Microwave Accelerated Wittig Reactions of Stabilized Phosphorus Ylides with Ketones under Solvent-Free Conditions

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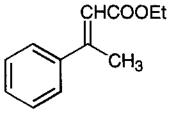
Received 21 October 1996

Abstract: Microwave irradiation accelerates some difficult Wittig reactions of stable phosphorus ylides (e.g. **1**) with ketones. Irradiation in a domestic microwave oven of the mixture of reactants, in absence of solvents, allowed to obtain, in shorter times, an improvement of tranformation yields over conventional heating method.

Microwave heating, together with high pressure and ultrasound, are the most promising non conventional methods used nowadays in organic synthesis. However, while high pressure[1] and ultrasound[2] applications are already at a good stage of development, microwave heating (MWH) potentiality[3,4] was not yet investigated enough.

In order to evaluate the applicability of MWH to Wittig reaction we have conducted some difficult reactions of stabilized phosphorus ylides with ketones under microwave irradiation under solvent-free conditions. It is well known that stabilized phosphorus ylides, such as carboethoxymethylentriphenylphosphorane (**1**), react with aldehydes under conventional[5,6] and non-conventional (high pressure[7] or microwave [8]) conditions, while reaction with ketones generally requires forcing conditions. Reactions conducted under reflux conditions, even after several hours or days, gave poor yields.[5,11] The catalytic action of benzoic acid has been also reported to improve the transformation.[9] However, conventional heating under solvent-free conditions gave satisfactory results only conducting the reactions at high temperature (100-170°C) for several hours.[10] For example the reaction of acetophenone (**2**) with the stable ylide (**1**) gave (**3**) in 58% yield on heating at 170°C for 10 hours. High pressure techniques have been also used but excellent yields were obtained only after several hours (at 9 kbar, 50°C , for 30 hours).[11]

We used a commercial domestic microwave oven to make this transformation easier and more efficient. Several experiments were performed, at various powers and irradiation times, in order to find the most adequate conditions for the reaction under microwave irradiation. In a typical experiment, ketone (1 mmol) was mixed to carboethoxymethylentriphenylphosphorane (**1**) (0.5 mmol) in a Ace Glass tube (Aldrich). The reactor was put in a glass beaker (600 ml) filled with vermiculite beads (50 g) and subjected to microwave heating. The use of vermiculite beads was very important, not only for safety reasons[12] but also for the thermal enhancement due to the absorption of microwave energy by the beads. In fact, without vermiculite the transformation yields were very low even at the highest microwave irradiation power (650 W). Using vermiculite, high temperatures were rapidly reached and the reactions were conducted more easily. The reaction mixtures obtained after irradiation were purified by chromatography on silica gel (Merck,70-230 mesh; petroleum ether-diethyl ether mixtures). A further purification by HPLC was performed, if necessary.[13] Acetophenone (**2**) (Table) reacts, under these conditions, at the irradiation power of 150 W, in only 20 min to give 73% of a mixture whose components were mainly *E* and *Z* isomers of 3-phenyl-but-2-enoic acid ethyl ester (**3**) and a small amount (6%) of isomer (**4**).[13] It seems likely that the origin of this isomer is due to an isomerization of 3-phenyl-but-2-enoic acid ethyl ester. However, when we put **3** in MWH condition, no isomerization to **4** was observed and we recovered the starting material.



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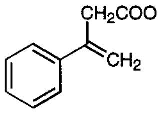

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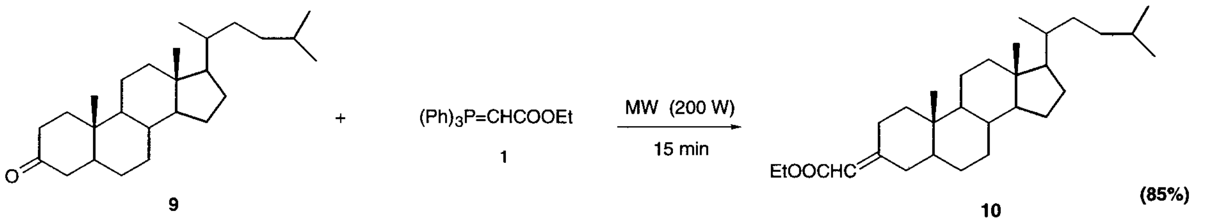
We have carried out microwave induced Wittig reaction with the same ylide (**1**) using other ketones such as benzophenone (**5**), 2-nonanone (**6**), *trans*-decalone (**7**) and β-ionone (**8**). The results are summarized in the Table.

Table. Reaction of Ylide (**1**) with Ketones under Solvent-Free Conditions.

Ketone	Conditions	Time	Tf ^{a} (°C)	Yield (%)^{b}	E/Z Ratio^{c}
acetophenone (**2**)	MWH (150W) ^{d}	20 min	210	67	2 : 1
	MWH(150W)^{d,e}	20 min	230	43	2 : 1
	MWH(150W)^{d,f}	20 min	85	17	2 : 1
	CH (Lit.)[10]	10 h	170	58	-
benzophenone (**5**)	MWH(150W)^{d}	15 min	210	69	-
	CH (Lit.)[10]	10 h	170	54	-
2-nonanone (**6**)	MWH(100W)^{d}	15 min	170	36	2 : 1
trans-decalone (**7**)	MWH(150W)^{d}	15 min	180	43	100 : 0
β-ionone (**8**)	MWH(100W)^{d}	15 min	150	36	3 : 1
5α-cholestan-3-one(**9**)	RMW (200W)^{d}	15 min	180	85	1 : 1

[a] Final temperature.[15] [b] Yields refer to the isolated products based on **1**. [c] Calculated by ^{1}H-NMR spectroscopy ($CDCl_3$, Bruker AM250). [d] Irradiation was conducted in a domestic microwave oven (Philips AVM 610). [e] With benzoic acid. [f] Without vermiculite.

A very interesting result was obtained with 5α-cholestan-3-one (**9**). In fact, it has been reported that this compound failed to react with carboethoxymethylentriphenylphosphorane (**1**) under the usual reaction



Scheme 1. Reaction of 5α-cholestan-3-one (**9**) with ylide **1** under microwave irradiation.

conditions.[14] In a microwave assisted reaction, using our condition, it was possible to obtain a good yield of **10** (85%) after only 15 minutes of irradiation (Scheme 1). Generally we noted that the use of higher power or longer time of irradiation caused a decrease in yield. Furthermore, the use of benzoic acid did not improve our results.

All the alkenes obtained exhibited satisfactory spectroscopic data (NMR, MS). The stereochemistry of the double bond of each product was assigned by the observation of n.O.e. effects in the ^{1}H-NMR spectra between the irradiated olefinic proton and the substituents at the new carbon-carbon double bond formed after the reaction. As expected,[5] (*E*)-alkenes were predominantly formed together with a considerable amount of (*Z*) isomer.

In conclusion, we have shown that the use of a commercial microwave oven allows conducting Wittig reactions of stable ylides with ketones, in a fast and easy way, with improved yield compared to conventional methods. On the ground of these results this new procedure proves to be of synthetic interest for its efficiency and cheapness.

Acknowledgements. The mass spectra were obtained from the " Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli". We gratefully acknowledge Prof. G. Sodano for the useful discussions and the encouragement during this work.

References and Notes

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13. Compound **4** was purified using HPLC (Spherisorb column; n-hexane-ethyl acetate 99 : 1) because it was recovered together with *Z* isomer of **3** after the column chromatography on silica gel. **4** : EIMS : m/z 190 (M^+), 145, 115, 105, 91; ^{1}H-NMR (250 MHz, $CDCl_3$, δ ppm) : 1.18 (t, J = 6.8 Hz, 3H), 3.51 (s, 2H), 4.12 (q, J = 6.8 Hz, 2H), 5.24 (s, 1H) , 5.54 (s, 1H), 7.28-7.42 (m, 5H); ^{13}C-NMR (62.9 MHz, $CDCl_3$, δ ppm) : 14.1, 41.3, 60.8, 116.2, 125.8, 127.7, 128.3, 139.8, 141.0, 171.3.
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15. Since it is difficult to measure temperature in a domestic microwave oven, the values reported refer to the temperature measured by introducing into the glass vessel a digital termometer at the end of the reaction.