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Kinetic study of microwave-assisted Wittig reaction of stabilised ylides with aromatic aldehydes

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Abstract—The Wittig reaction of a pool of stabilised ylides and aromatic aldehydes was carried out in a microwave oven. Only a few minutes were needed for high conversion rates under microwave heating in comparison to hour time with traditional methods. © 2001 Elsevier Science Ltd. All rights reserved.

The initial and empirical observation that some organic reactions proceed faster and with higher yields under microwave irradiation in comparison to conventional heating has resulted in intense and broad research in the field. Microwave-assisted synthesis is a new and quickly growing area in synthetic organic chemistry.[1] In most cases reactions that normally require many hours at reflux temperature under classical conditions can be completed within a few minutes or even seconds in a microwave oven, even at comparable reaction temperatures.

Although more recent methods have been made available in the last decades, the Wittig reaction remains one of the most robust and reliable tool for the formation of the carbon–carbon double bond in synthetic organic chemistry.[2]

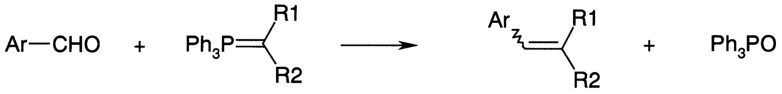
Very recently, a method based on the microwave heating in a simple domestic oven for the rapid preparation of phosphonium salts, precursor intermediates in the Wittig reaction, was described.[3] There are also some reports dealing with the formation of the double bond in the Wittig reaction from organophosphorus reagents under microwave conditions. These papers have mainly synthetic purposes as they describe different synthetic approaches of Wittig reactions with ketons and aldehydes.[4] Anyway, under conventional conditions the reaction time of stabilised ylides with aromatic aldehydes is normally long and it is strongly affected by the aromatic substitution pattern.

Our work describes the synthesis of a pool of olefins from stabilised ylides and aromatic aldehydes via a microwave accelerated Wittig reaction and the kinetic study of these reactions in different conditions at different times, with different reactive substrates. We have compared all the results in order to demonstrate that moving from traditional to microwave conditions, times are shorter and yields are better.

We have also compared the behaviour of two different solvents, one more commonly used for Wittig reactions (THF) and a more suitable one for microwave conditions (DMSO).

Here we report the results of our investigation on this reaction when carried out under microwave and normal conditions (see Scheme 1).

Four benzaldehydes substituted both with electron releasing or withdrawing groups and one heteroaromatic aldehyde were reacted in a domestic oven with five ylides stabilised by the traditional carbonyloxy,



Scheme 1. Wittig reaction of stabilised ylides with aromatic aldehydes.

Keywords: microwave heating; Wittig reaction; stabilised ylides.

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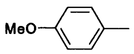
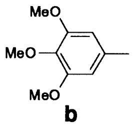
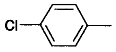
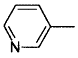
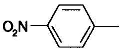
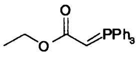
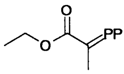
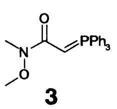
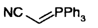
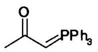
cyano and carbonylmethyl groups and by the less common *N*-methyl-*N*-methoxy carbonylamino group.[5]

Along with a standard microwave protocol (DMSO, 5 min, 280 W potency), as a comparison different traditional conditions were tested (THF, 5–60 min, room temperature or reflux). An additional method bridging the gap between traditional and microwave conditions was investigated as well (THF/DMSO drops, 15 min, 280 W potency). The conversion rate of the aldehydes into the expected olefins was determined by monitoring the reactions at a fixed time with HPLC chromatography.[6] In 20 cases, out of the 25 investigated, a substantial and positive effect was always observed both in terms of reaction time and conversion percentage (Table 1).

Aldehydes **b**–**e** are fully converted (100%) into the expected olefins after just 5 minutes microwave heating (**1**–**4**, **b**–**e**). *p*-Methoxy benzaldehyde under similar conditions shows a reduced reactivity (51–70%) with all five ylides (**1**–**5**,**a**). Analogously, *p*-chloro and 3,4,5 trimethoxy benzaldehyde react to only about 50% extent being this effect limited to coupling to ylide **5** (**5**, **b**–**c**). Under traditional conditions in THF the conversion rate of the aldehydes **a**, **b**, **c**, **d** with all ylides never equals that observed with the microwave oven even after one hour reflux. The only case in which both methods are similar as far as the reaction time is concerned (5 minutes), refers to *p*-nitro benzaldehyde (**1**–**5**, **e**; methods A and D). The conversion rates are mostly affected by the substitution pattern of aldehydes; the ylides seem to play a minor role, even if considering the lower conversion for compounds **5**, **a**–**c** one could speculate on a lower reactivity for ylide **5**. It is worthwhile noting that when method C is applied (THF as a solvent, times lasting up to 15 minutes, 280 W potency), the results with microwave chemistry are closely similar to that obtained under conventional conditions (**1**–**5**, **a**–**c**). This confirms the crucial and pivotal role played by the solvent used to carry out the microwave reactions.

In conclusion we have set up a rapid and general method for the Wittig reaction between aromatic aldehydes and stabilised ylides taking advantage of

Table 1. Wittig reaction of stabilised ylide and aromatic aldehyde (% of conversion of aldehyde into products)

	 **a**					 **b**					 **c**			 **d**			 **e**		
	Cpd	A	B	C	D	Cpd	A	B	C	D	Cpd	A′[f]	D	Cpd	A′[f]	D	Cpd	A′[f]	D
 **1**	**1a**	19	28	18	54	**1b**	67	84	93	100	**1c**	79	100	**1d**	56	100	**1e**	100	100
 **2**	**2a**	36	55	33	65	**2b**	81	92	82	100	**2c**	90	100	**2d**	65	100	**2e**	100	100
 **3**	**3a**	36	60	33	70	**3b**	73	87	79	100	**3c**[7]	60	100	**3d**[7]	50	100	**3e**	100	100
 **4**	**4a**	27	31	14	51	**4b**	50	60	65	100	**4c**	67	100	**4d**	64	100	**4e**	100	100
 **5**	**5a**	n.r.	16	30	56	**5b**	n.r.	23	25	50	**5c**	10	46	**5d**	35	100	**5e**	100	100

(a), (b), (c), (d), (e): The same results were obtained in classical conditions under refluxing for 24 hours. (f): in these cases the reaction rate is high even in classical conditions, so we have to compare the reactions at shorter times. Method A, A′, B, C, D: see Ref. 5.

microwave chemistry. Carrying out these reactions under this unconventional heating in the presence of an appropriate solvent (DMSO) has the major advantage of very shortened reaction times (5 minutes in most cases) coupled with high yields.

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5. *Methods:* (A) 60 mg aldehyde, 1 equiv. ylide, 2 ml THF, magnetic stirring, room temperature, 1 h; (A′) 60 mg aldehyde, 1 equiv. ylide, 2 ml THF, magnetic stirring, room temperature, 5 min; (B) 60 mg aldehydes, 1 equiv. ylide, 2 ml THF, magnetic stirring, reflux, 1 h; (C) 20 mg aldehyde, 1 equiv. ylide, 500 μl THF/10 μl DMSO, 15 min in a domestic microwave oven at 280 W potency; (D) 20 mg aldehyde, 1 equiv. ylide, 200 μl DMSO, 5 min in a domestic microwave oven at 280 W potency.
6. *HPLC method*: eluent $CH_3CN:H_2O = 50:50$ (plus HCOOH 10%); flux: 1 ml/min; analysis and integration of the chromatographic peaks at 254 nm; instrument: HP series 1100.
7. The following two compounds are not known in the literature. Their structure was identified and confirmed by LC–MS and NMR analysis. LC–MS analysis: LC: C8 reverse phase column (Symmetry Waters 4.6×15 cm) gradient method (from H_2O/0.2% formic acid:$CH_3CN = 80:20$ to H_2O/0.2% formic acid:$CH_3CN = 20:80$ in 20 min) 1 ml/min for 20 min; mass spectrometry was performed on a Finnigan SSQ7000 in APCI+mode, Heater temp. = 450°C. ^{1}H NMR (Varian 200 MHz, $CDCl_3$). Compound **3c**: 3.31 ppm (3H, s); 3.77 ppm (3H, s); 7.01 ppm (1H, d); 7.35 ppm (2H, d); 7.50 ppm (2H, d); 7.68 ppm (1H, d). Compound **3d**: 3.33 ppm (3H, s); 3.78 ppm (3H, s); 7.13 ppm (1H, d); 7.38 ppm (1H, m); 7.72 ppm (1H, d); 7.93 ppm (1H, m); 8.60 ppm (1H, m); 8.82 ppm (1H, d).