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Microwave irradiation in organophosphorus chemistry. Part 2: Synthesis of phosphonium salts[1]

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Abstract

Several phosphonium salts have been prepared using a domestic microwave oven. The microwave enhanced reaction of triphenylphosphine and an organic halide shows a remarkable rate acceleration under microwave irradiation and allows the general and facile synthesis of both stabilized and non-stabilized phosphonium salts.

Keywords: microwave heating; phosphonium salts; Wittig reaction; ylide.

Since its development the Wittig reaction has remained one of the primary routes utilized in synthetic organic chemistry for the construction of carbon–carbon double bonds.[2] The Wittig reagent, or ylide, necessary for the reaction is produced by deprotonation of the corresponding phosphonium salt generated by the quaternization of a phosphine with an organic halide (Scheme 1). While deprotonation of the phosphonium salt occurs readily, utilizing a variety of bases, its synthesis often requires forcing conditions. Frequently, the phosphine and organic halide must be heated to reflux for several hours, and in some cases days, to obtain the desired phosphonium salt, conditions which are not usually compatible with sensitive organic halides.[3]

Scheme 1. Formation of phosphonium salts

Since the appearance of the first papers[4] on the application of microwave irradiation in organic synthesis, the field has seen a steady growth to the point where a variety of transformations are now possible with microwave heating.[5] Carrying out reactions using microwave heating, as opposed to conventional heating, has the major advantage of shorter reaction times because of the rapid heating.

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Table 1
Synthesis of phosphonium salts under microwave irradiation

entry	R	X	conventional heating time in hours (solvent)[3]	microwave heating time (min)	^{31}P NMR δ[9]	conditions	yield (%)	m.p. (C)
a	CH_3CH_2	I	24 (toluene)	4	26.2	neat	87	169-173° (dec)
b	$CH_3CH_2CH_2$	I	48 (benzene)	4	23.8	neat	92	218-224° (dec)
c	$NCCH_2$	Br	336 (benzene)	3	21.4	xylene	99	221-223°
d	$CH_3CH_2OC(O)CH_2$	Br	0.5 (benzene)	2	20.8	xylene	86	151° (dec)
e	$PhCH_2$	Br	6 (chloroform)	3	23.1	xylene	83	287-291°
f	4-NO_2-$PhCH_2$	Br	12 (benzene)	3	24.0	xylene	94	288-290° (dec)
g	$PhCH=CHCH_2$	Br	12 (xylene)	2	20.9	xylene	96	250-252°

^{1}H and ^{13}C NMR Data for Phosphonium Salts

a ^{1}H NMR δ: 7.84-7.79 (7H, m), 7.74-7.69 (5H, m), 7.35-7.28 (3H, m), 3.76 (2H, m), 1.40 (3H, dt, *J* = 20.0, 7.5 Hz). ^{13}C NMR δ: 135.09 (d, *J* = 3.0 Hz), 133.65 (d, *J* = 9.7 Hz), 130.56 (d, *J* = 12.7 Hz), 118.11 (d, *J* = 86.2 Hz), 17.36 (d, *J* = 54.6 Hz), 6.96 (d, *J* = 5.5 Hz).

b ^{1}H NMR δ: 7.87-7.79 (7H, m), 7.74-7.69 (5H, m), 7.35-7.29 (3H, m), 3.72 (2H, m), 1.73 (2H, m), 1.28 (3H, dt, *J* = 7.2, 1.8). ^{13}C NMR δ: 135.04 (d, *J* = 2.9 Hz), 133.52 (d, *J* = 9.6 Hz), 130.49 (d, *J* = 12.3 Hz), 118.10 (d, *J* = 85.8 Hz), 24.45 (d, *J* = 50.9 Hz), 16.50 (d, *J* = 5.6 Hz), 15.34 (d, *J* = 14.8 Hz).

c ^{1}H NMR δ: 8.04-7.98 (4H, m), 7.88-7.83 (2H, m), 7.76-7.65 (4H, m), 7.36-7.29 (5H, m), 6.39 (2H, d, *J* = 15.3 Hz). ^{13}C NMR δ: 136.09 (d, *J* = 2.7 Hz), 133.98 (d, *J* = 10.8 Hz), 130.69 (d, *J* = 13.3 Hz), 115.95 (d, *J* = 89.0 Hz), 111.57, -0.10.

d ^{1}H NMR δ: 7.95-7.88 (5H, m), 7.82-7.77 (3H, m), 7.71-7.64 (5H, m), 7.35-7.28 (2H, m) 5.58 (2H, d, *J* = 13.8 Hz), 4.04 (2H, q, *J* = 7.1 Hz), 1.07 (3H, t, *J* = 7.2). ^{13}C NMR δ: 164.39 (d, *J* = 3.5 Hz), 135.16 (d, *J* = 2.9 Hz), 133.95 (d, *J* = 10.6 Hz), 130.25 (d, *J* = 13.1 Hz), 117.91 (d, *J* = 89.0 Hz), 62.83, 33.18 (d, *J* = 56.3 Hz), 13.71.

e ^{1}H NMR δ: 7.79-7.71 (8H, m), 7.67-7.60 (5H, m), 7.41-7.29 (2H, m), 7.25-7.20 (1H, m), 7.14-7.08 (4H, m), 5.40 (2H, d, *J* = 14.4 Hz). ^{13}C NMR δ: 134.96 (d, *J* = 2.9 Hz), 134.35 (d, *J* = 9.9 Hz), 131.47 (d, *J* = 5.7 Hz), 130.11 (d, *J* = 12.5 Hz), 128.78 (d, *J* = 3.5 Hz), 128.36 (d, *J* = 3.9 Hz), 127.08 (d, *J* = 8.6 Hz), 117.75 (d, *J* = 85.8 Hz), 30.83 (d, *J* = 46.8 Hz).

f ^{1}H NMR δ: 7.86-7.70 (12H, m), 7.63-7.56 (6H, m), 7.50-7.46 (2H, m), 6.01 (2H, d, *J* = 15.8 Hz). ^{13}C NMR δ: 147.29 (d, *J* = 4.4 Hz), 135.78 (2H, d, *J* = 8.7 Hz), 135.02 (2H, d, *J* = 2.9 Hz), 134.51 (d, *J* = 10.1 Hz), 132.91 (d, *J* = 5.4 Hz), 130.10 (d, *J* = 12.8 Hz), 123.12 (d, *J* = 3.1 Hz), 117.27 (d, *J* = 86.1 Hz), 29.64 (d, *J* = 46.6 Hz).

g ^{1}H NMR δ: 7.86-7.80 (6H, m), 7.77-7.72 (3H, m), 7.66-7.60 (6H, m), 7.22-7.14 (5H, m), 6.74 (1H, dd, *J* = 15.9, 5.6 Hz), 5.95 (1H, ddt, *J* = 15.2, 7.5, 5.6 Hz), 4.93 (2H, ddd, *J* = 15.3, 7.5, 0.9 Hz). ^{13}C NMR δ: 140.16 (d, *J* = 13.4 Hz), 135.73 (d, *J* = 3.9 Hz), 135.03 (d, *J* = 3.0 Hz), 134.00 (d, *J* = 9.8 Hz), 130.33 (d, *J* = 12.5 Hz), 128.59 (d, *J* = 3.3 Hz), 128.35 (d, *J* = 10.4 Hz), 126.51 (d, *J* = 1.9 Hz), 117.95 (d, *J* = 85.6 Hz), 113.63 (d, *J* = 10.7 Hz), 28.26 (d, *J* = 49.2 Hz).

Consequently, reactions exhibit cleaner products and more facile work-up procedures. Although few papers have shown the application of microwave heating with a limited scope to the synthesis of the carbon–carbon double bond[6] using organophosphorus reagents, none of the work has examined the formation of phosphonium salts, the precursors to the ylides utilized in the Wittig reaction. This communication describes a general and facile preparation of phosphonium salts using microwave heating to accelerate the reaction.

The desired phosphonium salts were synthesized by microwave-heated quaternization of triphenylphosphine with an organic halide (Table 1).[7] Several representative organic halides (**2a**–**g**) were treated with triphenylphosphine (**1**), either neat or with xylene as the solvent, to afford the phosphonium salts (**3a**–**g**) in excellent yields.[8] In each case, the reaction times were reduced to 4 min or less from conventional heating times ranging from 30 min to 14 days.[3]

In conclusion, we have demonstrated a rapid and general synthesis of phosphonium salts accomplished using a variety of organic halides with heating in a domestic microwave oven. In addition to the phosphonium salts being produced in excellent yields, the short reaction times should make this method applicable to more sensitive organic halides used in the synthesis of Wittig reagents.

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7. ***Caution*!** It is hazardous to rapidly heat organic reactions in closed vessels by either traditional means or with microwave irradiation. Therefore, caution should be exercised when conducting reactions of this type. A typical procedure for the synthesis of the phosphonium salts follows: Organic halide (1 equiv.) and triphenylphosphine (1 equiv.) are added either neat or in 5 ml of xylene to a pressure tube with a threaded Teflon cap (Ace Glass). The threaded cap on the pressure tube is sealed finger tight, and the tube placed in a beaker surrounded by glass wool. The glass wool not only serves to evenly heat the tube, but to absorb the reaction mixture if the tube were to shatter. The tube and beaker are then placed in the microwave oven (Panasonic) and heated for the appropriate time on high power (1100 watts). Once the heating cycle is complete and the beaker and tube have cooled to ambient temperature, the tube is opened and the phosphonium salts are removed and purified by recrystallization from an appropriate solvent.
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