A SYNTHESIS OF 1,2,4-TRIAZOLO[1,5-f]PHENANTHRIDINES BY REARRANGEMENTS OF 1,2,5-OXADIAZOLES INVOLVING AN NCN SEQUENCE WITH THE IMINE NITROGEN IN AN AROMATIC HETEROCYCLIC RING

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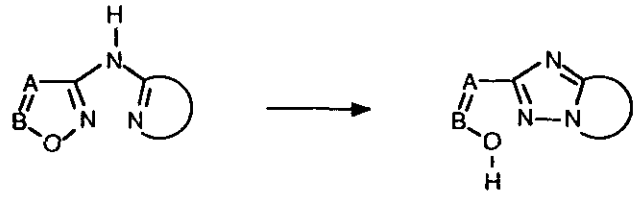
Abstract — A synthetic pathway to 1,2,4-triazolo[1,5-f]phenanthridine system by a base catalyzed rearrangement of 3-(6-phenanthridine)-amino-1,2,5-oxadiazoles (**5a,b**) has been investigated. This ring transformation is the first example of the applicability of the mononuclear heterocyclic rearrangement involving an **NCN** sequence to the synthesis of bridged nitrogen systems.

In previous researches, we have reported a new method for the synthesis of nitrogen containing polycondensed heterocyclic systems, through an initial 6 π electrocyclic reaction involving a hydrazone side chain of a five membered heterocycle, followed by ring opening and ring closure processes.[1-4]

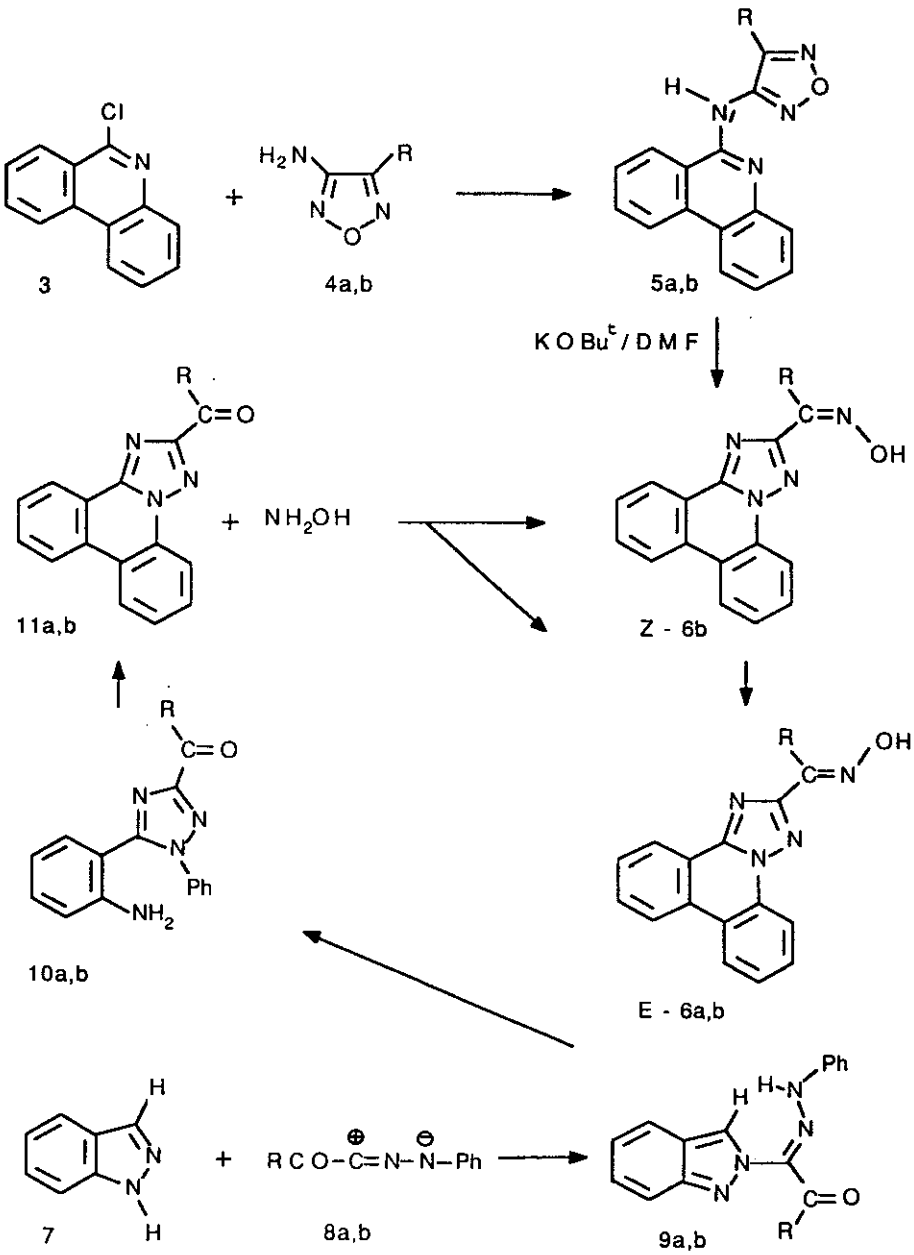
The present paper describes the results of our researches aimed to annelate polycondensed heterocyclic ring through an alternative synthetic route. The key step of this new method, as depicted in the Scheme 1, is the rearrangement of the type **1** ——> **2**.



1 2

Scheme 1

This rearrangement shows a close resemblance with the previously reported rearrangement of arylformamidinoazoles into 1,2,4-triazole derivatives.[5-8] In the present case the nucleophilic imine nitrogen of the formamidino side-chain is incorporated in an aromatic heterocyclic ring.



a: R = Me; b: R = Ph

Scheme 2

As an approach to examine the proposed route to azapolycondensed systems attention was directed towards the study of the rearrangement reactions leading to the known 1,2,4-triazolo[1,5-f]phenanthridine system, previously synthesized through the addition - rearrangement method.[1]

An access to the starting 3-(N-heteroaryl)aminoazoles involved the nucleophilic replacement of halogen atom by 3-aminoazoles. Taking into consideration that such nucleophilic substitution takes place from 6-chlorophenanthridine (3) only when the reactants are heated beyond their melting point[9] and that the 1,2,5-oxadiazole ring has a low reactivity towards mononuclear heterocyclic rearrangements,[8] we thought of heating 3-amino-1,2,5-oxadiazoles (**4a,b**) and **3** to obtain the intermediate 3-(6-phenanthridine)amino-1,2,5-oxadiazoles (**5a,b**). Compounds (**5a,b**) should not rearrange in such thermal conditions.

In fact the amino derivatives (**5a,b**) were obtained in high yield from equimolar amounts of 6-chlorophenanthridine (**3**)[10] and 3-amino-4-methyl-1,2,5-oxadiazole (**4a**)[11] or 3-amino-4-phenyl-1,2,5-oxadiazole (**4b**)[12] by heating the mixture in an oil bath at 110-140 °C for 1 h and subsequently at 160-180 °C for 1 h.

The transformation of the amino derivatives (**5a,b**) was carried out by refluxing in anhydrous DMF with equimolar amounts of potassium t-butoxide and the products (**6a,b**) were obtained in 90-92% yield (see Experimental). In order to verify the structures of the rearrangement products, the oximes (**6a,b**) were synthesized by oximation reaction of 2-acyl-1,2,4-triazolo[1,5-f]phenanthridines (**11a,b**), obtained by the addition-rearrangement method outlined in Scheme 2. The rearrangement of **5a** afforded only the oxime (**E-6a**) identical with the oxime obtained through the oximation reaction of **11a**; on the other hand, the rearrangement of **5b** led to a mixture of **E-** and **Z-6b** identical with the oximation mixture of 2-benzoyl-1,2,4-triazolo[1,5-f]phenanthridine (**11b**).[13] In the ir spectra of compounds **6**, the O-H stretching bands at 3270 cm^{-1} and 3180 cm^{-1} are indicatives for E and Z isomers, respectively. However, in the ^1H nmr spectra in DMSO solution, the OH protons of both **E** and **Z** isomers of the oxime (**6b**) appeared as a broad signal at low field.

The present ring transformation is the first example of the applicability of the mononuclear heterocyclic rearrangement of type **1** ——> **2** to the synthesis of bridged nitrogen systems. The success of this method seems to depend on the ease of the formation of an **N-N** bond through an electrocyclic reaction of the conjugate anion of compounds **5**.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mull) were recorded on a Perkin-Elmer infrared spectrophotometer (model 297); uv spectra (ethanol) were determined with a Varian Superscan 3 spectrophotometer; ^{1}H nmr spectra were recorded on a Varian EM 360 spectrometer. Chemical shifts are reported as δ values (ppm) relative to TMS as internal standard. Hplc analyses were performed with a Perkin-Elmer Series 10 instrument, by using a C-18 SIL-X-10 Perkin-Elmer column, eluting with methanol, and a Silica 50-10 Perkin-Elmer column, eluting with dichloromethane/ethyl acetate.

General Method for the Preparation of the 3-(6-Phenanthridine)amino-1,2,5-oxadiazoles (**5a,b**).

A mixture of 6-chlorophenanthridine (**3**)[10] (300 mg, 1.4 mmol) and equimolar amounts of 3-amino-4-methyl- (**4a**)[11] or 3-amino-4-phenyl-1,2,5-oxadiazole (**4b**)[12] was heated in an oil bath at 110° or 140° for 1 h. The reaction mixture was then kept for 1 h at 160° or 180°. After cooling this mixture was triturated with a minimum amount of chloroform and the resultant solid filtered off.

Compound **5a** (R = Me) colourless needles from DMF/H_2O (yield 77%), mp 170°C; ir: ν_{max}: 3270, 3190 cm^{-1} (NH), 1635, 1605 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6) δ : 2.40 (s, 3H, CH_3), 7.2-8.1 (m, 5H, H-2,3,4,8,9), 8.2-8.9 (m, 3H, H-1,7,10), 10.90 (broad s, 1H, NH). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.37; H, 4.27; N, 20.33.

Compound **5b** (R = Ph) colourless needles from DMF (yield 71%), mp 245°C; ir: ν_{max}: 3260, 3190 cm^{-1} (NH), 1625, 1605 cm^{-1} (C=N). Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.48; H, 4.21; N, 16.61.

Rearrangement of the Amine (**5a**) into the **E** Oxime of 2-Acetyl-1,2,4-triazolo-[1,5-f]phenanthridine (**6a**).

A mixture of **5a** (200 mg, 0.72 mmol) and equimolar amounts of potassium t-butoxide (81 mg, 0.72 mmol) in dry DMF (10 ml) was heated at 120-140° for 5 min. After cooling, the **E**-oxime of 2-acetyl-1,2,4-triazolo[1,5-f]phenanthridine (**6a**) (180 mg, 90%) was filtered off. Colourless needles from DMSO/H_2O, mp 270°C;

ir: ν_{max}: 3270 cm^{-1} (OH), 1610, 1595 cm^{-1} (C=N); ^1H nmr (DMSO-d_6) δ : 2.40 (s, 3H, CH_3), 7.5-8.1 (m, 4H, H-5,8,9,12), 8.3-8.9 (m, 4H, H-6,7,10,11), 11.80 (very broad, 1H, NOH). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.43; H, 4.41; N, 20.37.

Rearrangement of the Amine (**5b**) into the **E** and **Z** Oximes of 2-Benzoyl-1,2,4-triazolo[1,5-f]phenanthridine (**6b**).

A mixture of **5b** (200 mg, 0.59 mmol) and equimolar amounts of potassium t-butoxide (66 mg, 0.59 mmol) in dry DMF (10 ml) was heated at 120-140° for 2 h. After cooling, dilution with water (10 ml) gave a crude product which turned out (hplc) to be a mixture of the **E** and **Z** isomers of the oxime of 2-benzoyl-1,2,4-triazolo[1,5-f]phenanthridine (**6b**) (184 mg, 92%), mp 283-285°C; ir: ν_{max}: 3270, 3180 cm^{-1} (E and Z OH), 1610, 1590 cm^{-1} (C=N); ^1H nmr (DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 7.2-8.2 (m, 9H, H-7,8,10,11 and C_6H_5), 8.2-9.0 (m, 4H, H-5,8,9,12), 12.20 (broad s, 1H, NOH). A sample of this product was crystallized from DMF/H_2O, mp 282°C. Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.63; H, 4.24; N, 16.51.

Preparation of 2-Acylindazole Phenylhydrazones (**9a,b**).

Phenylhydrazones (**9a,b**) were prepared according to the procedure described previously for **9a**,[1] by treatment of indazole with equimolar amounts of suitable hydrazidoyl chloride[14] and threefold excess of triethylamine.

Compound **9a** (R = Me) was crystallized from ethanol (yield 93%), mp 140°C.[1]

Compound **9b** (R = Ph) was purified by column chromatography on silica gel (eluent cyclohexane/dichloromethane 2:1) and recrystallized from ethanol (yield 75%), mp 136°C; ir: ν_{max}: 3180 cm^{-1} (NH), 1640 cm^{-1} (CO); uv: λ_{max} nm (log ε): 244 (4.44), 298 (4.27), 377 (4.33); ^1H nmr ($CDCl_3$) δ : 6.7-8.6 (m, 10H, ArH), 7.72 (m, 2H, H-5 and H-6), 7.98 (m, 2H, H-4 and H-7), 8.92 (s, 1H, H-3), 13.20 (s, 1H, NH); (DMSO-d_6) δ : 8.70 (s, 1H, H-3), 11.73 (s, 1H, NH). Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.23; H, 4.78; N, 16.39.

Rearrangement of Phenylhydrazones (**9a,b**) into 1,2,4-Triazole Derivatives (**10a,b**)

Triazoles (**10a,b**) were prepared following the procedure previously described for **10a**[1] by refluxing **9a,b** (0.5 g) with conc. HCl (0.5 ml) in ethanol (20 ml) for two days. Evaporation of the solvent under reduced pressure, repeated additions of benzene to the residue and further evaporation under reduced pressure gave

10a,b as hydrochlorides. The corresponding free bases were obtained by column chromatography (eluent cyclohexane/ethyl acetate 4:1) of a chloroform solution of equimolar amounts of **10a** hydrochloride and triethylamine and by treating an ethanol solution of **10b** hydrochloride with aqueous ammonia (30%).

1-Phenyl-5-(o-aminophenyl)-3-acetyl-1,2,4-triazole (**10a**) (R = Me) : mp 139-141°C.[1]

1-Phenyl-5-(o-aminophenyl)-3-benzoyl-1,2,4-triazole (**10b**) (R = Ph) : mp 150°C (ethanol) (yield 69%); ir: ν_{max}: 3420, 3320 cm^{-1} (NH_2), 1669 cm^{-1} (CO); uv: λ_{max} nm (log ε): 260(4.24), 323(3,64); ^1H nmr ($CDCl_3$) δ : 4.75 (br s, 2H, NH_2), 6.3-7.6 (m, 12H, ArH), 8.33 (m, 2H, ArH). Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.08; H, 4.71; N, 16.49.

Preparation of the 2-Acetyl- and 2-Benzoyl-1,2,4-triazolo[1,5-f]phenanthridines (**11a,b**)

Compounds **11a,b** were prepared by the procedure previously described for **11a**.[1]

2-Acetyl-1,2,4-triazolo[1,5-f]phenanthridine (**11a**) (R = Me) was crystallized from ethanol (yield 85%), mp 207-208°C.[1]

2-Benzoyl-1,2,4-triazolo[1,5-f]phenanthridine (**11b**) (R = Ph) was crystallized from ethanol (yield 94%), mp 225°C; ir: ν_{max}: 1620, 1595 cm^{-1} (C=N), 1665 cm^{-1} (CO); uv: λ_{max} nm (log ε): 242s (4.73), 248 (4.83), 278s (4.36), 312s (3.79), 328 (3.61); ^1H nmr ($CDCl_3$) δ : 7.2-7.9 (m, 7H, H-6,7,10,11, meta- and para-H of COC_6H_5), 8.1-8.8 (m, 6H, H-5,8,9,12 and ortho-H of COC_6H_5). Anal. Calcd for $C_{21}H_{13}N_3O$: C, 78.00; H, 4.05; N, 13.00. Found: C, 78.18; H, 4.03; N, 12.89.

General Procedure for the Preparation of the Oximes (**6a,b**) from Hydroxylamine on Ketones (**11a,b**).

To a solution of hydroxylamine hydrochloride (70 mg, 1 mmol) and sodium acetate (82 mg, 1 mmol) in ethanol (30 ml) 1 mmol of **11a** or **11b** was added and the *suspension heated under reflux for 8 h.* After cooling, the solid was filtered off and washed with ethanol to give **E** oxime (**6a**) (ir and hplc) or a mixture of **E** and **Z** isomers of the oxime (**6b**) (ir and hplc).

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