An efficient one-pot synthesis of dialkyl 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[α]indene-2,3-dicarboxylate derivatives

Mohammad Anary-Abbasinejad,*[a] Manouchehr Mazraeh-Seffid,[a] Ehsanorreza Poorhassan,[a] Alireza Hassanabadi,[a] and Forough Rastegari[b]

[a]*Department of Chemistry, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran*

[b]*Young Researchers Club, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran*

E-mail: mohammadanary@yahoo.com

Abstract

Ninhydrin reacts with amides in ethanol to produce *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide derivatives in nearly quantitative yields. Reaction between these adducts and electron-deficient acetylenic esters in the presence of triphenylphosphine leads to dialkyl 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[α]indene-2,3-dicarboxylate derivatives in good yields.

Keywords: Acetylenic esters, ninhydrin, amides, intramolecular Wittig reaction

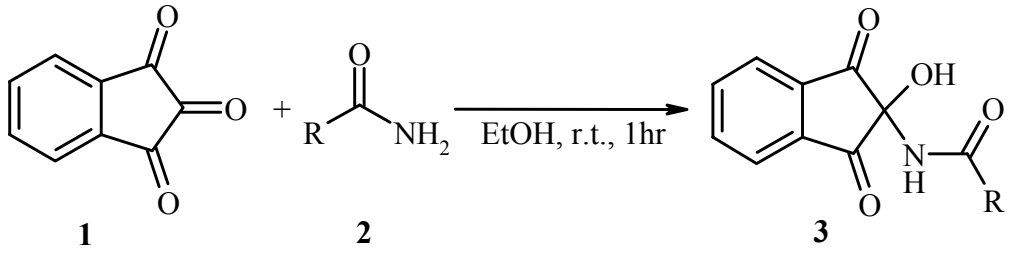
Introduction

Over the years, the Wittig reaction has evolved to include many variations that constitute some of the most powerful processes for the construction of carbon–carbon bonds.[1] The intramolecular Wittig reaction has become one of the favourites among the numerous methods of cycloalkene syntheses.[2-3] The importance of intramolecular Wittig reactions[2-3] in the synthesis of cycloalkenes and unsaturated heterocyclic compounds can hardly be overestimated. The three-component reaction between triphenylphosphine, acetylenic esters and an organic acidic compound has been reported to produce phosphorus ylides which may further undergo intramolecular Wittig reactions to produce unsaturated hetro-or carbo-cyclic compounds in a one-pot process.[4-6] In continuation of our previous work on the reaction between trivalent phosphorus nucleophiles and acetylene diesters in the presence of acidic organic compounds[7-14] we wish to report herein the results of our studies on the reaction between dialkyl acetylenedicarboxylates and triphenylphosphine in the presence of *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide derivatives **3**.

Results and Discussion

For the preparation of *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide derivatives an amide, such as acetamide, propionamide or benzamide was treated with ninhydrin in ethanol to afford the desired adducts **3a-c** in nearly quantitative yileds (Scheme 1). The structures of these products were confirmed by their spectral and analytical data. When di(*t*-butyl) acetylenedicarboxylate was treated in acetone with triphenylphosphine in the presence of *N*-(2-hydroxy-1,3-dioxoindan-2-yl)acetamide **3a,** di(*t*-butyl) 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta [α]indene-2,3-dicarboxylate **5a** was obtained in 78% yield (Scheme 2). The ^{1}H NMR spectrum of compound **5a** showed four sharp singlets at 1.43, 1.55, 2.20 and 5.82 ppm which are related to two *t*-butyl groups, methyl group and methine group protons, respectively. A singlet was observed at 6.42 ppm that disappeared after addition of a few drops of D_2O to $CDCl_3$ solution of compound **5a**. This signal was related to NH proton. The aromatic protons resonated between 7.61 and 8.31 ppm. The ^{13}C NMR spectrum of compound **5a** exhibited nineteen signals in agreement with the proposed structure. The above structural assignments based on NMR spectroscopy were supported by IR spectra. The IR spectrum of compound **5a** showed absorption bands at 1744, 1706 and 1667 cm^{-1} for carbonyl groups. Compound **5a** possesses two asymmetric centers and may exist as two diastereomers (Scheme 3). The *endo*-isomer is expected to suffer from steric crowding of the ester group and thus, we assign the *exo*-stereochemistry to product **5a**. Similar reaction with the same stereochemistry between ninhydrin, ethanol, dialkyl acetylenedicarboxylate and triphhenylphosphine has been recently reported for the stereoselective synthesis of functionalized 2*H*-Indeno[2,1-*b*]furans.[15] The reaction between hydrated ninhydrin with two eq of dialkyl acetylenedicarboxylates and triphenylphosphine was also reported for the diastereoselective synthesis of dihydrofuro[2',3':2,3]indeno[2,1-*b*]furan derivatives.[16] The configuration of the products of this reaction was also reported to be *exo*. The chemical shift of the methine proton in the ^{1}H NMR spectrum of compound **5a** is very similar to those obtained for the similar compounds reported in these two reports, confirming the *exo* stereochemistry for it.

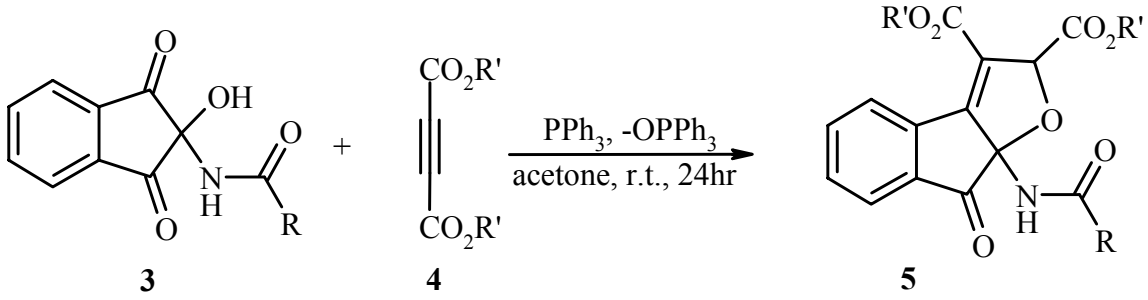
The NMR spectra of compounds **5b-d** indicated the presence of two diastereomers. Efforts to separate them by chromatography were unsuccessful. The ratio of *exo*/*endo* diastereomers could be obtained from the ^{1}H NMR spectra of compounds **5b-d**, assigning the signals related to the *exo* isomer by comparing their chemical shifts with those for compound **5a**.



1 **2** **3**

2, 3	R	%Yield
a	CH_3	98
b	C_2H_5	95
c	C_6H_5	95

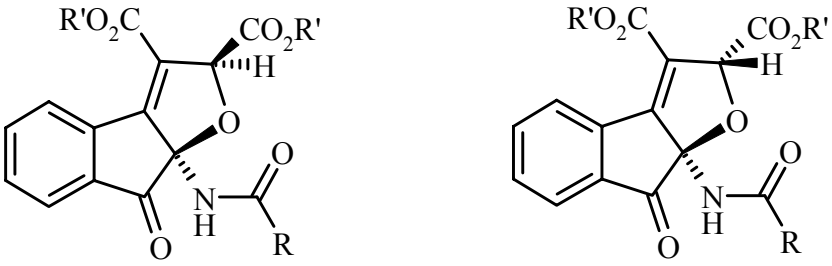
Scheme 1. Addition reaction between ninhydrin and amides.



3 **4** **5**

5	R	R'	%Yield	*exo/endo*
a	CH_3	t-Bu	78	100/0
b	CH_3	C_2H_5	75	80/20
c	C_2H_5	C_2H_5	80	75/25
d	C_6H_5	CH_3	75	84/16

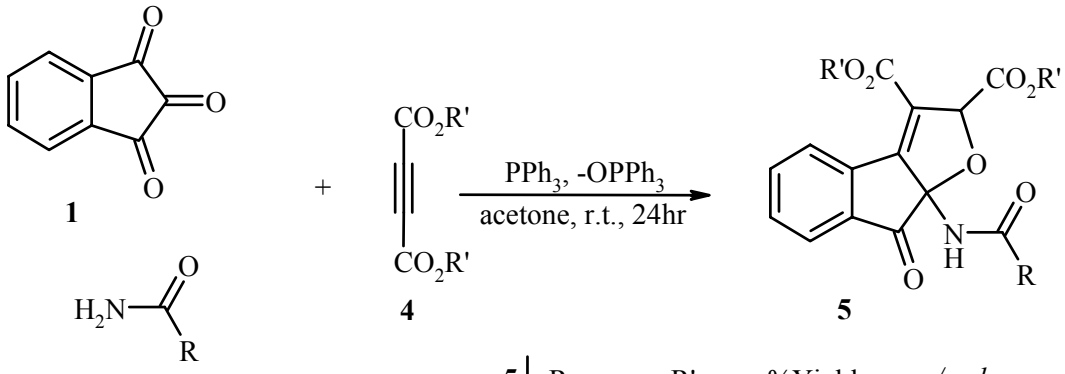
Scheme 2. Condensation of acetylenic esters and *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amides in the presence of triphenylphosphine.



Exo-**5** *Endo*-**5**

Scheme 3. Two diastereomers of compounds **5**.

We also examined the preparation of compounds **5a-d** by a one-pot reaction between ninhydrin, amide derivative, acetylenic ester and triphenylphosphine. Thus, the reaction between ninhydrin, acetamide, di(*t*-butyl) acetylenedicarboxylate and triphenylphosphine afforded compound **5a** in 73% yield. As shown in scheme 4 this method was also successful for preparing compounds **5b-d**. Yields and *exo*/*endo* diastereomer ratios obtained for this method were similar to those for the reaction between *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide derivatives and acetylenic esters in the presence of triphenylphosphine.

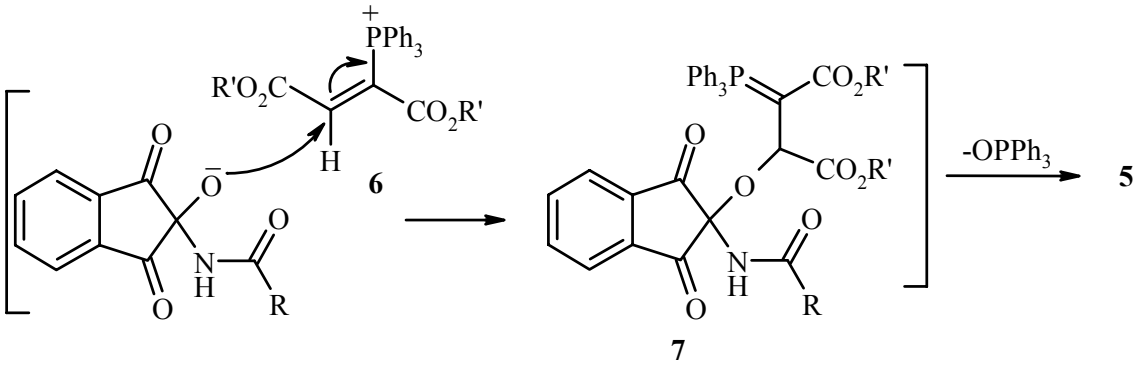


5	R	R'	%Yield	*exo/endo*
a	CH_3	t-Bu	73	100/0
b	CH_3	C_2H_5	70	80/20
c	C_2H_5	C_2H_5	72	75/25
d	C_6H_5	CH_3	70	84/16

Scheme 4. One-pot reaction between ninhydrin, amide derivative, acetylenic ester and triphenylphosphine.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[15, 16] it is reasonable to assume that compound **5** results from the initial addition of triphenylphosphine to

the acetylenic ester and subsequent protonation of the 1:1 adduct by *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide derivative (Scheme 5). Then the positively charged ion **6** is attacked by the conjugate base of the OH-acid to form phosphorane **7**, which undergoes an intramolecular Wittig reaction to produce triphenylphosphine oxide and the product **5**.



Scheme 5. Suggested mechanism for formation of compound **5**.

In summary, the present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also that the starting materials and reagents can be mixed without any activation or modification. The procedure described here provides an acceptable one-pot method for the preparation of dialkyl 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[α]indene-2,3-dicarboxylate derivatives.

Experimental Section

General Procedures. Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed at the analytical laboratory of the Islamic Azad University, the Science and Research Unit. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure for preparation of compounds 3a-c

To a magnetically stirred solution of ninhydrin **1** (2 mmol) in 20 ml ethanol was added amide **2** (2 mmol). After stirring for 1 hour at room temperature, the solvent was removed under reduced pressure and the residue was washed with cold diethyl ether (2×5 mL) to afford the product **3a-c**.

***N*-(2-Hydroxy-1,3-dioxoindan-2-yl)acetamide (3a).** Yield: 98%; White powder, m.p. 192-194˚C. IR (KBr) (ν_{max}, cm^{-1}): 3305 ,3015 (OH, NH), 1779, 1722, 1629 (C=O). MS (m/z, %): 219 (M, 5). ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.81 (s, 3 H, CH_3), 7.68 (s, 1 H, NH), 7.96-8.30 (m, 4 H, aromatic), 9.19 (s, 1 H, OH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 21.66 (CH_3), 80.34 (C), 124.26, 137.34 and 139.31 (aromatic), 170.35 (C=O amide), 197.51 (C=O ketone). Calcd. for $C_{11}H_9NO_4$: C, 60.57; H, 4.14; N, 6.39%. Found: C, 60.6 H, 4.2; N, 6.3 %.

***N*-(2-Hydroxy-1,3-dioxoindan-2-yl)-propionamide (3b).** Yield: 95%; White powder, m.p. 165-167˚C. IR (KBr) (ν_{max}, cm^{-1}): 3350 ,3115 (OH, NH), 1779, 1722, 1626 (C=O). MS (m/z, %): 233 (M, 3). ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 0.93 (t, $^3J_{HH}$ =7 H_Z , 3 H, CH_3), 2.14 (q, $^3J_{HH}$ =7 H_Z , 2 H, CH_2), 7.15 (s, 1 H, NH), 7.75-7.87 (m, 4 H, aromatic), 8.96 (s, 1 H, OH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 9.32 (CH_3), 27.85 (CH_2), 79.69 (C), 124.09, 136.29 and 139.52 (aromatic), 174.18 (C=O amide), 196.90 (C=O ketone). Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.74; N, 6.01%. Found: C, 61.9 H, 4.7; N, 6.2 %.

***N*-(2-Hydroxy-1,3-dioxoindan-2-yl)-benzamide (3c).**Yield: 95%; White powder, m.p. 138-140˚C. IR (KBr) (ν_{max}, cm^{-1}): 3395, 3250 (OH, NH), 1755, 1715, 1642 (C=O). MS (m/z, %): 281 (M, 6). ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 6.24 (s, 1 H, NH), 7.09-7.85 (m, 9 H, aromatic), 8.59 (s, 1 H, OH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 80.61 (C), 124.12, 128.10, 128.66, 131.81, 132.45, 136.34 and 139.45 (aromatic), 166.95 (C=O amide), 196.64 (C=O ketone). Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98%. Found: C, 60.4 H, 3.8; N, 5.1 %.

General procedure for preparation of compounds 5a-d by reaction between dialkyl acetylenedicarboxylates, triphenylphosphine and *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amides

To a magnetically stirred solution of *N*-(2-hydroxy-1,3-dioxoindan-2-yl)amide **3** (2 mmol) and dialkyl acetylenedicarboxylate **4** (2 mmol) in 10 ml acetone was added a mixture of triphenylphosphine (2 mmol) in 2 ml acetone at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was evaporated at reduced pressure and the residue was purified by silica gel column chromatography using hexane-ethyl acetate (4:1) as eluent. The solvent was removed under reduced pressure to afford the product.

General procedure for one-pot preparation of compounds 5a-d by reaction between ninhydrin, amides, dialkyl acetylenedicarboxylates and triphenylphosphine

A solution of ninhydrin **1** (2 mmol), amide **2** (2 mmol) and dialkyl acetylenedicarboxylate **4** (2 mmol) in 10 ml acetone was stirred for 5 min. Then, a mixture of triphenylphosphine (2 mmol) in 2 ml acetone was added at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was evaporated at reduced pressure and the residue was purified by silica gel column chromatography using hexane-ethyl acetate (4:1) as eluent. The solvent was removed under reduced pressure to afford the product.

Di(*t*-butyl) 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[*α*]indene-2,3-dicarboxylate (5a). Yield: 78%; White powder, m.p. 146 - 148^{o}C, IR(KBr) (ν_{max}, cm^{-1}): 3125 (NH), 1744, 1706, 1667 (C=O). MS (m/z, %): 429 (4) . ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.43 (9 H, s, *t*-

Bu), 1.55 (9 H, s, *t*-Bu), 2.20 (3 H, s, CH_3), 5.82 (1H, s, CH), 6.42 (1 H, broad s, NH), 7.61-8.31 (4 H, m, aromatic). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 28.14 and 28.48 (6 CH_3 of 2 *t*-Bu), 31.28 (CH_3), 82.40 and 83.01 (2 C of 2 *t*-Bu), 92.73 (CH), 101.92 (CN), 125.18, 126.06, 128.58, 131.72, 136.29, 138.43, 139.95 and 146.93 (aromatic and olefinic carbons), 161.24 (C=O amide), 171.40, 167.83 (2 C=O ester), 193.17 (C=O ketone). Analyses: Calcd. for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26%. Found: C, 64.4; H, 6.3; N, 3.3%.

Diethyl 8*a*-acetylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[*α*]indene-2,3-dicarboxylate (5b). Yield: 75%; Viscose oil**,** IR(KBr) (ν_{max}, cm^{-1}): 3085 (NH), 1751, 1720, 1635 (C=O). MS (m/z, %): 373 (7) . NMR data for *exo* isomer (80%) , ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.24 and 1.33 (6 H, 2 t, $^3J_{HH}$ = 7 H_Z, 2 CH_3), 1.94 (3 H, s, CH_3), 4.29 and 4.32 (4 H, 2 q, $^3J_{HH}$ = 7 H_Z, 2 OCH_2), 6.04 (1H, s, CH), 6.95 (1 H, broad s, NH), 7.59-8.29 (4 H, m, aromatic). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 14.32 and 14.38 (2 CH_3), 24.05 (CH_3), 61.76 and 62.08 (2 O*C*H_2), 91.21 (CH), 101.58 (CN), 125.45, 128.41, 128.53, 132.19, 136.55, 138.61, 139.61 and 148.57 (aromatic and olefinic carbons), 161.77 (C=O amide), 171.75, 168.91 (2 C=O ester), 192.75 (C=O ketone). Analyses: Calcd. for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75%. Found: C, 61.2; H, 5.2; N, 3.8%. NMR data for *endo* isomer (20%), ^{1}H NMR: δ 1.08 and 1.39 (6 H, 2 t, $^3J_{HH}$ = 7 H_Z, 2 CH_3), 2.15 (3 H, s, CH_3), 4.25 and 4.36 (4 H, 2 q , $^3J_{HH}$ = 7 H_Z, 2 OCH_2), 5.68 (1H, s, CH), 6.81 (1 H, broad s, NH), 7.59-8.29 (4 H, m, aromatic). ^{13}C NMR: δ 14.48 and 14.52 (2 CH_3), 23.28 (CH_3), 62.08 and 63.03 (2 O*C*H_2), 89.10 (CH), 102.26 (CN), 124.52, 125.18, 128.41, 133.22, 135.30, 136.43, 142.43 and 151.27 (aromatic and olefinic carbons), 161.72 (C=O amide), 171.44, 168.99 (2 C=O ester), 190.24 (C=O ketone).

Diethyl 8*a*-propionylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[*α*]indene-2,3-dicarboxylate (5c). Yield: 80%; Viscose oil**,** IR (KBr) (ν_{max}, cm^{-1}): 3163 (NH), 1737, 1705, 1667 (C=O). MS (m/z, %): 387 (5) . NMR data for *exo* isomer (75%) , ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.06 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.24 and 1.32 (6 H, 2 t, $^3J_{HH}$ = 7 H_Z, 2 CH_3), 2.21 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.26 and 4.34 (4 H, 2 q , $^3J_{HH}$ = 7 H_Z, 2 OCH_2), 6.06 (1 H, s, CH), 6.72 (1 H, broad s, NH), 7.60-8.30 (4 H, m, aromatic). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 9.19 (CH_3), 14.29 and 14.34 (2 CH_3), 29.52 (CH_2), 61.73 and 62.01 (2 O*C*H_2), 89.03 (CH), 101.44 (CN), 124.74, 125.45, 128.59, 133.26, 135.17, 136.60, 139.76 and 148.60 (aromatic and olefinic carbons), 161.76 (C=O amide), 168.87, 175.11 (2 C=O ester), 190.25 (C=O ketone). Analyses: Calcd. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62%. Found: C, 62.6; H, 5.4; N, 3.7%. NMR data for *endo* isomer (25%), ^{1}H NMR: δ 0.88 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.18 and 1.39 (6 H, 2 t, $^3J_{HH}$ = 7 H_Z, 2 CH_3), 2.42 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.17 and 4.24 (4 H, 2 q , $^3J_{HH}$ = 7 H_Z, 2 OCH_2), 5.67 (1H, s, CH), 6.84 (1 H, broad s, NH), 7.60-8.30 (4 H, m, aromatic). ^{13}C NMR: δ 9.40 (CH_3), 14.49 and 14.64 (2 CH_3), 30.03 (CH_2), 62.17 and 63.03 (2 O*C*H_2), 91.26 (CH), 102.31 (CN), 121.44, 125.20, 128.41, 132.13, 136.31, 138.46, 142.66 and 151.53 (aromatic and olefinic carbons), 161.82 (C=O amide), 171.52, 172.32 (2 C=O ester), 192.94 (C=O ketone).

Dimethyl 8*a*-benzoylamino-8-oxo-8,8*a*-dihydro-2*H*-1-oxacyclopenta[*α*]indene-2,3-dicarboxylate (5d). Yield: 75%; White powder, m.p. 121 - 123°C, IR(KBr) (ν_{max}, cm^{-1}): 3225 (NH), 1744, 1706, 1667 (C=O). MS (m/z, %): 407 (3) . NMR data for *exo* isomer (84%) , ^{1}H NMR

(500 MH_Z, $CDCl_3$): δ 3.78 and 3.88 (6 H, 2 s, 2 OCH_3), 6.23 (1H, s, CH), 6.96 (1 H, broad s, NH), 7.41-8.61 (9 H, m, aromatic). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 52.11 and 52.65 (2 O*C*H_3), 89.46 (CH), 102.17 (CN), 127.23, 128.73, 130.04, 132.23, 136.55, 138.09, 138.88 and 149.83 (aromatic and olefinic carbons), 122.18, 123.72, 129.44, 138.85 (phenyl moiety), 165.77 (C=O amide), 172.33, 169.24 (2 C=O ester), 195.87 (C=O ketone). Analyses: Calcd. for $C_{22}H_{17}NO_7$: C, 64.86; H, 4.21; N, 3.44%. Found: C, 64.9; H, 4.1; N, 3.5%. NMR data for *endo* isomer (16%), ^1H NMR: δ 3.75 and 3.93 (6 H, 2 s, 2 OCH_3), 5.79 (1H, s, CH), 7.06 (1 H, broad s, NH), 7.41-8.61 (9 H, m, aromatic). ^{13}C NMR: δ 52.86 and 53.09 (2 O*C*H_3), 90.08 (CH), 101.62 (CN), 126.88, 128.46, 129.94, 131.86, 136.71, 138.23, 138.97 and 149.25 (aromatic and olefinic carbons), 122.38, 124.03, 129.11, 138.36 (phenyl moiety), 165.29 (C=O amide), 173.68, 170.15 (2 C=O ester), 192.47 (C=O ketone).

References and Notes

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