Sci. J. Fac. Sci. Monoufia Univ Vol. VIII (1994). (179-189)

STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: 2-PHENYL-4-P-TOLYLHYDRAZONO-2-OXAZOLIN-5-ONE AS A PRECURSOR FOR THE SYNTHESIS OF SUBSTITUTED 1,2,4-TRIAZOLES, CINNOLINES AND PYRIDINES.

Mohamed Hilmy Elnagdi[a] Abdalla Mohamed Negm[b], Ayman Wahba Erian[b] and Salah El-Kousy[c]

a. Chemistry Department; Faculty of Science: University of Kuwait: P. O. Box 5969, Safat 13060 Kuwait.
b. Chemistry Department; Faculty of Science; Cairo University; Giza Egypt.
c. Chemistry Department; Faculty of Science; Menoufia University, Shibin El-Kom, Egypt.

2-Phenyl-4-p-tolylhydrazon-2-oxazolin-5-one (III) rearranged by action of phenols and naphthols into 1,2,4-triazole-5-carboxylic esters (V) that rearranged further on reflux with AcOH-$ZnCl_2$ into triazolyl ketones (VII). Rearrangement of (III) into 1,2,4-triazole derivatives could also be effected by action of 2-thionaphthol, heterocyclic amines and 1-naphthylamine. Compound (III) rearranged into cinnoline on reaction with sodium dioxane.

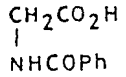
Polyfunctionally substituted heteroaromatics are interesting as potential pharmaceuticals[1,2] agrochemicals[1-5] and dye intermediates[6]. Since neither classical synthetic approaches of heterocycles nor functionalization reactions of aromatics can be easily applied for preparation of this class of compounds[3] developing new approaches for the synthesis of these compounds has received considerable

interest.[9-11] In the last few years we were involved in programme aimed at developing new approaches for polyfunctionally substituted heteroaromatics utilising simple, Inexpensive and readily obtainable starting materials. The synthesised compounds were required for testing either as agrochemicals[12,13] or as male fertility regulants[14]. Inconjunction of this work, samples of certain substituted 1,2,4-triazole derivatives were required. Although 2-phenyl-4-phenylhydrazono-2oxazolin-5-ones have been reported to rearrange readily into 1,2,4-triazoles on treatment with acids, alkalies, amines and thiophenol.[15-17] The exact synthetic scope of these reactions have never been explored. In fact the reported procedures for synthesis of the starting oxazolones are rather tedious and inefficient[15]. This difficulty is most likely beyond lack of interest in synthetic application of these compounds. In the present paper we report an efficient synthesis of 2-phenyl-4-p-tolylhydrazono-2-oxazolin-5-one (III) and results of investigations aiming to explore its chemistry. Thus, 2-phenyl-2-oxazolin-5-one (II) was generated in situe by heating hippuric acid (I) in acetic anhydride for short period. This insitue generated oxazolone could be coupled with p-toluidine-diazonium chloride in acetic acid in presence of sodium acetate to yield the hydrazone (III). Compound (III), so formed, reacted with phenol and 1-naphthol to yield products that may be formulated as the ester V resulting from attach of ring carbonyl with oxygen nucleophile affording intermediated IV that cyclizes into V via water elimination. Structure V could be established for the reaction product based on the conversion of product of reaction of III with phenol into the acid VI on hydrolysis with NaOH. Compounds Va,b rearranged according to Fries like rearrangement. On heating with acetic acid in the presence of $ZnCl_2$ to yield the ketones VIIa,b.

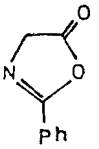
Compound III also rearranged by action of 2-thionaphthol to yield the thioester Vc.

Similar to reported rearrangement by aromatic amines[15-17], compound III afforded Vd on treatment with 1-naphthylamine. The latter compound is rearranged into VIIc on heating in AcOH/ZnCl2.

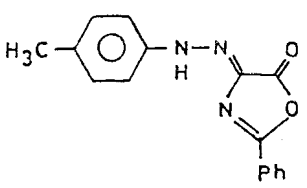
Compound III reacted with 1H-1,2,4-triazole-5amine (VIII) to yield the acylamino derivative IX. Althernate structures which may result by initial attack with ring nitrogens on the carbonyl group were excluded based on the absence of NH_2 group in the spectra of product. Also ^{1}H-NMR that revealed triazole ring H at δ 8.05 ppm which is almost the same field at which this proton resonates in VIII. Structure IX was further established on the basis of spectral data. ^{13}C NMR was in good agreement with the proposed structure IX (cf. the assignment on structure IX). Similar to the behavior of III toward VIII, it also reacted with the aminopyrazole derivative X to yield XI. Evidently the reactions of III with the amines VIII and X occur via initial attack of exocyclic amino function at ring carbonyl group. Compound III also reacted with 2-aminopyridine to yield XII.



I

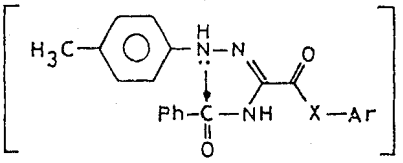


II



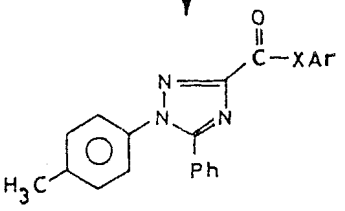
III

ArXH



IV

$-H_2O$



V

a, Ar = C_6H_5 , X = O

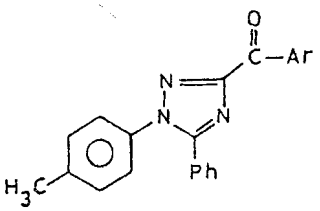
b, Ar = 1-naphthyl , X = O

c, Ar = 1-naphthyl , X = S

d, Ar = 1-naphthyl , X = NH

AcOH

$ZnCl_2$

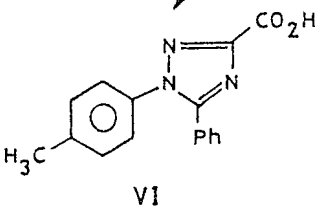


VII

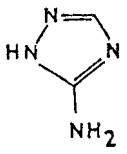
a, Ar = o-C_6H_4OH

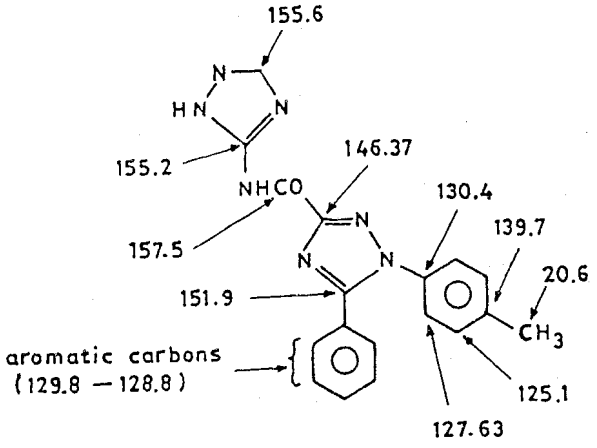
b, Ar = 1-naphthol-2yl

c, Ar = 1-naphthylamine-2yl

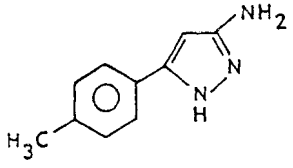


VI

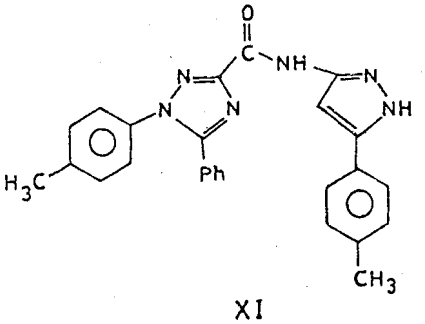



155.6
155.2
146.37
NHCO
157.5
130.4
139.7
20.6
151.9
CH3
aromatic carbons
(129.8 – 128.8)
125.1
127.63

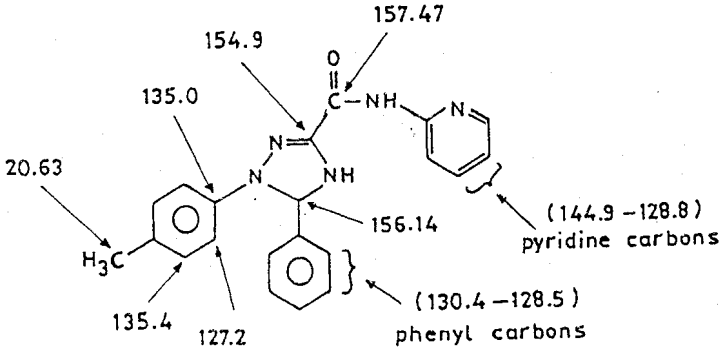
IX



X


O
NH
NH
Ph
CH3

XI


157.47
154.9
O
135.0
NH
20.63
NH
156.14
(144.9 –128.8)
pyridine carbons
135.4
127.2
(130.4 –128.5)
phenyl carbons

XII

Experimental

IR spectra were recorded for KBr discs on a Perkin Elmer 1430 spectrophotometer, ^{1}H, ^{13}C NMR were obtained on an EM-390 200 MHz spectrophotometer, using Me_4Si as internal indicator and chemical shifts are expressed as δ ppm.

2-Phenyl-4-tolylhydrazono-2-oxazolin-5-one (III): A solution of I (18 g. 0.1 mol) in acetic anhydride (30 ml) was heated on water bath for 20 min. then left to cool at 0°C. To the solution formed, 15 g of sodium acetate and 5 ml acetic acid was added with stirring. An ice cold solution of p-tolyldiazonium chloride (o.1 mol), prepared by adding NaNO2 (0.1 mol) to the appropriate quantity of p-toluidine in HCl with stirring, was added. After 30 min. The solid product was collected by filtration and crystallized from dioxane ethanol mixture as red crystals m.p. =180°C (8 g, 30%); IR (KBr) ν_{max} / cm^{-1}, 3320 (NH), 1720 (C=O) (Found: C, 68.8: H. 4.5; N. 15.1; $C_{16}H_{13}N_3O_2H$; requires C, 68.81; H. 4.65; N; 15.05%).

5-Phenyl-1-p-tolyl-1,2,4-triazole-3-carboxylate (V): (General procedure). A mixture of III (.4 g, 0.02 mole) and the phenol (0.02 mol) was fused over sand bath at 170°C for 10 min. The reaction mixture was triturated with ethanol and crystallized from ethanol.

Compound (Va): Pale yellow crystals. m.p. 165°C: IR (KBr.). ν_{max} /cm^{-1}, 1760 (C=O). ^{1}H NMR / (DMSO) δ = 2.1 (s. 3H. CH_3): 6.71-7.3 (m. 14H. aromatic protons) (Found: C, 73.6: H, 4.9; N, 12.2; $C_{21}H_{17}O_2N_3$ requires C, 73.43: H, 4.95: N, 12.24%).

Compound (Vb): Orange crystals, m.p. 150°C: IR (KBr), V_{max} /cm^{-1}, 1750 (C=O) (Found C, 77.1; H, 4.5; N, 10.4; $C_{26}H_{19}N_3O_2$ requires: C, 77.03; H, 4.69; N, 10.37%)

Compound (Vc), Buff crystals. m.p. 138°C: IR (KBr) ν / cm-1, 1740 (C=O) (Found: C, 74.0; H, 4.51; N, 9.8; S, 7.6; $C_{26}H_{19}N_3OS$ requires: C, 74.10: H, 4.51: N, 9.97; S, 7.6%).

Reaction of III with 1-naphthylamine (Vd):

A mixture of III (5.4 g. 0.02 mol) and 1-naphthyl amine (2.9 g, 0.02 mol) was triturated fused over sand bath at 180°C for 15 min. The reaction mixture was with ethanol and crystallized from ethanol as pale yellow crystals m.p. 188°C. IR (KBr) ν / cm^{-1} 3400 (NH). 1690 (C=O) (Found: C, 77.3; H, 4.9: N, 13.9; $C_{26}H_{20}N_4O$ requires C 77.22; H. 4.95; N. 13.86%).

5- Phenyl-1-p-tolyl-1,2,4-triazole-3-carboxylic acid (VI).- A solution of V (0.01 mole) in ethanol (20 ml) and 10% sodium hydroxide (10 ml) was refluxed for 5 h then evaporated in vacuo. The remaining solid product was triturated with water, collected by filtration and crystallized from ethanol as buff crystals m.p. 130°C, IR (KBr). ν/cm^{-1}; 3480, 3350 (COOH) (Found: C, 77.7; H, 5.3; N, 17.2; $C_{16}H_{13}N_3$ requires C. 77.73; H. 5.26; N, 17.0%)

Rearrangment of Va,b,d with acetic acid/zinc chloride to the ketone VIIa-c (General procedure:) A solution of V (0.01 mole) in acetic acid (20 ml) was treated with $ZnCl_2$ (1 g) and heated under reflux for 3h. The solid product, so formed by dilution, was collected by filteration and crystalized from ethanol.

Compound VIIa. Yellow crystals. m.p. 167°C: IR (KBr) ν / cm^{-1} 3400 (OH), 1700 (C=O) (Found: C, 73.6: H, 4.8 N, 12.2: $C_{21}H_{17}O_2N_3$ requires C 73.43; H. 4.95; N, 12.24%)

Compound VII b, Pale yellow crystals. m.p. 140 C; IR (KBr) ν / cm^{-1} 3450 (OH), 1710 (C=O) (Found: C, 77.1: H, 4.5: N, 10.3; $C_{26}H_{19}N_3O_2$ requires C. 77.03: H, 4.69; N. 10.37%).

Compound (VIIc). - Pale yellow crystals m. p. 207°C. IR (KBr) ν / cm^{-1} 3450-3330 (NH_2) 1710 (C=O) (Found: C. 77.2; H, 4.8; N, 13.8; $C_{26}H_{20}N_4O$ requires C. 77.22; H. 4.95: N. 13.86%).

Reaction III with heterocyclic amines (IX XI, XII). - (General procedure). -A mixture of III (5.4 g. 0.02 mol) and VIII, X or 2-amino pyridine (0.02 mole) was fused over sand bath at 180°C for 15 min. The reaction mixture was triturated with ethanol and crystalized from ethanol.

5-Phenyl-1-p-olyl-1,2,4-triazole-3-N(1`-H-1`,2`,4`-triazole-5-yl) carboxamide (IX). Pale yellow crystals m.p. 242°C IR (KBr) ν / cm^{-1} 3300-3250 (NH), 1690 (C=O) ^{1}H NMR (DMSO). δ = 2.38 (s, 3H.CH_3). 7.30-7.55 (m, 10H, aromatic protons), 8.05 (s, 1H, tirazol NH), 12.22 (br. 1H. carboxamide NH).- ^{13}C NMR (See structure XI) (Found: C 62.7:H, 4.3: N,28.3; $C_{18}H_{15}N_7O$ requires C, 62.60: H, 4.34; N, 28.40%).

5-Phenyl-1-p-tolyl-1,2,4-triazole-3-N-(5`-tolylpyrazole-3`-yl)-carboxamide (XI).-Pale yellow crystals m.p.>300°C-IR(KBr) ν/cm^{-1} 3400-3800 (NH) -1680 (C=O) (Found: C, 71.7; H, 5.0; N, 19.4; $C_{26}H_{22}N_6O$ requires C. 71.88: H. 5.06: N. 19.35%).

5-Phenyl-1-p-tolyl-1,2,4-triazole-3-N(pyridine-3`-yl) carboxamide (XII)- Pale yellow crystals m.p: 245°C, IR (KBr); ν/cm^{-1} 3250 (NH), 1690 (C=O). ^{1}H NMR (DMSO); δ = 2.37 (s. 3H, CH_3). 7.31-7.47 (m. 8H, aromatic protons), 7.51- 7.57 (m, 2H, aromatic protons), 8.23-8.35 (m, 2H, pyridyl protons), 9.04 (s, 1H, pyridyl proton), 10.55 (s, 1H, NH). ^{13}C NMR (see structure XII) (Found: C, 70.9; H. 4.7; N. 19.7; $C_{21}H_{17}N_5O$ requires C. 70.98; H, 4.78; N, 19.71 %).

REFERENCES

1- Mulder R., Wellinga K. and Van Daalen J. J.: Naturwissenschaften. 62. 531 (1975).

2- Wellinga K., Grosscurt A. C., Van Hes R.; J. Agric Food Chem., 25. 988 (1977).

3- Grosscurt A.C. Van Hes R., Welling K.: J. Agric. Food Chem., 27 406 (1979).

4- Scheek B.; Chemosphere 9, 483 (1980).

5- Fuhr F., Mittelstaedt W. and Wieneke J.: Chemosphere. 9, 469 (1980).

6- Webster O.W.: U.S. Pat. 3, 770, 764 (1973) [C.A. 80, 47996 (1973)].

7- Cirrincione G., Almerico A. M. and Aiello E. : Advances in Heterocyclic Chemistry, 48, 65 (1990).

8- Elnagdi M. H., Negm A. M., Hassan E. M., El-Boreriy E.; J. Chem. Research (s). 130 (1991).

9- Schafer H., Gewald K., Bellmann P., and Gruner M.: Monatshefte fur Chemie 122. 195 (1991).

10- Lenaga K., Hasegawa T., Brown J. D., Pfleiderer W. ; J. Chem. Soc. Perkin Trans I, 593 (1988).

11- Huddleston P. R., Barker J. M., Adamczewska Y. Z., Wood M. L. and Holmes D.; J. Chem. Research (s). 72 (1993).

12- Elangdi M. H., Abdelrazek F. M., Ibrahim N. S. and Erain A. W., Tetrahedron. 45. 3597 (1989).

13- Elangdi M. H. ad Erain A. W.: Liebigs Ann. Chem., 1215(1990).

14- Elnagdi M. H., Ghozlan S. A. S., Abdelrazek F. M. and Selim M. A: J. Chem. Res(s). 116 (1991).

15- Mustafa A., Khattab S. A. and Asker W.: Canadian Journal of Chemistry. 41. 1813 (1963).

16- Harhash A. H., Elnagdi M. H. and El-Banani A. A. Tetrahedron. 291, (1974).

17- Harhash A. H., Kassab N. L. and Banani A. A.: Indian J. Chem. 9, 789 (1971).

دراسات على الحلقات غير المتجانسة عديدة المجموعة الوظيفية: ٢-فينيل-٤-توليل هيدرازونو-٣-اوكسازولينون كبادئ تخليق مشتقات من ١و٢و٤-تريازول والسينولين والبريدين

محمد حلمى النجدى[أ] -عبدالله محمد نجم[ب] -ايمن وهبة عريان[ب] -صلاح القوصى[جـ]

أ- قسم الكيمياء - كلية العلوم - جامعة الكويت

ب- قسم الكيمياء - كلية العلوم - جامعة القاهرة

قسم الكيمياء - كلية العلوم - جامعة المنوفية

يتفاعل المركب ٢-فينيل-٤-توليل هيدرازونو أوكسازولينون مع الفينول و النافثول ليتكون ١و٢و٤-تريازول حمض كربوكسيلى والذى يعاد تشكيل تركيبه إلى ترايازوليلكيتون عندما يتفاعل مع حمض الخليك وكلوريد الزنك.

أمكن أيضا إعادة تشكيل نفس المركب عندما تفاعل مع ٢-ثيوفينول أمينات حلقية غير متجانسة و١-نفثيل أمين لتتكون مشتقات من السينولين و البريدين.