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Novel Syntheses of Pyrrolone and Pyrrolopyridine Derivatives

Zaghloul E. Kandeel, Ebtisam A. Hafez,* Maghraby A. Sleim, Fawi M. Abdelatif, and Mohamed H. Elnagdi

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

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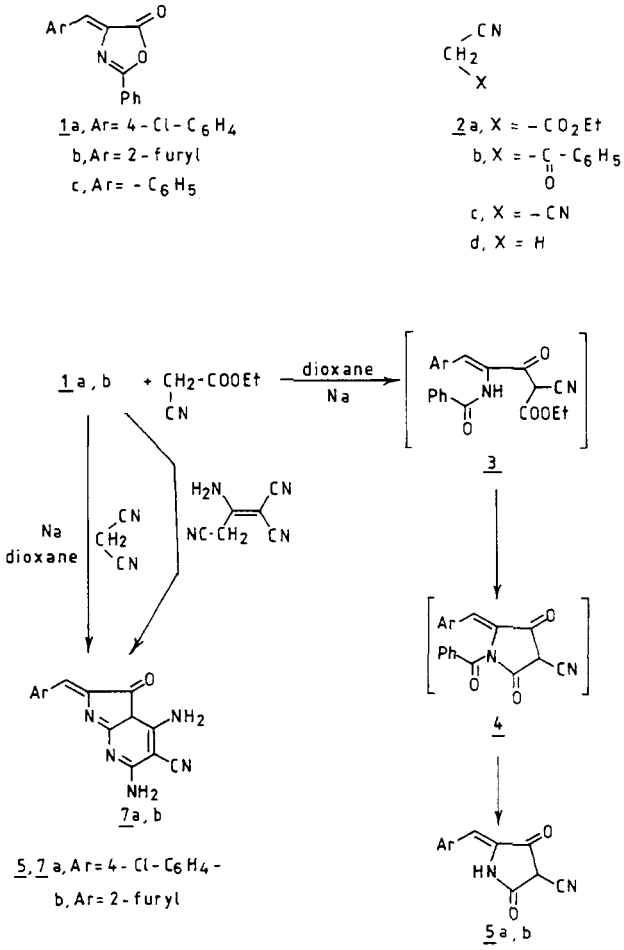
ABSTRACT

4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **1a,b** *reacted with some active methylene reagents to afford pyrrolidine-3,5-dione, pyrrolo[2,3-b]pyridine and pyrrolinone derivatives. The cinnamate ester, obtained from* **1a** *and sodium ethoxide, could be converted into a pyrrolidinone derivative having an active methylene group. This compound coupled with diazonium salts to afford the corresponding azo coupling products.*

Polyfunctionally substituted pyrrolones are interesting as potential pharmaceuticals [1–3] and intermediates in the dye industry [4]. In previous work, it has been reported that 4-phenylmethylene-2-oxazolin-5-one (**1c**) reacts with ethyl cyanoacetate (**2a**) in benzene in the presence of potassium metal to yield an acyclic β-ketoester, which could readily be cyclized to give an amino pyrrolone or pyrrolidine-3,5-dione, depending on the reaction conditions [5]. Attempted extension of this synthesis, utilizing benzoylacetonitrile (**2b**), afforded only products of a Michael addition across the double bond in **1** [5]. In continuation of our previous work [6,7], we report here results of our further investigations on reactions of **1a,b** with carbanions. Thus, refluxing equimolar amounts of **1a,b** and sodio ethyl cyanoacetate in dioxane resulted in their direct conversion into pyrrolidine-3,5-dione derivatives **5a,b**. The structures of com-



SCHEME 1

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

*To whom correspondence should be addressed.

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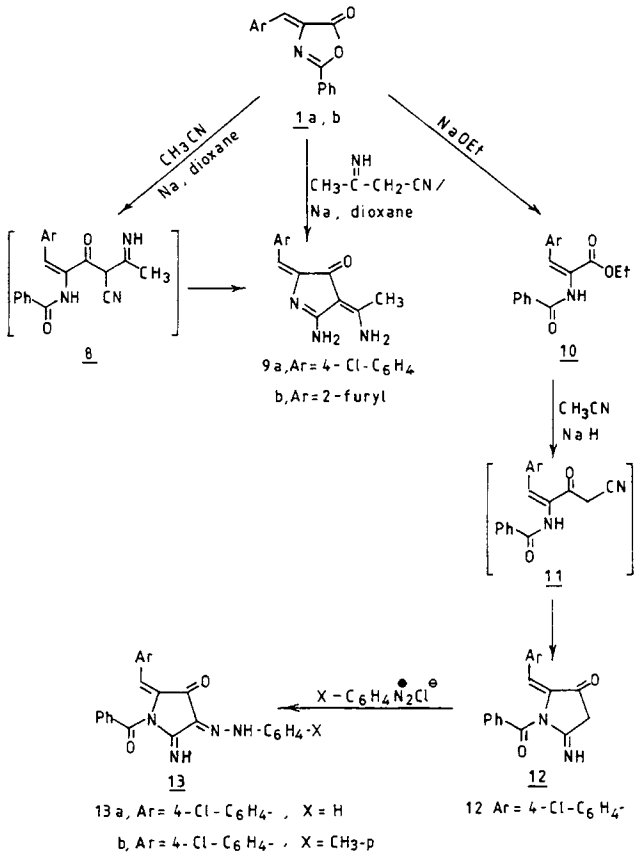
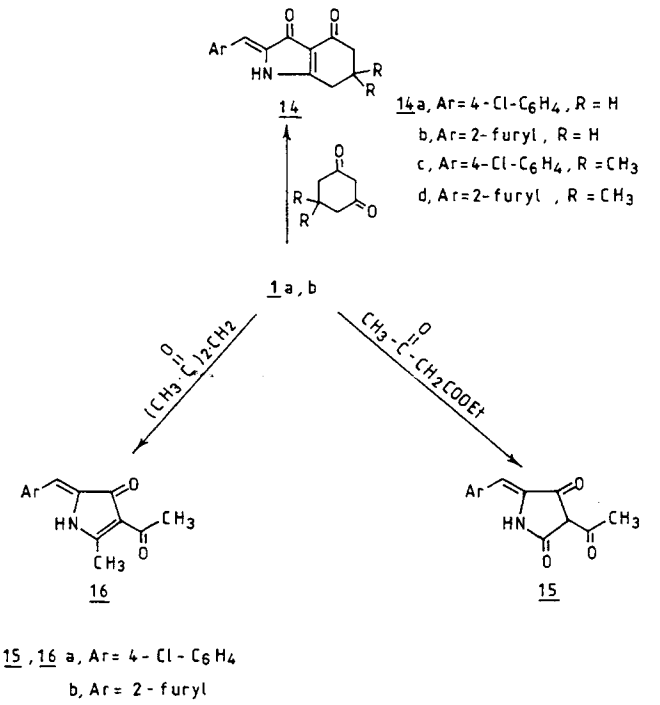


SCHEME 2



SCHEME 3

pounds **5a,b** were established on the basis of their elemental analyses and spectral data. The IR spectra showed the presence of NH group stretching at 3350 cm^{-1}, CN group stretching at 2220 cm^{-1}, and carbonyl group stretching at 1690 and 1648 cm^{-1}. ^1H NMR spectroscopy revealed the olefinic singlet at δ 6.0, the NH singlet at δ 11.2, and the aromatic multiplet at δ 7.2–7.65, respectively.

The formation of each compound **5a,b** is assumed to take place via the corresponding nonisolable intermediate **3**, which readily cyclizes under the reaction conditions to give the appropriate **4**. The latter undergoes debenzoylation to give each final isolable product **5a,b** (Scheme 1).

In contrast to the behavior of ethyl cyanoacetate (**2a**), compounds **1a,b** reacted with malononitrile (**2c**) under the same experimental conditions to yield the pyrrolo[2,3-b]pyridine derivatives **7a,b**. The formation of each compound **7a,b** is assumed to take place on the basis that malononitrile first dimerizes under the reaction conditions to give the malononitrile dimer (**6**) which then reacts with each **1a,b** to afford the corresponding pyrrolo[2,3-b]pyridine derivative **7a,b**. This result was confirmed by reacting **1a,b** with **6** to give the same isolable products **7a,b** in better yields. Similarly, compounds **1a,b** reacted with acetonitrile **2d** in dioxane in the presence of sodium metal to afford pyrrolone derivatives **9a,b**. The same products were obtained by reacting **1a,b** with 3-aminocrotononitrile.

It has been reported earlier that Z-4-arylmethylene-2-phenyl-2-oxazolin-5-ones (**1c**) afford the Z-α-acylaminocinnamic esters **10** in almost quantitative yields when treated with alkoxide ions [8]. Thus, when compound **1a** was treated with sodium ethoxide, the cinnamate ester **10** was formed. This could be successfully converted into the iminopyrrolidinone derivative **12** upon treatment with acetonitrile in the presence of sodium hydride via the intermediacy of **11**, which underwent cyclization under the reaction conditions, affording **12**. The mass spectrum of the reaction product revealed molecular ion peaks m/z 324 (M^+) and 326 (M^+ + 2). The iminopyrrolidinone structure **12** was assigned for this product on the basis of its IR spectrum, which revealed the absence of any cyano absorption. The ^1H NMR spectrum revealed the methylene singlet at δ 2.81, the olefinic proton at δ 6.0 in addition to the resonances of the aromatic and imine protons. The methylene group in compound **12** proved to be highly reactive; thus, compound **12** coupled with arenediazonium salts to afford the corresponding azo coupling products **13a,b** in excellent yields (Scheme 2).

Also, compounds **1a,b** reacted with cyclic and acyclic dicarbonyl compounds in dioxane in the

TABLE 1 Physical and Analytical Data of the New Compounds

Compound	Mp (°C) (Solvent)	Yield (%)	Molecular Formula (MW)	Found (Calcd)	Analysis % C	H	N	Cl
5a	280–281	77	$C_{12}H_7N_2O_2Cl$		58.5	3.0	11.4	14.3
	(EtOH)		(246.65)		58.43	2.86	11.36	14.37
5b	268–269	75	$C_{10}H_6N_2O_3$		59.6	3.0	14.0	—
	(EtOH)		(202.17)		59.41	2.99	13.86	—
7a	220–221	66	$C_{15}H_{10}N_5OCl$		57.6	3.5	22.5	11.2
	(DMF)		(311.73)		57.80	3.23	22.47	11.37
7b	207	68	$C_{13}H_9N_5O_2$		58.7	3.1	26.2	—
	(DMF)		(267.25)		58.43	3.39	26.21	—
9a	206	71	$C_{13}H_{12}N_3OCl$		59.5	4.6	16.2	13.4
	(EtOH)		(267.71)		59.66	4.62	16.06	13.55
9b	210	73	$C_{11}H_{11}N_3O_2$		60.7	4.9	20.1	—
	(EtOH)		(217.23)		60.82	5.10	19.94	—
12	128	60	$C_{18}H_{13}N_2O_2Cl$		66.4	4.0	8.7	11.0
	(EtOH)		(324.77)		66.57	4.03	8.63	10.92
13a	158–160	90	$C_{24}H_{17}N_4O_2Cl$		67.3	4.0	13.1	8.2
	(EtOH)		(428.88)		67.21	3.99	13.06	8.27
13b	165–166	85	$C_{25}H_{19}N_4O_2Cl$		67.6	4.4	12.4	8.2
	(EtOH)		(442.90)		67.80	4.32	12.65	8.00
14a	188	70	$C_{15}H_{12}NO_2Cl$		65.7	4.5	5.0	13.1
	(EtOH)		(273.72)		65.82	4.42	5.12	12.95
14b	210	71	$C_{13}H_{11}NO_3$		68.0	5.0	6.2	—
	(EtOH)		(229.24)		68.11	4.84	6.11	—
14c	192	62	$C_{17}H_{16}NO_2Cl$		67.8	5.4	4.5	12.0
	(EtOH)		(301.77)		67.66	5.34	4.64	11.75
14d	179	57	$C_{15}H_{15}NO_3$		70.0	6.1	5.3	—
	(EtOH)		(257.29)		70.02	5.88	5.44	—
15a	195	81	$C_{13}H_{10}NO_3Cl$		59.0	4.0	5.1	13.2
	(AcOH)		(263.68)		59.22	3.82	5.31	13.45
15b	190	85	$C_{11}H_9NO_4$		60.2	4.1	6.2	—
	(AcOH)		(219.20)		60.27	4.14	6.39	—
16a	140	63	$C_{14}H_{12}NO_2Cl$		64.3	4.5	5.6	13.3
	(EtOH)		(261.71)		64.25	4.62	5.35	13.55
16b	132	74	$C_{12}H_{11}NO_3$		66.1	4.9	6.7	—
	(EtOH)		(217.22)		66.35	5.10	6.45	—

presence of sodium metal to yield the indoline derivatives **14a–d**, the pyrrolidinediones **15a,b**, and the pyrrolinone derivatives **16a,b** (Scheme 3). Such reactions are assumed to take place via attack by carbon nucleophiles on the oxazoline moiety. Thus, the reaction of **1a,b** with 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione afforded the indoline derivatives **14a–d** in high yields. The structures of **14a–b** were confirmed based on their elemental analyses and spectral data. ^{1}H NMR spectra of compounds **14a–d** revealed the presence of olefinic protons at δ 5.9 in addition to the NH proton near δ 11.2 besides other signals due to methylene and aromatic protons (Table 2). The mass spectrum of compound **14a** demonstrates a molecular formula $C_{15}H_{12}NO_2Cl$ (*m/z* 273, M^+ and 275 $M^+ + 2$). Similarly, ethyl acetoacetate reacted with **1a,b** to give the pyrroledinediones **15a,b**. Also, acetylacetone reacted with **1a,b** under the same experimental conditions to yield the pyrrolinone derivatives **16a,b**.

Thus, several new polyfunctional pyrrolones could be prepared. The obtained compounds carry several functional substituents and are promising for further utility in syntheses of pyrrole derivatives.

EXPERIMENTAL

Melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were taken as KBr discs on a Pye-Unicam Sp 1100 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) instrument

TABLE 2 Spectral Data of the New Compounds

Compound	*IR, ν (cm^{-1})*	*^1H NMR (δ)*
5a	3350 (NH), 2990 (CH), 2220 (CN), 1690, 1648 (CO), 1580 (C = C)	11.2 (s, 1H, NH), 7.65–7.20 (m, 4H) (arom. H), 6.0 (s, 1H, olefinic H), 3.62 (s, 1H, CH)
5b	3340 (NH), 2990 (CH), 2222 (CN), 1690, 1640 (CO), 1570 (C = C)	11.0 (s, 1H, NH), 7.4–6.8 (m, 3H furyl H), 6.10 (s, 1H, olefinic CH), 3.37 (s, 1H, CH)
7a	3400 (NH_2), 3010 (CH), 2225 (CN), 1690 (CO), 1580 (C = C)	7.85–7.45 (m, 4H, arom. H), 6.0 (s, 1H, CH), 4.22 (s, 5H, two NH_2 + CH)
7b	3450 (NH_2), 3000 (CH), 2222 (CN), 1695 (CO), 1580 (C = C)	7.4–6.8 (m, 3H, furyl H), 6.0 (s, 1H, CH), 4.20 (s, 5H, two NH_2 + CH)
9a	3400 (NH_2), 2995 (CH), 1790 (CO), 1640 (C = N), 1580 (C = C)	7.92–7.41 (m, 4H, arom. H), 5.93 (s, 1H, olefinic CH), 4.36 (s, 4H, two NH_2), 2.0 (s, 3H, CH_3)
9b	3294 (NH), 2846 (CH), 1698 (CO), 1647 (CO), 1510 (C = C)	7.5–6.9 (m, 3H, furyl H), 5.9 (s, 1H, CH), 4.22 (s, 4H, two NH_2), 1.9 (s, 3H, CH_3)
12	3294, 3300 (NH), 2900 (CH), 1760 (CO), 1660 (CO), 1640 (C = N)	8.7 (s, 1H , NH), 7.9–7.3 (m, 9H, arom. H), 6.0 (s, 1H, CH), 2.8 (s, 2H, CH_2)
13a	3340, 3290 (NH), 1700 (CO), 1670 (CO), 1650 (C = N)	8.9 (s, 1H, NH), 8.2–7.6 (m, 16H, arom. H + NH)
13b	3340, 3290 (NH), 1700 (CO), 1670 (CO), 1650 (C = N)	8.8 (s, 1H, NH), 8.1–7.6 (m, 15H, arom. H + NH), 2.3 (s, 3H, CH_3)
14a	3290 (NH), 2890 (CH), 1700, 1680 (CO)	11.2 (s, 1H, NH), 7.9–7.5 (m, 4H, arom. H), 5.9 (s, 1H, CH), 2.7–2.6 (m, 2H, CH_2), 2.3–2.2 (m, 2H, CH_2), 1.9–1.8 (m, 2H, CH_2)
14b	3340 (NH), 2920 (CH), 1720 (CO), 1680 (CO), 1580 (C = C)	11.0 (s, 1H, NH), 7.8–7.3 (m, 3H, furyl H), 5.9 (s, 1H, CH), 2.63 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 1.95 (m, 2H, CH_2)
14c	3350 (NH), 2950 (CH), 1710, 1680 (CO), 1580 (C = C)	11.1 (s, 1H, NH), 7.7–7.4 (m, 4H, arom. H), 5.9 (s, 1H, CH), 2.6 (s, 2H, CH_2), 2.4 (s, 2H, CH_2), 1.3 (s, 6H, two CH_3)
14d	3345 (NH), 2930 (CH), 1710, 1690 (CO), 1580 (C = C)	11.0 (s, 1H, NH), 7.8–7.3 (m, 3H, furyl H), 5.85 (s, 1H, CH), 2.64 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 1.25 (s, 6H, two CH_3)
15a	3400 (NH), 2910 (CH), 1680, 1670 (CO), 1590 (C = C)	10.9 (s, 1H, NH), 7.8–7.4 (m, 4H, arom. H), 5.9 (s, 1H, CH), 2.09 (s, 3H, CH_3), 2.4 (s, 1H, CH)
15b	3360 (NH), 2950 (CH), 1675, 1660 (CO)	10.8 (s, 1H, NH), 7.7–7.4 (m, 3H, furyl H), 5.9 (s, 1H, CH), 2.1 (s, 3H, CH_3), 2.4 (s, 1H, CH)
16a	3400 (NH), 2970 (CH), 1695, 1670 (CO), 1580 (C = C)	10.7 (s, 1H, NH), 7.8–7.5 (m, 4H, arom. H), 5.9 (s, 1H, CH), 2.28 (s, 3H, CH_3), 1.78 (s, 3H, CH_3)
16b	3390 (NH), 3010 (CH), 1680, 1665 (CO), 1580 (C = C)	10.7 (s, 1H, NH), 7.7–7.3 (m, 3H, furyl H), 6.0 (s, 1H, CH), 2.3 (s, 3H, CH_3), 1.97 (s, 3H, CH_3)

for solutions in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard. Mass spectra were obtained on a GCMS-QP 1000 Ex mass spectrometer with ionization potential 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University. 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones were prepared according to literature procedures [9,10].

Reaction of 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones (**1a,b**) *with the Active Methylene Reagents; General Procedure*

To a solution of 0.01 mol of the active methylene reagent (ethyl cyanoacetate, malononitrile, malononitrile dimer, acetonitrile, 3-iminocrotononitrile, 1,3-cyclohexandione, 5,5-dimethylcyclohexandione, ethyl acetoacetate or acetylacetone) in dioxane (25 mL) was added finely divided sodium metal (0.23 g, 0.01 mol), and the mixture was stirred at room temperature for 24 hours, 0.01 mole of either **1a** or **1b** being added. The reaction mixture was heated under reflux for 6–8 hours. The solvent was removed under reduced pressure, and the residue was poured into ice-water, acidified with concd HCl. The solid products, so formed, were collected by filtration, washed with water, and crystallized from the appropriate solvent (Table 1). The yields of compounds **7a** and **7b** obtained from reaction

of **6** with **1a** and **1b** were 82 and 78%, respectively.

Reaction of the β-Unsaturated Ester **10** *with Acetonitrile; Formation of the Iminopyrrolone Derivative* **12**

To a solution of the ester **10** (32.99 g, 0.1 mol) in dry toluene (300 mL) was added sodium hydride (2.64 g, 0.11 mol), acetonitrile (4.1 g, 0.1 mol), and DMF (10 mL). The reaction mixture was warmed gently with continuous stirring for 2 hours, and then heated under reflux for 4 hours. A very vigorous reaction took place, which started to subside after about 30 minutes. The reaction mixture was allowed to cool, and then left to stand at room temperature overnight with continuous stirring. The crystalline solid product that had formed was collected by filtration, washed with petroleum ether (60–80°C, 100 mL), dried, and dissolved in ice-water and filtered again; then, the filtrate was acidified with concd HCl, whereby a colorless solid was formed, collected by filtration, washed with water, and crystallized from ethanol (Table 1).

Coupling of **12** *with Arenediazonium Salts; General Procedure*

To a cold solution of **12** (3.25 g, 0.01 mol) in ethanol (50 mL) was added sodium acetate (5 g), and then the equivalent amount (0.01 mol) of the appropriate arenediazonium chloride [prepared by diazotization of aniline or *p*-toluidine (0.01 mol) using concd HCl (37.5%, 3 mL) and sodium nitrite (0.7 g, 0.01 mol, at 0–5°C)] was added portionwise over a period of 30 minutes. After complete addition, the mixture was stirred for a further 30 minutes and then left for 2 hours in an ice bath. The precipitated reddish products were collected by filtration, washed with water, and crystallized from ethanol to afford **13a** and **13b**, respectively (Table 1).

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