

Behaviour of the hetero-ring in butenolides toward nucleophiles

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ABSTRACT

Some α -benzylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides (I) were synthesised and their reactions with different nucleophiles were investigated. The attempt to prepare the corresponding acyl azides (V) from the starting butenolides, via the acid hydrazides (II), failed. This led to an alternative route where the azides (V) were prepared from the corresponding acid chlorides. The behaviour of these azides under different experimental conditions was also investigated.

INTRODUCTION

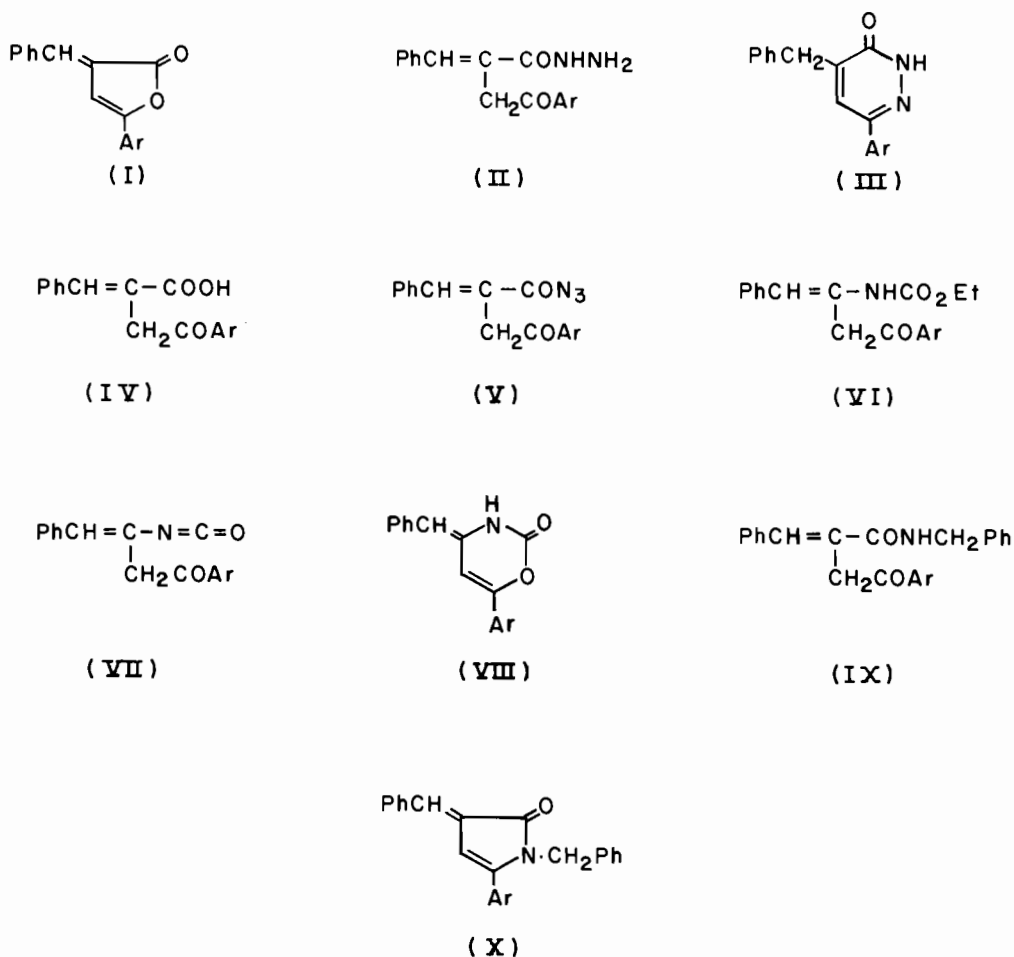
Schueler & Hanna (1951) prepared a number of butenolides by the condensation of benzaldehyde and some of its derivatives with β -benzoyl-propionic acid in sodium acetate-acetic anhydride mixture. The reaction of α -benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide with aqueous base, with methanol and with primary and secondary amines was investigated by Filler & Hebron (1959), Mustafa *et al.* (1963) and Awad *et al.* (1975).

The aim of the present work is to generalise the previous investigations to differently substituted butenolides using hydrazine and other nucleophiles as reagents. Besides these studies, the behaviour of the corresponding cinnamic acid azides, synthesised via these butenolides, under different experimental conditions has also been investigated.

RESULTS AND DISCUSSION

The α -benzylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides (Ia-e) were synthesised in an average yield of 85% following the procedure reported by Schueler & Hanna (1951). Compounds (I) reacted at room temperature with hydrazine hydrate in ethanol to give α -(substituted phenacyl) cinnamic acid hydrazides (II) (Scheme 1). The analytical and spectral data of compounds of series (II) were in accordance with the structures assigned (Tables 1 and 2).

When the reaction of (Ia-e) with hydrazine hydrate was repeated at elevated temperatures, 4-benzyl-6-aryl-3(2H)-pyridazinones (IIIa-e) were isolated (Tables 1 and 2). It seems in this case that the hydrazides (II) are formed as intermediates which



Ar = a , H ; b , p-CH₃ ; c , p-OCH₃ ; d , p-Cl ; e , p-Br .

Scheme 1.

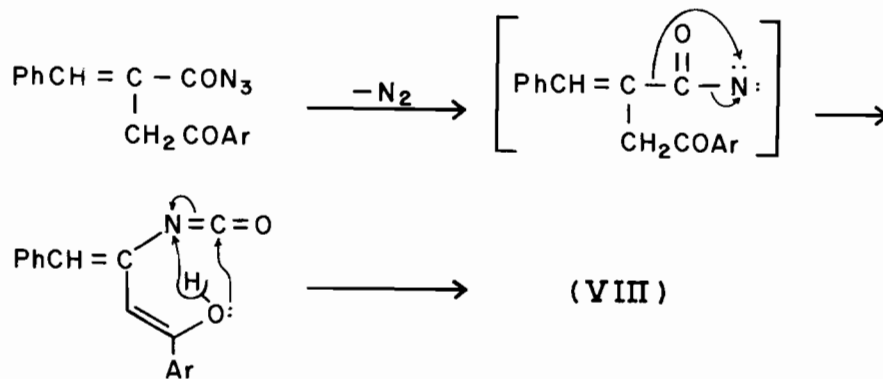
then undergo further condensation, intramolecularly, to give the pyridazinones (III). This was proved by treating the hydrazides (II) with a mixture of glacial acetic acid and hydrochloric acid where the compounds isolated matched in every respect (m.p., analytical and spectral data) with the pyridazinones (III) prepared earlier.

Furthermore, on treatment with sodium nitrite and hydrochloric acid the hydrazides (II) underwent, unexpectedly, ring closure to give the pyridazinones (III), instead of forming the corresponding azides. The failure of this hydrazide-azide route reported by Vangelovici & Moise (1941) to effect the conversion of (II) into the corresponding azides led to an alternative method in which the acyl azides were prepared from the corresponding acid chlorides by the action of sodium azide. Thus, the butenolides (Ia-c) were treated with 6N sodium hydroxide, as reported by Filler & Hebron (1959), to give α -(substituted phenacyl) cinnamic acids (IVa-c) (Table 1). The acids (IV) reacted smoothly with thionyl chloride to give the corresponding unisolated

acid chlorides, which on treatment with sodium azide in dry acetone yielded the azides (Va-c). All compounds of series (V) showed in their i.r. spectra the characteristic band of the azido group at 2100–2150 cm^{-1} (Tables 1 and 2).

When heated in ethanol the azides (Va-c) gave the corresponding urethane derivatives (VIa-c), while the thermolysis of compounds (V) in dry benzene gave the corresponding isocyanates (VII). These showed a band in their i.r. spectra (Table 2) characteristic of the asymmetric stretching mode of the $\text{N}=\text{C}=\text{O}$ group (Bellamy 1960). The pyrolysis of (V) at their melting point yielded the 4-phenylidene-2(3H)oxo-6-aryl-1,3-oxazines(VIIIa-c). The structure of all compounds of (VI), (VII), and (VIII) were inferred from their analytical and spectral data (Tables 1 and 2).

The mode of formation of compounds (VIII) is similar to the reported formation of oxadiazine derivatives from the corresponding hippuric acid azides (Awad & Fahmy 1968). It is also to be mentioned that the pyrolysis of the isocyanates (VII) at their melting points yielded the corresponding oxazines (VIII). Thus, it is concluded that compounds (VII) are intermediates in the formation of (VIII), which implies that the pyrolysis of (V) may thus involve Curtius rearrangement followed by cyclisation to give (VIII) (Scheme 2).



Scheme 2.

On the other hand, benzylamine reacted rapidly with the butenolides (Ia-e) to form the γ -ketoamides (IX-e). When compounds (IX) were heated either with dilute hydrochloric acid, glacial acetic acid, or acetic anhydride, orange needles of the corresponding β,γ -unsaturated- γ -lactams (Xa-e) were isolated. Analytical and spectral data of compounds (IX) and (X) were consistent with their proposed structures (Tables 1 and 2).

EXPERIMENTAL

All melting points were determined on an Electrothermal melting point apparatus, and are uncorrected. Elemental analyses were performed by Professor Dr. H. Malissa and G. Reuter, Elbach über Engelskirchen, West Germany. Infrared spectra (KBr wafer technique) were recorded using a Unicam SP1000 spectrophotometer, and ultraviolet spectra (ethanol as solvent) were obtained using a Unicam SP8000 spectrophotometer. $^1\text{H-n.m.r.}$ spectra in CDCl_3 or dioxan- d_8 were recorded on a Varian T-60A spectrometer using TMS as external standard.

α -Benzylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides (Ia–e) were prepared from benzaldehyde and the appropriate β -aroylpropionic acid according to the procedure reported by Schueler & Hanna (1951), Table 1.

Reaction of (I) with hydrazine hydrate

(A) At room temperature: A mixture of the butenolide (Ia–e) (1 g), hydrazine hydrate (4 ml), and ethanol (30 ml) was stirred at room temperature till a white precipitate separated. The reaction mixture was allowed to stand for 30 min, filtered, the solid washed with alcohol, and crystallised from a suitable solvent to give α -(substituted phenacyl) cinnamic acid hydrazides (IIa–e) (Tables 1 and 2).

(B) At elevated temperatures: The above-mentioned procedure was repeated but with refluxing for 2 hr. The reaction mixture was cooled and the solid formed was filtered, washed with alcohol and recrystallised from ethanol to give 4-benzyl-6-aryl-3(2H)-pyridazinones (IIIa–e) (Tables 1 and 2).

Cyclisation of (II) to (III)

A mixture of the hydrazide (IIa–e) (0.5 g), glacial acetic acid (7 ml), and conc. HCl (3.5 ml) was refluxed for 1 hr. Pouring the reaction mixture onto ice gave a solid which was filtered, washed with water, and recrystallised from ethanol to give the same pyridazinones (IIIa–e) prepared earlier.

Attempted conversion of (II) into the azides (V)

The hydrazide (IIa–e) in hydrochloric acid (100 ml, 1 N) was cooled in an ice-bath at 5°C, and a cold solution of sodium nitrite was added dropwise with stirring. After complete addition, the reaction mixture was left at room temperature for 30 min, the solid filtered, washed, and recrystallised to give a product whose i.r. spectra revealed the absence of the $\bar{N}-\overset{+}{N}\equiv N$ absorption at 2100 cm^{-1} . Analytical and spectral data of these products showed them to be the pyridazinones (IIIa–e).

Reaction of the butenolides (Ia–c) with sodium hydroxide

A mixture of the butenolide (Ia–c) (2 g) and sodium hydroxide (25 ml, 6 N) was refluxed for 2 hr. The cooled reaction mixture was neutralised with HCl (20%) and evaporated to dryness using a rotary evaporator. The solid left was crystallised from $\text{C}_6\text{H}_6\text{—CCl}_4$ (1:1 mixture) to give the α -(substituted phenacyl) cinnamic acids (IVa–c) (Tables 1 and 2).

Preparation of α -(substituted phenacyl) cinnamoyl azides (Va–c)

The acid (IVa–c) (2 g) was mixed with thionyl chloride (25 ml) and refluxed for 5 hr. Excess SOCl_2 was distilled off and the acid chloride that remained as a yellow oil was dissolved in dry acetone (12 ml) and sodium azide (2 g) added. The reaction mixture was stirred for 5 hr at room temperature and poured onto ice whereby a yellow solid separated. The solid was filtered, washed with water, and recrystallised from ether–petroleum ether (40–60°C) to give the azides (Va–c) (Tables 1 and 2).

Action of ethanol on the azides (Va-c)

The azide (Va-c) (0.5 g) and ethanol (20 ml) were refluxed for 2 hr. The solid obtained was filtered, washed, and recrystallised from ethanol to give the urethane derivatives (VIa-c) (Tables 1 and 2).

Thermolysis of the azides (Va-c)

A suspension of the azide (Va-c) (1 g) in dry benzene (25 ml) was refluxed for 4-5 hr. Cooling of the reaction mixture afforded a solid which was filtered, washed with petroleum ether (60-80°C) and recrystallised from ether-petroleum ether (60-80°C) to give the isocyanates (VIIa-c) (Tables 1 and 2).

Pyrolysis of the azides (Va-c)

The azide (Va-c) (1 g) was heated at its melting point under reduced pressure (5 mmHg) for 30 min, after which the evolution of gases ceased. The product was recrystallised from ethanol to give the 4-phenylidene-2(3H) oxo-6-aryl-1,3-oxazines (VIIIa-c) (Tables 1 and 2).

Pyrolysis of the isocyanates (VIIa-c)

The reaction was carried out as described above using the isocyanates (VIIa-c) (1 g). The product in each case was found to be the oxazine (VIIIa-c) obtained earlier, as proved by analytical and spectral data.

Reaction of the butenolides (Ia-e) with benzylamine

A mixture of the butenolide (Ia-e) (1 g) in dry benzene (20 ml) and benzylamine (0.8 g) was heated under reflux for 1 hr, then cooled. The colourless crystals separated were washed with petroleum ether and recrystallised from ethanol to give the α -(substituted phenacyl)-N-benzylcinnamic acid amides (IXa-e) (Tables 1 and 2).

Lactamization of (IXa-e)

A suspension of the N-benzylamide (IXa-e) (1 g) in HCl (25 ml, 6 N) was heated under reflux for 1 hr, then cooled. The orange-coloured solid formed was filtered, washed with water, and recrystallised from dilute ethanol to give the β,γ -unsaturated- γ -lactam (Xa-e) (Tables 1 and 2). The same results were obtained when (IX) was heated with acetic anhydride or glacial acetic acid.

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Table 1. Physical and analytical data

Compound	m.p. (°C)	Yield (%)	Mol. formula (mol. wt)	%C	%H	%N
				found/calculated		
Ia	154 ^{1,2}	75				
Ib	150 ^{1,2}	76				
Ic	172 ^{1,2}	96				
Id	211 ²	71	C ₁₇ H ₁₁ ClO ₂ (282·7)	72·30 72·22	3·71 ³ 3·82	
Ie	214 ²	75	C ₁₇ H ₁₁ BrO ₂ (327·3)	62·45 62·38	3·37 ⁴ 3·38	
IIa	175	85	C ₁₇ H ₁₆ N ₂ O ₂ (280·2)	72·78 72·82	5·72 5·75	10·01 9·99
IIb	157	90	C ₁₈ H ₁₈ N ₂ O ₂ (294·2)	73·95 73·43	6·10 6·16	9·49 9·52
IIc	160	95	C ₁₈ H ₁₈ N ₂ O ₃ (310·2)	69·63 69·64	5·88 5·84	9·06 9·03
IIId	149	80	C ₁₇ H ₁₅ ClN ₂ O ₂ (314·6)	64·47 64·54	4·76 4·80	8·94 8·90
IIe	182	80	C ₁₇ H ₁₅ BrN ₂ O ₂ (359·1)	56·73 56·82	4·19 4·21	7·82 ⁵ 7·80
IIIa	191 ^{1,2}	70	C ₁₇ H ₁₄ N ₂ O (262·1)			10·56 10·68
IIIb	220 ^{1,2}	72	C ₁₈ H ₁₆ N ₂ O (276·1)			10·06 10·14
IIIc	221-3 ²	96	C ₁₈ H ₁₆ N ₂ O ₂ (292·2)	73·72 73·98	4·99 5·52	9·98 10·04
IIId	240(dec.) ²	75	C ₁₇ H ₁₃ ClN ₂ O (296·6)	68·72 68·78	4·37 4·42	9·55 ⁶ 9·44
IIIe	266(dec.) ²	80	C ₁₇ H ₁₃ BrN ₂ O (341·6)	59·98 59·77	3·78 3·84	8·12 ⁷ 8·20
IVa	172(171-3) ⁸	74	C ₁₇ H ₁₄ O ₃ (266·3)	76·55 76·67	5·30 5·30	
IVb	189	79	C ₁₈ H ₁₆ O ₃ (280·3)	77·03 77·12	5·69 5·75	
IVc	152-3	85	C ₁₈ H ₁₆ O ₄ (296·3)	72·81 72·96	5·40 5·44	
Va	127(dec.) ⁹	67	C ₁₇ H ₁₃ N ₃ O ₂			
Vb	141(dec.) ⁹	69	C ₁₈ H ₁₅ N ₃ O ₂			
Vc	103-4(dec.) ⁹	73	C ₁₈ H ₁₅ N ₃ O ₃			

Table 1 (cont.)

Compound	m.p. (°C)	Yield (%)	Mol. formula (mol. wt)	%C	%H	%N
				found/calculated		
VIa	163-4 ²	81	C ₁₉ H ₁₉ NO ₃ (309·3)	73·58 73·78	6·11 6·19	4·58 4·53
VIb	174-5 ²	74	C ₂₀ H ₂₁ NO ₃ (323·3)	74·08 74·30	6·49 6·55	4·32 4·33
VIc	152 ²	83	C ₂₀ H ₂₁ NO ₄ (339·3)	70·70 70·79	6·13 6·24	4·18 4·13
VIIa	185 ⁹	67	C ₁₇ H ₁₃ NO ₂ (263·3)	77·32 77·54	4·89 4·98	5·25 5·32
VIIb	176 ⁹	72	C ₁₈ H ₁₅ NO ₂ (277·3)			4·91 5·05
VIIc	160 ⁹	72	C ₁₈ H ₁₅ NO ₃ (293·3)			4·67 4·77
VIIIa	193 ²	66	C ₁₇ H ₁₃ NO ₂ (263·3)	77·51 77·54	4·88 4·98	5·33 5·32
VIIIb	183-184 ²	68	C ₁₈ H ₁₅ NO ₂ (277·3)			5·11 5·05
VIIIc	167 ²	76	C ₁₈ H ₁₅ NO ₃ (293·3)			4·80 4·77
IXa	173 ^{1,2}	91	C ₂₄ H ₂₁ NO ₂			
IXb	169 ²	89	C ₂₅ H ₂₃ NO ₂ (369·4)	80·83 81·28	6·23 6·28	3·67 3·79
IXc	192 ²	90	C ₂₅ H ₂₃ NO ₃ (385·4)	77·78 77·91	5·99 6·02	3·51 3·63
IXd	230 ²	78	C ₂₄ H ₂₀ ClNO ₂ (389·9)	73·91 73·93	5·06 ¹⁰ 5·17	
IXe	234 ²	85	C ₂₄ H ₂₀ BrNO ₂ (434·3)	66·32 66·36	4·56 4·64	3·17 ¹¹ 3·22
Xa	143 ^{1,2}	89	C ₂₄ H ₁₉ NO			
Xb	139 ²	93	C ₂₅ H ₂₁ NO (351·4)	85·32 85·44	5·97 6·02	3·88 3·98
Xc	161 ²	92	C ₂₅ H ₂₁ NO ₂ (367·4)			3·79 3·81
Xd	200 ²	84	C ₂₅ H ₁₈ ClNO (383·8)			3·58 ¹² 3·65
Xe	203-204 ²	87	C ₂₅ H ₁₈ BrNO (428·3)	69·95 70·10	4·31 4·24	3·30 ¹³ 3·27

Notes: ¹ Identical with literature m.p. ² Crystallised from ethanol. ³ Cl, found: 12·78, calcd: 12·64%. ⁴ Br, found: 24·35, calcd: 24·44%. ⁵ Br, found: 22·13, calcd: 22·25%. ⁶ Cl, found: 11·88, calcd: 11·95%. ⁷ Br, found: 23·75, calcd: 23·42%. ⁸ Filler & Hebron (1959). ⁹ Crystallised from ether-petroleum ether (40-60°C). ¹⁰ Cl, found: 8·87, calcd: 9·09%. ¹¹ Br, found: 18·34, calcd: 18·40%. ¹² Cl, found: 9·21, calcd: 9·24%. ¹³ Br, found: 18·63, calcd: 18·66%.

Table 2. Spectral data*

Compound	i.r. (KBr)		u.v. (ETOH)		n.m.r. (CDCl ₃)	
	Cm ⁻¹	ν	λ_{\max} (nm)	l g ϵ	δ	Assignment (No. of protons)
I _{a-e}	1770-1760	C=O	403-385	4.33-3.41	5.3-5.2(s)	(1) —CH=
	1608-1602	C=C			6.8-6.6(s)	(1) —CH=
II _{a-e}	3300-3140(br.)	NH	300-280	4.77-4.47	8.73-7.2(m)	(10-9) ArH ¹
	1700-1680	C=O			3.4-3.2(t)	(1) —NH
	1640-1620	C=O			4.00(s)	(2) —CH ₂
					5.9-5.5(s)	(2) —NH ₂
III _{a-e}	3200-3020(br.)	NH	315-330	3.9-3.2	6.9(s)	(1) —CH=
	1690-1650	C=O			7.87-7.23(m)	(10-9) ArH ²
	1530	C=N or C=C			3.8(s)	(2) —CH ₂
					6.0-5.8(s)	(1) —CH=
IV _{a-c}	3090-2980(br.)	OH	270-250	3.3-3.0	8.0-7.4(m)	(10-9) ArH ³
	1750-1710	C=O			10.74-9.65(br.)	(1) NH
V _{a-c}	2200-2100	N ₃	270-265	3.8-3.75	3.67(s)	(2) —CH ₂
	1780-1760	C=O			6.48(s)	(1) —CH=
VI _{a-c}	3320-3150	NH	270-265	3.8-3.75	8.27-7.23(m)	(10-9) ArH ⁴
					1760	C=O
	1730-1715	C=O				
					4.0(s)	(2) —CH ₂
	5.5-5.3(s)	(1) —NH				
	6.9-6.7(s)	(1) —CH=				
VII _{a-c}	2275-2250	NCO	270-265	3.8-3.75	8.33-8.10(m)	(10-9) ArH
	1760-1750	C=O			4.10-3.95(s)	(2) —CH ₂
					6.55-6.43(s)	(2) —CH=
VIII _{a-c}	3350-3250	NH ⁶	270-265	3.8-3.75	8.11-7.54(m)	(10-9) ArH ⁵
	1790-1750	C=O ⁶			5.5-5.3(s)	(1) —CH=
					6.7-6.54(s)	(1) —CH=
IX _{a-e}	3230-3200	NH ⁶	410-405 ⁷	4.90	8.23-7.42(m)	(10-9) ArH
	1670-1665	C=O ⁶			10.75-10.3(br.)	(1) —NH
	1645-1640	C=O ⁶				
X _{a-e}	1680-1675	C=O ⁶	305-302 ⁷	3.88-3.80		
				258-250 ⁷	3.71-3.65	

* The data have been assembled into groups in order to save space. Detailed data for each compound can be supplied by the authors if requested.

Notes: ¹ I_b, δ 2.5(s) (3) Ar—CH₃; I_c, δ 3.87(s) (3) —OCH₃. ² II_b, δ 2.3(s) (3) Ar—CH₃; II_c, δ 3.85(s) (3) —OCH₃. ³ III_b, δ 2.35(s) (3) Ar—CH₃; III_c, δ 2.93(s) (3) —OCH₃. ⁴ V_b, δ 2.4(s) (3) Ar—CH₃. ⁵ VII_b, δ 2.38(s) (3) Ar—CH₃. ⁶ Bellamy (1960). ⁷ Scheuler & Hanna (1951).

سلوك الحلقة غير المتجانسة في البيوتينوليدات
تجاه الكواشف النيوكليوفيلية

نامق فرحات عويس وصديقة غلوم حسين
قسم الكيمياء بجامعة الكويت

خلاصة

تم تحضير بعض α - بنزايليدين γ - آريل $\Delta^{6,7}$ - بيوتينوليدات ودراسة تفاعلاتها مع
كواشف نيوكليوفيلية مختلفة. وقد أدى الفشل في تحويل هذه المركبات إلى الآسيل أزيدات
المقابلة عن طريق هيدرازيدات احماضها إلى اتباع طريق كلوريدات الأحماض ، كما تمت دراسة
سلوك هذه الآزيدات تحت ظروف تجريبية مختلفة .

