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Applications of High-Temperature Aqueous Media for Synthetic Organic Reactions

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Preparative organic synthesis was investigated in aqueous media at temperatures up to 300 °C. Experiments were conducted with a recently disclosed pressurized microwave batch reactor (MBR) or in conventionally heated autoclaves. Thirty-six examples are presented. Among these, methods were developed for a Fischer synthesis, an intramolecular aldol condensation that was scaled up, decarboxylation of indole-2-carboxylic acid, Rupe rearrangement of 1-ethynyl-1-cyclohexanol, isomerization of carvone to carvacrol, and conversion of phenylacetylene to acetophenone. The applicability of high-temperature water was also demonstrated for biomimetic processes important in food, flavor, and aroma chemistry and for tandem reactions such as formation of 2-methyl-2,3-dihydrobenzofuran from allyl phenyl ether. When addition of acid or base was necessary, less agent was usually required for high-temperature processes than for those at and below boiling, and the reactions often proceeded more selectively. In some instances the requirement was orders of magnitude lower, with obvious consequences for safe, economic processing and for lowering costs of effluent disposal. The diversity of reactions indicates that high-temperature aqueous media could play an increasingly important role in the development of new preparative processes.

Introduction

The past decade has seen increasing use of water as a medium for nonenzymatic organic reactions.[1] Synthetic procedures developed by several groups have employed temperatures at and below boiling.[2] On the other hand, conditions near supercritical (T_c water = 374 °C) have been investigated mainly for production of liquid and gaseous fuels from biomass,[3] for geochemical modeling,[4−25] and for the destruction of waste and hazardous organic materials.[3−5] Jointly, the groups of Katritzky and Siskin conducted extensive studies[4−25] and found that superheated water not only was an effective solvent for organic reactions but also could react.

With temperature rise from ambient toward the critical point, the dielectric constant of water decreases substantially, yet the ionic product increases by 3 orders of magnitude.[4,26] These properties appear anomalous, the former implying a decrease in polarity with temperature rise, and the latter, an increase due to higher dissociation. This behavior suggests that the role of water may be complex and could vary with temperature of organic reactions in aqueous media. To support this interpretation, we have observed that for some reactions optimal

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conditions prevail over a narrow range of time and temperature, yet for others, sets of optima are possible.[27,28]

From other perspectives, including considerations for the environment, safety, and economics, efforts are being directed toward decreasing the usage of organic solvents in chemical laboratories and industrial processes.[29] Also, since relatively few solvents are suitable for organic reactions above 200 °C anyway, further alternatives would be desirable. The above factors combine to indicate that, as well as for degradative applications,[3−5] water could become a solvent of choice for high-temperature synthetic organic reactions if its behavior under various conditions were better understood and hence more predictable.

To explore these aspects, over recent years we have investigated synthesis in aqueous environments at temperatures up to 300 °C. Notwithstanding work by the Siskin group[30,31] and by Parsons and her co-workers,[32] there have been few reports dealing with synthesis under such conditions. Furthermore, examples from our publications on microwave-assisted organic chemistry[27,28,33−35] may not have been readily recognized in the present context. This paper co-ordinates some of our published results with several additional findings.

Results and Discussion

Methodology. Stirred reactions were carried out in a microwave batch reactor (MBR)[33] with an upper operating limit of 260 °C or in commercial conventionally heated autoclaves that could accommodate higher temperatures. To avoid the slow heating up of reactions in the autoclaves,[36] the aqueous medium was preheated to the designated temperature when necessary, and the starting material was then injected under pressure of argon. Since reactions could be brought to temperature within a few minutes in the MBR, aqueous mixtures of the starting material were merely added to the vessel under an argon atmosphere at ambient and then heated.

By contrast, most of the work of the Katritzky and Siskin groups was carried out with small sealed metal tubes held in a fluidized sand bath for up to several days at a time.[5,9] When alternative conditions were investigated for a given reaction, usually temperatures differing by between 50 and 100 °C, and times differing by days, were selected.[9] Although that methodology was suitable for the degradative reactions studied,[5] it would not have been ideal for preparative studies owing to the constraints of scale, lack of stirring and sampling during reactions, large increments in temperature, and the lengthy times employed.

More recently, the Siskin group reported several classical organic reactions in superheated water.[30] They ensured that all starting materials were water soluble at the reaction temperature and avoided reactions in which there could be product-induced pH changes during heating. The scale was limited (total reaction volume 4.9 mL; concentration of organics 0.3−0.5 M), but reaction times (30−75 min) were convenient. Rapid and selective conversions were obtained for pinacol rearrangements, cleavage/hydrolysis, and hydrogen exchange reactions.[30,31] Jerome and Parsons[37] carried out their work in supercritical water, on an even smaller scale than that used by the Siskin group. Reaction times were up to several hours, and they concluded that supercritical water could act as a benign solvent even when the chemistry involved extremely hydrophobic reagents.

In the present work, the MBR (maximum capacity, 100 mL) had capabilities for rapid heating and cooling, control of heating, concurrent heating and cooling, and differential heating and was convenient to use.[27,33] Not all of these benefits are realizable with traditional equipment. However, pressurized microwave reactors are not yet widely available for organic synthesis, so for broad applicability of the findings, we employed the MBR and a conventional autoclave (maximum capacity, 500 mL on the laboratory scale) interchangeably where practicable.

It is important to recognize, however, that with conventional conductive heating, thermal gradients develop by convection, and even when mixtures are stirred, only part of the sample will be at the temperature of the applied heat. Accordingly, the measured temperature in the autoclave depended upon the positioning of thermal sensors. In calibrations of the vessel, differences of ±7 °C were observed within the sample. On the other hand, with the MBR, microwave energy is primarily absorbed by the stirred sample directly. Since the vessel was fabricated from polytetrafluoroethylene (PTFE), conductive heat losses would have been minimal. Further, owing to bulk heating by microwaves, the whole of the sample was irradiated simultaneously. These factors, combined with efficient stirring, minimize temperature gradients. Hence, differences between the nature and properties of conventional and microwave heating would have given some variability between results obtained with the autoclave and the MBR. For this reason, the heating method has been indicated for the examples presented in Table 1.

To study some reactions in detail, small increments in temperature and heating time were used. Advantages of this methodology have been demonstrated and discussed previously,[28] and in the interests of brevity, comprehensive lists of variations in conditions have not been included here.

Examples. Examples in Table 1 include condensations, isomerizations, addition of water to alkenes and alkynes, dehydration of alcohols, decarboxylations, hydrolyses of esters, amides, and nitriles, a Cannizzaro reaction, *ortho* Claisen, Rupe, and Meyer−Schuster rearrangements, biomimetic transformations, and tandem reactions.

Condensations. At temperatures below boiling, highly selective condensations can be promoted in water.[1] This applies particularly when negative activation volumes are involved,[38] as with Diels−Alder[39] and Baylis−Hill-

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Table 1. Example Reactions and Conditions

entry no.	starting material(s)	*T* (°C)	time (min)	medium	major product(s)	yield (%)	lit. ref
1	MeCOCH$_2$CH$_2$COMe (**2**)	200[a]	15	0.01 M NaOH	3-methylcyclopent-2-enone (**1**)	81[b]	48
2	PhNHNH$_2$ + EtCOMe	222[c]	30	water	2,3-dimethylindole (**3**)	67[b]	27
3	β-ionone (**4**)	250[c]	20	water	ionene (**5**)	30[d]	34
4	carvone (**7**)	250[c]	10	water	carvacrol (**6**)	95[b]	
5	indole-2-carboxylic acid (**8**)	255[c]	20	water	indole (**10**)	100[b]	27
6	2-carbethoxyindole (**9**)	255[c]	20	water	indole (**10**)	20[d]	27
7	2-carbethoxyindole (**9**)	200[c]	10	0.2 M NaOH	indole-2-carboxylic acid (**8**)	94[b]	27
8	2-carbethoxyindole (**9**)	255[c]	20	0.2 M NaOH	indole (**10**)	93[b]	27
9	PhCH=CHCOOEt (**11**)	250[a]	60	water	PhCH=CHCOOH (**12**)	51[d]	
10	PhCH=CHCOOEt (**11**)	290[a]	360	water	PhCH=CH$_2$ (**13**)	69[e]	
11	4-[(4-*tert*-butyl-1-cyclopenten-1-yl)-carbonyl]morpholine (**15**)	200[c]	10	2 M HCl	4-*tert*-butyl-1-cyclopentene-1-carboxylic acid (**14**)	70[b]	33
12	PhCN (**16**)	250[a]	60	water	PhCONH$_2$ (**17**) + PhCOOH (**18**) (5:4)	79[d]	
13	PhCN (**16**)	280[a]	60	water	PhCONH$_2$ (**17**) + PhCOOH (**18**) (1:1)	88[d]	
14	PhCN (**16**)	280[a]	360	water	PhCONH$_2$ (**17**) + PhCOOH (**18**) (1:25)	94[d]	
15	*n*-octanonitrile (**19**)	290[a]	60	water	*n*-octylamide + *n*-octanoic acid (**20**) (1:1)	29[d]	
16	*n*-octanonitrile (**19**)	290[a]	360	water	*n*-octylamide + *n*-octanoic acid (**20**) (1:18)	63[d]	
17	*n*-hexyl acetate	295[a]	180	water	hexanol + acetic acid	94[d]	
18	*n*-pentyl benzoate	298[a]	180	water	*n*-pentanol + PhCOOH (**18**)	84[d]	
19	PhCOOCH$_2$Ph	250[a]	60	water	PhCH$_2$OH + PhCOOH (**18**)	98[d]	
20	PhOCH$_2$CH=CH$_2$ (**21**)	240[c]	10	water	2-allylphenol (**22**)	84[b]	33
21	PhOCH$_2$CH=CH$_2$ (**21**)	245[a]	60	water	**22** + **24** + **25** (3:2:1.5)	98[d]	28
22	PhOCH$_2$CH=CH$_2$ (**21**)	250[c]	60	water	2-methyl-2,3-dihydrobenzofuran (**25**)	72[d]	28
23	PhOCH$_2$CH=CH$_2$ (**21**)	248[a]	10	0.4 M NaOH	2-(prop-1-enyl)phenols (**26** and **27**) (1:3.5)	77[d]	
24	PhOCH$_2$CH=CH$_2$ (**21**)	200[a]	60	1.29 M NaOH	2-prop-1-enylphenols(**26** + **27**) + *cis*-prop-1-enyl phenyl ether (5:3)	60[d]	
25	(*S*)-(+)-isomer of carvone (**7**)	210[c]	10	water	(*S*)-(+)-8-hydroxy-*p*-6-menthen-2-one (**28**)	21[b]	
26	8-hydroxy-*p*-6-menthen-2-one (**28**)	230[c]	10	water	carvone (**7**) + carvacrol (**6**) (1:1)	66[d]	
27	phenylacetylene (**29**)	280[a]	60	0.5 M H$_2$SO$_4$	PhCOMe (**30**)	90[b]	
28	geraniol (**31**)	220[c]	10	water	linalool (**33**); α-terpineol (**34**); monoterpene hydrocarbons (1:1:3)	91[d]	34
29	linalool (**33**)	220[c]	10	water	α-terpineol (**34**); monoterpene hydrocarbons (1:30)	89[d]	34
30	1-ethynyl-1-cyclohexanol (**42**)	290[a]	60	water	1-acetyl-1-cyclohexene (**44**)	45[b]	
31	1-ethynyl-1-cyclohexanol (**42**)	200[a]	60	water	1-acetyl-1-cyclohexene (**44**)	6[d]	
32	1-ethynyl-1-cyclohexanol (**42**)	200[a]	60	0.1 M NaOH	cyclohexanone	76[d]	
33	2-phenyl-3-butyn-2-ol (**43**)	200[a]	60	water	3-phenyl-2-butenaldehydes (**45** and **46** in the ratio 2:3)	34[b]	
34	1-phenylprop-1-yne	280[a]	60	0.1 M H$_2$SO$_4$	EtCOPh	80[b]	
35	1-heptyne	280[a]	60	0.5 M H$_2$SO$_4$	*n*-heptan-2-one	78[d]	
36	PhCHO	290[a]	60	0.1 M NaOH	PhCOOH (**18**) + PhCH$_2$OH (1:1)	56[d]	

[a] Autoclave heating. [b] Isolated yield of purified product. [c] MBR heating. [d] Conversion based on GC peak areas. [e] Conversion based on GC peak areas, adjusted to allow for nonvolatile components, mass balance discrepancies, or differences in molecular weight for individual components, as applicable. For some structures, see Figure 1.

man[40] reactions and Claisen rearrangements of allyl vinyl ethers.[41] Such reactions are facilitated by hydrophobic effects,[42] brought about by the tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon–water interfacial area. At high temperature though, hydrophobic effects diminish along with the disruption of hydrogen bonding in water[43] and would have been insignificant under the conditions employed in this work. Therefore, reactions were conducted to explore other potential benefits from high-temperature aqueous media, including lower levels of catalyst than would normally be required or, preferably, no addition of catalyst.

Such advantages were demonstrated for the aldol condensation, which is a valuable procedure for carbon–carbon bond formation, but presents problems associated with reversibility and lack of selectivity.[44–46]

We required 3-methylcyclopent-2-enone (**1**; for some structures, see Figure 1) in high purity, on the hundreds of gram scale for other work. Ketone **1** can be prepared by intramolecular aldol condensation of 2,5-hexanedione (**2**), and published preparations have used aqueous base at reflux, sometimes in the presence of an organic solvent.[47] Concentrations of alkali metal hydroxide ranging from 1 to 20% have been tried, along with reaction times between 15 min and 20 h. However, the yield has usually been moderate and the product contaminated with starting material, which has proved difficult to separate.[47]

Katritzky *et al.* reported that **2** did not react in water, even after 1 h at 250 °C.[5] Our results were consistent with this, but we also found that in 0.013 M (*i.e.* 0.05%) aqueous NaOH, within 15 min at 200 °C, dione **2** afforded enone **1** in high yield (entry 1, Table 1).[48] This relatively

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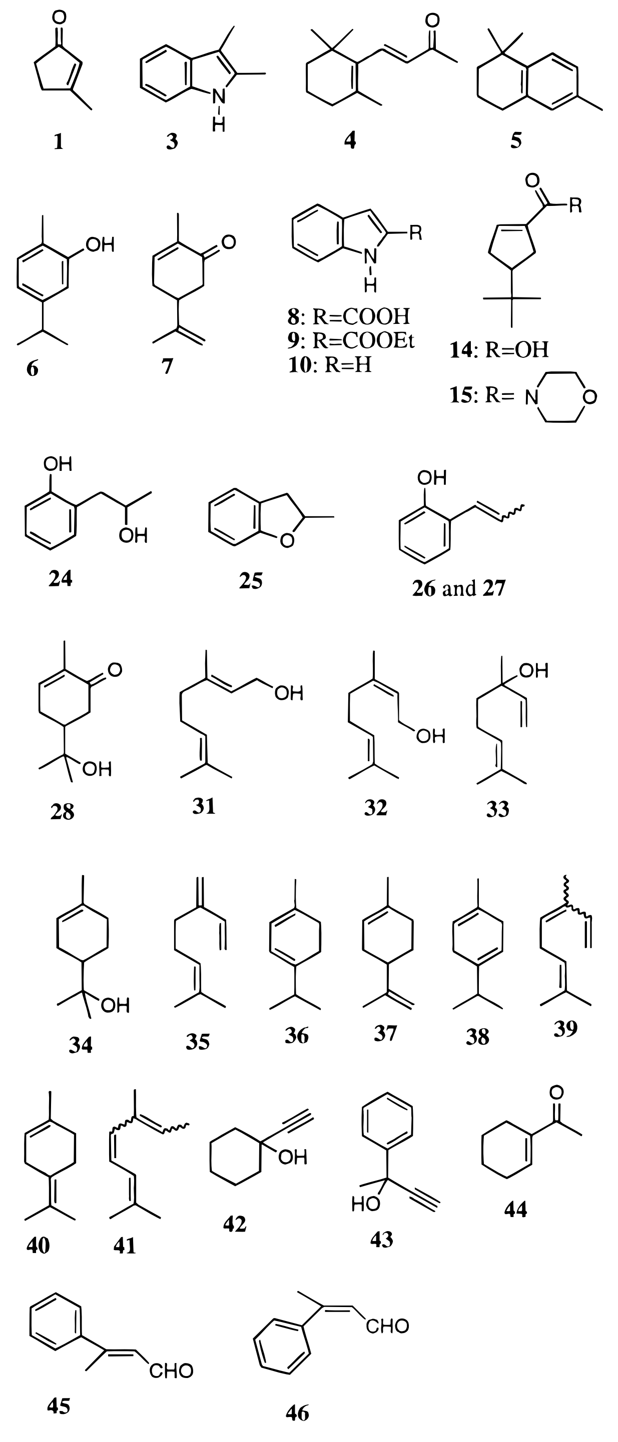

Figure 1. Structures referred to in this work.

subtle change in the medium indicates that although base was required for reaction to occur, only a trace was necessary to give an outcome clearly better than that obtained from conventionally heated processes employing 20−400 times more concentrated hydroxide and lower temperature.[47] Significantly, in 0.013 M aqueous NaOH at reflux, the condensation did not proceed as cleanly as it had at higher temperatures in less time. After 18 h, the conversion was only 57%, and considerable polymeric material was present. The synthetic utility of the high-temperature method was confirmed when the reaction was successfully conducted on the 250 g scale in a 3 L autoclave.[48]

In other examples, a one-step Fischer indole synthesis of 2,3-dimethylindole (**3**) was obtained from phenylhydrazine and butanone under optimal conditions at 222 °C for 30 min (entry 2, Table 1).[27] Although such syntheses have been reported in organic solvents without added catalyst,[49] and in the presence of mineral acids,[50] this appears to be the first example of the reaction in unacidified water. Also, in an unoptimized reaction, β-ionone (**4**) cyclized to ionene (**5**) with 30% conversion in water at 250 °C for 20 min (entry 3, Table 1).[34] As distinct from an established literature method,[51] addition of catalyst was not required and exhaustive washing was not necessary in the isolation step.

Isomerization. For an industrial project we required carvacrol (**6**), which Sattar *et al.* had prepared in moderate yield by heating an acidified aqueous mixture of carvone (**7**) on a steam bath for several hours.[52] We had previously employed aqueous conditions at temperatures of about 170 °C for this reaction, but added emulsifying agent to assist in phase transfer.[35] The conversion, although high, was incomplete. We now report that **7** isomerized almost quantitatively to **6** in water at 250 °C, within 10 min (entry 4, Table 1). This facile procedure thus improved upon earlier methods, through higher conversion, and in avoidance of added acidulant and emulsifying agent. At lower temperatures, addition of water across the 8,9-double bond of **7** occurred instead of aromatization, and this aspect is discussed below.

Decarboxylation. Indoles unsubstituted in the 2-position have been prepared by classical routes requiring removal of a 2-carboxyl group. Decarboxylation has been achieved by several methods, including pyrolysis, or heating with various derivatives of copper, in quinoline.[53] Difficulties usually have involved decomposition of the product during lengthy thermolysis or purification and have even led some workers to turn to multistep decarbonylative processes instead.[54]

However, in a simple procedure, indole-2-carboxylic acid (**8**) was quantitatively decarboxylated after 20 min at 255 °C in water (entry 5, Table 1). Conversely, 2-carbethoxyindole (**9**) underwent low conversion to indole (**10**) under these conditions (entry 6, Table 1). The presence of only traces of **8** in the product mixture indicated that ester hydrolysis was rate-limiting.[27] Reactivities of **8** and **9** were also investigated in aqueous base at high temperature. High selectivities were obtained under carefully controlled conditions. In 0.2 M NaOH solution, ester **9** underwent hydrolysis at 200 °C to afford acid **8** within 10 min (entry 7, Table 1). However, at 255 °C within 20 min, ester **9** hydrolyzed to give acid **8**, which decarboxylated to produce indole (**10**), also in excellent yield (entry 8, Table 1).

Analogously, after 1 h at 250 °C in water, ethyl cinnamate (**11**) afforded cinnamic acid (**12**; entry 9, Table 1), but after 6 h at 290 °C ester **11** had hydrolyzed, and the product acid **12** had decarboxylated to give styrene (**13**; entry 10, Table 1).

Hydrolyses. Tertiary amides can be difficult to hydrolyze, owing to steric factors and/or low solubility. Unsurprisingly, 4-*tert*-butylcyclopent-1-enoic acid (**14**) was obtained in only 48% yield from its morpholide derivative **15** after refluxing for 4 h in 2 M HCl.[55]

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However, at 200 °C in 2 M HCl, acid **14** was obtained in higher yield after only 10 min (entry 11, Table 1). Significantly, the MBR was used for this preparation, its wettable components being fabricated from PTFE and quartz,[33] thereby precluding corrosion of stainless steel fittings by chloride ions.[30]

Katritzky and his co-workers found that, in water at 250 °C for 5 days, benzonitrile (**16**) and benzamide (**17**) each afforded benzoic acid (**18**) as the major product, with amide **17** accounting for the bulk of the remaining material.[20] This indicates that acid **18** and amide **17** were in equilibrium. In the present work, benzonitrile (**16**) was heated in water for 1 or 6 h. At 250 °C, after 1 h, amide **17** was the major product (entry 12, Table 1). At 280 °C, the ratio of **18** to **17** was near unity after this time (entry 13, Table 1), but 25:1 in favor of the acid after 6 h (entry 14, Table 1). These results suggest that selective conditions could be found for each hydrolytic step, if required. In an aliphatic example, *n*-octanonitrile (**19**) was hydrolyzed more slowly than was benzonitrile (**16**), possibly owing to lower solubility in water (entries 15 and 16, Table 1). Amide formation appeared to be rate-limiting, on the path to *n*-octanoic acid (**20**).

The esters hexyl acetate, pentyl benzoate, and ethyl cinnamate (**11**) all hydrolyzed to significant extents in water within 1−3 h at 250−300 °C (entries 9, 17−19, Table 1). As hydrolysis progressed, the liberated acids would have been expected to autocatalyze the reactions.[5]

When heat is necessary for a reaction to proceed, but the product is thermally labile, it is essential to remove that compound from the energy source as soon as possible afterward. Microwave heating can be beneficial in this regard, and the hydrolysis of polysaccharides with dilute sulfuric acid is illustrative. High temperatures were necessary for cleavage of glycosidic linkages, but the monosaccharides and oligosaccharides produced were susceptible to decomposition under the conditions. In the optimal conditions found, the temperature was raised from ambient to 215 °C within 2 min, maintained at 215 °C for 30 s, and then rapidly decreased to 50 °C. Only 1 min was spent above 200 °C.[27]

Claisen Rearrangement. Although White and Wolfarth[56] found that the reaction rate of the Claisen rearrangement was enhanced in polar solvents, Grieco *et al.*[41] were first to demonstrate the benefits of water for the rearrangement of allyl vinyl ethers, at moderate temperatures. In our work, allyl phenyl ether (**21**) was heated in water at 200 and 240 °C, respectively, for 10 min.[33] Only 10% conversion to 2-allylphenol (**22**) was obtained at the lower temperature, but this increased to 84% at 240 °C (entry 20, Table 1). To our knowledge this was the first example of a Claisen rearrangement of an allyl aryl ether in water. In a subsequent indepth study, ether **21** was found to be relatively unreactive at 180 °C and below after a reaction time of 1 h.[28] With increments in temperature, however, **21** gave the *ortho* Claisen rearrangement product **22**, and then an array of other compounds including phenol (**23**), 2-(2-hydroxyprop-1-yl)phenol (**24**), 2-methyl-2,3-dihydrobenzofuran (**25**), and *cis*- and *trans*-2-(prop-1-enyl)phenols (**26** and **27**). A pathway was proposed, in which dihydrobenzofuran **25** was recognized as the thermodynamic product (entries 20−22, Table 1).[28]

Conversely, neat ether **21** rearranged to the phenol **22** almost exclusively, even at 290 °C. In the absence of water, **22** exhibited enhanced stability, presumably because it was not sufficiently acidic to readily promote autocatalytic reactions.[28] These results indicated that water facilitated tandem processes which culminated in the formation of dihydrofuran **25** from ether **21** (entry 22, Table 1).

We have now treated **21** in aqueous base at high temperature. With dilute NaOH (0.4 M) at 248 °C for 10 min, the ether presumably rearranged to **22**. Obviously this product could not undergo acid-catalyzed reaction under the conditions. Allylic rearrangement of the side-chain double bond occurred instead, and the isomeric 2-(prop-1-enyl)phenols (**26** and **27**) were obtained in 77% conversion, with the *trans* isomer predominating (entry 23, Table 1). Higher strength base (1.29 M) and lower temperature (200 °C) were employed to retard Claisen rearrangement and promote enol ether formation. Although the rationale was partially reflected by the outcome, the conversion and selectivity were only moderate (entry 24, Table 1). At lower temperatures, the extent of reaction was less because of poor solubility of **21** in the aqueous medium. Addition of phase-transfer catalyst had little effect. As the aqueous conditions were inappropriate for allylic rearrangement of **21**, treatment with methanolic KOH (1.7 M) at 170 °C for 60 min facilitated solubility and gave *cis*-1-propenyl phenyl ether in 45% conversion, contaminated only by traces of the isomeric 2-(prop-1-enyl)phenols (**26** and **27**).

Addition of Water to Alkenes and Dehydration of Alcohols. At elevated temperature, hydration of some olefins occurred readily, without the addition of catalyst. In such cases, equilibria were rapidly established but conversions were usually low. For example, treatment of the (*S*)-(+)-isomer of **7** in water for 10 min at temperatures between 180 and 250 °C afforded 8-hydroxy-*p*-6-menthen-2-one (**28**) as an intermediate on the pathway to carvacrol (**6**; entries 25 and 26, Table 1). Addition of water to the 8,9-double bond of **7** proceeded at lower temperature than did aromatization, was regioselective, and accorded with the Markovnikov rule. This was suggestive of an ionic mechanism and was consistent with the conclusions of Katritzky and Siskin for other reactions in superheated water.[4] An increase in the reaction time to 30 min had a minimal effect on the product distribution at 180 °C, indicating that an equilibrium between **7** and **28** was rapidly established.

As evidenced by the high optical purity of **28**, racemization had not occurred during the hydration step. This was predictable on mechanistic grounds, and corresponded with results of Buchi and Wuerst for the acid-catalyzed hydration.[57] In high-temperature water, the conversion of **7** to **28** was lower than that obtained in concentrated acid at ambient,[57] but the reaction time was far shorter (*i.e.* 10 min instead of 43 h). Since the product was readily isolable by differential extraction from the recyclable starting ketone, the reaction of carvone with water could be considered as a clean, simple, and practical synthetic route to **28**, in spite of the low conversion.

Formation of 2-(2-hydroxyprop-1-yl)phenol (**24**) as a kinetic product from allyl phenyl ether (**21**) or 2-allyl phenol (**22**) in high-temperature water has been discussed elsewhere.[28]

Although an aqueous environment may not seem convenient for elimination of the elements of water from alcohols, such transformations proceed well at high temperature. The formation of cyclohexenes from cyclo-

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hexanols was recently reported,[30] and we have presented other examples.[28,34]

Manufacture of alcohols by direct addition of water to olefins was considered 60 years ago at least, but calculations of the thermodynamics indicated that hydration was favored by low temperatures and high pressures, and that acceptable yields would only come about with catalysis.[58] The present results indicate that addition of water to olefinic bonds, and elimination of it from alcohols, can be facile under aqueous conditions at high temperature and under pressures up to 50 atmospheres, sometimes even in the absence of added acid or base. Clearly though, potential practical applications would require satisfactory conversions, and these depend on the position of equilibria, as well as on efficient and selective methods for removal of products.

Addition of Water to Alkynes. Katritzky *et al.* heated phenylacetylene (**29**) in water at 250 °C for up to 5 days.[14] Their best reported result showed acetophenone (**30**) in 51% conversion, along with dimeric and trimeric condensation products. Later, Jerome and Parsons[37] heated alkynes in supercritical water for up to 2 h. When catalyst was absent, they completely recovered starting 1-hexyne and 2-butyne, but obtained some low molecular weight oligomers from **29**. Acid-catalyzed hydrolysis of the alkynes to ketones occurred in the presence of acidic metal salts, such as $CuCl_2$ and $SnCl_2$.[37]

In the present work, dilute aqueous acid facilitated addition of water to alkynes, affording the corresponding ketones in moderate to high conversions (entries 27, 34, and 35, Table 1). By contrast with the addition of water to olefins, hydration of alkynes was not readily reversible. From the high regioselectivity of these reactions, initial protonation of the alkyne groups accorded with the Markovnikov rule.

Multiproduct Reactions. Synthetic procedures aim to deliver single substances in high yield. However, in the flavor and fragrance field, complex mixtures of volatiles can enhance the sophistication of products, increasing their appeal and hence their value. In those circumstances it may be desirable to form a broad array of compounds from a single starting material, provided that a consistent product distribution could be obtained. Water has potential in this regard, mainly because of enhanced solvent properties and greater dissociation at high temperature.

Geraniol (**31**), nerol (**32**), and linalool (**33**) have low solubility in water at ambient temperature. These terpenols are acid labile, but do not readily react at moderate temperature and neutral pH.[59] However, in unacidified water at 220 °C, **31** readily rearranged to α-terpineol (**34**) and linalool (**33**) and gave lesser amounts of the monoterpene hydrocarbons, myrcene (**35**), α-terpinene (**36**), limonene (**37**), γ-terpinene (**38**), the ocimenes (**39**), α-terpinolene (**40**), and alloocimenes (**41**; entry 28, Table 1).[34] Nerol (**32**; data not included in Table 1) and linalool (**33**) underwent considerably more elimination of water and hence afforded substantially less of the isomeric monoterpene alcohols than did geraniol (**31**), and a greater proportion of the above array of hydrocarbons (entry 29, Table 1). The major components and their relative proportions were consistent with those previously reported for the carbocationic rearrangement chemistry of derivatives of terpenols **31**, **32**, and **33** under acidic conditions at lower temperature.[60] Additionally, the product distribution from **31** was similar to that from acid-catalyzed degradation of naturally occurring linalyl and geranyl glycosides in fruit juices and wines.[61] These experiments showed that high-temperature water was a useful medium for biomimetic reactions, precluding requirements for addition of acid and derivatization of the starting materials with typical solubilizing groups such as phosphate esters or glycosidic units.

Rupe and Meyer−Schuster Rearrangements. The behavior of other potentially reactive molecules was next investigated. 1-Ethynyl-1-cyclohexanol (**42**) and 2-phenyl-3-butyn-2-ol (**43**) were appropriate since each possessed two functionalities (the hydroxyl group and the triple bond) that had been found to be susceptible to high-temperature aqueous conditions. At 290 °C for 1 h, alcohol **42** underwent Rupe rearrangement,[62] affording 1-acetylcyclohex-1-ene (**44**) in moderate yield (entry 30, Table 1). Even at 200 °C the same product predominated, although the conversion was low (entry 31, Table 1). At 290 °C acetylcyclohexene **44** was accompanied by small amounts of cyclohexanone derived from a retro-aldol type reaction and ethylbenzene probably resulting from elimination of water from the starting material, and aromatization. A literature rearrangement of 1-ethynyl-1-cyclohexanol (**42**) was conducted in refluxing 90% formic acid to give acetylcyclohexene **44** in 49% yield.[63] In the present work, only water was required, and at 290 °C within a comparable time, the yield was similar (*i.e.* 45%). However, at 200 °C, the Rupe rearrangement of **42** did not occur in dilute base. Elimination of acetylene proceeded instead, with cyclohexanone accounting for 76% of the product distribution (entry 32, Table 1).

Butynol **43** in water underwent Meyer−Schuster rearrangement[62] at 200 °C to give the 3-phenylbut-2-enaldehydes (**45** and **46**; in a *trans*/*cis* ratio of 2:3) predominantly, along with a small amount of **30** from retro-aldol reaction, and polymeric materials (entry 33, Table 1). Apparu and Glenat obtained a mixture of aldehydes **45** and **46** at subambient temperatures under acidic conditions but found that, at room temperature, the reaction was uncontrollably exothermic and only gave resin.[64] This result supports earlier conclusions that, for certain syntheses, elevated temperatures can provide an attractive alternative to the use of aggressive reagents at lower temperatures.[27,28,33,35]

Conclusion

Under high-temperature aqueous conditions, preparative methods were developed for the isomerization of carvone (**7**) to carvacrol (**6**; 95% yield), hydration of phenylacetylene (**29**) to acetophenone (**30**; 90% yield), Fischer synthesis of 2,3-dimethylindole (**3**; 67% yield), aldol condensation of dione **2** to 3-methylcyclopent-2-enone (**1**; 81% yield), decarboxylation of indole-2-carboxylic acid (**8**; quantitative), and formation of acetylcyclohexene **44** by the Rupe rearrangement of ethynyl-

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cyclohexanol **42** (45% yield). The applicability of high-temperature water also was demonstrated for biomimetic processes important in food, flavor, and aroma chemistry and for tandem reactions, such as those involving formation of dihydrobenzofuran **25** from ether **21** (72% conversion).

When addition of acid or base was necessary, less agent was usually required for high-temperature processes than for those at and below boiling, and the reactions often proceeded more selectively. In some instances the requirement was orders of magnitude lower, with obvious consequences for safe, economic processing and for lowering costs of effluent disposal.

As anticipated, water played different roles for given reactions. It acted as a solvent or medium for the *ortho*-Claisen rearrangement of ether **21** at 240 °C in 10 min (entry 20, Table 1) and the decarboxylation of carboxylic acid **8** (entry 5, Table 1). Clearly, it participated in hydrolyses of nitriles and esters, as well as in hydration of carbon−carbon double and triple bonds. It may have been both a catalyst and a medium for dehydration reactions in the absence of added acidulant, the cyclization of **4** (entry 3, Table 1), and the Fischer indole synthesis (entry 2, Table 1). It facilitated the tandem reaction sequence that afforded dihydrobenzofuran **25** from allyl phenyl ether (**21**) at 250 °C in 1 h (entry 22, Table 1).

In contrast with the alkene−arene coupling demonstrated by Parsons and co-workers,[32] our efforts have concerned mainly (but not exclusively) reactions involving single compounds, rather than those involving two or more different organic molecules. Furthermore, most examples in Table 1 regarded transformations of compounds containing a limited number of potentially reactive functional groups. This reflects the fledgling status of the field, and there is obviously considerable scope for broadening investigations. Nonetheless, the diversity of reactions discussed above, and the successful scale-up of an aldol condensation, indicate that high-temperature aqueous media could play an increasingly important role in the development of new preparative processes, for industrial as well as laboratory purposes.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR, EIMS, and GC analyses were carried out as previously described.[65] Authentic compounds were purchased if possible and synthesized when necessary. Spectral and other physical data for these materials agreed with literature values.

Apparatus and Methodology. The MBR has been previously described.[33] The stainless steel laboratory-scale autoclave, of maximum capacity 500 mL, was equipped with a magnetic stirring facility, thermocouple, pressure gauge, U-tube for cooling, over-pressure relieving rupture disk, and a pressurized tube for sample introduction. Reactions were generally conducted in a stainless steel liner, which reduced the effective volume of the heated zone to 400 mL. Heating was carried out electrically through a jacket attached to the outer wall. The upper operating temperature of the autoclave exceeded 300 °C. The system had considerable thermal inertia, owing to its high mass (8.5 kg), and temperatures of 200 °C and above were obtained from ambient only after heating for many minutes. Stirring was carried out by a rotating permanent magnet directly under the autoclave, and this was coupled to a magnetic follower inside the liner.

Initially, the autoclave was loaded with aqueous medium (typically 50 or 100 g), sealed, evacuated, and prepressurized with argon. The reactant was placed in a tared vessel with valves at both ends. The lower valve was connected to an inlet tube on the autoclave, and the upper valve was used to pressurize the vessel with argon. Reactions were started by opening the relevant valves so that the reactant was fed into the autoclave by the greater argon pressure in the reactant injection vessel. Reactions were terminated by circulation of coolant through the U-tube inside the autoclave. The pilot-scale autoclave (3 L capacity), fabricated from stainless steel, was jacket-heated with circulating oil. It was equipped with a mechanical stirrer and pressure and temperature sensors, but had no capability for rapid postreaction cooling.

Carvone Reactions. Aqueous mixtures (50 mL) containing the (*S*)-(+)-isomer of carvone (**7**; 2 mL; 1.93 g) were heated in the MBR for 10 min, at temperatures between 180 and 250 °C, and then rapidly cooled by means of the cold finger within the vessel. The aqueous phase was saturated with salt, and the organics were extracted into Et_2O (4 × 20 mL; recovery >95%) and subjected to qualitative and quantitative analysis, by GC−MS and by NMR spectroscopy (*e.g.* entry 4, Table 1).

No reference sample of 8-hydroxy-*p*-6-menthen-2-one (**28**) was available. Keto alcohol **28** was isolated by flash chromatography on silica gel[66] of the pooled extract from several experiments, using *n*-hexane/Et_2O (10:3, then 2:1 v/v), followed by Et_2O, as eluents. The ^{1}H and ^{13}C NMR spectra of the isolated (*S*)-(+)-isomer of **28** were in close agreement with literature data[67] [$[\alpha]^{22}_{D}$ +41° (*c* 6.9) *cf.* lit.[57] −42°] for (*R*)-(−)-8-hydroxy-*p*-6-menthen-2-one derived from (*R*)-(−)-carvone. MS (EI): *m/z* (relative intensity) 150 (12), 110 (50), 95 (35), 59 (100). This material was used for microwave heated reactions of **28** in water at 230 °C (entry 26, Table 1).

Meyer−Schuster Rearrangement of 2-Phenyl-3-butyn-2-ol (43). Molten **43** (mp 47−8 °C) was placed in the heated injection vessel of the autoclave. Water (100 mL) in the autoclave was preheated to 195 °C, and **43** (8.7 g) was introduced in one batch. The temperature reached 200 °C within 2 min after addition of reactant and was held within ±2 °C of this value for 60 min. The reaction was quenched by circulating cold water through the cooling loop. At ambient temperature, the argon was vented and the autoclave opened. The contents were removed, the solids were filtered off, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined ether solution was dried over $MgSO_4$, and the solvent was removed *in vacuo*. The volatile products, predominantly (*E*)- and (*Z*)-3-phenyl-2-butenal (**45** and **46** respectively, in the ratio 2:3), were isolated by bulb-to-bulb distillation under reduced pressure (3.0 g; 34% yield). ^{13}C NMR[68] and ^{1}H NMR[69] spectra were in close agreement with literature values. MS (EI): *m/z* (relative intensity) 146 (M^+, 40), 145 (100), 131 (25), for compound **45**, and 146 (M^+, 42), 145 (100), 131 (25), for **46**.

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