J IRAN CHEM SOC (2012) 9:503–506
DOI 10.1007/s13738-011-0061-4

ORIGINAL PAPER

Synthesis of functionalized 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-triones from primary amines, acetylenic esters and ninhydrin

Issa Yavari · Samira Arab-Salmanabadi · Ali Aminkhani

Received: 19 August 2011 / Accepted: 2 December 2011 / Published online: 13 January 2012

Abstract An effective route to functionalized 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-triones is described via tandem reaction of primary amines, acetylenic esters and ninhydrin.

Keywords Spiro compound · Primary amine · Acetylenic ester · Ninhydrin · Tandem reaction

Introduction

Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [1]. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [2–5].

We recently reported the formation of novel spiro compounds via the reaction of indane-1,3-dione with Huisgen's zwitterions formed in situ from *N*-heterocycles and activated acetylenes via cyclization [5, 6].

Experimental

Chemicals and apparatus

Amines **1**, acetylenic esters **2**, and ninhydrin (**3**) were obtained from *Merck* and were used without further purification. Melting points were obtained uncorrected using an Electrothermal-9100 apparatus. IR spectra were recorded with a *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a *Bruker DRX-300 Avance* instrument using $CDCl_3$ as the deuterated solvent containing tetramethylsilane as internal standard, at 300 and 75 MHz, respectively; δ in parts per million, J in hertz. EI-MS (70 eV) mass spectra were obtained with a *Finnigan-MAT-8430* mass spectrometer in *m/z*. Elemental analyses (C, H, N) were obtained with a *Heraeus CHN-O-Rapid* analyzer.

General procedure for the preparation of compound 4

To a stirred solution of amine **1** (2 mmol) and the acetylenic ester **2** (2 mmol) in toluene (10 mL), was added ninhydrin (**3**, 0.32 g, 2 mmol) at rt, then refluxed for 5–8 h. After completion of the reaction [TLC (AcOEt/hexane 1:4) monitoring], the solvent was removed under reduced pressure, and the residue was purified by column chromatography [silica gel (230–400 mesh; Merck), hexane/AcOEt 5:1: pure product].

*Methyl 4-(ethylamino)-1′,5-dioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4a**)*

Yellow oil, yield: 0.24 g (76%). IR (KBr): 3,352 (N–H), 1,784, 1,723, 1,689, 1,645 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 315 (M^+, 6), 227 (16), 171 (14), 105 (100), 59 (91), 58 (11), 44 (66), 29 (34). Anal. Calcd. for $C_{16}H_{13}NO_6$ (315.28): C, 60.95; H, 4.16; N, 4.44%. Found: C, 61.31; H, 4.11; N, 4.38%. ^{1}H NMR: δ = 1.30 (3H, t, ^{3}J = 7.2 Hz, Me), 3.44 (3H, s, MeO), 3.86 (2H, q, ^{3}J = 7.2 Hz, CH_2N), 6.78 (1 H, br s, NH), 7.97–8.11 (4H, m, 4CH). ^{13}C NMR: δ = 16.6 (Me), 29.6 (CH_2N), 51.9 (MeO), 109.4 (C), 120.3

I. Yavari (✉) · S. Arab-Salmanabadi · A. Aminkhani
Department of Chemistry Science and Research Branch, Islamic Azad University, Tehran, Iran
e-mail: yavarisa@modares.ac.ir

(C), 124.6 (2CH), 137.3 (2CH), 141.5 (2C), 148.7 (C), 166.7 (C=O), 170.3 (C=O), 194.0 (2C=O).

*Ethyl 4-(ethylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4b**)*

Yellow oil, yield: 0.24 g (72%). IR (KBr): 3,355 (N–H), 1,783, 1,720, 1,692, 1,649 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 329 (M^+, 11), 227 (17), 185 (14), 105 (100), 58 (11), 44 (70), 73 (91), 29 (46). Anal. Calcd. for $C_{17}H_{15}NO_6$ (329.30): C, 62.00; H, 4.59; N, 4.25%. Found: C, 61.75; H, 4.51; N, 4.20%. ^{1}H NMR: $\delta = 0.89$ (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, N–H), 7.96–8.10 (4H, m, 4CH). ^{13}C NMR: $\delta = 14.2$ (Me), 16.4 (Me), 29.5 (CH_2N), 61.0 (CH_2O), 109.1 (C), 120.1 (C), 124.5 (2CH), 137.2 (2CH), 141.3 (2C), 148.4 (C), 166.5 (C=O), 170.1 (C=O), 194.2 (2C=O).

*Methy 4-(butylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4c**)*

Yellow oil, yield: 0.29 g (85%). IR (KBr): 3,356 (N–H), 1,785, 1,725, 1,691, 1,646 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 343 (M^+, 11), 227 (13), 199 (8), 105 (90), 104 (7), 86 (19), 72 (100), 59 (98), 57 (17).Anal. Calcd. for $C_{18}H_{17}NO_6$ (343.33): C, 62.97; H, 4.99; N, 4.08%. Found: C, 62.61; H, 4.92; N, 4.01%. ^{1}H NMR: $\delta = 0.98$ (3H, t, $^3J = 7.2$ Hz, Me), 1.44 (2H, m, CH_2), 1.64 (2H, m, CH_2), 3.43 (3H, s, MeO), 3.83 (2H, t, $^3J = 7.2$ Hz, CH_2N), 6.78 (1 H, br s, N–H), 7.96–8.11 (4H, m, 4CH). ^{13}C NMR: $\delta = 14.1$ (Me), 14.5 (CH_2), 33.3 (CH_2), 42.8 (CH_2N), 51.9 (MeO), 109.2 (C), 120.2 (C), 124.6 (2CH), 137.3 (2CH), 141.5 (2C), 148.7 (C), 163.7 (C=O), 170.3 (C=O), 194.1 (2C=O).

*Ethyl 4-(butylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4d**)*

Yellow oil, yield: 0.28 g (78%). IR (KBr): 3354 (N–H), 1,786, 1,725, 1,689, 1,647 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 357 (M^+, 9), 227 (25), 213 (11), 105 (96), 104 (20), 86 (24), 73 (92), 72 (100), 57 (22).Anal. Calcd. for $C_{19}H_{19}NO_6$ (357.36): C, 63.86; H, 5.36; N, 3.92%. Found: C, 63.55; H, 5.30; N, 3.86%. ^{1}H NMR: $\delta = 0.97$ (3H, t, $^3J = 7.2$ Hz, Me), 1.29 (3H, t, $^3J = 6.9$ Hz, Me), 1.43 (2H, m, CH_2), 1.63 (2H, m, CH_2), 3.89 (2H, t, $^3J = 7.2$ Hz, CH_2N), 4.20 (2H, q, $^3J = 6.9$ Hz, CH_2O), 6.77 (1 H, br s, N–H), 7.96–8.11 (4H, m, 4CH). ^{13}C NMR: $\delta = 14.1$ (Me), 14.2 (Me), 14.6 (CH_2), 33.4 (CH_2), 42.9 (CH_2N), 61.2 (CH_2O), 109.3 (C), 120.2(C), 124.3 (2CH), 137.6 (2CH), 141.5 (2C), 148.5 (C), 163.6 (C=O), 170.5 (C=O), 194.2 (2C=O).

*Methyl 4-(cyclohexylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4e**)*

Yellow oil, yield: 0.28 g (75%). IR (KBr): 3,350 (N–H), 1,781, 1,721, 1,695, 1,647 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 369 (M^+, 9), 227 (17), 225 (32), 105 (100), 98 (80), 83 (46), 73 (88). Anal. Calcd. for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79%. Found: C, 65.42; H, 5.13; N, 3.73%. ^{1}H NMR: $\delta = 1.37$–2.19 (10 m, $5CH_2$), 3.43 (3H, s, MeO), 4.43 (1H, m, CHN), 6.77 (1 H, br s, N–H), 7.96–8.11 (4H, m, 4CH). ^{13}C NMR: $\delta = 24.9$ (CH_2), 25.6 (CH_2), 29.6 (CH_2), 34.9 (CH_2), 51.8 (MeO), 54.7(CHN), 109.5 (C), 120.6 (C), 124.6 (2CH), 137.2 (2CH), 141.4 (2C), 148.7 (C), 166.7 (C=O), 170.1 (C=O), 194.0 (2C=O).

*Ethyl 4-(cyclohexylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4f**)*

Yellow oil, yield: 0.27 g (70%). IR (KBr): 3,346 (N–H), 1,785, 1,720, 1,691, 1,645 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 383 (M^+, 8),239 (16), 227 (18), 112 (11), 105 (100), 104 (22), 98 (87), 83 (46), 73 (88). Anal. Calcd. for $C_{21}H_{21}NO_6$ (383.39): C, 65.79; H, 5.52; N, 3.65%. Found: C, 65.51; H, 5.45; N, 3.60%. ^{1}H NMR: $\delta = 1.27$ (3H, t, $^3J = 6.8$ Hz, Me), 1.36-2.35 (10H, m, $5CH_2$), 4.20 (2H, q, $^3J = 6.8$ Hz, CH_2O), 4.43 (1H, m, CHN), 6.78 (1 H, br s, N–H), 7.34–8.20 (4H, m, 4CH).^{13}C NMR: $\delta = 14.2$ (Me), 24.5 (CH_2), 25.4 (CH_2), 29.7 (CH_2), 34.8 (CH_2), 61.7(CH_2O), 54.8 (CHN), 109.4 (C), 120.6 (C), 124.4 (2CH), 137.3 (2CH), 141.2 (2C), 148.6 (C), 166.8 (C=O), 170.3 (C=O), 194.2 (2C=O).

*Methyl 4-(benzylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4g**)*

Yellow oil, yield: 0.30 g (80%). IR (KBr): 3,351 (N–H), 1,786, 1,724, 1,690, 1,648 (C=O) cm^{-1}. EI-MS: *m/z* (%) = 337 (M^+, 12), 233 (31), 227 (21), 120 (13), 105 (100), 104 (65), 91 (71), 59 (88). Anal. Calcd. for $C_{21}H_{15}NO_6$ (377.35): C, 66.84; H, 4.01; N, 3.71%. Found: C, 66.51; H, 3.96; N, 3.65%.^{1}H NMR: $\delta = 3.43$ (3H, s, MeO), 5.04 (2H, d, $^3J = 6.2$ Hz, CH_2N), 6.75 (1H, br s, N–H), 7.34–8.12 (9H, m, 9CH).^{13}C NMR: $\delta = 48.6$ (CH_2N), 52.0 (MeO), 109.7 (C), 120.9 (C), 124.7 (2CH), 128.1 (2CH), 128.3 (CH), 129.3 (2CH), 137.3 (2CH), 138.0 (C), 141.5 (2C), 148.7 (C), 166.7 (C=O), 170.2 (C=O), 193.8 (2C=O).

*Ethyl 4-(benzylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4h**)*

Yellow oil, yield: 0.30 g (78%). IR (KBr): 3,356 (N–H), 1,785, 1,728, 1,691, 1,650 (C=O) cm^{-1}.EI-MS: *m/z*

(%) = 391 (M^+, 9), 247 (19), 227 (14), 119 (18), 105 (100), 104 (34), 91 (69), 73 (84). Anal. Calcd. for $C_{22}H_{17}NO_6$ (391.37): C, 67.51; H, 4.38; N, 3.58%. Found: C, 67.32; H, 4.31; N, 3.52%.^{1}H NMR: $\delta = 1.29$ (3H, t, $^3J = 6.8$ Hz, Me), 4.12 (2H, q, $^3J = 6.8$ Hz, Me), 5.01 (2H, d, $^3J = 6.2$ Hz, CH_2N), 6.70 (1 H, br s, N–H), 7.30–8.13 (9H, m, 9CH).^{13}C NMR: $\delta = 14.2$ (Me), 48.7(CH_2N), 62.1 (MeO), 109.5 (C), 120.8 (C), 124.8 (2CH), 128.0 (2CH), 128.3 (CH), 129.5 (2CH), 137.4 (2CH), 138.2 (C), 141.4 (2C), 148.6 (C), 166.8 (C=O), 170.0 (C=O), 193.5 (2C=O).

*Methyl 1′,3′,5-trioxo-4-(phenylamino)-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4i**)*

Yellow oil, yield: 0.26 g (73%). IR (KBr): 3,355 (N–H), 1,784, 1,726, 1,693, 1,651 (C=O) cm^{-1}.EI-MS: *m/z* (%) = 363 (M^+, 8), 227 (23), 219 (14), 105 (100), 104 (17), 99 (54), 77 (89), 59 (61). Anal. Calcd. for $C_{20}H_{13}NO_6$ (363.32): C, 66.12; H, 3.61; N, 3.86%. Found: C, 66.59; H, 3.52; N, 3.80%.^{1}H NMR: $\delta = 3.45$ (3H, s, MeO), 6.78 (1 H, br s, N–H), 7.23–8.14 (9H, m, 9CH).^{13}C NMR: $\delta = 52.3$ (MeO), 109.1 (C), 120.2 (C), 123.1 (2CH), 124.4 (2CH), 126.7 (CH), 129.2 (2CH), 137.4 (2CH), 139.8 (C), 141.6 (2C), 145.3 (C), 165.5 (C=O), 170.1 (C=O), 193.3 (2C=O).

*Ethyl 1′,3′,5-trioxo-4-(phenylamino)-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylatee (**4j**)*

Yellow oil, yield: 0.26 g (70%). IR (KBr): 3,353 (N–H), 1,784, 1,726, 1,693. 1,652 (C=O) cm^{-1}.EI-MS: *m/z* (%) = 405 (M^+, 10), 233 (18), 227 (23), 105 (100), 104 (43), 92 (70), 77 (78), 73 (54). Anal. Calcd. for $C_{21}H_{15}NO_6$ (377.35): C, 66.84; H, 4.01; N, 3.71%. Found: C, 66.52; H, 3.94; N, 3.65%.^{1}H NMR: $\delta = 1.14$ (3H, t, $^3J = 6.8$ Hz, Me), 4.09 (2H, q, $^3J = 6.8$ Hz, CH_2O), 6.69 (1 H, br s, N–H), 7.20–8.14 (9H, m, 9CH).^{13}C NMR: $\delta = 14.1$ (Me), 61.4 (CH_2O), 109.3 (C), 120.4 (C), 123.3 (2CH), 124.6 (2CH), 126.8 (CH), 129.1 (2CH), 137.6 (2CH), 139.5 (C), 141.4 (2C), 145.2 (C), 165.7 (C=O), 170.3 (C=O), 193.8 (2C=O).

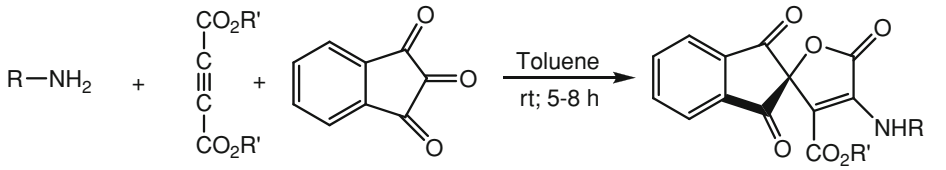
*Methyl 4-(benzo[d]thiazol-2-ylamino)-1′,3′,5-trioxo-1′,3′-dihydro-5H-spiro[furan-2,2′-indene]-3-carboxylate (**4k**)*

Pale yellow crystals, mp 165–167 °C, yield: 0.29 g (71%). IR (KBr): 3,356 (N–H), 1,785, 1,724, 1,693 (C=O) cm^{-1}.EI-MS: *m/z* (%) = 420 (M^+, 27), 276 (11), 227 (17), 162 (23), 149 (65), 134 (62), 105 (100), 73 (51). Anal. Calcd. for $C_{21}H_{12}N_2O_6S$(420.39): C, 60.00; H, 2.88; N, 6.66%. Found: C, 59.75; H, 2.83; N, 6.61%. ^{1}H NMR: $\delta = 3.70$ (3H, s, MeO), 6.86 (1 H, br s, N–H), 7.17–8.19 (8H, m, 8CH).^{13}C NMR: $\delta = 52.3$ (MeO), 114.0 (C), 118.3 (CH), 121.8 (CH), 122.1 (C), 125.3 (CH), 124.5 (CH), 125.8 (2CH), 130.8 (C), 133.0 (2CH), 141.2 (2C), 148.7 (C), 153.2 (C), 167.2 (C=O), 170.3 (C=O), 174.5 (C=N), 196.5 (2C=O).

Results and discussion

As part of our continuing interest in the construction of novel heterocycles [7–10], we now report the results of our studies involving the reactions of enamines derived from primary amines **1** and dialkyl acetylenedicarboxylates **2** in the presence of ninhydrin (**3**), which constitutes a synthesis of functionalized 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-trione **4** (Scheme 1).

Scheme 1



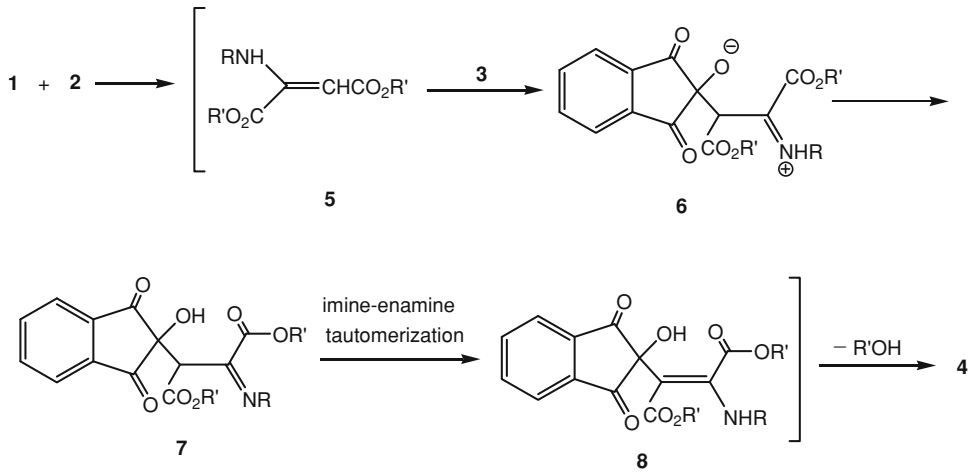
1a: R = Et
1b: R = *n*-Bu
1c: R = *c*-Hexyl
1d: R = Bn
1e: R = Ph

2a: R' = Me
2b: R' = Et

3

	R	R'	Yield %
4a	Et	Me	76
4b	Et	Et	72
4c	*n*-Bu	Me	85
4d	*n*-Bu	Et	78
4e	*c*-Hexyl	Me	75
4f	*c*-Hexyl	Et	70
4g	Bn	Me	80
4h	Bn	Et	78
4i	Ph	Me	73
4j	Ph	Et	70
4k	Benzo[d]thiazol-2-yl	Me	71

Scheme 2



The ^{1}H NMR spectrum of **4a** exhibited two singlets for methoxy ($\delta = 3.44$ ppm) and NH ($\delta = 6.78$ ppm) protons. The Et-N and phenyl groups showed characteristic multiplets in the appropriate regions of the spectrum. Compounds **4** possess C_s symmetry. Thus, the ninhydrin residue exhibits a complex AA'XX' spin system for the aromatic protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 12 distinct resonances which further confirmed the proposed structure. The ninhydrin residue shows only five ^{13}C resonances due to the presence of C_s symmetry in **4**. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**4k** were similar to those for **4a** except for the ester and alkyl(aryl)amino moieties.

A plausible pathway may be advanced to rationalize product formation (Scheme 2). Presumably, the enaminoester intermediate **5** is attacked by **3** to furnish the intermediate **6**, which undergoes proton-transfer reaction to produce imine derivative **7**. This intermediate undergoes imine-enamine tautomerization to generate **8**, which is converted to **4** by elimination of R'OH.

In conclusion, we have demonstrated a one-pot synthesis of functionalized 5*H*-spiro[furan-2,2′-indene]-1′,3′,5-triones via tandem reaction of primary amines, acetylenic esters and ninhydrin. Simple mixing of the starting materials and the potential diversity of this type of reaction are the advantages of this procedure.

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