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A high temperature investigation using microwave synthesis for electronically and sterically disfavoured substrates of the Newman–Kwart rearrangement

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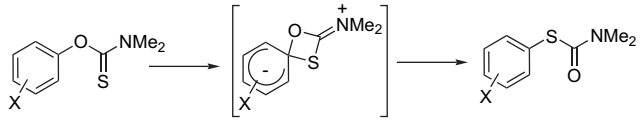
Abstract—Electronically deactivated and/or sterically hindered substrates undergo the Newman–Kwart rearrangement (NKR) at around 300 °C, beyond the range of most convenient and safe, small-scale laboratory equipment. We report here the convenient conversions of several difficult substrates using modern microwave technology, which has proven ideal for investigating this high temperature reaction in all but the most refractory of cases. In addition, several previously reported difficult examples were re-investigated, and found not to require high temperatures under these conditions, for various reasons which are elaborated upon.

1. Introduction

In our first report[1] on the Newman–Kwart rearrangement (NKR),[2] we commented that most synthetically useful examples require temperatures in the range of 200–300 °C since the NKR proceeds by an *O*- to *S*-aryl migration, which has a high activation energy (Scheme 1). Many literature examples feature electron withdrawing group (EWG) substituents, which are known to aid this rearrangement. Typical reaction temperatures for short reaction times are below 250 °C in these cases.[3] Substrates bearing electron-donating group (EDG) substituents on the other hand tend to require temperatures approaching 300 °C.[4] Furthermore, whilst one *ortho* substituent can enhance the reaction rate, doubly *ortho* and very sterically hindered substituents perturb the reaction and also require typically high temperatures and/or prolonged reaction times.[5]



O-thiocarbamate — *Proposed four-centre transition state intermediate* — *S*-thiocarbamate

Scheme 1.

Having proven the utility of microwave technology for heating this high temperature rearrangement in the general case,[1] we were interested to push the microwave capability above the general limit of 250 °C using difficult NKR substrates.[6] Since many phenols bearing useful substituents are available, it would broaden the scope and utility of the procedure by taking advantage of these substitution patterns. These difficult NKR compounds are electronically deactivated substrates bearing one or more MeO groups (**2a–f**); sterically crowded substrates (**2h–n**); or substrates incorporating both features (**2f**, **h–j**). We also decided to investigate the largely unknown fluoro series (**2o–s**) more comprehensively, which had previously proven to be sluggish at 'moderate' temperatures (i.e., around 250 °C).[1] Finally, in addition to examples **2d**, **h–k**, we specifically re-investigated two compounds in which the conversions were slow or the yields were low for the *O*- to *S*-rearrangement, suggesting that these might also be difficult substrates (**2t–u**).

All these substrates were expected to require temperatures at the upper end of the 250–300 °C range, which one or two modern scientific microwave instruments are capable of achieving.[7] Traditionally, many NKR reactions have been performed as melts in oils baths, autoclaves,[8] heating mantles,[9] metal[4c] or salt baths,[10] or under FVP conditions.[11] FVP is too specialised for most organic chemists to use,[12] and the other heating methods are also becoming less common due to their significant physical hazards. This is easily avoided by the use of modern microwave instrumentation.[13] Such microwaves effectively function as highly convenient, small-scale autoclaves. Safety concerns are reduced to

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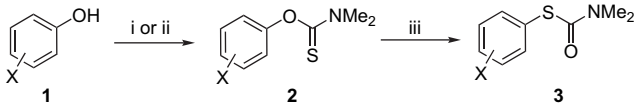
a minimum whilst accessing what are for the general organic chemist, very high temperatures. Furthermore, the direct heating capability of microwaves allows high temperatures to be accessed rapidly, without the delay in heating a bath or oven, or of conductive heating through a solid or molten sample. Compressed air cooling at the end of the reaction speeds up the cooling process. In addition, we were hopeful that the rapid heating/rapid cooling capability provided by microwave heating might also contribute to a cleaner reaction profile. Finally, it is worth noting that near critical water can be accessed in the 250–300 °C temperature range, which is of recent interest due to its unique reaction properties.[14]

2. Results and discussion

The starting *O*-thiocarbamates **2** could be readily prepared from available phenols in a single step, using our simplified procedure in most cases (DABCO, DMTCC and NMP) (Scheme 2).[1] The sterically hindered compounds **2h–j** could not generally be prepared in good yield by this method, but switching to the more forcing NaH/DMTCC conditions used by other workers,[2,4b,5] produced good yields for compounds **2h** and **i**. By either method, direct aqueous drown-out of the reaction mixtures gave high yields of highly crystalline compounds in excellent purity in the majority of cases (Table 1). Lower yields occurred only in the case of the low melting solid **2g**, where recovery was more difficult, and several of the *O*-alkyl substituted compounds, where conversions were lower although the products were highly crystalline.



Scheme 2. (i) DMTCC (1.1 equiv), DABCO (1.3 equiv), NMP, 50 °C, then water; (ii) NaH, DMTCC, NMP, rt, then water and (iii) solvent, MW.

The optimised conditions for conversion of each *O*- to *S*-thiocarbamate were screened using microwave heating on dilute samples, typically 0.4–1.2 M in NMP, and monitoring by HPLC initially. Although NMP heats very efficiently in the microwave field allowing high temperatures to be achieved, the reaction solutions often became very dark, which could complicate the workup; DMA was found to be a better solvent in these cases. When NMP and DMA both gave poorer impurity profiles, *ortho*-dichlorobenzene (DCB) was found to be a suitable replacement capable of reaching the high temperatures required (at high substrate concentrations). Although we have reported that there is a solvent dependency for this reaction,[1] there is no practical difference between NMP and DMA, and only a minor adjustment is required for the lower relative polarity of DCB. There is also no practical difference on the rates of reaction for the different concentrations used.

Once ideal conditions had been determined for >95% conversion after a 15–20 min heating time, purified samples were isolated on 200–500 mg scale from preparative procedures. Yields were comparable or better to existing literature data in all cases. Pressures at the high temperatures of ~300 °C were in the range 100–200 psi (7–14 bar) in most cases, depending on the solvent and the actual temperature required. This was well within the 300 psi (20 bar) operating limit of the microwave. The results are collected in Table 1. The unsubstituted compound **2g** was included as a baseline reference, showing >95% conversion at 290 °C after 20 min.

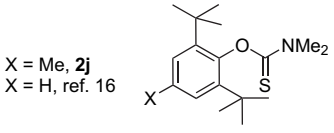
Table 1. Microwave conditions for conversion of **2** to **3**

	Substitution pattern (X=)	Yield[a] **2** (%)	Yield[a] **3** (%)	Microwave conditions for conversion of **2** to **3**					Ref.
				Temp[b] (°C)	Time (min)	Conv.[c] (%)	Solvent	Vol[d]	
a	2-MeO	75	80	300	20	99	NMP	10	2
b	3-MeO	68	86	295	20	98	NMP	10	4b
c	4-MeO	67	79	>300	40	99	NMP	10	2
d	3,5-DiMeO	66	86	295	20	99	NMP	4	19
e	3,4,5-TriMeO	81	64	300	15	100	NMP	4	23
f	2,6-DiMeO	77	78	300	20	100	DMA	4	24
g	4-H	56	82	290	20	97	NMP	10	5
h	2,6-DiMe	70	86	300	25	98	DMA	10	25
i	2,6-Di-*i*-Pr	64	91	>300	30	100	DMA	4	25
j	2,6-Di-*t*-Bu-4-Me[e]	n/a	n/a	335[e]	20[e]	13[e]	Neat[e]	n/a	2,5
k	1-Naph	77	84	300	15	100	NMP	4	17
l	2-Naph	72	75	280	20	97	DMA	4	18
m	2-Ph	76	80	300	15	100	DMA	4	5
n	2,6-DiPh	88	75	300	25	96	DMA	4	5
o	2-F	87	75	290	20	96	DMA	4	—
p	3-F	93	92	280	20	100	NMP	4	—
q	4-F	80	72	>300	20	97	DMA	4	1
r	2,4-DiF	94	71	290	20	100	DCB	4	21
s	3,4-DiF	90	89	300	20	100	DCB	4	—
t	2-Br-5-MeO	n/a	89	280	20	100	DCB	4	9
u	2,5-DiCl-4-I	93	85	230	20	97	DMA	4	22

n/a Not applicable.
[a] Isolated yields.
[b] For >300 °C, see text.
[c] Determined by LC at 254 nm.
[d] 10 vol=1 g in 10 mL.
[e] Data from Ref. 2.

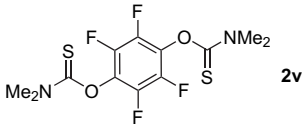
The results for singly and multiply substituted *O*-alkyl substituted compounds (**2a–f**) were as expected, being converted to their respective *S*-thiocarbamates in good yields in 15–20 min at ~300 °C. The conversion rates for the di- and tri-substituted compounds **2d** and **e**, and the doubly *ortho* compound **2f**, were equivalent to the mono-substituted **2a**, showing that *meta*-EWG substituents, and non-hindering *ortho* substituents do not make the reaction slower. However, the *para*-methoxy substituted compound (**2c**) proved particularly refractory. Rather than lengthening the reaction time significantly, however, **2c** could be heated well above 300 °C to achieve full conversion in 30–40 min by the expediency of not stirring the homogeneous reaction mixture. This lack of stirring means that the bulk heat in the unstirred liquid column is not adequately dissipated throughout the tube. This results in the microwave's IR pyrometer at the base of the microwave tube reading an artificially reduced temperature, which tricks the magnetron into supplying more power to the sample to reach the nominal set point of 300 °C, even though the bulk temperature above the pyrometer is already >300 °C. A semi-quantitative assessment from known reaction conversions at lower temperatures indicates that temperatures of ~30–40 K higher can typically be achieved by this procedure.[15]

The mildly electron-donating compounds **2h–i** needed slightly more forcing conditions, presumably due to their increased steric hindrance around the reacting centre. A slight lengthening of the reaction time to 25 min for **2h** (2,6-diMe) was required, and much more so for **2i** (2,6-di-*i*-Pr). Rather than increasing the reaction time excessively, which often leads to some degradation, the reaction temperature was again increased to >300 °C, as described for **2c** above. However, substrate **2j** (2,6-di-*t*-Bu-4-Me) proved too bulky to be synthesised in our hands, and it was not clear from the literature how this had been achieved in the past.[2,5] Rundel clearly had a similar problem with this and the simpler 2,6-di-*tert*-butyl-substituted compound.[16]



The aromatic substituents **2k–n** also proved to be readily converted to their *S*-thiocarbamates, despite their relatively bulky substituents. The sterically crowded **2m** (2-Ph) and **n** (2,6-diPh) were converted on a similar time scale to **2h** (2,6-diMe). The 1-naphthyl compound (**2k**) also underwent good conversion within the scope of the instrument, despite the expected steric constraint from the *peri*-proton and previously reported unsuccessful preparation by NKR.[17] The sterically unencumbered 2-naphthyl compound (**2k**) showed that these aromatic rings can function like EWG substituents when steric factors do not intervene, being relatively faster than the unsubstituted reference compound **2g**.[18]

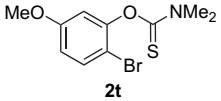
The fluoro-substituted compounds (**2o–s**) proved to be more difficult than reference substrate **2g** whilst exhibiting the expected trend for a mono-substituted series, i.e., 3-F>2-F>4-F. Indeed, compound **2q** (4-F) had to be heated unstirred above 300 °C as for sterically hindered **2i** to achieve >95% conversion after 20 min. With additional fluorine, the EWG effects appear to become dominant, and such extreme temperatures, although high, are no longer quite needed for compounds **2r** and **s**. This trend appears to be general, since the tetra fluoro-substituted bis-compound **2v** was reported to be converted at the relatively modest temperature of 195 °C after 45 min.[3d]



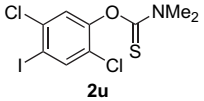
2v

Several compounds were studied in more detail, for which, in our experience, over-long reaction times and/or low conversions had been reported. For example, a recent re-synthesis of **2d** following Wolfers' procedure[19] required 6 h at 285 °C to give a modest yield of 47%.[20] Wolfers obtained 72% after 90 min at 265 °C, which compares well with our 86% yield after 20 min at 295 °C. Compound **2r** could also be prepared in slightly improved yield and at faster conversion in our hands than previously;[21] and compound **2k** has already been discussed above.

Finally, we specifically investigated two additional compounds for which long reaction times and/or low conversions had been reported. Both were halogen-substituted compounds, which should not have required particularly high temperatures. The first was from our own laboratories, whereby the 2-bromo-5-methoxy substrate (**2t**) had required 4 h at reflux in diethylaniline (bp 217 °C) to achieve full conversion with an isolated yield on scale-up of 90%.[9] This could be fully converted after 20 min in DCB at 280 °C to give an equivalent isolated yield. For an assumed first order rearrangement,[26] this increase in reaction rate at the higher temperature is roughly what would have been predicted from the Arrhenius equation. Comparison with the relevant 3-methoxy substituted analogue **2b** shows that the weakly EWG 2-bromo substituent does indeed facilitate this reaction moderately.

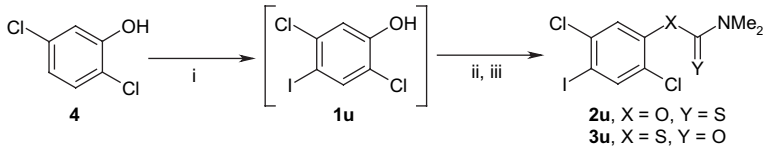


2t



2u

The alternative 2,5-dichloro-4-iodo substrate (**2u**) was more puzzling, giving an apparent isolated yield after reaction at 220 °C for 2 h of only 33%.[22] However, this yield was obtained from the starting phenol **4**, which required moderately selective iodination to give **1u** before formation of *O*-thiocarbamate **2u**, and then rearrangement to the *S*-thioicarbamate product **3u**, without purification during the intermediate steps (Scheme 3). The telescoped yield of 33% disguised the apparently low quality of the iodination product **1u**, which was used crude to form **2u**. We isolated and purified iodophenol **1u** in a modest 56% yield, from which the *O*-thiocarbamate could then be prepared in an excellent 93% yield. Conversion by NKR at the relatively modest temperature of



Scheme 3. (i) I_2, Ag_2SO_4, CH_2Cl_2; (ii) DMTCC, DABCO, NMP and (iii) DMA, 230 °C, MW.

230 °C for 20 min gave 97% conversion with an isolated yield of 85%. As with the other examples discussed above, including our own,[9] apparently lower than expected yields for the NKR step were all due to poor yields or selectivities in earlier chemistry steps whilst the NKR itself proved to be high yielding.

3. Conclusions

In summary, we have shown that electronically deactivated and/or sterically hindered substrates, which undergo the Newman–Kwart rearrangement (NKR) at ~300 °C can be safely and conveniently transformed in short reaction times using modern microwave technology. Significantly, microwave heating allowed access to temperatures substantially above solvent boiling points whilst under pressures that were comfortably within the operating limits of the microwave instrument. Of the substrates which could be prepared, none of the examples tested were beyond the scope of available instruments. In addition, we have re-investigated several examples which apparently required high temperatures and gave modest yields. In each case we found the NKR to be a reliable and high yielding reaction, often not requiring such high temperatures. In every case, the previously reported poor performance could be attributed to low conversions or non-optimised isolations in earlier chemical steps unrelated to the NKR.

4. Experimental

4.1. General

Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument as follows. *Method A*: 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. For the non-polar, sterically hindered substrates (**2**/**3h**–**j** and **n**), a longer running method was required. *Method B*: as for Method A, except at t=0 min, 0% eluent B; at t=13 min, 100% eluent B; at t=15 min, 100% eluent B; 5 min post time. Typical retention times (t_R) are noted in each case. 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 parts per million relative to TMS at δ=0. Electrospray (ES^+) mass spectra were performed on Micromass ZQ or Micromass Platform LC 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 was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Where not stated otherwise, assume standard practices have been applied.

4.2. Typical microwave procedure

Microwave reactions were exclusively performed in 10-mL sealed tubes in a regularly calibrated CEM *Discover* focused 300 W microwave reactor with IR temperature monitoring and non-invasive pressure transducer. In a typical procedure, 200 or 500 mg of *O*-thiocarbamate (**2**) was dissolved in NMP, DMA or DCB (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 90–120 s, depending on the maximum wattage supplied (250–300 W) and the temperature required (230–300 °C) (typically 300 W to heat to 300 °C in ~120 s). The heating time is not included in the quoted hold time for any given procedure; control studies show that the heating time is negligible for a 20 min reaction time. For substrates requiring more than 300 °C (**2c**,**i** and **q**), the same procedure was followed, except that the magnetic stirring was switched off. Pressures at the high temperatures of ~300 °C were in the range 100–200 psi (7–14 bar) when using DMA or NMP, and 200–250 psi (14–17 bar) when once using DCB at 300+ °C. This was well within the 300 psi (20 bar) operating limit of the microwave, and at no time for any solvent/substrate/temperature combination did the pressure exceed 250 psi (see also Ref. 15). The *S*-thiocarbamate (**3**) products were isolated either by precipitation by aqueous drown-out into water (for NMP and DMA solutions) or by partition with water and extraction into MTBE followed by flash silica gel chromatography. Yields in Table 1 are of purified samples from preparative procedures, typically performed on 200 or 500 mg of substrates **2** in 2.0 mL solvent.

4.3. Typical laboratory preparations

All compounds (**2a**–**u** and **3a**–**u**) were fully characterised by LC/TLC, ^{1}H and ^{13}C NMR spectroscopy, MS, and mp where applicable. The data are not reproduced here since most compounds are known in the literature (see Supplementary data for full experimental conditions and characterisations for previously unreported compounds). Typical preparations are given below.

4.3.1. Preparation of an *O*-thiocarbamate (2,6-dimethoxyphenyl-*O*-thiocarbamate, 2f). 2,6-Dimethoxyphenol (11.76 g, 75 mmol) and DABCO (11.30 g, 97.5 mmol, 1.3 equiv) were heated in NMP (60 mL) to 50 °C with mechanical stirring to give a dark brown solution. Dimethyl

thiocarbamoyl chloride (10.75 g, 82.5 mmol, 1.1 equiv) was dissolved in NMP (15 mL) and added dropwise to the previous solution over 18 min (N.B. A 3 K exotherm was typically seen on this scale). Some fine precipitate formed in the dark red solution during this addition. The reaction was monitored by LC and was complete within 90 min at 50 °C. Water (140 mL) was added over 15 min at 50 °C. The original solid dissolved readily, but a yellow precipitate formed later in the addition, which persisted to the end. The reaction mixture was cooled smoothly to 20 °C and the precipitate isolated by filtration. The product cake was slurry washed twice with water (24 mL each) and dried in vacuo at 50 °C to yield the title compound as a fine, off-white crystalline solid (14.25 g, 77% yield). HPLC (method A, t_R 2.53 min, 99.9%); mp 144–145.5 °C (lit.[24] 144–146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, t, J=8.7 Hz), 6.63 (2H, d, J=9.0 Hz), 3.83 (6H, s), 3.46 (3H, s), 3.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.69, 152.69, 132.21, 126.28, 105.01, 56.29, 43.35, 38.67; MS (ES^+) 242 (M+1, 100%).

4.3.2. Preparation of a sterically hindered *O*-thiocarbamate (2,6-dimethylphenyl-*O*-thiocarbamate, 2h). 2,6-Dimethylphenol (1.22 g, 10.0 mmol) was dissolved in NMP (18 mL) with mechanical stirring at 20 °C under N_2 to give a purple coloured solution over 30 min. Sodium hydride (440 mg, 11.0 mmol) was added in several portions over 15 min, to give a dark brown solution. There was effervescence on addition of each portion, and the temperature rose to a maximum of 37 °C. The reaction mixture was stirred for 30 min during which time it cooled back to 20 °C. Dimethyl thiocarbamoyl chloride (1.66 g, 13.0 mmol) was dissolved in NMP (6.0 mL) and added dropwise to the sodium phenolate solution over 3 min. The reaction was monitored by LC (method A) and judged complete after 60 min. Water (72 mL) was added over 15 min, which resulted in some precipitation of a pale brown solid and an exotherm to 33 °C on this scale. The reaction mixture was cooled to 20 °C and the precipitate isolated by filtration. The product cake was slurry washed twice with water (24 mL each) and dried in vacuo at 30 °C to yield the title compound as a light brown solid (2.11 g, 70% yield). HPLC (method B, t_R 10.34 min, 95%); mp 72–74 °C (lit.[5] 80–82 °C (ethanol)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (3H, s), 3.48 (3H, s), 3.38 (3H, s), 2.17 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 186.23, 151.16, 130.87, 128.46, 125.81, 43.28, 38.40, 16.52; MS (ES^+) 210 (M+1, 100%).

4.3.3. Preparation of an *S*-thiocarbamate (2,6-dimethoxyphenyl-*S*-thiocarbamate, 3f). 2,6-Dimethoxyphenyl-*O*-thiocarbamate (500 mg) was dissolved in DMA (2.0 mL) and heated at 300 W in a microwave tube to 300 °C for 20 min. After compressed air cooling to rt, the dark reaction mixture was diluted with water (6 mL), from which a precipitate formed after about 5 min. The solid was isolated by filtration, washed with water (2×6 mL, then 2×3 mL) and dried in vacuo at 50 °C to give the title compound as a white solid (390 mg, 78%). HPLC (method A, t_R 1.94 min, 96.5%); mp 127–128 °C (lit.[24] 122–127 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, J=8.5 Hz), 6.62 (2H, d, J=8.5 Hz), 3.86 (6H, s), 3.18 (3H, s), 3.00 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.68, 161.38, 131.67, 104.85, 104.24, 56.35, 36.93; MS (ES^+) 242 (M+1, 100%).

4.3.4. Preparation of an *S*-thiocarbamate (2,6-dimethylphenyl-*S*-thiocarbamate, 3h). 2,6-Dimethylphenyl-*O*-thiocarbamate (203 mg) was dissolved in DMA (2.0 mL) and heated at 300 W in a microwave tube to 300 °C for 25 min with stirring. After compressed air cooling to rt, the dark reaction mixture was diluted with water (15 mL), and extracted with MTBE (1×15 mL, then 2×10 mL). The combined MTBE extracts were dried over $MgSO_4$ and concentrated to dryness to give an orange oil (709 mg), which was purified by flash silica gel chromatography eluting with 4:1 *iso*-hexane/ethyl acetate (R_f 0.27) to give the title compound as a light oil (174 mg, 86%). HPLC (method A, t_R 4.75 min, 99%); mp oil; (lit.[5] 35–37 °C (30–60 petrol ether)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, m), 7.13 (2H, m), 3.16 (3H, br s), 3.02 (3H, br s), 2.42 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.95, 143.63, 129.48, 128.08, 118.85, 36.89, 22.01; MS (ES^+) 210 (M+1, 100%).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.101.

References and notes

1. Moseley, J. D.; Sankey, R. S.; Tang, O. N.; Gilday, J. P. *Tetrahedron* **2006**, *62*, 4685–4689.
2. (a) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984; (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410–412.
3. For example, see: (a) Miyazaki, K. *Tetrahedron Lett.* **1968**, 2793–2798; (b) Kaji, A.; Araki, Y.; Miyazaki, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1393–1399; (c) Reineke, C.; Goralski, C. T. *J. Org. Chem.* **1977**, *42*, 1139–1142; (d) Raasch, M. S. *J. Org. Chem.* **1979**, *44*, 2629–2632; (e) Rahman, L. K. A.; Scrowston, R. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2973–2977; (f) Corral, C.; Lissavetzky, J.; Valedeolmillos, A. M. *Synthesis* **1984**, 172–173; (g) Hirano, M.; Miyashita, A.; Nohira, H. *Chem. Lett.* **1991**, 209–212; (h) Levai, A.; Sebok, P. *Synth. Commun.* **1992**, *22*, 1735–1750; (i) Brooker, S.; Croucher, P. D.; Roxburgh, F. M. *J. Chem. Soc., Dalton Trans.* **1996**, 3031–3037.
4. For example, see: (a) Cooper, J. E.; Paul, J. M. *J. Chem. Eng. Data* **1970**, *15*, 586–588; (b) Kurth, H.-J.; Kraatz, U.; Korte, F. *Chem. Ber.* **1973**, *106*, 2419–2426; (c) Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujimura, H.; Nozaki, M.; Niwa, M. *J. Med. Chem.* **1985**, *28*, 1656–1661; (d) Cossu, S.; De Lucchi, O.; Fabbri, D.; Cossu, S.; De Lucchi, O.; Fabbri, D.; Valle, G.; Painter, G. F.; Smith, R. A. J. *Tetrahedron* **1997**, *53*, 6073–6084; (e) Rao, P.; Enger, O.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Eur. J. Inorg. Chem.* **2000**, 1503–1508.
5. Relles, H. M.; Pizzolato, G. *J. Org. Chem.* **1968**, *33*, 2249–2253.
6. It is worth noting the pioneering work of Strauss in the mid 1990s, who reported on the design of both prototype batch

and continuous flow microwave reactors, which were capable of reaching 260 °C. This was judged to meet the needs of most organic chemistry reactions and so ~250 °C is the limit that most commercial microwave reactors have subsequently followed. See: Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.

7. The only small-scale scientific microwave instrument capable of reaching the 250–300 °C window is the CEM Discover (www.cem.com). The semi-preparative scale Anton Paar Synthos 3000 has a set of quartz glass vessels capable of reaching 300 °C (www.anton-paar.com) (see Ref. 14c also). Milestone has a special rotor, the NOVA-10, for use with the Milestone Ethos, which will reach 280–300 °C on a similar scale (www.milestonsrl.com). Other microwave suppliers include Biotage (www.biotage.com).
8. Lau, C. K.; Belanger, P. C.; Dufresne, C.; Scheigetz, J. *J. Org. Chem.* **1987**, *52*, 1670–1673.
9. Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J.; Young, M. J. *Org. Process Res. Dev.* **2004**, *8*, 33–44.
10. Sorrell, T. N.; Cheesman, E. H. *Synth. Commun.* **1981**, *11*, 909–912.
11. Nicholson, G.; Silversides, J. D.; Archibald, S. J. *Tetrahedron Lett.* **2006**, *47*, 6541–6544.
12. For a recent modification on FVP conditions required for very sterically hindered but temperature sensitive NKR substrates, see: Higgs, T. C.; Carrano, C. J. *Eur. J. Org. Chem.* **2002**, 3632–3645. Although successful in this case, this required bespoke equipment to generate temperatures well above 300 °C, and so has limited general utility for the organic chemist at the present time.
13. (a) Kappe, O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005; (b) *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; Blackwell: Oxford, 2005; (c) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002.
14. (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Kluwer Academic: Dordrecht, 1997; (b) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750; (c) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672–3679.
15. Caution: This procedure takes the temperature (and potentially the pressure) above the standard operating limits of the CEM Discover's reaction tubes, which are rated to 300 °C and 300 psi (20 bar). However, we have suffered no failures using this technique on a small scale (2–4 mL), probably because this reaction generates no pressure other than the mechanical pressure of the solvent. This procedure is only possible on the CEM Discover due to the placement of the IR pyrometer at the base of the reaction tube. Some larger-scale instruments also have IR pyrometers reading the temperature at the base of their respective reaction tubes, but these are not intended to be accurate, and are for approximate temperature monitoring between reaction vessels in multiple vessel instruments (e.g., Anton Paar Synthos 3000, CEM Mars).
16. Rundel, W.; Köhler, H. *Chem. Ber.* **1972**, *105*, 1087–1091.
17. Daub, G. H.; Whaley, T. W. *J. Org. Chem.* **1978**, *43*, 4659–4661.
18. Newman, M. S.; Hetzel, F. W. *Org. Synth.* **1971**, *51*, 139–142.
19. Wolfers, H.; Kraatz, U.; Korte, F. *Synthesis* **1975**, 43–44.
20. Gallardo-Godoy, A.; Fierro, A.; McLean, T. H.; Castillo, M.; Cassels, B. K.; Reyes-Parada, M.; Nichols, D. E. *J. Med. Chem.* **2005**, *48*, 2407–2419.
21. Scheigetz, J.; Zamboni, R.; Roy, B. *Synth. Commun.* **1995**, *25*, 2791–2806.
22. Springer, D. M.; Luh, B.-Y.; Goodrich, J.; Bronson, J. J. *Bioorg. Med. Chem.* **2003**, *11*, 265–279.
23. Samreth, S.; Millet, J.; Bellamy, F.; Bajgrowicz, J.; Barberousse, V.; Renaut, P. European Patent EP 0 365 397 B1, 1994.
24. Traxler, J. T. *J. Org. Chem.* **1979**, *44*, 4971–4973.
25. Cooper, J. E.; Paul, J. M. *J. Org. Chem.* **1970**, *35*, 2046–2048.
26. Newman and Karnes demonstrated that the rearrangement of the 4-nitrophenyl-*O*-thiocarbamate was first order up to ~0.2 M, and assumed that this would be true for other substrates (Ref. 2a). We have confirmed this for several other compounds in dilute solutions (up to ~0.4 M); Moseley, J. D.; Cox, B. G. Unpublished results.