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Superoxide Ion Induced Multicomponent Synthesis of Spirooxindole Fused 4H-Chromenes

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Abstract: The present report demonstrates an efficient use of insitu generated superoxide ion to bring about multicomponent synthesis of spirooxindole fused 4H-chromenes 4a-h under the mild reaction conditions at room temperature.

Keywords: Superoxide ion, multicomponent synthesis, spirooxindole, 4H-chromenes

Introduction

The chemistry of superoxide ion has come to the forefront of current interdisciplinary research due to its demonstrated biochemical applications and as a species of relatively unexplored chemical reactivity [1].

The ability of superoxide ion to function as a multipotent reagent [2] has made the chemistry of this radical anion somewhat enigmatic. Although some progress has been made in the understating of the chemistry of superoxide ion but an important aspect involving the use of superoxide ion in multicomponent synthesis still remains untouched and warrants study in this direction.
Multicomponent reactions (MCR) have been proved an important tool for organic transformations due to their ability to incorporate three or more substrates into a single target in one operation [3].

In recent years, these are widely used in drug discovery [4] as well as in the total synthesis of natural products [5]. The spirooxindole ring system is a widely distributed structural framework present in numerous pharmaceuticals and natural products [6], including such cytostatic alkaloids as spirotryprostatins A, B, and strychnophylline [7].

Due to the unique structural array and the

highly pronounced biological activity, spirooxindoles have become attractive synthetic targets for many scientists and researchers [8].

Among the oxygen-containing heterocycles, 4*H*-chromenes heterocyclic scaffolds represent a "*privileged*" structural motif well-distributed in natural products with a broad spectrum of strong biological activities [9].

Substituted 4*H*-chromenes have received considerable attention due to their broad range of pharmacological properties, such as spasmolitic, diuretic, anticoagulant, anticancer and antianaphylactic activities [10, 11].

Several methodologies have been reported in literature for the synthesis of spirooxindole fused 4*H*-chromenes [12-15], but superoxide ion induced multicomponent synthesis of spirooxindole fused 4*H*-chromenes is still not fully explored.

Results and discussion

In light of the above, and as a part of our ongoing research on the application of the superoxide ion in organic synthesis [16], we report herein a mild and efficient one-pot synthesis of spirooxindole fused 4*H*-chromenes. In the present course of reaction superoxide ion was generated *in situ* by phase transfer reaction of potassium superoxide and 18- Crown- 6 in dry DMF at room temperature and was subsequently allowed to react with isatin derivatives **1a-f**, cyclic 1,3-diketone **2** and malononitrile/ethylcyanoacetate **3a,b** (**Scheme 1 and Table 1**).

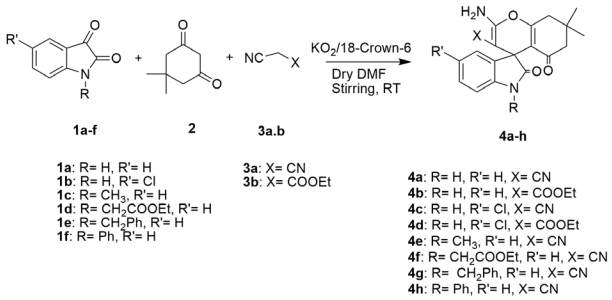

Table 1: Synthesis of spirooxindole derivatives **(4a-h).**

Entry	R	R'	X	% Yield
4a	H	H	CN	88
4b	H	H	COOEt	87
4c	H	Cl	CN	88
4d	H	Cl	COOEt	90
4e	CH_3	H	CN	82
4f	CH_2COOEt	H	CN	90
4g	CH_2Ph	H	CN	89
4h	Ph	H	CN	90

In order to achieve the optimum yield of the products, the effect of various parameters such as effect of solvents (DMF, DMSO, and CH_3CN) and molar proportion of the reactants were investigated in detail. The multicomponent reaction of isatin, dimedone and ethylcyanoacetate was taken as reference reaction. The best result was obtained using dimedone, isatin, ethylcyanoacetate, KO_2 and 18-Crown- 6 in the molar proportion **1:1:1:1:1** at room temperature in dry DMF in 4- 6 h (**Table 1**, **entry 2**). Under the optimized set of reaction conditions, isatin derivatives **1a-f** were made to undergo smooth coupling with cyclic 1,3-diketone **2** and malononitrile/ethylcyanoacetate **3a,b** in the presence of superoxide ion at room temperature to afford spirooxindole fused 4*H*-chromenes **4a-h.**

In this investigation, Superoxide ion is assumed to initiate the reaction by proton abstraction from the malononitrile /ethyl cyanoacetate followed by nucleophilic attack at isatin moiety and hydroxide-promoted Michael addition of cyclic 1,3-diketone to electron deficient Knoevenagel adduct followed by intramolecular cyclization leads to spirooxindole fused 4*H*-chromenes **4a-h** under significantly mild reaction conditions in aprotic medium at room temperature. Chemical structure of all synthesized compounds was fully established by their physical and spectral data.

Conclusions

In conclusion, a novel and mild approach for the one-pot synthesis of spirooxindole fused 4*H*- chromenes has been achieved by using superoxide ion in non-aqueous medium employing isatin derivatives, cyclic 1,3-diketone and malononitrile /ethyl cyanoacetate under room temperature in good to excellent yield. The utility of the described methodology in multicomonent reactions is highly promising as it allows for the combination of synthetic virtues of conventional MCRs with biochemical species i.e. superoxide ion.

Experimental

General: All chemicals were procured from Aldrich, USA, and E. Merck, Germany and used without further purification. TLC was carried out on SiO_2 gel (HF254, 200 mesh). The solvent system employed was ethyl acetate: n hexane (2: 1) and the spots were identified by placing the plate in Iodine chamber. IR spectra were recorded on a PerkinElmer FT/IR version 10.03.05 spectrometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE- 440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected.

General procedure for synthesis of compounds 4a-h

Potassium superoxide and 18- Crown-6 (1:1) were weighed under nitrogen atmosphere using an atmosbag and were transferred into a three necked R. B. flask, dry DMF (20 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of superoxide ion. To the stirred reaction mixture, were added ethylcyanoacetate/ malononitrile **3a,b** (0.01 mol). After 10 min, the isatin derivatives **1a-f** (0.01 mol) and dimedone 2 (0.01mol) were introduced, and the stirring was continued 4-6h. After the reaction was over as indicated by TLC, mixture was treated with cold brine solution (2 mL) followed by saturated sodium hydrogen carbonate solution (2 mL) to decompose the unreacted KO_2. The mixture was then extracted with dicholoromethane (3 × 15 mL) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to give the products **4a-h**, which were purified by column chromatography.

2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4a): White solid; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 0.98 (3H, s, CH_3),

1.06 (3H, s, CH_3), 2.10- 2.16 (2H, m, CH_2), 2.55-261 (2H, m, CH_2), 6.79–7.21 (4H, m, ArH), 7.22 (2H, s, NH_2), 11.02 (1H, s, NH). ^{13}C NMR (75.45 MHz, DMSO-d6): δC (ppm) 27.4, 28.2, 32.6,47.2, 50.5, 57.8, 109.8, 111.2, 117.8, 122.1, 123.4, 128.6, 134.8, 142.4, 159.2, 164.6, 178.5,195.3. IR (KBr), ν_{max},: 3400, 3290, 2893, 2206, 1710, 1660, 1241. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.0; H, 5.16; N, 12.53. Found: C, 67.94; H, 5.27; N, 12.60.

Ethyl-2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (4b): White solid; ^{1}H NMR (300 MHz,DMSO-d6): δH (ppm) 0.77 (3H, t, *J*= 6.5 Hz, CH_3), 0.99 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.04- 2.11 (2H, m,CH_2), 2.61-2.65 (2H, m, CH_2), 3.84 (2H, q, *J*= 6.9 Hz, CH_2), 6.66–7.06 (4H, m, ArH), 7.76 (2H, s, NH_2), 10.54 (1H, s, NH). ^{13}C NMR (75.45 MHz, DMSO-d6): δC (ppm) 13.6, 28.0, 28.7, 32.0, 47.7, 51.0, 58.9, 76.7, 108.8, 114.0, 122.0, 123.6, 128.0, 137.1, 144.4, 160.0, 162.7, 168.3 , 180.1, 193.1. IR (KBr), ν_{max},: 3399, 3216, 2932, 1661, 1623, 1235. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.00; H, 5.77; N, 7.3. Found: C, 65.80; H, 6.03; N, 7.65%.

2-Amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4c): White solid; ^{1}H NMR (300 MHz, DMSO-d6) δ 0.97 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.16-2.22 (m, 2H, CH_2), 2.47-2.54 (m, 2H, CH_2), 6.80 -7.21(3H, m, ArH), 7.24 (s, 2H, NH_2), 11.11 (s, 1H, NH). ^{13}C NMR (75.45 MHz, DMSO-d6) δ: 28.1, 28.9, 31.9, 48.5, 50.9, 57.0, 111.6, 111.8, 116.9, 124.9, 127.1, 128.5, 137.0, 142.5, 160.3, 164.1, 180.0, 193.1. IR (KBr), ν_{max},: 3425, 3300, 2911, 1678, 1621, 1257. Anal. calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.61; H, 4.45; N, 11.37. Found: C, 61.62; H, 4.47, N, 11.40.

Ethyl-2-amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4d): White solid; ^{1}H NMR (300 MHz, DMSO-d6) δ 0.80 (t, *J* = 6.9 Hz, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.10-2.16 (m, 2H, CH_2), 2.51- 2.58 (m, 2H, CH_2), 3.68 (q, *J* = 7.2 Hz, 2H, CH_2), 6.67- 7.12 (3H, m, ArH), 7.84 (s, 2H, NH_2), 10.51 (s, 1H, NH). ^{13}C NMR (75.45 MHz, DMSO-d6) δ 14.6, 28.0, 28.9, 31.0, 46.6, 50.8, 60.1, 77.0, 110.2, 114.0, 122.9, 123.9, 128.1, 139.0, 144.2, 160.2, 164.0, 168.1, 179.0, 195.0. . IR (KBr), ν_{max},: 3393, 3203, 2941, 1684, 1610, 1224. Anal. calcd. For $C_{21}H_{21}ClN_2O_5$: C, 60.50; H, 5.10; N, 6.71. Found: C, 60.52; H, 5.08, N, 6.74.

2-Amino-1',7,7-trimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-indole]-3-carbonitrile (4e): White solid; ^{1}H-NMR (300 MHz, DMSO-d6) δH 0.99 (6H, s, 2 CH_3), 2.22-2.18 (2H, m, CH_2), 2.48-255 (2H, m, CH_2), 3.84 (3H, s, NCH_3), 6.84–7.11 (4H, m, ArH), 7.30 (2H, s, NH_2) ppm; δC (75.45 MHz, DMSO-d6) 22.0, 26.9, 27.4, 32.1, 40.0, 48.1, 50.0, 56.9, 109.2, 110.0, 118.2, 122.2, 123.1, 128.5, 134.1, 144.2, 159.5, 164.0, 176.6, 193.0 ppm. IR (KBr): ν_{max}, 3368, 3224, 3116, 2938, 2193, 1698, 1644, 1258 $cm^{-1.}$ Anal. Calcd for $C_{20}H_{19}N_3O_3$ calcd: C 68.70, H 5.53, N 12.03; found: C 68.68, H 5.50, N 12.00.

1'-Acetyl-2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-

indole]-3-carbonitrile (**4f**): White solid; ^{1}H-NMR (300 MHz, DMSO-d6) δH 0.98 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.08–2.16 (2H, m, CH_2), 2.52-2.58 (2H, m, CH_2), 2.77 (3H, s, CH_3CO), 7.16–7.36 (3H, m, ArH), 7.50 (2H, s, NH_2), 8.08 (1H, d, *J*= 7.2 Hz, ArH) ppm; δC (75.45 MHz, DMSO-d6) 20.0, 27.1, 28.0, 32.1, 39.0, 46.1, 50.5, 59.1, 110.1, 113.3, 119.1, 122.2, 126.0, 128.4, 132.1, 139.3, 160.0, 164.0, 171.4, 180.0, 195.2 ppm. IR (KBr): ν_{max}, 3399, 3164, 2928, 2201, 1724, 1680, 1611, 1272 cm^{-}1. Anal. Calcd for $C_{21}H_{19}N_3O_4$ calcd: C 65.80, H 7.07, N 14.16; found: C 65.78, H 7.14, N 14.04.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3$^{'}$-(3$^{'}$*H*)-1$^{'}$-benzyl-indol]-(1$^{'}$*H*)- 2$^{'}$-one-3-carbonitrile (4g): White solid; ^{1}H NMR (DMSO-d6, 300 MHz): 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10-2.20 (2H, m, CH_2), 2.48–2.54 (m, 2H, CH_2), 4.88 (s, 2H, CH_2) 6.77- 7.21 (m, 4H, ArH), 7.30–7.36 (m, 5H, ArH, NH_2), 7.47 (d, 2H, ArH). IR: 3422, 3301, 3217, 2962, 2203, 1998, 1660, 1635, 1487, 1220 cm^{-}1. Anal. Calcd for $C_{26}H_{23}N_3O_3$: C, 74.38; H, 5.46; N, 8.88. Found: C, 74.27; H, 5.40; N, 8.78.

2-Amino-1',2',5,6,7,8-hexahydro-7,7-dimethyl-2',5-dioxo-1'-phenylspiro[4*H*-1-benzopyran-4,3'-[3*H*]-indole]-3-carbonitrile (4h): White solid; ^{1}H-NMR: 1.01 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.30–2.38 (2H, m, CH_2), 2.59–2.65 (2H, m, CH_2), 6.90-7.35 (4H, m, ArH), 7.60–7.65 (4H, m, ArH, NH_2), 7.70-7.84 (3H, m, ArH). IR: 3437, 3332, 2971, 2200, 1703, 1644, 1218, 1057. Anal. calc. for $C_{25}H_{21}N_3O_3$: C 71.98, H 6.14, N 10.21; found: C 71.74, H 6.25, N 10.29.

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