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Application of Focused Microwaves to the Scale-Up of Solvent-Free Organic Reactions

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Abstract:

A series of typical solvent-free reactions have been safely and beneficially scaled-up to several hundred grams in a larger batch reactor (Synthewave 1000) with yields equivalent to those obtained under similar conditions (temperature, reaction time) in laboratory-scale experiments (Synthewave 402). They concern potassium acetate alkylation, regioselective phenacylation of 1,2,4-triazole, deethylation of 2-ethoxy-anisole, and typical examples in carbohydrate chemistry (peracetylation, glycosylation, saponification, halogenation, and epoxidation of D-glucopyranosides).

Introduction

Extensive improvements have been described in organic synthesis, resulting from microwave (MW) irradiation by use of either domestic ovens[1] or, more recently, monomode reactors.[2] In the latter case, numerous reactions were performed using the Synthewave 402 apparatus,[3] with noticeable success achieved by using a maximum of 30−40 g of reactants, a limit imposed by the reactor size.

Due to the evident industrial interest, we describe herein the extension of the method to increased amounts of products for typical solvent-free organic reactions using a convenient larger apparatus recently developed by Prolabo: the Synthewave 1000. This reactor was essentially designed for scale-up with focused microwaves, fitted with a 1-L vessel, a mechanical stirrer, and eventually a dropping funnel, making it possible to perform reactions under controlled atmospheres. The reactor operates with an adjustable power between 40 and 800 W and may be monitored either in power or in temperature, or both (Figure 1).

Some experiments were previously described that used this reactor, including esterification of acetic acid with *n*-propanol in "dry media",[4] the solvent-free synthesis of dioxolanes, dithiolanes, and oxathiolanes on K10 montmorillonite,[5] and the synthesis of 4-alkoxyquinazoline-2-carbonitriles and aryl thiocarbamates in different alcohols.[6] In these cases, the reactions could be safely and beneficially scaled up to multigram levels with similar yields and conditions (reaction time, temperature) from the Synthewave 402 (300 W) to the Synthewave 1000 (800 W).

In this report, we describe the systematic study of significant organic reactions, performed either in the presence or in the absence of solvent under microwaves, scaled up to at least 100 g. To check the possible specific effect (nonpurely thermal) of microwaves, results obtained in the Synthewave 402 apparatus are compared with those resulting from conventional heating (△) under identical conditions (amounts, time, temperature, etc.) and thus are not optimized in this case.

Results and Discussion

Alkylations. *(a) Potassium Acetate Alkylation with n-Bromooctane* (Scheme 1). This reaction was first realized under solid−liquid phase-transfer catalysis (PTC) without any solvent using a multimode domestic oven.[7] Yields were quasi-quantitative (>95%) within 1 min on a 10−500 mmol scale (i.e., from 3.21 to 160.5 g of total starting materials).

Scheme 1

1

The reaction was reconsidered with accurate control of temperature, monitoring of the operations from 50 mmol (Synthewave 402) to 2 mol (Synthewave 1000). The study was completed by considering the medium effect in the presence of solvent (either a polar one, DMF, or a nonpolar one, 1,2-dichlorobenzene) or in its absence either under PTC or in "dry media" conditions by impregnation of reactants on basic alumina.[8]

The main results are given in Tables 1−3, with GC yields in octyl acetate **1** (determined by use of a capillary column).

The profiles obtained upon raising the temperature are presented in Figure 2, which also shows the evolution of emitted power necessary to maintain a constant temperature.

Scale-up was realized without any problem under identical conditions using the same time and temperature (5 min, 160

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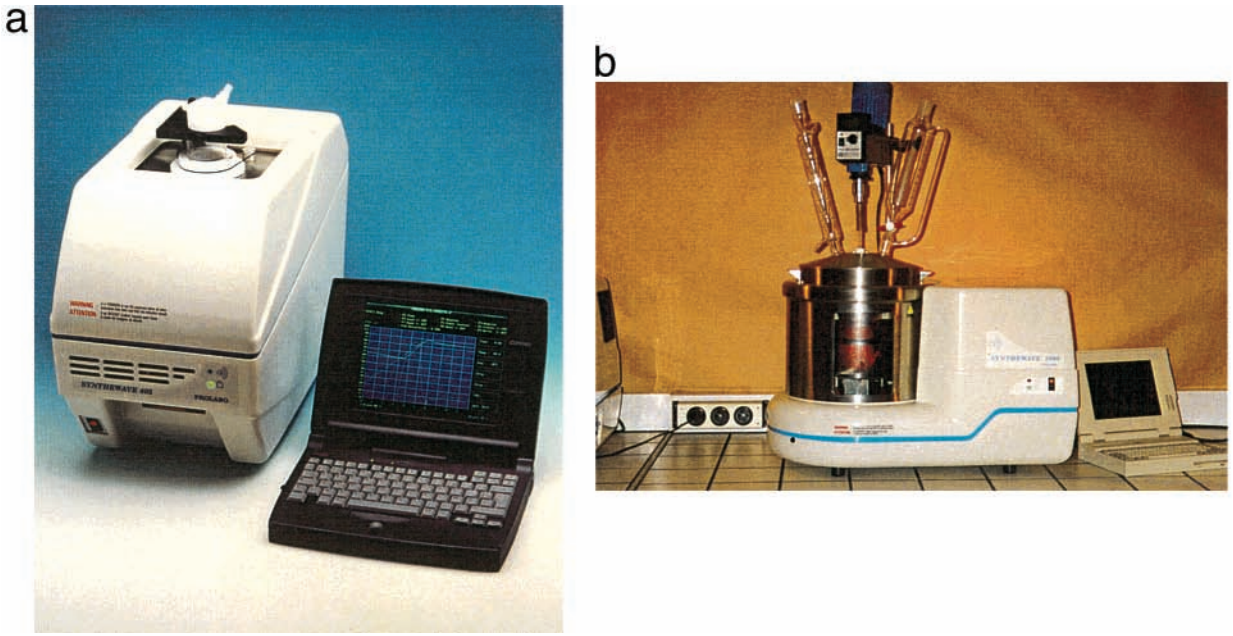


Figure 1. **Photograph of Synthewave equipment. (a) Synthewave 402 (optimal power = 300 W); (b) Synthewave 1000 (optimal power = 800 W).**

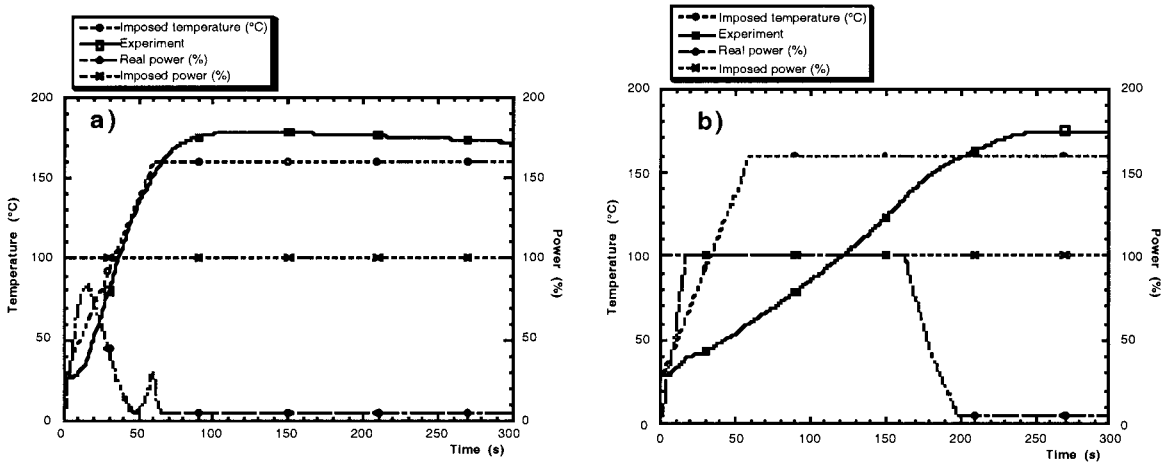


Figure 2. **Thermal behaviour for *n*-octylation of potassium acetate under solid−liquid PTC conditions and MW irradiation. (a) S402; (b) S1000.**

Table 1. **Synthesis of 1 under solvent-free PTC conditions in the presence of Aliquat 336 (5% mol); 5 min, $T_{imposed}$ = 160 °C**

activation method	amount of materials [g (mol)]			total amount (g)	final temp (°C)	yield of **1** (%)[b]
	CH_3COOK	nOctBr	Aliquat 336			
MW, S402	4.9 (0.05)	9.7 (0.05)	1 (0.0025)	15.6	172	98
△, oil bath	4.9	9.7	1	15.6	172	98
MW, S1000	196 (2)	386 (2)	40.4 (0.1)	622.4	174	98 (96)[a]

[a] In parentheses, yield in isolated product after distillation. [b] Yields evaluated by GC with internal standard (undecane).

Table 2. **Synthesis of 1 in the presence of DMF (5 min at 160 °C)**

activation method	amount of materials [g (mol)]			total amount (g)	yield of **1** (%)[a]
	CH_3COOK	nOctBr	DMF		
MW, S402	4.9 (0.05)	9.7 (0.05)	9.4 (10 mL)	24	88
△, oil bath	4.9	9.7	9.4	24	83
MW, S1000	4 (0.5)	96.5 (0.5)	94.4 (100 mL)	239.9	94

[a] Yields evaluated by GC with internal standard.

°C). Despite a quite large difference in the profiles obtained upon raising the temperature (3.5 min was necessary to reach the plateau value when using the Synthewave 1000 reactor, versus only 2 min with the 402 one), yields were equivalent in both situations.

Yields in ester remain very similar after extension of the scale for the same reaction times at identical temperatures. Results are equivalent under solvent-free PTC (Table 1) whatever the activation method and equipment and slightly better than those obtained by use of supported reagents on basic alumina. In this last case, the presence of 1,2-dichlorobenzene allowed more efficient stirring without any effect on the reactivity.

All of the reactions were repeated under traditional heating (oil bath), and equivalent results were obtained, respectively

Table 3. **Synthesis of 1 with potassium acetate impregnated onto neutral alumina (1:5 w/w) with or without 1,2-dichlorobenzene (DCB) (30 min at 160 °C)**

activation method	amount of materials [g (mol)]				total amount(g)	yield of **1** (%)[a]
	CH_3COOK	nOctBr	alumina	DCB		
MW, S402	4.9 (0.05)	14.5 (0.075)	24.5		43.9	48
△, oil bath	4.9	14.5	24.5		43.9	50
MW, S402	2.45 (0.025)	7.25 (0.0375)	12.25	6.55 (5 mL)	28.5	53
△, oil bath	2.45	7.25	12.25	6.55	28.5	49
MW, S1000	24.5 (0.25)	72.5 (0.375)	122.5		219.5	54
MW, S1000	24.5 (0.25)	72.5 (0.375)	122.5	65.5 (50 mL)	285	50

[a] Yields evaluated by GC with internal standard.

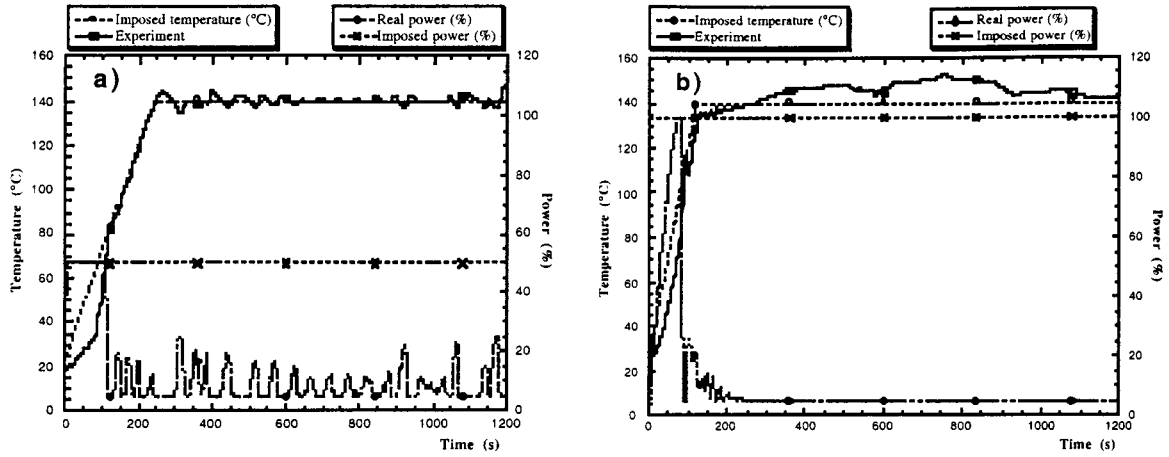


Figure 3. **Thermal behaviour for the phenacylation of 1,2,4-triazole under MW irradiation. (a) S402; (b) S1000.**

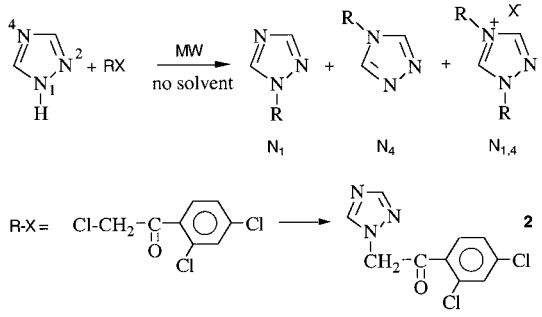
98, 83, and 50% for the three types of experiments (instead of 98, 88, and 53% obtained under MW). No specific MW effects are revealed under these conditions.

(b) Phenacylation of 1,2,4-Triazole. Selective alkylation by substituted phenacyl halides at position 1 of 1,2,4-triazole is an important goal, leading to the synthesis of biologically active molecules such as fungicides (fluconazole, flutriafole,[9] hexaconazole,[10] epiconazole, etc.).

Under classical heating, direct alkylation gave a mixture of 1- and 4-alkylated triazoles as well as quaternary salts resulting from alkylations at both positions 1 and 4.[11] We have shown that MW-assisted benzylation[11] and phenacylation[12] occurred selectively at position 1 without any base and under solvent-free conditions (Scheme 2).

The reaction was extensively studied with (2,4-dichloro)-phenacyl chloride (Table 4).

Scheme 2



Under microwave irradiation, both reactivity and selectivity were enhanced, and total regioselectivity in favour of N_1-alkylation was obtained due to specific MW effects. Scale-up gave the same results regardless of the amount of reactants involved. The profiles obtained upon raising the temperature are rather comparable, and the power involved remains quasi-identical (from 15 to 60 W using Synthewave 402, and 40 W with Synthewave 1000) (Figure 3).

Table 4. **Phenacylation of 1,2,4-triazole with (2,4-dichloro)phenacyl chloride (20 min at 140 °C)**

activation method	amount of materials [g (mmol)]		total amount (g)	yield of **2** (%)[a]	N_1/N_4/$N_{1,4}$[b]
	triazole	R−X			
MW, S402	0.414 (6)	1.12 (5)	1.534	92	100/0
Δ, oil bath	0.414	1.12	1.534	35	36/27/37
MW, S1000	37.3 (540)	100.6 (450)	137.9	89	100/0

[a] Yields evaluated by GC with internal standard. [b] Measured by ^{1}H NMR.

(c) Selective Deethylation of 2-Ethoxy-anisole. Alkylation−dealkylation is one of the most important protective−deprotective processes of hydroxyl moieties of alcohols and phenols. Dealkylation is generally performed under harsh conditions, either acidic (i.e., $AlCl_3$ or BX_3)[13] or basic,[14]

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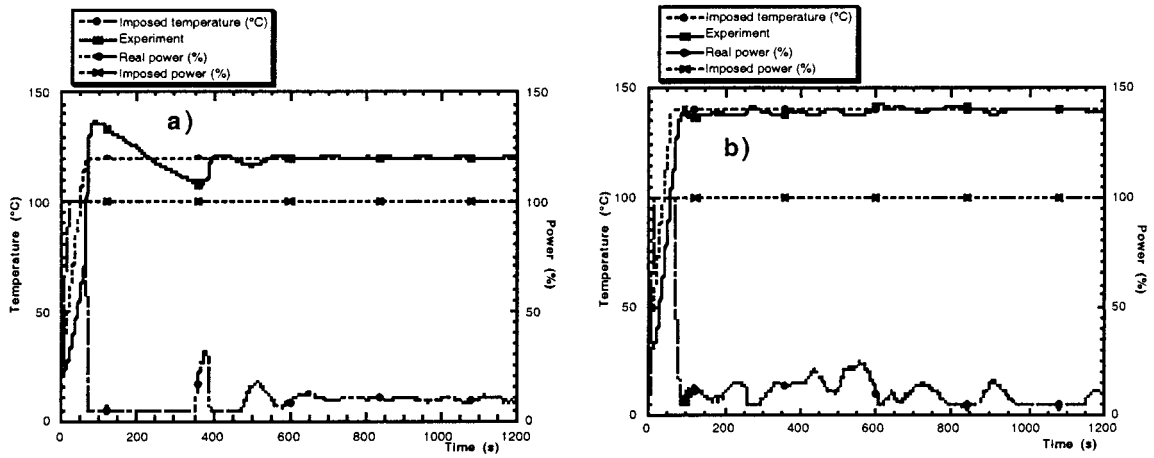
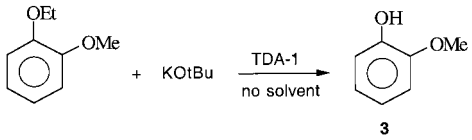


Figure 4. **Thermal behaviour for the deethylation of 2-ethoxy-anisole under MW irradiation. (a) S402; (b) S1000.**

including dry media using KF/alumina.[15]

Selective dealkylation was recently described under MW using PTC conditions induced by KOtBu as a base and TDA-1 as a phase-transfer agent [16] (Scheme 3).

Scheme 3



The reaction was studied under MW using Synthewave 402 or 1000 reactors, depending on the amount of reactants involved, and the results were compared with those obtained by conventional heating (△) (Table 5).

Table 5. **Deethylation of 2-ethoxy-anisole in 20 min (KOtBu (2 equiv), TDA-1 (10%))**

activation method	temp (°C)	amount of materials [g (mmol)] ethoxy-anisole	KOtBu	TDA-1	total amount (g)	yield of **3** (%)[a]
MW, S402	120	0.76 (5)	1.12 (10)	0.324 (1)	2.206	90
△, oil bath	120	0.76	1.12	0.324	2.206	50
MW, S1000	140	37.24 (245)	54.98 (490)	15.9 (49)	108.12	82

[a] Yields in isolated product.

A strong specific MW effect was evidenced as yields are enhanced from 50 to 90% under MW after 20 min at 120 °C. Scale-up proved very satisfactory, requiring only a slight modification of the temperature (140 instead of 120 °C) to obtain a similar result (82−90%) (Figure 4).

Examples in Carbohydrate Chemistry. *(a) Glycosylation of Monosaccharides with a Three-Step Procedure.* The interest in alkyl- or aryl-glycosides is connected to their physical properties (as liquid crystals and as nontoxic and biodegradable surfactants).[17] To obtain long-chain aliphatic alcohols, previous butylation and subsequent transacetalization at high temperatures were needed.[18] Because D-glucosylation with 1-decanol in acidic medium is not convenient (due to glucoside decomposition), a three-step microwave-assisted solvent-free synthesis of decyl D-glucopyranoside was established (peracetylation, glucosylation, and saponification).[19] Rate enhancements and reduction of the reaction time were observed in comparison to those observed with conventional heating under the same conditions.

Peracetylation of D-Glucose. Peracetylation of D-glucose with a slight excess (1.8 equiv per OH function) of acetic anhydride catalyzed by zinc chloride (0.13 equiv) was performed either under classical heating or under MW activation in the Synthewave 402 equipment (11.1 mmol) or Synthewave 1000 (200 mmol) (Scheme 4, Table 6).

Scheme 4

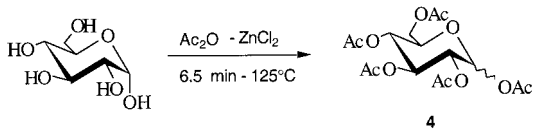


Table 6. **Peracetylation of D-glucose at 125 °C within 6.5 min**

activation method	amount of materials g (mmoles) D-glucose	Ac_2O	$ZnCl_2$	total amount (g)	yield of **4** (%)[a]
MW, S402	2 (11.1)	10.2 (100)	0.2 (1.47)	12.4	98[b]
△, oil bath	2	10.2	0.2	12.4	83[c]
MW, S1000	36 (200)	183.8 (1800)	3.5 (26)	223.3	86[b]

[a] Yields in isolated product. [b] $\alpha/\beta = 1/1$. [c] $\alpha/\beta = 7/3$.

Whatever the conditions, the yields were rather similar with MW or classical heating and equivalent in scale-up.

Glucosylation of D-Glucose Pentaacetate with 1-Decanol. It was previously shown that zinc chloride is a catalyst of

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Table 9. **Chlorination of 7 in 10 min at 100 °C**

activation method	amount of materials [g (mmol)]					total amount (g)	yield of **8** (%)[a]
	7	CCl_4	PPh_3	KCl	pyridine		
MW, S402	0.39 (2)	1.23 (8)	0.79 (3)	1.49 (20)	0.78 (0.8 mL)	4.68	78
△, oil bath	0.39	1.23	0.79	1.49	0.78	4.68	68
MW, S1000	20 (103)	63.4 (412)	40.5 (154.5)	74.6 (1030)	39.1 (40 mL)	237.6	92
△, oil bath	20	63.4	40.5	74.6	39.1	237.6	82

[a] Yields in isolated product.

choice for this reaction. Results are compared with those obtained under similar conditions by classical heating or MW activation (Scheme 5, Table 7).

Scheme 5

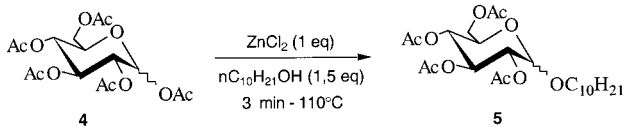


Table 7. **$ZnCl_2$-catalyzed glycosylation of 1-decanol with peracetyl D-glucopyranoside 4 at 110 °C**

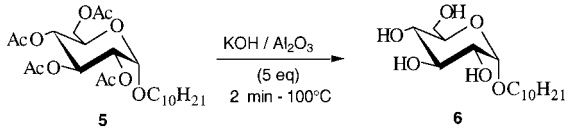
activation method	reaction time (min)	amount of materials [g (mmol)]			total amount (g)	yield of **5** (%)[a]
		4	1-decanol	$ZnCl_2$		
MW, S402	3	1.95 (5)	1.19 (7.5)	0.68 (5)	3.82	74[c]
△, oil bath	3	1.95	1.19	0.68	3.82	0[b]
MW, S1000	4	97.5 (250)	59.4 (375)	34.1 (250)	191	72[d]

[a] Yields in isolated product. [b] After 5 h, yield is only 25%. [c] Yields of anomers (%): $\alpha/\beta = 64/10$. [d] Yields of anomers (%): $\alpha/\beta = 62/10$.

An important specific (non-purely thermal) MW effect here is involved when one considers the 72−74% yield compared to the absence of reaction under classical heating. Scale-up under MW is fairly interesting, giving similar yields under very close conditions (72−74% within 3 or 4 min).

*Saponification of Decyl 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranoside **5***. Saponification was attempted with potassium hydroxide impregnated on alumina (1:3 w/w) in dry conditions (Scheme 6, Table 8).

Scheme 6



The effect of MW irradiation here is highly decisive because with classical heating no reaction occurred after 2 min at 100 °C, whereas the yield was nearly quantitative under MW. By extension of the reaction by a factor 50, scale-up led to satisfactory results under the same conditions using the Synthewave 1000 equipment (85% yield within 2 min).

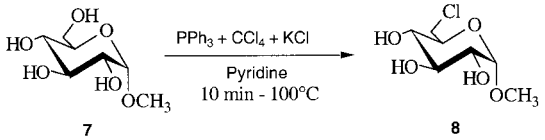
*(b) Chlorination of Methyl α-D-Glucopyranoside **7***. It was previously shown[20] that halogenation could be performed efficiently in highly concentrated solutions under MW irradiation. Chlorination using triphenylphosphine/carbon tetrachloride was realized in the presence of pyridine after addition of an excess of potassium chloride (Scheme 7, Table 9).

Table 8. **Saponification of decyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside 5 in 2 min at 100 °C**

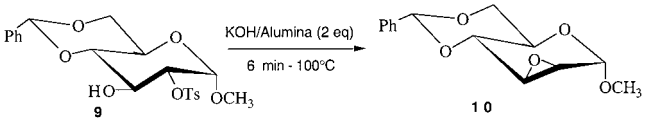
activation method	amount of materials [g (mmol)]		total amount (g)	yield of **6** (%)[a]
	5	KOH/ alumina		
MW, S402	1.09 (2.24)	2.91 (11.2)	4	96
△, oil bath	1.09	2.91	4	<2
MW, S1000	54.5 (112)	145.5 (560)	200	85

[a] Yields in isolated product (α anomer).

Scheme 7



Scheme 8



9).

Scale-up led in this case to improvements in yields as well as by classical heating (△) and under MW activation. The specific MW effect here is rather reduced, with only a 10% difference in yield in favour of the reaction with MW activation.

*(c) Epoxidation of a Protected Tosyl α-D-Glucopyranoside **9***** (Scheme 8). By treatment of the 2-*O*-tosylate **9** under microwave at 100 °C for 6 min in the presence of KOH/alumina (1:3 w/w, 2 equiv), epoxide **10** was obtained in good yield.[21] Under classical heating (same conditions), the required epoxide was obtained in only 25% yield (Table 10).

Table 10. **Epoxidation of 9 in 6 min at 100 °C**

activation method	amounts of materials [g (mmol)]		total amount (g)	yield of **10** (%)[a]
	9	KOH/Al_2O_3		
MW, S402	1 (2.3)	2.1 (9.2)	3.1	99
△, oil bath	1	2.1	3.1	25
MW, S1000	20 (46)	41.2 (184)	61.2	95[b]

[a] Yields in isolated product. [b] Reaction time = 10 min.

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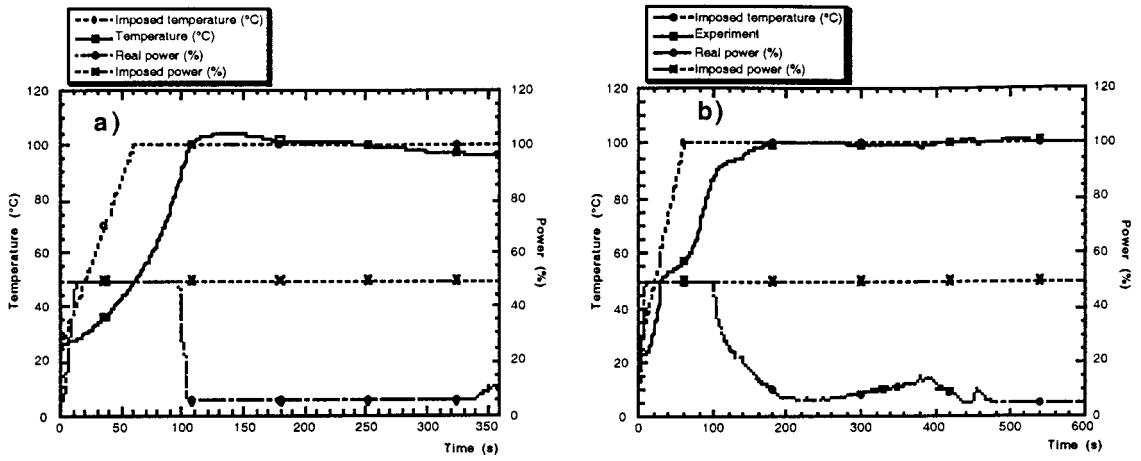

Figure 5. **Thermal behaviour for epoxidation of 9 under MW irradiation. (a) S402; (b) S1000.**

The profiles obtained upon raising the temperature were recorded under MW with both the Synthewave 402 and the Synthewave 1000 equipment (Figure 5). They are rather comparable for 6 min using the Synthewave 402 equipment (yield = 99%) and 10 min with the Synthewave 1000 (yield = 95%).

Conclusions

MW-enhanced synthetic organic chemistry is, at the present time, experiencing considerable growth and has the potential to greatly improve the image of chemistry and, in particular, the chemical industry. In this paper we have shown how it is possible to move from small-scale synthesis (grams) to the multigram level (100−300 g). Furthermore, these MW syntheses could be fairly applied under environmentally benign solvent-free conditions, i.e., according to new rules of so-called "green chemistry".

Experimental Section

Alkylation of Potassium Acetate by *n*-Bromooctane. (*1) Under PTC Conditions or in DMF as a Solvent.* In an adapted microwave vessel (matras) were added successively the potassium acetate, Aliquat 336 (methyl trioctylammonium chloride), and *n*-bromooctane in relative amounts as indicated in Table 1. The mixture was mechanically stirred and then exposed to microwaves for 5 min (imposed temperature = 160 °C) or heated using a thermostated oil bath at 172 °C. After the mixture was cooled to room temperature, organic products were extracted with diethyl ether (50 mL or 1 L, depending on scale). After filtration on a sintered glass, the *n*-octyl acetate yield was measured by gas chromatography (GC) using an internal standard (capillary column CP Sil 5CB, 25 m, isothermal 90 °C, pressure = 70 kPa, standard = undecane).

In the presence of DMF (Table 2), the order of introduction remained the same, and DMF was finally added. Reaction, treatment, and evaluation of product were identical to those in the previous case.

(2) On Basic Alumina. Potassium acetate was previously impregnated onto basic alumina (1:5 w/w relative to support) via an aqueous solution and subsequent removal of water under reduced pressure. The dried powder was introduced in the matras together with *n*-bromooctane and sometimes 1,2-dichlorobenzene (DCB) (Table 3). The reaction mixture was then submitted to MW or immersed into a thermostated oil bath at 160 °C for 30 min under stirring. Treatment and analysis remain identical to those in the above cases.

Phenacylation of 1,2,4-Triazole. In the matras, 1,2,4-triazole was added to the pure alkylating agent [(2,4-dichloro) phenacyl chloride]. Under mechanical stirring, the mixture was submitted to MW or immersed in a thermostated oil bath (under the conditions indicated in Table 4). At the end of the reaction, the mixture was dissolved in methanol and analyzed by GC (capillary column CP Sil 19CB, 10 m, temperature program from 160 (5 min) to 230 °C at 7 °C/min gradient, pressure = 50 kPa, internal standard = phthalimide).

Deethylation of 2-Ethoxy-anisole. In the matras adapted to the MW reactor were introduced successively 2-ethoxy-anisole, KOtBu, and TDA-1. After 5 min of mechanical stirring, the mixture was either submitted to MW or immersed into a thermostated oil bath (under the conditions indicated in Table 5). After cooling to room temperature, the mixture was treated with diluted sodium hydroxide (0.5%) for 5 min with stirring to recover unreacted 2-ethoxy-anisole. After concentration, the crude product was purified by silica gel column chromatography (eluent = pentane−diethyl ether) to give pure **3**.

Peracetylation of D-Glucose. In the matras, D-glucose, acetic anhydride, and zinc chloride were introduced. This mixture was either submitted to MW or immersed into a thermostated oil bath under the conditions indicated in Table 6. After cooling to room temperature, the mixture was diluted with methylene chloride. Powdered $NaHCO_3$ (3 or 50 g) was added, and the reaction mixture was stirred for 10 min and then filtered on silica gel. After solvent removal, pure **4** was obtained by precipitation in pentane.

Glucosylation of D-Glucose Pentaacetate with 1-Decanol. D-Glucose pentaacetate, 1-decanol, and zinc chloride were introduced in the MW reactor under mechanical stirring. This mixture was either exposed to MW or immersed into a thermostated oil bath under the conditions indicated in Table

(21) Hladezuk, I.; Olesker, A.; Cléophax, J.; Lukacs, G. *J. Carbohydr. Chem.* **1998**, *17*, 869.

7. After cooling to room temperature, the mixture was diluted with methylene chloride. Powdered $NaHCO_3$ (1 or 25 g) was added, and reaction mixture was stirred for 10 min before filtration over silica gel. The filtrate was evaporated to dryness. Thin-layer chromatography (TLC) allowed the detection of some amount of deacetylated compounds. To peracetylate these compounds, acetic anhydride in pyridine (3 mL/6 mL or 75 mL/150 mL) was added at 0 °C and allowed to react for 3 h at room temperature. After elimination of solvent and reactants by coevaporation with toluene, the pure product **5** was isolated by silica gel column chromatography (eluent = ethyl acetate−heptane).

Saponification of Glucoside 5. Glucoside **5** and impregnated KOH on alumina (1:3 w/w) were introduced in the MW reactor. Under mechanical stirring, this mixture was either exposed to MW or immersed in a thermostated oil bath under the conditions indicated in Table 8. After cooling to room temperature, the mixture was diluted in methanol and filtered through a silica gel bed. The filtrate was concentrated to dryness and purified by silica gel column chromatography (eluent = ethyl acetate-ethanol) to give pure **6**.

Chlorination of α-D-Methyl Glucopyranoside 7. Glucopyranoside **7**, PPh_3, and KCl were mixed in the MW matras. CCl_4 and pyridine were subsequently added. The mixture was either introduced in the MW reactor or immersed in a thermostated oil bath under the conditions indicated in Table 9. After cooling to room temperature, the heterogeneous mixture was diluted with methylene chloride/ethyl acetate/ethanol (1:1:1) (20 mL or 1 L) and then filtered on silica gel. The filtrate was evaporated to dryness and the residue suspended in water. The aqueous phase (containing the monohalide) was extracted twice with methylene chloride, concentrated, and purified by silica gel column chromatography (eluent = ethyl acetate−heptane) to give pure **8**.

Epoxidation of Tosyl α-D-Glucopyranoside 9. Tosyl α-D-glucopyranoside **9** was added to KOH impregnated on alumina (1:3 w/w). Under mechanical stirring, the mixture was either submitted to MW or immersed in a thermostated oil bath under the conditions indicated in Table 10. After cooling to ambient temperature, the mixture was diluted with ethyl acetate and filtered on silica gel. Pure epoxide **10** was obtained after solvent removal.

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