Pyridopyridazines, Benzimidazolopyrimidines Triazolopyrimidines, 9-Oxo-2,3,6,7-tetraazabicyclo[3.3.1]nona-3,7-diene and Aroylcnolinones from 2-Arylhdyrazono-3-oxopropanals

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The reaction of the 2-arylhydrazonopropanal 3a with 2-amino1,1,3-tricyanopropene 4 afforded the pyridopyridazines 6. On the other hand, reaction of 3b with 4 afforded 7. Compounds 3a,b also condensed with 2-aminobenzimidazole and 3(5)-amino-1,2,4-triazole to yield azolopyrimidines 10 and 13. Refluxing compounds 3a,b in acetic acid in the presence of ammonium acetate afforded 2,3,6,7-tetraazabicyclo[3.3.1]nona-3,7-diene 14 and aroylcnoline 15 respectively.

Key words: 2-Arylhdyrazonopropanals, Pyridopyridazines, Aminotriazole, Azolopyrimidines, Aroylcnoline

Introduction

Significant commercial interest in the development of benzopyridazine derivatives, in particular with regard to pharmaceutical applications of pyridazines and cinnolines is shown by the large number of patents filed in this area [1]. For example, cinoxacine 1 [2] is a cinnoline analogue of quinoline antibacterials used for urinary tract infection. ICI-D-7569 2 [3] is an anxiolytic agent. 2-Arylhdyrazono-3-oxopropanals are versatile reagents and their utility in heterocyclic synthesis has recently received considerable interest [4 – 6]. In previous work from our laboratories, we have reported a high yield synthesis of o-substituted-2-arylhdyrazonopropanals and reported on their potential as building blocks in heterocyclic chemistry [7 – 9].

Results and Discussion

In conjunction with this work we report here results of our further investigation aimed at exploring the potential of 2-arylhdyrazonopropanals 3a,b, in heterocyclic synthesis [10, 11]. It has been found that 3a readily condenses with 2-amino-1,1,3-tricyanopropene (4) yielding product of condensation via water elimination. Based on spectral data, IR and 13C NMR, compound 5 was established. On the other hand reaction of 3b with 4 afforded 6 (Scheme 1).

The reaction of 3a,c with 2-aminobenzimidazole (7) in refluxing ethanol afforded a condensation product, which was assigned as 8a,b based on 1H NMR spectral data which revealed the absence of a formyl signal.
When this product was refluxed in AcOH it cyclized smoothly via water elimination affording 9a,b (Scheme 2).

The reaction of 3a,c with 5-amino-1H-1,2,4-triazole (10) afforded the condensation product 11. 1H NMR data revealed the presence of two singlet at \( \delta = 8.5 \) trizol NH and \( \delta = 15.2 \) for hydrazone NH (Scheme 3).

Refluxing 11 in AcOH afforded the 1,2,4-triazololo[1,5-a]pyrimidene structure 12. The 1H NMR spectrum indicated a triazole singlet at \( \delta = 8.8 \) ppm shifted to lower field by almost \( \delta 1.0 \) ppm compared to the triazole signal in the parent amino triazole.

It could thus be demonstrated that compounds 3a,c are variable precursors of condensed pyridazines and also of arylazo azolopyrimidines (Scheme 3).

In an attempt to condense 3a with 5-methyl-2,4-dihydro-pyrazol-3-one 13 in the presence of acetic acid and ammonium acetate a new compound with the molecular formula C\(_{32}\)H\(_{20}\)N\(_6\)O\(_2\) was obtained based on mass spectra MS = 536 and X-ray analysis. The reaction takes place via condensation of two molecules of 3a. The hydrazone NH of one molecule attacks the formyl carbonyl carbon of a second molecule, followed by elimination of water to give 14 (Scheme 4). The initial step in this cyclization is the condensation of the formyl group with the amine to yield an intermediate enaminoazo product which then undergoes 6\(\pi\)-electrocyclization into a dihydrcinnoline which in turn aromatizes to the final product. A similar mechanism has been recently established by Al-Awadi et al. [12].

In contrast to this behavior compound 3b cyclized into 15 [12, 13]. The different behavior of 3a and 3b may be effected by the nature of the substituent of the aryl moiety.

To our knowledge, this is first reported example of the formation of 4,8-dibenzoyl-2,6-di(2-cyanophenyl)-9-oxo-2,3,6,7-tetra-azabicyclo[3.3.1]nona-3,7-dienes such as 14. The reactions took place without involvement of 5-methyl-2,4-dihydro-pyrazol-3-one. When the reactions were repeated in the absence of 5-methyl-2,4-dihydro-pyrazol-3-one, the products obtained were found identical with those obtained before (mp, mix.
mp, and TLC). Product 14 was recrystallized and its structure was solved by X-ray diffraction (Fig. 1).

**Experimental Section**

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP-300 Spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d$_6$) at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as an internal reference. Results are expressed as $\delta$ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The crystal and molecular structure was determined by X-ray diffraction from a single crystal.

**General procedure for the preparation of 5, 6**

A solution of compound 3a,b (0.1 mol) in ethanol (30 ml) was treated with 2-amino-l-propane-1,1,3-tricarbonitrile 4 (0.1 mol) in the presence of few drops of piperidine. The reaction mixture was refluxed for 3 h. The solid products were isolated by filtration, washed with ethanol and dried. Products were recrystallized from a single crystal.

**5-Amino-3-benzoyl-1-(2-cyanophenyl)-7-imino-l,7-dihydro-pyrido[2,3-c]pyrimidine-6-carbonitrile (5)**

Compound 5 was obtained as dark red crystals (85%), m. p. > 300 °C. IR: $\nu_{\text{max}}$(KBr) 3460(NH$_2$), 3377(NH), 3174(NH), 3064, 2930, 2864, 1973 cm$^{-1}$ (C=O); MS [EI, 70 eV]: $m/z$ = [M$^+$]$^+$ (77(398), 105(30.8%), 118(13.9%), 222(28.0%), 313(100%).) $\delta$ = 8.18 – 8.20 (m, 13H, arom-H); 9.4 (s, 1H, CH olefinic), 12.13 (s, 1H, NH imidazole) and 15.9 ppm; (s, H, NH). General procedure for the preparation of 8a,b

**8a**

A solution of compound 3a,c (0.1 mol) in acetic acid (10 ml) was refluxed for 3 h. The solid products were isolated by filtration, washed with ethanol and dried. Products were recrystallized from ethanol.

**2-(2-Cyanophenylhydrazono)-3-(benzimidazol-2-ylamino)-l-phenyl-l-propanone (8a)**

Compound 8a was obtained as orange crystals (84%), m. p. 193 °C. IR: $\nu_{\text{max}}$(KBr) (show complex spectra due to H-bond between O and NH), 3354 (NH imidazole), 2220 (CN), 1640 cm$^{-1}$ (C=O ketone); $^1$H NMR (200 MHz, DMSO-d$_6$): $\delta$ = 6.97 – 8.03 (m, 13H, arom-H); 9.4 (s, 1H, CH olefinic), 12.13 (s, 1H, NH imidazole) and 15.9 ppm; (s, H, NH). General procedure for the preparation of 9a,b

**9a**

A solution of 8a or 8b (0.1 mol) in acetic acid (10 ml) was refluxed for 2 h, then left cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol.

**3-Amino-1-cyano-2-(2-benzoyl-6-oxopyridazino[2,3-c]pyridazine 723**
3-(2-Cyanophenylazo)-4-phenylpyrimidino[1,2-a]benzimidazole (9a)

Compound 9a was obtained as orange crystals (78%), m.p. 148 °C. 1H NMR (200 MHz, DMSO-d6): δ = 7.15 – 7.94 (m, 13H, arom-H), 9.36 ppm (s, 1H, H-2); 13C NMR (200 MHz, DMSO-d6): δ = 151.8 (C-2), 144.2 (C-3), 142.6 (C-4), 137.9 (C-5a), 127.0 (C-6), 122.9 (C-7), 118.4 (C-9), 143.7 (C-10a), 116.5 (C=N), 129.0 (13.01, 134.3, 136.7 (phenyl carbons); 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 ppm (C6H4CN); MS [E]I, 70 eV): m/z = [M+1] (374). Analysis for C23H14N6: calcd. C 66.30, H 3.18, N 30.52; found C 66.30, H 3.04, N 30.52. General Procedure for the preparation of 11a, b

A mixture of compounds 3a,c (0.1 mol) and 3-amino-1,2,4-triazole (0.1 mol) was refluxed in ethanol or dioxan (30 ml) for 2 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol.

2-(2-Cyanophenylhydrazone)-3-(1,2,4-triazol-3-ylimino)-1-phenylpropanone (11a)

Compound 11a was obtained as yellow crystals (87%), m.p. 235 °C. IR: νmax(KBr) (show complex spectra due to keto-enol forms with H-bond between O and NH); 1H NMR (200 MHz, DMSO-d6): δ = 6.97 – 8.03 (m, 9H, arom-H); 8.12 (s, 1H, CH olefinic), 8.54 (s, 1H, 1,2,4-triazole NH), 9.35 (s, 1H, 1,2,4-triazole H-5) and 15.26 ppm (s, 1H, NH triazole), 2220 (C≡N) and 1640 cm⁻¹ (C≡O ketone); 1H NMR (200 MHz, DMSO-d6): δ = 7.23 – 7.97 (m, 5H, thienyl H-5 and 4H, arom-H), 8.18 – 8.20 (m, 2H, thienyl H-3, H-4), 8.42 (s, 1H, OHolefinic), 8.74 (s, 1H, 1,2,4-triazole NH), 9.35 (s, 1H, 1,2,4-triazole H-5) and 15.26 ppm (s, 1H, NH hydrazone); 13C NMR (200 MHz, DMSO-d6): 116.0 (C=N), 116.80, 117.18, 124.87, 131.98, 133.96, 135.41 (C6H4-CN), 122.8, 125.3, 127.5, 142.6 (thienyl carbons), 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 ppm (C6H4-CN); MS [E]I, 70 eV): m/z = [M+1] (380). Analysis for C18H12N7O: calcd. C 62.97, H 3.18, N 30.0. General Procedure for the preparation of 14, 15

A mixture of compounds 3a,b (0.1 mol) and 5-methyl-2,4-dihydro-pyrazol-3-one (0.1 mol) in glacial acetic (30 ml) and (0.1 mol) of ammonium acetate, was refluxed for 3 h. The precipitated material was isolated by filtration and recrystallized from ethanol.
4,8-Dibenzoyl-2,6-di(2-Cyanophenyl)-9-oxo-2,3,6,7-tetraazabicycle[3.3.1]nona-3,7-diene (14)

Compound 14 was obtained as dark yellow crystals (87%), m.p. 260 °C. 1H NMR (200 MHz, DMSO-d6): δ = 4.01 (2s, 2H, CH); 6.41 – 8.03 ppm (m, 18H, arom-H); 13C NMR (200 MHz, DMSO-d6): δ = 190.0 (CO), 77.8 (C-1), 154.0 (C-4), 117.8 (C≡N), 96.3, 113.0, 117.0, 132.8, 134.8, 147.0 (G2H3CN); 129.0, 130.1, 134.3, 136.7 ppm (phenyl carbons); MS [EI, 70 eV]: m/z = [M+] (536). Analysis for C32H20N6O3: calcd. C 71.89, H 3.81, N 15.71; found C 71.63, H 3.76, N 15.66.

4-Amino-3-benzoyl-cinnoline-8-carboxylic acid methyl ester (15)

Compound 15 was obtained as pale brown crystals (85%), m.p. 210 °C. 1H NMR (200 MHz, DMSO-d6): δ = 4.2 (s, 3H, CH3), 5.21 (b, s, 2H, NH2), 7.53 – 8.60 ppm (m, 8H, arom-H); 13C NMR (200 MHz, DMSO-d6): δ = 50.0 (CH3), 168.0 (CO), 137.4 (C-3), 141.0 (C-4), 118 (C-4a), 127.6 (C-5), 130.4 (C-6), 138.4 (C-7), 128.8 (C-8), 151.4 (C-8a), 193.6 (C-9), 137.0 (C-10), 131.8 (C-11), 129.3 (C-12), 134.3 ppm (C-13); MS [EI, 70 eV]: m/z = [M+] (307). Analysis for C17H13N3O3: calcd. C 66.23, H 4.27, N 13.70; found C 66.44, H 4.26, N 13.67.