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Synthesis of Some Novel γ-Spirolactones

Javad Azizian*, **Ali R. Karimi, Hamedeh Arefrad, Ali A. Mohammadi,** and **Mohammad R. Mohammadizadeh**

Department of Chemistry, Faculty of Science, Shahid Beheshti University, P.O. Box 19395-4716, Tehran, Iran

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Summary. We report on the addition of dialkyl acetylenedicarboxylate to 1-alkylisatins or tryptanthrine in the presence of triphenylphosphine which leads to highly functionalised novel unsaturated γ-spirolactones.

Keywords. γ-Spirolactones; Triphenylphosphine; 1-Alkylisatin; Tryptanthrine.

Introduction

γ-Spirolactones are an important class of molecules owing to their interesting structures and biological activities [1]. The lactone moiety is also present in many natural products [2], especially in insect pheromones [3], antifungal substances, and flavor components that occur in essential oils [4]. Recently, γ-spirolactones have been the subject of interest because of their effect as aldostrone inhibitors [5].

Systematic investigations of spiroindoles and indoloquinazolines are of interest due to their broad spectrum of biological activities [6]. Because of the pharmacological interest in these compounds, which belong to the indole and indoloquinazoline family [7] we have synthesized some novel γ-spirolactone derivatives from 1-alkylisatins and tryptanthrine. These molecules might show enhanced biological activities because they incorporate both indole and indoloquinazoline or lactone moieties.

The stochiometric as well as the catalytic use of phosphines and a variety of other organophosphorus compounds has become an integral part of organic synthesis [8]. In particular, triphenylphosphine (*TPP*) acts as a catalyst in various isomerization reactions of alkynes and allenes [9], and in the nucleophilic addition of malonate to methyl propiolate [10]. The addition of *TPP* to electron deficient

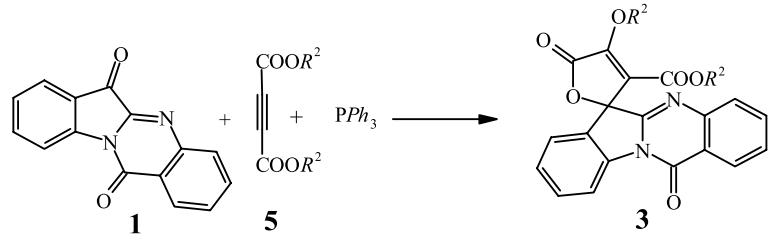
* Corresponding author. E-mail: J-Azizian@cc.sbu.ac.ir

alkynes, leading to zwitterionic compounds and the subsequent reactions of the latter species, notably dimerization, has become known from the work of *Tebby* and co-workers [11]. Very recently, dimethyl acetylenedicarboxylate (*DMAD*) has been reported to add to activated carbonyl compounds such as α-keto esters, α-keto nitriles, and 1,2-benzoquinones under the influence of *TPP* to afford γ-lactones [12].

Results and Discussion

In view of our general interest in the chemistry of isatin and tryptanthrine [13] and because of their bioactivity effects we examined the reaction of *DMAD* with isatin derivatives or tryptanthrine in the presence of *TPP* and our results are reported.

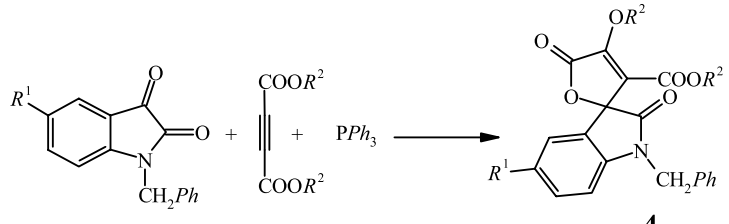
We observed that mixtures of 1-alkylisatin derivatives or tryptanthrine and dialkyl acetylenedicarboxylates at room temperature in benzene or toluene when treated with *TPP* afforded the products that were characterised as **3** and **4** (Scheme 1). γ-Spirolactones formation can be rationalized as shown in Scheme 2.



1 **5** **3**

5a R^2=*Me* **3a** R^2=*Me*

5b R^2=*Et* **3b** R^2=*Et*



2 **5** **4**

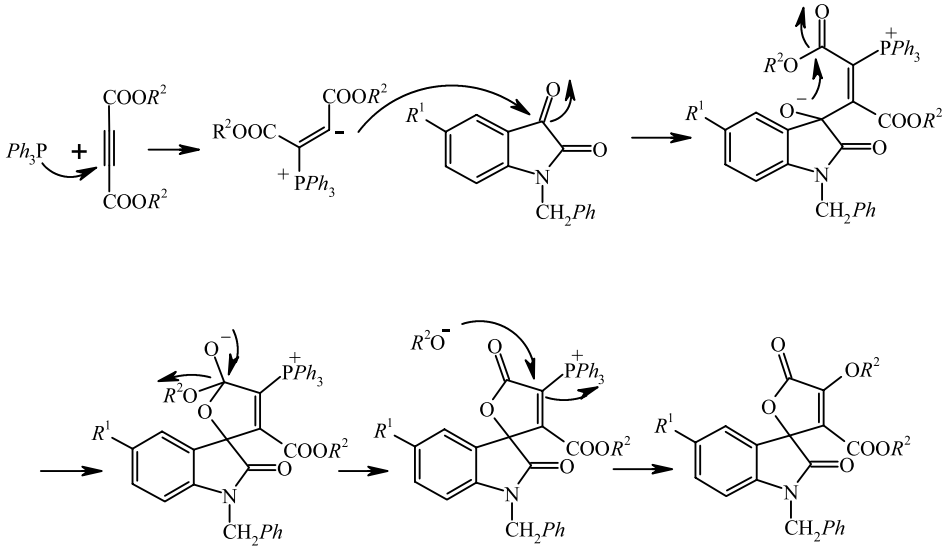
5a R^2=*Me* **4a** R^1=H; R^2=*Me*

5b R^2=*Et* **4b** R^1=H; R^2=*Et*

4c R^1=Br; R^2=*Me*

4d R^1=Br; R^2=*Et*

Scheme 1



Scheme 2

Experimental

Melting points were measured on a Mettler FP5. IR spectra were recorded with KBr pellets on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker 500 DRX AVANCE instrument at 500 and 125 MHz. Mass spectra were recorded on a Shimadzu QP 1100 EX equipment. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer. Their results agreed favourably with the calculated values.

General Procedure

To a stirred mixture of **1** or **2** (2 mmol) and dialkyl acetylenedicarboxylate (2.2 mmol) in 10 cm^3 of anhydrous benzene at room temperature 1 mmol of triphenylphosphine was added and the stirring was continued for 4 h. The solvent was removed under vaccum and the residue was chromatographed on silica gel with an 80:20 light petroleum ether:ethyl acetate mixture to afford the spirolactones **3** or **4**.

Methyl 5′-oxo-4′-methoxyspiro[indolo[2,1-b]quinazolin-12-one-6,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**3a**, $C_{21}H_{14}N_2O_5$)

White crystalline solid, yield 45%; mp 211–217°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.54$ (s, O–CH_3), 4.51 (s, $COOCH_3$), 7.28–8.63 (m, 8H arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 52.91$ ($COOCH_3$), 61.08 (OCH_3), 86 (spiro carbon), 118.40, 119.81, 122.69, 124.28, 125.70, 127.33, 127.98, 128.67, 132.78, 135.10, 138.77, and 147.19 (arom), 118.00 and 154.10 (C=C), 154 (C=N), 159.75, 160.93, and 165.66 (C=O) ppm; IR (KBr): $\bar{\nu} = 1780$, 1720, and 1684 (C=O), 1640 (C=N) cm^{-1}; MS: m/z (%) = 390 (M^+, 100), 331 (75), 263 (18), 216 (18), 59 (18).

Ethyl 5′-oxo-4′-ethoxyspiro[indolo[2,1-b]quinazolin-12-one-6,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**3b**, $C_{23}H_{18}N_2O_5$)

White crystalline solid, yield 44%; mp 100–109°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.089$ and 1.55 (2t, $2CH_3$), 3.74, 3.80, 3.90, and 4.071 (4dq, $2CH_2$), 1.25–8.65 (m, 8H arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.84$

and 13.98 ($2CH_3$), 62.11 and 62.43 ($2CH_2$), 82 (spiro carbon), 115.69, 118.84, 121.90, 124.02, 125.26, 126.93, 128.00, 128.81, 131.95, 136.03, 137.78, and 150.32 (arom), 115.25 and 151.01 (C=C), 160.80, 162.95, and 168.80 (C=O) ppm; IR (KBr): $\bar{\nu} = 1763$, 1718, and 1675 (C=O), 1640 (C=N) cm^{-1}; MS: m/z (%) = 418 (M^+, 38), 345 (18), 273 (15), 249 (50), 248 (100), 220 (38), 192 (25), 102 (18), 71 (31), 43 (70).

Methyl 5′,2-dioxo-4′-methoxyspiro[1-benzylindol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**4a**, $C_{21}H_{17}NO_6$)

White crystalline solid, yield 41%; mp 195–197°C; ^1H NMR ($CDCl_3$): $\delta = 3.52$ (s, OCH_3), 4.42 (s, $COOCH_3$), 4.82 and 5.13 (AB-system, CH_2), 6.80–7.41 (m, 9H arom) ppm; ^{13}C NMR($CDCl_3$): $\delta = 45.02$ (C–N), 52.72 ($COOCH_3$), 60.91 (O–CH_3), 83 (spiro carbon), 119.31, 123.87, 124.82, 127.85, 128.37, 128.78, 129.32, 129.47, 134.88, 135.33, 144.51, and 150.01 (arom), 110.56, 158.69 (C=C), 160.96, 165.91, and 170.62 (C=O) ppm; IR (KBr): $\bar{\nu} = 1783$, 1736, and 1700 (C=O) cm^{-1}; MS: m/z (%) = 379 (M^+, 43), 320 (18), 293 (13), 288 (18), 146 (13), 91 (100), 65 (18), 44 (18).

Ethyl 5′,2-dioxo-4′-ethoxyspiro[1-benzylindol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**4b**, $C_{23}H_{21}NO_6$)

White crystalline solid, yield 42%; mp 182–183°C; ^1H NMR ($CDCl_3$): $\delta = 0.84$ and 1.49 (2t, $2CH_3$), 3.83 (dq, CH), 4.09 (dq, CH), 4.26 and 4.33 (m, CH_2), 4.90 and 5.01 (AB-system, CH_2N), 6.79–7.50 (m, 9H arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.92$ and 14.01 ($2CH_3$), 45 (C–N), 61.97 and 62.25 ($2CH_2$), 79.9 (spiro carbon), 118.89, 124.30, 125.19, 127.70, 128.42, 128.85, 129.01, 130.51, 133.90, 135.65, 142.17, and 147.77 (arom), 111.53 and 157.45 (C=C), 162, 168, and 174.09 (C=O) ppm; IR (KBr): $\bar{\nu} = 1767$, 1721, and 1700 (C=O) cm^{-1}; MS: m/z (%) = 407 (M^+, 44), 316 (40), 237 (88), 180 (40), 146 (100), 91 (80), 43 (38).

Methyl 5′,2-dioxo-4′-methoxyspiro[1-benzyl-5-bromoindol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**4c**, $C_{21}H_{16}NO_6Br$)

White crystalline solid, yield 65%; mp 183–184°C; ^1H NMR ($CDCl_3$): $\delta = 3.59$ (s, O–CH_3), 4.43 (s, $COOCH_3$), 4.81 and 5.10 (AB-system, CH_2), 6.66 (d, 1H arom), 7.28–7.43 (m, 7H arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 45.13$ (C–N), 52.88 ($COOCH_3$), 60.92 (O–CH_3), 82 (spiro carbon), 116.42, 118.92, 125.55, 127.79, 127.99, 128.53, 129.41, 129.43, 134.81, 134.85, 134.89, and 143.54 (arom), 112.06 and 150.12 (C=C), 160.87, 165, and 171 (C=O) ppm; IR (KBr): $\bar{\nu} = 1782$, 1725, and 1698 (C=O) cm^{-1}; MS: m/z (%) = 461 (M^++2, 5), 459 (M^+, 44), 457 (46), 368 (88), 366 (100), 300 (25), 298 (25), 226 (13), 224 (13), 91 (70), 65 (13).

Ethyl 5′,2-dioxo-4′-ethoxyspiro[1-benzyl-5-bromoindol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate (**4d**, $C_{23}H_{20}NO_6Br$)

White crystalline solid, yield 35%; mp 176–177°C; ^1H NMR ($CDCl_3$): $\delta = 0.84$ and 1.11 (2t, $2CH_3$), 3.64 (dq, CH), 3.75 (2dq, CH_2), 4.1 (dq, CH), 4.57 and 5.18 (AB-system, CH_2N), 5.97–7.44 (m, 8H arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.86$ and 14.00 ($2CH_3$), 45.03 (C–N), 62.08 and 62.27 ($2CH_2$), 78.89 (spiro carbon), 115.58, 127.49, 127.97, 128.07, 128.20, 129.16, 129.23, 132.23, 132.31, 135.84, 143.84, and 147.87 (arom), 110.84 and 161.10 (C=C), 161.31, 167.33, and 174.37 (C=O) ppm; IR (KBr): $\bar{\nu} = 1778$, 1724, and 1682 (C=O) cm^{-1}; MS: m/z (%) = 489 (M^++2, 10), 487 (M^+, 13), 471 (30), 469 (30), 397 (25), 395 (25), 277 (100), 183 (13), 91 (50), 43 (20).

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References

[1] Trost BM, Balkoves JM, Mao MKT (1983) J Am Chem Soc **105**: 6755
[2] For a review, see Kano S, Shibuya S, Ebata TA (1980) Heterocycles **14**: 661
[3] Paolucci C, Mazzini C, Fava A (1995) J Org Chem **60**: 169–175
[4] Dubs P, Stussi R (1978) Helv Chim Acta **61**: 990
[5] Ogliaruso MA, Wolfe JF (1993) Synthesis of Lactones and Lactams. John Wiley & Sons, New York
[6] Grieco PA (1975) Synthesis 67
[7] Billimoria AD, Cava MP (1996) Heterocycles **42**: 453
[8] Kosolopoff GM, Maier L (1973) Organic Phosphorus Compounds. Wiley, NewYork
[9] Trost BM, Kazmeir U (1992) J Am Chem Soc **114**: 7933
[10] Trost BM, Martinez JA, Kulawiec RJ, Indolesa AF (1993) J Am Chem Soc **115**: 10402
[11] a) Shaw MA, Tebby JC, Ward RS, Williams DH (1968) J Chem Soc (C) 1609; b) Butterfields PJ, Tebby JC (1979) J Chem Soc Perkin Trans 1 1189; c) Tebby JC, Wilson IF (1979) J Chem Soc Perkin Trans 1 2133
[12] a) Nozaki K, Sato N, Ikeda K, Takaya H (1996) J Org Chem **61**: 4516; b) Nair V, Somarajan Nair J, Vinod AU, Nigam P Rath (2000) Synthesis **12**: 1713
[13] a) Azizian J, Karimi AR, Mohammadi AA (2003) Synth Commun **33**: 383; b) Azizian J, Mehrdad M, Jadidi K, Sarrafi Y (2000) Tetrahedron lett **27**: 5265; c) Azizian J, Jadidi K, Mehrdad M, Sarrafi Y (2000) Synth Commun **30**: 2309; d) Azizian J, Sarrafi Y, Mehrdad M, Jadidi K (2000) Indian J Chem **39B**: 304; e) Azizian J, Asadi A, Jadidi K (2001) Synth Commun **31**: 2727