

TOWARDS WATER-BORNE ORGANIC SYNTHESIS: AN EDUCATION IN CHEMISTRY RESEARCH

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Abstract. Though undeniably indispensable, organic synthesis has been unfortunately burdened with its toxicity facet. The use of an organic medium in this synthesis has made its toxic aspect acute and more fearful. Mostly, the public image vis-à-vis to chemistry has been awesome. Fortunately, this image is now being whitened as water is being thought as an organic medium surrogate, and comparative results are quite unexpected and even surprising. In this paper, a glance at some water-borne and on-water organic reactions is delineated, aiming at sweeping off and eradicating the general belief from minds: "*organic reactions work only or better in organic media*". Being acquainted with this new synthetic medium-related approach, one may dauntlessly and confidently present his chemistry to the public without any reservation.

Keywords: dispersions, aqueous media, organic reactions, water

ORGANIC SYNTHESIS, WHERE IT STANDS

At the close of 20th century and at the dawn of the 21st, would it be understandable and righteous to divulge that the outcome of organic synthesis is coming of age and reaching its zenith? Shall we assuredly and confidently assert by now that organic synthesis is at its apex? If not so, at what stage is its development standing? Shall we appraise its huge achievement as an embryonic, a halfway, or an in-between state? And, henceforth, more remains to be accomplished.

A retrospective scrutinizing look over the weighty and flourishing era of organic synthesis would make one fall into trance. Not only could the unprecedented applications of some organic molecules of robust architecture witness to the attained level of organic synthesis, but also the weighty and wealthy chemistry it created and used. As a mere consequence, it is of no surprise that one can be fond of synthetic chemists. Organic synthesis has grown at a more stupendous pace, due to the outburst of creativity and to the advent of technology overall. The literature is replete with a plethora of masterly review papers and accounts on this issue, which are but endorsing this witnessing. An epoch-making review paper is the one that appeared at the dawn of 21st century, elegantly penned by Nicolaou et al. [1]; the authors made a sound and *terse* analysis of the expansion of organic synthesis, from the Wöhler's urea synthesis to the remarkable and lively total syntheses, crossing the wonders of Woodward and Corey syntheses endeavors. The triumph of making the naturally occurring molecules of demonic, astounding and unusual structures such as Vitamin B₁₂ and CP molecules, may obviously lead to think that the organic synthesis science is drawing near its end. This feeling is not new, as one may read the Professor Herbert C. Brown's words [2], an eminent organic chemist of the 20th century: *'In 1938, when I received my Ph.D. degree, I felt that organic chemistry was a relatively mature science, with essentially all of the important reactions and structures known. There appeared to be little new to be done except the working out of reaction mechanisms and the improvement of reaction products. I now recognize that I was wrong. I have seen major new reactions discovered. Numerous new reagents are available to us....'*

That organic synthesis is an onerous and intricate task can be weighted by the indented track that the chemists strove in preparing *Quinine*; from the first attempt of William H. Perkin in 1856 to its complete synthesis by Gilbert Stork in 2000 [3], ending the culminating endeavors of the well-delved chemists. Avowedly and indubitably, the striking achievement in the multistep-faceted total synthesis is the synergism of the human sagacity and ingenuity, the sophisticated tools made available throughout, the abundance of reagents discovered throughout, and the new reactions set out throughout [4]. For the chemical synthesis work-up, the solvent is an inevitable component of the reaction recipe; the solvent-based organic reactions have been the easiest and the most studied ones. In fact, appropriately and judiciously chosen solvents play major roles in organic synthesis as they provide the homogenous phase for the reaction systems, promoting their feasibility, and ensuring faster kinetics and better yields. Unequivocally, the success of an organic reaction is partly due to its organic solvent-based liquid phase, obeying to the common belief: *corpora non agunt nisi soluta*, that is, substances do not interact unless dissolved, and *like needs (dissolves) like*. To recall a trivial example, the bimolecular nucleophilic substitution S_N2 occurs more favorably in organic polar aprotic solvents such as DMF, DMSO, and DMAc, com-

monly known as modern solvents. To circumvent the hampering immiscibility of aqueous and organic phases, a medium system for S_N2 in case of an ionic nucleophile, phase transfer catalysis (PTC) was ingeniously invented.

Needless to praise the immense contribution of synthetic organic chemistry to the human welfare and its near boundless influence on human actions, but this comes with a price tag of pollution. The uniqueness of the organic solvents in organic reactions is smeared with their cost and their *per se* toxicity, coupled with their volatility. Thus, the environment is deleteriously affected and a rallying call for mild surrogates is imposing and evident. It is incumbent on chemists at the academic level and the chemical industry to seek for friendly and benign solvents for the preservation of the environment. Fortunately, the chemists' commitments, awareness, and their expended efforts within the last few decades entail some hope and positive outlook.

WATER, A BLESSING MOLECULE!

With no reservation, we might assert that water is a divine molecule because it is ubiquitous (about 70% of Earth is covered with water, and the main component of all living things is water in nearly 80%) and the only substance that no one can fear. As known, it is the living molecule to which we usually resort; unequivocally, no drinking liquid can quench our thirst better than water. It is the natural and convenient medium for the occurrence of metabolic bio-reactions. For safer uptakes, and to name but a few pharmaceutical forms, most of the medication pills must be taken with a plenty of water.

Although the advent in science has indubitably outgrown and is by now and by no means an unshakable reality, the water molecule is still concealing mysteries and enigma, and ravel its roles and intricacies. For example, there is a need to understand the role that water plays in some electron-initiated process for diverse fields such as waste remediation and environmental cleanup, radiation processing, nuclear reactors, and medical diagnosis and therapy [5]. Water is unique by not only the following main parameters: 1) the floating ability of its solid form, 2) its larger heat capacity, 3) its high surface tension, and 4) its boiling and freezing points, but also its structure, although simple as it appears. Indeed, the peculiar properties of water is strongly related to its structure, and a hot and controversial debate about how tight is water bound, is going on. Two antagonist schools on this issue are led by Richard James Saykally (University of California, Berkely) and Anders R. Nilsson (Stanford Linear Accelerator Center, Stanford University). Some statements said about the water structure are but revealing [6]:

Anders Nilsson: *"It's amazing we don't really understand the structure of water. Liquid water has a structure totally at odds with what textbooks say and what scientists have believed for more than a century."*

Rustum Roy: *"People have ignored the possibility that liquid water can have multiple structures, but there is good evidence."*

William Titter: *"Water can indeed have its properties affected and hence its structure changed rather easily."*

Another everlasting event of water is its claimed *"memory effect"*. It is the explanation attributed to the results of studies that have shown that solutes subjected to dilution show biological effects different from those apparent using just the water employed for the dilutions [7]. This effect is otherwise defined by Professor Martin F. Chaplin as [8]: *"The 'memory effect' is a concept by which the properties of an aqueous preparation are held to depend on the previous history of the sample."* Truly, too much ink has been spilled for more than a decade, detracting its discovery and considering it a delusion, a non-science, and a mere heresy. Nowadays, it is being resuscitated and scientific evidence is rather surprisingly arising [8]. The impact of the meaning of a word or the type of a musical melody uttered in water on the crystal-line structure of its solid form is quite startling, as demonstrated by Dr. Emoto Masaru; nevertheless, scientists are still sceptical. Shall we stand as fans behind Dr. Jacques Benveniste and his collaborators, the initiators of this effect, and firmly assert that no scientific result should be underrated [9]? Because the subject seriously matters, the journal of Homeopathy devoted a special issue to *'the memory of water'* [10]. Professor Chaplin, one of the contributors to this issue, commented as follows: *"Science has a lot more to discover about such effects and how they might relate to homeopathy, as some scientists do, just because we don't have a full understanding of how it works."*

The new discovery made by South Korean researchers is that cluster size of solutes increased steadily with increasing dilution in water [11]. In contrast, no clustering of the molecules occurs in organic solvents. The solutes examined were cyclodextrin-fullerene complex, β -cyclodextrin by itself, sodium chloride, disodium guanosine monophosphate and a DNA oligonucleotide. The diameter of the clusters was found to increase from 0.55 nm at a starting concentration of 0.216 mM to 3.255 nm at 0.01mM.

Would the changes of the structure of water molecule, its hydrogen bond-structure relationship, its memory effect, and/or other properties not yet deciphered, account, at least partly, for the below effects of water in organic synthesis?

WATER IN MOLECULAR ORGANIC SYNTHESIS

Indeed, about two decades ago chemists began to retrieve the benefits of water as a lively substitute to the conventional solvents, as far as not only is the environment concerned but also the organic reaction outcome. Solventless or neat reactions, solid-state reactions, ultrasound and microwave-promoted aqueous reactions, reactions in

ionic liquids, and reactions in supercritical fluids (SCF) such as the supercritical CO₂ were also conceived as friendly alternatives. Synthetic chemists are indebted to Professor Ronald Breslow who first resuscitated the use of water as a medium in Diels-Alder (DA) reactions; he carried out the cycloaddition of cyclopentadiene with methyl vinyl ketone in water and found its rate to be unexpectedly enhanced by a factor of more than 700 compared with the reaction in isooctane [12]. Rather evidently, on seeing water daily before their eyes and being aware of its ubiquity and abundance, chemists would have been undoubtedly tempted or wished to use it as a medium, but the lingering belief of its man-created enmity for organic reactions impeded any attempt. However, switching to water should be deemed not as a significant achievement but a rational and normal return to the realm of life, that is, to follow the nature lead. Therefore, one should not be stunned by the fact that water-promoted *in vitro* organic reactions afford better results compared with those in organic solvents, as a startling number of *in vivo* organic reactions occur entirely in water. Fairly noting is that organic reactions were essentially realized in water a century ago, before the emergence of the afore-mentioned organic polar solvents.

Novel mechanistic views of water-mediated organic reactions are being elicited. In fact, new terms and new reactivity coupled with some new effects that are thought to be the promoting forces for the reactions course, has cropped up. Yet it is fair to mention that the development of these reactivity and effects owes to the chemistry already founded by the organic solvent-based synthesis. A new chemistry termed as "*Green chemistry*" or "*Sustainable chemistry*" has emerged [13,14] and water is unanimously viewed as a *greener solvent*. Of these effects are *hydrophobic effect*, *hydrophobic packing*, *antihydrophobic effect*, *pro-hydrophobic effect*, *dichotomous salts effect*, For example, the rate enhancement of a pericyclic reaction in water is explained by hydrophobic effect, stemming from the unique structure of water. Breslow noticed that lithium chloride (LiCl) and guanidinium chloride (GnCl) acted, respectively, as *pro*- and *anti*-hydrophobic agents in the cycloaddition reaction, otherwise termed as salting-out and salting-in agents; while the former promotes the water structure by increasing the number of hydrogen bonds and accelerates the reaction, the latter disrupts it and slows down the reaction. The high cohesive energy density (CED) of water (22,000 atm) exerts an external pressure on the organic reactants and, thus, lowering the transition state energies.

Organic reactions in water have mostly been performed using a cosolvent to engender some solubility. Today's status, the insolubility of organic reactants in water, once considered a drawback, turns out to be advantageously a leading factor for the success of organic reactions in pure water. In the present essay, the below-described examples are but a few of the many in-water reactions of the wealthy literature [15-17]. In 2005, Sharpless coined "*on-water*" to this type of heterogeneous reactions [18]. He carried out some pericyclic reactions (one of the many examples is

shown in Eq.1) in aqueous suspension (on-water systems) and found that both kinetics and yields were extremely enhanced in most cases, compared with those in organic solvents. Quite interesting is that a protic organic solvent (MeOH) is better than a nonprotic one (toluene, CH₃CN, DMF) as shown in Table 1.

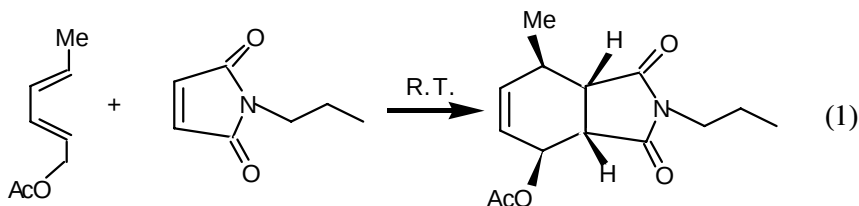
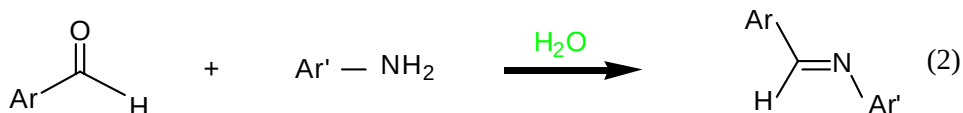


Table 1. Experimental results of the cycloaddition of Eq. 1.

Solvent	Time (h)	Yield (%)
Toluene	144 (6 days)	79
CH ₃ CN	> 144	43
MeOH	48	82
H₂O	8	81

Before Sharpless' work, "on-water" strategy was already employed by Tanaka and Shiraishi in making Schiff's bases (N-substituted imines) (Eq.2) [19]. The latter substances have customarily been prepared by condensing aromatic aldehydes with aromatic amines in organic solvents under azeotropic conditions to eliminate the water formed. The features of this "on-water"-run reaction were the non-use of acid catalyst, an efficient product isolation by simple filtration, a quantitative yield (higher than 86%), and a lower reaction time (≤ 3 h). Adversely, the analogous reactions in benzene afforded lower yields after several hours.

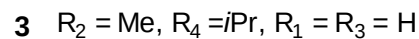
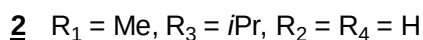
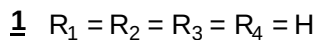
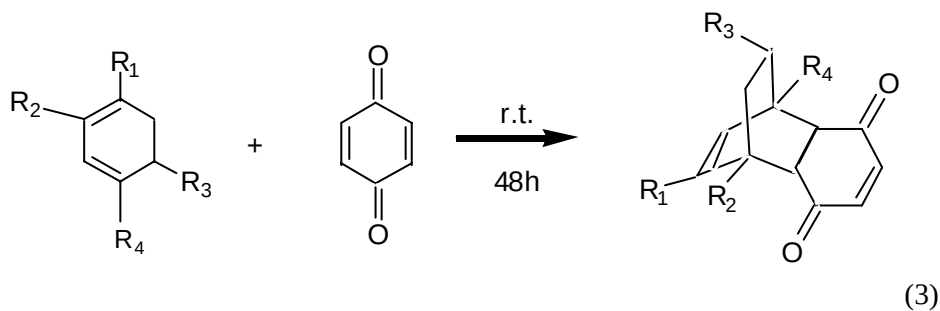


The DA reactions in water have been widely studied and coherent explanations were advanced for the unexpected results [20]. Comparison of the rates of reaction of some substituted naphthoquinones with cyclopentadiene in water with those in *n*-hexane was reported [21]; water was found to accelerate the DA reactions 1180-12780 times than *n*-hexane. The hydrophobic effect and the hydrogen bonding of water were thought to account for these results. A common observation is that, in contrast to the reaction in organic solvents, the water-based DA reactions proceed with higher *endo/exo* selectivities [22,23]. For example, the DA reaction of vinyl methyl ketone with cyclopentadiene yielded the Diels-Alder adduct with an *endo/exo* ratio higher in water than in methanol and *n*-butanol [21]. Besides, the thermodynamic parameter $\Delta G^\ddagger$ (Gibbs energy of activation) was found to be about 10-15 kJ/mol greater in water than in *n*-propanol. A quite featuring is that even the retro-Diels-Alder reactions proceeded much faster in water than in classical media [24].

The DA reactions of the cyclohexa-1,3-diene **1** and two of its derivatives, α -phellandrene **2** and α -terpene **3**, with 1,4-benzoquinone, Eq. 3 [25] showed hydrophobic and steric hindrance effects on yields. Still, water promoted better reaction yields than did the organic solvent (toluene) as illustrated in Table 2.

In the case of the cyclohexa-1,3-diene **1**, the yield and the reaction time were improved to 83% and 20 h, respectively, using Ti(IV) Lewis acid as a catalyst [26].

The occurrence of a hydrophobic packing of the diene and the dienophile in the transition state would account for the greater yields of the water-promoted DA reactions, particularly in the case of **1**. However, the relatively lower yields in the case of **2** and **3** were imputed to the steric interactions imposed by the methyl and the *isopropyl* radicals, disfavoring the packing phenomenon. Examination of the effects of NaCl (a salting-out additive) and GnCl (a salting-in additive) showed distinct acceleration and retardation, respectively, for **3**.



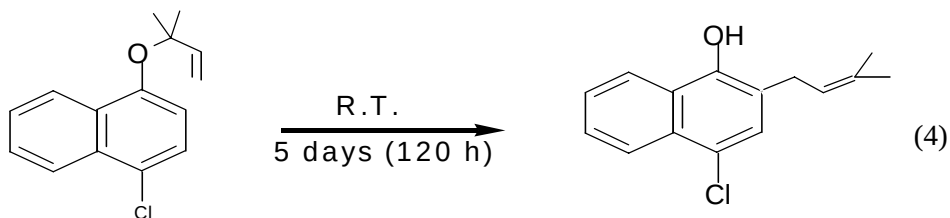
Sharpless extended the "on-water" protocol to the Claisen rearrangement of the naphthyl ether (Eq. 4) and noticed a higher yield and an accelerated reaction rate at ambient temperature, compared with the reactions in organic solvents (Table 3) [18].

Table 2. Yields (%) of the DA reactions of cyclohexadienes with 1,4-benzoquinone

	H ₂ O	Toluene
<u>1</u>	67	15
<u>2</u>	27	15
<u>3</u>	28	3

Table 3: Results of the Claisen rearrangement

Solvent	Yield (%)	Time (h)
Toluene	16	>>120
DMF	21	>>120
H ₂ O	100	120



A far-reaching challenge of the water as a medium surrogate resides in the realization of the non water-tolerating organic reactions in aqueous systems. In fact, one of the reasons for avoiding water is its reaction with some reactants or products and its poisoning ability by annihilating the activity of a catalyst, thus very tight measures must be adequately taken. For example, Grignard-type reactions are very water-sensitive and require stringently anhydrous conditions; a trace of moisture inhibits the reaction course.

Water, a by-product of esterification reaction, hydrolyzes the ester formed unless it is continuously removed by distillation or by a dehydration process; thus, the esterification in water was unconceivable. Propitiously, new approaches have made these reactions and others very plausible to occur in aqueous media. Indeed, the use of a Brønsted acid-surfactant-combined catalyst (BASC) such as dodecylbenzenesulfonic acid (DBSA), secured the esterification in water as depicted in Eq. 5 [27]; DBSA provides both the acid catalysis via the sulfonic group and the micellar organic core (emulsion droplet) for the ester formed via the hydrophobic segment (surfactant-type structure) as illustrated in Fig. 1. Water molecules formed during the esterification are displaced from a droplet due to the hydrophobic nature of its core, hence the equilibrium is shifted towards the ester product. DBSA was also employed to effect the etherification and thioetherification in water and the yields were quantitative at a temperature of 80 °C and a time of 24 h.

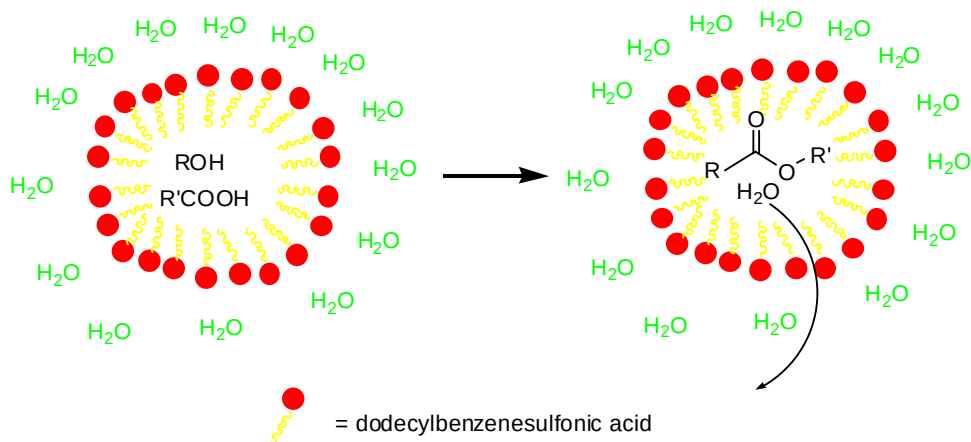
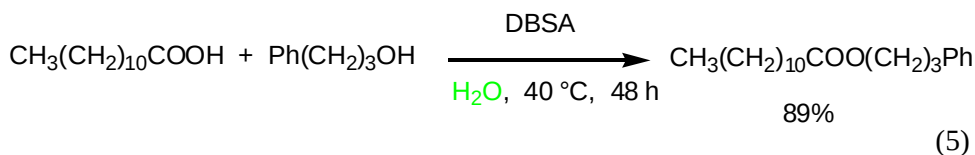
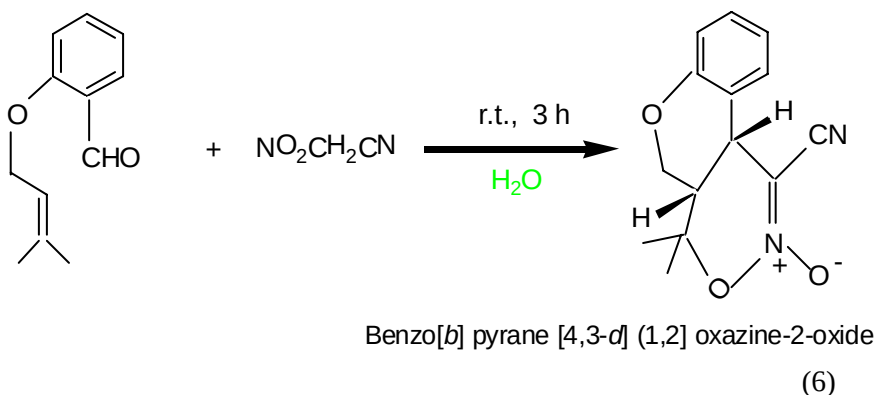
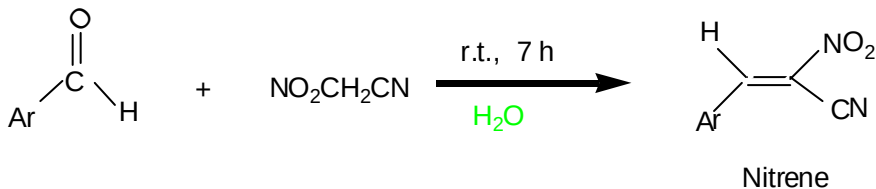


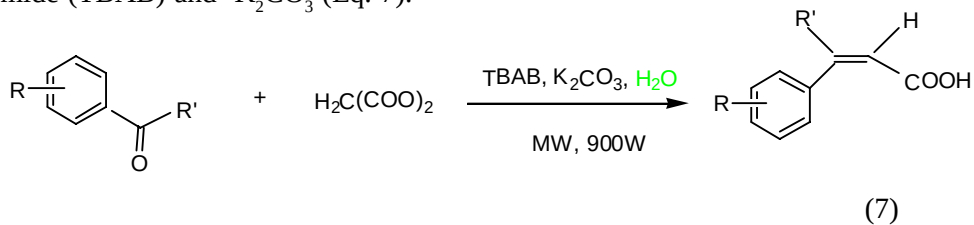
Fig. 1. Depiction of the esterification course in water in the presence of DBSA.

Many condensation reactions other than the esterification have been successfully attempted in water. Knoevenagel condensation of aryl aldehydes with nitroacetonitrile in water (first reaction of Eq. 6) afforded nitrenes in higher yields, 88-95%. This reaction protocol was featured by: 1) being a one-pot procedure, 2) yielding

an exclusive diastereoselectivity (only *E* was formed), 3) the non-use of a catalyst, and 4) the re-usability of the water medium (almost four runs giving appreciable yields) [28]. Following this strategy, benzo[*b*] pyrano [4,3-*d*][1,2] oxazine-2-oxide with a higher *cis* epimer, a more complex molecule, was synthesized in 60 % via a Knoevenagel-Diels-Alder domino process (second reaction of Eq. 6).

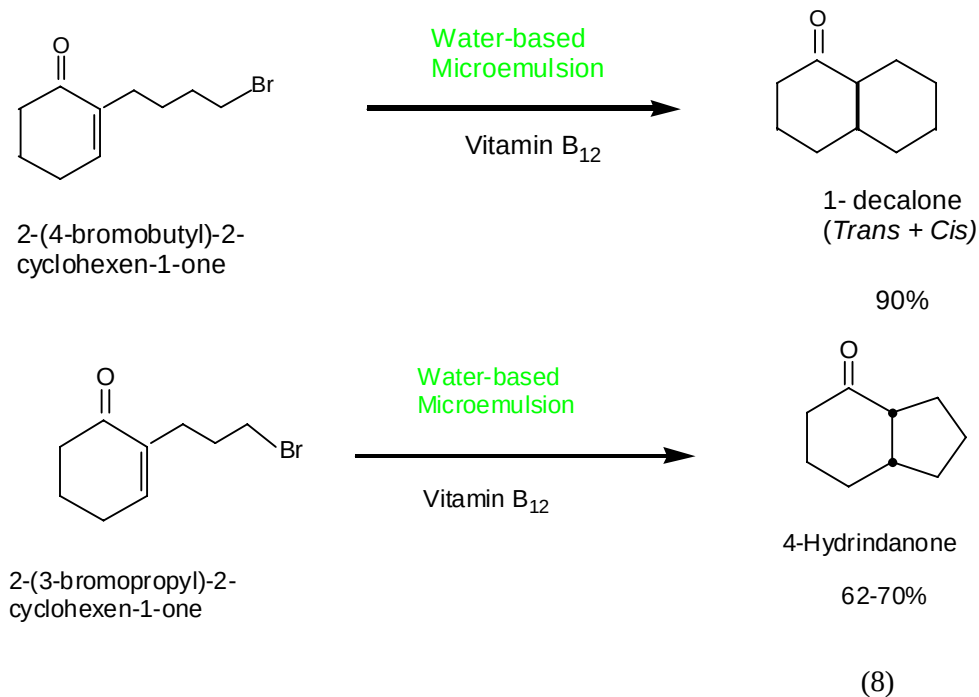


Also, a series of cinnamic acid derivatives were prepared in quantitative yields (> 70%) within shorter reaction times (< 8 min) by means of Knoevenagel condensation in water using microwave (MW) irradiation [29]; the reactions involved aromatic aldehydes or ketones and malonic acid in the presence of tetrabutylammonium bromide (TBAB) and K_2CO_3 (Eq. 7).

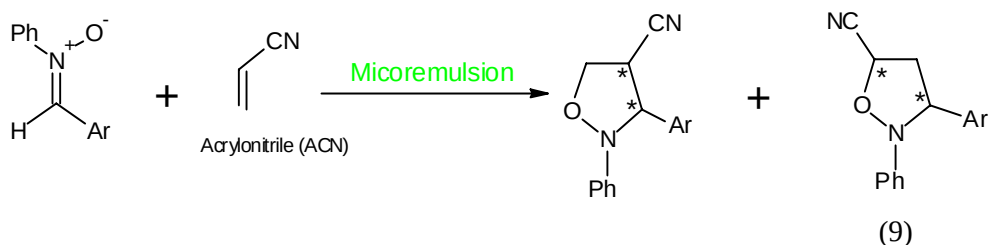


The O/W microemulsion, a highly ordered water-borne medium, has been exploited in organic synthesis and neat differences from the ordinary reactions were observed [30]. Electrosynthesis or organic synthesis in an electrochemical cell has gained a paramount interest since the 1980s [31]. Rusling conducted an elegant

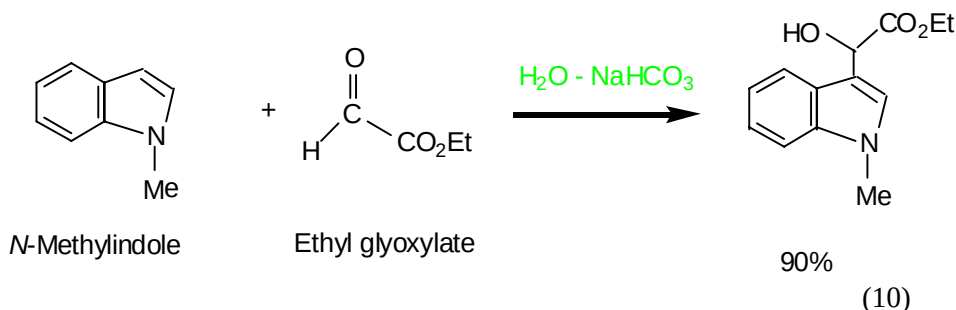
electrosynthetic work in O/W microemulsions [32]. Of these were the electrochemical cyclizations, mediated by vitamin B₁₂, of 2-(3-bromopropyl)-2-cyclohexen-1-one and 4-(bromobutyl)-2-cyclohexen-1-one into 4-hydrindanone and 1-decalone, respectively, (Eq. 8). Interesting is that the former cyclization, being forbidden by Baldwin's rules, took place affording the corresponding product in 62-70% in a microemulsion medium; only 7% of 4-hydrindanone was formed in DMF. However, the latter cyclization in a microemulsion led to a mixture of *trans* and *cis*-1-decalone in 90%, with a 93:7 *trans* : *cis* ratio; in DMF, this ratio was only 3:1.



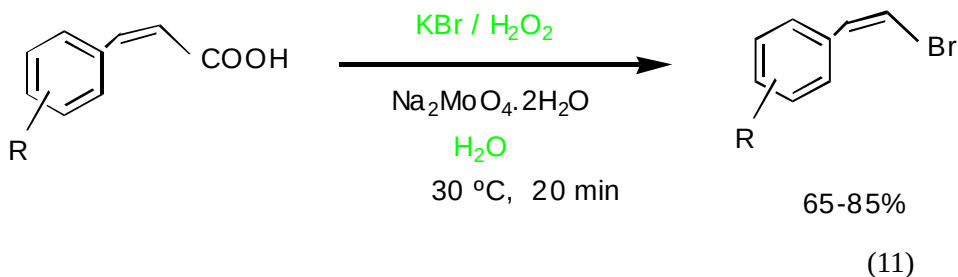
A study on 1,3-dipolar cycloaddition reactions of aromatic nitrones with acrylonitrile (ACN), affording isoxazolidines, was undertaken in O/W microemulsion medium, ACN being the oily component, (Eq. 9) [33]. The results were that not only were the yields enhanced (80-100%), but also the reactions rates were unexpectedly higher, particularly when triflate-based Lewis acids were employed. The main feature of this work was temperature-dependence of the reaction time; indeed, a 25° C temperature rise induced a 90% drop in the reaction time. However, the yields of the reactions in toluene, a conventional reaction medium, were rather moderate (31-69%) after refluxing for 12 h.



A good example of the Friedel-Crafts reactions that were run in water is the one depicted in Eq. 10, the reaction of ethyl glyoxylate with *N*-methylindole [34]. The intriguing feature of this reaction is that no conventional Lewis or Brønsted acid was required and the yield was surprisingly quantitative. This reaction, however, did not proceed in DCM unless an acid catalyst was added.



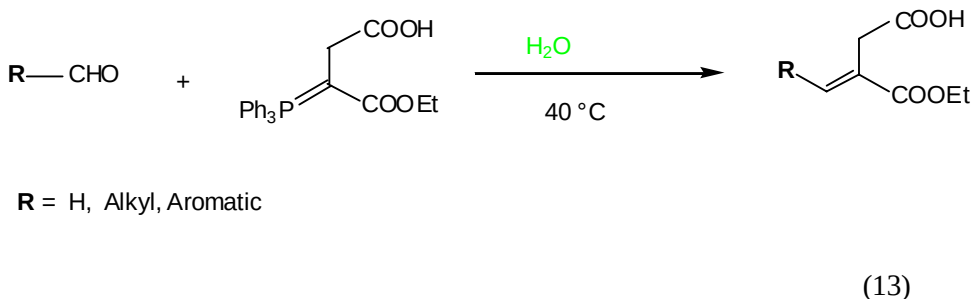
One efficient way to make organic halides, namely the alkyl bromides, is through the Hunsdiecker reaction. The conventional conditions include bromine and CCl_4 as reagent and solvent, respectively; both of the latter substances are highly toxic and the reaction yields are generally poor. Application of Hunsdiecker reaction to the α,β -unsaturated aromatic carboxylic acids in aqueous media successfully produced β -bromostyrenes in an appreciable yields (65-85%), (Eq. 11) [35]; the reaction conditions were milder, a temperature of 30°C and time of 20 min. While the classical Hunsdiecker reaction occurs by a free radical mechanism, an ionic mechanism has been suggested for the water-based present reaction [36].



Reports on water-based Wittig reactions started on the year 2005 [37]. Bergadhl and his coworkers presented 13 examples in which water promoted higher yields (up to 98%), higher reaction rates, and higher stereoselectivity (E/Z up to 99:1); the aldehydes experimented were aromatics and heteroaromatics. A good example is shown in Eq. 12 where a poorly-water soluble ylide reacts with veratraldehyde in water.



The water-mediated Wittig reaction was applied to a series of aldehydes to afford alkylidenesuccinic acids, exemplified by the reaction shown in Eq. 13. The outcome of the reaction depends on the chemical nature of **R** group of the aldehyde [38]. Indeed, in case of formaldehyde (**R** = H), the reaction yield was 81% after a reaction time of only 2 h. However, when **R** is an alkyl, the reaction yields were in the range of 62-73% after a reaction time as long as 24 h. The aromatic aldehydes were more resistant and afforded the corresponding products in 34-80% but after 2-5 days. The main feature of these water-borne reactions was that there was no need of purification of the products by column chromatography. Whereas, the products of the reactions (**R** = alkyl) in organic solvent (DMSO) were isolated in 50-60% after 24 h after purification by column chromatography.



R = H, Alkyl, Aromatic

A practical catalytic aldol-surrogate reaction was achieved via the hydrative amide synthesis in aqueous medium [39]. In fact, the reactions of a wide range of alkynes with sulfonyl azides were successfully carried out in water to afford sulfonamide products in high yields (72-99%) within only one hour. The reaction shown in Eq. 14 is but illustrative; the reaction outcome gives an insight into the superiority of the aqueous medium (Table 4).

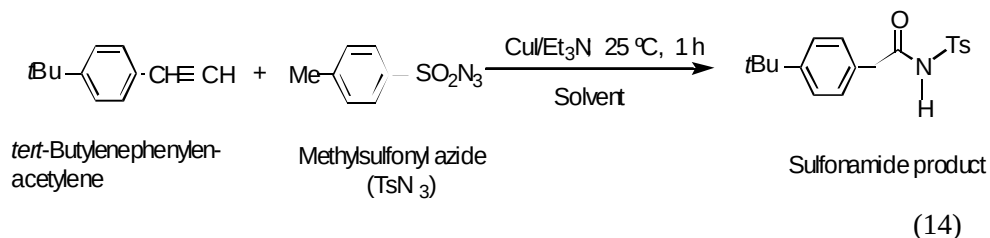


Table 4. Results of the reaction in Eq. 14 in different media

Solvent	Conversion (%)	Yield (%)
CHCl ₃	38	35
CHCl ₃ / H ₂ O (2:1)	64	55
H ₂ O	>99	87

Synthetic chemists did not delay to apply, wherever adequate, the "on-water" strategy to the preparation of some natural products. Shortly after the revival work of Breslow, Grieco embarked on the total synthesis of vernolepin (a potent cytotoxic sesquiterpene), *dl*-pyroangolensolide, and *dl*-epi-pyroangolensolide, applying the water-promoted DA reaction in one of the steps of the synthesis [40, 41]. The total synthesis of gambogin, a biological active molecule, involved steps where Diels-Alder reactions and Claisen rearrangement were performed in aqueous solutions and dramatic rate acceleration was observed [42].

WATER IN POLYMERIZATION

Another aspect of organic synthesis is the polymerization of monomers to afford useful polymeric materials. Vinyl polymers are the leading ones amid the large spectrum of these materials. The solution polymerization, a homogeneous procedure, of a vinyl monomer involves the use of an organic solvent. However, the polymerization of vinyl monomers bearing carboxylic acid, hydroxyl or amino groups can be advantageously run in aqueous system, providing water-soluble radical initiators; of these monomers are acrylic acid, methacrylic acid, hydroxylalkyl acrylates and acrylamides. Despite the pitfalls of the solution technique that reside in the cost and the toxicity of the organic solvent, it is generally recognized that the solvent profitably remedies to the high viscosity and the high exothermicity, which are encountered in the mass polymerization; the solvent fluidizes the system and absorbs the heat evolved. In the mass or neat polymerization, while the reaction is simpler and cleaner and the polymer obtained is purer, it enormously suffers from the above-mentioned drawbacks. On an industrial scale, the latter polymerization technique engenders thus a real danger. Fortunately, the use of water as a medium wards off the shortcomings of both the solution and the mass polymerizations; dispersion polymerization (emulsion and suspension polymerizations (Fig. 2) was consequently emerged, featured with ease of mixing and good heat transfer. Profitably, the industry manufactures a variety of polymeric materials using these two heterogeneous water-based techniques [43]. Indeed, the ion-exchange resins are mostly produced by the suspension polymerization. The synthetic elastomers are made by emulsion polymerization; latexes are employed in water-based paints and paper sizing. About 10 millions tons of polymer latexes are used in such applications and others. It is worth recalling that nature makes the natural rubber (*Hevea Brasiliensis*) in form of a latex, a special emulsion [44, 45], without the use of all the many ingredients that are necessary for producing synthetic rubbers by emulsion polymerization [46].

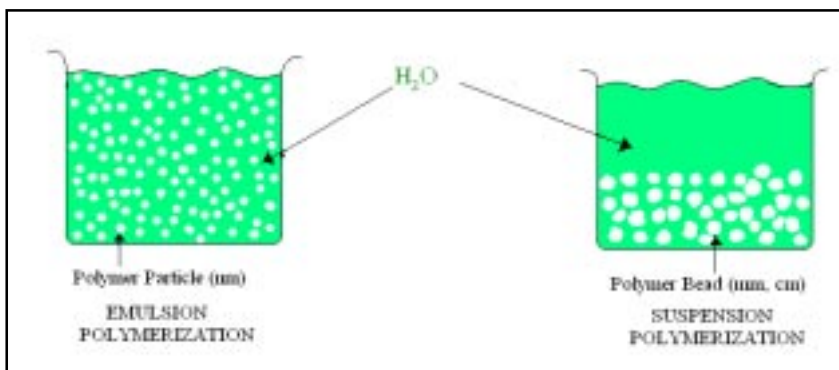


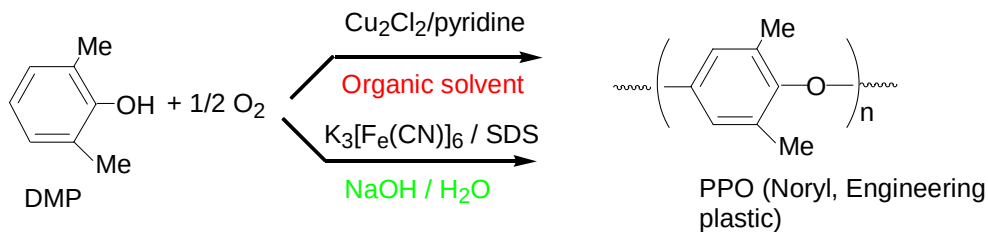
Fig. 2. Water-based dispersion polymerization (water as a green medium)

Research has brought forth emulsion polymerization processes characterized by smaller loci size affording smaller polymer particles: miniemulsion and microemulsion polymerizations [47,48]. They involve oil droplets of 50-500 nm and 10-100 nm, respectively, giving nanoparticles. As for emulsion polymerization, the miniemulsion technique has found a very interesting application in coating industry [49]. Miniemulsion polymerization allows copolymerizing very highly hydrophobic monomers in water-borne systems. For example, soybean oil-based vegetable oil macromonomer (VOMM) was efficiently copolymerized with other organic monomers, giving water-borne coating resins [50].

In the last decade, the use of water-borne microemulsion (oil-in-water, O/W) as a medium for polymerization of several vinyl monomers was reported [47]. This technique is featured by small monodisperse particles, fast polymerization rates, high conversions, and, best of all, very high molecular weights; size of the polymer in the order of over than 20 millions Daltons is very common. The microemulsion polymerization of styrene gave a $15 \cdot 10^6$ molecular weight polystyrene, while the homogenous free radical polymerization yielded only $2 \cdot 10^6$. Kaler patented the polymerization of some methacrylate derivatives by means of this medium [51].

Quite interesting is that aqueous dispersions (suspension, emulsion and miniemulsion) have gained a foothold even in the new polymerization routes called "controlled radical polymerizations" (CRP), versatile techniques for making tailor-made polymeric materials: atom transfer radical polymerization (ATRP), stable free radical polymerization (SFRP), reversible addition fragmentation transfer polymerization (RAFT) [52-56].

Saito was able to carry out the aqueous oxidative coupling polymerization of 2,6-dimethylphenol (DMP) or 2,6-xylenol to afford polyphenylene oxide (PPO) or polyxylenol in 98% yield, using potassium ferricyanide as a catalyst [57]; compare the green conditions versus the red ones of an old process as shown in Eq.15. The aqueous process is distinguished by the easy isolation of PPO by a simple filtration; the polymer precipitates from the medium as it forms, and the medium can be then profitably recycled for the next batch.



(15)

CONCLUSION

The aforementioned few examples are but encouraging and incentive for the on-water changeover while in its embryonic state; however, truly saying, organic synthesis stands far distant from its end, as the global outcome of this approach requires time and wherewithal. The words of the E. J. Corey (2003) are very inspiring in situating the today's organic synthesis status [58]: *"How many challenging and worthy synthetic targets remain to be discovered? How many truly powerful and general synthetic strategies and synthetic reactions remain to be discovered? Is there a prospect for the development of entirely new ways of planning or executing synthesis? In my judgment the opportunities for new developments and discoveries are so vast that today's synthesis is best regarded as a youngster with a brilliant future."*

Therefore, chemistry in water is challenging and more needs to be done and elicited. Is it, by remaking the countless organic solvent-run chemical reactions in water, that one can deem synthetic chemistry will reach its height? Synthetic chemists are now compelled to embark on making new synthetic strategies and techniques for the use of water as a reaction medium. Optimistically, some miracles would be expected and an achievement summit would be attained from the water-turnover. "On-water" approach could make the difficult reactions work, as proved by the successful rearrangements that were once considered rebellious [59].

By thriving to avoid using organic solvents and to work in aqueous systems would certainly annihilate the chemophobia from the public image and would hopefully set in lieu the chemophilia. Would the 21st be the century of organic synthesis in aqueous media? This is indubitably the every chemist's wish, but to fulfill it, one has to direct his own organic synthetic research towards the on-water strategy.

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