In the Name of Allah

the Beneficial the Merciful

Razi University

Faculty of Chemistry

Department of Organic Chemistry

M. Sc. Thesis

Title of Thesis

Organic cascaede reactions promoted with ionic liquids and solid-supported catalysts

Supervisors:

Prof. M. M. Khodaei

Dr. A. Alizadeh

By:

Somayeh Ostovar

July2011

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Evaluated and approved by thesis committee: as .....Exellent.....

Supervisor: Professor Mohamad Mehdi Khodaei …….....…….

Supervisor: Associated Professor Abdolhamid Alizadeh ……..…..……

External Examiner: Assistant Professor Hadi Adibi …….....……...

Internal Examiner: Assistant Professor Ebrahim Soleymani …….....….

July 2011

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Somayeh ostovar

Dedicated to:

My Dear Family

Abstract

In first part of this project, the use of a new and biguanid-like catalyst supported on silica as a recyclable catalyst provides a new route for the synthesis of a variety of arylalkylidene rhodanine derivatives through Knoevenagle reaction in at present of solvent at room temperature. Rhodanine derivatives and especially arylalkylidene rhodanines have proven to be attractive compounds due to their outstanding biological activities and have undergone rapid development as anticonvulsant, antibacterial, and antidiabetic agents.

In continue, For the synthesis of 4, 4'-(arylmethylene)-bis-(1H-pyrazol-5-ols) and 4-[(indol-3-yl)-arylmethyl]-1-phenyl-3-methyl-5-pyrazolones, using of a new and inexpensive ionic liquid provides in the cascade reaction in the absence of solvent at room temperature. 2-, 4-dihydro-3H-pyrazol-3-one derivatives are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds. This new ionic liquid has been used as an efficient catalyst for the first time and causes a remarkable decrease in the reaction time. Therefore, we believe that the work reported here would have the potential application in green chemistry.

Finally, we described for the first time a mild, efficient and green process was developed for synthesis new compounds of (6-hydroxy-5-((5-hydroxy-1-phenyl-3-methyl-5-pyrazolo-4-yl)(arylmethyl)-1,3-dimethyl barbituric utilizing relatively novel and cost effective synthesized acidic ionic liquid. Isolation of the product was simple and did not require solvent work-up. We described the application of cascade reactions for products synthesis under mild condition.

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Chapter one

Introduction

1.1. Organic cascade reactions

Cascade reactions constitute a fascinating branch of organic chemistry, and one which has been the subject ofintense research in recent years, as witnessed by the number of reviews that have appeared covering various aspects ofthese processes. (1) The undeniable benefits of cascade reactionsare well established, having been recounted on numerousoccasions, and include atom economy (2)as well aseconomies of time, labor, resource management, and wastegeneration. As such, cascade reactions can be considered tofall under the banner of "green chemistry". (3)For example, only asingle reaction solvent, workup procedure, and purificationstep may be required to provide a product that wouldotherwise have to be made over the course of severalindividual steps. Target-oriented synthesis provides the ultimate test ofreaction design and applicability. The design of cascades toprovide specific targeted molecules of considerable structural and stereo chemical complexity poses a significant intellectualchallenge and can be one of the most impressive activities innatural product syntheses.

Different authors use varying definitions as to what constitutes a cascade process. A variety of terms, including "cascade", "domino", "tandem", and "sequential", are used in the literature, often seemingly interchangeably and with liberal abandon, although efforts have been made to restore order to this area of reaction terminology. For our subjective purposes, we shall employ the term "cascade" to encompass all of the above descriptors. (4)

1.2.Multicomponent Cascade Reactions

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product (Figure1.1). (5) In a MCR, a product is assembled according to a cascade of elementary chemical reactions.

Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct a MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.

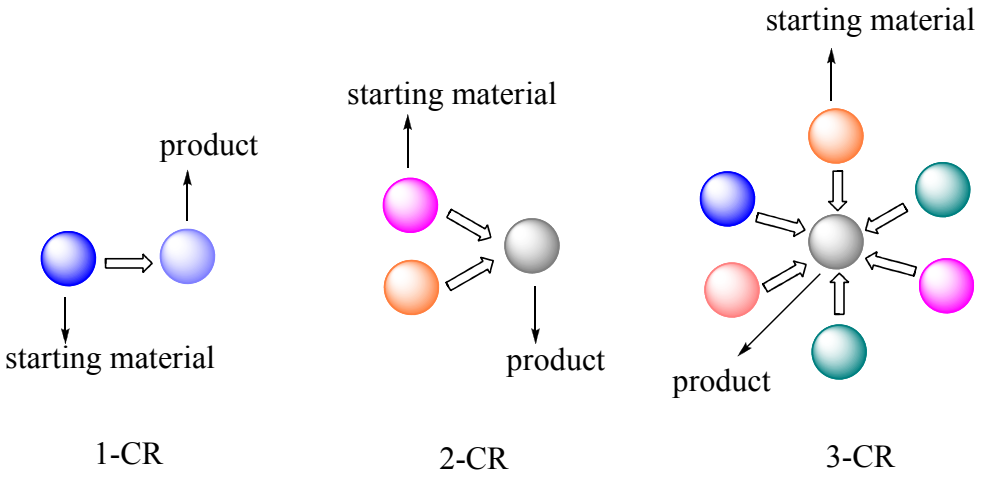
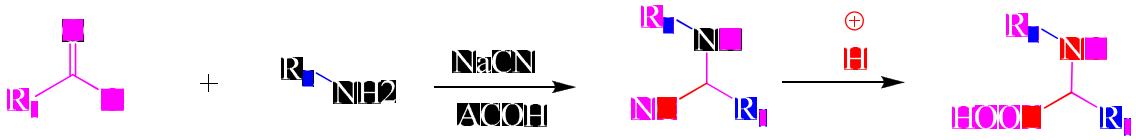


Figure 1.1

Multicomponent reactions have attracted considerable attentionsince an initial report in 1850 by Strecker, whointroduced a novel method for the synthesis of amino acids (Scheme 1.1).



Scheme 1.1

Applications of MCRs in all areas of applied chemistry are very popular because they offer a wealth of products, while requiring only a minimum of effort. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one-pot.Multicomponent cascade reactions are useful method for the construction of polycyclic skeletons, which are important cores for biological activities and this is important from the economical point view and from the

green chemistry (Figure 1.2).

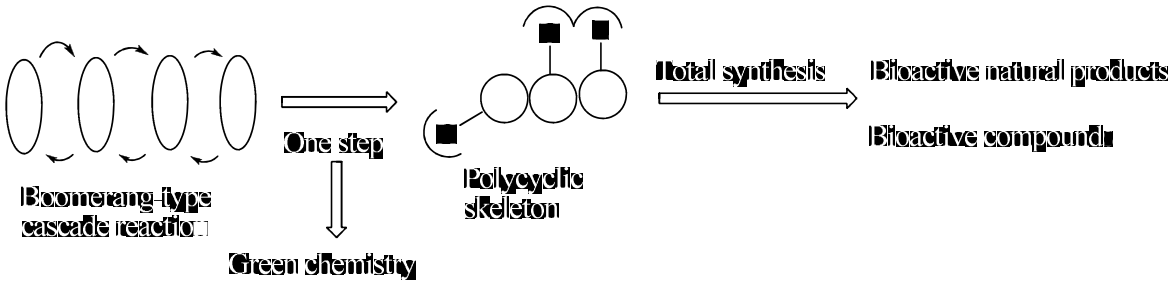
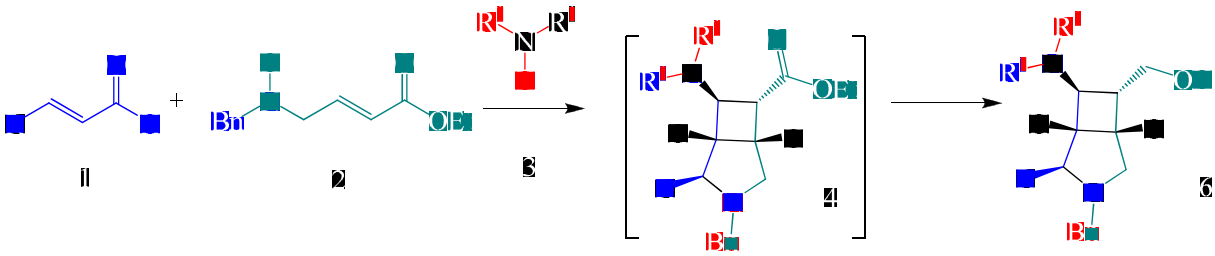


Figure1.2

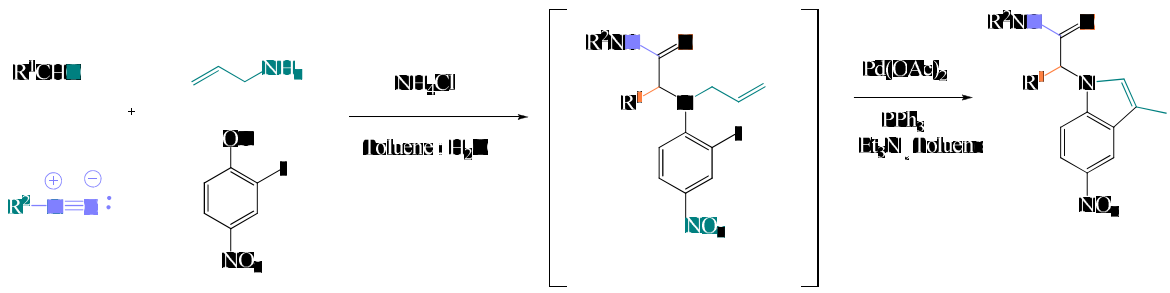
A variety of cascade reactions carried out under multiple reaction conditions, such as pericyclic, polar double Michael reaction, aza double Michael reaction, Michael–aldol reaction, and radical and transition metal catalyzed reaction conditions, has been investigated. (6) As a typical example of the application of this methodology, a synthetic plan of 3-azabicyclo [3.2.0] heptane derivatives is shown in scheme 1.2.



Scheme 1.2

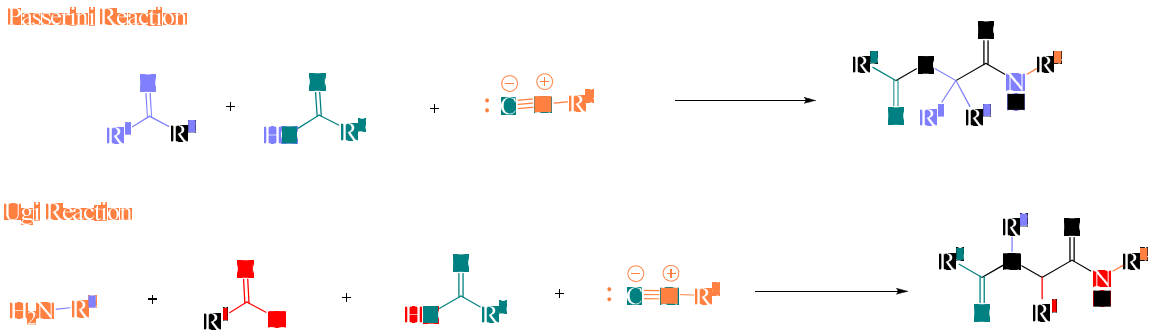
As it is seen, a novel multicomponent cascade reaction leads to the formation of a strained 3 azabicyclo [3.2.0] heptane derivative 4. This unstable esteris reduced in a one-pot procedure to a stable alcohol 6. The formation of the bicyclic product is highly diastereoselective, predominantly affordingone diastereoisomer. The obtained azabicycloheptanes are important pharmacophores. (7)

Laurent El Kaim reported that synthesis of ortho-iodonitrophenol in Ugi-Smiles reaction coupled with Heck cyclization gives new access to indole scaffolds. The sequence can be performed in a one-pot reaction if the residual isocyanides is neutralized prior to the addition of the palladium catalyst (Scheme 1.3). (8)



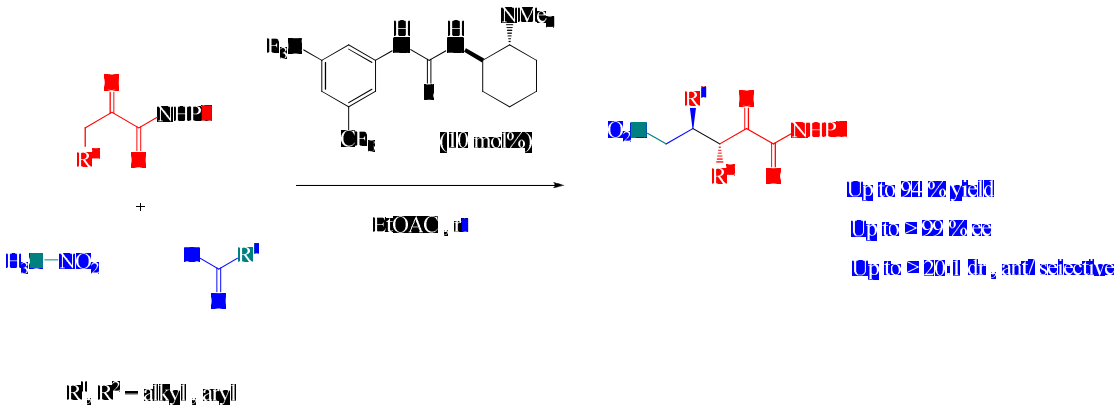
Scheme1.3

The Ugi reaction was first reported by Ivar Ugi in 1959 andalong with the Passerini reaction, it is classified as an isocyanides-based multicomponent reaction.The prototypical reaction (Scheme 1.4) results in the formation of a α-N-acylamino amide. The reaction is usually conducted in a polar protic solvent such as methanol, and some success in water has also been shown. (5)



Scheme 1.4

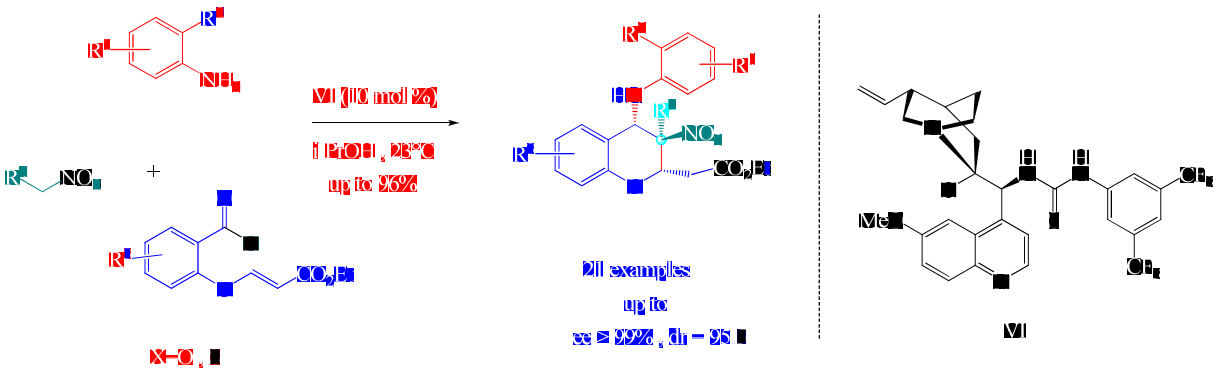
The first organocatalytic enantio- and diastereoselective conjugate addition of α'-ketoamides to nitroalkenes has been achieved using a bifunctionalamino thiourea catalyst (Scheme 1.5).



Scheme 1.5

In this new approach, the substrate amide proton plays a critical role in the formation of the Michael *anti*-adducts inhigh yields and high stereoselectivities. To illustrate the high synthetic potential of this methodology, the diastereo- and enantioselectivesynthesis of a hexasubstituted cyclohexane via a Michael-Michael-Henry cascade reaction is described. (9)

A catalytic asymmetric aza-Michael-Michael addition cascade of anilines to nitroolefin enoates in the presence of chiral bifunctional thioureacatalysts has been disclosed (Scheme 1.6).



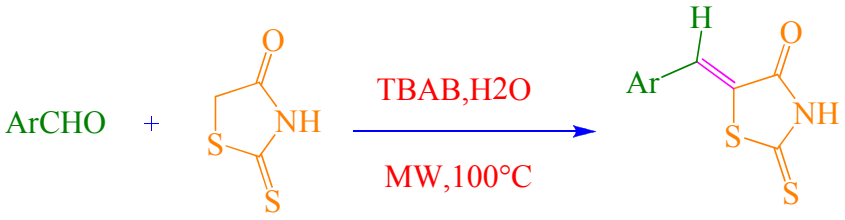
Scheme 1.6

This reaction provides a mild and efficient approach to polysubstituted chiral 4-aminobenzopyrans bearing threeconsecutive stereocenters in high yields with excellent stereoselectivities. (10)

1.3. Arylalkylidenerhodanine derivatives

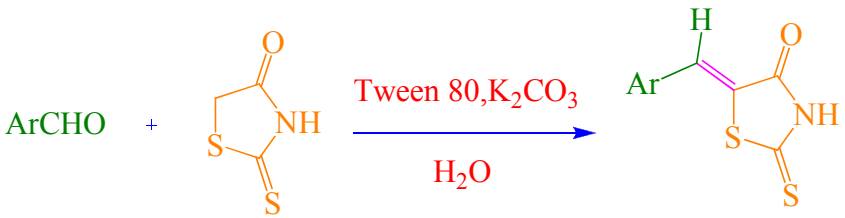
Rhodanine derivatives and especially arylalkylidene rhodanines have proven to be attractive compounds due to their outstanding biological activities and have undergone rapid development as anticonvulsant, antibacterial, and antidiabetic agents. (11) A series of arylalkylidene rhodanines have also been reported as Hepatitis C Virus (HCV) protease inhibitors (12) or as novel inhibitors of UDP N-acetylmuramate/L-alanine ligase. (13) Also rhodanine derivatives have attracted considerable pharmaceutical interest. Therefore, the preparation of this heterocyclic core unit haattracted the attention of many organic chemists. Following, few synthetic routes to rhodanine derivatives are represented. (14)

A series of benzylidenerhodanine derivatives were synthesized by the crossed-aldolcondensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide(TBAB) as phase transfer catalyst in water under microwave irradiation (Scheme 1.7). (15)



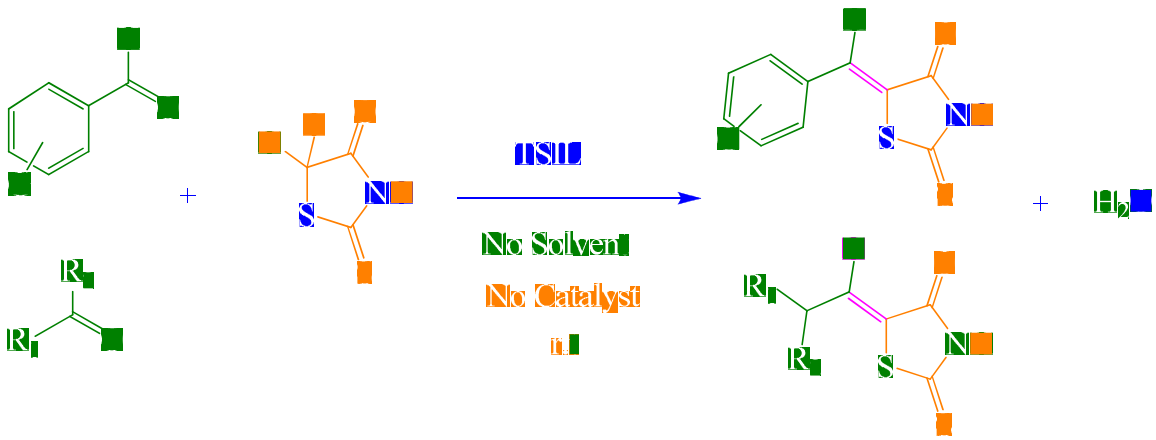
Scheme 1.7

Luo et al. (16) reported different types of aromatic aldehydes, containing electronreleasingor electron-withdrawing groups were subjected to condensation with rhodanine, inthe presence of potassium carbonate in Tween (scheme 1.8). (17)



Scheme 1.8

Alizadeh etal. (14) reported that2-hydroxyethylammonium formate acts as a task-specific ionic liquid (TSIL) for the Knoevenagelcondensation of carbonyl compounds with rhodanine to afford arylalkylidene rhodanines under solvent-free conditions in good to excellent yields. Additionally, compared with those in organic solvents, the yields obtained in thepresence of the ionic liquid were significantly increased (Scheme 1.9).

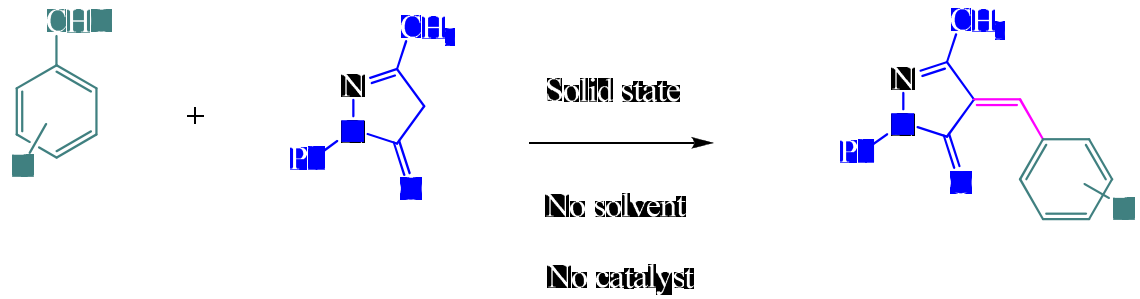


Scheme 1.9

1.4. Arylalkylidenepyrazolon derivatives

The pyrazole ring is a prominent structure motif found in numerous pharmaceutically activecompounds. This is mainly due to the easy preparation and important biological activity.Pyrazoleframework plays an essantial role in biologically active compounds and therefore represents anintrasting template for combinatorial as well as medicinal chemistry.The pyrazole nucleusis a ubiquitous feature of fertile source of medicinal agents such as antibacterial, antifungal, antiviral, antitubercular,antiamoebic, antiandrogenic etc. Someofthesecompoundshavealsoexhibitedantiinflammatory,antidiabetic,anaesthetic,analgesic and antiparasitic properties.Manypyrazoles have been found to be luminescent and fluorescentagents.In addition pyrazoles haveplayed a crucial role in the development of theory in heterocyclic chemistry and also usedextensively as useful synthon in organic synthesis. (18)It is interesting to note that pyrazoles arereported as well known pharmacophores.Pyrazole derivatives have a long history of application in agrochemicals and pharmaceuticalindustry as herbicides and active pharmaceuticals.It exhibits high chemical reactivity; especially, the C_2 can easily undergo electrophilic reactions in solution due to its high electron density.1-Phenyl-3-methyl-4-arylmethylene-5-pyrazolones are very useful intermediates in the synthesis of substituted pyrazolones, generally, which are prepared by the condensation of 3-methyl-1-phenyl-5-pyrazolone with aromatic aldehydes. Recently, some new methods such as microwave irradiation, supported solid catalyst, solid state reaction, *etc.* have been applied to facilitate this reaction. (19)

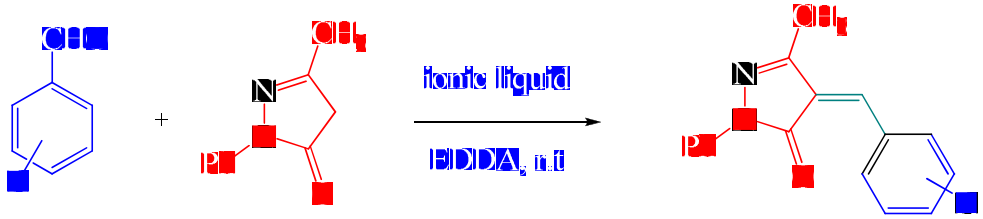
Li Xireported in 1996 a simple and straightforward procedure using mild conditions for solid-state combinatorial synthesis of 4-arylidene-3-methyl-1-phenyl-5-pyrazolon (yield 50%-70%) (Scheme1.10). (20)



Scheme1.10

An efficient and environmental benign method is reported for the condensation of3-methyl-1-phenyl-5-pyrazolone with carbonyl compounds in ionic liquids [Bmim] BF_4

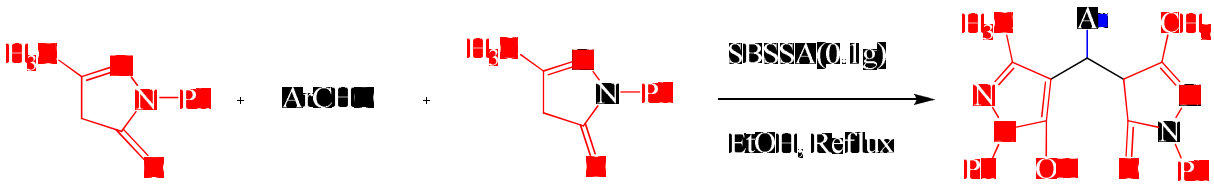
and[Bmim] PF_6 catalyzed by ethylenediammonium diacetate (Scheme 1.11). (19)



Scheme 1.11

1.5. The synthesis of 4, 4'-(arylmethylene)-bis-(1H-pyrazol-5-ols)

The conventional chemical approach to 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidenepyrazolones and its base-promoted Michael reaction, and also one-pot tandem Knoevenagel–Michael reaction of arylaldehydes with 2 equiv of 5- methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one performed under a variety of reaction conditions. (21-22)2,4-Dihydro-3H-pyrazol-3-one derivatives including 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) have a broadspectrum of approved biological activity, being used as antiinflammatory (23),antipyretic (24),gastric secretion stimulatory (25),antidepressant (26),antibacterial (27), and antifilarial agents. (28) Silica-bonded S-sulfonic acid (SBSSA) is employed as a recyclable catalyst for the condensation reaction ofaromatic aldehydes with 3-methyl-l-phenyl-5-pyrazolone. This condensation reaction was performed inethanol under refluxing conditions giving 4, 4'-alkylmethylene-bis-(3-methyl-5-pyrazolones) in 75–90% yields (Scheme 1.12). (28)



Scheme 1.12

Ionic liquid [HMIM] HSO4is shown to be an efficient catalyst for the synthesis of 4, 4'-alkylmethylene-bis-(3-methyl-5-pyrazolones) through the condensation reaction of arylaldehydes and 3-methyl-1-phenyl-5-pyrazolone underultrasonic irradiation at room temperature (scheme 1.13). (29)