Microwaves - Ultrasound Coupling:A tool for Process Intensification in Organic Synthesis

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Abstract

Chemists have always looked for synergism, that is, a combination of tools, reagents, or processes producing a larger effect than the sum of their individual effects. It is expected that in the future organic synthesis will undergo increased automation and require the construction of continuous-flow systems capable of rapid, efficient and scalable automated processes. In this context, our aim is to show how two of the most important, green activation techniques (microwaves and power ultrasound), may be combined to provide a reliable and cost-effective strategy for an increasing number of synthetic transformations.

Process intensification in organic synthesis is expected to require an increased automation, with rapid, efficient and scalable protocols to be implemented in continuous-flow reactors. The design and development of routes for manufacturing fine chemicals or pharmaceuticals must conform to strict criteria concerning not only efficiency and selectivity, but also time frame, safety, cost, and environmental impact. In this context the specific advantages of microwaves (MW) (1) and power ultrasound (US) (2), particularly their power to enhance reaction rates, yields and specificity (3), may become additive when they are used in combination (4). At a first glance, the idea of combining these two kinds of irradiation looks odd, as they basically differ in their physical nature, being quantum and non-quantum, respectively. While for electromagnetic radiation (such as

microwaves) quantum energy and frequency stand in a direct relationship, the cavitational energy is not directly proportional to US frequency; in fact, the relationship is quite complex due to nonlinear effects of cavitational collapse. Despite these considerations, in the light of recent advances we can ignore non-thermal microwave effects (5); this means that the observed enhancements can be fairly accounted for by purely thermal effects of dielectric heating on the one hand, and from pyrolytic mechanisms and powerful stirring arising from cavitation on the other (6).

Starting from the established fact that MW and US have both emerged as efficient and irreplaceable energy sources in organic synthesis, the present, short review aims to highlight synergic or additive effects resulting from their combined use (7). Several recent examples from the literature shall make this concept evident. No doubt technical hurdles and safety considerations have hampered so far the use of simultaneous MW and US irradiation. The ultrasonic energy generated by a transducer is usually delivered to the reaction vessel through a horn made of titanium alloy. However, a piece of metal placed inside a MW chamber would cause arcing and possibly result in vessel rupture, or perhaps an explosion when flammable compounds are present. Electric arcs can also be formed in the cavity if the microwave input is excessive (the efficiency of MW absorption decreasing as temperature rises); therefore temperature, pressure, stirring rate and power input should all be monitored and controlled for safe operation (8).

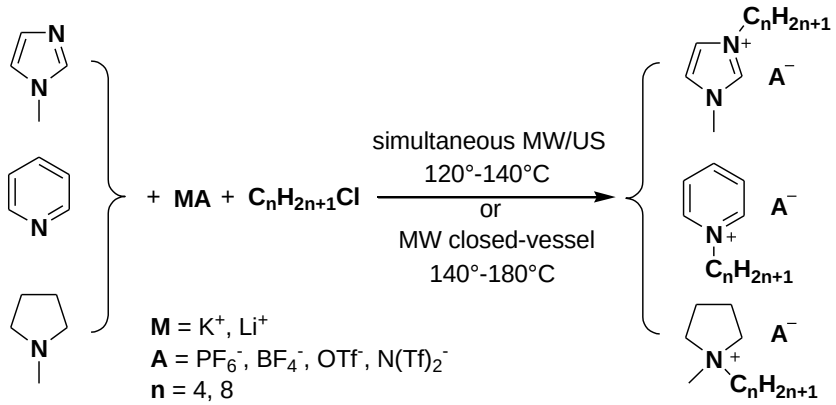
To overcome the main hurdle standing in the way of simultaneous MW/US irradiation, US can be conveyed inside a modified MW oven by inserting through its wall and down into the reaction vessel a horn made of quartz, even though this material is far from ideal because of its fragility. Pyrex also shares the same drawback, while ceramic horns may be more expensive. Cravotto's group experimented with various non-metallic horns and found that a particular type of PEEK containing a small amount of glass fibers offered the best solution to the problem.

Simultaneous US/MW irradiation usually requires a cooling system to keep the temperature under strict control so as to avoid superheating that would decrease cavitation. An efficient cooling can be achieved by circulating a refrigerated fluid that is transparent to MW, e.g. silicone oil or Galden® (Solvay-Solexis), a perfluoropolyether with a high boiling point and a low viscosity (Figure 1).

Figure 1. Simultaneous US/MW irradiation with a cooling system.

Combined irradiation can otherwise be achieved by the use of flow reactors for *sequential* MW/US treatment that do allow the employ of commercially available metallic horns. In these reactors a pump circulates the reacting mixture through two separated reaction cells, one placed inside the MW oven and the other (fitted with a US probe) standing outside it (9).

Maeda and Amemiya can be considered as the originators of the technique (10), as they first described the synergic effect of simultaneous US/MW irradiation. Chemat *et al.* avoided subjecting the horn to the electromagnetic field by using decaline (a low-viscosity apolar liquid) to convey US waves inside the oven and to the reaction mixture that was placed in a double-jacketed pyrex vessel (11). *Peng* and *Song* employed a modified domestic MW oven and inserted in it a probe fitted with a detachable horn (whose material, obviously not a conductor, was however unspecified by the authors) (12). They used this set-up for a solventless hydrazinolysis of esters, to synthesize ethers (Williamson) (13), for Knoevenagel-like reactions (14) as well as Mannich reactions (15). Synthetic applications of combined irradiation were reported by Cravotto and co-workers for preparing aromatic azo and/or azoxy compounds by selective reduction of nitroarenes (16), for the nucleophilic opening of epoxides (17), C-C aryl couplings through Suzuki-Miyaura (18) or Heck type reactions (19) and one-pot synthesis of second-generation ionic liquids (20). The last, patented protocol (21) combining in one step the Menshutkin reaction and anion metathesis, paved the road for a straightforward access to a wide range of ionic liquids, dramatically reducing their preparation times and costs. It made even possible to use as starting materials poorly reactive alkyl chlorides that are inexpensive and widely available (Scheme 1) (22).



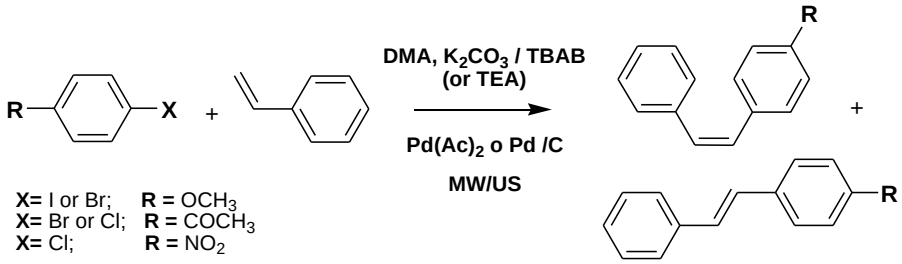
Scheme 1. One-pot synthesis of second-generation ionic liquids starting from alkyl chlorides.

Pd-catalyzed homo- and cross-couplings of boronic acids and aryl halides could be successfully performed in aqueous media under combined US (20.5 kHz, 40 W/cm^2) and MW (700 W) irradiation. Reactions were carried out in a sequential-flow reactor at 45ºC, using 10% Pd/C as catalyst. Under these conditions the expected biaryls were obtained after 1h irradiation as the sole products, in higher yields than could be achieved under either US or MW used separately (Table 1) (9).

Aryl halide	Boronic acid	US alone, yield %	MW alone, yield %	MW/US yield %
3-Bromoanisole	$PhB(OH)_2$	54	64	88
2-Iodothiophene	$PhB(OH)_2$	40	37	59
4-Chloronitrobenzene	$PhB(OH)_2$	22	30	57
None	thianthrene-1-boronic	48	55	69
None	4-*t*-butylboronic	68	74	86

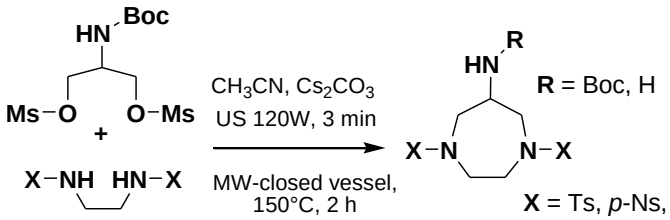
Table 1. Suzuki-type homo- and cross-couplings under US and MW, alone or combined.

Very recently Cravotto *et al.* showed that Heck reactions could conveniently be carried out under simultaneous MW/US irradiation to afford high product yields while using very low ligandless catalyst loads (Scheme 2) (19). With styrene, electron-poor aryl chlorides, such as 4-chloroacetophenone and 4-chloronitrobenzene, gave good yields after 1 h in the presence of 0.25 mol % $Pd(OAc)_2$ and a co-catalyst (Wilkinson 0.005 mol % or CuBr 4.0 mol %) or 2.0-3.0 mol % Pd/C. In most cases MW heating gave comparable results (although yields were 5-20% lower) in somewhat longer times, whereas under conventional heating acceptable yields were achieved only after 18 h.



Scheme 2. Heck reactions under MW/US irradiation using very low ligandless catalyst loads.

Favourable US/MW effects on a chemical reaction may be additive even when the two irradiations are applied sequentially, as was done in the synthesis of 6-aminoperhydro-1,4-diazepine (Scheme 3). Cesium or potassium ions catalyzed ring closure by coordinating the sulphonamide groups. Protected ethylenediamine derivatives and *N*-Boc-serinol mesylate underwent rapid cyclization to give 6-aminoperhydro-1,4-diazepine in excellent yields with high selectivity, whereas the same reaction failed or gave negligible yields under conventional heating. Even when just one of the two irradiation treatments was omitted (sonication being replaced with high-speed stirring and MW irradiation with conventional heating at the same temperature) the reaction outcome was negatively influenced (23).



Scheme 3. One-pot 6-aminoperhydro-1,4-diazepine under sequential US and MW treatments.

Scale-up of Pd-catalyzed protocols under combined US/MW irradiation shall probably resort to sequential-flow reactors (24) and require of course a careful analysis of costs, including energy consumption.

Conclusions

The above examples clearly show that microwaves - ultrasound coupling is a promising tool for process intensification in organic synthesis. Being practically hazard-free, this emerging technological innovation deserves widespread attention in fine-chemicals and pharmaceutical research. Although the mechanisms of cavitation and microwave effects are not fully understood, processes requiring enhanced heat transfer and mass transport (especially heterogeneous reactions) will greatly benefit from this green technique. Combinations of MW and US may be simultaneous or sequential; for optimal results conditions have to be tailored to each specific reaction.

Acknowledgments

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