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Ionic liquids as reagents and solvents in conjunction with microwave heating: rapid synthesis of alkyl halides from alcohols and nitriles from aryl halides

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Abstract—We show that using ionic liquids as reagents in conjunction with microwave heating it is possible to prepare primary alkyl halides from the corresponding alcohols rapidly. Using ionic liquids as solvents in conjunction with microwave heating it is possible to prepare aryl nitriles from the corresponding aryl bromides or iodides. The scope and limitations of using microwave-promotion as a tool in these reactions is discussed. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Microwave-mediated synthesis is a fast growing area of research interest as evidenced by the increasing numbers of papers and patents published in the area.[1,2] This is because it is often possible to reduce reaction times from many hours to a few minutes and it is also opening up avenues for new chemistry.[3] Microwave-mediated chemistry is often performed in high boiling polar solvents such as 1-methyl-2-pyrrolidone (NMP), DMSO and DMF. The high dipole moments of these solvents means that they can be heated very rapidly using microwave irradiation. Building on an idea first presented by Ley and co-workers,[4] we have recently explored a methodology for heating non-polar solvents very rapidly and well above their boiling points by addition of a small quantity of an ionic liquid to the medium.[5] Ionic liquids made of organic cations and appropriate anions have attracted much recent attention as solvents for chemistry because of the fact that they have melting points close or near to room temperature.[6] They have negligible vapor pressure and are immiscible with a range of organic solvents meaning that organic products can be removed and the ionic liquid recycled. As well as being used as solvents, a recent report has shown that they can be used as reagents for synthesis.[7] From the perspective of microwave chemistry the key properties of ionic liquids that can be exploited are their polarity (around that of methanol) and, with the appropriate material, their stability at high temperatures.

In this paper we present the first findings from our study into the scope and limitations of microwave-promotion as a tool for accelerating organic transformations. The potential speed and ease of product purification offered by the microwave/ionic liquid methodology would clearly be of use when preparing compound libraries. In addition, the process would be amenable to automation. We focus on the conversion of alcohols to alkyl halides and the conversion of aryl halides to nitriles. In the former case, the ionic liquid acts as a reagent and a solvent and in the latter just as a solvent. There is precedent in the literature for both these transformations using ionic liquids as reaction media but performing the reactions at room temperature or using conventional heating methods.[7,8]

2. Results and discussion

2.1. Synthesis of alkyl halides from alcohols

Ren and Wu have shown that, using 1,3-dialkylimidazolium halide-based ionic liquids, it is possible to convert alcohols to alkyl halides in the presence of either an organic or inorganic acid.[7] However, reaction times are very long generally being between 24 and 48 h. The ionic liquid is acting as a nucleophile as well as a solvent for the reaction. When investigating the use of ionic liquids as microwave heating agents, we found that with those comprising of an alkylimidazolium cation and a halide anion, when heated above 200°C decomposition occurs to give an alkyl halide and an alkyl imidazole as shown in Figure 1. The halide ion, X^-, acts as a nucleophile in attacking the cation with the subsequent elimination of alkyl-X. This decomposition at elevated temperatures is not totally unexpected. Vacuum

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Keywords: ionic liquids; alkyl halides; nitriles.

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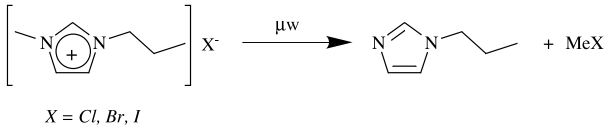
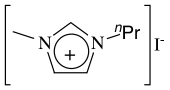


Figure 1. Decomposition of ionic liquids on microwave heating.

pyrolysis of 1-methyl-3-alkyl-imidazolium halides in the range 300–600°C leads to a similar decomposition, again forming the corresponding methyl halide and alkylimidazole.[9] We wanted to exploit and control this reactivity in the rapid microwave-promoted conversion of alcohols to alkyl halides.

Our first objective was to develop a set of working conditions for the microwave mediated process. Focusing on 1-octanol, we screened a range of reaction conditions, varying the microwave irradiation time, the ionic liquid (IL) and acid used and also investigated the effects of adding a toluene co-solvent. CAUTION!![10] The results are shown in Table 1. The ionic liquids chosen for use in our experiments were **1–3**. The temperature of the reaction mixture was carefully controlled. A microwave power of 100 W was used, this heating the ionic liquids to 200°C in a matter of a few seconds (≤15 s). The reactions performed using a co-solvent (2 mL of toluene) took a little longer to heat up but still reached 200°C within a matter of 30–40 s. We then held this temperature for the allotted time.



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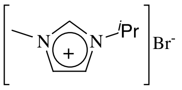

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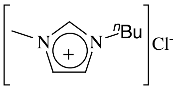

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The results show that *p*-toluene sulfonic acid is superior to sulfuric acid in the reactions involving the iodo- bromo- and chloro-ionic liquids. This concurs with the observations of Rex and Wu[7] for the reactions of iodo- and chloro-ionic liquids in the conversion of alcohols to alkyl halides at room temperature but differs for bromo-ionic liquids where they found mineral acids were better than organic acids. As expected, reaction times using our microwave method are greatly reduced over those for the room temperature reactions but follow the same trend i.e. reaction times increase in going from iodo to bromo to chloro substitutions, the optimum times being 30 s, 3 min and 10 min, respectively. An important point to note however is that the control of the reaction time when using **1** is very important. At 30 s a yield of 1-iodooctane of 81% is obtained, but if the reaction is left for a further 30 s then product decomposition is observed. For the reactions involving **1–3** the best product yields were obtained in the absence of co-solvent. The use of 2 mL of toluene as a co-solvent decreased the yield of product formed.

Table 2. Conversion of alcohols to alkyl halides using ionic liquids

Entry	Alcohol	IL	Time	Yield (%)[a]
1		1	30 s	77
2	1-Heptanol	2	3 min	95
3		3	10 min	75
4		1	30 s	73
5	1-Decanol	2	3 min	98
6		3	10 min	52
7		1	30 s	73
8	10-Undecen-1-ol	2	3 min	89
9		3	3 min	54
10		1	3 min	53[b]
11	1,8-Octanediol[c]	2	3 min	86[b]
12		3	10 min	50[b]
13	2-Propyn-1-ol	2	3 min	Dec[d]
14		1	30 s	Dec[d]
15	Geraniol	2	3 min	47[b]
16		3	10 min	30[b]
17		1	1 min	46[b] (72)[e]
18		2	3 min	68[b]
19	Benzyl alcohol	3	10 min	17[b]

Reactions were run using 1 mmol alcohol, 1 mmol ionic liquid and 1 mmol acid. Reactions were run using a power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Times shown represent hold times at the target temperature of 200°C.

[a] Isolated yield.

[b] With co-solvent (2 mL toluene).

[c] 0.5 mmol alcohol used.

[d] Dec=decomposition observed.

[e] 3 min.

Having found suitable conditions for the reaction we proceeded to screen a range of different alcohols the results being shown in Table 2. As with octanol, it is possible to prepare alkyl halides in good yield from other simple primary alcohols (entries 1–9). It is also possible to dihalogenate 1,8-octanediol (entries 10–12) but we find that this is best achieved with **1–3** using the co-solvent method.

Table 1. Screening of conditions for the reaction of 1-octanol

Entry	IL	Time	Acid[a]	Yield (%)[b] without co-solvent	Yield (%)[b,c] with co-solvent
1	1	30 s	PTSA	81	56
2	1	1 min	PTSA	53	38
3	1	30 s	H_2SO_4	3	55
4	1	1 min	H_2SO_4	38	15
5	2	30 s	PTSA	68	42
6	2	3 min	PTSA	95	32
7	2	30 s	H_2SO_4	73	59
8	2	1 min	H_2SO_4	42	40
9	3	3 min	PTSA	32	0
10	3	3 min	H_2SO_4	49	8
10	3	10 min	PTSA	42	35

Reactions were run using 1 mmol alcohol, 1 mmol ionic liquid and 1 mmol acid. Reactions were run using a power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Times shown represent hold times at the target temperature of 200°C.

[a] PTSA=*p*-toluene sufonic acid, H_2SO_4=95% sulfuric acid.

[b] Isolated yield.

[c] Co-solvent is 2 mL toluene.

We believe that the co-solvent method is better because the organic product is more soluble in the organic solvent than in the ionic liquid and that once formed it moves to the organic layer and is protected from decomposition which can occur in the higher-temperature, acidic ionic liquid environment. When attempting to use propargyl alcohol as a substrate in conjunction with **2**, significant decomposition occurred (entry 13). We attribute this to the thermal instability of the halide product. It is possible to use allylic and benzylic substrates although yields of product are lower than in the case of simple primary alcohols. Again we find that the co-solvent method offers the best route to these products, for the same reasons. With geraniol (entries 14–16), not unexpectedly geranyl iodide cannot be isolated but the bromide and chloride can both be obtained. With benzyl alcohol (entries 17–19), it is possible to obtain the iodide in moderate yield, the bromide in good yield but only a low yield of the chloride.

Our results with primary alcohols compliment those obtained from the room temperature studies. For simple aliphatic primary alcohols, our product yields are comparable if not better than those obtained at room temperature although our reaction times are much shorter (30 s–3 min instead of 5–48 h). Our work with geraniol and benzyl alcohol represents the first reported attempt to use allylic or benzylic substrates in the reaction. Our attempts to use secondary and tertiary alcohols as substrates however have not met with success; rapid decomposition occuring. This clearly is a disadvantage of the microwave-methodology since both secondary and tertiary alcohols can be converted to the corresponding halides at room temperature albeit with long reaction times. It could be that when using our microwave methodology, the product is formed rapidly but then decomposes, explaining the observation that a mixture of unreacted starting material and decomposition is all that is observed at the end of the reaction.

2.2. Synthesis of aryl nitriles from aryl halides

The Rosenmund-von Braun reaction (reaction between aryl halides and copper cyanide to give aryl nitriles) has been known for over 80 years (Fig. 2).[11] The reaction is usually carried out at high temperatures (150–250°C) using solvents such as nitrobenzene, however recently there has been a report of the use of ionic liquids as solvents.[8] When using 1,3-dialkylimidazolium halide-based ionic liquids it is possible to obtain moderate isolated yields of product when performing the reaction using aryl iodides, 2 or 3 equiv. of CuCN and heating at around 90–130°C for 24 h. We were keen to investigate the possibility of decreasing the reaction time and increasing the substrate scope using microwave promotion.

Our starting point was to develop a set of working conditions for the microwave mediated process. We screened a range of reaction conditions, varying the microwave irradiation time and the IL used. The results are shown in Table 3. We chose as ILs, **2** and **4**. These differ in the anion and were chosen because they were most easily manipulated at room temperature, the PF_6 salts of **1** or **2** being on the solid/liquid inerface at room temperature.

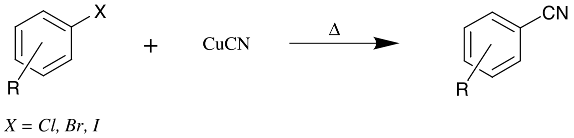


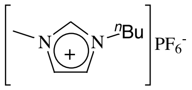
Figure 2. The Rosenmund-von Braun reaction.

Table 3. Screening of conditions for the Rosenmund-von Braun reaction

Entry	IL	Substrate	Time	Product yield (%)[a]
1	2	4-Iodotoluene	1 min	17
2	2	4-Iodotoluene	3 min	75
3	2	4-Iodotoluene	5 min	37
4	2	4-Bromotoluene	3 min	23
5	2	4-Bromotoluene	6 min	41
6	2	4-Bromotoluene	10 min	63
7	4	4-Iodotoluene	3 min	0

Reactions were run using 1 mmol 4-iodotoluene, 2 mmol CuCN and 0.5 mL ionic liquid. Reactions were run using a power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Times shown represent hold times at the target temperature of 200°C.

[a] Isolated yield.



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We found that the optimum reaction time for iodo-substituted substrates is 3 min, leading to a 75% yield of product, representing a significant improvement over the isolated yields obtained using similar substrates by heating using conventional methods (44%). For bromo-substituted substrates a reaction time of 10 min was required, this giving a lower yield than in the case of the iodo analogue. Of particular interest is that only the reactions using the halide-based ionic liquid worked. Other halide-based ionic liquids could be used but did not lead to any improvement in product yields. We have not been able to offer a rationale for why the reaction using **4** was unsuccessful, but it is rather surprising. At the temperatures used in these experiments, the PF_6 would be expected to be more robust and our expectation was that this would be a better reaction medium. It could be that the halide anion in **2** is non-innocent in the reaction, or offers the optimum ionic environment for facilitating the reaction. The work-up procedure is very important. In order to remove all the product from **2** at the end of the reaction it is necessary to wash the ionic liquid repeatedly (up to six times) with a hexane: ethyl acetate mixture. This highlights one of the problems that can be encountered when using ionic liquids as solvents, namely product extraction. Although by GC/MS analysis, quantitative yields may be reported, actual isolated yields are often significantly lower. We screened a range of organic solvents for their potential for product removal and found that a 4:1 hexane: ethyl acetate mixture was best. This mixture allowed satisfactory extraction of the product without solublising the ionic liquid and contaminating the product. The reactions were run using an excess of CuCN because the addition of cyanide to aryl halides in the reaction is known to be reversible so a high concentration of cyanide is key to driving the reaction towards completion.

Having found suitable conditions for the reaction we proceeded to screen a range of different aryl halides the

Table 4. Conversion of aryl halides to nitriles

Entry	Alcohol	Reaction time (min)	Yield (%)[a]
1	4-Iodotoluene	3	75
2	4-Bromotoluene	10	63
3	4-Chlorotoluene	10	0
4	4-Iodoanisole	3	65
5	4-Bromoanisole	10	40
6	4-Bromoacetophenone	10	64
7	4-Iodonitrobenzene	3	55[b]
7	4-Bromonitrobenzene	10	16
8	4,4′Dibromobiphenyl	10	19

Reactions were run using 1 mmol aryl halide, 2 mmol CuCN and 0.5 mL ionic liquid. Reactions were run using a power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Times shown represent hold times at the target temperature of 200°C.

[a] Isolated yield.

[b] Reaction run at 150°C.

results being shown in Table 4. We found that as well as being able to use aryl iodide substrates it was also possible to use aryl bromides and obtain moderate to good yields of product. This opens up the substrate scope of the reaction. In the conventional heating experiments, only bromonapthalenes have been activated. In the cases of the aryl iodides we are able to obtain higher isolated product yields than when the reaction is run using conventional heating and we also have the advantage of significantly reduced reaction times. The fact that chloro substrates cannot be activated is not surprising.

3. Conclusions

We have shown here that is is possible to greatly accerate the rate of reactions performed in ionic liquids as solvents by using microwave promotion. In the case of the synthesis of alkyl halides from alcohols, we find that reaction times can be reduced from 24–48 h down to 3 min. The reaction works well for primary alcohols but fails when using secondary or tertiary alcohols as substrates. In the case of the synthesis of aryl nitriles from the corresponding halides, we find that reaction times can again be reduced from 24 h down to 3 min. The reaction works for a range of aryl iodide and bromide substrates.

4. Experimental

4.1. General experimental

Microwave experiments were conducted using a CEM Discover™ Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled by a load cell connected to the vessel via a 14-gauge needle, which penetrates just below the septum surface. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In the reactions presented here, a target temperature was set together with a maximum microwave power. This maximum power was then used to heat the reaction mixture to the target temperature and once there, the microwave power was varied to hold the mixture at this temperature. This is defined as the ‘hold time’. A maxiumum pressure of 200 psi is set, this being a safety precaution since the tubes hold, at a maximum, a pressure of 250 psi. At the end of a reaction, the tube and contents were cooled rapidly using a stream of compressed air. All chemicals used in the reactions were reagent grade and used as purchased. ^{1}H and ^{31}P NMR spectra were recorded at 250 MHz and 293 K.

4.1.1. Preparation of 1-*n*-propyl-3-methylimidazolium iodide, 1.[12] To a toluene solution (30 mL) of 1-methylimidazole (5.1 g, 5.0 mL, 62.1 mmol) was added 1-iodopropane (10.8 g, 7.20 mL, 63.9 mmol) whilst stirring vigorously. The mixture was then heated for 3 h during which time the ionic liquid product **1** separated as a phase under the toluene solution. After allowing the reaction mixture to cool, the toluene was decanted off the ionic liquid and the orange viscous liquid product washed with ethyl acetate (4×20 mL) and dried under vacuum. (97% yield). ^{1}H NMR ($CDCl_3$, ppm): ^{1}H 9.80 (s, 1H, NC*H*N), 7.57 (d, 1H, J=1.4 Hz, NC*H*=), 7.54 (d, 1H, J=1.4 Hz, NC*H*=), 4.22 (t, J=7.1 Hz, 2H, $CH_2CH_2CH_3$), 3.94 (s, 3H, N-CH_3), 1.87 (m, 2H, $CH_2CH_2CH_3$), 0.89 (t, 3H, J=7.3 Hz, CH_3).

4.1.2. Preparation of 1-*i*-propyl-3-methylimidazolium bromide, 2. An analogous route to that for **1** was employed but using 2-bromopropane in the place of 1-iodopropane. The yellow viscous product was isolated in 81% yield. ^{1}H NMR ($CDCl_3$, ppm): δ 10.14 (s, 1H, NC*H*N), 7.60 (d, 1H, J=1.8 Hz, NC*H*=), 7.55 (d, 1H, J=1.8 Hz, NC*H*=), 4.67 (sep, J=6.7 Hz, 1H, $CH(CH_3)_2$), 3.94 (s, 3H, N-CH_3), 1.43 (d, 6H, J=6.7 Hz, $CH(CH_3)_2$).[5,12]

4.1.3. Preparation of 1-*n*-butyl-3-methylimidazolium chloride, 3.[13] To a 1-chlorobutane solution (32 mL) of 1-methylimidazole (5.1 g, 5.0 mL, 62.1 mmol) was added and then the mixture heated at reflux for 24 h during which time the ionic liquid product **3** separated as a phase under the chlorobutane solution. After allowing the reaction mixture to cool, the chlorobutane was decanted off the ionic liquid and the colourless viscous product washed with ethyl acetate (4×20 mL) and dried under vacuum (73% yield). ^{1}H NMR ($CDCl_3$, ppm): ^{1}H NMR ($CDCl_3$, ppm): δ 10.14 (s, 1H, NC*H*N), 7.79 (d, 1H, J=1.8 Hz, NC*H*=), 7.63 (d, 1H, J=1.8 Hz, NC*H*=), 4.37 (t, 2H, J=7.2 Hz, $CH_2CH_2CH_2CH_3$), 4.16 (s, 3H, N–CH_3), 1.92 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.40 (m, 2H, $CH_2CH_2CH_2CH_3$) 0.98 (t, J=7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$).

4.1.4. Preparation of 1-*n*-butyl-3-methylimidazolium hexafluorophosphate, 4.[14] A solution of **3** (5.24 g, 30 mmol) in water (10 mL) was cooled to 0°C and to this was added slowly HPF_6 (4.5 mL of a 60% solution in water, 30.5 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. After separation, the viscous liquid product was washed with water until the washings were neutral to universal indicator and then dried under vacuum. **4** was obtained in 61% yield. ^{1}H NMR

(CDCl$_3$, ppm): δ 9.08 (s, 1H, NC*H*N), 7.74 (d, 1H, J=1.7 Hz, NC*H*=), 7.67 (d, 1H, J=1.7 Hz, NC*H*=), 4.15 (t, 2H, J=7.2 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 3.84 (s, 3H, N–C*H*$_3$), 1.79 (m, 2H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.25 (m, 2H, CH$_2$CH$_2$CH$_2$ CH$_3$) 0.90 (t, 3H, J=7.3 Hz, CH$_2$CH$_2$CH$_2$C*H*$_3$). ^{31}P NMR (CDCl$_3$, ppm): −142.9.

4.2. General procedure for the synthesis of alkyl halides from alcohols using ionic liquids and microwave promotion

The ionic liquid of choice (1 mmol) was placed into a 10 mL glass microwave tube and to this was added alkyl alcohol (1 mmol) and acid (1 mmol). After sealing the tube, the mixture was irradiated in the microwave reactor. Reactions were run using a maximum microwave power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Once the temperature threshold was reached, the reaction mixture was held there for the requisite time. After the reaction mixture was cooled, the product was extracted from the ionic liquid. In the case when no co-solvent is used this was achieved by washing the ionic liquid with two aliquots of hexane (2 mL each). When a co-solvent was used, the organic layer was first decanted before the ionic liquid was washed with the aliquots of hexane (2 mL each) and the organics combined. Removal of the solvent by rotary evaporation gave product. Reaction products were characterised by comparison of ^{1}H NMR data with that in the literature: 1-bromoheptane,[15] 1-iodoheptane,[16] 1-chloroheptane,[17] 1-bromodecane,[18] 1-iododecane,[18] 1-chlorodecane,[19] 1-bromo-10-undecene,[20] 1-iodo-10-undecene,[21] 1-chloro-10-undecene,[22] 1,8-dibromooctane,[23] 1,8-diiodooctane,[17] 1,8-dichlorooctane,[17] 1-bromooctane,[7] 1-chlorooctane,[24] 1-iodooctane,[25] geranyl bromide,[26] geranyl chloride,[27] benzyl iodide,[28] benzyl bromide,[29] benzyl chloride,[30] 1-bromo-2-propyne.[31]

4.3. General procedure for the synthesis of nitriles from aryl halides using ionic liquids and microwave promotion

Ionic liquid **2** (0.5 mL) was placed into a 10 mL glass microwave tube and to this was added aryl halidel (1 mmol) and CuCN (2 mmol). After sealing the tube, the mixture was irradiated in the microwave reactor. Reactions were run using a maximum microwave power of 100 W, a temperature threshold of 200°C and a pressure threshold of 200 psi. Once the temperature threshold was reached, the reaction mixture was held there for the requisite time. After the reaction mixture was cooled, the product was extracted from the ionic liquid by washing the ionic liquid repeatedly with aliquots of 1:4 hexane/ethyl acetate (2 mL each time). Combination of the organic washings and removal of the solvent by rotary evaporation gave product. Reaction products were characterised by comparison of ^{1}H NMR data with that in the literature: 4-methoxybenzonitrile,[32] 4-cyanobenzonitrile,[33] 4-cyanotoluene,[34] 4-cyanoacetophenone[35] biphenyl-4,4′-dicarbonitrile.[36]

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10. Organic reagents and co-solvents are heated well above their boiling point so all necessary precautions should be taken when performing such experiments. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective metal cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to a temperature below the boiling point of the solvent before removal from the microwave cavity and opening to the atmosphere.
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