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Research Article

Rapid microwave-assisted cleavage of methyl phenyl ethers: new method for synthesizing desmethyl precursors and for removing protecting groups

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Summary

A new microwave-enhanced method for rapid demethylation of methyl phenyl ethers using neat methanesulfonic acid (CH_3SO_3H) is presented. Using a monomodal microwave cavity, cleavage of anisole (1), used as model compound, to phenol (2) was achieved with high conversions (ca 80%) in very short reaction times (10–20 s). The feasibility of cleaving one or both of two methoxy groups was illustrated with 4-(3-bromoanilino)-6,7-dimethoxyquinazoline (PD153035, 3). High conversions ($\geqslant$82%) of 3 were attained with four different conditions (i.e. combination of input effect (35–125 W) and time (15 s–2 min)). 4-(3-Bromoanilino)-7-hydroxy-6-methoxyquinazoline (4), 4-(3-bromoanilino)-6-hydroxy-7-methoxyquinazoline (5) and 4-(3-bromoanilino)-6,7-dihydroxyquinazoline (6), the possible mono- or di-demethylated compounds, were obtained. Methods for rapid demethylations are of interest in radiochemistry for post-labeling deprotections of hydroxyl containing aromatic rings and also provide a more direct route for synthesizing precursor compounds for labeling by alkylation. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: demethylation; deprotection; precursor synthesis; PD153035

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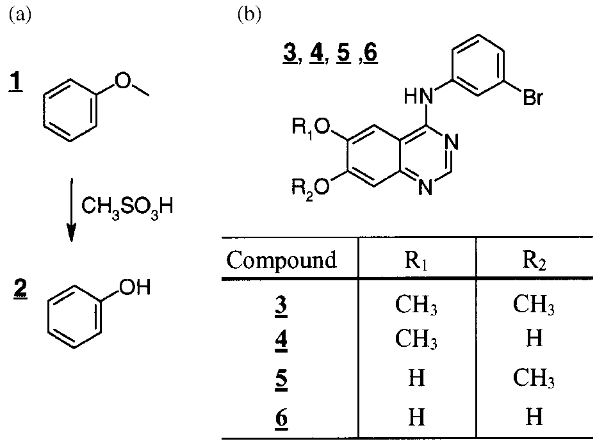
Introduction

The usefulness of microwaves for accelerating organic syntheses has been recognized since the mid-1980s and the number of synthetic publications involving microwave techniques is rapidly increasing. Reviews[1–3] are available that summarize microwave applications in different types of reactions, such as oxidations, condensations, heterocyclizations and carbon–carbon couplings. Reactions that usually require conventional heating, often proceed equally well or better, but more rapidly with microwave heating. The reductions in reaction times achievable are particularly important for syntheses with short-lived radionuclides and microwave techniques have been successfully applied in many radiolabelings.[4,5] In addition to the labeling step, many tracer preparations require additional transformations such as functional group protection and deprotection that might also profit from the accelerations achieved with microwave heating. For example, phenols are often protected as ethers during aromatic radiofluorinations and the ethers must be removed post-labeling (review on ether clevage).[6,7] A typical example is the synthesis of [6-^{18}F]6-fluorodopa in which the catechol hydroxyls must be deprotected after the labeling step.[8] Such multi-step syntheses are more common in fluorine-18 chemistry, but efficient and fast conditions for demethylation of N, O and S could also be potentially beneficial for carbon-11 radiochemical strategies.

Microwave-assisted deprotections of aromatic methyl ethers have previously been performed with pyridine hydrochloride,[9] KOBu-*t* and crown ether[10] and with lithium iodide and solid supports.[11] These methods were either not fast enough and/or the reagents used did not lend themselves well to the handling constraints of fluorine-18 and carbon-11 chemistry. We have examined here the use of monomodal microwave heating to speed up the cleavage of methylphenylethers with methanesulfonic acid[12] (CH_3SO_3H). Since CH_3SO_3H is very polar, it would be expected to interact strongly with the oscillating electromagnetic field. Its high boiling point (167°C at 10 mm Hg) suggested that high temperatures could be employed without the pressure increase typically observed in microwave heating of the more volatile mineral acids.

We report the use of this deprotection method in a model reaction (Scheme 1a) in which methyl phenyl ether (anisole, $\underline{1}$) was converted to phenol ($\underline{2}$). Furthermore, the mono- and di-demethylation of PD153035 (4-(3-bromoanilino)-6,7-dimethoxyquinazoline, $\underline{3}$, Scheme 1b), a tyrosine



Compound	R_1	R_2
3	CH_3	CH_3
4	CH_3	H
5	H	CH_3
6	H	H

Scheme 1. Methyl phenyl ether cleavage with methanesulfonic acid was studied in: (a) the conversion of anisole (1) to phenol (2); and (b) the conversion of PD153035 (3) to the two monomethoxy compounds (4 and 5) and the dihydroxy product, 6

kinase inhibitor selective for the epidermal growth factor receptor,[13] was also studied. Finding feasible routes for rapidly synthesizing the desmethyl counterparts of potentially interesting pharmaceuticals can expedite the tracer developmental process. Directly demethylating the parent compound avoids the alternative development and optimization of sometimes complex and lengthy organic pathways. In compounds with multiple methyl groups, access to all the different desmethyl compounds may be desirable for labeling in different positions so that the metabolism of the parent compound can be examined.

Experimental

General

All reagents, unless otherwise specified, were of analytical grade and commercially available. Anisole (1) and CH_3SO_3H were obtained from Aldrich and phenol (2) from Merck. 4-(3-Bromoanilino)-6,7-dimethoxyquinazoline (PD153035, 3) was synthesized as described previously[14] based on the method of Rewcastle *et al.*[15] HPLC analyses were performed using a Shimadzu SPD-6A spectrophotometric detector, a Shimadzu C-R4AX integrator and two Shimadzu LC-10AD pumps. LC/MS-analysis were performed using a VG Platform II, Fisons

Instrument. The monomodal microwave cavity used was a Microwell 10 (Personal Chemistry AB, Uppsala, Sweden).

Demethylation procedures

In pyrex vessels[16] **1** (15 μl, 138 μmol) or **3** (1.5–20 mg,. 4.2–55.5 μmol) was dissolved in CH_3SO_3H (200 or 500 μl, respectively). The samples were vortexed, the tube openings were covered with parafilm (to prevent loss of sample in case of bumping) and they were subsequently treated with microwaves of different input power (35–125 watts (W)) for different times (10 s–2 min). Immediately after irradiation (EOR, end of reaction) the temperature in the reaction mixture was measured using a mercury thermometer (measuring interval 70–360°C). The demethylation of **3** was also performed with conventional heating at 200 ± 5°C (silicon oil bath). Aliquots (5 μl) taken were diluted in distilled water (dH_2O, 200–400 μl depending on the initial concentration of **3**) for HPLC analysis. In the model reaction aliquots (and reference **2**) were diluted in ethanol.

Analysis

The conversion of **1** to **2** was followed at 270 nm using a PRP-1 column (300 × 7.0 mm, 10 μm) and a mobile phase of A (acetonitrile (MeCN) containing 0.085 vol% trifluoroacetic acid (TFA)) and B (dH_2O containing 0.1 vol% TFA). At a flow rate of 2.0 ml/min, the mobile phase composition was changed by increasing A in a linear gradient from 40 to 60% during 14 min and then an isocratic elution at 75% A from 14 to 25 min. The demethylation of **3** was followed at 249 nm using a C18 μBondapak™ column (Waters, 3.9 × 300 mm, 10 μm), isocratic elution with MeCN:dH_2O:TFA-30:70:0.1 at 1.5 ml/min.

The product of the demethylation of **1** was identified by coelution on HPLC with reference **2**. The products **4**–**6** obtained in the demethylation reaction of **3** were identified by LC/MS-analysis (positive (50–100 V) electrospray ionization (ESI)) performed at the Swedish Pharmacy's Central Laboratory (Kungens Kurva, Sweden). The unfragmented $[M+H]^+$ ions (m/z) were 359.8, 345.8, 345.8 and 331.8 for **3**–**6**, respectively, based on the bromine-79 peak.

Conversions were estimated from the total area (area units, AU) of the peaks deemed to be derived from the starting material. In the demethylation of **1**, the AUs for **1** and **2** were related to the total AUs

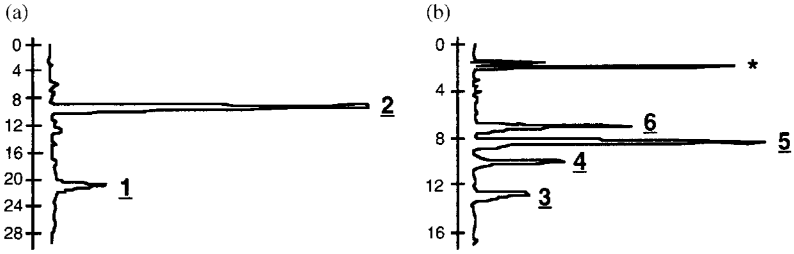


Figure 1. HPLC chromatograms from the product distribution analyses (UV-absorbance) for: (a) 1 ($t_R \approx 21.3$ min) cleaved to 2 ($t_R \approx 9.4$ min); and (b) 3 cleaved to the two mono demethylated products, 4 and 5 and the didemethylated product, 6. The approximate t_R for 3–6 were 12.4, 9.7, 8.1 and 6.8 min, respectively. The unidentified hydrophilic byproduct ($t_R \approx 1.8$–1.9 min) is marked with an asterisk

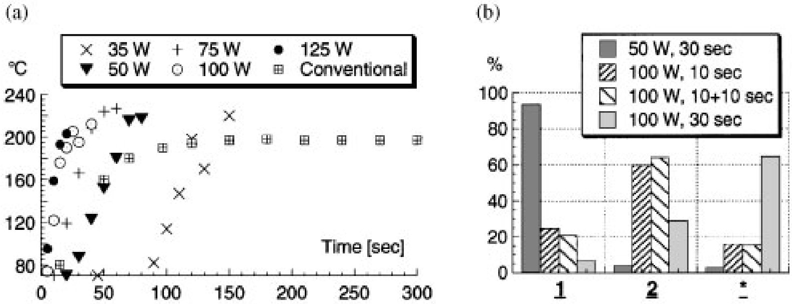


Figure 2. (a) The temperature of CH_3SO_3H (500 μl) as a function of time measured after microwave irradiation with different input power or during conventional heating in an oil bath of 195–200°C; (b) A bar diagram showing the conversions of 1 to 2 for different microwave input powers and times. Unidentified byproducts are indicated with an asterisk

calculated (see a typical HPLC chromatogram in Figure 1(a)). The molar absorptivities at 270 nm of 1 and 2 are nearly the same, with that of 1 being slightly larger than that of 2. Thus, conversions to 2 might be slightly underestimated. All peaks other than 1 and 2 were considered as unidentified byproducts (marked with an asterisk in Figure 2b). Since independently synthesized references 4–6 were either not available at all or in very small quantities, the amounts of 3–6 were calculated based on their area as related to the initial concentration of 3. An unidentified polar byproduct (marked with an asterisk in Figure 1b) was also produced in increasing amounts at longer times or higher input power.

To facilitate comparison of the different conditions, the total amounts of **3**–**6** together with the unidentified byproduct (*) were normalized to the original area of **3** (set as 100% with a correction factor range: 1.0 ± 0.2), without adjustment for individual molar absorptivities at 249 nm.

Results and discussion

This new microwave-assisted method for rapidly cleaving methyl phenyl ethers to phenols with CH_3SO_3H gave good conversions in <1 min reaction time. Conditions were identified which are suitable for removing methyl protecting groups post-labeling and for rapidly synthesizing the desmethyl precursors required for labeling with alkyl halides or triflates.

The temperatures achieved when heating CH_3SO_3H (500 μl) for different times and microwave input powers are shown in Figure 2a. The expected pattern of faster heating at higher input power was observed. It is noteworthy that the temperature curves for different input powers are similar, i.e. there seems to be a delay before the temperature increases at lower power but once the heating has started the rise per unit time is fairly similar.

The conversion of **1** to **2** proceeded with good yields at very short reaction times. After only 10 s with 100 W, the conversion of **1** was ca. 75%. In addition to **2** (ca. 60%), other unidentified byproducts were observed, as shown in Figure 2b. The byproducts eluted at retention times between those of **1** and **2** on the PRP-1 column and were not observed when CH_3SO_3H alone was heated under similar conditions. Further heating with 100 W did not improve the yield of **2**, nor did prolonged heating at lower input powers. For example, very little **1** (ca. 7%) remained after treatment with 100 W for 30 s, but the ratio of **2** to byproducts had also decreased (28%/65%). Apparently, once the optimum reaction temperature is reached, demethylation occurs very readily, but the phenol formed can be further transformed unless the microwave heating is quickly stopped.

The demethylating ability of CH_3SO_3H was further examined with the more complex PD153035 (**3**). With its vicinal methoxy groups (Scheme 1b) this compound provides an opportunity for investigating the method's regioselectivity, as well as multiple demethylation capability. HPLC analysis of reaction aliquots clearly showed the formation of three new compounds (4–6) (see the chromatogram in Figure 1b). They were identified by LC/MS analysis as the didemethylated 6 and the two monomethoxy compounds (4 and 5) arising from the monodemethylation of 3. Compounds 4 and 5 can be easily separated on the C18-HPLC column (Figure 1b). However, their fragmentation patterns in the ESI-MS analysis were identical. The major fragments were $[M+H^+-CH_3]$, $[M+H^+-CH_3-CO]$, $[M+H^+-CH_3-CO-CO]$, $[M+H^+-CH_3-Br]$ with *m*/*z* of approximately 331, 302, 274 (based on bromine-79) and 251, respectively. The identities of 4 and 5 were established based on coelution with reference compounds on HPLC. Compound 4 coeluted with 4-(3-bromoanilino)-7-hydroxy-6-methoxyquinazoline that we have synthesized previously by a multi-step pathway (data not shown) starting with production of 2-amino-4-benzyloxy-5-methoxybenzoic acid which was further transformed by basically the same route as used in the synthesis of 3 and then finishing with selective cleavage of the benzyl group. Compound 5 coeluted with the desmethyl precursor compound of 3 synthesized (by demethylation using BBr_3) as previously reported[14] and then realkylated with $[^{11}C]$iodomethane to afford $[^{11}C]$-3, and is thus assigned as 4-(3-bromoanilino)-6-hydroxy-7-methoxyquinazoline.

Figure 3 summarizes the demethylation results at different reaction times for four different microwave input powers. For each input power, the reaction time was selected so that an EOR temperature of ca. 180–200°C would be achieved (Figure 2a), since initial screening had

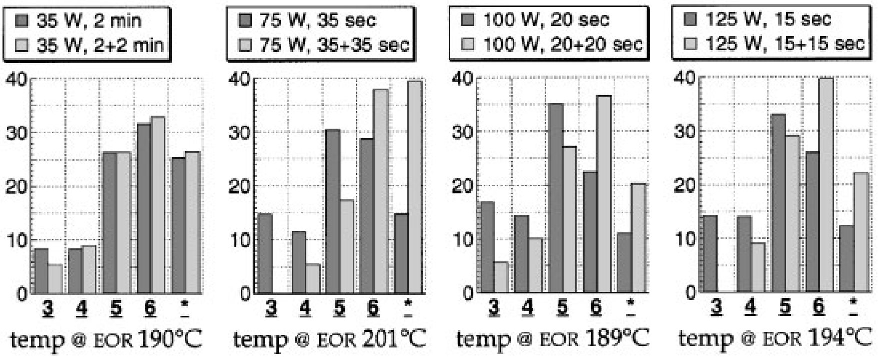


Figure 3. Compound distribution (expressed as percent with respect to starting concentration of 3) after the demethylation reaction of 3 (1.5–2.5 mg) in CH_3SO_3H at various microwave input powers and for different times. The asterisk indicates the unidentified byproduct

indicated that those temperatures were required for demethylations of 3 to occur (data not shown). The actual EOR temperatures measured for each reaction time and effect are indicated in Figure 3. Conversion of 3 was efficient ($\geqslant$82%) in all four trials (Figure 3), with the best conversion ($>$90%) obtained after 2 min with 35 W. All of the possible products 4–6 were obtained, though a certain degree of regioselectivity favoring 5 was observed. Prolonged heating gave the most didemethylation to 6, along with a more hydrophilic byproduct ($t_R \approx 1.8$–1.9 min, marked with an asterisk in Figure 1b). Both monomethoxy compounds were obtained in all four trials, with around 8–14% and 26–35% of 4 and 5, respectively, after the first heating period. During the second heating period, 3–5 decreased while the didemethylated 6 and the unidentified byproduct increased. Highest yields of 6 (40%) were obtained with 125 W for 30 s. These conditions can be attractive for use in radiosyntheses in which multiple demethylations must be performed.

To test whether the reaction could be scaled up, 10 and 20 mg of 3 were also subjected to the same conditions as for 1.5–2.5 mg in the series above. As seen in Figure 4, similar conversions of 3 were observed for these 4- to 10-fold increases in concentration, with 5 obtained in the highest yields under the conditions tested. These results indicate the feasibility of using this method as a quick preparative route to the desmethyl compounds.

The reaction of 3 with CH_3SO_3H was also performed with conventional heating in an oil bath at 200 ± 5°C. No demethylation

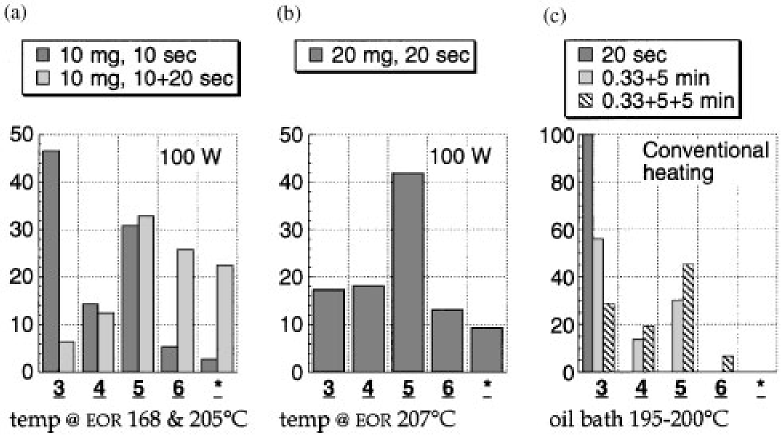


Figure 4. Conversions (expressed as percent with respect to starting concentration of 3) for: (a and b) scaled-up microwave reactions; and (c) after conventionally heating 3 (1.8 mg) with CH_3SO_3H in an oil bath

of 3 was detectable after the first 20 s, in contrast to the microwave experiments. After 10 min, 30% of 3 had still not reacted and only small amounts of the didemethylated product, 6, were produced. Other byproducts were not detected.

The demethylation of 3 was thus faster with microwave heating (conversions $\geqslant 82\%$ in $\leqslant 2$ min) than with conventional heating (ca. 70% at 10 min). Regioselectivity favoring 5 was essentially the same for both heating methods, while the extent of didemethylation differed considerably. The temperature of the sample increased much more slowly when it was convectively heated in the oil bath (Figure 2a), but had reached 190°C (the EOR temperature of the microwave experiments) by 1.5 min. The sample temperatures were not continuously measured in the microwave experiments nor were they corrected for possible cooling of reaction mixture by the thermometer. It is likely that the temperatures reached during the 'flash' microwave heating were somewhat higher than the temperature measured at EOR. It has also been proposed[17] that local 'hot spots' may form during microwave heating and that the rapid rate of heating can contribute to the accelerations reported and may also have affected the differing extents of didemethylation and byproduct formation observed here.

Conclusions

Cleavage of methyl phenyl ethers with CH_3SO_3H has been accomplished with the aid of monomodal microwave heating. Multiple demethylations could be rapidly performed in good yields with microwave, but not with conventional heating. The speed of this method makes it attractive for post-labeling deprotections in both fluorine-18 and carbon-11 labeling chemistry. The capability for quickly preparing multi-milligram quantities of desmethyl compounds for labeling in alternative positions may reduce the necessity for alternative, protracted synthetic procedures. These results are particularly convincing considering our previous experiences that the demethylation of 3 is difficult to accomplish with more commonly used cleavage conditions.[14]

Acknowledgements

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References

1. Abramovitch RA. *Org Prep Proced Int* 1991; **23**: 683–711.
2. Caddick S. *Tetrahedron* 1995; **51**: 10 403–10 432.
3. Lidström P, Tierney J, Wathey B, Westman J *Tetrahedron* 2001; **57**: 9225–9283.
4. Elander N, Jones JR, Lu S-Y, Stone-Elander S. *Chem Soc Rev* 2000; **29**: 239–249; and references therein.
5. Stone-Elander S, Elander N. *J Label Compd Radiopharm* 2002, in press; and references therein.
6. Bhatt MV, Kulkarni SU. *Synthesis* 1983; **4**: 249–282.
7. Tiecco M. *Synthesis* 1988; **10**: 749–759.
8. Luxen A, Guillaume M, Melega WP, Pike VW, Solin O, Wagner R. *Nucl Med Biol* 1992; **19**: 149–158.
9. Kulkarni PP, Kadam AJ, Mane RB, Desai UV, Wadgaonkar PP. *J Chem Res. (S)* 1999; **6**: 394–395.
10. Oussaïd A, Thach LN, Loupy A. *Tetrahedron Lett* 1997; **38**: 2451–2454.
11. Stone-Elander S, Fredriksson A, Elander N. *J Label Compd Radiopharm* 2001; **44**: S1029–S1031.
12. Fujii N, Irie H, Yajima H. *J Chem Soc Perkin Trans I* 1977; 2288–2289.
13. Fry DW, Kraker AJ, McMichael A, Ambroso LA, Nelson JM, Leopold WR, Connors RW, Bridges AJ. *Science* 1994; **265**: 1093–1095.
14. Johnström P, Fredriksson A, Thorell J-O, Stone-Elander S. *J Label Compd Radiopharm* 1998; **41**: 623–629.
15. Rewcastle GW, Denny WA, Bridges AJ, Zhou H, Cody DR, McMichael A, Fry DW. *J Med Chem* 1995; **38**: 3482–3487.
16. Stone-Elander SA, Elander N, Thorell J-O, Solås G, Svennebrink J. *J Label Compd Radiopharm* 1994; **34**: 949–960.
17. Galema SA. *Chem Soc Rev* 1997; **26**: 233–238.