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ORIGINAL ARTICLE

Melamine trisulfonic acid as an efficient catalyst for the synthesis of 2,6-dimethyl-4-substituted-1,4-dihydropyridine-3,5-diethyl/dimethylcarboxylate derivatives *via* Hantzsch reaction in solvent free condition

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KEYWORDS

Melamine trisulfonic acid;
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Abstract A facile and highly efficient one-pot synthesis of 1,4-dihydropyridine derivatives (1,4-DHPs) is reported *via* three component condensation reaction of aldehydes, ethyl acetoacetate or methyl acetoacetate and ammonium acetate using environmentally benign melamine trisulfonic acid (MTSA) as a catalyst in solvent free condition at 60 °C. The method presented here is applied to the tenets of green chemistry to the generation of biologically interesting products under solvent-free media that is less expensive and less toxic than those with organic solvents. Also, the catalyst is recyclable and could be reused without significant loss of activity. Even after three runs for the reaction, the catalytic activity of MTSA was almost the same as that of the freshly used catalyst.

The method also offers several advantages including high yields and simple work-up procedure.

1. Introduction

In recent years, an increasing interest has been focused on the synthesis of Hantzsch 1,4-dihydropyridines, a class of model compounds of NADH coenzyme, due to the biological pertinence of these compounds to NADH redox process (Miri et al., 2006; Tewari et al., 2004). 1,4-dihydropyridines have been reported as anticancer (Tsuruo et al., 1983), neurotropic (Krauze et al., 1999), glycoprotein inhibitors (Zhou et al., 2005), anticoagulant (Kumar et al., 2011a), antioxidant (Vijesh et al., 2011), anti-inflammatory and anti-microbial agents (Kumar et al., 2011b). Calcium entry into the cytosol is mediated by multiple types of calcium channel, each with a distinct physiological role. Dihydropyridines are commercially used as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension (Zamponi, 1998). Recently, the synthesis of dihydropyridines with respect to multidrug resistance (MDR) reversal in tumour cell gave a new dimension to their applications (Tanabe et al., 1998; Tasaka et al.,

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2001). Tuberculosis (TB) is a common and often deadly infectious disease caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis*. Tuberculosis has been considered to be a disease of poverty for many years with quite rare occurrences in the developed countries. Recently, studies showed that 3,5-dicarbamoyl derivatives of 1,4-dihydropyridine (DHP) with lipophilic groups have considerable antitubercular activity against *M. tuberculosis* H37Rv (Trivedi et al., 2011; Khoshneviszadeh et al., 2009).

Generally, the basic skeleton of DHP was first discovered by Hantzsch in 1882 (Hantzsch, 1882). Due to the biological importance of these compounds several methods have been reported for the improvement of 1,4-dihydropyridine ring and polyhydroquinoline derivatives. Different approaches for the syntheses of 1,4-dihydropyridine derivatives using various catalysts, such as cellulose sulphuric acid (Safari et al., 2011), triphenylphosphine (Debache et al., 2009), silica supported 12-tungstophosphoric acid (Rafiee et al., 2009), Iron (III) trifluoroacetate (Adibi et al., 2007), ionic liquid [tbmim]Cl_2/$AlCl_3$ (Reddy et al., 2011), organo catalyst (Baghbanian et al., 2010), cerric ammonium nitrate (Reddy and Raghu, 2008), nickel nanoparticle (Saikia et al., 2012), aluminium phosphate (Purandhar et al., 2012), bismuth nitrate (Bandyopadhyay et al., 2012), gadolinium triflate (Mansoor et al., 2012a), titanium dioxide nanoparticles (Tajbakhsh et al., 2012), ferric fluoride (Surasani et al., 2012) and silica sulphuric acid (Kolvari et al., 2011), MgO nanoparticles (Mirzaei and Davoodnia, 2012), visible light (Ghosh et al., 2013) and protic pyridinium ionic liquid (Tajbakhsh et al., 2013) have been reported. Many of these reported methods involve the use of expensive reagents, hazardous solvents, long reaction times and tedious workup procedures. Thus, the search for new reagents and methods is still of growing importance.

Melamine trisulfonic acid is effectively used as a catalyst in organic reactions, such as regioselective nitration of aromatic compounds (Albadi et al., 2012), N-formylation of amines (Yang and Zhang, 2012), aryldithienylmethanes (Wu et al., 2012), spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives (Yang et al., 2012), acetylation of alcohols, phenols and amines (Shirini et al., 2010a), trimethylsilylation of alcohols and phenols (Wu et al., 2011), solvent free synthesis of coumarins (Shirini et al., 2010b), chemoselective methoxymethylation of alcohols (Shirini et al., 2010c), synthesis of chromen-6-ones (Ma et al., 2011) and synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (Shirini et al., 2011).

To the best of our knowledge, there are no examples on the use of melamine trisulfonic acid as a catalyst for the synthesis of 1,4-dihydropyridine derivatives. In continuation of our investigation with the one-pot synthesis of biologically active molecules, such as 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones/imines (Mansoor et al., 2011), β-amino ketone compounds (Mansoor et al., 2012b), amidoalkyl naphthols (Mansoor et al., 2012c), 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives (Mansoor et al., 2012d) and α-amino nitriles (Mansoor et al., 2012e), herein, we wish to report the one-pot condensation of aldehydes, ethyl/methyl acetoacetate and ammonium acetate under solvent free conditions at 60 °C using melamine trisulfonic acid as a reusable catalyst for the synthesis of 1,4-dihydropyridine derivatives *via* Hantzsch reaction. Melamine trisulfonic acid is safe, easy to handle and environmentally benign.

2. Experimental

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. The benzaldehydes used were with substituents H, *p*-OCH_3, *p*-CH_3, *p*-Cl, *p*-NO_2, *p*-Br, *p*-OH, *m*-Cl, *m*-NO_2 and *m*-OH. Heterocyclic aldehydes like Furfural and 2-Thienal were also used for the synthesis. The solid aldehydes were used as such and the liquid aldehydes were used after vacuum distillation. Ethyl acetoacetate and methyl acetoacetate were used as 1,3-dicarbonyl compounds. Ammonium acetate was used as the nitrogen source. Solvents like THF, methanol, ethanol, dichloromethane, acetonitrile, cyclohexane and benzene were used. Melamine and chlorosulfonic acid were used for the preparation of MTSA. All yields refer to isolated products unless otherwise stated.

2.1. Preparation of melamine trisulfonic acid (MTSA)

Melamine trisulfonic acid was prepared from melamine and chlorosulfonic acid as reported previously in the literature by Shirini et al. (2010a) Scheme 1.

*2.2. General experimental procedure for the synthesis (compounds **4a–p**)*

A mixture of aldehyde **1** (1 mmol), ethyl acetoacetate **2** (2 mmol), ammonium acetate 3 (1.5 mmol) and MTSA (5 mol%) was taken in a 50 ml flask and heated at 60 °C under solvent-free condition for the appropriate time monitored by TLC. The reaction mixture, after being cooled to room temperature was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over Na_2SO_4. The crude products were purified by crystallization from ethanol to afford 1,4-dihydropyridines. The catalyst was filtered and washed with methanol for reuse (see Scheme 2).

2.3. Spectral data for the synthesized compounds

*2.3.1. 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diethylcarboxylate (**4a**)*

White solid; mp 157–159 °C; IR (KBr, cm^{-1}): 3342, 1691, 1643, 1489, 1210, 779.

^1H NMR (500 MHz, DMSO-d_6) δ: 1.19 (t, J = 7.2 Hz, 6H, $2CH_3CH_2$), 2.33 (s, 6H, $2CH_3$), 4.08 (q, J = 7.0 Hz, 4H, $2CH_3CH_2$), 4.96 (s, 1H, CH), 5.97 (s, 1H, NH), 7.16–7.33 (m, 5H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.0, 19.4, 39.6, 59.5, 104.0, 121.8, 129.0, 131.0, 144.4, 146.5, 166.8 ppm; MS (ESI): m/z 330 $(M + H)^+$. Anal. Calcd. for $C_{19}H_{23}NO_4$ (%): C, 69.30; H, 6.99; N, 4.25. Found: C, 69.22; H, 6.94; N, 4.23.

*2.3.2. 2,6-Dimethyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-diethylcarboxylate (**4b**)*

Yellow solid; mp 135–137 °C; IR (KBr, cm^{-1}): 3338, 1698, 1653, 1480, 1200, 789.

^1H NMR (500 MHz, DMSO-d_6) δ: 1.24 (t, J = 7.4 Hz, 6H, $2CH_3CH_2$), 2.28 (s, 6H, $2CH_3$), 4.09 (q, J = 7.2 Hz, 4H, $2CH_3CH_2$), 5.00 (s, 1H, CH), 5.90 (s, 1H, NH), 7.10–7.43 (m, 4H, Ar-H), 2.22 (s, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.3, 19.5, 38.9, 60.0, 103.5, 119.3,