Pergamon

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Lactam Analogues of Pentalene. A new One-Pot Synthesis of Pyrrolo[3,2-b]pyrrole-2,5-diones deriving from Pulvinic Acid

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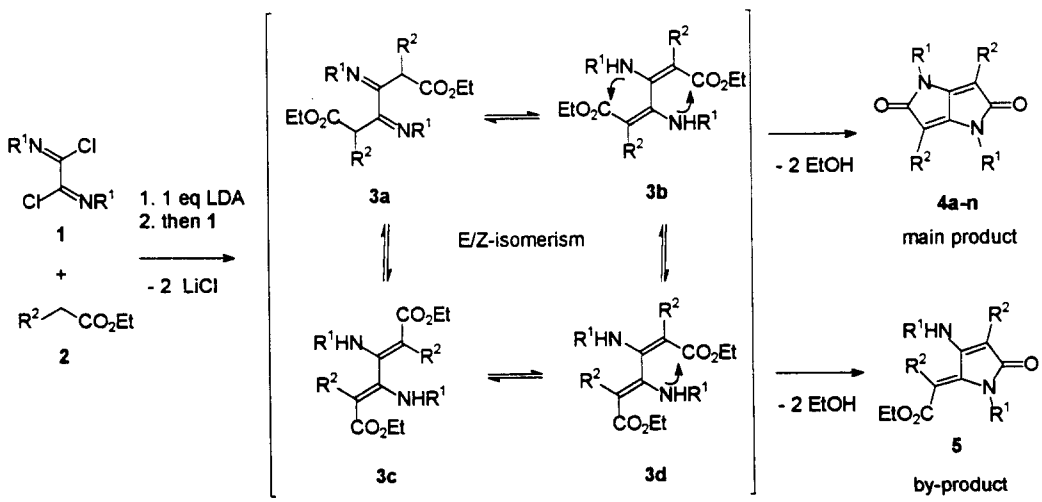
Abstract: A new and convenient one-pot synthesis of a variety of N-aryl lactam analogues **4** of pentalene has been developed. Pulvinic acid dilactams **4** are of interest due to their electronic and optical features and as synthetic pigments. © 1997 Elsevier Science Ltd.

Pyrrolo[3,2-b]pyrrole-2,5-diones **4** are dilactams of pulvinic acid, which is a natural dye found in lichens.[1] Vinylogue amides **4** also are lactam analogues of pentalene. Regioisomeric pyrrolo[3,4-c]pyrrole-1,4-dione [2] has recently been used for the preparation of substituted 2,5-diazapentalenes and of Azafulvens.[3] Pyrrolopyrrole-diones also are used as synthetic pigments.[4] Oxa-analogue pulvinic acid dilactones are analogues of biological active derivatives of pulvinic acid.[5] Previously, selected pulvinic acid dilactams were obtained in a three step protocol starting with (N-phenylacetyl)-acetic acid amino ester[6] or in one step from pulvinic acid using relatively harsh reaction conditions (autoclave reaction, 140-180 °C).[7] Herein, we describe a new one-pot synthesis of a variety of substituted N-aryl pulvinic acid dilactams **4a-n**.



Scheme 1

One molar equivalent of bis(imidoyl) chlorides of oxalic acid **1**[8] were treated with two molar equivalents of monoanions of acetic acid ester derivatives **2** at -78 °C in THF (Scheme 1). The ester enolates were generated by means of one molar equivalent of $(i\text{-}C_3H_7)_2NLi$ (LDA) or $(Me_3Si)_2NNa$ in THF. A variety

of substituted pulvinic acid dilactams **4** were obtained in moderate to good yields (Table 1).[9] The best yields of **4** were observed using aryl-stabilized ester enolates. [10]

Table 1: Yields and physical properties of pyrrolo[3,2-b]pyrrole-2,5-diones **4** prepared

R^1	R^2	N°:	$\lambda_{(max)}$ (lgε) (Acetonitrile / nm)			yield	mp.
			λ_1	λ_2	λ_3	(%)	(°C)
C_6H_5	C_6H_5	**4a**	246 (4.42)	344 (4.35)		75	370-71
4-$C_6H_4CH_3$	$CH_2C_6H_5$	**4b**	247 (4.50)	300 (4.51)	397 (2.60)	35	216-18
4-$C_6H_4CH_3$	$C(CH_3)_3$	**4c**	241 (4.46)	296 (4.64)	385 (2.68)	25	250-51
4-$C_6H_4CH_3$	H	**4d**	247 (4.51)	294 (4.53)	387 (2.72)	32	256-58
4-$C_6H_4CH_3$	4-$C_6H_4OCH_3$	**4e**	249 (4.82)	378 (4.53)		72	330-31
4-$C_6H_4CH_3$	1–$C_{10}H_7$	**4f**	246 (4.47)	295 (4.42)	363 (4.09)	63	376-78
4-$C_6H_4CH_3$	4-$C_6H_4N(CH_3)_2$	**4g**	272 (3.92)		457 (3.67)	67	364-66
4-$C_6H_4CH_3$	Pyrid-3-yl	**4h**	245 (4.38)	336 (4.27)	446 (2.80)	62	430-31
4-$C_6H_4CH_3$	$N(CH_3)$pyrrole-2-yl	**4i**	246 (4.49)	302 (4.21)	423 (4.28)	37	314-16
4-$C_6H_4CH_3$	Thien-2-yl	**4j**	261 (4.32)	302 (4.34)	536 (4.38)	76	425-26
4-$C_6H_4CH_3$	$N(CH_3)_2$	**4k**	254 (4.62)		414 (4.46)	21	288-89
4-$C_6H_4OCH_3$	C_6H_5	**4l**	244 (4.61)	341 (4.36)		68	318-20
4-$C_6H_4NO_2$	C_6H_5	**4m**	236 (3.93)	337 (4.05)		35	420-24
3-$C_6H_4CF_3$	C_6H_5	**4n**	243 (4.35)	345 (4.22)		64	284-86

Pyrrolo[3,2-b]pyrrole-2,5-diones **4a-n** are the main products isolated in all reactions. However, pyrrolidenone **5** was isolated as by-product (15 % yield) in case of **4b**. Thus, we believe that the reaction involves two-fold attack of the ester enolate on the oxalic acid bis(imidoyl) chloride to give the open-chain intermediate **3a**, which rapidly equilibrates with enamine-tautomers **3b**, **3c** and **3d** (E/Z-isomerism). Pulvinic acid dilactams **4** are formed by a two-fold cyclization of tautomer **3b** and are removed from the equilibrium due to low solubility in THF.[11] It would appear that pyrrolidenone **5** is obtained by mono-cyclization of tautomer **3d**.[12]

Open-chained products derived from tautomer type **3c** were observed in the reaction of **1** with ketone enolates only.[13] However, the reaction of malonic acid diethylester with oxalyl chloride was reported to produce open-chain oxalyl-bismalonic acid diethyl esters.[14] This striking difference to the formation of pyrrolo[3,2-b]pyrrole-2,5-diones **4** from ester enolates seems to be an effect of the enhanced nucleophilicity of nitrogen as compared with that of oxygen.

The X-ray crystallographic analysis of pyrrolo[3,2-b]pyrrole-2,5-dione **4c** (Figure 1)[15] shows that the heterocyclic moiety is planar and centro-symmetric. Alternation of the bond-lengths within the bicyclic system indicates that double and single bonds localized.

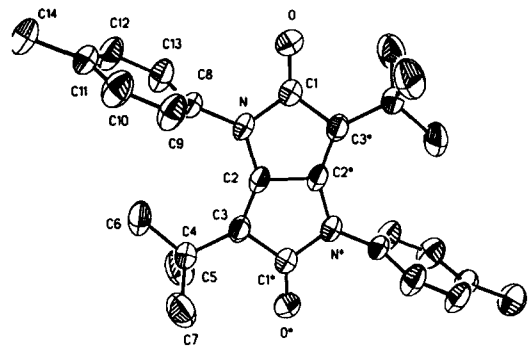


Figure 1: ORTEP plot of the crystal structure of **4c**, selected bond lengths (Å): C2-C2*, 1.489 (4); N-C2, 1.388 (3); C2-C3, 1.342 (3); N-C1, 1.412 (3); C1-C3*, 1.502 (3); C1-O, 1.206 (3).

As shown in Table 1, the n→π*-transition (λ_1) is not significantly influenced by the exocyclic substituents. In contrast, the π→π*-transition (λ_2 and λ_3) is influenced: a change in substituents R^2 effects different colors of the products (varying from slight yellow in case of **4f** and deep red in case of **4j**). The influence of N-substitution (R^1) on π→π*-absorption is small. These results are in agreement with the substituent effects in diazapentalenes.[16]

In summary, the reaction of anions of ethyl acetats with bis(imidoyl) chlorides of oxalic acid offers access to a variety of novel pulvinic acid dilactams. Our current studies are directed towards exploring the preparative scope of the concept presented.

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9. Data for compound **4i**: mp 314-16°C; IR (Nujol) 1737 (C=O), 1657 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz / CD_2Cl_2): δ (ppm): 2.30 (s, 6H, tolyl); 3.16 (s, 6H, N-methyl); 5.99 (m, 4H, 2 x 2 pyrrole); 6.52 (t, 2H, 2 x pyrrole, J = 2.1Hz); 6.94-7.28 (m, 8H, tolyl). ^{13}C-NMR (200 MHz / CD_2Cl_2): δ (ppm): 21.0 (tolyl-CH_3); 34.6 (pyrrole-CH_3); 108.6 (C3 -pyrrole); 113.6 (C4-pyrrole); 120.1 (C5-pyrrole); 121.1 (C4); 124.8; 129.3; 131.4; 137.2 (tolyl); 129.9 (C3); 145.5 (C2-pyrrole); 145.5 (CO). MS (CI/H_2O), *m/z* 475 (M+H). Anal: Calc. for $C_{30}H_{26}N_4O_2$:C, 75.93; H, 5.52; N, 11.81. Found: C, 75.01; H, 5.56; N, 11.93.
10. Other by-products observed were oxalic acid bis(imidoyl) diethyl esters (5 % to 50 % yield) deriving from alcoholysis of **1** with ethanol formed during the reaction.
11. Pyrrolo[3,2-b]pyrrole-2,5-diones **4** proved almost insoluble in a variety of organic solvents which is, in fact, an important feature of synthetic pigments.
12. Compound **5**: mp 328-330°C; IR(Nujol) 3240 (N-H), 1651 (C=O), 1603 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz / $DCON(CD_3)_2$): δ (ppm) 0.69 (t, 3H, CH_3-ester, J = 6.9Hz); 2.22; 2.35 (s, 3H, tolyl); 3.35 (q, 2H, ester-CH_2, J = 6.9Hz); 6.93-7.73 (m, 18H, tolyl); 10.41 (s, 1H, NH). ^{13}C-NMR (200 MHz / $DCON(CD_3)_2$): δ (ppm) 15.2 (ester-CH_3); 20.9; 21,5 (tolyl-CH_3); 69,8 (ester-CH_2); 115-144 (tolyl, pyrrolidenone); 160,2 (ester-CO); 163,7 (CO). MS (CI/H_2O): *m/z* 515 (M+H). Anal: Calc. for: $C_{34}H_{30}N_2O_3$: C, 79.35; H, 5.88; N, 5.40. Found: C, 79.50; H, 6.05; N, 5.14.
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15. The crystal was measured on Enraf-Nonius CAD4 four circle diffractometer using ω-2θ scan mode. The structure was solved by direct methods (SHELXS) and refined against F_o^2 (SHELXC-93).
    Crystal data for **4c**: $C_{28}H_{32}N_2O_2$, yellow quader, size 0.41 X 0.38 x 0.38 mm^3, Mr = 428.6 $gmol^{-1}$, monoclinic, space group $P2_1/c$, a = 11.086(2), b = 11.203(2), c = 10.030(2) Å, β = 107.93(3)°, V = 1185.2 (4) $Å^3$, Z = 2, $\rho_{calcd.}$ = 1.201 gcm^{-3}, μ (Mo-K_α) = 0.75 cm^{-1}, F(000) = 460, 4327 reflections in ±h, +k, -l, measured in the range 2.20° ≤ Θ ≤ 27.40°, 4122 independent reflections, R_{int} = 0.036, 1775 reflections with Fo > 4σ(Fo), 149 parameters, R = 0.064 and wR^2 = 0.149, GOOF = 1.20, largest difference peak: 0.25 $eÅ^{-3}$. The atomic co-ordinates for this work are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
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