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A rapid and high efficient microwave promoted multicomponent domino reaction for the synthesis of spirooxindole derivatives

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ABSTRACT

A simple, efficient and rapid method has been developed for synthesis of 6,6-dimethyl-4-phenyl-6,7-dihydro-1*H*-spiro[furo[3,4-*b*]quinoline-9,3′-indoline]1,2′,8(3*H*,4*H*,5*H*)-trione derivatives. These heterocycles were prepared through domino one-pot and multicomponent condensation reactions of isatins, dimedone, and anilinolactones in the presence of alum (15 mol%) as an inexpensive, nontoxic, convenient, and available Lewis acid catalyst under microwave irradiation. The corresponding products have been obtained in excellent isolated yields between 78% and 90%, with high purity, in short reaction times about 10–12 min and easy work up.

1. Introduction

The development of efficient formation of multifunctionalized complex products such as natural products and analogs, drugs, diagnostics and etc. by using simple reactants has been an important issue in organic synthesis [1]. In this regard, multi-component domino reactions have become increasingly attractive and the best tools in modern organic synthesis and medicinal chemistry, because of their green characteristics of atom-economy, bond-forming economy, and structural economy [2,3]. These reactions can be avoided energy and time-consuming, costly processes for the purification, tedious work-up procedures, isolation of intermediate and environmentally friendly methods [4]. Therefore; the design of novel and efficient multi-component domino reactions is a continuing challenge at the forefront of organic chemistry.

Nowadays, the employment of adapted tools and techniques considering operational, economic and environmental advantages over traditional methods have greatly developed in organic, combinatorial, and medicinal chemistry mainly the synthesis of complicated molecules earned in a very fast, efficient, and time-saving manner [5]. The use of microwaves as a valuable and powerful technology has become a major motivation for both industry and academia. Replacing the oil bath with a microwave reactor, opens a new window to perform reactions in dramatically shortened time as well as increasing yields and the involved reactions are often very cleaner [6]. Many organic reactions have been explored under microwave activation [7–9].

Oxindole derivatives for decades have drown great attention because these compounds are characterized by extensive applications in biology and pharmacology as well as the presence of this framework in a number of natural products [10,11]. A great number of compounds that carry oxindole moieties are reported to have significant properties such as antiprotozoal, antibacterial, anti-inflammatory, antitumor properties and new targets for cancer chemotherapy [12–14]. They have been widely served as synthetic intermediates for alkaloids, many kinds of clinical pharmaceuticals, and drug candidates especially, compounds containing the spirooxindole ring system. Spirooxindoles and their derivatives occupy a special place in heterocyclic chemistry as these structural frameworks form the core units of many naturally occurring molecules for example; *Spirotryprostatin A*, *B*, and *Horsfiline*, (Fig. 1). These compounds possess highly pronounced biological activities and pharmacological properties [15–17], so various strategies have been used to obtain these structure containing compounds [18–20].

In this research, due to the diverse range of the pharmacological and biological activities of spirooxindoles, and in continuation of our research in this field for the preparation of these compounds [21–23], we report herein a simple, efficient and high speed

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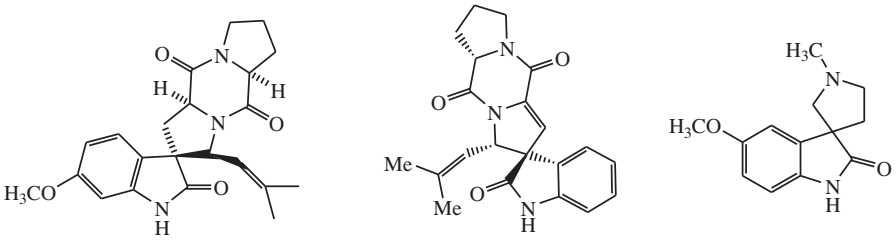

Fig. 1. Selected spirooxindolic natural products.

method for the preparation of 6,6-dimethyl-4-phenyl-6,7-dihydro-1*H*-spiro[furo[3,4-*b*]quinoline-9,3′-indoline] 1,2′,8(3*H*,4*H*,5*H*)-triones using $KAl(SO_4)_2{\cdot}12H_2O$ (alum) as an inexpensive, nontoxic, and available Lewis acid catalyst under microwave irradiation.

2. Experimental

2.1. Materials

The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

2.2. 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. Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 Ex mass spectrometer operating at an ionization potential of 70 eV. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.3. 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, 0.15 g), dimedone (1 mmol, 0.14 g), 4-(*p*-tolylamino)furan-2(5*H*)-one (1 mmol, 0.19 g), alum (15 mol%, 0.071 g), with few drops of DMSO, in an open tall beaker was irradiated inside microwave oven at 100 °C with the power level at 900 W for an appropriate time (monitored by TLC). After completion of the reaction, 5 ml of cold water was poured into the mixture. The precipitate was filtrated and the cream precipitate was collected, dried and recrystallized from ethanol to afford the pure product. Due to very low solubility of the products **4d**, **4g**, **4l** and **4o**, we cannot report the ^{13}C NMR data for this product.

2.3.1. 4-(4-Chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-spiro[furo[3,4-b]quinoline-9,3′-indoline]-1,2′,8(3H,4H,5H)-trione (**4a**)

Cream powder (Yield: 82%). *mp* > 300 °C. (Ref. [23b]). IR (KBr) (ν_{max}/cm^{-1}): 3436, 2958, 1741, 1662‘, 1620; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3*H*, s, CH_3), 1.02 (3*H*, s, CH_3), 2.00–2.68 (4*H*, m. 2 CH_2), 4.94–5.03 (2*H*, m, OCH_2), 6.97–7.65 (8*H*, m, ArH), 10.33 (1*H*, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.3, 29.3, 34.5, 36.1, 49.2, 51.2, 65.9, 92.3, 117.3, 121.0, 121.2, 124.0, 127.6, 129.0, 129.9, 130.1, 132.8, 133.7, 137.1, 159.4, 159.9, 171.2, 179.9, 190.6; Anal. Calcd for $C_{26}H_{21}ClN_2O_4$: C, 67.75; H, 4.59; N, 6.08%; Found C, 67.71; H, 4.64; N, 6.13%; MS: *m*/*z* 462, 460.

2.3.2. 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**)

Cream powder (Yield: 89%). *mp* > 300 °C, (Ref. [23b]). IR (KBr) (ν_{max}/cm^{-1}): 3439, 2960, 1740, 1665, 1620; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3*H*, s, CH_3), 1.02 (3*H*, s, CH_3), 2.01–2.63 (4*H*, m. 2 CH_2), 2.36 (3*H*, s, CH_3), 4.91–4.98 (2*H*, m, OCH_2), 6.94–7.36 (8*H*, m, ArH), 10.29 (1*H*, 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%; MS: *m*/*z* 440.

2.3.3. 4-(4-Bromophenyl)-6,6-dimethyl-6,7-dihydro-1H-spiro[furo[3,4-b]quinoline-9,3′-indoline]-1,2′,8(3H,4H,5H)-trione (**4c**)

White powder (Yield: 86%). *mp* > 300 °C. (Ref. [23b]). IR (KBr) (ν_{max}/cm^{-1}): 3277, 2959, 1739, 1662; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3*H*, s, CH_3), 1.02 (3*H*, s, CH_3), 2.00–2.68 (4*H*, m. 2 CH_2), 4.92–5.03 (2*H*, m, OCH_2), 6.95–7.78 (8*H*, m, ArH), 10.33 (1*H*, s, NH), ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.0, 28.8, 34.8, 35.7, 50.0, 51.4, 66.5, 92.0, 117.9, 121.8, 121.4, 123.8, 128.1, 129.6, 130.4, 130.9, 133.2, 134.0, 137.8, 160.1, 160.9, 172.0, 180.4, 190.2; Anal. Calcd for $C_{26}H_{21}BrN_2O_4$: C, 61.79; H, 4.19; N, 5.54%; Found C, 61.85; H, 4.24; N, 5.59%; MS: *m*/*z* 506, 504.

2.3.4. 4-(4-Methoxyphenyl)-6,6-dimethyl-6,7-dihydro-1H-spiro[furo[3,4-b]quinoline-9,3′-indoline]-1,2′,8(3H,4H,5H)-trione (**4d**)

White powder (Yield: 91%). *mp* > 300 °C. (Ref. [23b]). IR (KBr) (ν_{max}/cm^{-1}): 3454, 3240, 2961, 1736, 1662, 1607; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3*H*, s, CH_3), 1.01 (3*H*, s, CH_3), 2.00–2.62 (4*H*, m, 2 CH_2), 3.80 (3*H*, s, OCH3), 4.91–5.00 (2*H*, m, OCH_2), 6.94–7.31 (8*H*, m, ArH), 10.29 (1*H*, s, NH); Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14%; Found C, 71.10; H, 5.24; N, 6.19%; MS: *m*/*z* 556.

2.3.5. 6,6-Dimethyl-4-phenyl-6,7-dihydro-1H-spiro[furo[3,4-b]quinoline-9,3′-indoline] 1,2′,8(3H,4H,5H)-trione (**4e**)

Pail yellow powder (Yield: 87%). *mp* > 300 °C. (Ref. [23b]). IR (KBr) (ν_{max}/cm^{-1}): 3437, 2960, 1724, 1660; ^{1}H NMR (DMSO-d_6, 400 MHz): δ: 0.99 (3*H*, s, CH_3), 1.01 (3*H*, s, CH_3), 2.01–2.66 (4*H*, m. 2 CH_2), 4.91–5.00 (2*H*, m, OCH_2), 6.96–7.57 (9*H*, m, ArH), 10.32 (1*H*, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.4, 29.3, 34.5, 36.2, 49.1, 51.2, 65.8, 92.4, 117.3, 120.9, 121.3, 124.0, 127.5, 128.1, 129.0, 129.2, 130.0, 133.9, 137.1, 159.4, 160.3, 171.2, 180.0, 190.6; Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20; N, 6.57%; Found C, 73.18; H, 5.24; N, 6.63%; MS: *m*/*z* 426.