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Suitable Multicomponent Organic Synthesis using Heteropolycompounds as Catalysts

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Abstract: Nowadays, scientists need to work with non-contaminating technologies. Some approaches include the use of multicomponent reactions (MCRs), and solid and reusable catalysts. Through MCRs it is possible to work without isolating intermediate products, so the use of auxiliary solvents is minimized.

Furthermore, catalysis by heteropolycompounds is a field of increasing importance worldwide. Heteropolycompounds are effective, reusable and stable solid catalysts that have intrinsic multifunctionality: they can be designed in order to enhance their redox or superacidic properties by varying the atoms in their formula.

The present review presents recent advances in the synthesis of organic compounds through multicomponent reactions by using heteropolycompounds as catalysts. Some of these compounds are: dihydropyrimidinones, quinazolinones, naphthol derivatives, pyridines, xanthenones, azabicyclo[2.2.2]octan-5-ones, dispiroheterocycles, imidazoles, spirofused heterocycles, and 1,4-dihydropyridines.

Keywords: Green chemistry, heterocycles, heteropolycompounds, multicomponent reaction, organic synthesis.

INTRODUCTION

There are many organic compounds that have remarkable biological applications and are constantly being prepared around the world. Some preparation methods involve the use of large quantities of mineral acids as stoichiometric catalysts, long reactions times, high temperatures, contaminating solvents and as a result, these processes generate environmentally hazardous substances. Sometimes, these processes also give unsatisfactory yields. Therefore, there is a real need for the use of non-contaminating technologies. One possible approach is the application of the principles that forms the basis of Green Chemistry.

As Deligeorgiev and co-workers have extensively described [1], Green Chemistry consists of a set of 12 principles, which were proposed by Anastas and Warner [2-4]. They give a new approach to the synthesis, processing and application of chemical substances, thus diminishing the hazards for human health and environmental pollution.

Multicomponent reactions (MCRs) are convergent reactions that maximize the participation of reactant atoms in the final product, so they enable proceeding according to the second principle (also known as 'atom economy principle'). MCRs allow working without isolating intermediate products, so they minimize the use of auxiliary solvents. Biginelli, Ugi, Hantzsch, Passerini and Mannich reactions are some examples of MCRs [5-15].

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According to the ninth principle, the use of reaction catalysts increases reactions rates, yields and selectivity to the desired product. In some other cases, reactions do not take place without a catalyst. Catalysis by both bulk and supported heteropolycompounds is a field of increasing importance worldwide. Numerous developments are being carried out in basic research as well as in fine chemistry processes. Heteropolycompounds are effective, reusable and stable solid catalysts that have intrinsic multifunctionality: they can be designed in order to enhance their redox or superacidic properties by varying the atoms in their formula.

Some recent advances in the application of heteropolycompounds as catalysts for multicomponent organic reactions are presented in the following sections.

NAPHTHOL DERIVATIVES

Heravi and co-workers presented two methods using silica-supported Preyssler nanoparticles as catalyst [16]. Amidoalkyl naphthols were prepared with high yields through two methods: heating at 90°C under solvent-free conditions and using acetonitrile (as reactant and as solvent) at 80°C. The catalyst can be reused after a simple work-up, with a gradual decline of its activity being observed (Scheme **1a**). Using the same Preyssler nanoparticles, Heravi also prepared carbamatoalkyl naphthols by heating at 90°C under solvent-free conditions for the appropriate time (Scheme **1b**) [17].

Khabazzadeh and collaborators prepared 1-amidoalkyl-2-naphthols using $Cu_{1.5}PMo_{12}O_{40}$ and $Cu_{1.5}PW_{12}O_{40}$ as catalysts [18]. The reactions were conducted in molten tetrabutylammonium bromide (TBAB) as ionic liquid at 100°C (Scheme **1c**). The reactions were catalyzed by 5 mol% of $Cu_{1.5}PMo_{12}O_{40}$ and 2 mol% of $Cu_{1.5}PW_{12}O_{40}$ in 90 and 80

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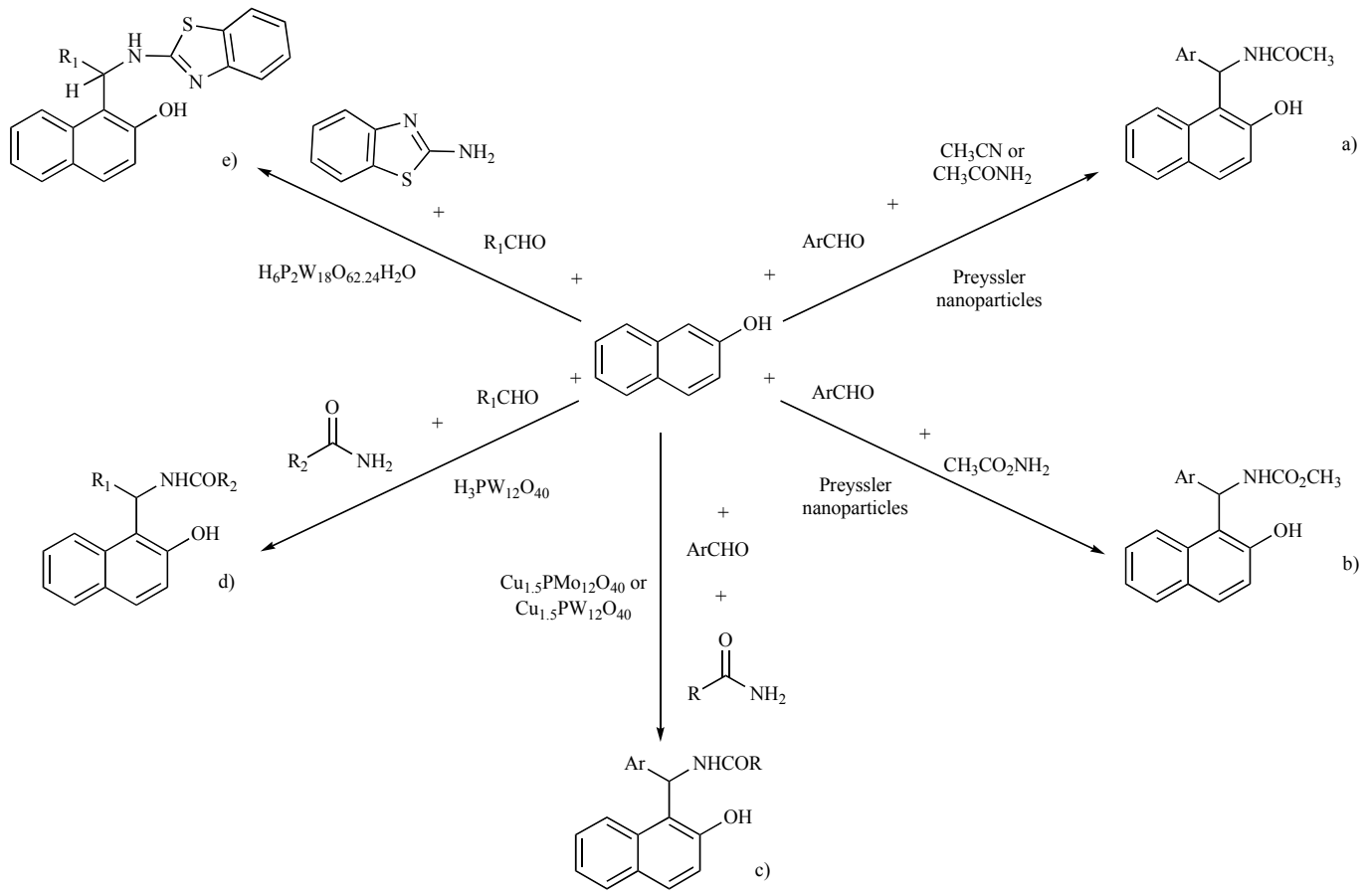


Scheme 1. Preparation of naphthol derivatives through five different ways.

min, respectively, giving product yields ranging from 74% to 95%. After three catalytic cycles, product yields decreased slightly, which indicates that the catalyst can be reused without significant loss of activity.

Dorehgiraee and co-workers presented a method to prepare 1-amidoalkyl-2-naphthols using 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$, 2 mol%) as catalyst, and the system was heated at 100°C for 80 min (Scheme **1d**) [19]. Moderate to high yields were obtained for the reaction of virtually all the aryl aldehydes examined.

Ohanian and collaborators prepared 2'-aminobenzothiazolomethylnaphtholes in high yields using Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$) as catalyst in water at 60°C for 5 h (Scheme **1e**) [20]. The products were recrystallized from acetone/water.

β-ACETAMIDO KETONES

Acetamido ketone derivatives are versatile intermediates in the synthesis of important biological and pharmacological organic compounds such as the natural nucleoside antibiotics nikkomycins, neopolyoxins, and several antibiotic drugs [21-24].

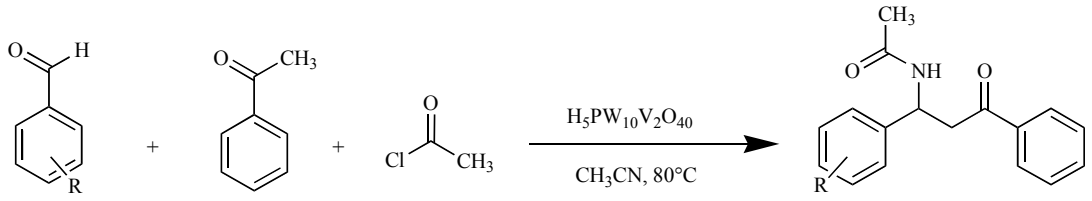
Tayebee and Tizabi did extensive research into β-amino ketone synthesis using Keggin, Wells-Dawson and Preyssler heteropolycompounds [25]. The reaction conditions were at reflux of acetonitrile, and the authors were especially interested in vanadium (V)-containing heteropolyacid activity. Some examples of the tested catalysts include: $H_5PW_{10}V_2O_{40}$; $H_7SiW_9V_3O_{40}$; $H_3PW_{12}O_{40}$; $H_6P_2W_{18}O_{62}$; $H_5PMo_{10}V_2O_{40}$; $H_6P_2Mo_{18}O_{62}$; $H_{14}NaP_5W_{30}O_{110}$; $H_5SiW_9Mo_2VO_{40}$; $2Na_2O{\cdot}P_2O_5{\cdot}12WO_3$. The best results were obtained by using 2.5 mol% of $H_5PW_{10}V_2O_{40}$.The synthesis of β-acetamido-β-(4-chlorophenyl) propiophenone is shown in Scheme **2**.

DIHYDROPYRIMIDINONES

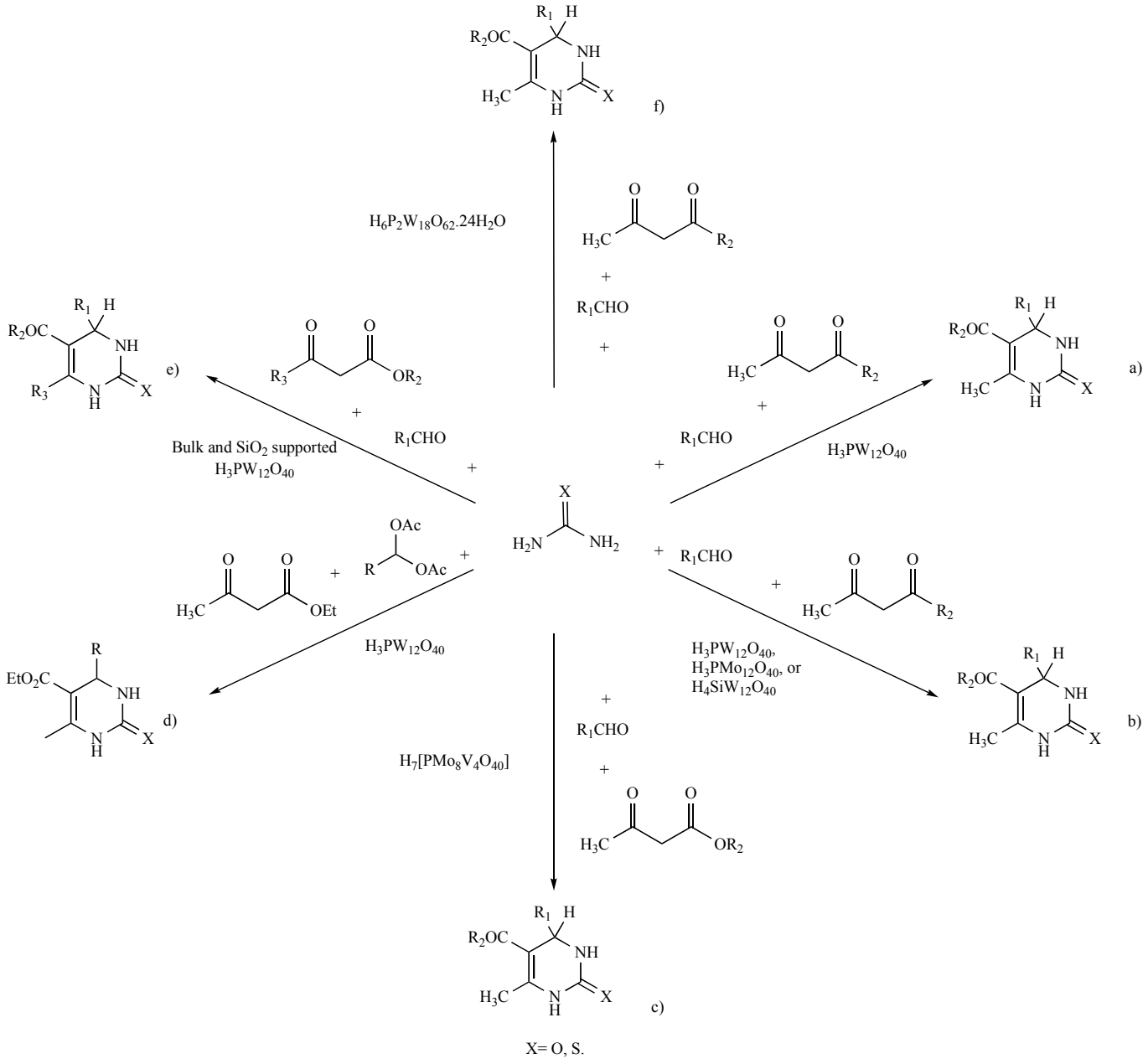
Biginelli compounds, 3,4-dihydropyrimidin-2(1H)-ones (DHPMs), are medicinally important as antibacterial, antitumor, antiviral and anti-inflammatory agents [26-28]. More recently, these compounds have emerged as potential calcium channel blockers, antihypertensives, α1a-adrenergic antagonists and neuropeptide antagonists [29]. In addition, the 2-oxodihydropyrimidine-5- carboxylate core unit is found in nature and in potent HIV gp-120-CD4 inhibitors [30-32].

Heravi and co-workers presented a method to prepare Biginelli compounds using 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$, 2 mol%) as catalyst, and the system was refluxed in glacial acetic acid for 6-7 h (Scheme **3a**) [33]. The product yields obtained by varying the reactants were between 40% and 75%, and after five runs under the same reaction conditions, the catalyst activity was almost the same as that of the fresh material.

Rafiee and Jafari tested three catalysts ($H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$) using four different solvents (ethanol, toluene, acetonitrile and chloroform) at 80°C [34]. They selected acetonitrile as the best choice for the reaction



Scheme 2. Preparation of acetamido ketone derivatives.

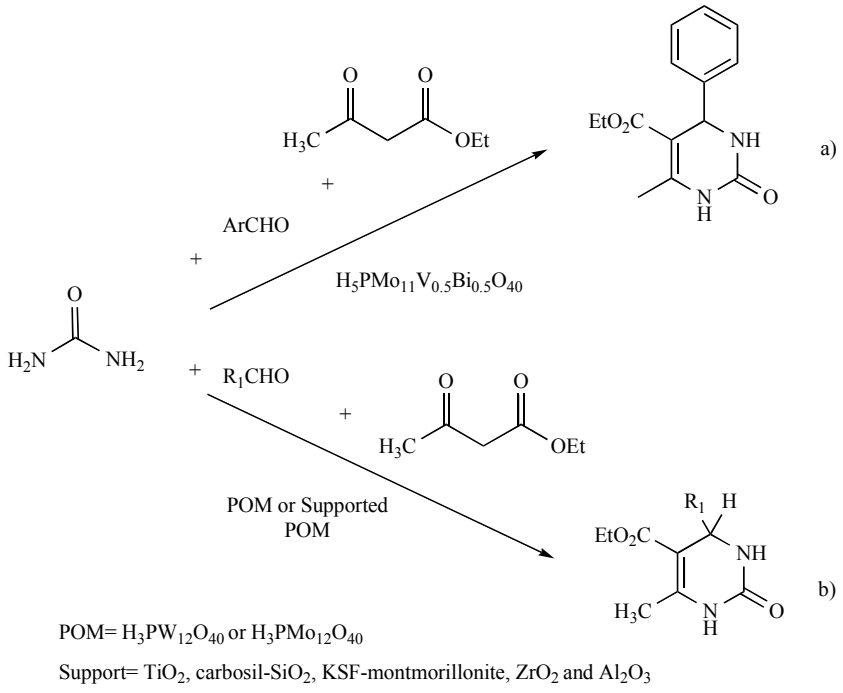


Scheme 3. Preparation of dihydropyrimidinone derivatives through six different ways.

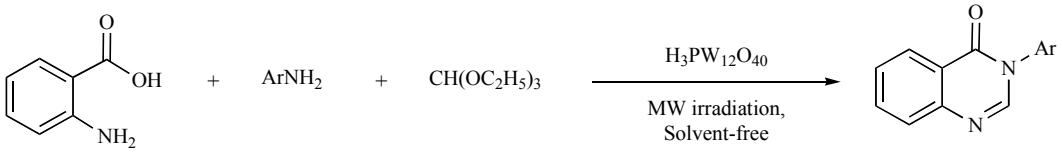
solvent and then synthesized a series of DHPMs obtaining yields ranging from 52% to 97% in 1 h (Scheme **3b**).

Gharib and collaborators used thirteen different catalysts (nine of them were Keggin-type heteropolyacids) and ten different reaction solvents [35]. The catalyst-free and solvent-free conditions were also tested. The best results were found with $H_7[PMo_8V_4O_{40}]$ under water reflux for 6 h (Scheme **3c**). After five catalytic cycles under the same reaction conditions, product yields were almost constant: up to 90%.

Khabazzadeh and collaborators presented a method to prepare Biginelli compounds using 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) as catalyst, in which the system was heated under solvent-free conditions at 100°C (Scheme **3d**). They obtained thirteen different compounds with yields greater than 66% in reaction times from 10 to 60 min [36].



Scheme 4. Preparation of dihydropyrimidinone derivatives by two methods.



Scheme 5. Preparation of quinazolinones.

Amini and co-workers also used 12-tungstophosphoric acid under solvent-free conditions [37]. DHPMs were prepared by heating at 80°C from 1 to 1.5 h using bulk $H_3PW_{12}O_{40}$, and for 2 h in the case of silica-supported $H_3PW_{12}O_{40}$. For both cases product yields were greater than 86% (Scheme **3e**).

Our research group presented two methods for DHPM preparation using Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$) as catalyst: under solvent-free conditions at 80°C for 1.5 h and at reflux of acetonitrile for 8 h (Scheme **3f**) [38]. For both methods product yields are from good to excellent.

Our investigation group tested four catalysts ($H_4PMo_{12}O_{40}$, $H_4PMo_{11}VO_{40}$, $H_6PMo_{11}BiO_{40}$, and $H_5PMo_{11}V_{0.5}Bi_{0.5}O_{40}$) under solvent-free conditions at 80°C for 1 h [39]. The reactivity order was: $H_5PMo_{11}V_{0.5}Bi_{0.5}O_{40}$> $H_4PMo_{11}VO_{40}$> $H_6PMo_{11}BiO_{40}$> $H_4PMo_{12}O_{40}$. In this reaction, $H_5PMo_{11}V_{0.5}Bi_{0.5}O_{40}$ can be recycled without loss of the catalytic activity. Then, twelve compounds were obtained with very good yields (80%-98%) (Scheme **4a**).

Fazaeli and co-workers studied a series of heterogeneous catalytic systems for DHPM preparation [40]. The materials were metal oxides (TiO_2, carbosil-SiO_2, KSF-montmorillonite, ZrO_2 and Al_2O_3) used as inorganic supports with Keggin-type polyoxometalates, $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ (Scheme **4b**). The products were obtained with high yields in short reaction times. The catalysts were recovered and reused: they presented almost constant activity.

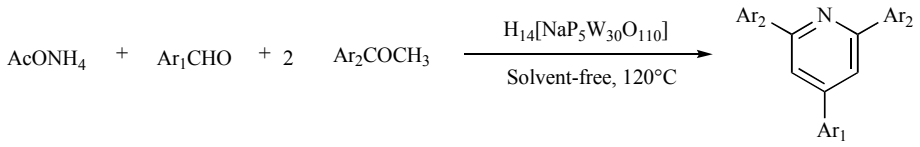
QUINAZOLINONES

Quinazolinones and their derivatives have very important biological properties such as antihypertensive, anticonvulsant, anti-inflammatory and antimalarial activity [41-44]. Moreover, the 4(3*H*)-quinazolinone moiety is found in several bioactive natural products [45, 46].

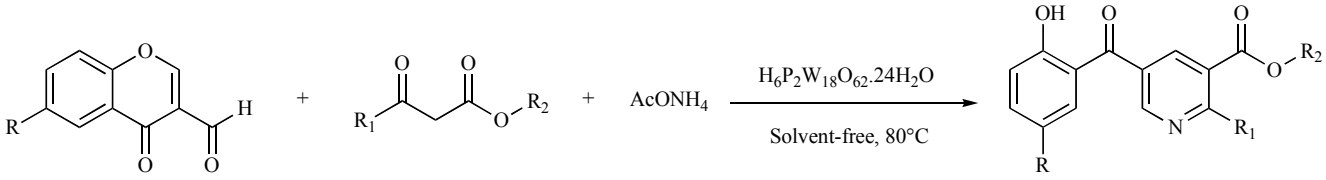
Ighilahriz and collaborators studied four catalysts ($H_3PW_{12}O_{40}$, $H_3SiW_{12}O_{40}$, $H_3SiMo_{12}O_{40}$, and $H_3PMo_{12}O_{40}$) under three different methods for quinazolinone derivative preparation: under reflux of toluene for 2 h with conventional heating, with 2-ethoxyethanol as reaction solvent under microwave irradiation, and using microwave irradiation under solvent-free conditions [47]. The most convenient reaction conditions are the third ones: although in all cases product yields were almost the same, the reaction time was tenfold shorter than in the other two cases. Regarding catalyst activity, product yields decreased in the following order: $H_3PW_{12}O_{40}$> $H_3SiW_{12}O_{40}$> $H_3PMo_{12}O_{40}$> $H_3SiMo_{12}O_{40}$. The best method is summarized in Scheme **5**.

PYRIDINES

Pyridines are present in the important niacin and B6 vitamins, and also in highly toxic alkaloids such as nicotine. They are important as anti-inflammatory, antiasthmatic, antidepressant, antitubercular and antibacterial agents. There are also examples of pyridines that act as potent HIV protease inhibitor, and some pyridine derivatives and their metal complexes are important building blocks for the construction



Scheme 6. Preparation of pyridine derivatives.



Scheme 7. Preparation of pyridine derivatives.

of chemosensors, self-organized assemblies, or photoactive molecular devices [48-54].

Heravi and co-workers prepared 2,4,6-triarylpyridines in the presence of Preyssler-type heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$) by heating at 120°C under solvent-free conditions (Scheme **6**) [55]. Most of the product yields were greater than 80% for reaction times from 3.5 to 7 h.

Our investigation group prepared substituted pyridine derivatives using Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$) as catalyst under solvent-free conditions at 80°C from 15 to 30 min (Scheme **7**) [56]. The products were obtained with excellent yields (60%-99%) and selectivity, and were also free of secondary products. Recycling of the catalyst showed that its activity is almost constant after three catalytic cycles.

The original idea was to prepare 1,4-dihydropyridines through the multicomponent Hantzsch reaction. In contrast with what takes place by using simple aldehydes, 3-formylchromones showed an alternative direction of the Hantzsch condensation reaction. Functionalized pyridine in the 2-, 3- and 5- positions was formed by opening the γ-pyrone ring after nucleophilic attack and subsequent cyclodehydration. So, we decided to optimize the method in order to prepare pyridine derivatives in good yields.

XANTHENONES

Xanthene derivatives have various important applications: as dyes in fluorescent materials for visualization of biomolecules and in laser technologies due to their useful spectroscopic properties [57]. They are also useful as bactericides [58] in photodynamic therapy [59], as anti-inflammatory [60] and antiviral agents [61].

Hassakhani and co-workers prepared 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones using 12-tungstosilicic acid ($H_4SiW_{12}O_{40}$, 3.5 mol%) as catalyst, and the system was heated at 100°C under solvent-free conditions for 15-40 min (Scheme **8a**) [62]. The products were obtained in yields greater than 82%, and the catalyst showed almost constant activity after four catalytic cycles.

Heravi and collaborators presented a method to prepare xanthene derivatives under solvent-free conditions by using a Preyssler-type heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$, 0.4 mol%) and heating at 120°C (Schemes **8b** and **8c**) [63]. The products were recrystallized from absolute ethanol, giving yields greater than 80% for reaction times of less than 2 h.

IMIDAZOLES

Imidazoles are one of the most important substructures found in a large number of natural products and pharmacologically active compounds. They are present in histidine, histamine and biotin, and they are also present as active components in several drug molecules: antiallergenic drugs, a hypnotic agent (Etomidate), a proton pump inhibitor (Omeprazole), and in the benzodiazepine antagonist Flumazenil. Therefore, imidazole and its derivatives are attractive compounds for organic chemists [64-68].

Heravi and collaborators prepared tetrasubstituted imidazoles at reflux of ethanol using 1 mmol% of Keggin heteropolyacids such as $H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $HNa_2[PMo_{12}O_{40}]$ [69]. In reaction times from 5 to 120 min, all catalysts achieved reaction yields greater than 83%, and $H_4PMo_{11}VO_{40}$ showed the highest activity (Scheme **9a**). The desired products could be easily separated: the heteropolyacid was soluble in ethanol at room temperature, but the products were not.

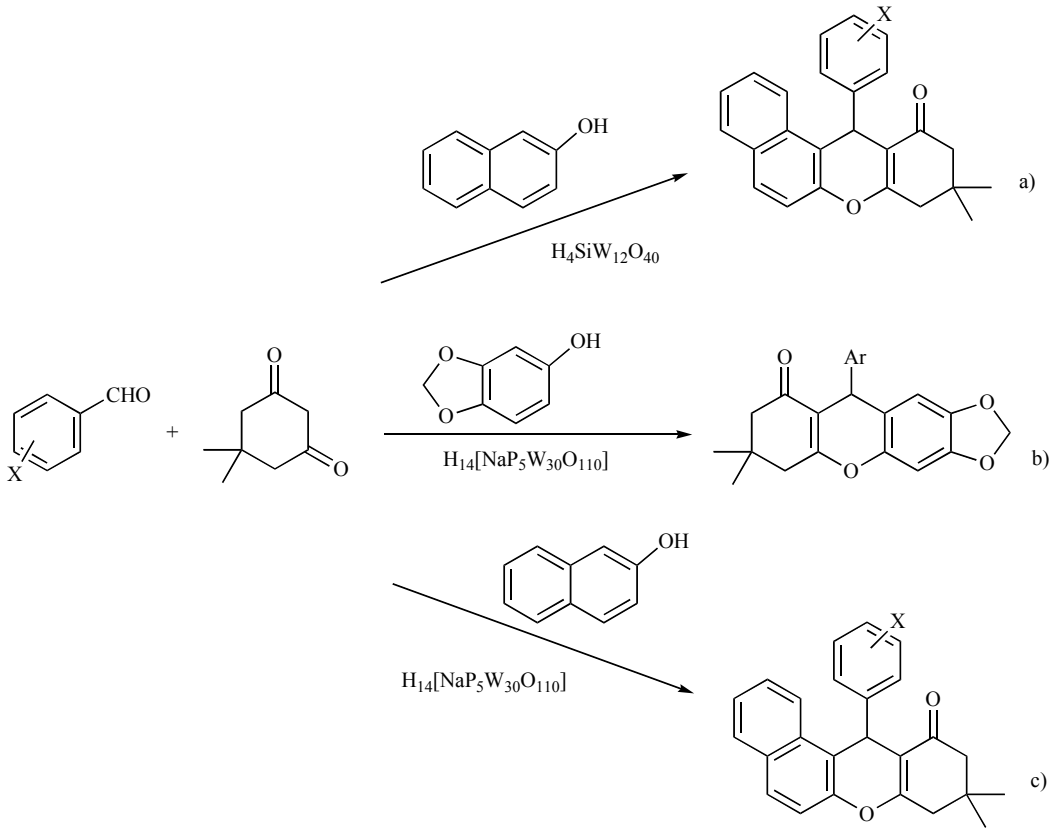
Heravi also presented a publication in collaboration with Kakhorani in which they described the preparation of tetrasubstituted imidazoles by using $K_7Na_3P_2W_{18}Cu_4O_{68}$ as catalyst in solvent-free conditions [70]. The products were obtained in excellent yields using 0.2 mol% of catalyst and heating at 140°C for 90 min (Scheme **9b**). The catalyst was reused and after five catalytic cycles, its activity was almost constant.

Javid and co-workers presented the tetrasubstituted imidazole synthesis using 1 mol% of a Preyssler-type heteropolyacid ($H_{14}NaP_5W_{30}O_{110}$) [71]. The reactions were carried out in ethanol at reflux temperature for 10-30 min (Scheme **9c**). The products were obtained with good to excellent yields, and after four catalytic cycles the loss of catalyst activity was low.

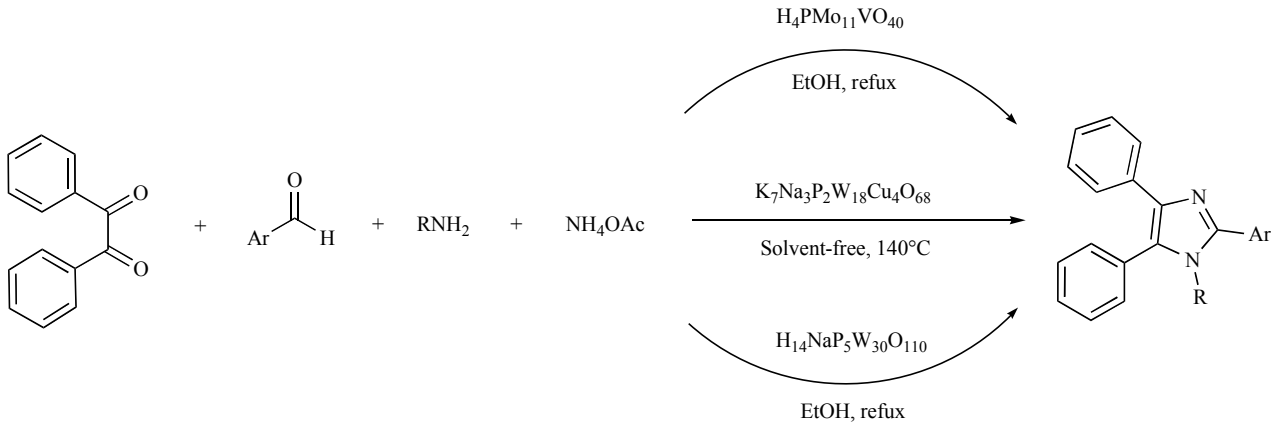
Chaskar prepared 1*H*, 3*H*- thiazolo [3, 4-a] benzimidazole derivatives using phosphomolybdic acid ($H_3PMo_{12}O_{40}$) in ionic liquid at 70°C for 45 min [72]. The desired products, which could act as potential HIV-1RT inhibitors as well, were obtained in good yields. The catalyst was reused in three catalytic cycles, showing almost constant activity (Scheme **10**).

PYRANOPYRAZOLES

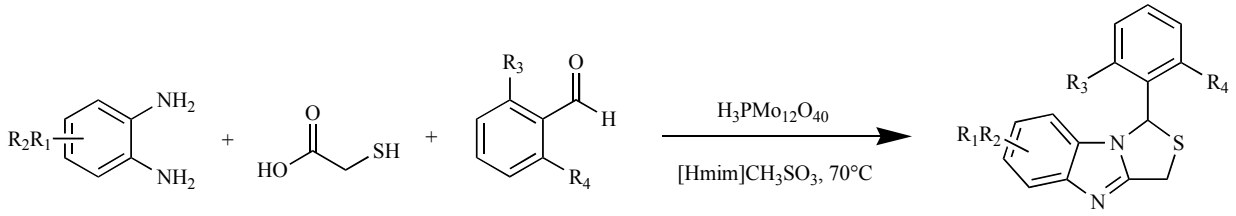
Pyranopyrazoles are bioactive compounds with important applications as anticancer, antimicrobial, anti-inflammatory,



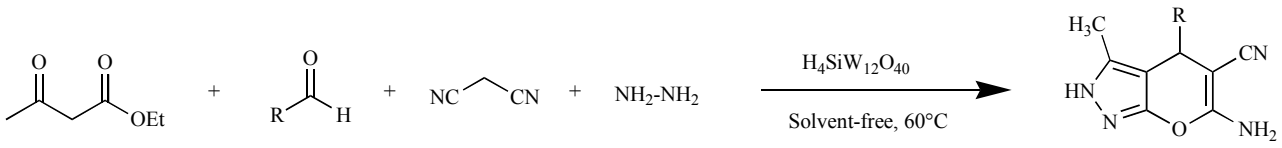
Scheme 8. Preparation of xanthenone derivatives.



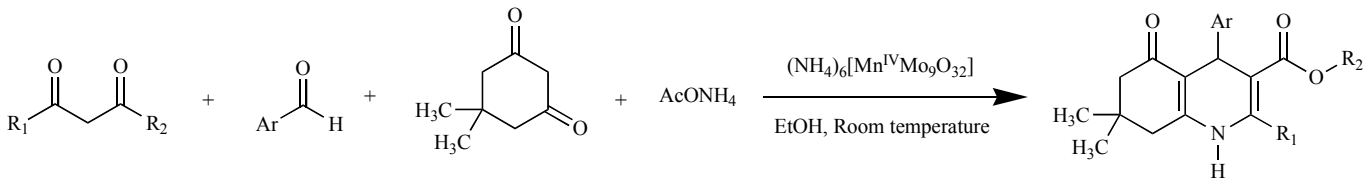
Scheme 9. Preparation of tetrasubstituted imidazoles through three different ways.



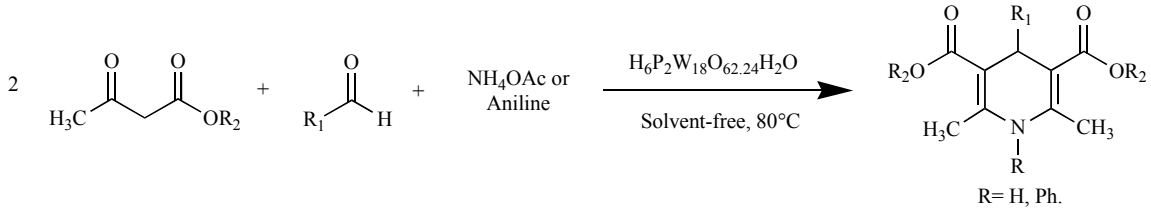
Scheme 10. Preparation of benzimidazole derivatives.



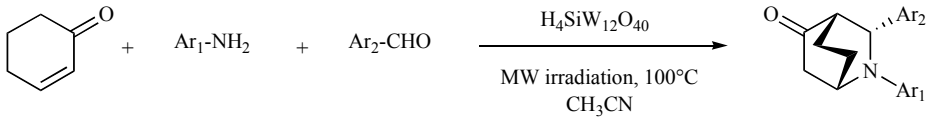
Scheme 11. Preparation of pyranopyrazole derivatives.



Scheme 12. Preparation of polyhydroquinoline derivatives.



Scheme 13. Preparation of 1,4-dihydropyridine derivatives.



Scheme 14. Preparation of azabicyclo[2.2.2]octan-5-ones.

insecticidal, and molluscicidal agents. They are also used as pharmaceutical ingredients and biodegradable agrochemicals [73-81].

Chavan and co-workers prepared pyranopyrazole derivatives through a one-pot four-multicomponent reaction using 2 mol% silicotungstic acid ($H_4SiW_{12}O_{40}$) as catalyst under solvent-free conditions at 60°C for 10 min (Scheme **11**). Twenty-two different pyranopyrazoles were prepared with yields ranging from 58% to 96 % [82].

1,4-DIHYDROPYRIDINES

1,4-Dihydropyridine (1,4-DHP) derivatives have significant biological activity. They function as calcium channel blockers and hence, they are suitable for the treatment of cardiovascular diseases, as vasodilators, antiatherosclerotic, antitumor, geroprotective, antidiabetic, neuroprotective, antianginal, anti-inflammatory, antitubercular, analgesic and antithrombotic agents, among other applications [48, 49, 83-94].

Supale and Gokavi reported a method to prepare polyhydroquinoline derivatives by using enneamolybdomanganate (IV) ($(NH_4)_6[Mn^{IV}Mo_9O_{32}]$) as catalyst in ethanol at room temperature. This material is one of the stable heteropolymolybdates containing Mn^{IV} as a heteroatom and is noncentrosymmetric [95]. In reaction times from 1.5 to 2 h products were obtained in yields greater than 82% (Scheme **12**).

Our research group presented a method for 1,4-DHPs preparation using Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$) as catalyst under solvent-free conditions at 80°C for 25 to 120 min (Scheme **13**) [96]. Product yields are from good to excellent, and after three catalytic cycles, catalyst activity is almost constant.

AZABICYCLO[2.2.2]OCTAN-5-ONES

Borkin and co-workers prepared azabicyclo[2.2.2]octan-5-ones using 12-tungstosilicic acid ($H_4SiW_{12}O_{40}$, 3.5 mol%) as catalytic material under microwave irradiation and acetonitrile as reaction solvent for 10 min at 100°C (Scheme **14**) [97]. The products were obtained in good yields and were pre-evaluated in two processes that are thought to be important in the development of Alzheimer's disease. Some compounds showed promising activity in these assays, raising the possibility of using them as lead scaffolds for the synthesis of dual target inhibitors.

DISPIROHETEROCYCLES

Spiro compounds are an important class of naturally occurring substances characterized by their pronounced biological properties [98-103] such as potent aldose reductase inhibitors, polio and rhinovirus 3C-proteinase inhibitors.

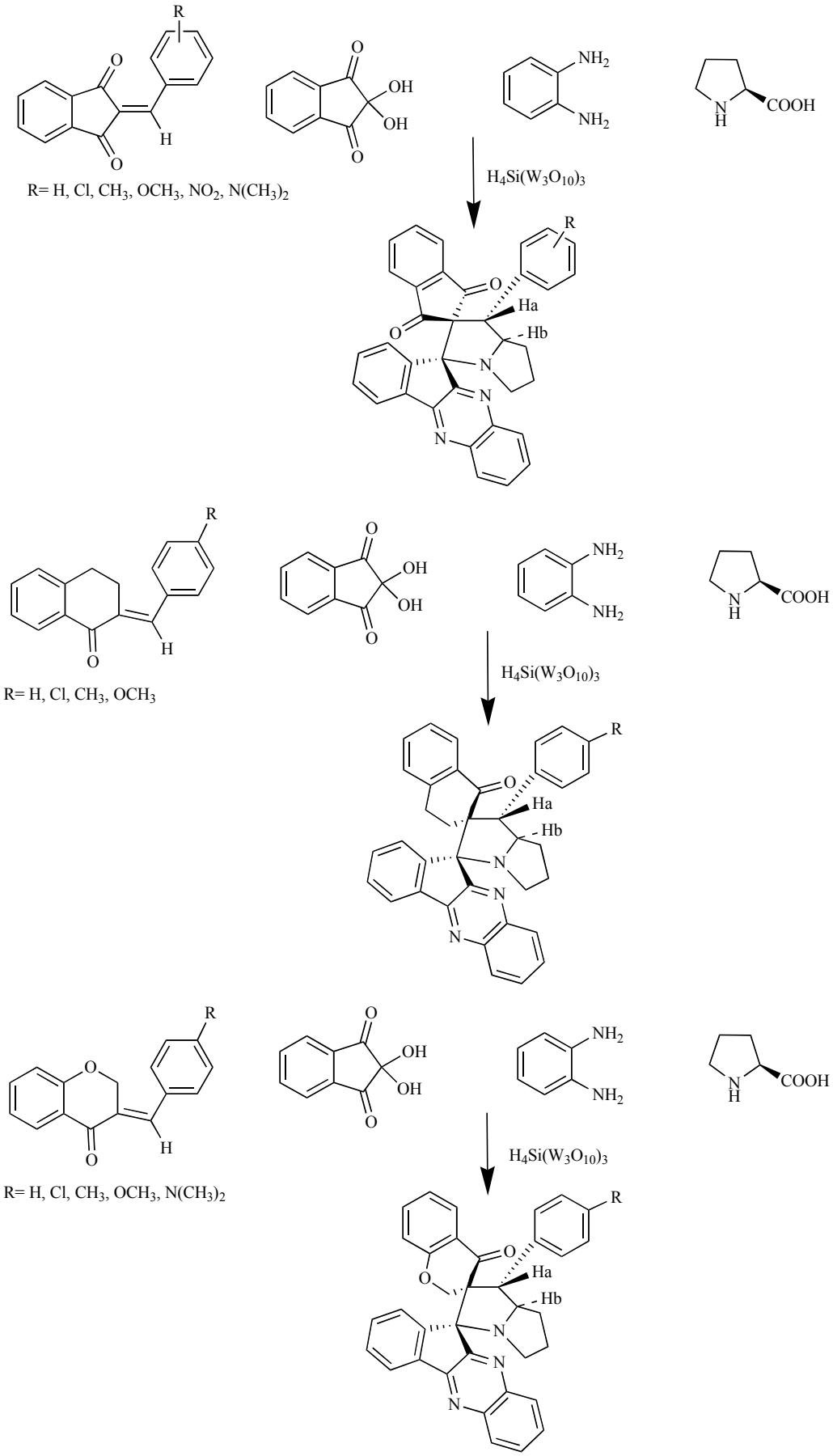
Babu and Raghunathan used $H_4Si(W_3O_{10})_3$ as catalyst in a one-pot four-component reaction to prepare dispiroindenoquinoxaline pyrrolizidine derivatives [104]. They tested the catalyst activity through three methods: $H_4Si(W_3O_{10})_3$ in methanol at reflux, $H_4Si(W_3O_{10})_3$ in acetonitrile at reflux, and $H_4Si(W_3O_{10})_3$-silica in acetonitrile at reflux. All methods presented good to excellent yields in reaction times of less than 4 h. Some reactions are presented in Scheme **15**.

SPIROFUSED HETEROCYCLES

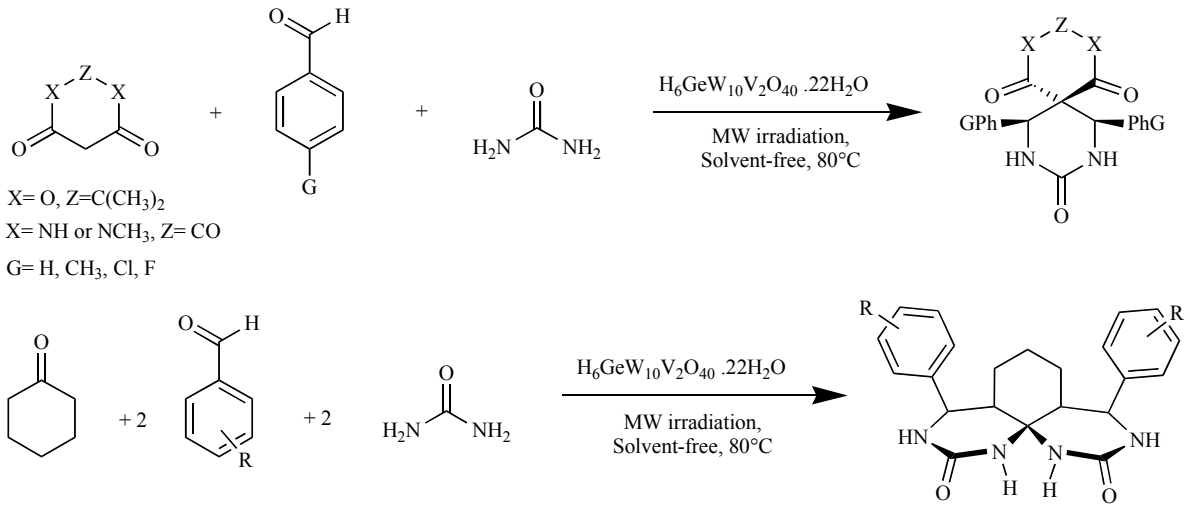
Jetti and collaborators used decatungstodivanadogermanic acid ($H_6GeW_{10}V_2O_{40}{\cdot}22H_2O$) for the synthesis of spirofused heterocycles under microwave irradiation in solvent-free conditions at 80°C [105]. The catalyst can be used for subsequent cycles without appreciable loss of activity (Scheme **16**).

In this work we have presented a compilation of modern and greener pathways, by using heteropolycompounds as catalysts, to prepare organic compounds. In most cases product yields are from good to excellent, and catalysts maintain their activity along several catalytic cycles.

Many researchers have used microwaves as an alternative energy source, lower reaction temperatures, green solvents



Scheme 15. Preparation of dispiroindenoquinoxaline pyrrolizidine derivatives.



Scheme 16. Preparation of spirofused heterocycles.

such as ethanol and water, and even some reactions under solvent-free conditions.

All the above-mentioned modifications help generate already known and new organic structures, maximizing the ecocompatibility of the systems. Those approaches are nothing more and nothing else than what the scientific community should adopt in their laboratories, greener and efficient chemistry to obtain organic products with minimal environmental contamination.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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