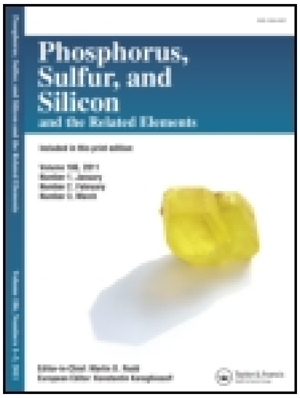

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

RAPID AND EFFICIENT ARBUZOV REACTION UNDER MICROWAVE IRRADIATION

Didier Villemin [a] , Fabrice Simeon [a] , Hugues Decreus [a] & Paul-Alain Jaffres [b]

[a] Ecole Nationale Supérieure d'lngéfnieurs de Caen (ISMRA) Université de Caen, UMR 6507, 6 Boulevard du Marichal Juin, F-14050, Caen, Cedex, France

[b] University of St Andrews, School of Chemistry, College Gate, Fife, KY16 9AJ, Scotland

Version of record first published: 24 Sep 2006.

To cite this article: Didier Villemin , Fabrice Simeon , Hugues Decreus & Paul-Alain Jaffres (1998): RAPID AND EFFICIENT ARBUZOV REACTION UNDER MICROWAVE IRRADIATION, Phosphorus, Sulfur, and Silicon and the Related Elements, 133:1, 209-213

To link to this article: http://dx.doi.org/10.1080/10426509808032465

Phosphorus, Sulfur and Silicon, 1998, Vol. 133, pp. 209-213
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RAPID AND EFFICIENT ARBUZOV REACTION UNDER MICROWAVE IRRADIATION

DIDIER VILLEMIN[a*], FABRICE SIMEON[a], HUGUES DECREUS[a] and PAUL-ALAIN JAFFRES[b]

[a]*Ecole Nationale Supérieure d'Ingénieurs de Caen (ISMRA) Université de Caen, UMR 6507, 6 Boulevard du Maréchal Juin F-14050 Caen Cedex, France and* [b]*University of St Andrews, School of Chemistry, College Gate, Fife KY16 9AJ, Scotland*

(Received 30 September, 1997)

Diethyl alkylphosphonates are efficiently and rapidly prepared in good yields (75–99%) from trialkylphosphates and alkyl halides under short microwaves irradiations.

Keywords: microwaves irradiation; alkylphosphonates; Arbuzov reaction

INTRODUCTION

One of the methods commonly used for the synthesis of diethyl alkylphosphonates is the Michaelis-Arbuzov reaction,[1–2]. These phosphonates are widely used as synthon for Wittig-Horner reactions[3] and for the synthesis of pharmaceutical products and other physiologically active organophosphoric compounds.[4] Over the last twenty years, phosphonates have attracted considerable attention as precursors of phosphonic acids which are used in the synthesis of new hybrid organic-inorganic supports and catalysts.[5]

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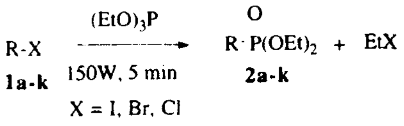
* Corresponding author.

RESULTS AND DISCUSSION

Various functionalized phosphonates can easily be prepared by the Arbuzov reaction (scheme 1), which is a cheap and very efficient method. The fact that an ionic intermediate of the reaction was postulated,[6] allowed us to think that the use of microwaves might improve the yield and the rate of the reaction.[7] According to our previous works[8], we employed a focused microwave with a monomode cavity. A sample has been taken out of the mixture periodically for analysis by ^{31}P NMR spectroscopy. Disappearance of the NMR singlet of triethylphosphite (at 138 ppm) was proportional to the increase of the phosphonate signal (from 28 to 32 ppm). The medium time of reaction was found to be 5 minutes at 150 Watts of irradiation.

The results are summarised in Table I. Entries **a** to **e** report the phosphonation of monohalide substrates while entries **f** to **k** report the monophosphonation of polyhalide substrates.



$$\underset{\mathbf{1a\text{-}k}}{R\text{-}X} \xrightarrow[\substack{150W,\ 5\ min \\ X\,=\,I,\ Br,\ Cl}]{(EtO)_3P} \underset{\mathbf{2a\text{-}k}}{R\text{-}\overset{O}{P}(OEt)_2} + EtX$$

SCHEME 1

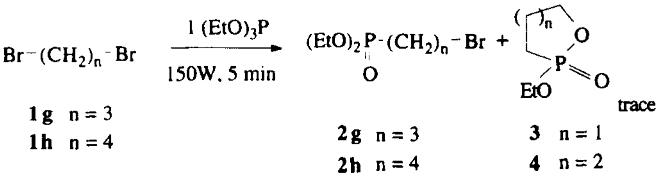
TABLE I Reaction of triethylphosphite with halogenide under focused microwave irradiation (M.W.)

N°	*Substrat 1*	*Products(1) 2*	*^{31}P NMR ($CDCl_3$)*	*M.W. Heating 5 min yield %$^{(2)}$[lit.]*
a	I-CH_3	**P**-CH_3	30.2	99$^{(5)}$[1]
b	Br-$(CH_2)_3$Ph	**P**-$(CH_2)_3$Ph	30.6	90[9]
c	B_r-CH_2P_h	**P**-CH_2Ph	26.3	95[11]
d	Br-CH_2-CH=CH_2	**P**-CH_2-CH=CH_2	26.7	89[12]
e	Br-$(CH_2)_3$CN	**P**-$(CH_2)_3$CN	29.2	75
f	CCl_4	**P**-CCl_3	5.4	78[13]
g	Br-$(CH_2)_3$Br$^{(3)}$	**P**-$(CH_2)_3B_r$	30.3	91[14]
h	Br-$(CH_2)_4$-Br$^{(3)}$	**P**-$(CH_2)_4B_r$	31.1	90[14]
i	Br-$(CH_2)_5$-Br$^{(3)}$	**P**-$(CH_2)_5$-Br	31.7	94[14]
j	Br-$(CH_2)_9$-Br$^{(3)}$	**P**-$(CH_2)_9$-Br$^{(4)}$	32.4	91
k	Br-$(CH_2)_{10}$-Br$^{(3)}$	**P**-$(CH_2)_{10}$-Br$^{(4)}$	32.6	88

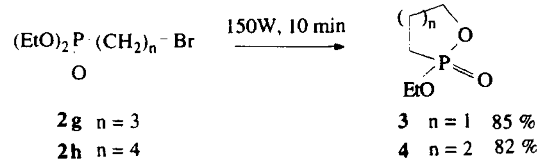
(1) **P** = P(O)$(OEt)_2$; (2) Purified by distillation ; (3) 3 equivalents ; (4) for characterisation see ref. [15] (5) heating for 3 min.

In all these examples after 5 minutes under microwave irradiation all the triethylphosphite reacts and no trace of it was detected by ^{31}P NMR. The times required are shorter by microwave irradiation than by thermal activation. The yields are equivalent or better than those obtained under classical conditions. In order to compare microwave activation to thermal heating we monitored by ^{31}p NMR the phosphonation of 3-phenylethylbromide **1b** during a thermal heating reaction. We showed that at least 35 minutes were required in order to have a total disappearance of triethylphosphite in the solution. When the substrate is iodomethane (**1a**) only 3 minutes of microwave irradiation is required. By a thermal heating[9] the same reaction is polluted with diethylethylphosphonate which is difficult to separate from the main product. In this case microwave heating, because of the shorter reaction time, allows to avoid the formation of by-products.

With dibromoalcane (**1g** to **1k**) an excess of substrate was employed in order to avoid a double Arbuzov reaction which formed diphosphonate. With compounds **1g** and **1h** as substrate traces of oxaphospholane **3** or oxaphosphane **4** were observed (scheme 2). These compounds result from cyclisation which required a thermal heating at 180°C for 2 hours.[10] Under microwave activation, compounds **3** and **4** have been isolated in very good yield by 10 min. irradiation of a pure sample of 3-bromopropylphosphonate **2g** or 4-bromobutylphosphonate **2h** (scheme 3).



SCHEME 2



SCHEME 3

The conclusion of this work is that microwave activation decreases-hugely the time of the Arbuzov reactions. Such process can be used for large scale synthesis of alkylphosphonates (see experimental section). This work was realised with triethylphosphite as starting substrate but we can expect to have a similar activation by microwave with other alkyl phosphites.

EXPERIMENTAL

Focused microwaves : cavity TE_{01} at 2450 MHz with a universal generator MES 73–800.[8] ^1H and ^{13}C NMR spectra were recorded on a BRUKER AC 250 spectrometer in $CDCl_3$ as solvent. These spectra were measured with $SiMe_4$ as inernal standard. ^{31}P NMR was recorded on a BRUKER WP 80 SY with H_3PO_4 as external standard. Mass spectra were recorded on Nermag R10.10H spectrometer.

General Procedure

Example : iodomethane **1a** (3.55 g ; 0.025 mol) and triethylphosphite (4.15 g ; 0.025 mol) are placed in a quartz tube. The solution is irradiated at 150 W for 3 minutes. NMR analyses (^{31}P and 1H) show that methyl diethylphosphonate is obtained with a good purity.

In the case of polyhalide substrates **(1f-1k)** 3 equivalents of substrate **(1f-1k)** are used. At the end of the heating (5 min.) the phosphonates are purified by distillation under vacuum and the excess of dibromide substrate is recovered. This methodology is suitable for scale up to 0.2 mole of monohalide substrate or 0.12 mole of polyhalide substrate.

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[15] NMR spectra of new products :
2j: ^{1}H NMR 1.32 (t, $^3J_{HH}$ = 7.0 Hz, $C\mathbf{H}_3CH_2O$, 6H) 1.39 (m, 8H), 1.51–1.65 (m, 4 H), 1.77–1.88 (m, 4H) ; 3.40 (t, J = 6.8 Hz , $-C\mathbf{H}_2-Br$, 2H), 4.09 (dqd, J = 7.2 Hz, J = 7.1 Hz, $CH_3C\mathbf{H}_2O$, 4H); ^{13}C NMR 16.55 (d, $^3J_{CP}$ = 6,1 Hz, CH_3CH_2O), 22.47 (d, $^3J_{CP}$ = 4.5 Hz, $-CH_2-(CH_2)_2-P$), 22.68 (C), 26.91 (C), 28.19 (C), 28.71 (C), 28.75 (C), 29.05 (C), 30.61 (d, $^2J_{CP}$ = 16.2 Hz, $-CH_2-CH_2-CH_2-P$), 33.43 (d, $^1J_{CP}$ = 70.9 Hz, CH_2-P), 61.45 (d, $^2J_{CP}$ = 6.4 Hz, CH_3CH_2O).
2k : ^{1}H NMR 1.32 (t, $^3J_{HH}$ = 7.1 Hz, $C\mathbf{H}_3CH_2O$, 6H), 1.33–1.42 (m, 6H), 1.60–1.90 (m, 12H), 3.40 (t, J = 6.8 Hz, $-C\mathbf{H}_2-Br$, 2H), 4.08 (dqd, $^3J_{HP}$= 7.2 Hz , $^3J_{HH}$ = 7.1 Hz, $CH_3C\mathbf{H}_2O$, 4H) ^{13}C NMR 16.55 (d, $^3J_{CP}$ = 6.02 Hz, $\mathbf{C}H_3CH_2O$), 22.46 (d, $^3J_{CP}$= 5.35 Hz, $-CH_2-CH_2-CH_2-P$), 24.66 (C), 26.90 (C), 28.22 (C), 28.78 (C), 29.12 (C), 29.37 (C), 29.42 (C), 30.64 (d, $^2J_{CP}$ =17.0 Hz, $\mathbf{C}H_2-CH_2-P$), 33.46 (d, $^1J_{CP}$ = 71.7 Hz, $-\mathbf{C}H_2-P$), 61.49 (d, $^2J_{CP}$ = 6.54 Hz, CH_3CH_2O).