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Potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$): A mild and efficient reusable catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles under conventional heating and microwave irradiation

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Abstract

An efficient method for the synthesis of 1,2,4,5-tetrasubtituted imidazoles by four-component condensation of benzil or benzoin, aldehydes, amines and ammonium acetate under microwave irradiation or classical heating conditions using potassium dodeca tungstocobaltate trihydrate [$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.1 mol%)] as catalyst is reported. The catalyst exhibited remarkable reusable activity.

Keywords: Tetrasubstituted imidazoles; $K_5CoW_{12}O_{40}\cdot 3H_2O$; Solvent-free conditions; Microwave irradiation or classical heating

In the mainstream of current interest, multicomponent reactions permitted rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery. One such reaction, which falls in this category was reported by Debus [1] in 1858, a reaction that pioneered a novel synthetic route to imidazole. Over the century, imidazoles have received significant attention due to their synthesis, reactions and biochemical properties. Even today, research in imidazole chemistry continues undebated. Compounds with imidazole moiety have biological and pharmaceutical importance [2]. Several substituted imdazoles are known as inhibitors of P 38 kinase [3]. Eprosartan is one of the series of 1-(carboxy benzyl)imdazole-5-acrylic acids, which is a potent and selective angiotensin II receptor antagonist [4]. Highly substituted imidazoles like lepidilines A and B [5] exhibit micromolar cytotoxicity against several human cancer cell lines. Trifenagrel [6] is a potent 2,4,5-triaryl imidazole that reduces platelet aggregation in several animal species and humans. Thus, the prevalence of imidazole moiety in several naturally occurring and synthetic biologically active compounds has rekindled an increased interest in obtaining tri- and tetra-substituted imidazoles via regiocontrolled process.

In the literature, there exist few reports on the direct synthesis of tetrasubstituted imidazoles. General methods rely on the synthesis of trisubstituted imidazoles followed by installation of the fourth substituent via *N*-alkylation [7], metal activated coupling [8] or imidazole-*N*-oxides [9]. Tetrasubstituted imidazoles can be directly prepared from cycloaddition of munchnone derivatives but this methodology is limited to *N*-methyl imidazoles [10]. Another direct method involves a four-component condensation of 1,2-diketones, aldehydes, amines and NH_4OAc in AcOH or on various supports such as acidic, basic and neutral alumina, bentonite, montimorillonite K10, montimorillonite KSF, silica gel and florisil under microwave irradiation [11]. The condensation of α-hydroxy ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in presence of MW has been reported recently [12]. However, these synthetic methods have limitations of harsh reaction conditions, use of hazardous and often expensive acid catalysts, long reaction time and moderate yield. Moreover, the synthesis of these heterocycles have been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also

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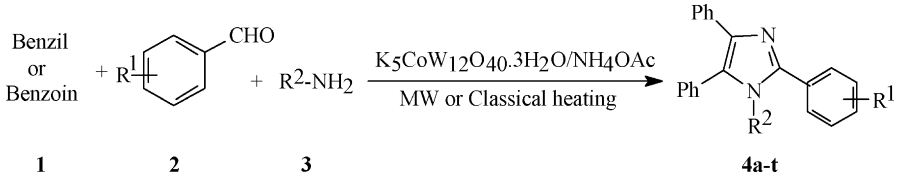

Scheme 1.

generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off. Consequently, there is a scope for further improvement towards lower reaction time and improved yields, employing non-sophisticated and recoverable catalyst.

In recent years, polyoxometalates have proved to be good catalysts in various oxidations [13]. They are applied in bulk or supported forms, both homogenous and heterogenous catalysis is possible. Due to their acidic and redox properties, heteropoly compounds (heteropoly acids and salts) are useful and versatile catalysts in a number of transformations [14]. In continuation of our study [15] in exploring application of polyoxometalates in fine organic chemistry, we have developed a method, for solvent free synthesis of 1,2,4,5-tetrasubtituted imidazoles by using inexpensive and reusable $K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.1 mol%) catalyst [16] under microwave irradiation or classical heating in a highly efficient manner.

To the best of our knowledge, however, the generality and applicability of potassium dodecatangsto cobaltate (PDTC) to accomplish these reactions has not been reported in the literature. This method not only affords the products in excellent yield but also avoids the problems with catalyst cost, handling, safety and pollution. This catalyst is water tolerant, recoverable, reusable, non-explosive, easy to handle and thermally robust. In view of emerging importance of the heterogenous catalyst, we wish to explore the use of PDTC as a recoverable and reusable catalyst for the synthesis of 1,2,4,5-tetrasubtituted imidazoles (Scheme 1; Table 1).

The typical procedure [17] for 1,2,4,5-tetrasubtituted imidazoles involve impregnating the mixture of $K_5CoW_{12}O_{40}\cdot 3H_2O$ and ammonium acetate (ammonia source) with a dichloromethane solution of benzil, aldehyde and amine, evaporating the solvent, and heating the solid residue in a microwave oven or oil bath (at 140 °C). The reactions proceeded in high yields and the results are summarized in Table 3. The general applicability of the method is demonstrated by using amines both aliphatic and aromatic. Aldehydes bearing various functional groups such as Cl, OH, NO_2, Br, etc., have been used and reactions proceeded smoothly with high yields. Imidazoles having cyclohexyl group (entry 12) as one of the substituent has been prepared without any difficulty. Very good results were obtained when hydroxyl substituted benzaldehydes (entries 13–15) were used. Furthurmore, chiral imidazoles can be obtained by incorporating chiral amines as the amine counter part (entry 11). Compounds **4k**–**4t** (entries 11–20) are newely synthesized using PDTC catalyst (Table 3).

Under the same conditions, this approach can be repeated for synthesis of these imidazoles when the benzoin was used instead of benzil as a starting material (Scheme 1). Thus, benzoin effectively participated in the condensation with aldehyde, amine and ammonium acetate in presence of PDTC to give corresponding tetrasubstituted imidazoles but the yields were found to be low (15–30%). The structures of the imidazoles were confirmed from ^{1}H NMR and ^{13}C NMR and IR spectral data and melting points [18].

The four-component condensation of benzil, *p*-bromobenzaldehyde, benzyl amine and ammonium acetate was also performed in the absence of $K_5CoW_{12}O_{40}\cdot 3H_2O$ under microwave irradiation; however, the yield of **4p** was low (30%). Carrying out the condensation in refluxing CH_3CN or EtOH for 3 h catalysed by PDTC resulted **4p** with 45% yield.

The possibility of recycling the catalyst is of concern, especially for large-scale operations. For this purpose, the reaction of benzil, *p*-methylbenzaldehyde, benzyl amine and ammonium acetate at 140 °C as a model reaction was again studied. When the reaction completed, the catalyst was recovered and reused for the similar reaction. This process was carried out over six runs without appreciable reduction (95–86%) in the catalytic activity of the catalyst (Table 2).

In conclusion, we have reported here in several noteworthy features of a new catalyst for the synthesis of tetrasubstituted imidaoles through the four-components condensation of benzil, aldehydes, amines and ammonium acetate using PDTC. This protocol offers many attractive features such as reduced reaction times, higher yields and economic viability of the catalyst. The reaction proceeds under solvent free conditions and isolation of the catalyst is easily achieved. This method can be applied to large-scale processes with high efficiency and

Table 1
Optimization of catalyst for the synthesis of **4d** (Table 3, entry 4) at 140 °C

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.01)	2.0	76
2	$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.05)	2.0	65
3	$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.1)	2.0	95
4	$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.15)	4.0	93

Table 2
Reuse of the catalyst for the synthesis of **4d** (Table 3, entry 4)

Entry	Yield (%)
0	95
1	95
2	93
3	92
4	90
5	88
6	86