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Sonochemically synthesis of 1,4-dihydropyridine derivatives using nano-silica supported tin tetrachloride as a reusable solid acid catalyst

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ABSTRACT

A simple and general synthetic method for the synthesis of 1,4-dihydropyridines *via* three- or four-component condensation of aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate was developed. In this procedure, nano-silica supported tin tetrachloride as an efficient solid acid catalyst was used under sonication condition. Short reaction times, excellent yields, simple work-up and reusability of catalyst are some advantages of this method.

1. Introduction

1,4-dihydropyridines are an important class of nitrogen heterocycles. The most feasible position is 4th which exhibits various activities such as the calcium channel blockers or calcium antagonists [1]. Moreover, this compound emerged as one of the most important classes of drugs for the treatment angina pectoris, hypertension and other cardiovascular diseases [2,3]. The heterocyclic ring is the common feature for various pharmacological activities such as antihypertensive [4], antitumor [5], antiinflammatory activity [6], antitubercular activity [7], analgesic activity [8], antithrombotic and [9,10] also behave as neuroprotectants, cerebral antiischemic agents and chemosensitizers [5,11]. A recent analysis of the comprehensive medicinal chemistry database found that the dihydropyridine framework is the most prolific chemotypes [12]. Therefore, it is not surprising that 1,4-dihydropyridines have received increasing interest as synthetic targets and their synthesis remains an area of intense current interest to the chemical community [13–18]. Up till now, numerous literature citations exist relating to various attempts to improve the synthesis of these compounds [19–25]. Although most of these processes offer advantages, they suffer drawbacks such as longer reaction times, tedious work-up, unsatisfactory yields, the use of volatile organic solvents and the use of stoichiometric expensive reagents. Furthermore, the main drawbacks of existing methods are that the catalysts are destroyed in the work-up and cannot be recovered. Therefore, we prompted towards further investigation in the search for a better catalyst for the synthesis of 1,4-dihydropyridines, which will carry out the synthesis under simpler experimental set up reusability, economic viability and eco-friendly conditions.

In recent years, the progress in the field of heterogeneous catalyst due to several advantages associated such as low cost, easy separation, recycling ability was occurred [26,27]. Tin tetrachloride ($SnCl_4$) which is a powerful Lewis acid and a highly volatile, corrosive liquid is used as homogeneous catalyst in organic reactions [28–31]. When $SnCl_4$ is grafted on the surface of silica, does not need special precautions for toxic and handling, or storage. Silica-supported $SnCl_4$ is a mild solid Lewis acid, which promotes acid catalyzed organic reactions [32–34]. Silica-supported $SnCl_4$ can be stored at ambient temperatures for months without losing its catalytic activity [35]. In this regard, nano-scale materials in modern organic chemistry exhibit higher activity and selectivity than their corresponding bulk materials due to theirs present high specific surface area of the active component. Our research group recently prepared nano-silica supported tin tetrachloride ($SnCl_4$-nano-SiO_2) as a nano catalyst in organic reactions [35,36]. Furthermore, the progress in the field of greener process which is based on sonochemistry has increasingly been considered as a simple, clean and convenient method in synthetic organic chemistry. Thus, chemists are focusing on its use for the synthesis of compounds [37–40]. Sonochemistry has advantages such as shorter reaction time, milder reaction condition, higher yield, improved selectivity

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and clean reaction in comparison to classical methods [41,42]. The use of ultrasound to promote chemical reaction is titled sonochemistry. Ultrasound irradiation offers energy source by acoustic cavitation phenomenon, which is a physical process that creates, enlarges and collapses gases in an irradiated liquid [43].

In this study, we report $SnCl_4$-nano-SiO_2 promoted three or four components coupling reaction of aldehydes, 1,3-dicabonyl compounds, and ammonium acetate in ethanol under ultrasound irradiation (Scheme 1). This green method is a rapid ultrasonic assisted route for the synthesis of a wide variety of 1,4-dihydropyridines.

2. Experimental

2.1. Chemicals and apparatus

Chemicals were purchased from Merck company and used without further purification. Benzaldehyde was purified by distillation. Commercial nano silica gel (20 nm) was purchased from Sigma-Aldrich company.

FT-IR spectra were run on a Nicolet Magna 550 spectrometer using KBr pellets. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Bruker DRX-400 Avance spectrometer in CDCl3 as a solvent. A multiwave ultrasonic generator (Sonicator 3000; Bandelin MS 72, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 60 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. Scanning electron microscopy (SEM) images of nano particles were determined with VEGA/TESCAN electron microscope. Transmission electron microscopy (TEM) photographs of nano particles were performed with a LEO 912 AB OMEGA instrument (Germany) with a LaB6 cathode and accelerating voltage of 100 kV. X-ray diffraction (XRD) patterns were recorded on a Philips Xpert MPD diffractometer equipped with a Cu Kα anode (λ = 1.54 A°) in the 2θ range from 5 to 80°.

2.2. Preparation of $SnCl_4$-nano-SiO_2

$SnCl_4$ (0.35 g, 0.16 ml, 1.34 mmol) was added dropwise to a mixture of $CHCl_3$ (5 ml) and nano-silica gel (0.65 g). The resulting suspension was stirred for 1 h at room temperature. The reaction mixture was filtered, washed with chloroform, and dried at room temperature. $SnCl_4$-nano-SiO_2 was obtained as a white powder which can be kept for several months in air at room temperature without losing its activity.

2.3. General procedure for the synthesis of 1,4-dihydropyridines

2.3.1. Typical reflux method (Method A)

A mixture of aryl aldehydes (1 mmol), 1,3-dicarbonyl compounds (2 mmol), ammonium acetate (1.5 mmol) and $SnCl_4$-nano-SiO_2 (30 mg) was refluxed in ethanol (5 ml) for the stipulated time mentioned in Table 3. The progress of the reaction was monitored by TLC (EtOAc:petroleum ether 7:3). After completion of the reaction, the hot mixture filtered to separate the catalyst. The heterogeneous catalyst was recovered by washing with $CHCl_3$ and drying. The filtrate poured into crushed ice and obtained solid products, which recrystallized from ethanol to get pure crystalline dihydropyridines derivatives.

2.3.2. Ultrasound irradiation method (Method B)

In a round-bottom flask, a mixture of aryl aldehydes (1 mmol), 1,3-dicarbonyl compounds (2 mmol), ammonium acetate (1.5 mmol) and $SnCl_4$-nano-SiO_2 (20 mg) in ethanol (5 ml) was sonicated at 20 kHz frequency and 40 W power for the stipulated time which was confirmed by TLC (EtOAc:petroleum ether 7:3). After completion of the reaction, the catalyst was separated by filtration. The filtrate poured into crushed ice and the solid product, which separated was filtered recrystallized from ethanol to get pure crystalline dihydropyridine derivatives. The heterogeneous catalyst was recovered by washing with $CHCl_3$ and drying.

2.4. Spectral data for selected compounds

2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diethylcarboxylate (**4a**) Yellowish solid, FT-IR (KBr, υ cm^{-1}): 3342 (NH), 1689 (C=O, ester), 1487 (C=C, aromatic), 1212 (C-O). ^{1}H NMR ($CDCl_3$, 400 MH) δ: 7.28 (*d*, *J* = 7 Hz, 2H. Ar–H), 7.21 (*t*, *J* = 6.9 Hz, 2H. Ar–H), 7.13 (*d*, *J* = 6.9 Hz, 1H, Ar–H), 5.54 (*s*, 1H, NH), 4.99 (*s*, 1H, CH), 4.09 (*q*, *J* = 6.8 Hz, 4H, 2 OCH_2), 2.34 (*s*, 6H, 2CH_3), 1.22 (*t*, *J* = 6.8 Hz, 6H, 2CH_3CH_2).

2,6-Dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-diethylcarboxylate (**4b**) Yellow solid, FT-IR (KBr, υ cm^{-1}): 3343 (NH), 1689 (C=O, ester), 1489 (C=C, aromatic), 1211 (C-O). ^{1}H NMR ($CDCl_3$, 400 MH) δ: 7.20 (*d*, *J* = 7.9 Hz, 2H. Ar–H), 6.75 (*d*, *J* = 7.9 Hz, 2H, Ar–H), 5.54 (*s*, 1H, NH), 4.93 (*s*, 1H, CH), 4.10 (*q*, *J* = 7.4 Hz, 4H, 2 OCH_2), 3.76 (*s*, 3H, OCH_3), 2.33 (*s*, 6H, 2CH_3), 1.23 (*t*, *J* = 7.4 Hz, 6H, 2CH_3CH_2).

2,6-Dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-diethylcarboxylate (**4c**) Yellowish solid, FT-IR (KBr, υ cm^{-1}): 3356 (NH), 1695 (C=O, ester), 1486 (C=C aromatic), 1214 (C-O), 1117 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MH) δ: 7.22 (*d*, *J* = 8 Hz, 2H. Ar–H), 7.17 (*d*, *J* = 8 Hz, 2H, Ar–H), 5.55 (*s*, 1H, NH), 4.96 (*s*, 1H, CH), 4.08 (*q*, *J* = 7.2 Hz, 4H, 2 OCH_2), 2.34 (*s*, 6H, 2CH_3), 1.22 (*t*, *J* = 7.2 Hz, 6H, 2CH_3CH_2)

2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-diethylcarboxylate (**4d**) Colorless solid, FT-IR (KBr, υ cm^{-1}): 3327 (N-H), 1696 (C=O, ester), 1517 (NO_2), 1486 (C=C, aromatic), 1345 (NO_2), 1213 (C-O); ^{1}H NMR ($CDCl_3$, 400 MH) δ (ppm): 8.09 (*d*, *J* = 7.9 Hz, 2H, Ar–H), 7.45 (*d*, *J* = 7.9 Hz, 2H, Ar–H), 5.63 (*s*, 1H, NH), 5.10 (*s*, 1H, CH), 4.08 (*q*, *J* = 7.4 Hz, 4H, 2 OCH_2), 2.37 (*s*, 6H, 2 CH_3), 1.24 (*t*, *J* = 7.4 Hz, 6H, 2 CH_3CH_2).

3,3,6,6-Tetramethyl-9-4-phenyl-3,4,6,7-tetrahydroacridine 1,8(2H,5H,9H,10H)-dione (**4e**) Yellowish solid, FT-IR (KBr, υ cm^{-1}): 3279(NH), 1641 (C=O, dimedone), 1484 (C=C, aromatic). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (*d*, *J* = 7.5 Hz, 2H, Ar–H), 7.19 (*t*, *J* = 7.5 Hz, 2H, Ar–H), 7.07 (*t*, *J* = 7.5 Hz, 1H, Ar–H), 6.68 (*s*, 1H, NH), 5.08 (*s*, 1H, CH), 2.14–2.39 (*m*, 8H, 4 CH_2), 1.08 (*s*, 6H, 2 CH_3), 0.97 (*s*, 6H, 2 CH_3).

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8 (2H,5H,9H,10H)-dione (**4f**) Yellow solid, FT-IR (KBr, υ cm^{-1}) 3279 (NH), 1640 (C=O, dimedone), 1482 (C=C aromatic), 1224 (C-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.23 (*d*, *J* = 8.3 Hz, 2H, Ar–H), 6.72 (*d*, *J* = 8.3 Hz, 2H, Ar–H), 6.51 (*s*, 1H, NH), 5.02 (*s*, 1H, CH), 3.70 (*s*, 3H, OCH_3), 2.14–2.37 (*m*, 8H, 4 CH_2), 1.08 (*s*, 6H, 2 CH_3), 0.96 (*s*, 6H, 2 CH_3).

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-3,4,6,7-tetrahydroacridine1,8(2H,5H,9H,10H)-dione (**4 g**) Yellow solid, FT-IR (KBr, υ cm^{-1}) 3279 (NH) , 1644 (C=O, dimedone), 1486 (C=C, aromatic), 1145 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (*d*, *J* = 8 Hz, 2H, Ar–H), 7.17 (*d*, *J* = 8 Hz, 2H, Ar–H), 6.79 (*s*, 1H, NH), 5.05 (*s*, 1H, CH), 2.13–2.37 (*m*, 8H, 4 CH_2), 1.08 (*s*, 6H, 2 CH_3), 0.96 (*s*, 6H, 2 CH_3).

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (**4 h**) Yellow-orange solid, FT-IR (KBr, υ cm^{-1}) 3384 (NH), 1643 (C=O, dimedone), 1514 (NO_2), 1481 (C=C, aromatic), 1344 (NO_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (*d*, *J* = 8.3 Hz, 2H, Ar–H), 7.51(*d*, *J* = 8.3 Hz, 2H, Ar–H), 6.13 (*s*, 1H, NH), 5.15 (*s*, 1H, CH), 2.14–2.45 (*m*, 8H, 4 CH_2), 1.10 (*s*, 6H, 2 CH_3), 0.96 (*s*, 6H, 2 CH_3).

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