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A Comparison of Commercial Microwave Reactors for Scale-Up within Process Chemistry

Jonathan D. Moseley,*,† Philip Lenden,† Mark Lockwood,† Katinka Ruda,§ Jon-Paul Sherlock,‡ Anthony D. Thomson,† and John P. Gilday†

AstraZeneca, Process Research and Development, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, U.K., AstraZeneca, R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, U.K., and AstraZeneca, R&D Södertälje, S-151 85 Södertälje, Sweden

Abstract:

Seven commercially available microwave reactors designed for limited scale-up have been investigated using a highly reliable and robust reaction (the Newman−Kwart rearrangement). The use of a single reaction has enabled the comparison to be made across the range of different reactor types and scales. Overall, all reactors gave reliable scale-up from small scale, and performance equivalent to one another on large scale. A more detailed comparison between them is given in the concluding section.

Introduction

Microwave-assisted organic synthesis (MAOS) was first reported in 1986 by Gedye and Giguere using domestic microwave ovens.[1] However, it was not until small-scale, monomode scientific microwaves became commercially available around 2001/2002 that microwave synthesis really began to be more widely used by the general organic chemist. Since then MAOS has been so successful that most pharmaceutical discovery departments now routinely use microwave synthesis for initial drug discovery synthesis.[2] The features of small scale, fast reaction time, and ready automation marry well with combinatorial and library synthesis techniques and have provided a step change in drug discovery programmes. Furthermore, the availability of cheap microwave reactors is also beginning to be felt in universities, where fast reaction times for multiple small-scale reactions is a boon in undergraduate teaching laboratories.[3] The other advantages of microwave heating are familiar and have been presented many times elsewhere.[2,4,5]

Of particular interest to process chemists are the claimed cleaner reaction profiles of microwave heating, usually accompanied by and probably linked to improved yields. The cleaner reaction profiles are usually attributed to lack of thermal wall effects, which can be an issue in conventional laboratory glassware when compared to narrow microwave test tubes. On the larger scale, the longer heating times required for jacketed plant reactors compared to laboratory-scale reactors and the tendency to char materials thrown above the solvent line can contribute to reduced purity and lower yields on scale-up. In addition, the possible energy savings that might be achieved by use of microwave heating on a plant scale are of significant interest, although there are still few studies at present.[6]

Therefore, process chemists have as much potential interest in microwave synthesis as their medicinal chemistry colleagues. However, a limiting factor is the penetration depth of the microwave field, which is only a few centimeters in most solvents (at 2450 MHz). This has so far limited attempts to scale up microwave synthesis, and nearly all serious investigations have concluded that a continuous flow system of some description will have to provide the solution.[7,8] A modest scale-up can, however, be achieved by a variety of options, and all

* To whom correspondence should be addressed. E-mail: jonathan.moseley@astrazeneca.com.

† Avlon Works.

‡ R&D Charnwood.

§ R&D Södertälje.

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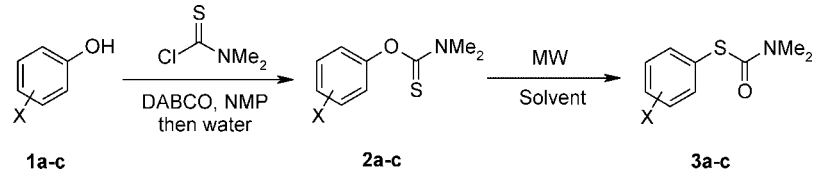
Scheme 1



major scientific microwave manufacturers[9] have designed microwave reactors in the past few years capable of providing a 10–100 g scale option. A number of studies have compared these various reactors. The early studies focussed more on the reliability of scaling small-scale reactions in monomode microwave reactors to larger-scale reactions in multimode instruments,[10] whilst more recent comparisons have been between the larger-scale microwave reactors.[11] These studies had concluded that microwave reactions could be scaled from test tubes in monomode microwave reactors to large-scale vessels (typically 100 mL) in multimode reactors without the need to change the chemistry, thus confirming a key advantage of microwave chemistry on scale-up. Since the chemistry does not need to be developed for initial scale-up, this brings a further benefit for process chemistry in saving vital laboratory time and resources in the early stages of a project.

As part of our study into the potential use of microwave chemistry for scale-up in process chemistry, we decided to evaluate each reactor as it became available. This report presents our initial findings of a single reaction in seven microwave scale-up reactors. These include single batch, multibatch, stop-flow, and true continuous flow reactors, under both pressurized and atmospheric pressures. Individual (noncomparative) reports have been made on most of these reactors, and these will be highlighted in the discussion below. Of the comparative studies, only a maximum of three reactors had been compared at any one time.[10,11] Kappe's excellent recent review covers all instruments as part of an overview of progress towards scale-up of MAOS.[7] To our knowledge however, this is the first research report to compare the same reaction in all currently available commercial large-scale microwave reactors (see also the accompanying critical comparison by Leadbeater).[12] Note also that this report will focus only on commercially available equipment and will not discuss the interesting developments from the groups of Bogdal (Krakow), Ondruschka (Jena), and Strauss (Monash) amongst others, working on bespoke or prototype microwave reactors for scale-up, even up to true pilot plant scale.

Results and Discussion

Choice of Reaction. Due to the ongoing debate over nonthermal microwave effects,[13] we felt it would be prudent to concentrate our instrument evaluation studies on a completely reliable reaction for which there were no claims of any microwave effect and which was reliable under a wide range of known parameters (temperature, pressure, solvent, etc.). We have already reported our findings on re-evaluating the Newman−Kwart rearrangement (NKR)[14] under both microwave and conventional thermal heating and shown that there is no difference between the two under easily achieved and well-controlled conditions.[15] The NKR is a first-order, unimolecular rearrangement converting an *O*-thiocarbamate to an *S*-thiocarbamate (Scheme 1; **2** to **3**). The rate of reaction is dependent on the aromatic substituent, somewhat dependent on solvent polarity, and slightly dependent on concentration but only at higher values.[16] A homogenous reaction solution is readily obtained, so there are no complex kinetics, phase transitions, or surface effects. In a well-stirred homogenous solution, localized superheating, a potential problem with microwave heating,[17] does not occur. Given the general problems with measuring physical parameters in microwave reactors, we thought this would prove to be an ideal model reaction with which to make valid comparisons, not only when comparing alternative microwave reactors with their different vessel geometries, microwave fields and operating parameters but also when changing scale between them.

Preparation of Materials. The required *O*-thiocarbamates **2** were synthesized from phenols **1** as described previously,[15] generally in a 4-L jacketed reactor, to provide ∼300 g per batch on a convenient laboratory scale (Scheme 1). This acylation reaction was not subjected to microwave heating as it requires only mild heating. We concentrated on *O*-thiocarbamates **2a**−**c** with strong electron-withdrawing group substituents, since these are converted to their *S*-thiocarbamates **3a**−**c** at the lower end of the temperature range for the NKR, around 180–220 °C. Substrates requiring higher temperatures have been investigated on the smaller scale,[15,18] but this temperature was convenient for initial thermal comparisons and for the subsequent scale-up studies.

General Notes on Instrument Evaluations. Technical and operating details for each microwave reactor evaluated can be

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Table 1. **Microwave reactors: numerical data**

make and model	general description	power (W)	mode	reaction volume (per cycle)	vessel size (mL)	max temp (°C)	max pressure (bar)	overall size[a] (kg)
Anton Paar								
Synthos 3000	autoclave, multiple (16)	1400	multi	1000	16 × 100	240	40	M (74)
with XQ80	autoclave, multiple (8)	1400	multi	400	8 × 80	300	80	M (74)
Biotage								
Advancer	autoclave, single vessel	1200	multi	250	350	250	20	L (450)
CEM								
Voyager	autoclave, stop-flow	300	mono	50	80	250	20	S (29)
MARS (open)	cavity for lab glassware	1600	multi	3000	5000	solvent bp	1	M (54)
MARS (a/c)	autoclave, various	1600	multi	700	14 × 75	200	20	M (54)
Milestone								
FlowSYNTH	continuous flow	1000	multi	unlimited	200	200	30	L (110)
MicroSYNTH (open)	cavity for lab glassware	1000	multi	1000	2000	solvent bp	1	M (90)
MicroSYNTH (a/c)[b]	autoclave, various	1000	multi	1200	6 × 300	200	20	M (90)
Ultraclave	autoclave, various	1000	vari	2000	3500	300	200	L (400)

[a] Small (S) <50 kg; medium (M) 50−100 kg; large (L) >100 kg and floor-standing. [b] a/c, autoclave mode.

Table 2. **Microwave reactors: functional parameters**

make and model	general description	reaction volume (per cycle)	agitation	automated charging	continuous addition/ sampling	hetero geneous	active cooling
			Anton Paar				
Synthos 3000	autoclave, multiple (16)	1000	magnetic	no	no	yes	air
with XQ80	autoclave, multiple (8)	400	magnetic	no	no	yes	air
			Biotage				
Advancer	autoclave, single vessel	250	mechanical	no	yes	yes	adiabatic flash cooling
			CEM				
Voyager	autoclave, stop-flow	50	magnetic	yes	no	no	compressed air
MARS (open)	cavity for laboratory glassware	3000	both[a]	no	yes	yes	air
MARS (a/c)	autoclave, various	700	magnetic	no	no	yes	air
			Milestone				
FlowSYNTH	Continuous flow	unlimited	mechanical	yes	yes	no	water jacket
MicroSYNTH (open)	cavity for laboratory glassware	1000	magnetic	no	no	yes	air jacket
MicroSYNTH (a/c)	autoclave, various	1200	both[a]	no	yes	yes	air jacket
Ultraclave	autoclave, various	2000	magnetic	no	no	yes	water jacket

[a] Can use either magnetic or mechanical agitation.

found in Tables 1 (numerical data) and 2 (functional parameters) with additional technical data given in Supporting Information. To save space in the discussions that follow, descriptions will highlight the key advantages and operating principles of each instrument; noncritical aspects can be found in Tables 1 and 2.

Each instrument is briefly described before a discussion of the chemistry is presented. It should be noted that where cycle times are quoted, these exclude the work-up in most cases, which is assumed to occur off-line, probably with multiple (small) batches being combined in a single work-up vessel. Work-ups are generally typical of process chemistry, involving only aqueous drown-outs or simple extractions, to give isolable solids of high quality (typically 98–100%) and so should be taken as suitable for process scale-up. Yields may vary due to the concentration and efficiency of the work-up but are generally typical of process yields. The overall cycle time (heat up, reaction time, and cool down) gives an indication of what the throughput might be, and calculations are made on the assumption of a fully usable 8 h working day. Throughputs naturally vary with concentration, yield, and cycle time, which we have tried to standardise across the range of reactions and reactors. However, this work was conducted over a period of more than 2 years (although mostly in 2006) and in a number of laboratories. In addition, the chemistry has been improved over this period; mimicking the early results has not always been possible or desirable, so that absolutely rigorous comparisons cannot easily be made.

For compounds **2a,b**, small-scale microwave and thermal data had already been reported;[15] for compound **2c**, equivalent small-scale microwave data were gathered for this study. Each compound was trialed where possible (material allowing) in one or more of the large-scale microwave reactors under

Table 3. **Data for conversion of 2a to 3a (2-nitro)**

reactor type	scale (mL)	input/bx (g)	vol[a]	solvent	temp (°C)	time (min)	cycle time (min)	conversion (%)	yield (%)
thermal	2–4	various	4–10	DMA/NMP	180	20	n/a[h]	99	n/a
small MW[b]	2	0.4	4	NMP	180	20	n/a	98	n/a
small MW[b]	2	0.2	10	NMP	180	30	n/a	100	n/a
small MW[b]	2	0.4	4	DMA	200	10	n/a	100	n/a
small MW[b]	2	0.2	10	DMA	170	40	n/a	96	n/a
Advancer	120	30	4	NMP	180	15	n/k	96	n/a
Advancer	240	60	4	NMP	160	15	n/k	73	n/a
FlowSYNTH	(500)[c]	(50)[c]	10	DMA	200	10	n/a	97	(64)[c]
MARS	1000	100	10	DMA	170[d]	40	90	>99	85
MultiSYNTH	250	25	10	DMA	200	10	33[e]	100	84
MultiSYNTH	250	25	10	DMA	180	20	45[e]	>99	89
MultiSYNTH	200	50	4	DMA	200	10	36[e]	100	90
Synthos	8 × 60	12.5	4	DMA	200	10	40	95–99	97
Voyager	5 × 50	10	4	DMA	200	10	16	>99	77
Voyager	3 × 50	16.5	2	DMA	200	10	16	>99	93
Ultraclave	1500	150	10	NMP	180	30	n/k	>100[f]	n/a
small MW[b]	2	0.2	10	xylene	160	30	n/a	45	n/a
Ultraclave	1500	150	10	xylene	160[g]	30	n/k	55	n/a

[a] Expressed as L/kg. [b] Biotage Initiator or CEM Discover. [c] For this experiment only; batch size effectively unlimited. [d] Limited by solvent bp of 166 °C. [e] Cooled to 120−130 °C before removing vessel. [f] >100 indicates some degradation had occurred. [g] Weflon coils used as passive heating elements. [h] n/a = not applicable; n/k = not known.

Table 4. **Data for conversion of 2b to 3b (4-nitro)**

reactor type	scale (mL)	input/bx (g)	vol[a]	solvent	temp (°C)	time (min)	cycle time (min)	conversion (%)	yield (%)
small MW[b]	2	0.2	10	DMA	200	20	n/a[e]	98	n/a
small MW[b]	2	0.4	5	DMA	200	20	n/a	98	n/a
MARS	750	75	10	DMA	170[c]	160	200	98	91
Voyager	6 × 50	8	5	DMA	200	20	27[d]	>99	79

[a] Expressed as L/kg. [b] Biotage Initiator or CEM Discove. [c] Limited by solvent bp of 166 °C. [d] Including aqueous drown-out. [e] n/a = not applicable.

Table 5. **Data for conversion of 2c to 3c (3-methyl-4-nitro)**

reactor type	scale (mL)	input/bx (g)	vol[a]	solvent	temp (°C)	time (min)	cycle time (min)	conversion (%)	yield (%)
small MW[b]	2	0.4	4	DMA	210	20	n/a	98	n/a[f]
small MW[b]	2	0.4	4	DMA	220	20	n/a	100	n/a
small MW[b]	2	0.2	10	NMP	200	40	n/a	98	n/a
FlowSYNTH									
pass 1	(500)[c]	(50)[c]	10	DMA	200	6	n/a	68	n/a
pass 2	(500)[c]	(50)[c]	10	DMA	200	6	n/a	87	(87)[c,d]
MARS	850	85	10	NMP	200[e]	40	90	>99	83
MultiSYNTH	200	50	4	DMA	210	20	46	>99	93
Synthos	8 × 60	12.5	4	DMA	220	20	51	>99	93
Voyager	5 × 50	10	4	DMA	210	20	28	95	82

[a] Expressed as L/kg. [b] Biotage Initiator or CEM Discover. [c] For this experiment only; batch size effectively unlimited. [d] Mass recovery of 2c and 3c combined. [e] Limited to solvent bp of 202 °C. [f] n/a = not applicable.

conditions identical or similar to those for the small-scale microwave reactions. The results are collected in Tables 3 (2-nitro, **2a/3a**), 4 (4-nitro, **2b/3b**), and 5 (3-methyl-4-nitro, **2c/3c**). The standard reaction times for essentially full conversion under small-scale microwave conditions are shown at the top of each table. All conversions were determined by HPLC at 254 nm and are corrected for relative response factors (RRFs) since the UV response of the *O*-thiocarbamates is generally significantly higher than that of the product *S*-thiocarbamates.[15] Values for RRFs are given in Table 6.

Table 6. **Relative UV response of 2x over 3x at 254 nm**

ref no.	substitution	RRF
2/3a	2-nitro	3.20
2/3b	4-nitro	3.04
2/3c	3-methyl-4-nitro	3.62

It will be seen that for a given substrate, the reaction volume (expressed in L solvent/kg input) varies between 2 and 10; however, this has little significant effect on the reaction rate. There is also effectively no difference between the two polar aprotic solvents, NMP and DMA, except that the reaction mixture is physically much darker in NMP and has an unpleasant odour. The reaction is slower in a nonpolar solvent, for example, in xylene (Table 3). Reaction times and temper-

atures were kept as close as possible to the small-scale preparations, but some adjustments had to be made where the required temperature could not be reached (open vessel systems). Where heating and cooling times became significant compared to the reaction time, this was cut down to compensate and hence avoid degradation due to overheating. The figure for conversion is the most important in this case, since the yield was dependent on the work-up procedure, which was not always the same. However, the yield does give an indication of what should be achievable for these reactions on scale-up without chromatography.

Anton Paar Synthos 3000. This is a multiple vessel autoclave of robust construction that has been reviewed previously.[10c,11d] It has multiple configurations, but the instrument available to us at the time had 16 100-mL PTFE lined tubes in ceramic cases, allowing a maximum load of ~60 mL per tube or 1000 mL total volume per run. The XQ80 option uses eight 80-mL quartz glass tubes with a total usable volume of 400 mL per run and can reach near critical water temperatures requiring 300 °C and 80 bar,[19] as demonstrated by Kappe[20] and Leadbeater.[21] Since it uses sealed tubes, it cannot accommodate continuous additions, sampling, or automated charging, which with up to 16 tubes could be tedious. However, it would be ideal in a setting requiring 5–10 g quantities of related compounds, such as an advanced medicinal chemistry programme, where useful quantities of up to 16 analogues could quickly be produced per run, or where 100–200 g of a single compound could be produced in a couple of runs. It does not really meet the 1 kg scale required for our initial scale-up projects, but with a wide operating envelope, it can handle most thermal chemistries at large laboratory scale without significant change from small scale.[10c,11c,20–22]

Compound **2a** was trialed at half-load (i.e., eight tubes at full volume) but at high concentration (4 vol) at 200 °C for 10 min. Conversions for each tube were between 95% and 99%, and an optimized extractive work-up gave an excellent isolated yield of 97% of high quality product **3a**, approximately 100 g per run. Although the reaction time was identical to that of the small-scale runs, the cycle time was longer mainly due to the longer cool down. Cooling is provided by low pressure air, but the reaction mixture is insulated inside a PTFE sheath, ceramic liner, and large plastic carousel. This typifies the problems of supplying microwaves to reaction mixtures through microwave-transparent materials that have sufficient mechanical strength for pressure vessels; all of these materials are typically thermal insulators. Even so, a fully loaded carousel should be able to process ~200 g product in an estimated cycle time of 45 min or 2.1 kg per 8 h day, albeit for a highly concentrated and simple reaction (excluding work-up).

Compound **2c** was also processed on the same scale and concentration as **2a** above, but requiring 20 min at 220 °C rather than 210 °C for the small-scale tubes. Conversions were excellent across all tubes (>99%) and an isolated yield of 93% was achieved on aqueous drown-out. Allowing for a full load (16 tubes at 60 mL) with a cycle time of 60 min, 1.5 kg of **3c** could be produced per 8 h day at the same concentration.

Biotage Advancer. This is a multimode microwave based heavily on the prototype developed by Strauss.[23] It functions as a single vessel autoclave with a slim cylindrical PTFE pot of 350 mL total volume, with a working volume of ~250 mL, and is fitted with a narrow mechanical stirrer. There are a number of ports on the lid, and consequently it is one of the few microwaves that can accommodate continuous addition and be sampled whilst under pressure. Operating parameters are typical (250 °C and 20 bar). An interesting feature is adiabatic flash cooling of the reaction mixture, whereby the pressure generated by the solvent is used to rapidly evacuate the reaction vessel into another (low pressure) sealed vessel; this avoids the potentially long cooling time inherent in other microwaves, thus speeding up the cycle time considerably. As with other instruments, the software controls are well-developed and easy to use, and it has some impressive safety features. A drawback is perhaps its size and weight (it is in a large cabinet), which requires a walk-in fume cupboard for what is essentially quite a modest-sized reaction vessel. However, it can probably handle most thermal chemistries, including the charging of slurries and the processing and discharging of heterogeneous mixtures.[10d,24] Automating the charging would probably bring it into the 1 kg range of interest to process departments; at present, it is good for 100 g scale deliveries of interest to medicinal chemists.

This instrument was the first to be formally trialed, and being less confident at this early stage about the impact of concentration, we chose to run experiments at 4 vol, which used much material. However, we did take advantage of the option to take multiple samples from the same run whilst the experiment was in progress. Three experiments were performed of 120-mL volume (30 g of **2a** each), at temperatures of 140, 160, and 180 °C, taking time points at 15 min intervals. The results are shown in Figure 1, and some time points are also incorporated into Table 3. Figure 1 shows the conversion rates as the temperature rises, which is as expected for a first-order reaction. These are in excellent agreement with the comparable small-scale microwave and thermal rate profiles, for which only the data at 140 °C are shown in Figure 1. A fully loaded vessel (60 g of **2a** in 240 mL of NMP) was run at 160 °C, again giving the expected reaction rate profile; the slight increase in rate during the middle phase of the reaction is attributed to more efficient coupling to microwaves when the vessel is full, a feature common to many microwave reactors, both large and small.

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(20) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672–3679.
(21) Kormos, C. M.; Leadbeater, N. E. *Tetrahedron* **2006**, *62*, 4728–4732.
(22) (a) For example, see: Kormos, C. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 65–68. (b) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2006**, 1663–1666. (c) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864–3870. (d) Kaval, N.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Org. Biomol. Chem.* **2004**, *2*, 154–156.
(23) (a) Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456–2460. (b) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.
(24) (a) Ekström, J.; Wettergren, J.; Adolfsson, H. *Adv. Synth. Catal.* **2007**, *349*, 1609–1613. (b) Carlsson, A.-C.; Jam, F.; Tullberg, M.; Pilotti, Å.; Toannidis, P.; Luthman, K.; Grøtli, M. *Tetrahedron Lett.* **2006**, *47*, 5199–5201. (c) Hoogenboom, R.; Paulus, R. M.; Pilotti, Å.; Schubert, U. *Macromol. Rapid Commun.* **2006**, *27*, 1556–1560. (d) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212–5218.

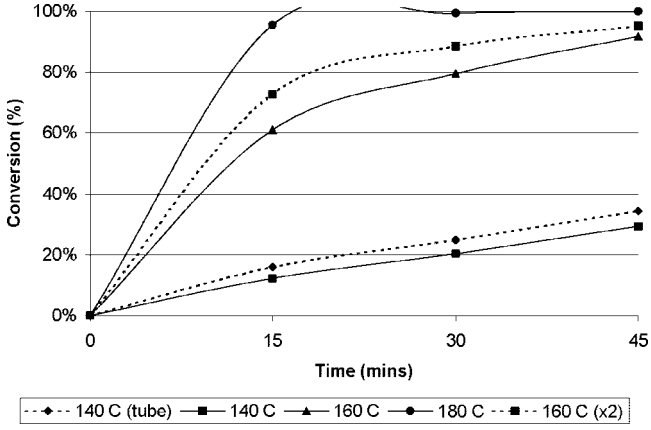

Figure 1. **Conversions for 2a to 3a at 140–180 °C on 120 mL scale in a Biotage Advancer.**

Since this trial was run remotely, no product was isolated. However, 60 g could be processed per 20 min run, so with an estimated cycle time of less than 30 min (allowing for heating and flash evaporation), ~1.0 kg could be run per day (at this temperature and concentration). The lack of a cooling period significantly reduces the cycle time and enables a moderately small reactor to deliver potentially kilogram scale quantities per week for this simple reaction. Our colleagues in Sweden have used this instrument for 100 g scale deliveries of pharmaceutical intermediates.

This trial also confirmed what many others have noted before,[10] that microwave heating can be linearly scaled from a small tube (5–10 mL) to a larger vessel (a 350-mL tube in this case) without changing other parameters. Having been run somewhat differently from the later trials in taking multiple time points of the same reaction, thus building a rate profile instead of just a fixed end-point, it has perhaps been more rigorous in comparing small- and large-scale microwave reactions, and thus showing their equivalence.

CEM MARS. This is a multimode microwave with a 1600 W magnetron, which can operate in either closed or open vessel mode. It has a set of sealed vessel tubes for pressure reactions, set in a carousel containing up to 14 80-mL glass tubes each supported by a Kevlar liner. Since this is similar to the Synthos 3000 and MicroSYNTH instruments also described herein, we did not trial it in this configuration, and only the open vessel mode is discussed below.

In open vessel mode, the cavity can accommodate up to a 5-L glass vessel, and some impressive results have recently been reported by Barnard and Leadbeater on this scale.[6b,25] Both magnetic and overhead mechanical stirring are possible, the latter being particularly useful for heterogeneous reactions heavily loaded with solids. In principle both continuous addition and sampling whilst running are possible with minor equipment modification and suitable glassware. Automated charging is not possible, but is less of an issue with a single large vessel. The ability to use standard laboratory glassware (of good condition and quality note) is a potential boon for the average synthetic organic chemist and may help to encourage the less adventurous chemist to try larger-scale microwave reactions. However, because it is an unpressurised open vessel system, the maximum operating temperature is of course limited to the boiling point of the solvent for the reaction. This may be a drawback when wanting to scale up the use of lower boiling solvents under sealed tube conditions, although suitable higher boiling replacements can usually be found. The larger volume with proportionately reduced surface area does mean that cooling times are longer, but lacking the thermal insulators used in pressure vessels, it is relatively quicker than in most autoclave type reactors. This instrument is capable of significant throughputs for a wide range of chemistries, and the use of familiar 1–5 L glass vessels will appeal to many chemists.

All three standard compounds **2a**−**c** were run in the MARS and at the more dilute 10 vol, simply to maximise the usage of the available material; in principle larger-scale runs could have been performed had materials been available. In open vessel mode all three required a lengthening of their reaction times to allow for the lower than desired solvent boiling limit. So **2a** was converted to **3a** over 40 min at 170 °C in DMA (5 K above its bp of 165 °C), doubling the reaction time to allow for the 10 K drop in temperature possible; **2b** required nearly eight times as long to allow for the 30 K discrepancy between the desired 200 °C and the achievable 170 °C; but **2c** required only a doubling of reaction time to allow for a drop from 210 to 200 °C (note change to NMP, bp 202 °C, since using the preferred DMA would have required too long a reaction time). Even so, the magnetron appeared to deliver the load required in all cases without any difficulty, including the 3-h run required for **2b**. The change to NMP for **2c/3c** was a trivial modification, the only drawback being the dark colour of the product, which was otherwise analytically identical (LC, NMR) to samples isolated from DMA. Lastly, it is worth noting that the conversions were all high in these reactions, but the yields appear suboptimal compared to other reactions as a result of the larger solvent volume used, thus making the work-up and isolations less efficient.

CEM Voyager. The CEM Voyager is essentially a unit consisting of a peristaltic pump and two valves with appropriate software control integrated with the versatile 300-W monomode Discover base unit.[10e] It is by far the smallest instrument reviewed here and will sit comfortably in the corner of a standard depth fume cupboard. It has an 80-mL vessel (50-mL operating capacity) and fibre optic temperature control and will operate across the standard temperature and pressure range. The Voyager unit in essence provides automated charging and discharging of the reaction cell in a stop-flow mode (Voyager SF) (a continuous flow instrument, the Voyager CF, is also available for use with homogenous reaction solutions). Therefore, although the reaction volume is relatively small, it can in principle be automated to charge, heat, cool, and discharge continuously, for as many batches as are required, and with a small footprint, multiple units can be accommodated easily if larger quantities are required (a scale-out option). Furthermore, once the reaction conditions are optimised, the automation reduces the interaction required by the chemist. A significant

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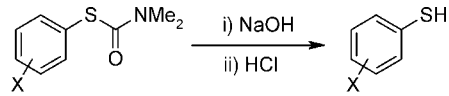
Scheme 2. **Hydrolysis of *S*-thiocarbamates**



3a-c **4a-c**

drawback is the need to have homogeneous or nearly homogeneous reaction solutions. Although the instrument uses a peristaltic pump that can in principle transfer slurries and is fitted with an anticlog device, in practice the lines (1.5 mm i.d.), valves, and pump are prone to blocking with slurries, as noted by Lehmann.[11c] However, it has been used successfully with fine slurries, as reported by others.[11b,26] Although continuous addition and sampling whilst heating are not formally possible, the multiple feed and exit lines could be used to mimic these techniques if required, although with the potential to isolate many small batches, this is probably of less interest. Finally, the small reaction mass in a glass-walled reactor heats and cools quickly (with compressed air), and so it has a good cycle time. Coupled with genuine automation for rapid charging and discharging, this small instrument has a lot to offer.

We trialed short automated sequences with all three of our standard compounds **2a**−**c**. For **2a** under the improved standard conditions (200 °C for 10 min), a five batch sequence gave >99% conversion for each batch and an unoptimised yield of 77%. The cycle time was just 16 min per batch, which included charging, heating to reaction temperature, cooling, and discharging. A three batch run of **2a** under similar but more concentrated conditions gave complete reaction with a 93% isolated yield. This equates to about 460 g per day (30 batches) for one instrument.

Compound **2b** required a slightly longer time and was run in a six batch cycle to give again complete conversion with an unoptimised 79% yield in a cycle time of 27 min. In this case, the discharge was slowed to the maximum possible (∼3 min) to mimic a direct aqueous drown-out of the product, which naturally lengthened the cycle time marginally. Lastly, compound **2c** was heated at 4 vol to 210 °C for 20 min in a five batch cycle to give ∼95% conversion for each batch with an overall isolated yield of 82%. Running the reactions below complete conversion proved beneficial in this case as the unreacted starting phenol **1c** was more readily removed on aqueous drown-out than some very minor impurities if the reaction was forced further. At this concentration with this yield and a cycle time of 28 min, 160 g per day could be produced.

In every case above, the quality of the products was excellent (>98%) with only aqueous drown-outs for purifications. Samples of all *S*-thiocarbamates **3a**−**c** were hydrolysed to their respective thiophenols **4a**−**c** in high yields to demonstrate further chemical utility (Scheme 2). Whilst some impressive throughputs have been quoted for this instrument, it should be noted that the NKR is a very concentrated high-yielding reaction and that these numbers are unlikely to be possible in most cases (although Leadbeater has reported the preparation of ∼800 mL[26a] in 2 h, albeit for a simple, neat esterification reaction). We agree with Leadbeater[26c] that this instrument does not reach kilogram scale in most cases, but for the right reaction or if only 100–200 g is required, the modest-sized Voyager can deliver suitable quantities in a day with minimal operator input.

Milestone FlowSYNTH. We have already reported an individual evaluation of the NKR in the Milestone Flow SYNTH.[8a] It is a multimode microwave based on the Milestone MicroSYNTH (vide infra).[8i,j,27] The unique feature of the FlowSYNTH is a vertically mounted reaction vessel of 200 mL capacity running through the centre of the cavity. A pump feeds the reaction solution into the bottom of the columnar vessel, which is irradiated in the cavity and exits from the top through a product cooler. Plug-flow characteristics of the reaction solution are controlled by an overhead motor driving an Archimedean screw, and heating inside the reaction vessel section is aided by Weflon baffles, which strongly absorb microwaves and hence transfer thermal energy. A back-pressure regulator controls the pressure at the exit such that solvents can be continuously fed in even if heated above their bp; consequently, operating parameters are good (i.e., 200 °C and 30 bar).

However, the back pressure regulator and the narrow inlet port (∼1.5 mm i.d.) do limit this reactor to homogeneous reaction solutions, and any small quantity of fine solid can block the system. The complete system requires bottom access to the microwave cavity, several ancillary units (pump, chiller unit, PC interface), and potentially large feed and receive vessels; this requires a large fume cupboard for safe operation since the system is under pressure. Although heterogeneous reactions cannot be tolerated, addition is continuous and effectively automated, and the small reaction volume exiting the top is cooled very efficiently. Once steady-state conditions have been achieved, throughputs for a homogeneous reaction solution will be high and virtually unlimited.

Compound **2a** was passed through this instrument at 10 vol in both NMP and DMA with a nominal residence time of 10 min at 200 °C and showed 96–97% conversions. Compound **2c**, however, required 10 min at 210 °C, 10 K above the limit of the FlowSYNTH. To simulate this heating, compound **2c** was trialed in 10 vol of DMA, the same batch being passed through twice at 200 °C for 10 min each. Unfortunately the pump settings had changed and the batch only received 6 min of heating on each pass, giving 68% and 87% conversions, respectively. However, this did establish the principle of effectively achieving higher temperatures by multiple passes through the reactor when longer reaction times were required. For more detailed discussion, see ref 8a.

Milestone MicroSYNTH. The Milestone MicroSYNTH provides the basic unit for the FlowSYNTH already discussed above. The basic unit is similar to the Synthos 3000 and MARS systems but has an even wider range of vessel arrays possible, from those small enough to meet medicinal chemistry require-

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(27) (a) Gellis, A.; Boufatah, N.; Vanelle, P. *Green Chem.* **2006**, *8*, 483–487. (b) Verhaeghe, P.; Rathelot, P.; Gellis, A.; Rault, S.; Vanelle, P. *Tetrahedron* **2006**, *62*, 8173–8176. (c) Heller, E.; Lautenschläger, W.; Holzgrabe, U. *Tetrahedron. Lett.* **2005**, *46*, 1247–1249.

ments up to a single 1000-mL sealed vessel.[10b,28] A feature of these cells is that they are jacketed reaction vessels through which compressed air can be pumped to aid the cooling cycle, which is long due to the thermal insulating materials used. In principal, other cooling fluids could be used to improve the cooling process. It can also be operated in open vessel mode as shown by Kappe.[29] Operating parameters are given in Tables 1 and 2 as for other instruments. This was briefly assessed using the single 500-mL vessel configuration for compounds **2a** and **2c**; as Tables 3 and 5 show, it performed exactly as expected compared to the small-scale tube results and would be ideal for scaling up medicinal chemistry from 10 to 100 g.

Milestone Ultraclave. The Milestone Ultraclave is a large, free-standing unit that has mainly been used for digestion, although some have been sold to pharma. Milestone claims the Ultraclave is a variable or mixed mode microwave, i.e., monomode at low fill and multimode when full. As with the MicroSYNTH, a wide variety of vessel sizes can be accommodated, up to a single vessel of 3.5-L capacity. An interesting feature is prepressurisation of the reaction cavity with nitrogen to high pressure; this means that many open vessels/tubes can be used in a single reaction without reflux but without danger of cross-contamination within the unit. Since this is a pressurised closed vessel system, continuous additions and sampling are not possible. Although the homogeneous NKR stirred well, separate stirring trials with sugar/water mixtures of known viscosity were not encouraging; the efficiency in heterogeneous reactions would have to be assessed on a case by case basis. The cooling profile was also long because of the large vessel size, low surface area, and lack of active cooling. Some of these drawbacks could in principle be off-set with modest improvements. Even so, the operating statistics are impressive (300 °C, 200 bar), and as with other instruments, the software controls and data capture are well-developed and easy to use.

Like the Advancer, this instrument was one of the first to be formally trialed. We tried a number of multiple vessel configurations in test tubes and small pots, all of which gave complete conversions of **2a** to **3a** under the standard conditions (Table 3). In fact, slight degradation was seen in some cases, supporting Milestone's claim that this multimode instrument actually heats more efficiently than other microwave instruments. We also performed some single vessel reactions in both NMP and xylene (Table 3), although to partial conversions in the latter case. Again, some signs of moderate degradation were observed for full conversions, but overall the results showed good agreement with tube-scale experiments. We believe this is the first reported use of MAOS using the Ultraclave. No isolations were possible as this trial was conducted off-site.

Overall Comparison. The individual evaluations above show from Tables 3–5 that each large-scale microwave reactor, irrespective of type, operating mode or scale, gave reliable and linear scale-up from microwave test-tube scale, as has been noted for other reactions.[10,11] We have endeavoured to highlight in the discussions above the key advantages and drawbacks in the use of each microwave reactor, not only for the simple and robust NKR but also for other potential reaction classes (e.g., those requiring continuous additions or containing heterogeneous reaction mixtures). However, of more interest is probably the direct comparison of throughputs between the instruments.

Table 7. **Instrument comparison: daily throughput for conversion of 2a to 3a**

reactor type	input/ bx (g)	vol[a]	cycle time (min)	bxs/day	total daily throughput (g)
Advancer	60	4	30[c]	16	960[b]
FlowSYNTH	200 g/h	10	2.1 L/h	continuous	1600
FlowSYNTH	500 g/h	4	2.1 L/h	continuous	4000
MARS	200	10	90	5	1000
MARS	500	4	96[d]	5	2500
Synthos	200	4	45[d]	10	2100
Voyager	10	4	16	30	300
Ultraclave	400	4	100[c]	5	1920

[a] Expressed as L/kg. [b] Assumes automated. [c] Good estimate. [d] Extrapolated from similar reaction conditions.

For the reasons already noted, it was not easy to obtain a complete set of rigorously comparable data. Most data is available for the conversion of **2a** to **3a** in 4 (or 10) vol of DMA/NMP at 180–200 °C for 10–20 min. To give an indication of how the instruments compare, a comparison of daily throughputs for **2a/3a** is shown in Table 7. Throughputs have been calculated on the basis of a fully usable 8 h day assuming 100% conversion for a 4 vol reaction. Differences in yield have been ignored since the work-up would be identical for a strict comparison. Where cycle times were not known, they were extrapolated from very similar reaction conditions (MARS, Synthos) or based on good estimates from the known operating conditions (Advancer, Ultraclave); inevitably some reasonable assumptions have to be made to achieve a comparison. No figures are shown for the MicroSYNTH since we did not have cycle times with cool down periods to equivalent temperatures. Two pairs of figures are shown for the FlowSYNTH and the MARS, extrapolating from the dilute 10 vol used to the concentrated 4 vol, only because these instruments demanded too much material to be trialed at 4 vol.

Unsurprisingly, the large continuous flow FlowSYNTH delivers the highest throughput; however, it can only tolerate completely homogeneous reaction solutions, and this is greatly limits the number of pharmaceutical reactions to which it can be applied. The MARS reactor in open vessel mode also has an excellent daily throughput, although is potentially limited by the solvent boiling point. However, we have only assumed a 3-L flask capacity (2-L working volume), and the data were based on a 40 min reaction in DMA at 170 °C. In a 5-L flask with NMP, the increased capacity with a shorter reaction time could give higher figures still, even allowing for the increased heating and cooling phases due to the extra reaction mass. Solvent heating trials suggest that this is within the capability of the 1600-W magnetron. The Synthos 3000 also has a potential throughput similar to that of the MARS, but unlike it is not limited by the solvent boiling point. For a more complex reaction mixture requiring multiple charges, however, this would be tedious to achieve in practice.

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(29) Razzaq, T.; Kappe, C. O. *Tetrahedron Lett.* **2007**, *48*, 2513–2517.

The Advancer could in theory produce ~1 kg/day for this reaction, taking advantage of the adiabatic flash cooling to process some high batch numbers. Ideally this would be automated, although there is no reason in principle why this could not be achieved now by a diligent operator, again, in somewhat tedious fashion. The Ultraclave can also in principle produce ~2 kg/day for this reaction. However, as noted in the discussion, it does have some disadvantages that would make this difficult to achieve pragmatically. The limited stirring capability also tends to limit it towards homogeneous reaction mixtures in our opinion. Lastly, what the diminutive Voyager lacks in volume, it makes up for by automatically processing many small batches reliably with little operator input. This will yield the user quantities in the low hundreds of grams per day, of interest to medicinal chemists. For those requiring larger quantities, this is probably the least user-intensive instrument that can be left running in a steady state for long periods; and with the smallest footprint, a scale-out option can be considered by the use of multiple instruments. However, although it has been heroically used to process slurries, it is best with homogeneous or near homogeneous reaction mixtures, putting it in a similar class to the FlowSYNTH.

Finally, note that although the actual daily throughput values shown in Table 7 look attractive, they are for a simple, highly concentrated rearrangement reaction. They are given to aid the comparison between microwave reactors, not to be indicative of generally achievable throughputs. A more realistic assessment would probably require these figures to be divided by 2-, 5-, or 10-fold, taking into account the more complex charging, higher dilutions, longer cycle times, and the less than perfect conversions and yields of typical pharmaceutical reactions. This would give throughputs in the range of low hundreds of grams, useful for the top end of medicinal chemistry scale-up but not properly in the process chemistry domain.

Conclusions

In summary, we have reported a survey of seven distinctly different microwave reactors designed for scale-up from four manufacturers. Although the need to develop a distinct market advantage and avoid competitor's patents are undoubtedly factors for these manufacturers, the diversity of approaches taken indicates to us that there is no obvious solution to the problem of microwave scale-up.[7] It is our assessment that there is at present no single commercially available scale-up microwave reactor capable of meeting the needs of the pharmaceutical industry for the wide range of reactions typically required on >1 kg scale. There are, however, several reactors that do cover a good range of chemistry and are suitable for subkilo scale deliveries that should be of interest for initial scale-up within medicinal chemistry departments. Within this wider context, we have also supplied full data on all of the reactors so that potential users can choose the instrument that is most suitable to their needs. Obviously we have left out one other important factor, namely, that of cost, which is outside the scope of this technical review and which prospective users will need to consider for themselves.

In addition, we have shown that microwave chemistry is linearly scalable, from test tube to >1 L. Many others have claimed this before,[10] but we have demonstrated a significant scale-up factor in these cases and across a range of diverse microwave reactors with different operating principles. And whilst we have shown throughputs of >1 kg for a best case scenario, it should be borne in mind that these results are based on a simple homogeneous reaction, for the reasons given in the introduction. For true process development and pilot scale, there is presently no commercial microwave scale-up solution. Investigations into more challenging and heterogeneous reactions are ongoing in our laboratories.

Experimental Section

General Procedures. Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument according to the following conditions: column, Genesis C18 100 mm × 3.0 mm i.d.; eluent A, 95% purified water, 5% acetonitrile, 0.1% v/v formic acid; eluent B, 95% acetonitrile, 5% purified water, 0.1% v/v formic acid; flow rate 0.75 mL/min.; wavelength 254 nm; temperature 35 °C; injection volume 10 μL; at $t = 0$ min, 40% eluent B; at $t = 5$ min, 70% eluent B; at $t = 7$ min, 70% eluent B; 3 min post time. Typical retention times (t_R) are noted in each case. Relative Response Factors (RRF) between *O*- and *S*-thiocarbamates were determined as described previously.[15] Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electrospray (ES^+) mass spectra were performed on Micromass ZQ (for *O*-thiocarbamates **2a**−**c**) and Micromass Platform LC (for *S*-thiocarbamates **3a**−**c**) mass spectrometers. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative-scale silica gel flash chromatography (for purification of analytical samples only) was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Where not stated otherwise, assume standard practices have been applied.

General Preparation of *O*-Thiocarbamates (2a−c). *Preparation of 2-Nitrophenyl-O-thiocarbamate (2a).* 2-Nitrophenol (182 g, 1.30 mol) was charged to a 4-L jacketed reactor vessel and dissolved in NMP (900 mL, 5.0 vol). DABCO (195 g, 1.70 mol, 1.30 equiv) was added, and the contents were heated to 50 °C with mechanical stirring to give an orange solution. In a separate vessel, dimethyl thiocarbamoyl chloride (183 g, 1.44 mol, 1.10 equiv) was dissolved in NMP (185 mL, 1.0 vols) and added dropwise to the reaction solution over 30 min. A fine orange precipitate formed, and an exotherm of 2–3 K was observed during this time. After 2 h, water (2190 mL, 12.0 vol) was added over 30 min, maintaining the temperature at 50 °C (after an initial exotherm of a few K). The original solid dissolved readily, to be replaced by a persistent yellow precipitate that formed half-way through the addition. The reaction mixture was cooled smoothly to 20 °C, and the precipitate was isolated by filtration. The product cake was slurry washed twice with water (728 mL, 4.0 vols each) and dried in a vacuum oven at 50 °C to yield the title compound as a fine sandy-coloured crystalline solid (284 g, 96%). HPLC (t_R

3.52 min, 99.9%); mp 120–121 °C (lit.[14a] 112–113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, d, J = 8.4 Hz), 7.67 (1H, t, J = 7.8 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.26 (1H, d, J = 8.0 Hz), 3.46 (3H, s), 3.41 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 185.90, 147.21, 142.01, 134.42, 126.55, 126.49, 125.68, 43.50, 39.09; MS (ZQ) (ES^+) 227 (M + 1, 100%).

Preparation of 4-Nitrophenyl-O-thiocarbamate (2b). *O*-Thiocarbamate **2b** was prepared on a 500 mmol scale according to the method used for compound **2a**, to yield the title compound as a pale yellow solid (113 g, 99%). HPLC (t_R 3.84 min, 99.6%); mp 140–142 °C (lit.[14a] 150–153 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 3.47 (3H, s), 3.38 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 186.21, 158.47, 145.38, 124.88, 123.86, 43.36, 38.96; MS (ZQ) (ES^+) 227 (M + 1, 100%).

Preparation of 3-Methyl-4-nitrophenyl-O-thiocarbamate (2c). *O*-Thiocarbamate **2c** was prepared on a 1.30 mol scale according to the method used for compound **2a**, to yield the title compound as a buff coloured solid (307 g, 98%). HPLC (t_R 4.52 min, 99.6%); mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, dd, J = 7.7, 1.8 Hz), 7.07 (1H, d, J = 1.8 Hz), 7.05 (1H, s), 3.46 (3H, s), 3.36 (3H, s), 2.63 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 186.33, 156.73, 146.30, 135.78, 126.83, 126.20, 121.51, 43.33, 38.91, 20.90; MS (ZQ) (ES^+) 241 (M + 1, 100%).

Typical Small-Scale Microwave Procedures. Small-scale microwave reactions were performed in thick-walled glass sealed tubes in CEM Discover or Biotage Initiator focused 300 W microwave reactors with IR temperature monitoring and noninvasive pressure transducer. In a typical procedure, 200 mg of *O*-thiocarbamate (**2a**−**c**) was dissolved in NMP (2.0 mL) and heated to the required temperature with stirring for a fixed time. The heating time to reach the set temperature was typically 45–90 s, depending on the scale, the maximum wattage supplied (100–300 W) and the temperature required (140–250 °C). The heating time is not included in the quoted hold time for any given procedure; control studies show that the heating time has a negligible effect on overall conversion during a 20 min reaction time. The *S*-thiocarbamate products (**3a**−**c**) were isolated either directly by aqueous drown-out from DMA or NMP solutions or by extraction into MTBE followed by flash silica gel chromatography and/or recrystallisation from methanol if required.

Physical and Spectroscopic Data on Analytically Pure *S*-Thiocarbamates (3a−c). *2-Nitrophenyl-S-thiocarbamate (3a).* A bright yellow oil or low melting solid. R_f 0.25 (2:1 isohexane/ethyl acetate); HPLC (t_R 2.67 min); mp 39–42 °C (lit.[14a] 30–32 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, J = 7.6, 1.2 Hz), 7.70 (1H, d, J = 7.6 Hz), 7.50–7.60 (2H, m), 3.19–2.95 (6H, bs); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.35, 152.34, 138.16, 132.18, 129.84, 124.76, 124.30, 37.09, 29.65; MS (ES^+) 227 (M + 1, 100%).

4-Nitrophenyl-S-thiocarbamate (3b). A pale yellow or buff solid. R_f 0.33 (2:1 isohexane/ethyl acetate); HPLC (t_R 3.38 min); mp 118–120 °C (lit.[14a] 122–124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz), 3.11 (3H, bs), 3.06 (3H, bs); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.58, 147.88, 137.65, 135.57, 123.54, 36.89 (2C); MS (ES^+) 227 (M + 1, 5%), 142 (60%), 101 (100%).

3-Methyl-4-nitrophenyl-S-thiocarbamate (3c). A light buff to mid brown solid. HPLC (t_R 4.18 min); mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 8.5 Hz), 7.49 (1H, m), 7.46 (1H, dd, J = 0.3, 1.8 Hz), 3.10 (3H, bs), 3.05 (3H, bs), 2.60 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.96, 149.03, 139.02, 135.30, 133.90, 133.31, 124.81, 36.97, 20.38; MS (ZQ) (ES^+) 241 (M + 1, 100%).

Representative Large-Scale Microwave Procedures. *Preparation in Anton Paar Synthos 3000.* Portions of *O*-thiocarbamate **2c** (12.5 g each, 52.0 mmol) were charged to eight PTFE tubes with DMA (50 mL each, 4 vol) with a magnetic stirring flea, sealed in ceramic cases evenly distributed inside a 16-position rotor, and placed in the cavity of an Anton Paar Synthos 3000 microwave reactor (total mass of **2c** was 100 g, 416 mmol in 400 mL of DMA). One tube was fitted with a gas-bulb thermometer; the temperature in the others was monitored by IR-pyrometer. The reaction mixtures were heated with magnetic stirring to 220 °C over 13 min with 1400 W available power, held at 220 °C for 20 min, then cooled by fan air to 70–80 °C over ~40 min. The reaction mixtures were worked up in two pairs of four combined tubes by adding water dropwise to each (150 mL, 12 vol). Beige solids were precipitated in both cases, which on cooling to room temperature were isolated by filtration, each washed with further water (150 mL, 12 vol), and dried in a vacuum oven at 50 °C to give *S*-thiocarbamate **3c** as a light beige solid (46.6 and 46.2 g respectively; combined yield 92.8 g, 93%). HPLC (t_R 4.18 min, 100%); other data as above.

Preparation in CEM MARS (example 1). *O*-Thiocarbamate **2b** (75 g, 331 mmol) was dissolved in DMA (750 mL, 10 vol) in a 3-L flask equipped with a fibre optic probe and placed in the cavity of a CEM MARS microwave reactor fitted with a water condenser externally. The reaction mixture was heated with magnetic stirring to a vigorous reflux at 170 °C over 10 min with 1200 W available power, held at 170 °C for 2 h and 40 min, then cooled by fan air to 70–80 °C over 30 min. Water (1500 mL, 20 vol) was added dropwise over 30 min, which precipitated a beige solid that on cooling to room temperature was isolated by filtration and washed with further water. The product was dried in a vacuum oven at 50 °C to give *S*-thiocarbamate **3b** as a light beige solid (68.2 g, 91%). HPLC (t_R 3.38 min, 99.1%); other data as above.

Preparation in CEM MARS (example 2). *O*-Thiocarbamate **2c** (85.2 g, 355 mmol) was dissolved in NMP (850 mL, 10 vol) in a 3-L flask equipped with a fibre optic probe and placed in the cavity of a CEM MARS microwave reactor fitted with a water condenser externally. The reaction mixture was heated with magnetic stirring to 200 °C over 9 min with 1200 W available power, held at 200 °C for 40 min, then cooled by fan air to 70–80 °C over 30 min. Water (1700 mL, 20 vol) was added and the reaction solution cooled to room temperature and left to stand overnight. A black solid formed that was isolated by filtration, displacement washed with water twice (250 mL each), and dried in a vacuum oven at 50 °C to give *S*-thiocarbamate **3c** as a black solid (71.1 g, 83%). HPLC (t_R 4.18 min, 99.8%); other data as above.

Preparation in CEM Voyager (example 1). Three batches of a solution of *O*-thiocarbamate **2a** in DMA were sequentially charged by automation through a CEM Voyager equipped with a fibre optic probe and magnetic stirrer bar (each batch contained 16.5 g of **2a** (72.9 mmol) in 33 mL DMA (2 vol)). Each batch was heated with magnetic stirring to 200 °C over 2 min with 300 W available power, held at 200 °C for 10 min, then cooled by compressed air to 70 °C over 4 min Once cool, the batch was discharged to a holding vessel, and the next batch charged automatically (total cycle time was 16 min). The combined reaction mixture was diluted with water (150 mL, 3 vol) and after cooling to room temperature extracted with MTBE (3 × 150 mL). The combined MTBE extracts were back-washed with water (5 × 150 mL), dried over $MgSO_4$, and concentrated to dryness to give *S*-thiocarbamate **3a** as a yellow oil (combined yield 46.6 g, 93%). HPLC (t_R 2.67 min, 96.5%); other data as above.

Preparation in CEM Voyager (example 2). Five batches of a warm solution of *O*-thiocarbamate **2c** in DMA held at 60 °C were sequentially charged by automation through a CEM Voyager equipped with a fibre optic probe and magnetic stirrer bar (each batch contained 10.0 g of **2c** (41.6 mmol) in 40 mL DMA (4 vol)). Each batch was heated with magnetic stirring to 210 °C over 3.5 min with 300 W available power, held at 210 °C for 20 min, then cooled by compressed air to 70 °C over 5 min. The individual batches were collected separately and drowned-out with varying quantities of water from which it was determined that 12 vol of water was most efficient to precipitate the product. The products were isolated by filtration, washed with more water, and dried in a vacuum oven at 50 °C to give *S*-thiocarbamate **3c** as a light orange solid (combined yield 41.2 g, 82%). HPLC (t_R 4.18 min, 96%); other data as above.

Preparation in Milestone FlowSYNTH. For full details, see ref 8a.

Preparation in Milestone MicroSYNTH. O-Thiocarbamate **2c** (50.0 g, 208 mmol) was slurried in DMA (200 mL, 4 vol) in a 500-mL PTFE jacketed reaction vessel equipped with a magnetic stirring bar and fibre optic probe and placed in the cavity of a Milestone MicroSYNTH microwave reactor. The reaction mixture was heated with magnetic stirring on 60% maximum speed to 210 °C over 4 min with 800 W available power, held at 210 °C for 20 min, then cooled by fan air to ~120 °C. After further cooling to room temperature, the clear brown reaction solution was diluted with water (600 mL, 12 vol) added dropwise over 30 min with stirring which precipitated some solid. After recooling to room temperature over 1 h, the brown precipitate was isolated by filtration, slurry washed twice with water (250 mL each, 5 vol), and dried in a vacuum oven at 50 °C to give *S*-thiocarbamate **3c** as a golden brown solid (46.4 g, 93%). HPLC (t_R 4.18 min, 100%); other data as above.

Conversion in Milestone Ultraclave (example 1). O-Thiocarbamate **2a** (150 g, 663 mmol) was dissolved in NMP (1525 mL, 10 vol) in a 3.5-L PTFE vessel equipped with a large magnetic stirring bar and carefully loaded into the stainless steel lined cavity of a Milestone Ultraclave microwave reactor. A shielded thermocouple was inserted, the reaction vessel sealed and then pressurised with nitrogen to 50 bar over 2–3 min The reaction mixture was heated with magnetic stirring to 180 °C over 10 min with full power available (1000 W), held at 180 °C for 30 min, then free cooled to ~120 °C. The instrument was depressurised and the reaction vessel carefully removed to a fume cupboard to free cool to room temperature more quickly in the extract. HPLC (t_R 2.67 min, 100%); no product was isolated in this case.

Converstion in Milestone Ultraclave (example 2). O-Thiocarbamate **2a** (150 g, 663 mmol) was dissolved in *o*-xylene (1500 mL, 10 vol) in a 3.5 L PTFE vessel. Weflon coils (total mass 90 g) were added to aid heating. The reaction mixture was heated as described for run 1 to 160 °C for 30 min HPLC (t_R 2.67 min, 55%); no product was isolated in this case.

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Supporting Information Available

Additional technical data on each microwave reactor. This material is available free of charge via the Internet at http://pubs.acs.org.

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