoxy-Thienyl Methan Derivatives

Maurizio D'Auria [a] , Franco D'Onofrio [a] & Floriana Sciarroni [a]

[a] CNR, Centre per lo Studio della Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Universita di Roma "La Sapienza", P. le A. Moro 2, 00185, Roma, Italy

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REACTIVITY OF THIENYL PHOSPHONYL CARBINOLS IN ACIDIC MEDIUM: SYNTHESIS OF ARYL- AND ALKOXY-THIENYL METHAN DERIVATIVES.

Maurizio D'Auria, Franco D'Onofrio*, and Floriana Sciarroni

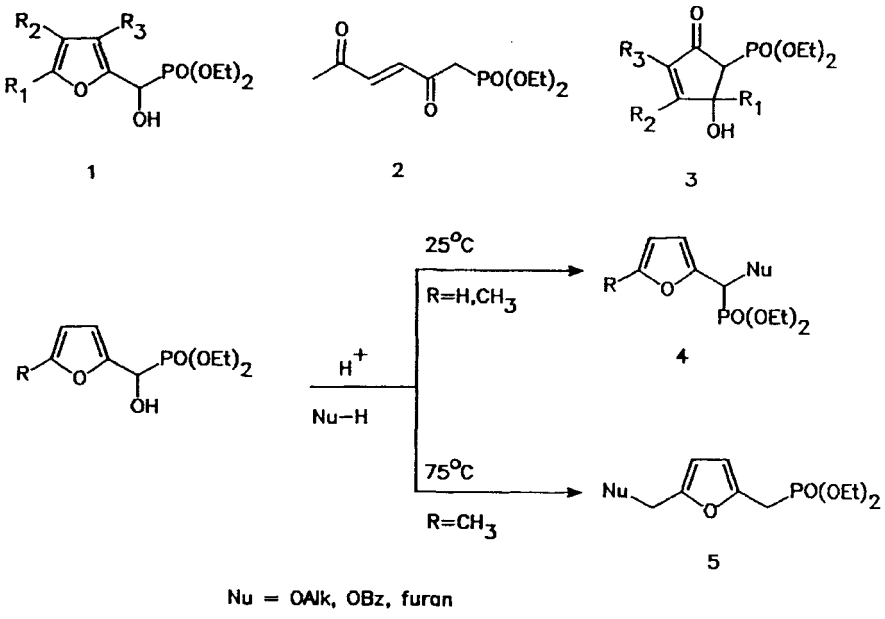
CNR, Centro per lo Studio della Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università di Roma "La Sapienza", P.le A. Moro 2, 00185 Roma, Italy

Abstract - 2-Thienyl-phosphonylcarbinols in acidic medium gave with alcohols and aromatic derivatives two classes of new compounds depending on the reaction temperature.

In previous papers some studies about the reactivity of 2-furyl-phosphonylcarbinols 1 in acidic medium have been reported. In hydrolitic conditions these compounds furnished ring opening reaction products such as 2 in drastic conditions, or, previa

*) To whom correspondence should be addressed

substitution of the hydroxyl group with chlorine, underwent a well-known rearrangement into the corresponding 4-hydroxy-cyclopent-2-enones 3 in buffered solution.[1,2] Otherwise, operating in anhydrous conditions to prevent both the rearrangement and the ring opening reaction, an unusual reactivity was observed.[3,4] In fact, in presence of nucleophiles different from water, such as alcohols or furan, two type of product, 4 and 5, were obtained, the distribution of which depending on the temperature.



Because our interest in the chemistry of heterocycles and their use as auxiliares in the synthesis of natural compounds, we decided to extend this study to analogous thiophene derivatives. In our mind the success of this methodology applied on thiopene could permit to obtain compounds both never described and potentially useful as precursors of bioactive natural substances.

Results and discussion

Starting materials 6a-g were easily prepared in near quantitative yield by reaction of the suitable aldehyde with diethyl (or dimethyl) phosphite in the presence of triethylamine. When not commercially available the starting aldehydes were prepared according with the described methods.[5] (Table 1)

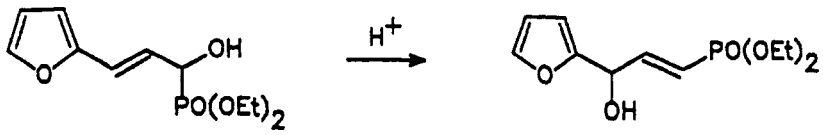
In similar manner phosphonyl-carbinols deriving from benzaldehyde, p-methoxybenzaldehyde, crotonaldehyde, 2,4-hexadienal, were prepered, but these compounds in acidic conditions and in the presence of various nucleophiles slowly decomposed. Furfurilidene-phosphonylcarbinol 7 showed only the isomerization of the double bond to yield the stable vinylphosphonate 8, according with the usual reactivity of similar compounds.[6]

TABLE 1 - Synthesis of thienyl-phosphonylcarbinols.

$$R^1\text{-CHO} \xrightarrow[Et_3N,\ 25^oC,\ 24\ h]{HOP(OR^2)_2} R^1\text{-CH(OH)-PO(OR}^2)_2 \quad \underline{6}$$

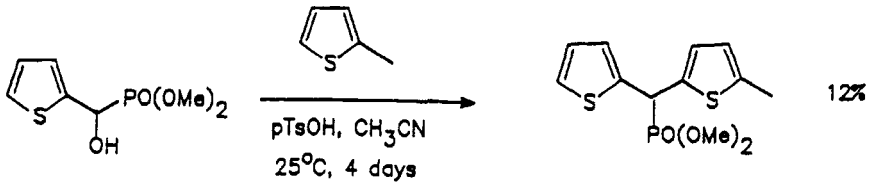
6	R^1	R^2	Yield (%)[a]
a	2-thienyl	Me	88
b	3-thienyl	Me	90
c	2-(3-methylthienyl)	Me	90
d	2-(4-methylthienyl)	Et	92
e	2-(5-methylthienyl)	Et	95
f	2-(3,5-dimethylthienyl)	Et	92
g	2-(4,5-dimethylthienyl)	Me	90

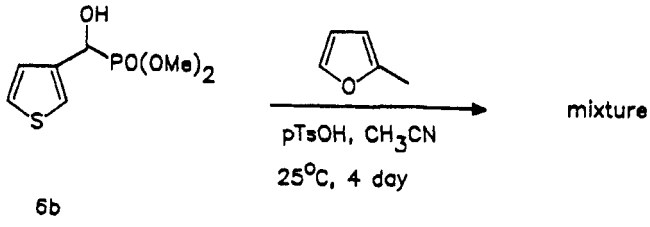
a) All the yields refer to the isolated chromatografically pure compounds



7 8

Low temperature reaction. In this set of experiments starting material 6a-f were dissolved in acetonitrile and treated with p-TsOH at room temperature (Table 2). These experiments allowed us to have some informations about the effects on the reactivity of a) the nature of the substrate, b) the acid catalyst, and c) the solvent used. In fact, on regard the thienylcarbinols 6, the presence of at least one methyl group on the ring is required (Table 2). Compounds 6a,b reacted very slowly giving after prolonged reaction time complex mixtures of products. Only poor yields of 9w were obtained.





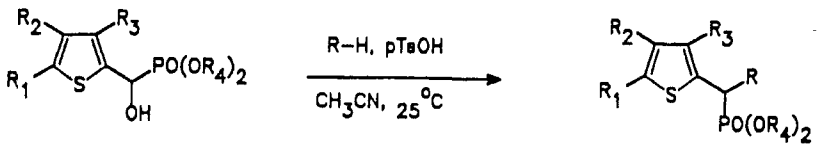
The behaviour of 6d is borderline (entry 18) whereas good results were obtained from 6c (entry 17), 6e

(entries 1 - 14), 6g (entry 19), 6f (entry 20), the last compound being the more reactive.

As regard the effect of both the solvent and the catalyst, the best results were obtained by using acetonitrile as solvent and p-TsOH in equimolecolar amount as catalyst. Among the most common solvents (acetone, chloroform, DMSO, DME, ethyl ether, HMPT, sulfolane) only chloroform gave similar results; prolonged reaction times (4 days) were observed using $BF_3 \cdot Et_2O$ instead of p-TsOH (24 h). Amberlyst 15, gaseous hydrochloric acid, zinc chloride, sulforic acid did not give good results. An excess of nucleophile was used.

In order to estimate the general validity of the method, model compound 6e was tested toward numerous substances. 6e furnishes generally good yields of the corresponding compounds 9a-p both in eterification process with simple alcohols (entries 1 and 2) and in alkylation reaction; when a possible competition between these two processes could be observed (entry 12), the eterification product was isolated only in trace. In the case of phenol (entry 3) only the formation of the para alkylation product was observed. In agreement with above reported results, when heteroaromatic compounds were used alkylation at the

TABLE 2 - "Low Temperature reactions"



6 9

Entry	R_1	R_2	R_3	R_4	Product	R	Yield (%)
1	Me	H	H	Et	**9a**	methoxy	92
2	Me	H	H	Et	**9b**	benzyloxy	80
3	Me	H	H	Et	**9c**	1-(4-hydroxy)-phenyl	88
4	Me	H	H	Et	**9d**	2-thienyl	64
5	Me	H	H	Et	**9e**	2-furyl	92
6	Me	H	H	Et	**9f**	2-(5-methylfuryl)	95
7	Me	H	H	Et	**9g**	2-(3-methylthienyl)	70

(continued)

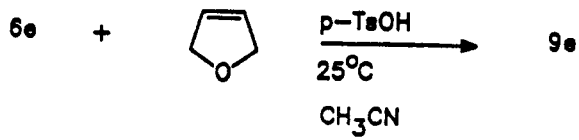
TABLE 2 - "Low Temperature reactions"(continued)

Entry	R_1	R_2	R_3	R_4	Product	R	Yield (%)
8	Me	H	H	Et	**9h**	2-(5-ethylthienyl)	90
9	Me	H	H	Et	**9i**	3-(2,5-dimethylthienyl)	92
10	Me	H	H	Et	**9j**	2-(5-bromothienyl)	45
11	Me	H	H	Et	**9k**	2-[5-(3-oxopropenyl)-furyl]	85
12	Me	H	H	Et	**9l**	2-(5-thienylethanol)	81
13	Me	H	H	Et	**9m**	2-(3-bromofuryl)	20
					9n	2-(4-bromofuryl)	40
14	Me	H	H	Et	**9o**	2-(3-hydroxymethylfuryl)	34
					9p	2-(4-hydroxymethylfuryl)	40
15	H	H	Me	Me	**9q**	benzyloxy	88
16	H	H	Me	Me	**9r**	2-(5-methylfuryl)	86

Entry	R_1	R_2	R_3	R_4	Product	R	Yield (%)
17	H	H	Me	Me	**9s**	2-(5-methylthienyl)	81
18	H	Me	H	Et	**9t**	2-(5-methylfuryl)	39
19	Me	Me	H	Me	**9u**	2-(5-methylfuryl)	76
20	Me	H	Me	Et	**9v**	2-(5-methylfuryl)	98

All the yields refer to isolated chromatographycally pure products.

free 2-position occurred. When α-positions are unaccessible (entry 9), good yields of the ß-alkylation product were obtained by using 2,5-dimethylthiophene. On the contrary 2,5-dimethylfuran did not furnish appreciable results. A mixture of two isomers was obtained when a substituent in ß-position on the heterocycles was present (entries 13 and 14) except for 3-methylthiophene (entry 7) where a good regioselectivity was observed favouring the alkylation product in 2-position 9g; analogous compound 9s was obtained from 6c and 2-methylthiophene (entry 17). It is noteworthy that using furan (entry 5) or 2,5-dihydrofuran, the same product 9e was obtained.

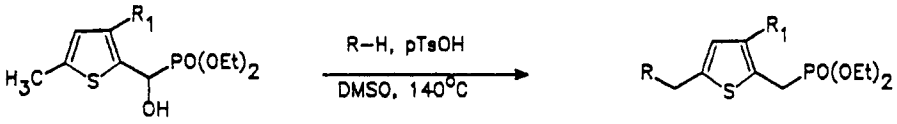


High temperature reaction. As reported above, when 2-furyl-phosphonylcarbinols 1 were treated at 75°C with a nucleophile, compounds 5 were obtained. When analogous thiophene derivatives 6 were treated in the same conditions higher temperature was required to obtain compounds 10. Probably this behaviour was due to the different aromaticity of thiophene and furan rings, according with the proposed mechanism.[3]

Complete regioselectivity was observed only using temperature higher than 120°C. This parameter was optimized and all the experiments were performed at 140°C in DMSO. Every other tested solvent (acetone, chloroform, diethylether, acetonitrile in autoclave, HMPT) gave bad results. The presence of a methyl group in 5-position is required to obtain 10. It is notewhorty that 6c, with a methyl group in 3-position, that in principle could have shown the same reactivity, did not furnish any product. Moreover 6g, with methyl groups in both 4 and 5-positions of the thienyl ring, did not yield the expected product 10. As observed in the case of "low temperature reactions", 6f showed to be more reactive than 6e: to use the same reaction time (20 min.), 6f required only an half quantity of acid compared to 6c. p-TsOH proved to be the best catalyst. In this type of reactions Lewis acids such as $ZnCl_2$, $BF_3 \cdot Et_2O$ and $AlCl_3$ did not give good yields: in fact $ZnCl_2$ was ineffective whereas $AlCl_3$ quickly destroyed the substrates. Worse yields were obtained by using $BF_3 \cdot Et_2O$ due the prolonged reaction time.

As showed in the Table 3 the best yields (54%) were obtained using benzyl alcohol as nucleophile (entries 1 and 7). The not high yields can be explained

TABLE 3 - "High temperature reactions"



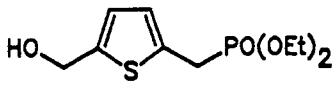
6 10

Entry	R_1	Product	R	Yield (%)
1	H	**10a**	benzyloxy	54
2	H	**10b**	1-(4-hydroxy)-phenyl	50
3	H	**10c**	2-furyl	45
4	H	**10d**	2-thienyl	40
5	Me	**10e**	2-furyl	52
6	Me	**10f**	2-(5-methylthienyl)	42
7	Me	**10g**	benzyloxy	54
8	Me	**10h**	1-(4-hydroxy)-phenyl	51
9	Me	**10i**	2-thienyl	38

All the yields refer to isolated chromatographycally pure products.

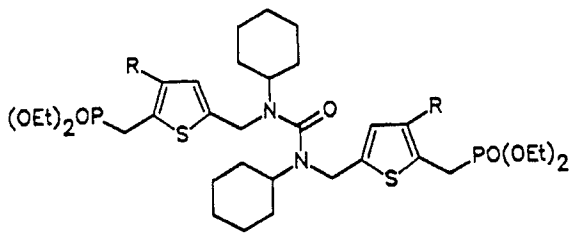
considering that two competitive process occurs. In fact, in so drastic conditions substrates 6e,f decomposed to give starting aldehydes and diethyl phosphite. Furthermore compound 11 was isolated in all

the experiments in 10-15 % yields. Probably this compound derived from the attack of water on the substrate. Water is present both in p-TsOH and as by product of the reaction. The possibility to use water as nucleophile was attractive, but all the attempts devoted to obtain 11 in appreciable yields failed.



11

In order to minimize the formation of 11, dicyclohexylcarbodiimmide (DCC) was added to the reaction mixture but in this case only the disubstituted urea 12 was isolated (48%).



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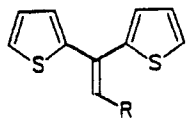
Conclusions

This work represents one of the rare cases in which a positive charge in α-position at a phosphonate group

is formed.[1,2,3,4,7] This behaviour does not seem to be generalizable to all phosphonylcarbinols and, as reported above, even using heterocyclic compounds the reactivity greatly depends on the substitution model on the ring. Moreover, at least as regard "high temperature reaction" the not high yields make the method not very useful. On the other hand, the achievement of products like 10a and 10g could be interest from a synthetic point of view, considering the easiness to remove the benzyl group, having realized a head-to-tail functionalization. The possibility to perform a Wittig-Horner reaction on thienyl or furyl methanephosphonate is well documented.[4,8] This make the method, in particular as regards the "low temperature reaction" potentially useful in the synthesis of a class of compounds having the structure 13, that are of farmacologically



13

interest.[9] Further studies on the application of new compounds 9 and 10 to organic synthesis are currently in progress.

Experimental

^{1}H-NMR spectra were recorded with a Varian Gemini 200 instrument using $CDCl_3$ as solvent. IR spectra were obtained on a Perkin-Elmer 457 spectrometer. Mass spectra were obtained with a Hewlett-Packard 5971A mass selective detector connected with a Hewlett-Packard 5890 gas chromatografic instrument and with a Hewlett-Packard 9000 central processor.

Starting materials

All the starting materials were obtained from the corresponding aldehydes by reaction with equimolecular amounts of diethyl or dimethylphosphite in presence of a equimolecolar amount of triethylamine.[10] The reaction mixtures were stirred for 24 h at 25°C. After removal under vacuum of the amine the crude products were chromatographed on SiO_2 using ethyl acetate as eluent. Pure compounds 6a-g were obtained as dense oils that solidified in refrigerator.

Diethyl 2-thienyl-hydroxymethyl-phosphonate 6a - ^{1}H-NMR ($CDCl_3$) δ: 1.23, 1.27 (2t, 6 H, J = 7 Hz), 4.0 - 4.2 (m, 4 H), 4.2 - 4.4 (m, 1 H), 5.20 (d, 1 H, J = 11 Hz), 6.97 (dd, 1 H, J_1 = 5 Hz, J_2 = 3.5 Hz), 7.16 (dd, 1 H, J_1 = 3.5 Hz, J_2 = 3 Hz), 7.27 (d, 1 H, J = 5 Hz); IR (CCl_4) ν_{max}: 3270 cm^{-1}; MS (m/z) 250 (M^+).

Diethyl 3-thienyl-hydroxymethyl-phosphonate 6b - ^{1}H-NMR ($CDCl_3$) δ: 1.19, 1.25 (2t, 6 H, J = 7 Hz), 3.9 - 4.2 (m, 4 H), 4.2 - 4.5 (m, 1 H), 5.06 (d, 1 H, J = 10 Hz), 7.17 (m, 1 H), 7.27 (dd, 1 H, J_1 = 5 Hz, J_2 = 3 Hz), 7.38 (m, 1 H); IR (CCl_4) ν_{max}: 3280 cm^{-1}; MS (m/z) 250 (M^+).

Dimethyl 3-methyl-2-thienyl-hydroxymethyl-phosphonate 6c - ^{1}H-NMR ($CDCl_3$) δ: 2.21 (d, 3 H, J = 2 Hz), 3.73 (d, 6 H, J = 10 Hz), 4.0 - 4.1 (m, 1 H), 5.31 (dd, 1 H, J_1 = 10 Hz, J_2 = 5 Hz), 6.79 (d, 1 H, J = 5 Hz), 7.22 (dd, 1 H, J_1 = 5 Hz, J_2 = 2 Hz); IR (CCl_4) ν_{max}: 3280 cm^{-1}; MS (m/z) 236 (M^+).

Diethyl 4-methyl-2-thienyl-hydroxymethyl-phosphonate 6d - ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.21 (2t, 6 H, J = 7 Hz), 2.21 (s, 3 H), 3.5 - 3.7 (m, 1 H), 4.0 - 4.2 (m, 4 H), 5.11 (d, 1 H, J = 11 Hz), 6.84 (m, 1 H), 6.97 (m, 1 H); IR (CCl_4) ν_{max}: 3260 cm^{-1}; MS (m/z) 264 (M^+).

Diethyl 5-methyl-2-thienyl-hydroxymethyl-phosphonate 6e - ^{1}H-NMR ($CDCl_3$) δ: 1.23, 1.27 (2t, 6 H, J = 7 Hz), 2.42 (s, 3 H), 3.9 - 4.2 (m, 5 H), 5.81 (d, 1 H, J = 11 Hz), 6.60 (d, 1 H, J = 3 Hz), 6.92 (dd, 1 H, J_1 = 3

Hz, J_2 = 3 Hz); IR (CCl_4) ν_{max}: 3270 cm^{-1}; MS (m/z) 264 (M^+).

Diethyl 3,5-dimethyl-2-thienyl-hydroxymethyl-phosphonate 6f - ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.25 (2t, 6 H, J = 7 Hz), 2.12 (d, 3 H, J = 3 Hz), 2.39 (m, 3 H), 4.0 - 4.2 (m, 5 H), 5.19 (d, 1 H, J = 11 Hz), 6.44 (s, 1 H); IR (CCl_4) ν_{max}: 3260 cm^{-1}; MS (m/z) 278 (M^+).

Dimethyl 4,5-dimethyl-2-thienyl-hydroxymethyl-phosphonate 6g - ^{1}H-NMR ($CDCl_3$) δ: 2.06 (s, 3 H), 2.27 (s, 3 H), 3.0 - 3.4 (m, 1 H), 3.73, 3.77 (2d, 1 H, J = 10 Hz), 5.07 (d, 1 H, J = 11 Hz), 6.85 (d, 1 H, 3 Hz); IR (CCl_4) ν_{max}: 3280 cm^{-1}. MS (m/z) 250 (M^+).

Low temperature reactions - General procedure

To a solution of 6a-g (2 mmol) and R-H (8 mmol, see table 2) in acetonitrile (15 ml) p-TsOH (2 mmol) was added. The mixture was stirred for 24 h at room temperature. Then the mixture was poured into water and extracted with Et_2O. Neutral extracts were dried over Na_2SO_4 and evaporated under reduced pressure to yield a crude product that was chromatographed on SiO_2 using Et_2O - hexane 9 : 1 as eluent. Pure compounds 9a-w were obtained as dense oils.

Diethyl (5-methyl-2-thienyl)-methoxy-methylphosphonate 9a - ^{1}H-NMR ($CDCl_3$) δ: 1.16, 1.23 (2t, 6 H, J = 7 Hz), 2.41 (s, 3 H), 3.73 (s, 3 H), 3.8 - 4.2 (m, 4 H), 4.58 (d, 1 H, J = 15 Hz), 6.59 (d, 1 H, J = 3 Hz), 6.87 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz); MS (m/e) 278 (M^+).

Diethyl (5-methyl-2-thienyl)-benzyloxy-methylphosphonate 9b - ^{1}H-NMR ($CDCl_3$) δ: 1.19, 1.25 (2t, 6 Hz, J = 7 Hz), 2.44 (s, 3 H), 3.9 - 4.2 (m, 4 H), 4.39 (d, 1 H, J = 12 Hz), 4.69 (d, 1 H, J = 12 Hz), 4.77 (d, 1 H, J = 16 Hz), 6.62 (d, 1 H, J = 3 Hz), 6.68 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.29 (s, 5 H); MS (m/z) 354 (M^+).

Diethyl (5-methyl-2-thienyl)-(4-hydroxy-1-phenyl)-methyl-phosphonate 9c - ^{1}H-NMR ($CDCl_3$) δ: 1.11, 1.21 (2 t, 6 H, J = 7 Hz), 2.30 (s, 3 H), 3.6 - 4.2 (m, 4 H), 4.49 (d, 1 H, J = 26 Hz), 6.57 (d, 1 H, J = 3 Hz), 6.70 (d, 2 H, J = 8 Hz), 6.95 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.23 (d, 2 H, J = 8 Hz), 8.0 - 8.8 (m, 1 H); IR = ($CHCl_3$) ν_{max}: 3250, 1615 cm^{-1}; MS (m/z) 340 (M^+).

Diethyl (5-methyl-2-thienyl)-(2-thienyl)-methylphosphonate 9d - ^{1}H-NMR ($CDCl_3$) δ: 1.15, 1.17 (2t, 6 H, J = 7 Hz), 2.38 (s, 3 H), 3.8 - 4.1 (m, 4

H), 4.81 (d, 1 H, J = 26 Hz), 6.57 (d, 1 H, J = 3 Hz), 6.93 (m, 2 H), 7.17 (m, 2 H); MS (m/z) 330 (M^+).

Diethyl (5-methyl-2-thienyl)-(2-furyl)-methylphosphonate 9e - ^{1}H-NMR ($CDCl_3$) δ: 1.18 (t, 6 H, J = 7 Hz), 2.38 (d, 3 H, J = 1 Hz), 3.8 - 4.1 (m, 4 H), 4.71 (d, 1 H, J = 26 Hz), 6.32 (dd, 1 H, J_1 = 3 Hz, J_2 = 2 Hz), 6.41 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.57 (dd, 1 H, J_1 = 3 Hz, J_2 = 1 Hz), 6.87 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.34 (d, 1 H, J = 2 Hz); MS (m/z) 314 (M^+).

Diethyl (5-methyl-2-thienyl)-(5-methyl-2-furyl)-methyl-phosphonate 9f - ^{1}H-NMR ($CDCl_3$) δ: 1.18 (t, 6H, J = 7 Hz), 2.22 (s, 3 H), 2.37 (s, 3 H), 3.8 - 4.1 (m, 4 H), 4.63 (d, 1 H, J = 26 Hz), 5.88 (d, 1 H, J = 3 Hz), 6.28 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.55 (d, 1 H, J = 3 Hz), 6.85 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz); MS (m/z) 328 (M^+).

Diethyl (5-methyl-2-thienyl)-(3-methyl-2-thienyl)-methyl-phosphonate 9g - ^{1}H-NMR ($CDCl_3$) δ: 1.16, 1.18 (2t, 6 H, J = 7 Hz), 2.19 (d, 3 H, J = 2 Hz), 2.37 (s, 3 H), 3.8 - 4.1 (m, 4 H), 4.85 (d, 1 H, J = 26 Hz),

6.54 (d, 1 H, J = 3 Hz), 6.73 (d, 1 H, J = 5 Hz), 6.96 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.09, 7.11 (2d, 1 H, J = 5 Hz); MS (m/z) 344 (M^+).

Diethyl (5-methyl-2-thienyl)-(5-ethyl-2-thienyl)-methyl-phosphonate 9h - ^{1}H-NMR ($CDCl_3$) δ: 1.17 (t, 3 H, J = 7 Hz), 1.23 (t, 3 H, J = 7 Hz), 2.39 (s, 3 H), 2.75 (q, 2 H, J = 7 Hz), 3.8 - 4.1 (m, 4 H), 4.73 (d, 1 H, J = 26 Hz), 6.58 (m, 2 H), 6.93 (m, 2 H); MS (m/z) 358 (M^+).

Diethyl (5-methyl-2-thienyl)-(2,5-dimethyl-3-thienyl)-methylphosphonate 9i - ^{1}H-NMR ($CDCl_3$) δ: 1.10, 1.18 (2t, 6 H, J = 7 Hz), 2.29, 2.30 (2s, 3 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 3.7 - 4.1 (m, 4 H), 4.53 (d, 1 H, J = 26 Hz), 6.53 (d, 1 H, J = 3 Hz), 6.88 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.90 (s, 1 H); MS (m/z) 358 (M^+).

Diethyl (5-methyl-2-thienyl)-(5-bromo-2-thienyl)-methyl-phosphonate 9j - ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.20 (2t, 6 H, J = 7 Hz), 2.40 (s, 3 H), 3.8 - 4.2 (m, 4 H), 4.71 (d, 1 H, J = 26 Hz), 6.58 (d, 1 H, J = 3 Hz), 6.87 (s, 2 H), 6.93 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz); MS (m/z) 408 (M^+), 410 (M^+ + 2).

Diethyl (5-methyl-2-thienyl)-[5-(3-oxopropenyl)-2-furyl]-methylphosphonate 9k - ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.20 (2t, 6 H, J = 7 Hz), 2.39 (s, 3 H), 3.8 - 4.2 (m, 4 H), 4.73 (d, 1 H, J = 26 Hz), 6.50 (dd, 1 H, J_1 = 16 Hz, J_2 = 8 Hz), 6.55 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.58 (d, 1 H, J = 3 Hz), 6.69 (d, 1 H, J = 3 Hz), 6.90 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.12 (d, 1 H, J = 16 Hz), 9.56 (d, 1 H, J = 8 Hz); IR (CCl_4) ν_{max}: 2705, 1730, 1630 cm^{-1}; MS (m/z) 368 (M^+).

Diethyl (5-methyl-2-thienyl)-[5-(2-ethanol)-2-thienyl]-methylphosphonate 9l - ^{1}H-NMR ($CDCl_3$) δ: 1.16 (t, 6 H, J = 7 Hz), 2.37 (s, 3 H), 2.92 (t, 2 H, J = 6.5 Hz), 3.72 (t, 2 H, J = 6.5 Hz), 3.8 - 4.1 (m, 4 H), 4.72 (d, 1 H, J = 26 Hz), 6.55 (d, 1 H, J = 3 Hz), 6.65 (d, 1 H, J = 3 Hz), 6.91 (t, 1 H, J = 3 Hz), 6.94 (t, 1 H, J = 3 Hz); IR (CCl_4) ν_{max}: 3400 cm^{-1}; MS (m/z) 374 (M^+).

Diethyl (5-methyl-2-thienyl)-(3-bromo-2-furyl)-methylphosphonate 9m - ^{1}H-NMR ($CDCl_3$) δ: 1.19, 1.22 (2t, 6 H, J = 7 Hz), 2.41 (s, 3 H), 3.8 - 4.2 (m, 4 H), 4.66 (d, 1 H, J = 26 Hz), 6.47 (d, 1 H, J = 2 Hz), 6.59 (d, 1 H, J = 3 Hz), 6.88 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz),

7.34 (d, 1 H, J = 2 Hz); MS (m/z) 392 (M^+), 394 (M^+ + 2).

Diethyl (5-methyl-2-thienyl)-(4-bromo-2-furyl)-methylphosphonate 9n - ^{1}H-NMR ($CDCl_3$) δ: 1.19, 1.20 (2t, 6 H, J = 7 Hz), 2.40 (s, 3 H), 3.8 - 4.2 (m, 4 H), 4.87 (d, 1 H, J = 26 Hz), 6.39 (m, 1 H), 6.58 (d, 1 H, J = 3 Hz), 6.96 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.40 (m, 1 H); MS (m/z) 392 (M^+), 394 (M^+ + 2).

Diethyl (5-methyl-2-thienyl)-(3-hydroxymethyl-2-furyl)-methylphosphonate 9o - ^{1}H-NMR ($CDCl_3$) δ: 1.16, 1.22 (2t, 6 H, J = 7 Hz), 2.40 (s, 3 H), 3.5 - 4.0 (m, 1 H), 3.8 - 4.1 (m, 4 H), 4.44 (s, 2 H), 4.93 (d, 1 H, J = 27 Hz), 6.39 (d, 1 H, J = 2 Hz), 6.59 (d, 1 H, J = 3 Hz), 6.98 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.32 (d, 1 H, J = 2 Hz); IR (CCl_4) ν_{max}: 3400 cm^{-1}; MS (m/z) 344 (M^+).

Diethyl (5-methyl-2-thienyl)-(4-hydroxymethyl-2-furyl)-methylphosphonate 9p - ^{1}H-NMR ($CDCl_3$) δ: 1.18, 1.19 (2t, 6 H, J = 7 Hz), 2.39 (s, 3 H), 2.5 - 3.0 (m, 1 H), 3.8 - 4.1 (m, 4 H), 4.46 (s, 2 H), 4.67 (d, 1 H, J = 26 Hz), 6.44 (d, 1 H, J = 3 Hz), 6.57 (d, 1 H, J =

3 Hz), 6.87 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.31 (s, 1 H); IR (CCl_4) ν_{max}: 3400 cm^{-1}; MS (m/z) 344 (M^+).

Dimethyl benziloxy-(3-methyl-2-thienyl)-methylphosphonate 9q - ^{1}H-NMR ($CDCl_3$) δ: 2.13 (d, 3 H, J = 3 Hz), 3.65, 3.74 (2d, 6 H, J = 11 Hz), 4.38 (d, 1 H, J = 12 Hz), 4.71 (d, 1 H, J = 12 Hz), 4.95 (d, 1 H, J = 16 Hz), 6.81 (d, 1 H, J = 5 Hz), 7.23 - 7.35 (m, 6 H); MS (m/z) 326 (M^+).

Dimethyl (3-methyl-2-thienyl)-(5-methyl-2-furyl)-methyl-phosphonate 9r - ^{1}H-NMR ($CDCl_3$) δ: 2.20 (m, 6 H), 3.59, 3.64 (2d, 6 H, J = 7 Hz), 4.81 (d, 1 H, J = 26 Hz), 5.89 (d, 1 H, J = 3 Hz), 6.35 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz) 6.76 (d, 1 H, J = 5 Hz), 7.11, 7.12 (2d, 1 H, J = 5 Hz); MS (m/z) 300 (M^+).

Dimethyl (5-methyl-2-thienyl)-(3-methyl-2-thienyl)-methyl-phosphonate 9s - ^{1}H-NMR ($CDCl_3$) δ: 2.20 (d, 3 H, J = 2 Hz), 2.39 (s, 3 H), 3.59, 3.65 (2d, 6 H, J = 11 Hz), 4.91 (d, 1 H, J = 26 Hz), 6.58 (d, 1 H, J = 3 Hz), 6.76 (d, 1 H, J = 5 Hz), 6.98 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.13, 7.14 (2d, 1 H, J = 5 Hz); MS (m/z) 316 (M^+).

Diethyl (4-methyl-2-thienyl)-(5-methyl-2-furyl)-methyl-phosphonate 9t - ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.19 (2t, 6 H, J = 7 Hz), 2.17 (s, 3 H), 2.23 (s, 3 H), 3.8 - 4.1 (m, 5 H), 4.65 (d, 1 H, J = 26 Hz), 5.89 (m. 1 H), 6.30 (m, 1 H), 6.73 (s, 1 H), 6.91 (m, 1 H); MS (m/z) 328 (M^+).

Dimethyl (4,5-dimethyl-2-thienyl)-(5-methyl-2-furyl)-methyl-phosphonate 9u - ^{1}H-NMR ($CDCl_3$) δ: 2.03 (s, 3 H), 2.23 (s, 6 H), 3.65 (d, 6 H, J = 11 Hz), 4.62 (d, 1 H, J = 26 Hz), 5.90 (d, 1 H, J = 3 Hz), 6.29 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.76 (d, 1 H, J = 3 Hz); MS (m/z) 314 (M^+).

Diethyl (3,5-dimethyl-2-thienyl)-(5-methyl-2-furyl)-methyl-phosphonate 9v - ^{1}H-NMR ($CDCl_3$) δ: 1.18, 1.21 (2t, 6 H, J = 7 Hz), 2.14 (d, 3 H, J = 3 Hz), 2.23 (s, 3 H), 2.35 (m, 3 H), 3.8 - 4.1 (m, 4 H), 4.73 (d, 1 H, J = 26 Hz), 5.89 (d, 1 H, J = 3 Hz), 6.34 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.42 (s, 1 H); MS (m/z) 314 (M^+).

Dimethyl (5-methyl-2-thienyl)-(2-thienyl)-methylphosphonate 9w - ^{1}H-NMR ($CDCl_3$) δ: 2.38 (s, 3 H), 3.60, 3.66 (2d, 6 H, J = 11 Hz), 4.81 (d, 1 H, J =

26 Hz), 6.58 (d, 1 H, J = 3 Hz), 6.93 (m, 2 H), 7.17 (m, 2 H); MS (m/z) 302 (M^+).

High temperature reaction - General procedure

To a solution of 6e,f (1.14 mmol) and R-H (5.7 mmol) in DMSO (9 ml) p-TsOH (1.14 mmol for 6e, 0.57 mmol for 6f) was added. The mixture was stirred for 10 min at 140 °C. Then the mixture was poured into water and extracted with Et_2O. Neutral extracts were dried over Na_2SO_4 and evaporated under reduced pressure to yield a crude product that was chromatographed on SiO_2 using Et_2O as eluent. Pure compounds 10a-i were obtained as dense oils.

Diethyl (5-benzyloxymethyl-2-thienyl)-methylphosphonate 10a - ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 6 H, J = 7 Hz), 3.22 (d, 2 H, J = 21 Hz), 4.07 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 4.53 (s, 2 H), 4.62 (s, 2 H), 6.84 (s, 2 H), 7.34 (s, 5 H); MS (m/z) 354 (M^+).

Diethyl [5-(4-hydroxybenzyl)-2-thienyl]-methylphosphonate 10b - ^{1}H-NMR ($CDCl_3$) δ: 1.23 (t, 6 H, J = 7 Hz), 3.25 (d, 2 H, J = 20 Hz), 3.95 (s, 2 H), 4.03 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 6.56 (d, 1 H, J

= 3.5 Hz), 6.74 (m, 3 H), 7.00 (d, 2 H, J = 8 Hz), 7.8 - 8.2 (m, 1 H); IR (CCl_4) ν_{max}: 3260 cm^{-1}; MS (m/z) 340 (M^+).

Diethyl [5-(2-furylmethyl)-2-thienyl]-methylphosphonate 10c - ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 6 H, J = 7 Hz), 3.19 (d, 2 H, J = 21 Hz), 3.8 - 4.2 (m, 6 H), 5.98 (d, 1 H, J = 3 Hz), 6.22 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.27 (d, 1 H, J = 3 Hz), 6.36 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 7.25 (d, 1 H, J = 3 Hz); MS (m/z) 314 (M^+).

Diethyl [5-(2-thienylmethyl)-2-thienyl]-methylphosphonate 10d - ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, 6 H, J = 7 Hz), 3.29 (d, 2 H, J = 21 Hz), 4.07 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 4.28 (s, 2 H), 6.71 (d, 1 H, J = 3 Hz), 6.79 (dd, 1 H, J_1 = 3 Hz, J_2 = 3 Hz), 6.87 (dd, 1 H, J_1 = 3.5 Hz, J_2 = 1 Hz), 6.93 (dd, 1 H, J_1 = 5 Hz, J_2 = 3.5 Hz), 7.16 (dd, 1 H, J_1 = 5 Hz, J_2 = 1 Hz); MS (m/z) 330 (M^+).

Diethyl [3-methyl-5-(2-furylmethyl)-2-thienyl]-methylphosphonate 10e - ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 6 H, J = 7 Hz), 2.10 (d, 3 H, J = 3 Hz), 3.17 (d, 2 H, J = 21 Hz), 4.02 (s, 2 H), 4.02 (dq, 4 H, J_1 = 7 Hz, J_2 = 7

Hz), 6.05 (d, 1 H, J = 3 Hz), 6.26 (dd, 1 H, J_1 = 3 Hz, J_2 = 2 Hz), 6.53 (s, 1 H), 7.29 (d, 1 H, J = 2 Hz); MS (m/z) 328 (M^+).

Diethyl [3-methyl-5-(5-methyl-2-thienylmethyl)-2-thienyl]-methylphosphonate 10f - ^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, 6 H, J = 7 Hz), 2.10 (d, 3 H, J = 3 Hz), 2.39 (s, 3 H), 3.18 (d, 2 H, J = 21 Hz), 4.02 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 4.11 (s, 2 H), 6.53 (m, 2 H), 6.61 (d, 1 H, J = 3.5 Hz); MS (m/z) 358 (M^+).

Diethyl (3-methyl-5-benzyloxymethyl-2-thienyl)-methylphosphonate 10g - ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 6 H, J = 7 Hz), 2.14 (d, 3 H, J = 3 Hz), 3.23 (d, 2 H, J = 21 Hz), 4.04 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 4.51 (s, 2 H), 4.56 (s, 2 H), 6.69 (s, 1 H), 7.31 (s, 5 H); MS (m/z) 368 (M^+).

Diethyl [3-methyl-5-(4-hydroxybenzyl)-2-thienyl]-methyl-phosphonate 10h - ^{1}H-NMR ($CDCl_3$) δ: 1.22 (t, 6 H, J = 7 Hz), 2.06 (d, 3 H, J = 3 Hz), 3.17 (d, 2 H, J = 20 Hz), 3.90 (s, 2 H), 4.01 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 6.41 (s, 1 H), 6.72 (d, 2 H, J = 8 Hz), 6.99 (d, 2 H, J = 8 Hz), 7.4 - 7.7 (m, 1 H); IR (CCl_4) ν_{max}: 3260 cm^{-1}; MS (m/z) 354 (M^+).

Diethyl [3-methyl-5-(2-thienylmethyl)-2-thienyl]-methyl-phosphonate 10i - ^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, 6 H, J = 7 Hz), 2.10 (d, 3 H, J = 3 Hz), 3.18 (d, 2 H, J = 21 Hz), 4.02 (dq, 4 H, J_1 = 7 Hz, J_2 = 7 Hz), 4.25 (s, 2 H), 6.54 (s, 1 H), 6.84 (d, 1 H, J = 3.5 Hz), 6.90 (dd, 1 H, J_1 = 5 Hz, J_2 = 3.5 Hz), 7.13 (d, 1 H, J = 5 Hz); MS (m/z) 344 (M^+).

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