Monatshefte für Chemie 121, 671 – 675 (1990)

Monatshefte für Chemie
Chemical Monthly

Reactions with Pyrrolidine-2,4-diones, II [1]: New Approaches to the Synthesis of Substituted 5,6-Dihydropyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)ones*

Mohamed G. Kassem, S. A. Shams El-Dine, Farid S. G. Soliman, and **Manal N. S. Saudi**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, A. R. Egypt

Summary. Approaches leading to 5,6-dihydro-5,6-diphenyl-2-substituted-pyrrolo[3,4-d][1,2,3]-triazol-4(2*H*,4*H*)-ones (**10**) are described. The first approach consists of cyclodehydrating 3(or 4)-hydroxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**4**, **7**) with boiling acetic anhydride. The second approach involves cyclization of 3(or 4)-acetoxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**8**, **9**) with elimination of acetic acid upon treatment with sodium hydroxide.

Keywords. 3(or 4)-Hydroxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones; 3(or 4)-Acetoxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones; 5,6-Dihydro-5,6-diphenyl-2-substituted-pyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)-ones.

Reaktionen mit Pyrrolidin-2,4-dionen, 2. Mitt.: Neue Ansätze zur Synthese von substituierten 5,6-Dihydropyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)-onen

Zusammenfassung. Es werden zwei neue Wege zur Synthese von 5,6-dihydro-5,6-diphenyl-2-substituierten Pyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)-onen (**10**) beschrieben. Der erste Weg besteht aus der Cyclodehydrierung von 3(oder 4)-Hydroxyimino-1,5-diphenyl-4(oder 3)-(4-subst.phenylhydrazono)pyrrolidin-2-onen (**4**, **7**) mit kochendem Essigsäureanhydrid. Der zweite Weg benutzt eine Cyclisierung von 3(oder 4)-Acetoxyimino-1,5-diphenyl-4(oder 3)-(4-subst.phenylhydrazono)-pyrrolidin-2-onen (**8**, **9**) unter Eliminierung von Essigsäure nach Behandlung mit Natriumhydroxyd.

Introduction

Only few reactions leading to examples of pyrrolo[3,4-d][1,2,3]triazoles have been described in the literature. Variously 1,5-disubstituted-3a,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(1*H*,5*H*)-diones have been synthesized [2–7] by 1,3-dipolar cycloaddition of organic azides with maleimide or N-substituted maleimides. On the other hand, 2-[(trialkyl or triphenyl-phorphoranylidene)amino]-5-substituted-

* Part of the work has been presented at the 8th International Congress of Heterocyclic Chemistry (August 1981), Graz, Austria

pyrrolo[3,4-d][1,2,3]triazole-4,6(2*H*,5*H*)-diones have been obtained from diazidomaleimides and alkyl- or aryl-phosphines [8]. 1-(4-Bromophenyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-d][1,2,3]triazole has been synthesized from 4-bromophenyl azide and 3-pyrroline [9]. Furthermore, the cycloaddition of several 4-substituted phenyl azides with 5-alkoxy-3-pyrrolin-2-ones afforded mixed products of the *trans*- and *cis*-1-(4-substituted phenyl)-6-alkoxy-3a,5,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-4(1*H*)-ones and their regioisomers [10].

Therefore it appeared desirable to develop new synthetic approaches to the bicyclic system enabling the preparation of a wider range of substituents for biological screening.

Results and Discussion

Continued interest in the chemistry of pyrrolidine-2,4-diones [1, 11] led us to study the usefulness of 1,5-diphenylpyrrolidin-2-one bearing two azomethine groups at the 3 and 4 positions (**4** and **7**) for the synthesis of 5,6-dihydro-5,6-diphenyl-2-substituted-pyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)-ones (**10**). Two methods were attempted for the synthesis of the desired compounds (see formula scheme). In the

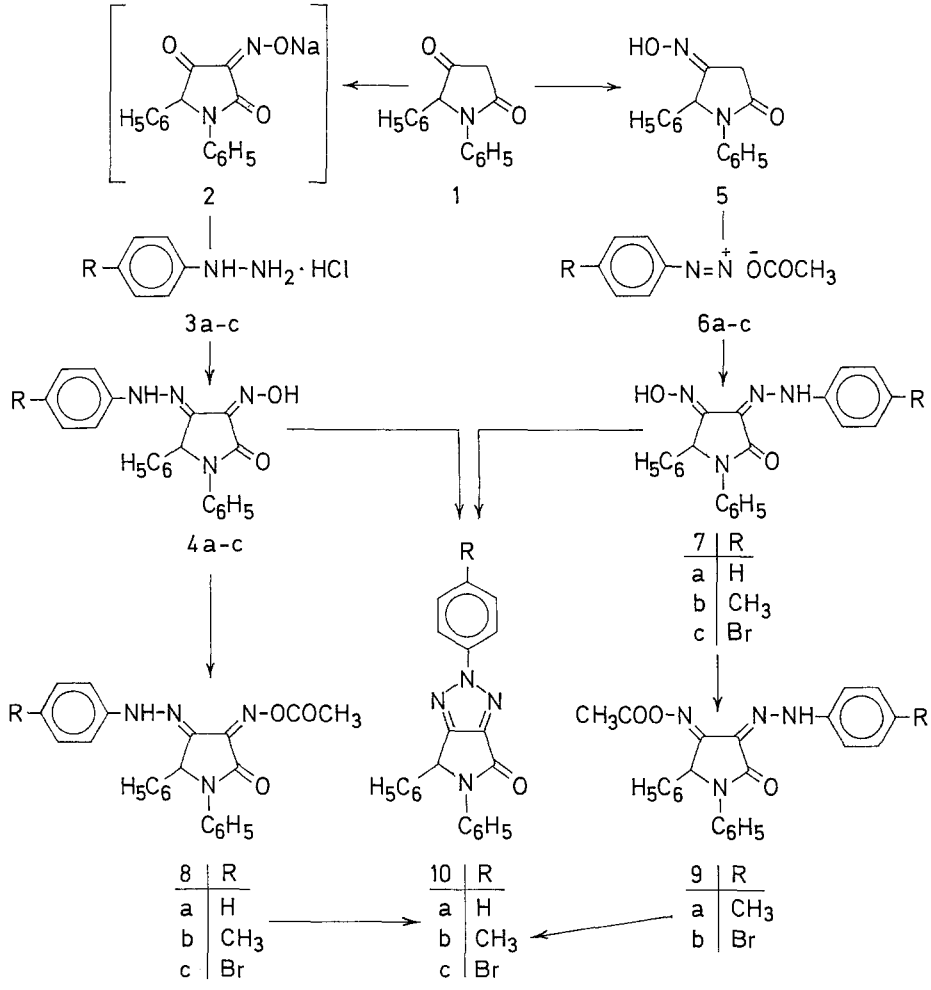

Table 1. 3(or 4)-Hydroxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**4** or **7**)

Compound	*R*	Yield %	M.p. °C	Recryst. solvent	Molecular formula
4a	H	70.2	206–208	*Et*OH	$C_{22}H_{18}N_4O_2$ (370.42)
4b	CH_3	70	300	C_6H_6-*Et*OH	$C_{23}H_{20}N_4O_2$ (384.44)
4c	Br	83.4	220	*Et*OH	$C_{22}H_{17}BrN_4O_2$ (449.32)
7a	H	45.9	227–228	aqu. *Et*OH	$C_{22}H_{18}N_4O_2$ (370.42)
7b	CH_3	36.4	256–257	C_6H_6-*Et*OH	$C_{23}H_{20}N_4O_2$ (384.44)
7c	Br	51.2	150–152	*Et*OH	$C_{22}H_{17}BrN_4O_2$ (449.32)

Table 2. 3(or 4)-Acetoxyimino-1,5-diphenyl-4(or 3)-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**8** or **9**)

Compound	*R*	Yield %	M.p. °C	Recryst. solvent	Molecular formula
8a	H	89.7	165–167	*Et*OH	$C_{24}H_{20}N_4O_3$ (412.46)
8b	CH_3	45.7	>300	*Et*OH-Et_2O	$C_{25}H_{22}N_4O_3$ (426.48)
8c	Br	45.8	115–117	C_6H_6-*Et*OH	$C_{24}H_{19}BrN_4O_3$ (491.36)
9a	CH_3	45.7	275–276	*Et*OH	$C_{25}H_{22}N_4O_3$ (426.48)
9b	Br	43.7	165	*Et*OH-Et_2O	$C_{24}H_{19}BrN_4O_3$ (491.36)

Table 3. 5,6-Dihydro-5,6-diphenyl-2-substituted-pyrrolo[3,4-d][1,2,3]triazol-4(2*H*,4*H*)-ones (**10**)

Compound	*R*	Method (Starting material)	Yield %	M.p. °C	Recryst. solvent	Molecular formula
10a	H	A (**4a**)	24.1	247–249	*Et*OH	$C_{22}H_{16}N_4O$ (352.4)
		(**7a**)	42.6			
		B (**8a**)	82.4			
		(**9a**)	42.6			
10b	CH_3	A (**4b**)	95.5	258–260	C_6H_6-*Et*OH	$C_{23}H_{18}N_4O$ (366.43)
		(**7b**)	75.0			
		B (**8b**)	42.3			
10c	Br	A (**4c**)	31.3	187–188	*Et*OH	$C_{22}H_{15}BrN_4O$ (431.31)
		(**7c**)	91.5			

first method (A), 3-hydroxyimino-1,5-diphenyl-4-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**4**) and their regioisomers 4-hydroxyimino-1,5-diphenyl-3-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**7**) were cyclized to **10** by refluxing with acetic anhydride. In the second method (B), 3-acetoxyimino-1,5-diphenyl-4-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**8**) and 4-acetoxyimino-1,5-diphenyl-3-(4-methylphenylhydrazono)pyrrolidin-2-one (**9a**) underwent cycloelimination of acetic acid to the corresponding **10a** and **b** upon heating with sodium hydroxide solution. The crude products were more easily purified than

Table 4. ^{1}H-NMR Data of some compounds of the **4**, **8**, and **10** series

Compound	δ (ppm)
4a	6.1 (s, H at C-5), 6.9–7.6 (m, 15 aromatic H)[a]
4c	5.95 (s, H at C-5), 6.8–6.7 (m, 14 aromatic H)[b]
8a	2.35 (s, CH_3), 6.32 (s, 1/2 H at C-4 in the phenylazo tautomer), 6.5 (s, H at C-5), 6.8–7.8 (m, 15 aromatic H), 10.15 (s, 1/2 H, NH in the phenylhydrazone tautomer)[c]
10a	6.3 (s, H at C-6), 7.0–8.1 (m, 15 aromatic H)[a]
10b	2.25 (s, CH_3), 6.12 (s, H at C-6), 6.8–7.8 (m, 14 aromatic H)[a]

[a] In trifluoroacetic acid
[b] In deuteriochloroform
[c] In hexadeuteriodimethylsulfoxide

those obtained by method A. Trials to prepare the bromo compound **10c** from **8c** or **9b** were unsuccessful. Excellent yields of compounds **10a**, **b** and **c** were obtained from their parent compounds **8a**, **4b** and **7c**, respectively. The parent 3-hydroxyimino-1,5-diphenyl-4-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**4**) were prepared by reacting **1** with sodium nitrite in aqueous ethanol followed by treating the intermediate 3-hydroxyimino-1,5-diphenylpyrrolidine-2,4-dione sodium salt (**2**) with 4-substituted phenylhydrazine hydrochlorides (**3**). The 4-hydroxyimino-1,5-diphenyl-3-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**7**) were also prepared from **1** by sequential oximation and coupling the oxime **5** with the proper diazotized amine **6**. Acetylation of **4** and **7b**, **c** under mild conditions afforded the corresponding acetoxyimino derivatives **8** and **9a**, **b**, respectively. Synthetic data for the compounds are summarized in Tables 1–3, the ^{1}H-NMR data of representative compounds of the **4**, **8** and **10** series are recorded in Table 4.

Experimental Part

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Beckman 4210 or a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The ^{1}H-NMR spectra were measured on a Varian EM 360 spectrometer using *TMS* as an internal standard. Microanalyses, for samples dried over phosphorus pentoxide at 70° under reduced pressure, were carried out at the Microanalytical Unit, University of Cairo, A. R. Egypt; they agree within experimental error with the values calculated.

3-Hydroxyimino-1,5-diphenyl-4-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**4a–c**, *Table 1*)

A solution of sodium nitrite (0.14 g, 2 mmol) in water (5 ml) was added to a solution of **1** [11] (0.5 g, 2 mmol) in ethanol (10 ml) and the mixture warmed for 5 min and cooled to room temperature. To the resulting wine-red reaction mixture, a solution of **3** (2 mmol) in water (5 ml) was added while stirring; an immediate turbidity was formed followed by precipitation of the product. After stirring for 2.5 h at room temperature, water was added (5 ml), the product filtered, washed with water, air dried and crystallized from the proper solvent. IR of **4a** and **c**: 3 500–2 800 bm (OH and NH), 1 685–1 670 s (CO), 1 595–1 590 m (C=N), 1 560–1 545 s cm^{-1} (C=C and aromatics).

4-Hydroxyimino-1,5-diphenyl-3-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**7a–c**, *Table 1*)

The appropriate aniline derivative (2 mmol) was dissolved in acetic acid (5 ml) and the solution was cooled to 5°. A cooled solution of sodium nitrite (0.14 g, 2 mmol) in water (2 ml) was added and the resulting diazonium acetate (**6**) solution was filtered onto a stirred solution of **5** [11] (0.53 g, 2 mmol) in glacial acetic acid (10 ml) at 10°. After stirring at room temperature for 1 h, water was added and the precipitated yellowish to orange product was filtered, washed with water, air dried and crystallized. IR of **7a** and **b**: 3300–2700 bm (OH and NH), 1670 s (CO), 1590 m (C=N), 1560 s cm^{-1} (C=C and aromatics).

3-Acetoxyimino-1,5-diphenyl-4-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**8a–c**, *Table 2*)

The appropriate **4** (2 mmol) was dissolved in acetic anhydride (3 ml) by gentle warming and the resulting solution was allowed to stand at room temperature for 24 h. Subsequently, water was added and the oily product was set aside to solidify. The crude product was filtered, washed with water, air dried and crystallized from the suitable solvent. IR of **8a** and **b**: 3040 w (NH), 1775 s (CO-acetyl), 1710 s (C_2O), 1600 m (C=N), 1550 m cm^{-1} (C=C and aromatics).

4-Acetoxyimino-1,5-diphenyl-3-(4-substituted phenylhydrazono)pyrrolidin-2-ones (**9a, b**, *Table 2*)

These were likewise prepared from **7b, c** (2 mmol) and acetic anhydride (3 ml). IR of **9b**: 3100–2800 w (NH), 1790 m (CO-acetyl), 1710 s (C_2O), 1600 w (C=N), 1550 m cm^{-1} (C=C and aromatics).

5,6-Dihydro-5,6-diphenyl-2-substituted-pyrrolo[3,4-d][1,2,3]triazol-4(2H,4H)-ones (**10a–c**, *Table 3*)

Method A for **10a–c**: The appropriate **4** or **7** (2 mmol) was refluxed with acetic anhydride (5 ml) for 30 min. Subsequently, the dark brown solution was poured onto cold saturated sodium bicarbonate solution and the precipitated dark colored product was filtered, washed with water, air dried and purified by repeated crystallizations from the proper solvent.

Method B for **10a** *and* **b**: The appropriate **8a, b** or **9a** (2 mmol) was warmed with 1 *N* sodium hydroxide (25 ml), while stirring, for 20 min. During this period the orange color of the starting material turned to pale yellow. After cooling, the product was filtered, washed with water, air dried and crystallized. IR: 1700–1710 s (CO), 1590–1600 m-w (C=N), 1550–1545 m-w cm^{-1} (C=C and aromatics).

References

[1] Part I: Soliman F. S. G., Kappe T. (1982) Monatsh. Chem. **113**: 475
[2] Mustafa A., Zayed S. M. A. D., Khattab S. (1956) J. Amer. Chem. Soc. **78**: 145
[3] Davis S. J., Rondestvedt Jr. C. S. (1956) Chem. Ind. (London): 845
[4] Awad W. I., Omran S. M. A., Nagieb F. (1963) Tetrahedron **19**: 1591
[5] Tamura Y., Chun M. W., Ohno K., Kwon S., Ikeda M. (1978) Chem. Pharm. Bull. (Japan) **26**: 2874
[6] Kartsev V. G., Pokidova T. S., Nabatov A. S., Dovgilevich A. V. (1984) Khim. Geterotsikl. Soedin.: 514; (1984) C. A. **101**: 90840e
[7] Washburne S. S., Peterson Jr. W. R., Berman D. A. (1972) J. Org. Chem. **37**: 1738
[8] Mosby W. L. (1966) U.S. Pat. 3,278,546; (1967) C. A. **66**: 11043k
[9] Scheiner P. (1968) Tetrahedron **24**: 2757
[10] Kasugi Y., Hamaguchi F. (1984) Heterocycles **22**: 2368
[11] Soliman F. S. G. (1977) Pharmazie **32**: 572

Received January 15, 1990. Accepted March 6, 1990