REVIEW ARTICLE

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The Q-tube System, A Nonconventional Technology for Green Chemistry Practitioners

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Abstract: Background: High-pressure chemistry offers the possibility to have faster and cleaner transformations thus addressing most of the green chemistry principles. Among the devices recently developed, Q-tube is worth mentioning since it is cheap, easy to handle, safe and highly versatile.

Methods: The most recent and interesting results obtained using such technique are reviewed in this study.

Results: Examples of the Q-tube assisted reactions in organic synthesis are presented in a critical manner making where possible, a comparison with conventional heating strategies and unconventional energy source such as microwave or ultrasounds assisted synthesis. The application of Q-tube pressure reactor in biofuels manufacture is also discussed.

Conclusion: The literature survey clearly revealed that Q-tube is a valid tool in organic synthesis.

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1. INTRODUCTION

In the course of our studies on the development of new green procedures in organic synthesis [1-3], we came across the device named Q-tube, recently. As usual, before starting the experimental work, we performed a deep literature analysis that culminates in this mini-review. This manuscript is not directed to specialists but rather for someone interested in becoming better acquainted with details and application of this innovative device.

Starting from 1981, when the Isaacs seminal book on High Pressure Chemistry (HPC) was published [4], several examples were reported in literature [5-7]. HPC allows to obtain faster and cleaner transformation by simply modifying some physical properties of solvents, reagents and final products. For liquids, the properties that are mostly modified are: boiling point, viscosity, density and dielectric constant, and in the case of protic media such as water, also the ion product constant is modified once the pressure changes [8]. The main advantage of carrying out a reaction under pressure is the possibility to overcome the boiling point of the solvent. The boiling point of a liquid is the temperature at which its vapour pressure equals the external pressure allowing the change of state. Considering a standard, mantel-heated, batch reaction, once the solvent boiling point is

reached, all of the energy that is administered to the system is dispersed through the evaporating molecules. By increasing the external pressure, the vapour pressure of the solvent increases as well, and thus its boiling point. As the boiling point is exceeded, the reaction rate increases according to the physical dependence given by Arrhenius equation which defines that every 10°C of temperature increment results in approximately double reaction rate [9]. In addition, the pressure increment reduces reaction volume, hence the concentration of reagents and their collision frequency are increased. When the desired reaction is accelerated, the competing decompositions of reagents could be also minimized enabling cleaner reactions profiles.

Among the devices developed for high-pressure chemistry, Q-tube[®] (hereafter referred to as Q-tube) provided by Q Labtech is surely the simplest and cheapest alternative (illustrations together with exhaustive technical details can be found at the website: <http://www qlabtech.com>). Q-tube is a patented, safe pressure reactor, featuring a pressure release and reseal system that prevents explosions due to overpressures. It is considered a viable alternative to expensive MW synthesizers, but at the same time, it is also suitable for those solvents that are MW transparent.

In this mini review, the utility of Q-tube in multicomponent reactions will be discussed, then examples in which it enabled the synthesis of heterocyclic systems will be given prior to deal with some catalytic approaches. Finally, recent reports in which this technology has been applied for the manufacturing of biofuels will be provided.

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2. MULTICOMPONENT REACTIONS

Multicomponent Reactions (MCRs) are convergent synthetic approaches whereby three or more starting materials react to form a final product that contains all or most of the atoms of the initial products [10, 11]. In a MCR, the product arises from a series of simple organic reactions and is the thermodynamically stable combination in a series of possible intermediate equilibria. The success of MCRs strongly depends on the minimization of the side products and this can be achieved by modulating the reaction conditions. With this in mind, Procopio and co-workers revisited the Biginelli reaction for the synthesis of pyrimidines using nonconventional technologies such as MW and Q-tube (Scheme 1) [12].

(Scheme 1). The Biginelli reaction.

The authors prepared a small set of Monastrol derivatives, which is a lead compound in the anticancer research field, by reacting variously functionalized dicarbonyl compounds, ureas and aldehydes at 120°C in solvent free conditions in the presence of catalytic amount of the Lewis acid ErCl_3 . All the reactions were carried out in both Q-tube and under MW irradiation. Surprisingly, Q-tube emerged not only as a valid alternative technique but also it provided a cleaner reaction profile in a shorter reaction time. Indeed, to get complete conversion the MW-assisted synthesis required 90 minutes while in the Q-tube the reactions needed just 30 minutes to be concluded. A head to head comparison of the reactions for the preparation of compound 1-3, is given in Table 1.

Table 1. Conversion and yields for compounds 1-3.^a

	Q-tube		MW Reactor	
	Conversion	Yield	Conversion	Yield
1	100	92	90	50
2	100	90	90	45
3	75	64	47 (75) ^b	5 (54) ^b

^aAll the reactions were conducted at 120 °C in 30 min; ^bcarried out in 90 min.

As evident from (Table 1), both methods worked well but the Q-tube apparatus afforded higher yields, this is particularly evident for the synthesis of compound 3 obtained by

comparable conversion and yields with MW but after 90 minutes of reaction time.

Starting from the assumption that the high pressure enhances reactions with negative activation volumes such as the [4+2] cycloadditions [13], Elnagdi *et al.* reported the Q-tube promoted synthesis of benzo[c]chromen-6-one and phenanthridin-6(5*H*)-one derivatives by reacting at 120 °C, ethylcyanoacetate with alkynes and acetophenones bearing amino or hydroxyl substituents in the *ortho* position. Under neat conditions, they obtained the desired compounds in moderate to good yields in just 25-30 minutes (Scheme 2) [14].

In order to test the versatility of the developed protocol, they replaced the alkyne with naphthoquinone preparing the pentacyclic compounds 6 in good yields.

Very recently, the same research group developed a Q-tube assisted procedure to synthesize highly substituted pyridazino[5,4,3-*de*][1,6]naphthyridines in moderate to good yields (Scheme 3) [15]. The reactions have been carried out in dioxane at 150 °C in 60 minutes. The reaction temperature is far above the solvent boiling point (101°C). An interesting aspect is that in this example Q-tube worked as an enabling technology, indeed the same reactions carried out under standard conditions did not gave the target compounds but other molecules derived from different reaction pathways.

3. SYNTHESIS OF HETEROCYCLES

The development of efficient and practical synthetic pathways for the construction of a variety of aromatic and heteroaromatic ring systems is one of the major goals in organic chemistry and the implementation of greener procedures is highly demanded. In keeping with this, Jha *et al.* turned their attention to elaborate a new and versatile procedure for the preparation of polycyclic heteroaromatic compounds which was also employed for the synthesis of thiopyrano [2,3-*b*:6,5-*b'*]diindoles (Scheme 4).

The synthetic method involves the reaction between variously functionalized indoles bearing an aldehydic group at the C-3 position and indoline-2-thione in the presence of ethylene diamine diacetyl (EDDA) in acetonitrile at 100 °C (20 °C above its boiling point). Interestingly, all of the reactions were found to occur instantaneously, indeed just 30 seconds were required for the complete conversion of starting indoles into the fused compounds. The use of Q-tube was found not to be an absolute requirement for the formation of the products 8. These derivatives could be obtained under standard conditions in refluxing CH_3CN but the reaction time was found to be longer (30 minutes) [16].

Indanones and related compounds are important bioactive molecules and for this reason they are considered synthetic targets by the organic chemistry community. These compounds have exhibited biological activities against cancer cells and Alzheimer's disease. The most famous drug which bears an indanone moiety is indeed donepezil hydrochloride, which has been approved by the United States Food and Drug Administration for the treatment of mild-moderate Alzheimer's disease [17]. Indanones are commonly obtained *via* intramolecular Friedel-Crafts acylation of 3-arylpropionic

(Scheme 2). Four component reaction toward heterocyclic scaffolds.

(Scheme 3). Three component reaction to pyridazino[5,4,3-*de*][1,6]naphthyridines.

(Scheme 4). Synthesis of pentacyclic compounds.

acids using harsh reaction conditions which usually employ strong acids as solvents. In order to develop a greener procedure Procopio and co-workers performed the Friedel-Crafts reaction in nonconventional conditions (Scheme 5) [18].

The intramolecular acylation was performed in the presence of triflic acid in DCM under MW irradiation, high-intensity ultrasound (US) [19] and high-pressure conditions using Q-tube. In Table 2, some results are collected to enable a head to head comparison of the three methods.

The MW-assisted and Q-tube assisted procedures allowed the complete conversion of the starting substrates into the final products in shorter reaction times (60-180 minutes) than the US-activated approaches (150-1200 minutes). On the other hand, US-assistance allowed the reactions to be conducted at a lower temperature (40 °C *vs* 110 °C of MW

and Q-tube) and afforded higher yields. In most of the cases, the Q-tube technology gave the same results as the MW-assisted protocol in term of conversion but with cleaner reaction profiles.

An interesting comparison between conventional heating and nonconventional conditions was very recently performed by AlMarzouq *et al.* [20]. The reaction between a diazene and some electron poor double and triple bonds in absolute ethanol gave the target structures **11-14** depicted in Scheme 6, this was used as model to compare the four different methodologies (Table 3). Unfortunately, the authors performed the MW-assisted reactions using a domestic instrument instead of a veritable MW synthesizer. However the outcomes clearly indicated that the best results in term of yield were obtained by using Q-tube, which afforded the

products in moderate to good yields. US assisted synthesis worked well for all of the substrates giving yields always above 70 %. From the reaction time point of view, MW-assisted synthesis proved to be the method of choice to get quantitative conversions in few minutes (1-4 minutes). Comparable results were obtained with Q-tube while the time required for US and conventional heating was of hours. Overall, among the 4 methods, Q-tube surely emerged as the best in class for the quick and efficient synthesis of these heterocyclic compounds.

(Scheme 5). Intramolecular Friedel-Crafts acylation to indanones.

4. CATALYTIC APPROACHES

Very few examples of catalytic approaches coupled with Q-tube device have been reported in literature. Porcheddu [21] and co-workers in 2013 developed a two-step procedure for the synthesis of indoles, that are considered privileged scaffolds from a medicinal chemistry point of view [22, 23]. As shown in Scheme 7, the Pd/C-catalysed reaction of primary amines and hydrazines, in the presence of crotonitrile as hydrogen acceptor, in toluene at 150 °C gave the corresponding hydrazones **15** even after 12 h.

In this first step, several palladium catalysts were tested and the best results were obtained with Pd on carbon, which was also recycled and reused for five consecutive cycles without reduction of catalytic efficacy. Beside toluene, the same reaction was also carried out in greener solvents such as water and under neat conditions with comparable yields of compounds **16**. Once prepared, the whole set of hydrazones was converted into indoles through the Fisher indolization reaction [24] catalysed by ZnCl₂ using 2-methyl-2-butanol (tert-amyl alcohol, TAA) as solvent. In one example the authors proved a single step approach by adding both catalyst together with the primary amine and the hydrazine without

isolating the hydrazone **16**. They eventually obtained the target indoles but in lower yields thus they preferred the two steps procedure for the library construction.

A p-toluenesulfonic acid (p-TSA) – catalysed strategy to modify aldehyde- containing indoles was developed by Blanchard *et al.* in 2013. In their study a comparative investigation was performed by carrying out the optimization of the reaction conditions not only in Q-tube but also in conventional heating and under MW irradiation (Scheme 8) [25].

Using catalytic amount of p-TSA and in presence of alcohols, the formyl indoles were easily converted into the corresponding enol ethers. Among the tested procedures, Q-tube emerged as the best system because allowed quantitative yields to be obtained in reasonable time where standard reflux and MW-assisted synthesis required longer reaction times.

In the medicinal chemistry research field Pd(OAc)₂ catalysed coupling reactions in Q-tube were recently reported [26, 27]. In one example, the use of such system was required, as the author stated, to reduce the reaction time [27].

5. BIOFUELS DEVELOPMENT

An interesting application of the Q-tube technology is in the biomass processing for the manufacturing of biofuels. Given the current energy crisis and the global warming there is an urgent need to exploit alternative and renewable energy sources, such as biomass [28, 29]. Therefore, new methods for biomass processing are highly demanded.

In 2017, Martinez-Palou used Q-tube in combination with ionic liquids (ILs) to promote a easier depolymerisation of the lignocellulosic biomass derived from Taiwan grass [30]. After a design of experiments-guided process optimization, the Q-tube/ILs was discovered as a synergistic couple, very efficient for the biomass pre-treatment, which was completed in 1 hour with high yields of reducing and total sugars after enzymatic hydrolysis. The authors initially screened a series of 24 ionic liquids, then with the best one an experiment was performed with conventional heating to prove the Q-tube effect. As expected, an improvement of the whole process, in terms of total free sugars, was observed as a result of pressure increment, which may allow easier depolymerisation of lignin-derived cellulose.

Recently, a new route for producing drop-in diesel or jet fuels, which combines the use of furfural, obtained by the catalytic dehydration of lignocellulosic pentose sugars, and

Table 2. Comparison between MW, US and Q-tube activated synthesis of indanones.

	US			MW Reactor			Q-tube		
	Time (min)	T (°C)	Yield (%)	Time (min)	T (°C)	Yield (%)	Time (min)	T (°C)	Yield (%)
9	150	40	99	60	110	99	60	110	99
10	1200	40	90	180	110	48	180	110	43

(Scheme 6). Synthesis of pyrazolopyrimidinones **11-13** and pyrazolopyrimidines **14**.**Table 3.** Comparison between MW, US and Q-tube activated synthesis of indanones.

	Conventional Heating ^a		US ^b		MW Reactor ^c		Q-tube ^d	
	Time (hours)	Yield (%)	Time (hours)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
11	6	85	3	82	1	60	5	90
12	7	75	4	84	1	55	10	80
13	7	70	4	78	4	66	30	80
14	5	68	3	73	2	65	5	76

^a The reaction has been carried out at reflux; ^bThe reaction has been carried out at 80°C; ^cThe reaction has been carried out in neat condition; ^dThe reaction has been carried out at 140°C.

(Scheme 7). Two step synthesis of indoles.

alcohols produced from a variety of bio or petroleum feedstocks has been reported by Bell, Scown, Toste *et al.* [31]. The dehydrogenative cross-coupling reaction of furfural and alcohols was found to be catalysed by a recyclable transition-metal-free hydrotalcite (HT) and led to high molecular weight furanyl adducts *via* a transfer hydrogenation–aldol condensation. The optimization studies, such as the catalyst screening along with the evaluation of the substrate scope for

the dehydrogenative cross-coupling reaction (Scheme 9) of various bioalcohols and lignocellulosic furfural were performed in Q-tube at high temperature in toluene.

The highly selective cross-condensation proceeded, as suggested, *via* a hydride transfer from butanol to furfural, consistent with the Meerwein–Ponndorf–Verley reaction [32], followed by an aldol condensation of the resulting bu-

tyraldehyde with a second molecule of furfural. The second step of the developed synthetic strategy to upgrade lignocellulosic furfural to high value biofuels involved the hydrogenation of adducts. The reaction was conducted in a Mini Parr reactor using Pt/NbOPO₄ as catalyst at elevated pressure and temperature. The hydrodeoxygenation of furanyl aldehydes **19** provided a mixture of cyclic and acyclic alkanes consisting of C8–C19 carbons in 75–78% total yield (Scheme 10), that can be applied as blendstocks for jet and diesel fuels.

(Scheme 8). Modification of indoles.

Other biofuel solutions such as biomass derived cycloalkanes, which offer up to 81% Greenhouse Gas (GHG) reduction benefits have also been proposed by the same research group [33]. It was exemplified by the reported novel method for selectively upgrading biomass-derived alkyl methyl ketones into trimer condensates. The latter of which can then

be hydrodeoxygenated in near-quantitative yields to give a new class of cycloalkane compounds for aviation fuels as well as lubricants applications. The developed strategy involves initial conversion of sugars in sugarcane-derived sucrose as well as the conversion of hemicellulose to ketones using a combination of chemical and biocatalytic processes. The self-condensation reaction of the biomass obtained ketones was first examined in order to optimize the reaction conditions and screen heterogeneous acid/base catalysts (Scheme 11, Table 4). The detailed catalyst screening for the condensation of 2-hexanone was also reported independently [34] and the calcined hydrotalcite, Mg–Al–O (Mg/Al=3) was found to be the most efficient heterogeneous species, which could selectively produce cyclic and aromatic trimer condensates. The reaction was conducted in a sealed Q-tube reactor at high temperature in toluene. It was demonstrated that ketones containing methyl functionality undergo selective trimerization to produce condensates of **27** and **28** in the presence of a base (MgAlO) and acid (Nb₂O₅) catalysts, whereas ketones with longer hydrocarbon chains at both ends condense to form mostly dimers (**26**). Furthermore, it was found that the selective formation of **27** and **28** was dependent on the nature of the catalyst (acid/base).

The hydrodeoxygenation of condensates (**26–28**) was accomplished in the liquid phase at 160 °C with 3.5 MPa of H₂ using Pt/NbOPO₄ for 5–12 h to produce quantitatively cyclic and acyclic alkanes **29–31** (Scheme 12), that serve as potential jet fuels (C12–C21) and synthetic lubricants (C33+).

(Scheme 9). Dehydrogenative cross-coupling reaction of furfural.

(Scheme 10). Hydrodeoxygenation of furanyl aldehydes.

(Scheme 11). Self-condensation reaction of the biomass obtained ketones.

Table 4. Self-condensation of ketones in the presence of solid acid/base catalysts.

Ketones			Cat.	Temp. [°C]	Time [h]	Conv. [%]	Yields [%]		
no	R ¹	R ²					26	27	28
1	Me	H	MgAlO	170	3	100	0	95	0
2	Et/Pr/ <i>n</i> -Bu	H	MgAlO	150	3	100	0	95-98	0
3 ^a	<i>n</i> -Pr	H	MgAlO	150	3	99	0	97	0
4	<i>n</i> -Pentyl→ <i>n</i> -Docecyl	H	MgAlO	180	12	100	0	96-99	0
5	Et	H	Nb ₂ O ₅	180	6	99	1	8	73
6	<i>n</i> -Bu	H	Nb ₂ O ₅	180	6	98	2	8	78
7	Et	Et	Nb ₂ O ₅	180	20	86	73	0	0
8	<i>n</i> -Bu	Et	Nb ₂ O ₅	180	20	79	69	0	0
9	<i>n</i> -Bu	<i>n</i> -Bu	Nb ₂ O ₅	180	20	61	54	0	0

Ketones (2 mmol), catalyst (200 mg), toluene (3 ml); ^a Cyclohexane (3ml) instead of toluene.

(Scheme 12). Reduction of the condensed products.

Another reported protocol which enables the kilogram scale production of high-value biofuel precursors from fermentation solvents consisted of the combination of the biological fermentation and chemical catalysis [35]. This two-step approach was achieved by the Acetone-Butanol-Ethanol (ABE) extractive fermentation of sugar using solventogenic strains of bacteria *Clostridium acetobutylicum*, followed, by the conversion of ABE mixture to long-chain ketones after a palladium-hydrotalcite (Pd-HT)-catalysed reduction. This catalytic reaction is carried out in Q-tube for 20 h at 250 °C, providing blends of ketones *via* dehydrogenation-aldol condensation in excellent overall yield (up to 86%). The more details on the experimental part along with the troubleshooting were described. The activity and recyclability of a number of catalysts in the chemical catalysis route to generate aliphatic ketones from a biomass-derived fermentation mixture (ABE or IBE) has been broadly explored in the procedures using previously reported Pd/C-K₃PO₄ [36] or transition metal based hydrotalcite catalysts [37].

6. OTHERS

Several papers have been published where the use of Q-tube is not the central subject of the research but it was employed just to speed up known processes. These examples will be cited briefly because the advantages associated to this device were not discussed in the original articles. In this context, the Q-tube was used to replace halogens with amino groups on inactivated substrates in the frame of a wider study aimed to develop estrogen analogues [38]. While a

series of reductive amination were performed under solvent free conditions to prepare anti-tubercular agents [39]. Q-tube was also recently used in inorganic synthesis to prepare iron and cadmium-based nanocrystals [40, 41].

CONCLUSION

In conclusion, the use of Q-tube to develop HPC is a field of interest that is becoming more and more important among the green chemistry practitioners. Here, we have collected the papers deliberately focused on the use of such technology but the scale of survey is certainly not exhaustive since in many articles the use of Q-tube is hidden in the experimental details or even in supplementary files. In the field of organic chemistry research, this device has been used in the development of MCRs, synthesis of heterocycles, transition metals-catalysed processes and biofuel manufacture, as a result Q-tube can be surely considered not only a mere alternative to the expensive MW synthesizers or the cheaper version of the high-pressure reactors but also a valuable tool, which will become indispensable in every chemical laboratory in the near future. Indeed, in almost every case in which it is used and compared with conventional heating and nonconventional technologies Q-tube emerged as the best alternative, affording high yields and clean reaction profiles.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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