A New Route for the Synthesis of 1,2,4-Triazole and 3,4-Disubstituted Cinnoline Derivatives

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Summary: The behaviour of 4-aryl-hydrazono-2-phenyl-2-oxozolin-5-one towards phenols, aromatic amines, 1,2,4-triazol-5-amino and acylhydrazines to give the 1,2,4-triazol derivatives have been studied. Fries rearrangement products have been obtained by refluxing the products resulting from the starting material and phenols or amines with anhydrous zinc chloride and acetic acid. Reactions of Fries rearrangement products with malononitrile have also been studied. Interestingly, reaction of oxazolinone derivative with or without acetophenone give one and the same product benzoylamino-6-methyl-cinnolin-4-ol. The mechanism of the later reaction has been discussed. The structure of the products has been studied by different spectroscopic methods.

Introduction

In continuation of the recent studies [1-3] to synthesize polyfunctionally substituted 1,2,4-triazoles through the reaction of 4-arylhydrazono-2-phenyl-2-oxazolin-5-ones with amines, carbanions and with thiophenol, the behaviour of 4-aryl-hydrazono-2-phenyl-2-oxazolin-5-one towards phenols, aromatic amines, 1,2,4-triazol-5-amino and acyl hydrazines to give the 1,2,4-triazol derivatives has now been studied.

In the present investigation, the authors used a newly developped efficient method for the preparation of 4-*p*-tolylhydrazono-2-phenyl-2-oxazolin-5-one (1) via cyclization hippuric acid by action of acetic anhydride and coupling the so-formed 2-phenyl-2-oxazolin-5-one (2) with diazotised *p*-toluidine in acetic acid in the presence of sodium acetate.

The 4-*p*-tolylhydrazino-2-phenyl-2-oxazolin-5-one (1) is used as starting material for the preparation of new heterocyclic compounds. The various compounds prepared are outlined in Scheme-1.

Thus, treatment of 1 with phenols, namely, phenol, resorcinol, 1-naphthol and/or 2-naphthol give rearranged product 1-*p*-tolyl-5-phenyl 1(H) 1,2,4-triazol carboxylate derivatives (**3a-d**). The structure of **3a-d** was derived from their IR* spectra which showed νC=O ester at 1725-1735 in addition to νOH for compounds **3b** at 3200. Structure of **3** was further established by refluxing **3a** with acetic acid in the presence of conc. HCl to give the hydrolysed products phenol and 1-*p*-tolyl-5-phenyl-1(H)-1,2,4-triazol-3-carboxylic acid (**3e**).

Rearrangement of compounds **3a-c** can be achieved by refluxing these compounds in acetic acid in the presence of anhydrous zinc chloride to give Fries rearrangement products, 1-*p*-tolyl-5-phenyl-1(H)-1,2,4-triazol-3-yl-2-hydroxylphenyl ketone derivatives (**4a,4b** and **5**), respectively. The IR spectra of **4a,4b** and **5** showed νOH at 3000-3600, and νC=O at 1670-1725. The ^{1}H-NMR (DMSO-d_6) of **4b** showed signal at δ 8.3 and 8.2 (2H, 2s, 2OH), 7.6-7.0 (12H, m, ArH), 2.2 (3H, s, CH_3).

The structure of the Fries rearrangement products **4a,4b** and **5** was further established by its reaction with malononitrile in boiling acetic acid and dry benzene containing ammonium acetate to give the corresponding 1-*p*-tolyl-5-phenyl-3-(3-cyanocoumarines)4-yl-1H-1,2,4-triazol derivatives (**6a, 6b** and **7**) respectively. Their IR spectra showed νC ≡N at 2200 and νC=O at 1630-1660. The ^{1}H-NMR (DMSO-d_6) of **6a** exhibited signals at δ 7.6-7.0 (13H, m, ArH) and 2.25 (3H, s, CH_3).

Compound **1** was also rearranged on treatment with aromatic amines namely, *p*-toluidine and 1-naphthylamine to give compounds 1-*p*-toly-5-phenyl-1-(H)-1,2,4-triazol-3-yl-3(carboxy-*p*-toluidine) (**8**) and 1-*p*-tolyl-5-phenyl-1(H)-1,2,4-triazol-3-yl-3(1-naphthylcarboxamide) (**9**). The IR spectra of **8** and **9** showed νC=O at 1700, νC=C at 1600 and νNH at 3400.

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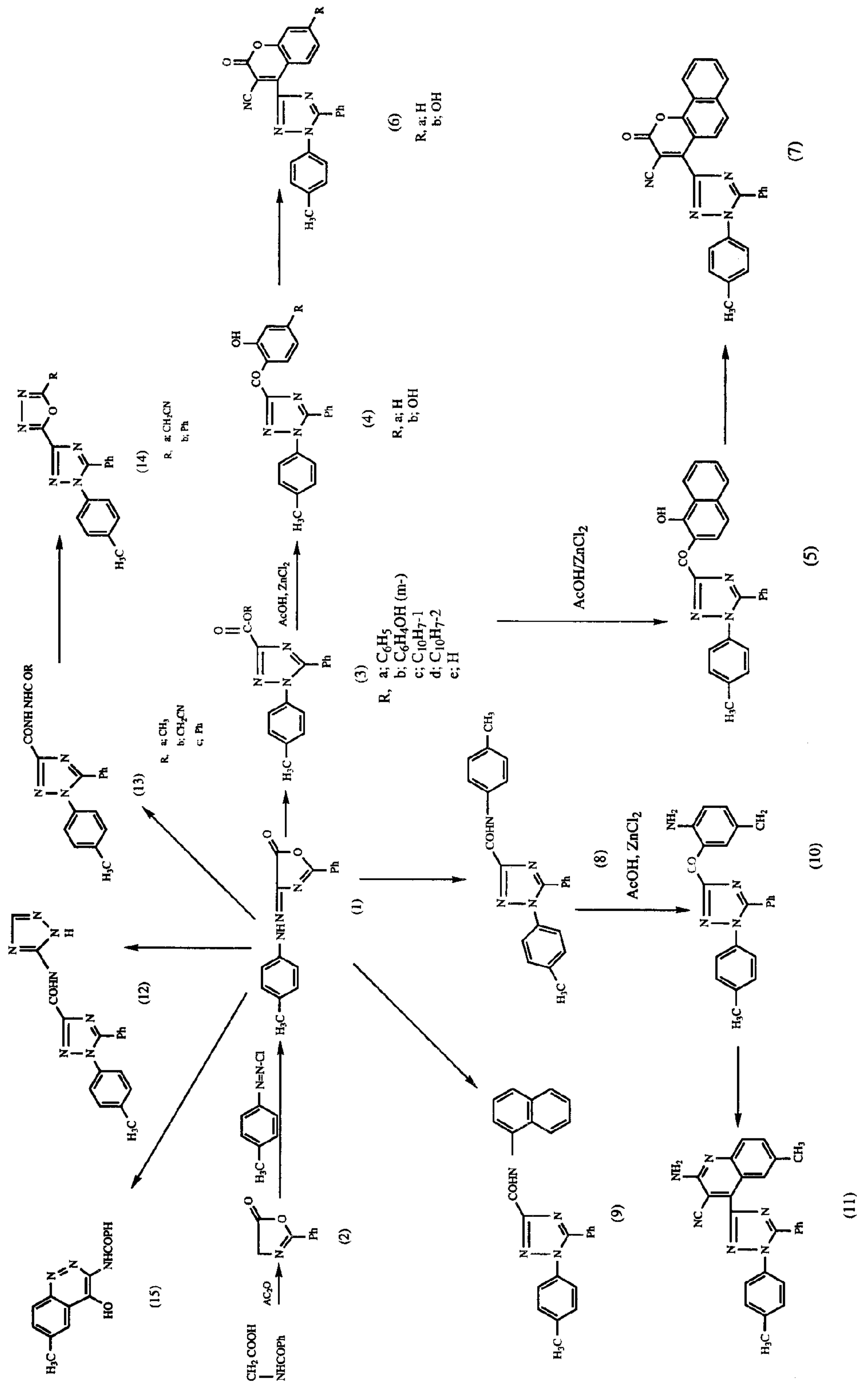
*IR λ_{max} here and elsewhere in the paper in cm^{-1}


(1)
(2)
Ac2O
(3)
R, a; C6H5
b; C6H4OH (m-)
c; C10H7-1
d; C10H7-2
e; H
AcOH, ZnCl2
(4)
R, a; H
b; OH
(5)
AcOH/ZnCl2
(6)
R, a; H
b; OH
(7)
(8)
AcOH, ZnCl2
(9)
(10)
(11)
(12)
(13)
R, a; CH3
b; CH2CN
c; Ph
(14)
R, a; CH2CN
b; Ph
(15)

Scheme-1.

Refluxing compound **8** in acetic acid containing anhydrous zinc chloride gave the Fries rearrangement product 1-*p*-tolyl-5-phenyl 1(H)-1,2,4-triazol-3-yl-2-amino-5-methyl phenyl ketone (**10**). The IR spectrum of **10** showed νC=O at 1700 and νNH at 3390. The ^{1}H-NMR (DMSO-d_6) of **10** exhibited signals at 8.25-7.4 (12H, m, ArH), 2.64 and 2.50 (2H, 2s, NH_2) and 2.46 and 2.50 (6H, 2s, CH_3).

Condensation of compound **10** with malononitrile under the previous mentioned conditions gave 2-amino-6-methyl-4(1-*p*-tolyl-5-phenyl-1(H)-1,2,4-triazol)3-yl-quinoline-3-carbonitrile (**11**). The IR spectrum of **11** showed νC≡N at 2200 and νNH at 3400.

Compound **1** also undergoes rearrangement when fused with 1,2,4-triazol-5-amino at 140°C and acylhydrazines at 100°C to give 1-*p*-tolyl-5-phenyl-1,2,4-triazol-3-yl-N-1(H)-1,2,4-triazol-5-yl-carboxamide (**12**) and the hydrazide derivatives **13a-c** respectively.

The IR spectrum of **12** showed νC=O at 1690 and νNH at 3400. The IR spectra of **13a-c** showed νC=O at 1640-1680 and νNH at 3040-3200. The ^{1}H-NMR (DMSO-d_6) of **13a** exhibited signals at δ 8.3-7.6 (9H, m, ArH), 2.4 (3H, s, CH_3), 2.2 and 2.6 (2H, 2s, 2NH) and 1.85 (3H, s, CH_3).

Structure of **13b** and **c** was further established by treatment with acetic acid-sulfuric acid mixture to give **2** (1-*p*-tolyl-5-phenyl 1(H)-1,2,4-triazol-3-yl)-1-oxo-5-cyano-methane-3,4-diazol (**14a**) and 2(1-*p*-tolyl-5-phenyl-1(H)-1,2,4-triazol-3-yl)-1-oxo-5-phenyl-3,4-diazol (**14b**). The IR spectrum of **14a** showed CH_2 at 2800 - 3300 and C≡N at 2200, while the IR spectrum of **14b** showed C=N at 1610.

Interestingly, attempted rearrangement of **1** by acetophenone in refluxing dioxane and in the presence of sodium metal, has resulted in the formation of 3-benzoylamino-6-methyl-cinnolin-4-ol (**15**), the reaction probably proceeds through the formation of an azine **16** which then cyclized into **17** followed by ring opening and rearrangement to give **15** (Scheme 2). Its IR spectrum showed νC=O at 1700 and νNH at 3100. The ^{1}H-NMR (DMSO-d_6) of (**15**) exhibited signals at δ 7.85-7.60 (9H, m, ArH), 2.20 (3Hs, s, CH_3) and 2.45 (1H, s, NH).

Alternatively compound **15** can be obtained by refluxing **1** in dioxane solution in the presence of sodium metal or in ethanolic sodium ethoxide.

Experimental

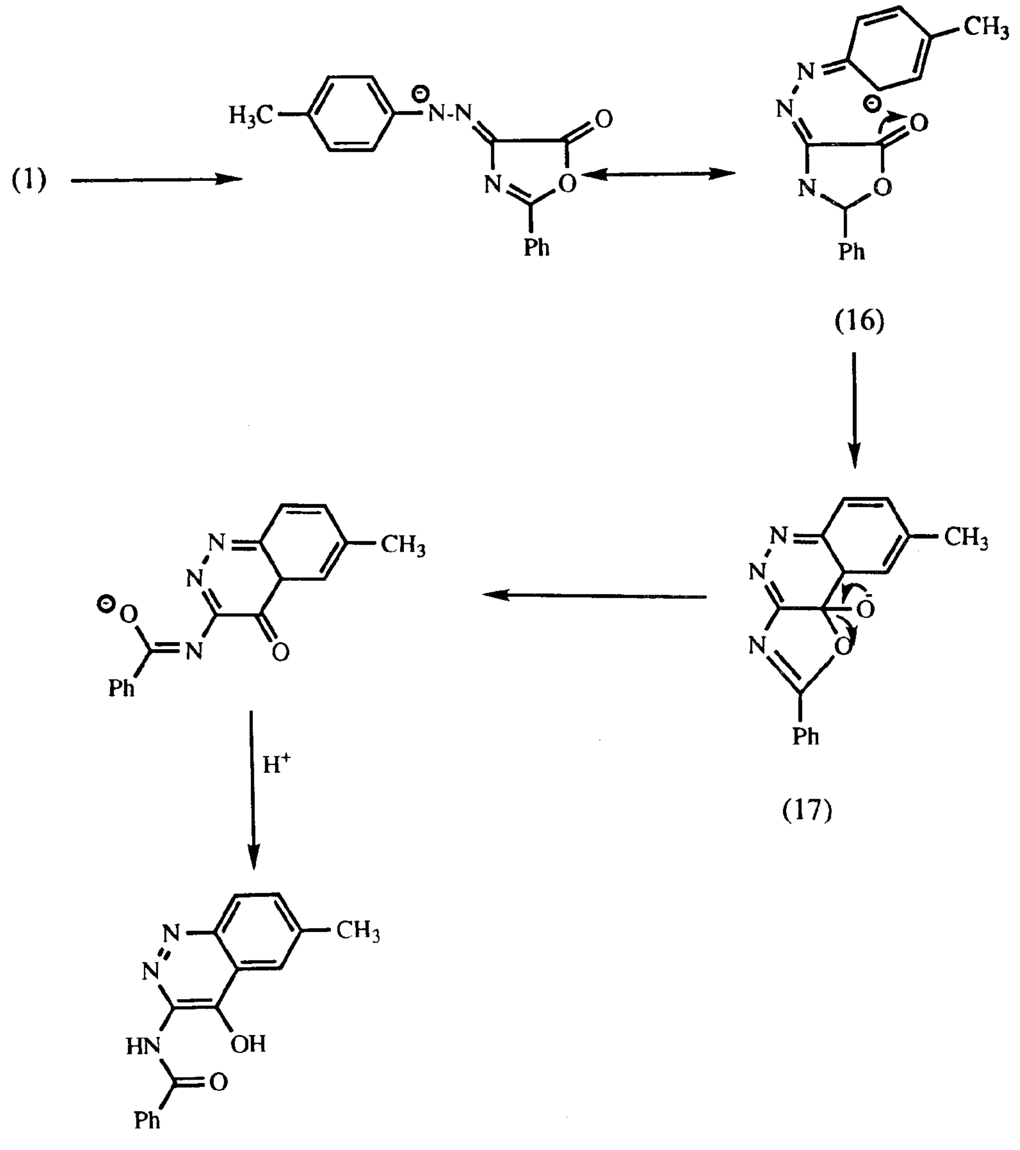
Melting points are uncorrected. IR spectra were recorded in KBr on Shimadzu No. 440 IR spectrometer, ^{1}H-NMR were performed in DMSO-d_6 on Varian 200 Hz using TMS as internal standard. Mass spectra were recorded on an AET-MS 902 mass spectrometer at 70eV electron energy, 6KV accelerating voltage at 130°C ion source temperature using a direct insertion probe. Analytical data were performed in analytical data unit at the National Research Centre in Cairo Dokki.

4-p-tolylhydrazono-2-phenyl-2-oxazolin-5-one (1)

A solution of hippuric acid (0.1 mol) in Ac_2O (30 ml) was heated at 100°C for 20 minutes and then poured into acetic acid (50 ml) containing anhydrous sodium acetate (5.0 g). The resulting solution was then treated dropwise over a period of 10 minutes with a solution of diazotised *p*-toluidine (prepared from 0.1 mol) and appropriate quantities of conc. HCl and sodium nitrite. The mixture was stirred for 30 minutes after complete addition of the diazonium salt and the resulting solid produced was collected by filtration and crystallised from ethanol - water mixture (1:1).

Reaction of 1 with phenols 1,2,4-triazol-5-amino and acylhydrazines: Formation of 3a-d, 12 and 13a-c

A mixture of **1** (0.01 mol) and appropriate phenol, namely phenol, resorcinol, 1-naphthol, 2-naphthol 1,2,4-triazol-5-amino, and/or acylhydrazines were fused at 140°C for 30 minutes then left to cool. The reaction mixture was triturated with ethanol. The solid product so formed, collected by filtration and crystallised from petroleum ether 60-80°C **3c, 13a, 13b**, petroleum ether 100-120°C **3a,3d** petroleum ether 100-120°C **13c**, ethanol **12** and benzene **3b**. **3a**: m.p. 175°C, yield 55% (Found: C, 73.52; H, 4.88 $C_{22}H_{17}N_3O_2$ Requires C, 74.36; H, 4.78%). **3b**: m.p. 220°C,



(15)

Scheme 2

yield 60% (Found: C, 71.15; H, 4.58 $C_{22}H_{17}N_3O_3$ Requires: C. 71.16; H, 4.58%). **3c**: m.p. 140°C, yield 57% (Found: C. 77.50; H, 5.00 $C_{26}H_{19}N_3O_2$ Requires: C, 77.03; H, 4.69%). **3d**: m.p. 135°C, yield 52% (Found: C, 77.00; H, 4.60 $C_{26}H_{19}N_3O_2$ Requires: C, 77.03; H, 4.69%). **12**: m.p. >300°C, yield 65% (Found: C, 62.90; H, 4.30 $C_{18}H_{15}N_7O$ Requires: C, 62.60; H, 4.34%). **13a**: m.p. 170°C; yield 60% (Found: C, 64.40; H, 5.30 $C_{18}H_{17}N_5O_2$ Requires: C, 64.47; H, 5.07%). **13b**: m.p. 145°C, yield 50% (Found: C, 63.40; H, 4.60 $C_{19}H_{16}N_6O_2$ Requires: C, 63.33; H, 4.44%). **13c**: m.p. 130°C, yield 75% (Found: C, 69.80; H, 4.60 $C_{23}H_{19}N_5O_2$ Requires: C, 69.52; H, 4.78%).

Hydrolysis of 3a: Formation of 3e

A solution of **3a** (2 g) in AcOH (20 ml) and HCl (10 ml) was heated under reflux for 3 h. The reaction mixture was then evaporated in vacuum and the remaining oil was washed several times with ether, evaporation of ether layer, phenol was isolated and could be characterized as its azo derivatives. The solid product left, was collected by filtration, crystallised from ethanol and identified by melting point and mixed melting point.

Fries rearrangement of 3a-c and 8. Formation of 4a, 4b, 5 and 10

A solution of **3a, 3b, 3c** and **8** (0.01 mol) in glacial acetic acid (10 ml) was treated with anhydrous zinc chloride. The reaction mixture was then refluxed for 5 h. then evaporated in vacuum, the remaining solid produced was triturated with water and the resulting solid produced was collected by filtration and crystallized from benzene - petroleum ether 60-80°C **4a**, ethanol **4b, 5, 10. 4a**: m.p. 160°C, yield 75% (Found: C, 74.40; H, 4.70 $C_{22}H_{17}N_3O_2$ Requires: C, 74.36; H, 4.78%). **4b**: m.p. 235°C, yield 70% (Found: C, 71.20; H, 4.52 $C_{22}H_{17}N_3O_3$ Requires: 71.15 H, 4.58%). **5**: m.p. 210°C, yield 78% (Found: C, 77.40; H, 4.70 $C_{26}H_{19}N_3O_2$ Requires: C, 77.03; H, 4.69%). **10**: m.p. 180°C, yield 65% (Found: C, 74.60; H, 5.60 $C_{23}H_{20}N_4O$ Requires: C, 75.00; H, 5.43%).

Reaction of 4a, 4b, 5 and 10 with malononitrile: Formation of 6a, 6b, 7 and 11

A mixture of **4a, 4b, 5** and **10** (0.01 mol), ammonium acetate (3g) malononitrile (0.01 mol) was treated with acetic acid 10 ml, the reaction mixture was then covered with dry benzene (20 ml) and heated using reflux condenser provided with a device for continual elimination of water, after no more water was eliminated the reaction mixture was evaporated with vacuum and the reaction solid was collected by filtration and crystallised from ethanol to give **6a, 6b, 7** and **11**, respectively.

6a: m.p. > 250°C; yield 65% (Found: C, 74.15; H, 4.00 $C_{25}H_{16}N_4O_2$ Requires: C, 74.25; H, 3.96%). **6b** m.p. > 250°C, yield 60% (Found: C, 71.10; H, 3.60 $C_{25}H_{16}N_4O_3$ Requires: C, 71.42; H, 3.80%). **7**: m.p. > 250°C, yield 50% (Found: C, 77.10; H, 4.30 $C_{29}H_{20}N_4O_2$ Requires: C, 76.65; H, 4.40%). **11**: m.p. 192°C; yield 66% (Found: C, 74.70; H, 5.30 $C_{26}H_{20}N_6$ Requires: C, 75.00; H, 4.80%).

Reaction of 1 with aromatic amines: Formation of 8 and 9

A mixture of **1** (0.01 mol) and *p*-toluidine or 1-naphthylamine (0.01 mol) was heated at 140°C for 1 h, resulting reaction products were triturated with ethanol and crystallized from ethanol to give **8** and **9** respectively.

8: m.p. 195°C yield 75% (Found: C, 75.07; H, 5.60 $C_{23}H_{20}N_4O$ requires: C, 75.00; H, 5.43%). **9**: m.p. 200°C, yield 70% (Found: C, 77.40; H, 5.20 $C_{26}H_{20}N_4O$ Requires: C, 77.22; H, 4.95%).

Cyclisation of 13b and 13c: Formation of 14a and 14b

A solution of **13b**, and **13c** (0.01 mol) in acetic acid (30 ml) with sulfuric acid (5 ml) was refluxed for 4 h, then evaporated in vacuum. The remaining product was collected by filtration and crystallised from benzene - petroleum ether 60 - 80°C **14a** and from benzene **14b.**

14a: m.p. 120°C, yield 60% (Found: C, 66.20; H, 5.20; $C_{19}H_{14}N_6O$ Requires: C, 66.66; H, 4.09%). **14b**: m.p. 180°C, yield 56% (Found: C, 72.40; H, 4.50 $C_{23}H_{17}N_5O$ Requires: 72.82; H, 4.48%).

Reaction of 1 with acetophenone: Formation of 15

A solution of **1** (0.01 mol) in dioxane (10 ml), acetophenone (0.01 mol) was treated with sodium metal (3 g), then refluxed for 4 h. The reaction mixture was treated with ethanol then evaporated in vacuum. The remaining product was acidified with conc. HCl, and the resulting solid produced was collected with filtration and crystallized from benzene to give **15**, m.p. 190°C, yield 40% (Fund: C, 69.20; H, 4.60, Requires: C, 68.81; H, 4.65%).

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