



Review Of Literature On Methodologies For Organic Reactions

* GARIMA SAINI and ** Dr. SUKEERTI SINGH

*Research Scholar, Department of Chemistry, SunRise University, Alwar, Rajasthan (India)

**Professor, Department of Chemistry, SunRise University, Alwar, Rajasthan (India)

Email: Garimasaini2040@gmail.com

Abstract: One central challenge for XXI century chemists is the development of sustainable processes that do not represent a risk either to humanity or to the environment. In this regard, the search for more efficient and clean alternatives to achieve the chemical activation of molecules involved in chemical transformations has played a prominent role in recent years. The use of microwave or UV-Vis light irradiation, and mechanochemical activation is already widespread in many laboratories. Nevertheless, an additional condition to achieve “green” processes comes from the point of view of so-called atom economy. The removal of solvents from chemical reactions generally leads to cleaner, more efficient and more economical processes. This review presents several illustrative applications of the use of sustainable protocols in the synthesis of organic compounds under solvent-free reaction conditions.

[Saini, G. and Singh, S. **Review Of Literature On Methodologies For Organic Reactions**. *N Y Sci J* 2024;17(11):23-26]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 04. doi:10.7537/marsnys171124.04

Keywords: solvent-free; mechanochemistry; biocatalysis; microwaveactivation; photocatalysis; green chemistry; sustainable synthesis

Introduction

Classic chemical activation strategies are often associated with highly energy-demanding processes, as well as with the use of solvents that often times are not friendly with the environment and are commonly associated with costly and time-consuming procedures for the preparation and isolation of the desired product.

In recent decades, the search for more environmentally friendly processes constitutes one central theme of research and development in both academic and industrial chemistry. In the 1990s, Anastas and Warner coined the concept of “Green Chemistry” in terms of the design of products and processes that imply the reduction or elimination of substances that are harmful to life or the environment. This philosophy is based on the 12 principles advanced by Anastas and Warner [1].

Following the postulation of the twelve Green Chemistry principles, a significant number of chemists in both academic and industrial settings have focused their efforts on the development of processes that meet those criteria.

Conceptually, one obvious approach to achieve more sustainable processes is by avoiding the use of solvents, since this strategy minimizes the use of chemical auxiliaries while simultaneously decreasing the generation of waste [2]. Indeed, already in 2005, Sheldon argued that “*the best solvent is no solvent*” [3]. Occasionally, this strategy takes advantage of the fact

that some of the reactants are actually liquids at ambient temperature, which helps to achieve a homogeneous reaction mixture. Occasionally, a slight excess of one liquid reagent may be used and the process can still be considered solvent-free. In this context, the use of liquid adjuvants or activators acting as reaction medium can be particularly convenient—salient examples are ionic liquids and deep eutectic solvents.

Another aspect that is essential for the eventual fulfillment of the principles of Green Chemistry refers to the chemical activation associated to the reaction of interest. According to conventional methodologies, chemical reactions involving high activation energy require heating for long periods of time that result in high inherent cost and the concomitant risk of decomposition of reagents and/or products. In the last two or three decades, organocatalysis, mechanochemical activation, microwave irradiation, and photocatalysis are among the most effective alternatives for efficient activation under sustainable conditions.

As a topic of great current relevance, Green Chemistry has recently generated a significant number of review articles and monographs describing successful approaches to achieve the activation of chemical transformations in sustainable processes. The present review focuses on the discussion of

several recent applications of non-conventional chemical activation strategies in organic synthesis in the absence of solvents.

Review of Literature

Many conventional chemical processes make use of large amounts of toxic and volatile organic solvents (VOs) [4]. Re placement of such a hazardous reaction solvent is one of the main goals of green chemistry [8]. With growing global environmental awareness; the design of solvent-free green processes has gained noticeable attention from the researcher [9]. By and large, many reactions with solvent-free or solid-state conditions have been designed to reduce pollution and cost. These reactions are much easier for procedural work up and proceed cleanly and efficiently, hence in short span of time these reactions gained vital importance and popularity [2]. In 1990, the Green chemistry campaign had been initiated in the USA under pollution prevention legislation by keeping in view that organic substances could be produced an environmentally clean manner.

Chalcones and flavonoids constitute one more essential class of natural compounds with various pharmacological applications. These compounds have been synthesized by classical methods via Claisen-Schmidt condensation between respective ketones and aldehydes in various organic solvents. The equimolar mixture of substituted acetophenones and aldehydes was ground in open mortar and pestle in the presence of a base (NaOH/KOH) for a period of 4-15 minutes. On completion of the reaction, as monitored by TLC, chalcones were formed. The resulting chalcones were further purified by crystallization from a suitable solvent. These grinding mode reactions take place efficiently and smoothly in short reaction time giving high yields of the desired product [10]. The solvent-free grinding mode of reaction between these carbonyl compounds leads to the development of flavonoid chemistry. Grinding mode synthesis became more interesting

Polyfunctionalized 4H-pyrans structurally similar to the biologically active 1,4-dihydropyridines constitute a structural unit of many natural products and also act as potential calcium channel antagonists [5]. The 4H-pyrans have a wide range of biological and pharmacological activities, such as spasmolytic, diuretic, anti-coagulant and anticancer properties. In the treatment of neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease pyrans are very valuable [6]. Recently, the multicomponent synthesis of 4H-pyran was conducted through the reaction of aryl aldehyde, malononitrile and ethyl acetoacetate in the presence of magnesium oxide as a basic catalyst under solvent-

free environment using grinding method [4]. The same reactions were conducted with silica nanoparticles supported catalyst in ethanol solvent [7] and Cu(II) oxymetasilicate reusable catalyst in methanol solvent [8]. Smits et al. reported 4H-pyran derivatives by one-pot method in the presence of ammonium acetate as catalyst under solvent-free environment at room temperature [9]. Initially, Knoevenagel condensation under solvent-free conditions by grinding of aryl aldehyde with a malononitrile in the presence of ammonium acetate leads to the formation of benzylidene malononitrile derivative. To this derivative ethyl acetoacetate was added in the same reaction vessel, followed by grinding, workup and recrystallization in ethanol affording 4H-pyran.

Cyclopropane derivatives have a considerable place in organic chemistry. They can undergo electrophilic, nucleophilic, radical and rearrangement reactions and found as key intermediates in a wide range of natural compounds [7]. Usually, these compounds were synthesized by Simmons-Smith reaction [1] and metal-catalyzed decomposition of diazo compounds [2] in the presence of alkene. These methods often give a mixture of cis and trans products with a higher yield. Recently, high yield stereoselective synthesis of 1 carbomethoxy-2-aryl-3,3-dicyanocyclopropane has been reported through the reaction of arylidene malononitrile and methoxycarbonyl methyltriphenyl arsonium bromide in dimethoxyethane solvent in the presence of K_2CO_3 [3]. The novel route of high stereoselective synthesis of cis-1-carbomethoxy-2-aryl-3,3-dicyanocyclopropanes i.e. tetrasubstituted cyclopropane was also described with excellent yield by grinding at room temperature [4]. The reaction was completed within 20 minutes and the acquired cyclopropane derivative was purified by silica gel column chromatography with petroleum ether-ethyl acetate.

Reaction between 1,3-diaryl-2-propene-1-one (chalcone) and dipolar molecule or 1,2-binucleophile leads to the formation of pyrazoles. A well-known approach for pyrrole synthesis is the reaction between high polar chalcones with dipolar diazoalkanes and hydrazine derivatives. The high polarity of the double bond in chalcones offers them to react with various dipolar molecules. The conventional and well-known approach for the synthesis of pyrazoles was described by the treatment of Chalcones with 1,2 binucleophilic compounds, such as hydrazines [9]. These one-step or two-steps transformations are usually carried in acidic conditions with ethanol or acetic acid as the most common solvents [9-10]. Recently our research group described an efficient, simple and useful solvent-free protocol for the synthesis of 3,5-disubstituted-2 pyrazolines to overcome the use of hazardous solvent [10, Scheme 14]. The significant

advantages of methods are clean and mild reaction conditions, short reaction period, easy workup and higher yields of the desired product. In an experimental procedure, the mixture of 2-hydroxychalcones and hydrazines was thoroughly mixed with a pestle in an open mortar at room temperature. To this reaction mixture, the catalytic amount of acetic acid was added and grinding was continued for 5 minutes. The resultant reaction mixture was collected through workup and recrystallized from ethanol to give the desired product 2-pyrazolines.

The electron deficient nitro alkenes, the Michael acceptor underwent conjugate addition by carbon nucleophiles. This conjugate addition of nucleophiles results in two chiral centers via tetrahedral intermediate in a single step. A greener and highly efficient protocol has been reported for the synthesis of nitro amines and nitro sulfides with approximately 100% yield [5]. The mixture of nitro alkenes and amines mixed thoroughly ground with pestle for only 1-3 minutes and the reaction was monitored on thin layer chromatography. After 5 minutes, the corresponding adducts were obtained. This novel procedure has a number of advantages such as reduction of costs, waste, energy use, materials consumption, risks and hazards, and non-renewables [9]. N-Containing 1,4-Dihydropyridines are the important six membered heterocyclic compounds. These compounds exhibit a wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme [10], angiotensin converting enzyme inhibition and blood pressure control on chronic, nondiabetic nephropathies [10]. Arthur Hantzsch was discovered and utilized 1,3-dicarbonyl derivatives for the synthesis of dihydropyridines and pyridines with symmetrical substitution patterns as potential multi-component substrate [6]. In the classical Hantzsch reaction, the cyclocondensation of β -keto esters and aldehyde with ammonia gave 1,4-dihydropyridines. Many modifications and verifications to the Hantzsch synthesis have been made with the use of molecular sieves and pyridine [10], Yb(OTf)₃ [108], Me₃Si [1], p-TSA [11], TBAHS [1], ionic liquid [2] and polymers [3]. One of the research groups described a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation by grinding the three ingredients at room temperature in solvent-free conditions [4]. A mixture of aldehyde, dimedone and β -ketoester was grinded thoroughly in the presence of ammonium acetate for 10-20 minutes till completion of the reaction and after workup and recrystallization from ethanol to give respective polyhydroquinoline [4, Scheme 16]. The same reaction was also carried out in ethanol as a reaction solvent and refluxed for 4 hrs to

give only 55% yield of polyhydroquinoline. Therefore, the key advantages of the grinding method for the synthesis of polyhydroquinoline are short reaction time, easy workup and high yields.

The combination of solvent-free and K₂O–Al₂O₃ catalyst was found to be an efficient route for the synthesis of ethyl α cyanocinnamates under grinding [8]. Usually, ethyl α cyanocinnamates are prepared via the Knoevenagel condensation [5] of ethyl cyanoacetate with aromatic aldehydes under homogeneous conditions. The catalysts are ammonia, organic amines and their salts [9], some Lewis acids and bases such as ZnCl₂ [1], CdI₂ [5], MgO and ZnO [2] have also been used as catalysts. Recently, the use of inorganic supported catalysts in organic synthesis has rapidly increased because these reactions often involve easier work-up procedures than those needed for homogeneous methods [6]. The applications of inorganic catalysts promote the researcher towards the synthesis of ethyl α -cyanocinnamates using K₂O–Al₂O₃ [1]. The reaction mixture of aldehyde and ethyl cyanoacetate was grinded in the presence of K₂O–Al₂O₃ for 5 minutes at room temperature to yield corresponding ethyl α -cyanocinnamates. The method has a few advantages such as simple reaction procedure, easy workup and high product yield.

References

1. Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998.
2. Tanaka, K.; Toda, F. Solvent-Free Organic Synthesis. *Chem. Rev.* **2000**, *100*, 1025–1074.
3. Sheldon, R.A. Green solvents for sustainable organic synthesis: State of the art. *Green Chem.* **2005**, *7*, 267–278.
4. Krištofiková, D.; Modroková, V.; Mečiarová, M.; Šebesta, R. Green Asymmetric Organocatalysis. *ChemSusChem* **2020**, *13*, 2828–2858.
5. Kerru, N.; Maddila, S.; Jonnalagadda, S.B. Design of Carbon-carbon and Carbon-heteroatom Bond Formation Reactions under Green Conditions. *Curr. Org. Chem.* **2019**, *23*, 3154–3190.
6. Zangade, S.; Patil, P. A Review on Solvent-Free Methods in Organic Synthesis. *Curr. Org. Chem.* **2019**, *23*, 2295–2318.
7. Sarkar, A.; Santra, S.; Kundu, S.K.; Hajra, A.; Zyryanov, G.V.; Chupakhin, O.N.; Charushin, V.N.; Majee, A. A decade update on solvent and catalyst-free neat organic reactions: A step forward towards sustainability. *Green Chem.* **2016**, *18*, 4475–4525.
8. Gawande, M.B.; Bonifácio, V.D.B.; Luque, R.; Branco, P.S.; Varma, R.S. Solvent-Free and

- Catalysts-Free Chemistry: A Benign Pathway to Sustainability. *ChemSusChem* **2014**, 7, 24–44.
9. Hernández, J.G.; Avila-Ortiz, C.G.; Juaristi, E. Useful Chemical Activation Alternatives in Solvent-Free Organic Reactions. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G.A., Eds.; Elsevier: Amsterdam, The Netherlands, 2014; pp. 287–314.
 10. Hernández, J.G.; Juaristi, E. Recent efforts directed to the development of more sustainable asymmetric organocatalysis. *Chem. Commun.* **2012**, 48, 5396–5409.
 11. Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, 39, 301–312.

11/2/2024