Journal of Molecular Liquids 219 (2016) 573–578

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Oxalic acid dihydrate and proline based low transition temperature mixture: An efficient synthesis of spiro [diindenopyridine-indoline] triones derivatives

Dattatray R. Chandam [a], Abhijeet G. Mulik [a], Dayanand R. Patil [a], Ajinkya P. Patravale [a], Digambar R. Kumbhar [b], Madhukar B. Deshmukh [a,b]

[a] Hetrocyclic Laboratory, Department of Chemistry, Shivaji University, Kolhapur 416004, India
[b] Department of Agrochemicals and Pest Management, Shivaji University, Kolhapur 416004, India

ARTICLE INFO

Article history:
Received 18 October 2015
Received in revised form 22 January 2016
Accepted 27 February 2016
Available online xxxx

Keywords:
Isatin
Indenone fused heterocycles
Spiro compounds
Low transition temperature mixture

ABSTRACT

The new facile approach has been developed for the synthesis of spiro [diindenopyridine-indoline] triones under the umbrella of green chemistry. The developed protocol is endowed with the use of low transition temperature mixture as a green reaction medium, operational simplicity, easy workup procedures, good to excellent product yields, and non-chromatographic purification procedure. Since indenone fused motifs have a broad spectrum of biological activities, this protocol is expected to find application in the combinatorial synthesis of biologically active compounds.

1. Introduction

In the advancement of green chemistry, during the last few years, considerable efforts have been made to design new protocols with less environmental hazards, higher atom economy [1]. In this esteem, multicomponent reactions have been used as a powerful, highly atom efficient tool to construct complex molecules starting from small molecules [2]. Multicomponent reactions (MCRs) comprise facile, fast, efficient synthesis of complex and bioactive molecules with reduction in number of step as well as waste [3,4]. Such protocols due to their easiness, efficacy along with high selectivity are found to be valuable asset in drug designing and discovery process [5]. Moreover, replacement of hazardous organic solvent with green or sustainable media is of great importance in the context of green chemistry [6]. In the recent years, low transition temperature mixtures (LTTMs) or deep eutectic solvent (DES) have been emerged as the powerful alternatives to conventional molecular solvent, ionic liquids. After inception by Abbott [7], Kroon et al. extended their work with introduction of new LTTMs based on diverse varieties of hydrogen bond donor and acceptor. The ease of preparation with 100% atom economy, nontoxic and biodegradable in nature, and its recyclability are the significant advantages of LTTMs over ionic liquids. As their physicochemical properties solely depend upon the nature and ratio of the counterparts, they can be considered as designer solvent. They radially dissolve CO_2 as well as worked as extraction media for proteins, potential lubricants [8]. LTTMs or DESs have been emerged as green reaction media for various organic transformations [9–13].

Indole and its derivatives are omnipresent in the plants of both marine and terrestrial origin. Heterocycles containing indole motif is an important target in synthetic and medicinal chemistry since this fragment is key moiety in various natural products as well as drug molecules [14]. Furthermore formation of spirooxindole ring system by the sharing of indole-3-carbon atom greatly enhances the biological activity. Spirooxindole ring system containing natural products like rhynchophylline, isorhynchophylline exhibit a broad range of biological activities [15,16] while spirotryprostatin A and B have been identified as novel inhibitors of microtubule assembly [17] (Fig. 1).

Indenone fused heterocycles are recognized as an important biological and medicinal frameworks (Fig. 1). Onychnine represents 4-azafluorenone group of alkaloids having indenopyridine skeleton. In addition to this, indenopyridines display numerous biological activities such as phosphodiesterase inhibition [18], adenosine A2a receptor antagonistic [19], anti-inflammatory [20], coronary dilating calcium-modulating activities [21]as well as they have been employed for the treatment of hyperlipoproteinemia [22], neurodegenerative diseases [23]. Indenopyrazoles act as ascyclin-dependent kinase inhibitors [24] while indenopyridazines act as selective monoamine oxidase B (MAO-B) inhibitors [25].

E-mail address: shubhlaxmi111@gmail.com (M.B. Deshmukh).

http://dx.doi.org/10.1016/j.molliq.2016.02.101
0167-7322/

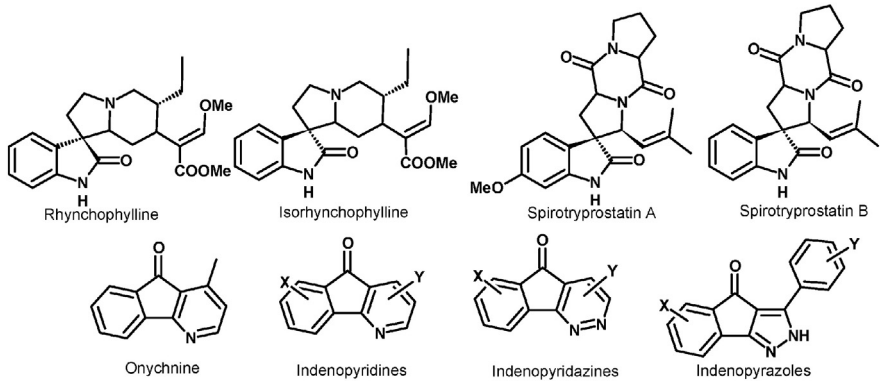


Fig. 1. Representative natural products having spirooxindole ring system and bioactive indenone fused heterocyclic compounds.

The literature survey reveals that there are few reports on the synthesis of indenone-fused heterocycles such as spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,3′-indoline]-trione from isatin, 1,3-indanedione and aromatic amine using PTSA [26,27], PEG-SO_3H and $[NMP]H_2PO_4$ [28] as catalyst under different condition. However, most of the reported methods are allied with the use of expensive catalyst, toxic solvent, and tedious preparation of catalyst. Therefore, there is a need to develop new eco-friendly methodology for bioactive indenone-fused heterocycles.

To our best of knowledge, there is no report on low transition temperature mixture prompted synthesis of indenone-fused heterocycles. Combining the greenness of low transition temperature mixture with multicomponent reaction and in continuation of our research work to develop new environmentally benign synthetic methodologies along with the biological screening of synthesized derivatives [29–31], we wish to report the synthesis of spiro[diindeno [1,2-b:2′,1′-e]pyridine-11,3′-indoline]-trione derivatives using oxalic acid: proline LTTM (Scheme 1).

2. Experimental

2.1. General

All chemicals and solvents were reagent grade and used as purchased without any further purification. Percolated silica gel 60-F254 plates were used to perform analytical thin-layer chromatography. IR spectra were recorded on a Jasco FT-IR-LE-4600 spectrophotometer. The routine nuclear magnetic resonance spectra were taken in DMSO d_6 using a Bruker 300 MHz spectrophotometer with TMS as an internal standard. Elemental analysis was done by using EURO elemental analyzer.

2.2. Preparation of LTTM

The LTTM has been synthesized according to reported method in literature [32]. The preparation of LTTM involves the heating of mixture of proline (11.5 g, 100 mmol) and oxalic acid dihydrate (12.6 g, 100 mmol) in the ratio of 1:1 at 80 °C for 1 h which afforded yellowish viscous liquid (LTTM) with 100% atom economy (Scheme 2).

2.3. Typical procedure for the synthesis of Spiro [diindenopyridine-indoline] triones (4a)

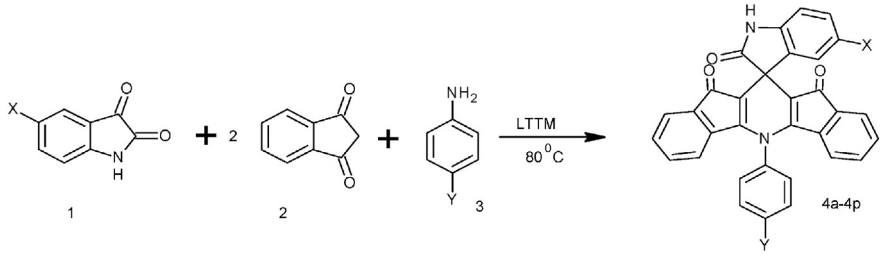
Isatin (0.147 g, 1 mmol), 1,3-indanedione (0.292 g, 2 mmol) and aniline (0.093 g, 1 mmol) were mixed in oxalic acid: proline LTTM (5 mL) as solvent and the resultant mixture was heated at 80 °C for appropriate time. After the completion of the reaction indicated by TLC, mixture was stirred at room temperature and 5 mL distilled water was added. The insoluble crude product was filtered, washed with distilled water and recrystallized from ethanol and acetonitrile to obtain pure product.

2.4. Recyclability of oxalic acid dihydrate: proline LTTM

The recyclability of LTTM was studied using the reaction of Isatin (0.147 g, 1 mmol), 1,3-indanedione (0.292 g, 2 mmol) and aniline (0.093 g, 1 mmol) in oxalic acid: proline LTTM under optimized conditions. After completion of the reaction, water (5 mL) was added to the reaction mixture and crude product was separated by filtration. Finally, LTTM was recovered by evaporating the water at 80 °C under vacuum and was reused for the next batch and recycled again.

2.5. Spectral data

1. 5-(4-chlorophenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione(4c).
   Red powder, M.P. > 300 °C, IR (KBr): 3372, 3048, 2913, 1688, 1601 cm^{-1}, ^1H NMR (300 MHz, DMSO d_6): δ_H (ppm) 5.56–5.58 (d, 2H, Ar-H), 6.85–6.92 (m, 2H, Ar-H), 7.16–7.23 (m, 2H, Ar-H), 7.27–7.29 (d, 4H, Ar-H), 7.41–7.43 (d, 2H, Ar-H), 7.88–7.92 (d, 2H, Ar-H), 8.03–8.06 (d, 1H, Ar-H), 8.23–8.26 (d, 1H, Ar-H), 10.66 (s, 1H, NH), Anal. Calcd for $C_{32}H_{17}N_2O_3Cl$: C (74.93%), H (3.34%), N (5.46%), Found: C (74.98%), H (3.30%), N (5.40%). Due to the very low solubility of 4c, we were unable to obtain ^{13}C NMR data.



Scheme 1. Oxalic acid dihydrate: proline (LTTM) promoted synthesis of spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,3′-indoline]-trione.