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Potassium hydrogen sulfate: An efficient catalyst in organic reactions

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ABSTRACT

Potassium hydrogen sulfate, $KHSO_4$, has been used in many organic preparations as a good solid catalyst. The $KHSO_4$ has received considerable attention since it is an inexpensive, eco-friendly, highly reactive, easy to handle and non-toxic catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. We wish to report some applications of this catalyst in organic reactions.

1. Introduction

In recent years, the use of solid acids as heterogeneous catalysts has received significant interest in different areas of organic synthesis [1]. Solid acids have many advantages such as ease of handling, decreased reactor and plant corrosion problems, and environmentally safe disposal [2]. Also, wastes and by-products can be minimized or avoided by developing cleaner synthetic routes [3]. There is current research and general interest in heterogeneous systems because of their importance in industry and in developing technologies [4,5]. Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically more viable. $KHSO_4$ is one of the components of a triple salt with the formula $2KHSO_5.KHSO_4.K_2SO_4$ which is known as Oxone and is used as a highly efficient oxidant in many organic reagents [6]. $KHSO_4$ is a reusable, green, inexpensive, convenient, easy to handle, non-toxic, available and efficient catalyst for various organic reactions and can be used as a solid catalyst under homogeneous and heterogeneous conditions. Some important organic transformations have been performed successfully in the presence of $KHSO_4$. The catalyst was recovered, activated and reused for three consecutive times with only slight variation in the yields of the products. We believe that a great number of acid catalyzed organic reactions could be performed by using this catalyst and its use has been growing rapidly.

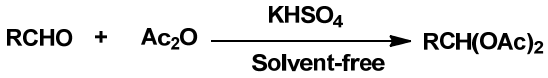
2. $KHSO_4$ and functional group transformation

2.1. Protection of carbonyl groups

2.1.1. Synthesis of 1,1-diacetates

1,1-Diacetates are synthetically useful as protecting groups for aldehydes due to their stability and easy conversion into parent aldehydes [7]. They are also important building blocks for the synthesis of dienes for Diels-Alder cycloaddition reaction [8].

A simple, mild, effective and green method to form acylals from aliphatic and aromatic aldehydes in good to excellent yields (85-98%) in the presence of $KHSO_4$ as a catalyst under solvent-free conditions were performed. Ketones are not affected under the reaction conditions. The method has advantages in terms of high yields, high selectivity, short reaction times, ease of operation, and use of a relatively non-toxic, available and inexpensive catalyst (Scheme 1) [9].



Scheme 1

2.1.2. Protection of carbonyls to acetals and ketals

The acetalization or ketalization reaction is a process that is widely used in organic synthesis to protect the carbonyl group of aldehydes and ketones [10]. The acetals are important reactants for synthesis of enantiomerically pure compounds, which were widely used as steroids, pharmaceuticals, and fragrances [11]. Various aldehydes and ketones were efficiently converted to the corresponding diethyl acetals with glycerols using potassium hydrogen sulfate ($KHSO_4$) as a catalyst. $KHSO_4$ was an efficient catalyst for the acetalization and ketalization with high conversion (90-98%) and selectivity in mild conditions. Simple workup, cost-efficient catalyst, and the recyclability of the catalyst are the features characteristic of this method (Scheme 2) [12].

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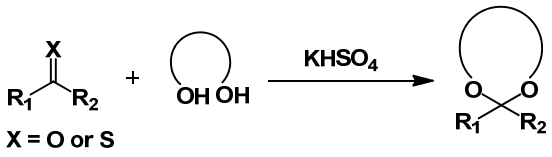
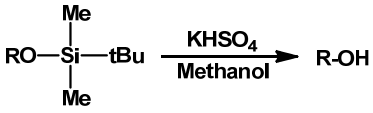


Scheme 2

2.2. Deprotection of functional groups

Selective protection and deprotection of functional groups is extremely useful in organic synthesis. $KHSO_4$ in methanol deprotects a variety of *tert*-butyldimethylsilyl ethers at room temperature in excellent yields (88-93%). This practical method has the advantages of mild reaction conditions, short reaction times, excellent yields of products, simple workup procedure, and low cost of catalyst (Scheme 3) [13].

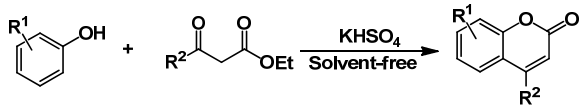


Scheme 3

2.3. $KHSO_4$-catalysed heterocyclic compounds synthesis

2.3.1. Pechmann reaction

Coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry [14]. Their applications range from additives in food, perfumes, cosmetics, pharmaceuticals and in the preparation of insecticides [14], optical brighteners [15] and dispersed fluorescent and tunable laser dyes [16]. $KHSO_4$ is used as an alternative to conventional acid catalysts in the Pechmann condensation of phenols with *β*-ketoesters leading to the formation of substituted coumarins in good yields (91-97%). The method is simple, cost-effective, solvent-free and gives good isolated yields (Scheme 4) [17].



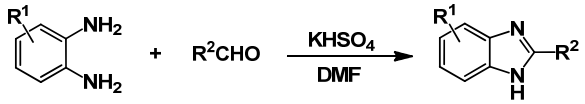
Scheme 4

2.3.2. Synthesis of benzimidazoles

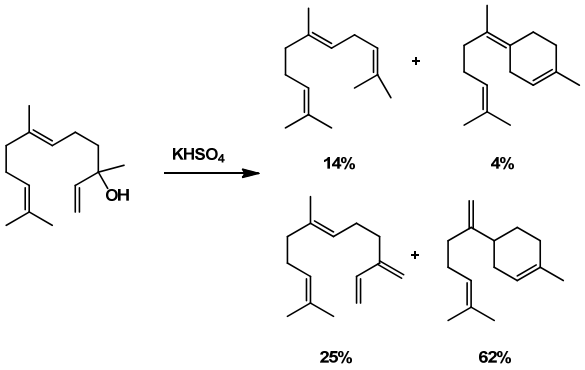
The importance of benzimidazole units arises, because they are found in many biologically active compounds [18]. Several publications reported benzimidazole-containing compounds showing biological activities such as selective neuropeptide YY_1 receptor antagonists [19], and as 5-lipoxygenase inhibitors for use as novel antiallergic agents [20], factor Xa (FXa) inhibitors [21], poly (ADP-ribose) polymerase (PARP) inhibitors [22] and as human cytomegalovirus (HCMV) inhibitors [23]. $KHSO_4$ is used to promote the oxidative condensation of *o*-phenylene diamine with aldehydes in DMF and afford corresponding 2-substituted benzimidazoles efficiently (87-93%). Simple and convenient procedure, use of inexpensive promoter, easy purification and shorter reaction time are the advantageous features of this method (Scheme 5) [24].

2.3.3. Dehydration of nerolidol

The $KHSO_4$ catalyzed dehydration of nerolidol and α- and β-farnesene, β-bisabolene, and γ-bisabolene were performed in good yields (Scheme 6) [25]. The features of mild and solvent-free conditions, cost-efficient catalyst, simple work-up, and the recyclability of the catalyst are some advantages of this method.



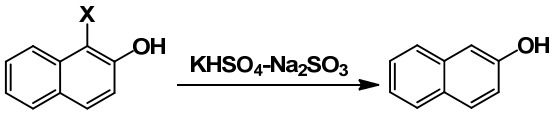
Scheme 5



Scheme 6

2.3.4. Elimination of halogens from halophenols

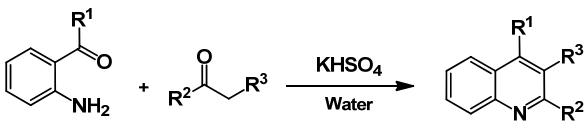
The $KHSO_4$-Na_2SO_3 system is found to be simple and inexpensive for reductive elimination of halogens from the corresponding halophenols under reflux conditions in dry methanol with good yields (97-98%) (Scheme 7) [26]. Mild conditions, cost-efficient catalyst, simple workup, and the recyclability of the catalyst are the features obtained in this method.



Scheme 7

2.3.5. Synthesis of quinolines

Quinoline is a well-known structural unit in alkaloids, therapeutics and synthetic analogues with interesting biological activities such as antimalarial, antibacterial, antiasthmatic, antihypertensive, anti-inflammatory and tyrokinase PDGF-RTK inhibiting agents [27,28]. They are also applied for the preparation of nano- and mesostructures having enhanced electronic and photonic properties [29]. A new green approach to the Friedlander quinoline synthesis was achieved for the preparation of polysubstituted quinolines using $KHSO_4$ as a acid catalyst in good yields (90-95%) (Scheme 8) [30].

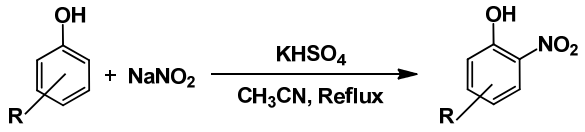


Scheme 8

2.3.6. Nitration of phenols

Aromatic nitro compounds are important starting materials for the manufacture of various industrial products such as pharmaceuticals, dyes and plastics. The nitration of aromatic

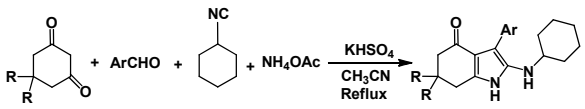
compounds is one of the oldest and most important processes in the chemical industry for the production of intermediates. Certain phenols and naphthols were nitrated regioselectively with $NaNO_2$ in the presence of $KHSO_4$ as a catalyst in good yields (64-94%) (Scheme 9) [31].



Scheme 9

2.3.7. Synthesis of 3-aryl-1H-indole-4(5H)-ones

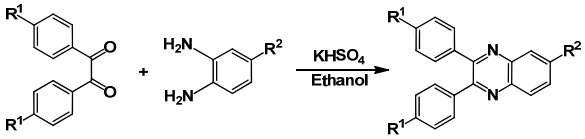
The indole nucleus is an important substructure found in numerous natural and alkaloids [32]. Thus, the development of high-throughput methods for the synthesis of indoles remains an important topic. A simple and efficient synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1H-indole-4(5H)-ones was achieved via a one-pot multi-component reaction of cyclohexyl isocyanide, an aldehyde, a 1,3-dicarbonyl compound, and ammonium acetate in the presence of a catalytic amount of $KHSO_4$ in acetonitrile. The advantages of the present procedure were experimental simplicity, easy work-up, use of an easy to handle and safe catalyst, and high yields of products (84-91%) (Scheme 10) [33].



Scheme 10

2.3.8. Synthesis of quinoxalines

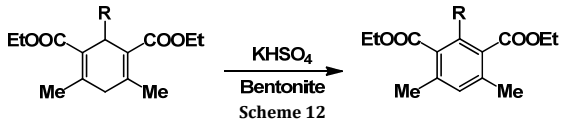
Quinoxalines are important heterocycles in medicinal chemistry [34] and display a broad spectrum of biological activity [35] which makes them privileged structures in combinatorial drug discovery libraries [36]. They have also found applications as dyes [37], efficient electroluminescent materials [38], organic semiconductors [39], dehydroannulenes [40], cavitands [41] and chemically controllable switches [42]. $KHSO_4$ has been used as an effective catalyst for the synthesis of quinoxaline derivatives at room temperature. Some of the major advantages of this procedure are the ambient conditions, very good yields (92-99%), very short reaction times, and use of an inexpensive, green, readily available, and easily to handle catalyst, simple work-up procedure, and absence of volatile and hazardous solvents (Scheme 11) [43].



Scheme 11

2.3.9. Synthesis of 1,4-dihydropyridines

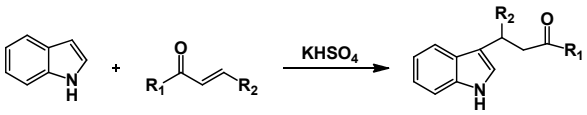
Hantzsch, 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and an important class of drugs [44]. The current literature reveals that 1,4-dihydropyridines exhibit several medicinal applications, which include neuroprotectant [45] and platelet anti-aggregratory activity [46], in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's disease [47], and also as a chemo sensitizer in tumor therapy [48]. Aromatization of Hantzsch 1,4-dihydropyridines was promoted by $KHSO_4$, a relatively green chemical, supported onto bentonite to yield the corresponding pyridine derivatives in excellent yields. The reaction was carried out under mild and convenient conditions with high yields (97-99%) (Scheme 12) [49].



Scheme 12

2.3.10. Addition of indoles

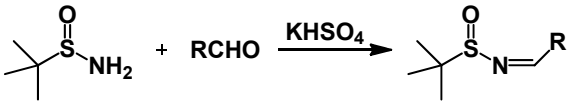
Indoles and their derivatives are an important class of compounds that are receiving increasing attention because of their therapeutic and pharmaceutical activities [50]. Conjugate addition of indoles to a variety of α,β-unsaturated ketones (chalcones) mediated by a catalytic amount of $KHSO_4$ at room temperature under ultrasonic conditions to afford the corresponding Michael adducts in good to excellent yields (90-96%) was reported. This protocol offers several advantages, such as higher yields, shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures (Scheme 13) [51].



Scheme 13

2.3.11. Synthesis of imino derivatives

Imino derivatives are the extremely important biologically active molecules and intermediates for synthesis of pharmaceuticals and natural products. Tert-butanesulfinyl aldimines were prepared by direct condensation of chiral *tert*-butanesulfinamide with aldehydes in high yields (90-95%) in the presence of $KHSO_4$. The main advantage of $KHSO_4$ is that it is applicable to the condensation reactions of a variety of aldehydes, including electron deficient and electron rich (hetereo) aromatic aldehydes, as well as aliphatic aldehydes (Scheme 14) [52].



Scheme 14

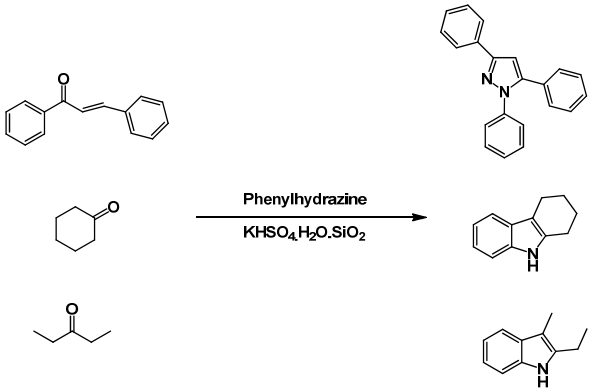
2.3.12. Preparation of pyrazolines, tetrahydrocarbazoles and indoles

Pyrazolines are an important class of heterocycles due to their biological importance. $KHSO_4.H_2O$ impregnated on SiO_2 has been applied as a new and efficient catalyst for preparation of pyrazolines, tetrahydrocarbazoles, and indoles under microwave irradiation. This work demonstrated a new high yielding (70-95%), operationally simple, solvent-free, and mild method for preparation of these compounds (Scheme 15) [53].

3. Conclusion

In this review, some applications of $KHSO_4$ have been discussed. $KHSO_4$ can be used as an acidic catalyst in various organic reactions and we believe that a great number of acid catalyzed organic reactions could be performed by using this catalyst. From the reported results it can be concluded that

$KHSO_4$ is reusable, green, inexpensive, convenience, easy to handle, non-toxic, available and efficient catalyst for various organic chemistry transformations and its use has been growing rapidly.



Scheme 15

Acknowledgements

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