Chemistry of Heterocyclic Compounds, Vol. 40, No. 11, 2004

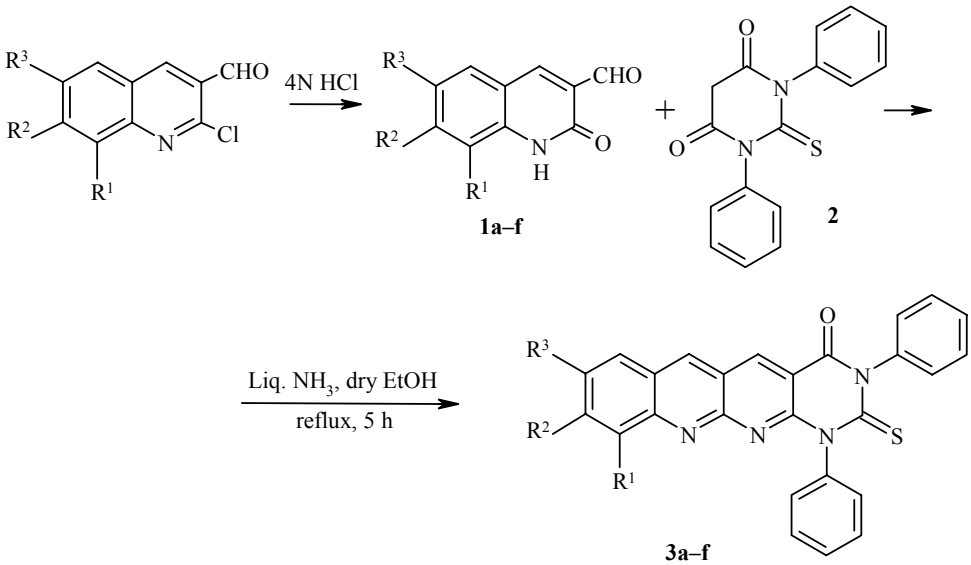
A CONVENIENT ONE-POT SYNTHESIS OF BENZOPYRIMIDO[1,8]NAPHTHYRIDINES BY KNOEVENAGEL CONDENSATION

R. Nandha Kumar, T. Suresh, and P. S. Mohan

A series of 1-oxo-2,4-diphenyl-3-thioxobenzo[g]pyrimido[6,5-b]-1,8-naphthyridines has been synthesized by Knoevenagel condensation from 3-formyl-2-oxoquinolines and N,N-diphenyl-2-thiobarbituric acid on refluxing with liquid ammonia in absolute ethanol.

Keywords: benzopyrimidonaphthyridines, N,N-diphenyl-2-thiobarbituric acid, 3-formyl-2-oxoquinoline, Knoevenagel condensation.

2-Aminonicotinaldehyde was used as a potential starting material for the synthesis of 1,8-naphthyridines *via* Friedlander condensation [1-3]. In the present work an alternative route for the synthesis of 1,8-naphthyridines from 3-formyl-2-oxoquinoline in a one-pot method by Knoevenagel condensation [4-7] is discussed. Quinoline derivatives [8-11], quinoline amines [12-15], and 1,8-naphthyridines [16-20] are pharmacologically important. So, these moieties attract considerable attention as active biocidal agents and prompted us to synthesize a series of 1,8-naphthyridines.



1a–f **2** **3a–f**

1, 3 a $R^1 = R^2 = R^3 = H$; **b** $R^1 = Me$, $R^2 = R^3 = H$; **c** $R^1 = R^3 = H$, $R^2 = Me$; **d** $R^1 = R^2 = H$, $R^3 = Me$; **e** $R^1 = OMe$, $R^2 = R^3 = H$; **f** $R^1 = R^2 = H$, $R^3 = OMe$

Departament of Chemistry, Bharathiar University, Coimbatore-641046, TamilNadu, India; e-mail: ps_mohan_in@yahoo.com. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 11, 1723-1725, November, 2004. Original article submitted September 2, 2002.

3-Formyl-2-oxoquinoline **1** [21, 22], N,N-diphenyl-2-thiobarbituric acid (**2**) [23, 24], and liquid ammonia were refluxed in absolute ethanol for 5 h to give the product (74% yield), whose IR spectrum showed strong absorption bands at 1325 cm^{-1} due to the C=S group, 1680 cm^{-1} for the C=O group, and 1620 cm^{-1} and 1595 cm^{-1} for the C=N groups. Its ^1H NMR and mass spectra as well as data of elemental analysis corroborated with the structure of 1-oxo-2,4-diphenyl-3-thioxobenzo[*g*]pyrimido[6,5-*b*]-1,8-naphthyridine (**3a**). Other compounds **3** were obtained similarly (Table 1).

In conclusion, the reaction proceeds smoothly through the Knoevenagel condensation between the formyl moiety and the active methylene group of N,N-diphenyl-2-thiobarbituric acid to give after elimination of a water molecule the desired substituted 1-oxo-3-thioxobenzo[*g*]pyrimido[6,5-*b*]-1,8-naphthyridines.

EXPERIMENTAL

Thin layer chromatography was used to access the reaction course and the 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 a Shimadzu-8201FT instrument in KBr discs and only significant absorption levels (reciprocal centimeter) are listed. ^1H NMR spectra were recorded in an AMX-400 MHz spectrometer in $CDCl_3$ solution; chemical shifts are expressed in ppm (δ) relative to TMS. Mass spectra were recorded on a Jeol-D-300 mass spectrometer. CHN analyses were carried out on Carlo Erba 106 and Perkin–Elmer Model 240 analyzers.

TABLE 1. Characteristics of Synthesized Compounds **3a-f**

Compound	Empirical formula (Mol. Wt.)	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm	Yield, %
		C	H	N				
3a	$C_{26}H_{16}N_4OS$ (432.46)	72.02 / 72.21	3.64 / 3.73	12.87 / 12.96	280	1680, 1620, 1595, 1325	8.1 (1H, s, C_{11}-H); 8.4 (1H, s, C_{12}-H); 6.8-7.9 (14H, m, Ar–H)	74
3b	$C_{27}H_{18}N_4OS$ (446.49)	72.71 / 72.63	4.13 / 4.06	12.48 / 12.55	183	1690, 1635, 1585, 1330	2.3 (3H, s, CH_3); 8.0 (1H, s, C_{11}-H); 8.5 (1H, s, C_{12}-H); 7.1-7.8 (13H, m, Ar–H)	82
3c	$C_{27}H_{18}N_4OS$ (446.49)	72.52 / 72.63	4.01 / 4.06	12.46 / 12.55	240	1685, 623, 1580, 1320	2.5 (3H, s, CH_3); 8.1 (1H, s, C_{11}-H); 8.7 (1H, s, C_{12}-H); 7.0-8.0 (13H, m, Ar–H)	68
3d	$C_{27}H_{18}N_4OS$ (446.49)	72.60 / 72.63	3.98 / 4.06	12.59 / 12.55	215	1670, 1610, 1590, 1323	2.4 (3H, s, CH_3); 8.2 (1H, s, C_{11}-H); 8.6 (1H, s, C_{12}-H); 7.0-7.9 (13H, m, Ar–H)	79
3e	$C_{27}H_{18}N_4O_2S$ (462.49)	70.02 / 70.12	3.80 / 3.92	12.17 / 12.12	174	1668, 1605, 1587, 1328	3.9 (3H, s, OCH_3); 8.3 (1H, s, C_{11}-H); 8.5 (1H, s, C_{12}-H); 7.1-8.1 (13H, m, Ar–H)	73
3f	$C_{27}H_{18}N_4O_2S$ (462.49)	70.16 / 70.12	3.86 / 3.92	12.08 / 12.12	195	1660, 1615, 1593, 1322	3.9 (3H, s, OCH_3); 8.2 (1H, s, C_{11}-H); 8.6 (1H, s, C_{12}-H); 6.9-8.0 (13H, m, Ar–H)	80

Synthesis of Benzopyrimido[1,8]naphthyridines. 3-Formyl-2-oxoquinoline **1a-f** (1 mmol) and N,N-diphenyl-2-thiobarbituric acid (**2**) (1 mmol) were dissolved in anhydrous ethanol with 2 ml of liquid ammonia and refluxed on a water-bath for about 5 h. After the completion of the reaction, inferred through TLC studies, the volume was reduced to half. The separated product was collected and recrystallized with chloroform–methanol. A series of compounds **3a-f** was synthesized and their characteristic data are presented in Table 1.

The authors thank CSIR, New Delhi for the award of Senior Research Fellowship (R.N.K.) and Bharathiar University for the award of University Research Fellowship (T.S.). SIF, Indian Institute of Science, Bangalore and Central Drug and Research Institute, Lucknow supported the spectral details.

REFERENCES

1. M. T. Chary, K. Mogilaiah, and B. Sreenivasulu, *J. Indian Chem. Soc*., **64**, 488 (1987).
2. K. R. Reddy, K. Mogilaiah, and B. Sreenivasulu, *J. Indian Chem. Soc*., **64**, 193 (1987).
3. K. R. Reddy, K. Mogilaiah, and B. Sreenivasulu, *J. Indian Chem. Soc*., **63**, 443 (1986).
4. G. Jones, *Org. Reactions*, **15**, 204 (1967).
5. P. S. Kwoi, Y. M. Kim, C. J. Kang, and T. W. Kwon, *Synth. Commun.*, **27**, 4091 (1997).
6. S. A. Ayoubi, F. Texier-Boullet, and D. Hamelin, *Synthesis*, 258 (1994).
7. A. K. Bose, M. S. Manhas, M. Ghosh, V. S. Raju, K. Tabei, and Z. Urbanczyk-Lipkowska, *Heterocycles*, **30**, 741 (1990).
8. M. Kidwai, N. Negi, and S. R. Chowdary, *Acta Pharm*., **45**, 511 (1995).
9. M. Kidwai, K. Kumar, Y. Goel, and K. C. Srivastava, *Bioorg. Med. Chem. Lett.*, **6**, 871 (1996).
10. M. Kidwai, N. Gupta, and K. C. Srivastava, *Indian Drugs*, **8**, 377 (1993).
11. M. Kidwai, S. Kohli, A. K. Goel, and M. P. Dubey, *Indian J. Chem*. (*B*), **37**, 1063 (1998).
12. K. Hino, Y. Nagai, and H. Uno, *Chem. Pharm. Bull*., **35**, 2819 (1987).
13. S. F. Campbell, J. D. Hardstone, and M. J. Palmer, *J. Med. Chem*., **31**, 1031 (1988).
14. H. Gilman, I. Zarember, and J. A. Beel, *J. Am. Chem. Soc*., **74**, 3177 (1952).
15. R. Rodriguez, US Pat. 3737540; *Chem. Abstr*., **79**, 42554 (1973).
16. G. B. Barlin and W. L. Tan, *Aust. J. Chem*., **37**, 1065 (1984).
17. J. Matsumoto, Y. Nishimura, and S. Nakamura, Fr. Pat. 2531084; *Chem. Abstr*., **101**, 505088 (1984).
18. P. L. Ferrarini, C. Mori, M. Badawneh, C. Manera, A. Martinelli, M. Miceli, F. Romagnoli, and G. Saccomanni, *J. Heterocycl. Chem*., **34**, 1501 (1997).
19. K. J. D. Gorecki and E. M. Hawes, *J. Med. Chem*., **20**, 124 (1977).
20. M. Kidwai and S. Kohli, *Indian J. Chem*. (*B*), **40**, 248 (2001).
21. O. Meth-Cohn and B. Narine, *Tetrahedron*, **19**, 2045 (1978).
22. M. M. Ali Tasneem, K. C. Rajanna, and P. K. Prakash, *Synlett*, 251 (2001).
23. S. C. Nagam, G. S. Saharia, and H. R. Sharma, *Def. Sci. J*., **31**, 15 (1981).
24. I. N. D. Das and S. Dutt, *Proc. Indian Sci. Acad*., **8A**, 145 (1938).