Asian Journal of Chemistry Vol. 14, Nos. 3–4 (2002), 1405–1408

A Simple One-Pot Synthesis of 4-Phenyl-3-Oxo Pyrimido [4,5-b] Quinolines and their Biocidal Studies

R. NANDHA KUMAR, T. SURESH and P.S. MOHAN*
Department of Chemistry, Bharathiar University, Coimbatore-641 046, India

A convenient one-pot synthesis of pyrimido [4,5-b] quinolines **3a–e** has been achieved from 2-chloro-3-formyl quinolines **1** and *N*-phenylurea **2**. All the synthesized compounds have been biologically screened for their antibacterial and antifungal activities.

Key Words: One-pot synthesis, 4-Phenyl-3-oxopyrimido [4,5-b] quinolines, Biocidal.

INTRODUCTION

4,5-Heteroannelated quinolines, particularly pyrimido [4,5-b] quinolines are of recent origin and are associated with varied pharmacological and chemotherapeutic properties[1–7]. 2-Chloro-3-formyl quinolines occupy a predominant position, as they are the key intermediates for the further [b] and [c] annelation for various ring systems and many functional group interconversions[8, 9]. Our interest in developing one-step synthesis for novel 2,3-heteroannelated[10,11] quinoline systems prompted us to pave a path for the synthesis of the title compounds. All the synthesized compounds were screened for their antibacterial and antifungal activities against different species.

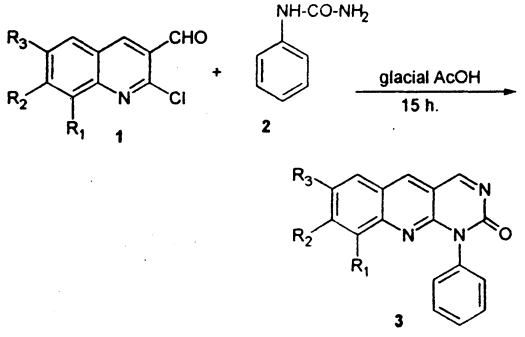
EXPERIMENTAL

Thin layer chromatography was used to access the reactions and purity of products. Melting points were determined on a Boetius microheating table and Mettler-FP5 melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu-8201-FT instrument in KBr pellets and only noteworthy absorption levels (reciprocal centimetre) are listed. ^{1}H NMR spectra were recorded on an AMX-400 MHz spectrometer in $CDCl_3$ solution (chemical shifts in δ, ppm relative TMS). Satisfactory microanalyses were obtained on Carlo-Erba 1106 and Perkin-Elmer models 240 CHN analyzer. Mass spectra were recorded on a Jeol-300 mass spectrometer.

Preparation of 3: General procedure: 2-Chloro-3-formyl quinoline **1** (0.002 mole) and N-phenylurea **2** (0.002 mole) were dissolved in 20 mL of glacial acetic acid and refluxed for 15 h. After the completion of the reaction inferred through TLC studies, it was poured into crushed ice and neutralized with 1% sodium hydroxide soultion. It was then extracted with ethyl acetate and dried over anhydrous sodium sulfate. The silica gel column chromatography yielded the product **3a** using pet-ether : ethyl acetate (95 : 5) as eluent. Compounds **3b–e** were prepared similarly.

RESULTS AND DISCUSSION

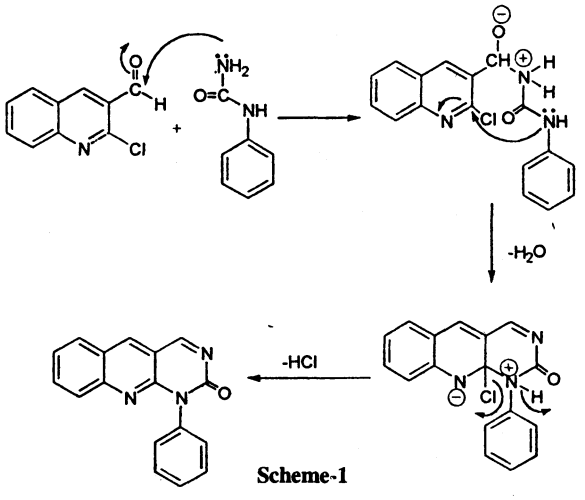
The reaction of 2-chloro-3-formylquinoline[12, 13] (**1**) with N-phenylurea (**2**) in glacial acetic acid at reflux temperature for 15 h afforded the product **3a** in 83% yield. Its IR spectrum showed strong absorption peaks at 1654 and 1590 cm^{-1} for ν(C=N) and at 1718 cm^{-1} for ν(C=O). The ^1H NMR spectrum revealed two fine singlets at δ 7.9 and δ 8.5 accountable to the C_1-H and C_{10}-H protons. Rest of the nine aromatic proton resonances showed their signals between δ 6.6–7.7 as an unresolved complex multiplet. The elemental analysis corroborated with the proposed m.f. $C_{17}H_{11}N_3O$ and the mass spectrum illustrated the molecular ion peak at m/z 273. All the above spectra supported the compound **3a** as 4-phenyl-3-oxo pyrimido [4,5-b] quinoline.



1 2 3

1,3 **a** : $R_1=R_2=R_3=H$ d : $R_1=OCH_3$, $R_2=R_3=H$
b : $R_1=CH_3$, $R_2=R_3=H$ e : $R_3=OCH_3$, $R_1=R_2=H$
c : $R_3=CH_3$, $R_1=R_2=H$

Mechanism



Scheme-1

The possible mechanistic pathway is shown in **Scheme-I.** Here the reaction proceeds through the anil intermediate for the formation of Schiff's base and the subsequent aromatization takes places by the elimination of a hydrochloride molecule. A series of similar compounds **3b–e** were obtained under identical conditions. The structures of all the compounds were confirmed by their analytical and spectroscopic data (Table-1).

TABLE-1
PHYSICAL AND SPECTRAL DATA OF COMPOUNDS **3a–e**

Compd.	m.p. (°C)	Yield (%)	m.f. (m.w.)	% Calcd. (Found)			^{1}H NMR
				C	H	N	
3a	166	83	$C_{17}H_{11}N_3O$ (273.294)	74.71 (74.63)	04.06 (04.14)	15.38 (15.29)	δ 6.6–7.7 (m, 9H, Ar-H), 7.9 (s, 1H, C_1-H), 8.5 (s, 1H, C_{10}-H)
3b	144	70	$C_{18}H_{13}N_3O$ (287.321)	75.25 (75.17)	04.56 (04.51)	14.63 (14.59)	δ 2.5 (s, 3H, CH_3), 6.9–7.6 (m, 8H, Ar-H), 7.8 (s, 1H, C_1-H), 8.5 (s, 1H, C_{10}-H)
3c	190	73	$C_{18}H_{13}N_3O$ (287.321)	75.25 (75.31)	04.56 (04.62)	14.63 (14.68)	δ 2.6 (s, 3H, CH_3), 6.8–7.7 (m, 8H, Ar-H), 7.9 (s, 1H, C_1-H), 8.6 (s, 1H, C_{10}-H)
3d	175	58	$C_{18}H_{13}N_3O_2$ (303.321)	71.28 (71.19)	04.32 (04.19)	13.85 (13.71)	δ 4.0 (s, 3H, OCH_3), 6.7–7.7 (m, 8H, Ar-H), 7.9 (s, 1H, C_1-H), 8.7 (s, 1H, C_{10}-H)
3e	212	67	$C_{18}H_{13}N_3O_2$ (303.321)	71.28 (71.22	04.32 (04.27)	13.85 (13.81)	δ 3.8 (s, 3H, OCH_3), 6.9–7.6 (m, 8H, Ar-H), 7.9 (s, 1H, C_1-H), 8.5 (s, 1H, C_{10}-H)

All the synthesized compounds were screened for their antibacterial activities against *Salmonella typhi, Escherichia coli* and *Aeromonas hydrophilla* by using the disc diffusion method[14, 15]. Bacteria were cultured in nutrient agar medium and used as inoculum for study. Streptomycin was used as standard. The compounds exhibited moderate activity against *Salmonella typhi* and *Aeromonas hydrophilla.* The activity towards *Escherichia coli* was found to be very low. According to the observation, the toxicity increases with the increase in concentration of test solution containing new compounds. Although, all the compounds are active, they did not reach the effectiveness of the conventional bacterostatic streptomycin. The variation in effectiveness of different compounds against different organisms depends either on impermeability of cells of the microbes or diffusion in ribosomes of microbial cells[16].

The compounds were also screened for their *in vitro* antifungal activities against *Fusarium oxysporum* and *Alternaria macrospora.* The fungi were cultured in Czapek-Dox medium and used as inoculum for study. The inhibitory activities

were compared with the commercial fungicide *Carbendazim* tested under similar conditions. The percentage inhibition, after incubation for five and seven days, was calculated by the following formula.

$$\% \text{ Inhibition} = (C - T) \times 100/C$$

where C is the diameter of the mycelial colony (in mm) on the control plate and T is the diameter of the mycelial colony (in mm) on the treated plate. From the results observed compounds were found toxic to both the test fungi at various concentrations.

Their activity decreases with dilution. Their toxicity was effective as that of the conventional fungicide *Carbendazim.*

ACKNOWLEDGEMENTS

One of the authors (RNK) thanks CSIR, New Delhi for the award of Senior Research Fellowship. Authors also thank SIF, IISc, Bangalore and CDRI, Lucknow for providing the spectral and analytical data.

REFERENCES

1. F. Yoneda and T. Sasaki, *Kokaki Tokkyo Koho, Japan* 0381, 276 (1991); *Chem. Abstr.*, 11525590f (1991).
2. E.H. Elgemeie Galal and A.W. Hussan Badria, *Tetrahedron*, **50**, 199 (1994).
3. F. Yonedo, K. Mori, Y. Sakuma and H. Yamaguchi, *J. Chem. Soc., Perkin Trans.*, **1**, 978 (1980).
4. D.E. O'Brien, L.T. Weinstock and C.C. Cheng, *J. Heterocyclic Chem.*, **7**, 99 (1970).
5. T. Nagamatsu, Y. Hashiguchi and F. Yonedo, *J. Chem. Commun.*, 1085 (1982).
6. F. Yonedo, Y. Sakuma, S. Nizamoto and R. Ito, *J. Chem. Soc., Perkin Trarns.*, **1**, 1085 (1976).
7. V.K. Ahluwalia, Ranjana Sahay and Umashankar Das, *Indian J. Chem.*, **38B**, 1136 (1999).
8. O. Meth-Cohn, *Heterocycles*, **35**, 539 (1993) and references cited therein.
9. S.P. Rajendran, M. Manonmani and S. Vijyalakshmi, *Org. Prep. Proced. Int.*, **26**, 383 (1994).
10. R. Nandha Kumar, T. Suresh, A. Mythili and P.S. Mohan, *Het. Commun*, **2**, 7, 193 (2001).
11. R. Nandha kumar, T. Suresh and P.S. Mohan, *Indian J. Chem.* (in press).
12. O. Meth-Cohn and B. Narine, *Tetrahedron*, **19**, 2045 (1978).
13. M.M. Ali Tasneem, K.C. Rajanna and P.K. *Prakash, Synth. Lett.*, **2**, 251 (2001).
14. C.H. Collins and P.M. Lyne, Microbial methods, University Park Press, Baltimore (1970).
15. T. Daniel Thangadurai and K. Natarajan, *Indian J. Chem.*, **40A**, 573 (2001).
16. P.G. Lawerence, P.L. Harold and O.G. Francis, *Antibiot. Chemother.*, 1597 (1980).

(*Received:* 28 February 2002; *Accepted:* 13 May 2002) AJC–2701