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Synthesis of 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-triones from tetrahydro-4-oxoindeno[1,2-*b*]-pyrroles

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Abstract: A simple approach to assembling of functionalized spiro-butenolide-indenetriones from oxoindeno[1,2-*b*]pyrrole derivatives in the presence of H_2SO_4 is described. Simplicity of the procedure, short reaction time and excellent yields are important features of this protocol.

Keywords: amines; dialkyl acetylenedicarboxylates; 2(5*H*)-furanones; ninhydrin.

Introduction

Five-membered oxygen-containing heterocycles have been referred to as privileged structural motifs owing to their wide distribution in pharmaceuticals and natural products [1–5]. In particular, 2(5*H*)-furanones have received increasing attention because of their biological and pharmacological activities, such as antitumor, antimicrobial, antiviral and anti-human immunodeficiency virus 1 (HIV-1) properties [6–8]. Furans are also present in agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers and flavoring and fragrance compounds [9, 10]. The presence of a sterically constrained spiro structure in heterocyclic compounds also adds to the versatility of the properties of spiro compounds [11, 12]. In continuation of our work on the development of efficient protocols for the synthesis of heterocyclic compounds [13–16], herein, a novel approach to the synthesis of spiro-2(5*H*)-furanone derivatives **2** is reported (Scheme 1). The products are unusual in that a different outcome could be expected based on the recent report of a closely related reaction [17].

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Results and discussion

Synthesis of indeno[1,2-*b*]pyrrole-2,3-dicarboxylate derivative **1a** by the reaction of ninhydrin, methyl acetylenedicarboxylate and aniline has been reported by Yavari and co-workers [18], but conversion of the product **1a** in the presence of concentrated sulfuric acid has not been studied. In this work, heating of compound **1a** with a catalytic amount of sulfuric acid in acetic acid for 3 h furnished 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-trione **2a**. In order to show the generality and scope of this new protocol, additional products **2b–f** were obtained, as summarized in Scheme 1. The structures of compounds **2a–f** are in full agreement with their infrared (IR) spectroscopy, mass spectrometry (MS), proton nuclear magnetic resonance (^{1}H NMR), and carbon-13 nuclear magnetic resonance (^{13}C NMR) data. A suggested mechanism is given in Scheme 2. The proposed sequence involves protonation of **1** in the first step and then is self-explanatory.

Conclusions

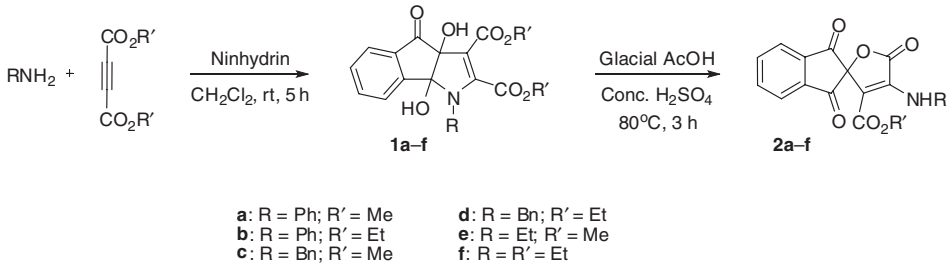
A convenient and efficient methodology for synthesizing diverse 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-triones with potential biological properties from commercially available materials was developed.

Experimental

IR spectra were recorded in KBr pellets on a Shimadzu 460 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer using $CDCl_3$ as solvent. Electron impact mass spectra were obtained at 70 eV on a Finnigan-MAT-8430 mass spectrometer. Elemental analyses for C, H and N were obtained on a Heraeus CHNO-Rapid analyzer. All commercially available chemicals and reagents were used without further purification.

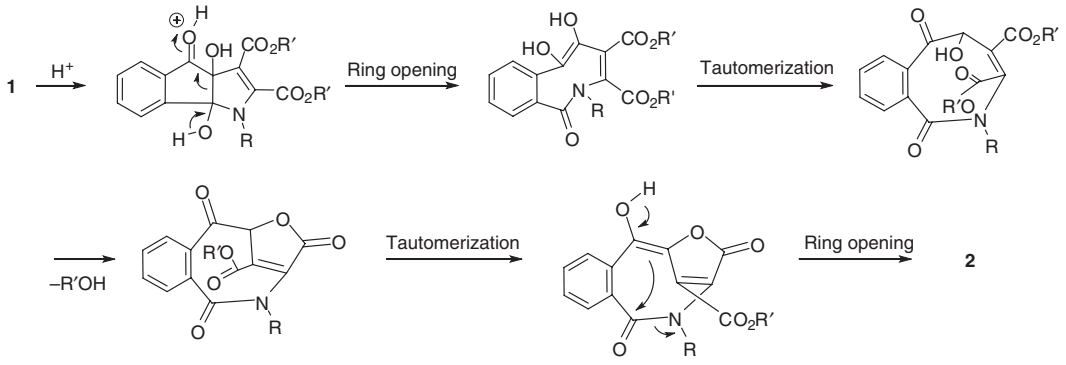
General procedure for the preparation of compounds 2a–f

Concentrated H_2SO_4 (20 mol%) was added to a solution of dihydroxyindenopyrrole **1** (1 mmol) in acetic acid (5 mL). The



a: R = Ph; R′ = Me
b: R = Ph; R′ = Et
c: R = Bn; R′ = Me
d: R = Bn; R′ = Et
e: R = Et; R′ = Me
f: R = R′ = Et

Scheme 1



Scheme 2

mixture was heated in a water bath at 80°C for 3 h. After completion of the reaction as monitored by thin layer chromatography (TLC), eluting with a mixture of ethyl acetate and hexanes (1:4), the mixture was cooled to room temperature and then poured into 5 mL of water. The product was extracted with CH_2Cl_2 (2×5 mL). The extract was concentrated under reduced pressure and the viscous residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and hexanes (1:6).

Methyl 1′,3′,5-trioxo-4-(phenylamino)-1′,3′-dihydro-5*H*-spiro-[furan-2,2′-indene]-3-carboxylate (2a) Yellow oil; yield 0.32 g (88%); IR: 3356, 1786, 1725, 1693 cm^{-1}; ^1H NMR: δ 3.45 (3H, s, OCH_3), 6.78 (1 H, br s, NH), 7.23–8.14 (9H, m, CH); ^{13}C NMR: δ 52.3, 109.1, 120.2, 123.1, 124.5, 126.8, 129.2, 137.4, 139.8, 141.6, 145.3, 165.5, 170.1, 193.3; EI-MS: *m/z* 363 (M^+, 9), 227 (23), 105 (100), 99 (54), 77 (90), 59 (61%). Anal. Calcd for $C_{20}H_{13}NO_6$: C, 66.12; H, 3.61; N, 3.86. Found: C, 66.28; H, 3.50; N, 3.81.

Ethyl 1′,3′,5-trioxo-4-(phenylamino)-1′,3′-dihydro-5*H*-spiro[furan-2,2′-indene]-3-carboxylate (2b) Yellow oil; yield 0.33 g (87%); IR: 3353, 1782, 1726, 1695 cm^{-1}; ^1H NMR: δ 1.14 (3H, t, ^3J = 6.8 Hz, CH_3), 4.11 (2H, q, ^3J = 6.8 Hz, CH_2O), 6.69 (1 H, br s, NH), 7.21–8.14 (9H, m, CH); ^{13}C NMR: δ 14.2, 61.2, 109.3, 120.3, 123.3, 124.6, 126.8, 129.1, 137.6, 139.5, 141.3, 145.2, 165.7, 170.2, 193.6; EI-MS: *m/z* 377 (M^+, 11), 227 (25), 105 (100), 104 (48), 92 (70), 77 (78%). Anal. Calcd for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.62; H, 3.94; N, 3.66.

Methyl 4-(benzylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5*H*spiro[furan-2,2′-indene]-3-carboxylate (2c) Yellow oil; yield 0.35 g (94%); IR: 3355, 1785, 1724, 1695 cm^{-1}; ^1H NMR: δ 3.43 (3H, s, MeO), 5.05 (2H, d, ^3J = 6.4 Hz, CH_2N), 6.75 (1H, br s, NH), 7.27–8.10 (9H, m, CH); ^{13}C NMR: δ 48.6, 52.2, 109.5, 120.3, 124.7, 128.1, 128.3, 129.3, 137.1, 138.0, 141.2, 148.7, 166.8, 170.2, 193.6; EI-MS: *m/z* 337 (M^+, 12), 233 (31), 227 (21), 120 (13), 105 (100), 104 (65), 91 (71), 59 (88%). Anal. Calcd for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.74; H, 3.95; N, 3.65.

Ethyl 4-(benzylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5*H*-spiro[furan-2,2′-indene]-3-carboxylate (2d) Yellow oil; yield 0.36 g (92%); IR: 3351, 1785, 1728, 1691 cm^{-1}; ^1H NMR: δ 1.28 (3H, t, ^3J = 6.8 Hz, Me), 4.12 (2H, q, ^3J = 6.8 Hz, Me), 5.03 (2H, d, ^3J = 6.2 Hz, CH_2N), 6.70 (1 H, br s, NH), 7.33–8.14 (9H, m, CH); ^{13}C NMR: δ 14.2, 48.7, 62.1, 109.5, 120.8, 124.8, 128.2, 128.3, 129.5, 137.4, 138.2, 141.4, 148.6, 166.8, 170.2, 193.2; EI-MS: *m/z* 391 (M^+, 11), 247 (21), 227 (16), 105 (100), 104 (38), 91 (64), 73 (87%). Anal. Calcd for $C_{22}H_{17}NO_6$: C, 67.51; H, 4.38; N, 3.58. Found: C, 67.32; H, 4.31; N, 3.52.

Methyl 4-(ethylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5*H*-spiro[furan-2,2′-indene]-3-carboxylate (2e) Yellow oil; yield 0.29 g (91%); IR: 3353, 1784, 1723, 1687, 1642 cm^{-1}; ^1H NMR: δ 1.30 (3H, t, ^3J = 7.2 Hz, Me), 3.44 (3H, s, MeO), 3.86 (2H, q, ^3J = 7.2 Hz, CH_2N), 6.78 (1 H, br s, NH), 7.97–8.12 (4H, m, 4CH); ^{13}C NMR: δ 16.6, 29.6, 51.8, 109.2, 120.3, 124.6, 137.3, 141.4, 148.7, 166.7, 170.1, 194.2; EI-MS: *m/z* 315 (M^+, 8), 227 (18), 105 (100), 59 (92), 44 (66%). Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16; N, 4.44. Found: C, 61.71; H, 4.14; N, 4.37.

Ethyl 4-(ethylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5*H*-spiro[furan-2,2′-indene]-3-carboxylate (2f) Yellow oil; yield 0.29 g (89%); IR: 3355, 1783, 1720, 1692, 1649 (C=O) cm^{-1}; ^1H NMR: δ 0.89 (3H, t, ^3J = 7.2 Hz, Me), 1.29 (3H, t, ^3J = 6.8, Me), 3.86 (2H, q, ^3J = 7.2 Hz, CH_2N), 4.20 (2H, q, ^3J = 6.8 Hz, CH_2O), 6.78 (1 H, br s, NH), 7.96–8.10 (4H, m, CH); ^{13}C NMR: δ 14.2, 16.5, 29.5, 61.4, 109.1, 120.0, 124.5, 137.2, 141.2, 148.2, 166.5, 170.0, 194.4; EI-MS: *m/z* 329 (M^+, 11), 227 (19), 105 (100), 44 (70), 73 (92), 29 (50%). Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.87; H, 4.50; N, 4.20.

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