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Neat reaction technology: A green tool

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A solvent free approach for organic synthesis is described which involve microwave exposure of neat reactants. A variety of cyclization and condensation are carried out including the efficient one pot assembly of heterocyclic molecules from *in situ* generated intermediates.

Keywords: Green chemistry, microwave irradiation, solid supported synthesis, heterocycles, neat reaction technology

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Green chemistry is a set of principles and practices that aim to reduce the generation, use of hazardous materials in chemical products and processes. It is some times characterized as preventive medicine for the environment. The concept of green chemistry is now widely adopted to meet the scientific challenges of protecting the human health and environment while simultaneously achieving commercial viability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. According to the work carried out by Paul T Anastas, the following basic principles[1] of green chemistry have been formulated.

(i) Prevention of waste,
(ii) Atom Economy,
(iii) Synthesis of less Hazardous Chemicals,
(iv) Designing of Safer Chemicals for Use,
(v) Use of safer solvents and auxiliaries,
(vi) Design of energy efficiency,
(vii) Use of renewable feedstock,
(viii) Reduction of unnecessary derivatization,
(ix) Use of catalytic reagents,
(x) Design of environment friendly and easily degradable products,
(xi) Real time analysis for pollution and prevention and
(xii) Inherently safer chemistry for accident prevention.

The target of these basic principles is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimum by-products or waste generation, as well as to eliminate the use of conventional organic solvents.

Role of microwave technology in Green chemistry

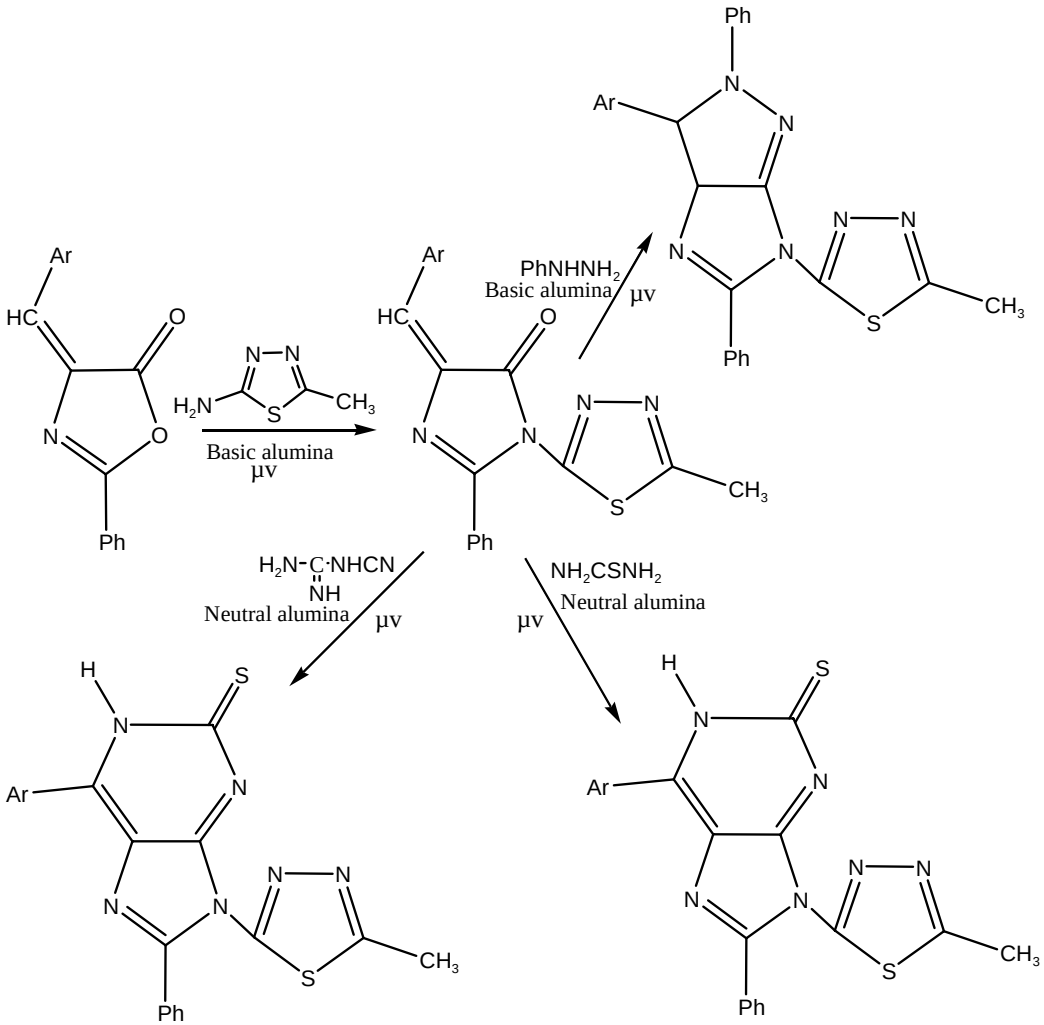
Microwave (MW) irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules[2]. The application of MV irradiation to provide enhanced reaction rate and improved product field in chemical synthesis has been extending to modern drug discovery in complex multi-step synthesis and it is proving quite successful in the formation of a variety of carbon-heteroatom bonds.

Choice of reaction vessel

Teflon, Polystyrene, Pyrex, or Borosilicates are the commonly used materials and are transparent to microwave *i.e.*; they do not have any effect of radiation. In case of sealed reaction vessel, very high temperature and high pressure are rapidly attained. This leads to a remarkable increase in the rate of reaction resulting in dramatic time saving. However the generation of high pressure also increases the risk of explosion during reaction irradiation, which is the chief constraint in the use of sealed reaction containers. Microwave reaction can be carried out in open vessel by using simple, inexpensive and safe equipment like open borosil beaker, conical flask or Erlenmeyer flask. Major disadvantage of open vessel is the loss of solvent.

Strict legal restrictions on pollution exposure have enforced the application of solvent-less conditions into practice. The reactions under solvent-free conditions are especially appealing as they provide the opportunity to work in an open vessel, thus circumventing the risk of generating high pressure in reaction vessels. In this endeavor, inorganic solid supports (alumina, bentonite, montmorillonite, *etc*.) have made a landmark, because reactions can be performed in a dry media or under solvent free conditions[3,4]. In addition, the use of solid supports[5] in conjunction with microwave leads to a higher yield, remarkable reactions rate enhancement, and high catalytic activity with the optimum utilization of energy. In this expeditious and solvent free approach the reactants were adsorbed over inorganic support/clays and exposed to microwave irradiation. This solvent-less approach provides an opportunity to conduct selective organic functional group transformations more efficiently and expeditiously, thereby increasing the potential of such reactions to be up scaled. This research group, during the synthesis of various pharmacologically active moieties, obtained similar results, which are now presented.

Solid supported synthesis of pyrazoline/imino pyrimidino/thioxo pyrimidino Solid supported synthesis of pyrazoline/imino pyrimidino/thioxo pyrimidino imidazoline[6]. An expeditious solvent free synthesis of pyrazoline/imino pyrimidino/thioxo pyrimidino imidazoline derivatives from oxazolines on solid support using microwaves has been described **(Scheme I)**. The reaction time was brought down from several hours to only a few minutes with improved yields as compared to conventional heating.



Scheme I—Solid supported synthesis of pyrazoline/imino/pyrimidino/thioxopyrimidino imidazoline[6]

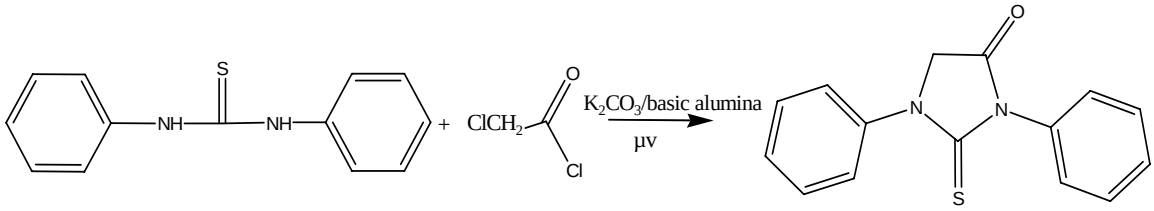
Solventless synthesis of thiohydantoin[7]. The problems associated with waste disposal of solvents and excess chemicals have been overcome by performing reaction without a solvent under microwave irradiation. The use of K_2CO_3 not only eliminates the need for external base to neutralize HCl evolved but also enables aqueous work-up **(Scheme II)**.

Neat reaction technology is a step forward in the direction of solvent free reactions and an alternative approach that eliminates the use of a solid support as well as solvent from the reaction. Solid supported reactions do not entirely meet the definition of no solvent as the usage of solvent is only eliminated at the primary reaction stage whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of products at the pre and post reaction stages respectively.

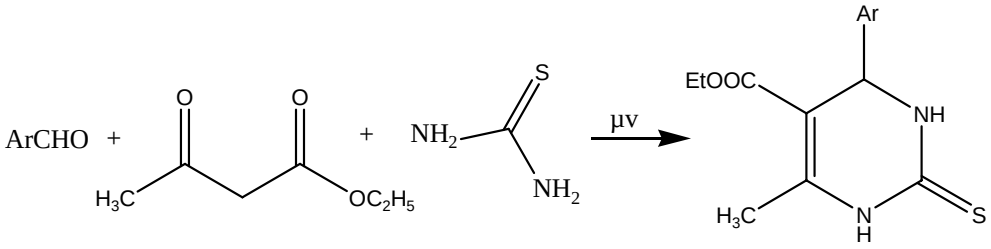
Synthesis of pyrimidines and pyridine derivatives[8]. 3,4-Dihydropyrimidine **(Scheme III)** and 1,4 dihydropyridine **(Scheme IV)** are readily prepared *via* modified Beginelli and Hantzsch reactions using environmentally benign process. Neat reactants subjected to microwave irradiation gave the required products more quickly and in better yield in comparison to the traditional methodologies.

Synthesis of 1,2-dihydrotriazine derivatives[9]. One pot neat synthesis of 1-aryl-4,6-diamino-1,2-dihydrotriazines using neat reaction technology under microwave is described **(Scheme V)**. Equimolar neat reactants *viz*. aldehyde, cyanoguanidine and aromatic amine when exposed to MW gave the required product in 2-3 min.

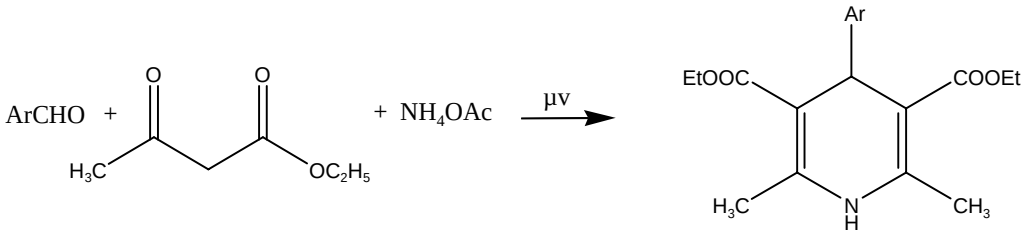
To broaden the scope of this MW assisted neat reaction technology accelerated heterocyclization approach, the assembly of ethylacetoacetate, aromatic aldehyde, and *o*-phenylenediamine for the synthesis of 1,5-benzodiazepines was investigated[19]. The 1,5-benzodiazepines have been studied for over a decade, largely because they show sufficient pharmacological[10] and clinical activity to warrant introduction as new drugs. Due to pharmacological utility of benzodiazepines several protocols have been reported for their synthesis. 1,5-benzodiazepines are synthesized by the condensation of diamine with α,β-unsaturated carbonyl compound[11], β-haloketone or



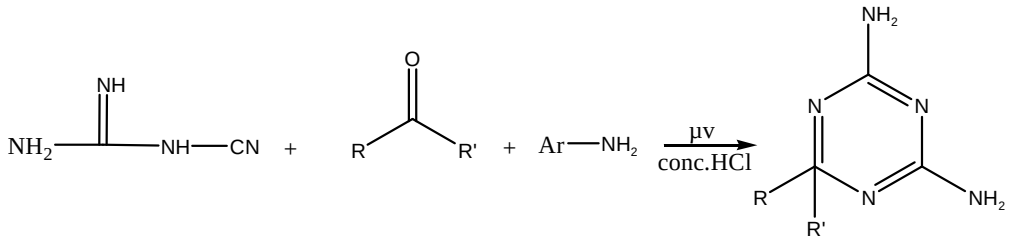
Scheme II—Solventless synthesis of thiohydantoin[7]



Scheme III—Synthesis of pyrimidines derivatives[8]



Scheme IV—Synthesis of pyridine derivatives[8]



Scheme V—Synthesis of 1,2-dihydrotriazine derivatives[9]

ketones[12]. A drawback to this reaction is the requirement of Lewis acids as well as protic acids as promoters. In order to improve the efficiency of synthesis, many catalysts have been tried such as BF_3-OEt_2[13], $NaBH_4$[14], polyphosphoric acid[15], SiO_2, $MgO/POCl_3$[16] and $Yb(Of)_3$[17]. Most of these processes suffer from major or minor limitations such as drastic reaction conditions, tedious work-up procedures, expensive and hazardous catalysts, stoichiometric amount of catalyst, and strong acidic conditions, thus rendering the procedure uneconomic and polluting one. This paper describes a facile synthesis of novel 1,5-benzodiazepines **4a-g** in microwave assisted neat reaction technology, eradicating the use of any acid or catalyst. Neutral conditions were tried in the light of our earlier work[18] on 1,5-benzodiazepines where *o*-phenylenediamine condenses with α,β-unsaturated carbonyls under neutral conditions, whereas rest of the reactions require acidic conditions. This is the first report on the synthesis of new series of 1,5-benzodiazepine **4a-g** using ethylacetoacetate **1**, aromatic aldehydes **2a-g** and *o*-phenylenediamine **3** without the use of any catalytic reagent at *p*H 7. One step synthesis was conducted for novel 2,3-dihydro-1*H*-1,5-benzodiazepines **4a-g** as shown in **Scheme VI**.

During the work, we obtained **5** as a side product in addition to the desired product. The formation of side product can be avoided by following the two step synthesis rather than one step condensation. Initially ethylacetoacetate **1** and aldehyde **2a-g** were added in equimolar ratio in an Erlenmeyer flask and irradiated for sufficient interval of time. Then *o*-phenylenediamine **3** was added which condenses with the intermediate and afforded the desired product exclusively **Scheme VII**.

Benzodiazepines were obtained in good yield within few minutes of irradiation. The results were summarized in **Table I**.

Conclusion

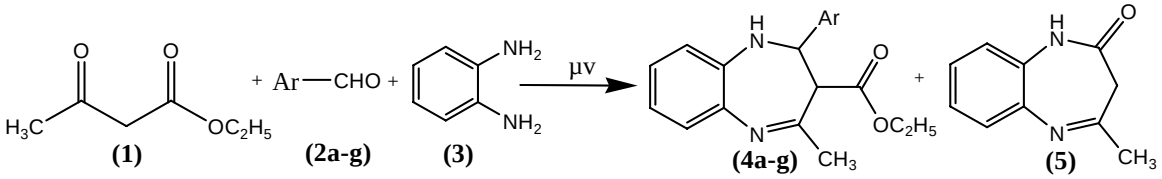
In conclusion, novel 3-ethylcarboxylate-4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepines **4a-g** are prepared in absence of any toxic and corrosive mineral acids or organic solvents. Interestingly, the two step synthesis leads to the formation of desired product only whereas the single step results in other side reactions also. The remarkable features of new procedure are high conversion, shorter reaction times, eliminations of hazardous reagents, cleaner reaction profile, solvent-free conditions and simple experimental and work-up procedure. Considering the advantages of this new methodology, various useful heterocyclic compounds can be synthesized. As a result a simple, economical and environmentally benign synthesis has been developed.

Experimental Section

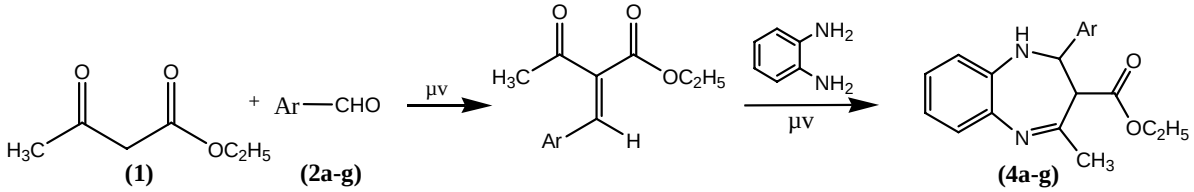
Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra (cm^{-1}) were obtained in KBr. ^1H NMR spectra were recorded in $CDCl_3$ on a FTNMR Hitachi R-600 spectrometer operating at 300 MHz using TMS as internal standard (chemical shift in δ, ppm). Elemental analyses were performed on a Heraues CHN Rapid Analyser. A Kenstar (Model No. OM-9925E) microwave oven (2450 MHz, 800 W) was used for all experiments. The purity of compounds was checked on silica gel coated aluminium plates (Merck). The approximate temperature, as measured by AZ, mini Non-contact Infrared Thermometer Model No. 8868, was 130°C to 150°C.

General procedure for the synthesis of 3-ethyl-carboxylate-4-methyl-2, 3-dihydro-1*H*-1, 5-benzo-diazepines 4a-g (ref. 19).

A. One step synthesis: Appropriated aromatic aldehyde **2a-g** (10 mmole), ethylacetoacetate **1** and *o*-phenylenediamine **3** were introduced in an Erlenmeyer flask. This was subjected to microwave irradiation for sufficient interval of time using resting intervals of 1 min after every 30 s of irradiation. Reaction progress was monitored by TLC. After cooling, the reaction mixture became sticky and the

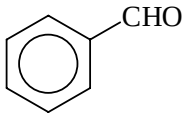
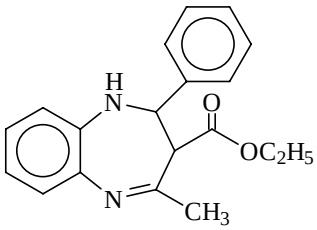
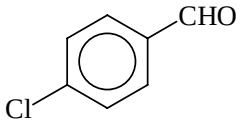
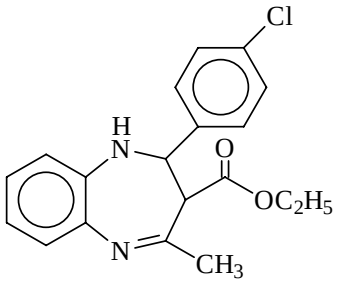
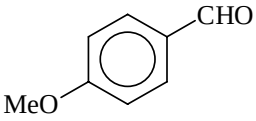
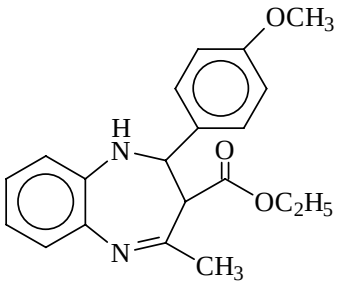


Scheme VI



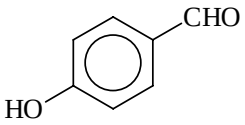
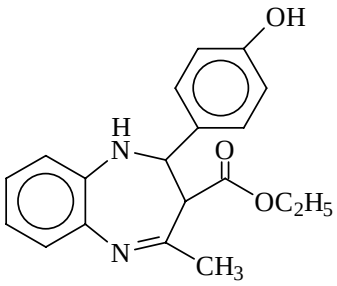
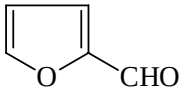
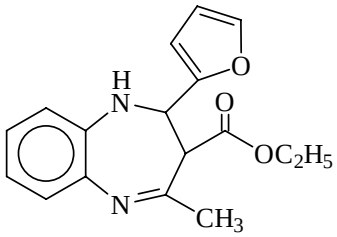
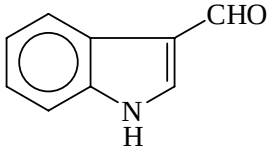
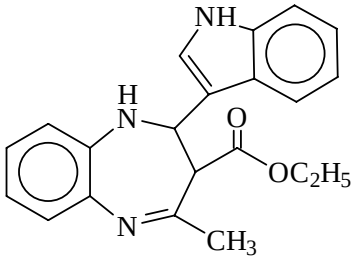
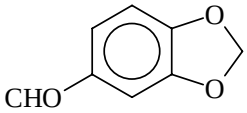
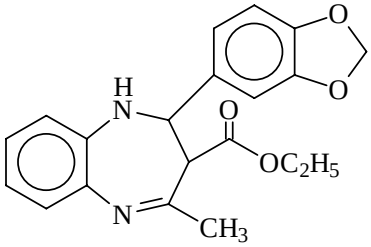
Scheme VII

Table I—Microwave synthesis of 1,5-benzodiazepines **4a-g** using two-step condensation

Entry	Aldehyde	Product	Yield (%)	Time of irradiation (min)
(i)			97	2.5
(ii)			94	3
(iii)			93	3

Contd

Table I—Microwave synthesis of 1,5-benzodiazepines **4a-g** using two-step condensation—*Contd*

Entry	Aldehyde	Product	Yield (%)	Time of irradiation (min)
(iv)			86	2
(v)			91	3.5
(vi)			87	2.5
(vii)			92	2.5

sticky solid was then triturated to afford the product. The product was purified using silica gel chromatography.

B. Two step synthesis: Equimolar amount of aromatic aldehyde **2a-g** (10 mmole) and ethylacetoacetate **1** were taken in an Erlenmeyer flask and irradiated in microwave oven. On formation of adduct as monitored by TLC examination, *o*-phenylenediamine **3** was added for further reaction. Reaction mixture was then mixed using a glass rod and again irradiated for the formation of pure desired product. The reaction mixture was worked-up in the same way as for method A.

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