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A Keggin heteropoly acid as an efficient catalyst for an expeditious, one-pot synthesis of 1-methyl-2-(hetero)arylbenzimidazoles

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Abstract—The Keggin heteropoly acid, silicotungstic acid, $H_4SiW_{12}O_{40}$, has been demonstrated to be highly efficient for an expeditious, one-pot synthesis of 1-methyl-2-(hetero)arylbenzimidazoles from *N*-methyl-1,2-phenylenediamine and (hetero)aryl aldehydes in ethyl acetate at room temperature. The catalyst works equally well for *N*-phenyl-1,2-phenylenediamine.

Benzimidazoles are useful pharmaceuticals,[1] and 2-substituted benzimidazoles are used as anthelmintics in veterinary medicine[2] and display significant anticancer, antiviral, antiallergic, antiulcer and anticoagulant properties in human therapeutics.[3] They are usually prepared by condensation of *ortho*-phenylenediamines (*o*-PDs) with either, (i) carboxylic acids or their equivalents, namely, nitriles, amidates or orthoesters under dehydrating conditions, or (ii) aldehydes under oxidative conditions via the Schiff bases generated in situ.[4]

Since methods using carboxylic acids or equivalents require strongly acidic reagents, harsh dehydrating conditions and high temperatures, for example, PPA, 170–180 °C,[5] aryl aldehydes are preferred as substrates. Thus, a large number of benzimidazoles have been prepared from aryl aldehydes employing L-proline, ionic liquids, iodobenzene diacetate, hydrogen peroxide–hydrochloric acid, potassium bisulfate, etc. as the catalysts.[6] However, the reactions of aldehydes with N-unsubstituted *o*-PDs mostly lead to a mixture of 1,2-disubstituted and 2-substituted benzimidazoles.[7] Since 1-alkyl-2-arylbenzimidazoles also exhibit a broad spectrum of biological activities,[8] these molecules have become improved synthetic targets.

1-Methyl-2-arylbenzimidazoles, the simplest members of this class, have been synthesised previously by N-methylation of 2-arylbenzimidazoles,[9] 2-arylation of 1-methylbenzimidazoles using rhodium or palladium catalysts,[10] intramolecular N-arylation of (*o*-bromophenyl)amidine precursors,[11] or more directly, by condensation of *N*-methyl-*o*-PD with either primary alcohols using active MnO_2 as oxidant,[12] or with polymer-bound esters.[13] These methods require the use of preformed reagents, employ very expensive and eco-unfriendly catalysts, involve prolonged reaction periods and furnish products in low and widely varying yields. To our knowledge, only one 1-methyl-2-arylbenzimidazole, namely, the 2-phenyl derivative has been prepared by the direct condensation of *N*-methyl-*o*-PD with an araldehyde (benzaldehyde in this case)—the preferred straightforward route—using ytterbium triflate as the catalyst.[14]

Clearly, a general method for the one-step preparation of 1-methyl-2-arylbenzimidazoles from *N*-methyl-*o*-PDs and aryl aldehydes was lacking. We have now developed one such method employing a heteropoly acid (HPA) as the catalyst. HPAs are economically attractive, environmentally benign, possess very high Brönsted acidity, involve a mobile ionic structure and absorb

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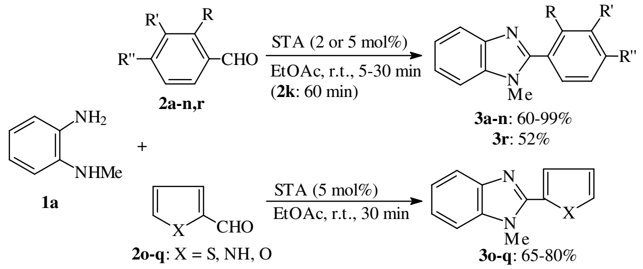
polar molecules easily in the bulk forming a ‘pseudo-liquid phase’.[15] As a result, both the surface protons and the bulk protons of HPAs participate in their catalytic activity, which significantly enhances the reaction rate, even at relatively low temperatures. The best known HPAs are the Keggin HPAs, $H_{8-n}XM_{12}O_{40}$, where X is the central atom (Si^{4+}, P^{5+}, etc.), n is the oxidation state of X and M is the metal ion (W^{6+} or Mo^{6+}). Of these, phosphomolybdic acid, phosphotungstic acid and silicotungstic acid, in particular, have been used in recent years for the synthesis of various heterocycles.[16] In continuation of our efforts[17] towards the development of more efficient synthetic routes to various classes of heterocycles employing eco-friendly catalysts, we have developed a general and expeditious one-pot synthesis of 1-methyl-2-(hetero)arylbenzimidazoles from *N*-methyl-*o*-PD and (hetero)aryl aldehydes using the Keggin HPA, silicotungstic acid (STA), $H_4SiW_{12}O_{40}$, as the catalyst. Our findings are presented herein.

Initially, the reaction of *N*-methyl-*o*-PD **1a** with one equivalent of benzaldehyde **2a** was to be carried out on a 1 mmol scale in a solvent-free manner using 2–5 mol % of STA as the solid support. However, because of the high molecular weight (2880) of dehydrated STA, which we used as catalyst, 0.02–0.05 mmol of STA was found to have too small a bulk to act as an effective support. The reaction of **1a** with **2a** was, therefore, examined separately in methanol, ethanol, acetonitrile and ethyl acetate solutions at room temperature in the presence of 2 mol % of STA, which furnished 1-methyl-2-phenylbenzimidazole **3a** in 39% (in 5 h), 46% (15 min), 60% (2 h) and 65% (2 h) yields, respectively. Ethyl acetate thus appeared to be the solvent of choice in terms of yield. However, when the reaction in ethyl acetate solution was repeated using 3 and 5 mol % of STA separately, **3a** was obtained in 68% (1 h) and 73% (0.5 h) yields, respectively.

Accordingly, the reaction of **1a** was carried out with several aryl aldehydes **2a–n,r** and three heteroaryl aldehydes **2o–q** in ethyl acetate at room temperature in the presence of 2 or 5 mol % of STA, as necessitated for expeditious completion of the reactions.[18] As a result, the corresponding 1-methyl-2-(hetero)arylbenzimidazoles **3a–r**[19] were isolated in 60–99% yields in 5–30 min (Scheme 1, Table 1) with two exceptions, namely, for anisaldehyde **2k** (which required 1 h for completion) and for 4-(*N*,*N*-dimethylamino)benzaldehyde **2r** (which furnished the corresponding benzimidazole **3r** in only 52% yield).

An analysis of the results (Table 1) revealed that the electronic nature of the substituents on the phenyl ring played a marked role on the amount of catalyst required for completing the reactions expeditiously. Thus, for benzaldehydes **2b–e** bearing electron-withdrawing groups or those **2f–h** with mildly electron-donating substituents, the reactions with **1a** were complete within 30 min with just 2 mol % of STA. However, for **2a** and benzaldehydes **2i–n,r** with electron-donating substituents, as well as for the three heteroaryl aldehydes **2o–q**, 5 mol % of the catalyst was required for completion of the reactions in 30 min with only one exception, **2k**, as stated earlier.

In order to check the range of applicability of STA, benzaldehyde was treated separately with *o*-PD **1b** and *N*-phenyl-*o*-PD **1c** on similar scales in ethyl acetate at



Scheme 1.

Table 1. Synthesis of 1-methyl-2-(hetero)arylbenzimidazoles from **1a** using STA as the catalyst

Entry	**2** R/R′/R″/X	mol % of STA	Product **3**	Mp (°C)	Time (min)	Yield (%)
1	**a**: R = R′ = R″ = H	5	**a**	97–98	30	73
2	**b**: R = NO_2; R′ = R″ = H	2	**b**	135–136	5	99
3	**c**: R = R″ = H; R′ = NO_2	2	**c**	155–157	5	92
4	**d**: R = R′ = H; R″ = NO_2	2	**d**	204–206	5	95
5	**e**: R = R′ = H; R″ = CN	2	**e**	228–230	15	90
6	**f**: R = R′ = H; R″ = Me	2	**f**	125–126	30	95
7	**g**: R = R′ = H; R″ = Cl	2	**g**	112–114	20	99
8	**h**: R = R′ = H; R″ = Br	2	**h**	109–110	30	99
9	**i**: R = OH; R′ = R″ = H	5	**i**	166–167	30	62
10	**j**: R = R′ = H; R″ = OH	5	**j**[a]	262–264	30	78
11	**k**: R = R′ = H; R″ = OMe	5	**k**	118–120	60	80
12	**l**: R = H; R′,R″ = OCH_2O	5	**l**[a]	157–158	30	74
13	**m**: R = H; R′ = R″ = OMe	5	**m**[a]	Gum	30	61
14	**n**: R = H; R′ = OMe; R″ = OH	5	**n**[a]	198–200	30	60
15	**o**: X = S	5	**o**	83–84	30	80
16	**p**: X = NH	5	**p**	208–209	30	79
17	**q**: X = O	5	**q**	75–77	30	65
18	**r**: R = R′ = H; R″ = NMe_2	5	**r**[a]	159–160	30	52

[a] New compounds.