

# Some Reactions with $\omega$ -Bromoacetophenone: Synthesis of $\Delta^{\alpha,\beta}$ -Butenolide and Its Transformation into Pyrrole Derivatives

Fathy M. Abdelrazek,\* Zaghoul E. Kandeel,  
and Abdellatif M. Salah

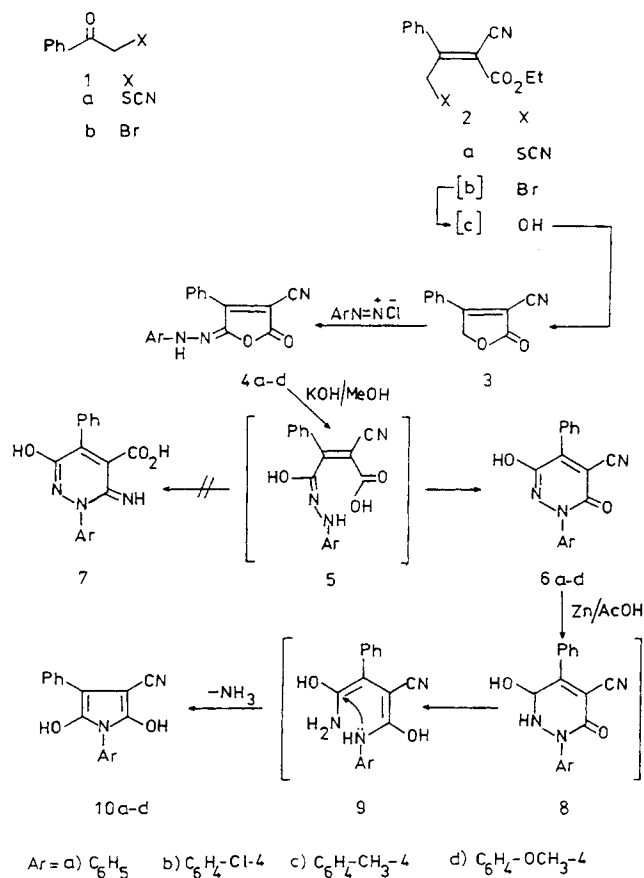
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Received 25 April 1994

## ABSTRACT

$\omega$ -Bromoacetophenone reacts with the sodium salt of ethyl cyanoacetate to afford  $\alpha$ -cyano- $\beta$ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide. This butenolide undergoes azo coupling with diazotized aromatic amines ( $\text{ArNH}_2$ ) to afford the hydrazo derivatives. These hydrazo derivatives ( $\text{Ar}=\text{Ph}$ , 4- $\text{ClC}_6\text{H}_4$ , 4- $\text{MeC}_6\text{H}_4$ , 4- $\text{MeOC}_6\text{H}_4$ ) were transformed into the corresponding 3(2H)-pyridazine derivatives on stirring in methanol in the presence of potassium hydroxide. These latter compounds were converted into the corresponding 3-cyano-2,5-dihydroxy-4-phenyl-N-arylpurrole derivatives on reduction with zinc dust in refluxing acetic acid, presumably via reductive cleavage of the N-N bond of the pyridazine followed by recyclization via loss of ammonia.

In the context of our search for new simple syntheses of azoles, azines, and their fused derivatives [1-4] utilizing readily available starting materials, we have previously reported [5] that phenacyl thiocyanate (1a) reacts with ethyl cyanoacetate (depending on the reaction conditions) to afford the Knoevenagel condensation product 2a in relatively low yield (Scheme 1). In an attempt to improve the yield of 2a, we attempted to pre-



SCHEME 1

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

\*To whom correspondence should be addressed.

pare the alkylidene derivative **2b** [6] via the reaction of  $\omega$ -bromoacetophenone **1b** with the sodium salt of ethyl cyanoacetate under mild conditions for a long period of time [7], and then to subject **2b** to the reaction with potassium thiocyanate (Scheme 1). However, on stirring of **1b** at room temperature for 24 hours with ethyl  $\alpha$ -sodiocyanacetate in absolute ethanol and after subsequent treatment (see experimental), a pale rose crystalline product of mp 161–162°C was obtained. Microanalyses and spectral data indicated that this product is  $\alpha$ -cyano- $\beta$ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide **3** [8].

The formation of **3** can be assumed to proceed via the intermediacy of the Knoevenagel condensation product **2b** which is formed, on long stirring of **1b** with the sodium salt of ethyl cyanoacetate, as the thermodynamically controlled product, which undergoes in situ hydrolysis to give the hydroxy intermediate **2c**. This intermediate then undergoes cyclization via loss of ethanol to afford the final isolable product **3**.

Compound **3** undergoes azo coupling with aryl diazonium salts to afford bright red coupling products. Spectral data (Table 2) revealed that these compounds are present predominantly in the hydrazo form **4**. Micro-analytical data of these products are in complete agreement with structures **4a**–

**d** (Table 1). Compound **4a** was also described in Ref. [8].

Compounds **4a**–**d** could be transformed into the corresponding 2,3-dihydropyridazin-3-one derivatives, respectively, upon stirring at room temperature in methanol containing potassium hydroxide solution presumably via ring opening and recyclization of the acyclic intermediate **5**, with loss of water. The IR spectra of the reaction products show absorption bands in the regions of  $\nu \sim 3500$ – $3400$ ,  $2228$ – $2205$ , and  $1690$ – $1670$   $\text{cm}^{-1}$  corresponding to hydroxy, cyano, and carbonyl groups, respectively. Structures **6a**–**d** were assigned to these products.  $^1\text{H}$  NMR spectra of **6a** and **6b** revealed signals at  $\delta = 7.2$ – $8.1$  and  $\sim 8.5$ , corresponding to aromatic and OH protons, respectively. Compounds **6c** and **6d** revealed, in addition, a methyl singlet (3H) at  $\delta$  2.42 and 3.78, respectively (Table 2). Based on these data as well as on elemental analyses (Table 1), the other possibility of cyclization of the intermediate **5** into **7** was ruled out. A similar behavior of butenolides has been previously reported [9].

Upon reflux in glacial acetic acid with zinc dust, the pyridazine derivatives **6a**–**d** could be transformed into the pyrrole derivatives **10a**–**d**, respectively. Structures **10a**–**d** were assigned on the basis of analytical as well as spectral data (Tables 1 and 2). The reaction presumably involves a reduc-

TABLE 1 Physical and Analytical Data of the New Compounds

Compound No.	Mp (°C) Solvent	Yield (%)	<i>m/e</i>	Molecular Formula (Mol. Wt.)	Calcd. Anal %		
					Found C	H	N
3	161-2	46	185	C <sub>11</sub> H <sub>7</sub> NO <sub>2</sub>	71.35	3.81	7.56
	AcOH			185.18	71.5	3.7	7.4
4a	248	65	289	C <sub>17</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	70.58	3.83	14.6
	DMF			289.29	70.3	4.0	14.6
4b	290	86	289	C <sub>17</sub> H <sub>10</sub> N <sub>3</sub> O <sub>2</sub> Cl	63.07	3.11	12.98
	DMF			323.74	63.1	3.3	12.7
4c	232	84	323	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	71.28	4.32	13.85
	DMF			303.32	71.0	4.5	14.0
4d	240	66	319	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub>	67.71	4.10	13.16
	DMF			319.32	67.4	4.3	13.3
6a	110	76	323	C <sub>17</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	70.58	3.83	14.53
	EtOH			289.29	70.8	4.1	14.4
6b	170	74	323	C <sub>17</sub> H <sub>10</sub> N <sub>3</sub> O <sub>2</sub> Cl	63.07	3.11	12.98
	EtOH			323.74	63.1	3.2	12.8
6c	192	76	319	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	71.28	4.32	13.85
	EtOH			303.32	71.5	4.3	13.7
6d	162	75	319	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub>	67.71	4.10	13.16
	EtOH			319.32	67.6	4.2	13.5
10a	185	72	290	C <sub>17</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	73.90	4.38	10.14
	EtOH			276.29	73.6	4.5	10.2
10b	153	78	290	C <sub>17</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> Cl	65.70	3.57	9.0
	EtOH			310.74	65.8	3.6	9.2
10c	176	68	290	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	74.47	4.86	9.65
	EtOH			290.32	74.5	4.6	10.0
10d	160	63	290	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	70.58	4.61	9.15
	EtOH			306.32	70.4	4.9	9.3

TABLE 2 IR and  $^1\text{H}$  NMR Data of the New Compounds

Compound No.	IR $\nu$ $\text{cm}^{-1}$ (Selected Bands)	$^1\text{H}$ NMR $\delta$ (DMSO- $d_6$ )
3	2230(CN); 1752(CO).	5.7 (s, 2H, CH <sub>2</sub> ); 7.5–8.0 (m, 5H, ar. H).
4a	3300–3200(NH); 2228(CN); 1760(CO).	7.3–8.2 (m, 10H, ar. H); 11.8 (s, 1H, NH).
4b	3280–3190(NH); 2224(CN); 1771(CO).	7.25–8.15 (m, 9H, ar. H); 11.9 (s, 1H, NH).
4c	3276–3195(NH); 2221(CN); 1743(CO).	2.4 (s, 3H, CH <sub>3</sub> ); 7.28–8.1 (m, 9H, ar. H); 11.65 (s, 1H, NH).
4d	3320–3210(NH); 2230(CN); 1765(CO).	3.7 (s, 3H, CH <sub>3</sub> ); 7.28–8.15 (m, 9H, ar. H); 11.7 (s, 1H, NH).
6a	3480–3270(OH); 2215(CN); 1680(CO).	7.28–8.1 (m, 10H, ar. H); 8.6 (s, 1H, OH).
6b	3444–3258(OH); 2228(CN); 1690(CO).	7.25–8.0 (m, 9H, ar. H); 8.4 (s, 1H, OH).
6c	3510–3375(OH); 2205(CN); 1672(CO).	2.42 (s, 3H, CH <sub>3</sub> ); 7.2–7.9 (m, 9H, ar. H); 8.7 (s, 1H, OH).
6d	3440–3260(OH); 2228(CN); 1690(CO).	3.78 (s, 3H, CH <sub>3</sub> ); 7.3–8.1 (m, 9H, ar. H); 8.9 (s, 1H, OH).
10a	3405–3320(OH); 2225(CN).	7.28–7.9 (m, 10H, ar. H); 8.1 (s, 1H, OH); 8.25 (s, 1H, OH).
10b	3400–3310(OH); 2224(CN).	7.3–7.9 (m, 9H, ar. H); 8.15 (s, 1H, OH); 8.28 (s, 1H, OH).
10c	3420–3320(OH); 2220(CN).	2.1 (s, 3H, CH <sub>3</sub> ); 7.25–8.0 (m, 9H, ar. H); 8.2 (s, 1H, OH); 8.3 (s, 1H, OH).
10d	3425–3315(OH); 2222(CN).	3.8 (s, 3H, CH <sub>3</sub> ); 7.28–8.0 (m, 9H, ar. H); 8.1 (s, 1H, OH); 8.22 (s, 1H, OH).

tive cleavage of the N–N bond in the pyridazines **6a–d**, followed by recyclization with loss of ammonia to afford the products via the intermediates **8** and **9** (Scheme 1). A similar transformation has been recently reported [10].

### EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 580 spectrophotometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker WH 90 and WP 200 spectrometers in DMSO- $d_6$  using TMS as an internal reference. Assignments were made by correlation of the off-resonance decoupled  $^{13}\text{C}$  NMR spectra and determination of the  $^1\text{H}$  NMR chemical shifts. Mass spectra were recorded on a GCMS-QP 1000 EX, Shimadzu (Japan), with ionization potential 70 eV. Elemental analyses were made in the Microanalytical Centre at Cairo University.

#### $\alpha$ -Cyano- $\beta$ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide **3**

To a suspension of 14.85 g (0.11 mole) of ethyl  $\alpha$ -sodiocynoacetate in 150 mL of absolute ethanol was added portionwise 19.9 g (0.1 mole) of phenacyl bromide (**1b**). The reaction mixture was stirred at room temperature for 24 hours, then was poured into ice-cold water and neutralized with dil HCl. The solid product that appeared was collected by filtration and recrystallized from acetic acid to afford 8.5 g of **3**.  $^{13}\text{C}$  NMR:  $\delta$  = 72.16 (t), 97.97 (s), 112.93 (s), 127.63 (s), 127.98 (d), 129.60 (d), 134.25 (d), 168.68 (s), and 172.75 (s).

#### Preparation of the Hydrazo Derivatives **4a–d**

To a cold solution of **3** (1.85 g, 0.01 mole) and sodium acetate (~3 g) in DMF/ethanol (50 mL, 1:1)

was added dropwise with stirring a solution of diazotized amine (aniline, *p*-chloroaniline, *p*-toluidine, or *p*-anisidine; 0.01 mole). The addition took ~30 minutes, after which stirring was continued for further 2 hours. The red solid precipitates so formed were collected by filtration, washed with cold water, dried, and recrystallized from DMF to afford 1.9 g of **4a**, 2.8 g of **4b**, 2.6 g of **4c**, and 2.1 g of **4d**.

#### 2-Aryl-4-cyano-6-hydroxy-5-phenylpyridazin-3(2H)-ones **6a–d**

To a suspension of each of **4a–d** (0.01 mole) in methanol (~30 mL) was added 5 mL of 20% aq potassium hydroxide solution. The reaction mixture was stirred for 10 hours at room temperature, at which time the dark red color faded. The mixture was then poured into cold water and neutralized with HCl, whereby orange precipitates appeared. These were filtered off and recrystallized to afford 2.2 g of **6a**, 2.4 g of **6b**, 2.3 g of **6c**, and 2.4 g of **6d**.

#### 1-Aryl-2,5-dihydroxy-4-phenyl-1H-pyrrole-3-carbonitriles **10a–d**

To a solution of each of the compounds **6a–d** (0.01 mole) in glacial acetic acid (20 mL) was added 2 g of zinc dust, and the mixture was refluxed for 2 hours during which the orange color disappeared. The mixture was then filtered while hot, the filtrate was cooled, and ice-water was added. The white solids that appeared were collected by filtration and recrystallized to afford 2, 2.4, 2, and 1.9 g of **10a**, **10b**, **10c**, and **10d**, respectively.

## REFERENCES

- [1] F. M. Abdelrazek, N. S. Ibrahim, Z. E. Kandeel, M. H. Elnagdi, *Synthesis* 1984, 970.
- [2] F. M. Abdelrazek, A. W. Erian, A. M. Torgoman, *Chem. Ind. (London)* 1988, 30.
- [3] F. M. Abdelrazek, *Z. Naturforsch.*, 44B, 1989, 488.
- [4] F. M. Abdelrazek, A. M. Salah, Z. E. Elbazza, *Arch. Pharm. (Weinheim)*, 325, 1992, 301.
- [5] F. M. Abdelrazek, H. Z. Shams, A. W. Erian, M. H. Elnagdi, *J. Chem. Res.*, 1985 (S)246, (M)2774.
- [6] Compound **4** has been previously prepared by M. Susse and S. Johnes, *J. Prakt. Chem.*, 323(4), 1981, 647; via bromination of the corresponding crotonitrile according to K. Gewald, *Chem. Ber.*, 98, 1965, 3571.
- [7]  $\alpha$ -Haloketones were reported to react with ethyl  $\alpha$ -sodiocyanoacetate in 30 minutes to afford ethyl phenacylcianoacetate as the kinetically controlled product by F. Korte, K. Trauner, *Chem. Ber.*, 95, 1962, 307.
- [8] Compound **3** has been previously prepared from sodium cyanoacetate and  $\omega$ -bromoacetophenone **1b** by J. A. Ford, Jr., C. V. Wilson, W. R. Young, *J. Org. Chem.*, 32, 1967, 173.
- [9] S. A. Khattab, A. S. Shawali, A. M. Farag, *J. Chem. Eng. Data*, 22, 1977, 104.
- [10] F. M. Abdelrazek, A. M. Salah, *Bull. Chem. Soc. Jpn.*, 66(6), 1993, 1722.