Heteroatom Chemistry
Volume 6, Number 6, 1995

# Studies with Polyfunctionally Substituted Heteroaromatics: 2-Phenyl-4-*p*-Tolylhydrazono-2-oxazoline-5-one as a Precursor for the Synthesis of Substituted 1,2,4-Triazoles and Pyridines

Mohamed Hilmy Elnagdi*

*Chemistry Department, Faculty of Science, University of Kuwait, P.O. Box 5969, Safat, 13060 Kuwait*

Abdalla Mohamed Negm and Ayman Wahba Erian

*Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt*

Salah El-Kousy

*Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt*

*Received 9 January 1995; revised 3 April 1995*

## ABSTRACT

*2-Phenyl-4-p-tolylhydrazono-2-oxazoline-5-one (3) was rearranged by the action of phenols and naphthols into 1,2,4-triazole-5-carboxylic esters (5) that were rearranged further on reflux in AcOH-$ZnCl_2$ into triazolyl ketones (7). Rearrangement of 3 into 1,2,4-triazole derivatives could also be effected by the action of heterocyclic amines and 1-naphthylamine. © 1996 John Wiley & Sons, Inc.*

Polyfunctionally substituted heteroaromatics are interesting as potential pharmaceuticals [1,2], agrochemicals [3–5], and dye intermediates [6,7]. Because neither classical synthetic approaches of heterocycles nor functionalization reactions of aromatics can easily be applied for preparation of this class of compounds [8], developing new approaches for the synthesis of these compounds has received considerable interest [9–11]. In the last few years, we were involved in a program aimed at developing new approaches for polyfunctionally substituted heteroaromatics utilizing simple, inexpensive, and readily obtainable starting materials. The synthesized compounds were required for testing either as agrochemicals [12,13] or as male fertility regulants [14]. In conjunction with this work, samples of certain substituted 1,2,4-triazole derivatives were required. Although 2-phenyl-4-phenylhydrazono-2-oxazolin-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 has never been explored. In fact, the reported procedure for synthesis of the starting oxazolones is rather tedious and inefficient [15]. In the present article, we report an efficient synthesis of 2-phenyl-4-*p*-tolylhydrazono-2-oxazoline-5-one (3) and the results of investigations aimed at exploration of its chemistry. Thus, 2-phenyl-2-oxazoline-5-one (2) was generated *in situ* by heating hippuric acid (1) in acetic anhydride for a short period. This, an *in situ* generated oxazolone, could be coupled with *p*-toluidinediazonium chloride in acetic

*To whom correspondence should be addressed.



1042-7163/96/060589-04

acid in the presence of sodium acetate to yield the hydrazone (3). Compound 3, thus formed, reacted with phenol and 1-naphthol to yield products that may be formulated as the ester 5 resulting from attack at the ring carbonyl group by an oxygen nucleophile, affording intermediate 4 that cyclizes into 5 via water elimination. Structure 5 could be established for the reaction product based on the conversion of the product of the reaction of 3 with phenol into the acid 6 on hydrolysis with NaOH. Compounds 5a,b were rearranged, according to a Fries-like rearrangement, by heating with acetic acid in the presence of $ZnCl_2$ to yield the ketones 7a,b. Similar to the reported rearrangement by the action of aromatic amines [15–17], compound 3 afforded 5c on treatment with 1-naphthylamine. The latter compound was rearranged into 7c on heating in AcOH/$ZnCl_2$. Compound 3 was also rearranged by the action of 2-thionaphthol to yield the thioester 5d.

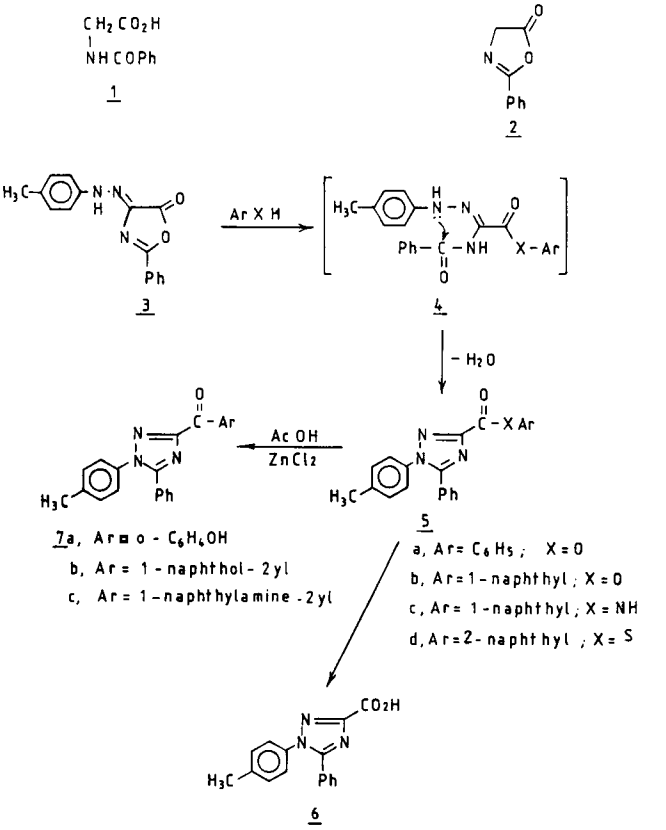
Compound 3 reacted with 1H-1,2,4-triazole-5-amine (8) to yield the acylamino derivative 9. Alternate structures that may result by initial attack of ring nitrogens on the carbonyl group were excluded based on the absence of an $NH_2$ group in the spectra of the product. Also, $^1$H-NMR spectroscopy revealed the triazole ring H at $\delta$ 8.05, which is almost the same field at which this proton resonates in 8. Structure 9 was further established on the basis of spectral data. $^{13}$C NMR spectra were in good agreement with the proposed structure 9 (cf. the assignment in structure 9). Similar to the behavior of 3 toward 8, 3 also reacted with the aminopyrazole derivative 10 to yield 11. Although the ring nitrogen in 8 and 10 is the most basic center in each molecule, it is also more hindered than the exocyclic amino group. Thus, the reactions of 3 with the amines 8 and 10 occur via initial attack by the exocyclic amino function at the ring carbonyl group. Compound 3 also reacted with 2-aminopyridine to yield 12.

## *EXPERIMENTAL*

All melting points are uncorrected. IR spectra were recorded for KBr discs on a Perkin Elmer 1430 spectrophotometer. $^1$H, $^{13}$C NMR spectra were obtained on an EM-390, 90 and 200 MHz spectrophotometer, using $Me_4Si$ as an internal standard, and chemical shifts are expressed as $\delta$ values. Microanalytical data were obtained by the microanalytical data unit at Cairo University.

### *2-Phenyl-4-p-tolylhydrazono-2-oxazoline-5-one* (3)

A solution of 1 (18 g, 0.1 mol) in acetic anhydride (30 mL) was heated on a water bath for 20 minutes, then left to cool at 0°C. To the solution formed, 15 g of sodium acetate and 5 mL of acetic acid were added with stirring. An ice-cold solution of *p*-tolyldiazonium chloride (0.1 mol), prepared by adding $NaNO_2$ (0.1 mol) to the appropriate quantity of *p*-toluidine in HCl with stirring, was added. After 30 minutes, the solid product that had formed was collected by filtration and crystallized from the dioxane/ethanol mixture to give red crystals, m.p. = 180°C (8 g, 30%); IR (KBr) $\nu_{max}$/cm$^{-1}$, 3320 (NH), 1720 (C=O). (Found: C, 68.8; H, 4.5; N, 15.1; $C_{16}H_{13}N_3O_2$ requires C, 68.81; H, 4.65; N; 15.05%.)




### *5-Phenyl-1-p-tolyl-1,2,4-triazole-3-carboxylate* (5)

*General Procedure.* A mixture of 3 (5.4 g, 0.02 mole) and each phenol (0.02 mol) was fused over a sand bath at 170°C for 10 minutes. The reaction mixture was triturated with ethanol and crystallized from ethanol.

*Compound* 5a. Pale yellow crystals, m.p. 165°C; IR (KBr), $\nu_{max}$/cm$^{-1}$, 1760 (C=O); $^1$H NMR $\delta$ = 2.1 (s, 3H, $CH_3$); 6.71–7.3 (m, 14H, aromatic 44 protons). (Found: C, 74.4; H, 4.8; N, 11.8; $C_{22}H_{17}N_3O_2$ requires C, 74.36; H, 4.78; N, 11.83%.)

*Compound* 5b. Orange crystals, m.p. 150°C; IR (KBr), $\nu_{max}$/cm$^{-1}$, 1750 (C=O); $^1$H NMR $\delta$ = 2.30 (s, 3H, $CH_3$); 6.71–6.90 (m, 5H, aromatic H); 6.94–7.12 (m, 4H, aromatic H); 7.20, 7.24, and 7.42 (m, 2H, m, 1H, and m, 4H). (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* **5c**. Pale yellow crystals, m.p. 188°C; IR (KBr), $\nu/cm^{-1}$, 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%.)

*Compound* **5d**. Buff crystals, m.p. 138°C; IR (KBr), $\nu/cm^{-1}$, 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, 7.60%.)

### *5-Phenyl-1-p-tolyl-1,2,4-triazole-3-carboxylic acid* (6)

A solution of **5** (0.01 mole) in ethanol (20 mL) and 10% sodium hydroxide (10 mL) was refluxed for 5 hours, then evaporated *in vacuo*. The remaining solid product was triturated with water, collected by filtration, and crystallized from ethanol to give buff crystals, m.p. 130°C, IR (KBr), $\nu/cm^{-1}$; 3480, 3350 (COOH) $^1H$ NMR $\delta$ = 2.3 (s, 3H, $CH_3$); 6.73–7.16 (m, 5H, Ph); 7.20–7.57 (m, 4H, aromatic H); 10.21 (s, 1H). (Found: C, 68.8; H, 4.7; N, 15.1; $C_{16}H_{13}N_3O_2$ requires C, 68.81; H, 4.65; N, 15.05%.)

### *Reaction of* **5a,b,d** *with Acetic Acid/Zinc Chloride to the Ketone* **7a-c**

*General Procedure* **2**. A solution of **5** (0.01 mole) in acetic acid (20 mL) was treated with $ZnCl_2$ (1 g) and heated under reflux for 3 hours. The solid product thus formed by dilution was collected by filtration and crystallized from ethanol.

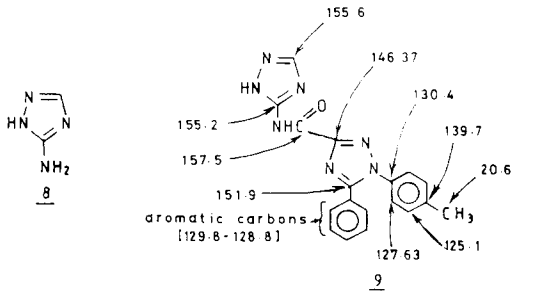
*Compound* **7a**. Yellow crystals, m.p. 167°C; IR (KBr), $\nu/cm^{-1}$, 3400 (OH), 1700 (C=O); $^1H$ NMR $\delta$ = 2.24 (s, 3H, $CH_3$); 3.20 (s, 1H, OH); 6.75–7.11 (m, 5H, aromatic H); 7.23–7.50 (m, 6H, aromatic H); 7.56–7.83 (m, 2H, aromatic H). (Found: C, 74.4; H, 4.8; N, 11.9; $C_{22}H_{17}N_3O_2$ requires C, 74.36; H, 4.78; N, 11.83%.)

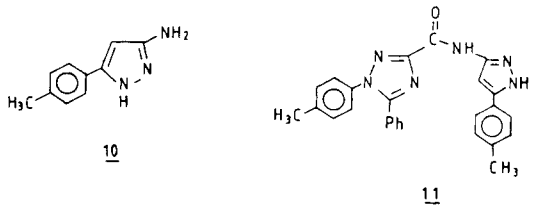
*Compound* **7b**. Pale yellow crystals, m.p. 140°C; IR (KBr), $\nu/cm^{-1}$, 3450 (OH), 1710 (C=O). (Found: C, 77.1; H, 4.5; N, 10.3; $C_{26}H_{19}N_3O_2$ requires C, 77.03; H, 4.69; N, 10.37%.)

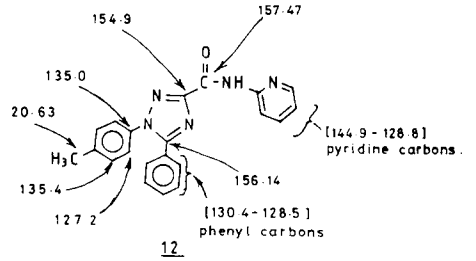
*Compound* **7c**. Pale yellow crystals, m.p. 207°C; IR (KBr), $\nu/cm^{-1}$, 3450–3330 ($NH_2$), 1710 (C=O); $^1H$ NMR $\delta$ = 2.30 (s, 3H, $CH_3$); 3.82 (br, 2H, $NH_2$); 6.69–6.92 (m, 5H); 6.95–7.20 (m, 4H, aromatic H); 7.12, 7.28, and 7.39 (m, 2H–2H and 2H via aromatic protons). (Found: C, 77.2; H, 4.8; N, 13.8; $C_{26}H_{20}N_4O$ requires C, 77.22; H, 4.95; N, 13.86%.)

### *Reaction of* **3** *with Aromatic Amines* (**5d, 9, 11**)

*General Procedure 1*. A mixture of **3** (5.4 g, 0.02 mol) and aromatic amines (0.02 mole) was fused over a sand bath at 180°C for 15 minutes. The reaction mixture was triturated with ethanol and crystallized from ethanol.




*5-Phenyl-1-p-tolyl-1,2,4-triazole-3-N(1'-H-1',2',4'-triazole-5-yl)-carboxamide* (**9**). Pale yellow crystals, m.p. 242°C; IR (KBr), $\nu/cm^{-1}$, 3300–3250 (NH), 1690 (C=O); $^1H$ NMR (DMSO), $\delta$ = 2.38 (s, 3H, $CH_3$); 7.30–7.55 (m, 10H, aromatic protons); 8.05 (s, 1H, triazole NH); 12.22 (br, 1H, carboxamide NH). $^{13}C$ NMR (see structure **11**). (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* (**11**). Pale yellow crystals, m.p. > 300°C; IR (KBr), $\nu/cm^{-1}$, 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* (**12**). Pale yellow crystals, m.p. 245°C; IR (KBr), $\nu/cm^{-1}$, 3250 (NH), 1690 (C=O); $^1H$ NMR (DMSO); $\delta$ = 2.37 (s, 3H, $CH_3$); 7.31–7.47 (m, 8H, aromatic protons); 7.54–7.57 (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 **17**). (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%.)

*ACKNOWLEDGMENT*

One of the authors (M.H.E.) is grateful to University of Kuwait for partial financial support through project SC071.

*REFERENCES*

[1] R. Mulder, K. Wellinga, J. J. Van Daalen, *Naturwissenschaften, 62,* 1975, 531.
[2] K. Wellinga, A. C. Grosscurt, R. Van Hes, *J. Agric. Food Chem., 25,* 1977, 988.
[3] A. C. Grosscurt, R. Van Hes, K. Wellinga, *J. Agric. Food Chem., 27,* 1979, 406.
[4] B. Scheek, H. Taurins, *Chemosphere, 9,* 1980, 483.
[5] F. Fuhr, W. Mittelstaedt, J. Wieneke, *Chemosphere, 9,* 1980, 469.
[6] O. W. Webster: U.S. Pat. 3, 770, 764 (1973) [C.A. *80,* 47996 (1973)].
[7] G. Cirrincione, A. M. Almerico, E. Aiello, *Adv. Heterocyclic Chem., 48,* 1990, 65.
[8] M. H. Elnagdi, A. M. Negm, E. M. Hassan, E. El-Boreiy, *J. Chem. Res.,* 1993, 130.
[9] H. Schafer, K. Gewald, P. Bellmann, M. Gruner, *Monatsh. Chem., 122,* 1991, 195.
[10] K. Ienaga, T. Hasegawa, J. D. Brown, W. Pfleiderer, *J. Chem. Soc. Perkin Trans I,* 1988, 593.
[11] P. R. Huddleston, J. M. Barker, Y. Z. Adamczewska, M. L. Wood, D. Holmes, *J. Chem. Res.,* 1993, 72.
[12] M. H. Elnagdi, F. M. Abdelrazek, N. S. Ibrahim, A. W. Erian, *Tetrahedron, 45,* 1989, 3597.
[13] M. H. Elnagdi, A. W. Erian, *Liebigs Ann. Chem.,* 1990, 1215.
[14] M. H. Elnagdi, S. A. S. Ghozlan, F. M. Abdelrazek, M. A. Selim, *J. Chem. Res.,* 1991, 116.
[15] A. Mustafa, S. A. Khattab, W. Asker, *Can. J. Chem., 41,* 1963, 1813.
[16] A. H. Harhash, M. H. Elnagdi, A. A. El-Banani Tetrahedron, *31(1),* 1975, 25.
[17] A. H. Harhash, N. L. Kassab, A. A. Banani, *Indian J. Chem., 9,* 1971, 789.