SHORT PAPER

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Effect of microwave irradiation on the formation of bicyclic cyclopropane derivatives

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Microwave irradiation changes the diastereomeric composition of the bicyclic cyclopropane carboxylic acid lactones obtained in the intramolecular cyclization of malonic acid allylic esters in a phase transfer catalysed reaction.

Numerous publications and reviews have shown the usefulness of microwave-facilitated organic syntheses.[1,2] Typically enhancement of chemical yields, increase in purity of the reaction products and shorter reaction times (often few minutes only) are described. In many cases, heterogeneous reactions, e.g. solid–liquid phase transfer catalytic reactions,[2] clay-,[3] zeolites-[4] or related minerals[5]-catalysed reactions are used in which the solid materials are good microwave absorbants but good effects were even observed with reagents adsorbed on solid supports[6] (silica or alumina) although these support materials are weak microwave absorbants.

Recently we reported a solid–liquid phase transfer catalytic intramolecular cyclization reaction of malonic acid allylic esters in toluene, using solid potassium carbonate, iodine, and a lipophilic quaternary ammonium salt (TCMC, Aliquat® 336) as catalyst, which yields bicyclic cyclopropane carboxylic acid lactones in a stereoselective manner in good preparative yield (65–90%) without any remarkable byproduct (Scheme 1).[7] In this communication we describe our results concerning an examination of this cyclization.

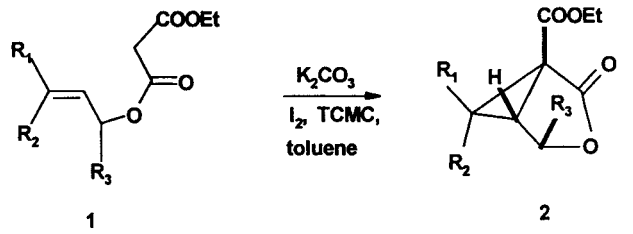
The experiments were performed in a Prolabo Synthewave 402 apparatus equipped with mechanical glass stirrer and reflux condenser. This apparatus works either in temperature control mode when the power of the microwave irradiation is controlled by the temperature of the reaction mixture or in power control mode when a constant irradiation power is produced independently of the inner temperature of the mixture.

In our case the power control mode was only applicable because in the other mode the temperature of the reaction mixture reached the assigned temperature in one minute and to keep it only irradiation with a very low microwave power was needed (2–3% of the maximal 300 W). The speed of the stirrer was 30 rpm. Without stirring, the reaction time increased significantly. Comparative results on cyclizations obtained under classical conditions (room temperature or oil bath-heated) are also summarized in Table 1.

There was no more than 3% difference between the chemical yields obtained in the classical reaction at 110 °C and the microwave-assisted reaction. The times in Table 1 indicate the minimum reaction time required for the 100% conversion. Using shorter reaction time TLC examination of the reaction mixtures (both the classical and the microwave-irradiated) showed the presence of some unreacted starting ester, the known iodomalonic ester intermediate[7] and the cyclization product.

In all cases the reaction time was significantly reduced using microwave irradiation. In some cases the temperature of the reaction mixture exceeded even the boiling point of the toluene, although toluene is a weak microwave absorber. Using xylene as solvent in the cyclization of **1a** the temperature of the reaction mixture increased to 130 °C (but did not reach the boiling temperature of the solvent) but there was no further decrease in the reaction time. These results unambiguously prove that the 2–3 sold decrease in the reaction time is not due to a simple thermal effect of the microwave irradiation. If a special microwave effect exists this might influence other parameters of the reaction, too.

This cyclization reaction is diastereoselective, the two rings are always in the *cis* configuration and the R_3 group always occupies the *exo* position. If R_1 and R_2 are different, the ratio of the endo/exo isomers at the cyclopropane C2 position (see



1 **2**

1	**2**
a R_1=R_2=Me, R_3=CCl_3	**a** R_1=R_2=Me, R_3=CCl_3
b R_1, R_2=H, Me, R_3=H	**b,** *exo* R_1=Me, R_2=R_3=H
	b, *endo* R_2=Me, R_1=R_3=H
c R_1=Ph, R_2=H, R_3=H	**c,** *exo* R_1=Ph, R_2= R_3=H
	c, *endo* R_2=Ph, R_1=R_3=H
d R_1=Ph, R_2=H, R_3=Me	**d,** *exo* R_1=Ph, R_2=H, R_3=Me
	d, *endo* R_1=H, R_2=Ph, R_3=Me
e R_1=Ph, R_2=H, R_3=Ph	**e,** *exo* R_1=R_3=Ph, R_2=H
	e, *endo* R_1=H, R_2=R_3=Ph
f R_1=Ph, R_2=H, R_3=$PhCH_2$	**f,** *exo* R_1=Ph, R_2=H, R_3=$PhCH_2$
	f, *endo* R_1=Ph, R_2=H, R_3=$PhCH_2$

Scheme 1
Phase transfer catalytic cyclopropanation reactions of malonic acid allylic esters

Table 1 Comparison of the reaction times of the classical[8] and microwave irradiated reactions at 240 W irradiation power

	Microwave			Classical				
	Temp.[a] [°C]	Time[b] [min]	Yield	Temp. [°C]	Time[b] [min]	Yield	Temp. [°C]	Time[b] [min]
2a	119	16	91	110	30	94	24	480
2b	108	10	66	110	26	68	24	840
2c	117	10	65	110	25	66	24	840
2d	107	10	71	110	24	68	24	600
2e	–[c]	–[c]	–[c]	110	28	70	24	–[c]
2f	103	10	67	110	25	65	24	720

[a]Maximal temperature detected in the microwave oven.
[b]Time required for 100% conversion.
[c]No cyclization product was observed.

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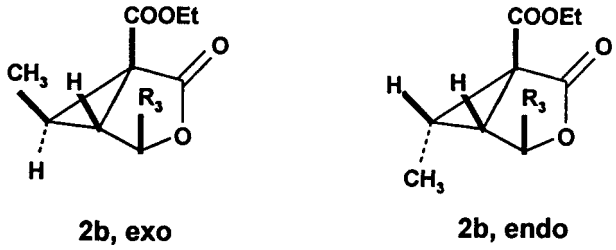
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2
Endo and *exo* diastereomers of compound **2b**.

Table 2 The percentage of *exo* isomer in the cyclization products **2b–f**[a,b]

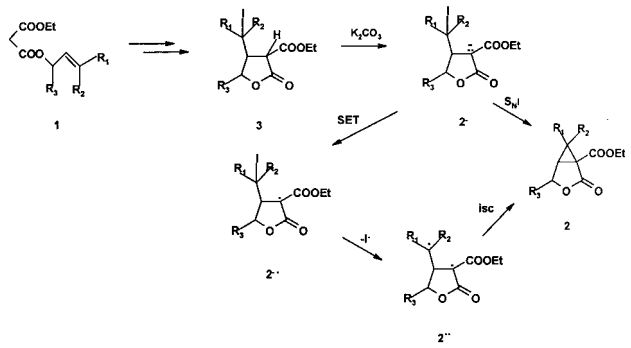
Compound	Microwave	Room temp.	110 °C
	exo%		
2b	72	65	60
2c	78	77	60
2d	55	45	62
2e	–[c]	–[c]	65
2f	63	40	30

[a]The *exo/endo* diastereomeric ratio was determined from the ^{1}H-NMR-spectra of the chromatographed products obtained at 100% conversion (see Experimental). [b]No change in isomeric ratio was observed upon neither longtime heating nor irradiating compounds **2b–f**. [c]No cyclization product was obtained.

Scheme 2) depends on the reaction temperature and the R_3 group.[8] Therefore, it was interesting to investigate further the diastereochemical composition of the products obtained in the microwave-assisted reactions. Significant differences in diastereomeric distribution of compounds **2b** and **2d–f** were observed, from classical and microwave-facilitated reactions (Table 2).

Although the reaction temperature in the microwave experiments in all cases exceeded 100 °C, surprisingly the diastereomeric composition of the products was generally more similar to that observed at room temperature in the classical reaction without irradiation. Even in the cases of **2b** and **2f** the *exo* selectivity exceeded the value obtained in the room temperature classical reaction. The most significant change was observed in the case of **2f**; the classical reaction showed *endo* isomer-preference both at room temperature and at 110 °C, while in the microwave-assisted reaction a significant *exo*-preference could be observed. As the classical cyclization at room temperature requires a longer reaction time, in the cases mentioned above the microwave-assisted reaction can generally provide a more convenient way to obtain products with high *exo*-diastereoselectivity not observed previously. In the case of **2e** surprisingly there was no cyclization product observed in the microwave-irradiated, or in the classical room temperature reaction, although the starting material was completely consumed. In the case of **2d** the two diastereomers were obtained in a nearly equal amount.

Based on literature precedents, since some solid mineral-like materials have good microwave absorption ability, strong local heating on the surface leads to elevated reaction rates. Taking into account these considerations we would have obtained diastereomeric composition similar to those obtained in the classical reaction at higher temperature. Examination of the reaction mechanism provides an interpretation of this unexpected effect. The cyclization is a complex, SET-induced radical-ionic reaction[7] with more than ten elemental steps, in which the formation of the iodolactone intermediate **3** is a



Scheme 3
The mechanism of the cyclization reaction

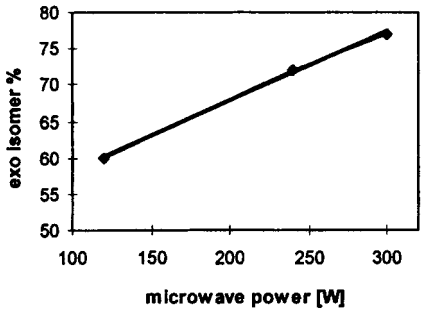


Fig. 1 The Effect of microwave power on the diastereoselectivity of compound **2b**

kinetically controlled process[9] but the stereochemistry of the product is probably determined only in the last steps in two possible ways[8] (Scheme 3), resulting in the final diastereoselective composition of the product. We suppose that the microwave irradiation influences these steps. As the diastereoselective composition of the products has changed in the microwave-assisted reaction the irradiation might influence the two ways differently.

We evaluated this hypothesis by studying the cyclization of **1b** at three different levels of microwave power. In all cases the temperature of the reaction mixture reached 100 °C in one minute and the final temperature was in the range of 105–108°C. The results showed a linear correlation in the examined area between increasing microwave power and increasing exo isomer in **2b** (see Fig. 1). Since there are no differences in reaction temperatures or in reaction times required for 100% conversion and only the irradiation levels differed, a new strategy for possibly influencing the diastereoselectivity in microwave-assisted cyclizations may be in hand.

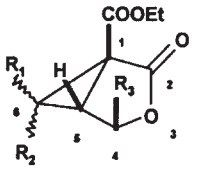
Experimental

General method for the preparation of the lactones **2a-f** *in microwave oven*: A mixture of 2 mmol of **1**, 1.3 g of iodine, 1.4 g of potassium carbonate, one drop of TCMC and 10 cm^3 of toluene was irradiated under stirring at 30 rpm in the reaction vessel of the microwave oven. The reaction was conducted until the complete consumption of the starting material which was checked by TLC (Merck Kieselgel 60 F_{254} plates, hexane-acetone 4:1). Then the mixture was diluted with toluene and filtered. The filtrate was washed with sodium thiosulphate solution and then with water, dried over magnesium sulphate and the solvent was evaporated. The residue was purified by column chromatography on Merck Kieselgel 60 to 200 mesh, eluent: hexane-acetone 4:1.

Determination of the diastereomeric composition of the products: This was determined by ^{1}H NMR spectroscopy. The spectra were recorded on a VARIAN INOVA UNITY plus 400 spectrometer at 400

MHz in $CDCl_3$ as solvent using TMS as internal standard. Chemical shifts are given on the δ scale, δ(TMS) = 0 ppm. The signals for the identification of the *endo* and *exo* isomers are summarized in Table 3. The diasteromeric ratio was calculated from the integral values of the appropriate pairs of signals. There was less than 5% difference between the corresponding individual calculated values. The data described in Table 2 are the average of the individual values.

Table 3 Selected ^{1}H NMR data of the compounds **2b–f**[a]



	$OCH_2\underline{CH_3}$	H-4	H-5	H-6	R_3
2b *exo*	–[b]	–[b]	2.55	1.71	
2b *endo*	–[b]	–[b]	2.74	2.35	
2c *exo*	0.94	–[b]	3.29	2.90	
2c *endo*	1.37	–[b]	3.02	3.59	
2d *exo*	0.92	–[b]	3.06	2.88	1.53
2d *endo*	1.37	–[b]	2.78	3.55	1.46
2e *exo*	0.87	5.42	3.31	3.02	
2e *endo*	1.33	5.13	2.96	3.64	
2f *exo*	0.88	4.72	3.03	2.86	
2f *endo*	1.28	4.47	3.48	2.81	

[a]chemical shifts are given in ppm; [b]overlaps with other signals

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