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Synthesis of novel spirooxindoles in water by using $MnFe_2O_4$ nanoparticles as an efficient magnetically recoverable and reusable catalyst

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ABSTRACT

An efficient, clean, atom-economical and simple method for the one-pot synthesis of novel spirooxindole derivatives *via* a three-component reaction of isatins, dimedone and anilinolactones was reported. This reaction was performed by using $MnFe_2O_4$ nanoparticles (5 mol%) as an efficient magnetically heterogeneous catalyst in water as green solvent. Prominent among the advantages of this method is the use of magnetically recoverable and reusable catalyst, simple work up procedure, good to high product yields and use of water as a solvent that is considered to be relatively environmentally benign.

1. Introduction

There has been a huge interest in development of highly efficient transformations to form novel structures from simple building blocks. Synthetic chemists are also in need of finding new, efficient, and simple synthetic routes leading to greater structural variation in short times with high yields and simple work-up procedures. Significant advances have been made on to chemical processes to achieve the hazard-free, waste-free, and energy-efficient syntheses as an ultimate goal. In this context, multicomponent reactions (MCRs) have played an important role in this area in which the starting materials in a single reaction vessel give a final product [1–3]. The development of novel, efficient and green MCRs that focus on a target product is one of the major challenges in organic synthesis. The use of water as green solvent in organic chemistry was rediscovered in the 1980s in Breslow's work, which was highlighted that hydrophobic effects could strongly enhance the rate of some organic reactions. In this effect, hydrophobic molecules in aqueous solution are surrounded by a cage of water molecules. The condensation of individual molecules to form local domains consisting of multiple hydrophobes surrounded by water cages is favored by the minimization of the surface area of contact between the hydrophobic and hydrophilic domains. Therefore, the acceleration of a reaction through the hydrophobic effect is expected to correlate with the hydrophobic surface area of the reactants [4]. The performance of organic reactions in water, without the use of any hazardous and flammable organic solvents are some of the current focuses today especially in our environmentally conscious society [5,6]. The extensive work has revealed that a variety of organic reactions can be realized in water especially in the presence of various catalysts [7–10].

Recently, the magnetic nanoparticles have been widely used as a useful group of heterogeneous catalysts for organic synthesis, due to their important advantages such as, the remarkable catalytic activity, easy synthesis, operation simplicity, eco-friendliness, and recoverability by external magnetic field. They can be separated from the reaction medium after being magnetized by an external magnet. Magnetic separation is an intriguing alternative to filtration or centrifugation as it prevents the loss of catalyst and enhances the reusability, rendering the catalyst cost-effective and it is promising for industrial applications [11–15]. These advantages encouraged us to utilize manganese ferrite nanoparticles as recoverable and reusable catalyst for the synthesis of novel spirooxindole structures.

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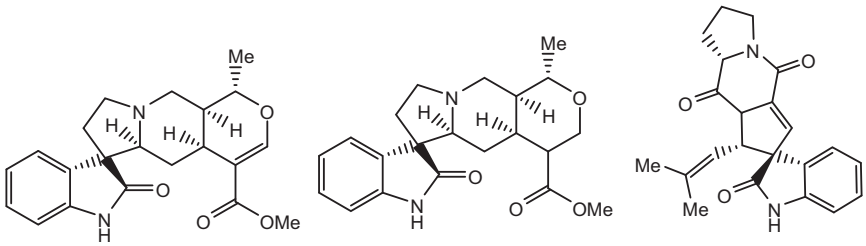

Fig. 1. Representatives of spirooxindole-containing compounds.

Spirooxindole structures are the central skeleton for numerous alkaloids and pharmacologically important compounds [16] with wide range of useful pharmacological properties and biological activities such as; antimicrobial [17], antitumoral [18], antibiotic agents [19], human NK-1 receptor inhibitors [20], and microtubule assembly inhibitors [21]. For example, *Spirotryprostatin B*, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel microtubule assembly inhibitor, also, *pteropodine* and *isopteropodine* have been shown to modulate the function of *muscarinic serotonin* receptors (Fig. 1) [22–24]. The unique structural array and highly prominent pharmacological activities have subsequently stimulated interest in the spirooxindole derivatives synthesis, consequently, much effort has been made to find efficient, new and simple synthetic methods so as to prepare compounds containing spirooxindole nucleus [25–28].

In order to evaluate the potential applications of MCRs in the field of heterocyclic chemistry, and to continue our research toward the development of novel spirooxindoles, employing environmentally benign reaction medium [29–34], herein we report a simple and efficient one-pot three-component protocol for the synthesis of new 4-phenyl-6,7-dihydro-[spiro[furo]quinoline-indoline]-triones.

2. Experimental

2.1. Reagents and materials

The used chemicals in this work were obtained from Fluka and Merck and used without purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO–d_6 solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) difractometer (Cu K, radiation, k = 0.154056 nm), at a scanning speed of 2°/min from 10° to 100°/(2θ). Scanning electron microscopy (SEM) micrographs have been collected by a FEI Quanta 200 SEM operated at a 20 kV accelerating voltage. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.2. Typical experimental procedure for the preparation of catalyst

Manganese ferrite nanoparticles have been synthesized *via* a number of different popular methods including co-precipitation, thermal decomposition and/or reduction, micelle synthesis, hydrothermal synthesis, and laser pyrolysis techniques that all of them can be directed in the synthesis of high-quality magnetic nanoparticles [35–37]. In this research, the $MnFe_2O_4$ nanoparticles have been prepared by following the reported standard protocol by co-precipitation of $MnCl_2$ and $FeCl_3$ in water in the presence of sodium hydroxide. Briefly, $MnCl_2{\cdot}4H_2O$ and $FeCl_3{\cdot}6H_2O$ were taken in molar ratio of Mn^{2+}:Fe^{3+} = 1:2 to prepare 0.3 mol L^{-1} metal ion solution of 100 ml containing 0.1 mol L^{-1} Mn^{2+} and 0.2 mol L^{-1} Fe^{3+}, which was then dropped slowly into 100 ml NaOH solution of 3 mol L^{-1} at the temperature of 95 °C. After aging for 2 h with continuous stirring, the mixture was filtered, washed and dried at 60 °C for 12 h [38].

2.3. Typical procedure for the preparation of 6,6-dimethyl-4-p-tolyl-6,7-dihydro-1H-spiro[furo[3,4-b]quinoline-9,3′-indoline]-1,2′,8(3H,4H,5H)-trione (4b)

A mixture of isatin (1 mmol, 0.147 g), dimedone (1 mmol, 0.140 g), 4-(*p*-tolylamino)furan-2(5*H*)-one (1 mmol, 0.189 g), catalyst (5 mol%, 0.011 g) and water (5 mL) was added in a round-bottomed flask and stirred at 90 °C. After completion of the reaction (monitored by TLC), the catalyst was easily separated from the reaction mixture with an external magnet. After separation of catalyst, the reaction mixture was filtered and the precipitate washed with water and recrystallized by EtOH to afford the pure product as cream powder (0.388 g, Yield: 88%); mp: >300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3439, 2960, 1740, 1665, 1620; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.01–2.63 (4H, m. 2 CH_2), 2.36 (3H, s, CH_3), 4.95 (2H, m, OCH_2), 6.94–7.36 (8H, m, ArH), 10.29 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 21.2, 27.4, 29.3, 34.4, 36.2, 49.1, 51.2, 65.8, 92.5, 117.2, 120.8, 121.4, 124.0, 127.4, 127.9, 129.0, 130.4, 131.3, 137.1, 138.9, 156.3, 160.6, 171.2, 180.1, 190.5; Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36; Found C, 73.68; H, 5.54; N, 6.31.

3. Results and discussion

Due to the unique properties of spirooxindole compounds, the development of environmentally benign synthetic methods which enable facile access to these useful entities will be an interesting challenge. To the best of our knowledge there are no reports in literature by using of anilinolactones for preparation of spirooxindoles, and this is the first report for the synthesis of these compounds by using of anilinolactones. Hence, in this research, firstly, the anilinolactones were prepared from the condensation reaction of tetronic acid with various anilines. As shown in Scheme 1, when tetronic acid was reacted with an equimolar amount of various anilines in 1,4-dioxane solution at room temperature, the corresponding products were obtained in excellent yields, appropriate reaction times and high purity [39].

In continuation of this research, considering the highly prominent pharmacological activities of spirooxindoles, we evaluated the MCR of isatins **1**, dimedone **2** and anilinolactones **3** for the synthesis of novel spirooxindole derivatives **4**. The choice of an appropriate reaction medium is of crucial importance for successful synthesis.