A Comparative Study of Conventional Conditions Versus Microwave Irradiation for the Preparation of Novel 1,2-Dihydro-2-imino-7-methyl-1,6(6*H*)-naphthyridin-5-ones

Dieter Heber [a]* and Edmont V. Stoyanov [b]

[a] Department of Pharmaceutical Chemistry, University of Kiel, Gutenbergstr. 76, D-24118 Kiel, Germany,
[b] Department of Industrial Pharmacy, Faculty of Pharmacy, Medical University of Sofia, Dunav 2, BG-1000 Sofia, Bulgaria

Received February 7, 2000

Dedicated to the memory of Professor Raymond Castle (✞ August 11, 1999)

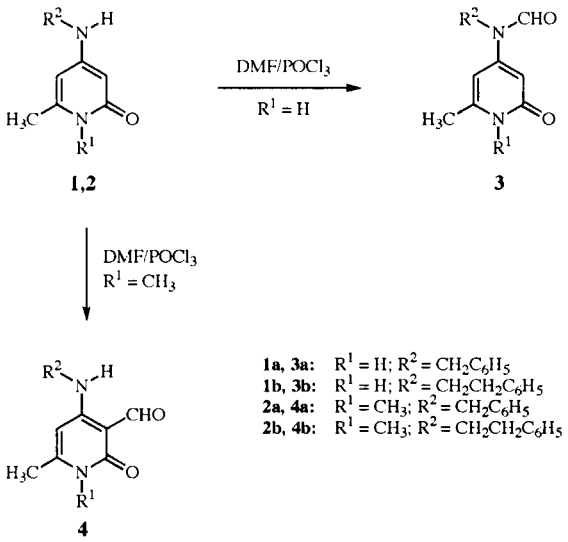
The synthesis of novel 1,6-naphthyridines **6** with potential activity against tuberculosis is described using the reaction sequence **2** → **4** → **6**. Depending on the ring *N*-substitution of the 4-alkylamino-6-methyl-2(1*H*)-pyridones **1** and **2** the electrophilic attack of the Vilsmeier reagent gives rise to the formation of the exocyclic *N*-formyl derivatives **3** from **1** and the corresponding 3-carbaldehydes **4** from **2**. 1,2-Dihydro-2-imino-7-methyl-1,6(6*H*)-naphthyridin-5-ones **6a-j** are prepared by the Knoevenagel reaction of **4** with CH-acidic nitriles **5**. These reactions are carried out using a comparative study of conventional conditions (room temperature or reflux) versus microwave irradiation.

J. Heterocyclic Chem., **37**, 871 (2000).

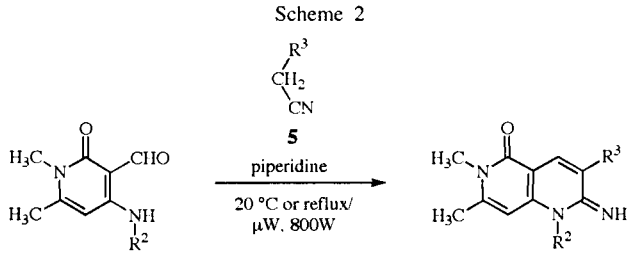
In a recent paper [1] one of us described the synthesis of substituted 2-imino-1,6-naphthyridin-5-ones from 4-alkylamino-2(1*H*)-pyridone-3-carbaldehydes. Some of the naphthyridines were found to cause inhibition of H37Rv tuberculosis strain in a minimal inhibitory concentration (MIC) from 3 to 12.5 μg/ml [2]. As to the best of our knowledge, antibacterial activity of 1,6-naphthyridines has not been previously described in the literature. In order to gain more insight in structure activity relationships we had to use a time saving method for the preparation of novel 1,6-naphthyridines **6** with varying substituents *via* the reaction sequence **2** → **4** → **6**. Microwave irradiation has been used to enhance a great number of classical organic reactions [3-8]. Since we applied successfully this modern method to transform 4-hydroxy-2(1*H*)-pyridones into the corresponding 4-alkylamino compounds **1**,**2** [9], we now tried the same approach to the synthesis of substituted 1,6-naphthyridines **6** comparing the results with those achieved under normal conditions.

The Vilsmeier-Haack formylation of the pyridones **1** and **2** was carried out by a method described in the literature [1] (Scheme 1) and gave surprisingly different new reaction products, namely the 4-*N*-formyl derivatives **3** exclusively from **1** and the corresponding 3-carbaldehydes **4** exclusively from **2** with very good yields (Table 1). An explanation for the formation of different products may be due to the blocking of the N-1 position with methyl group changing automatically the properties of the lactam group. The electrophilic attack of the Vilsmeier reagent preferentially occurs then at the C-3 carbon atom in the pyridone molecule.

Scheme 1



Scheme 2



The spontaneous cyclization to the final 1,6-naphthyridines **6** was achieved under Knoevenagel conditions by treatment of **4** with the CH-acidic nitriles **5** in the presence of a catalytic amount of piperidine. As described above we wanted to compare two procedures. First, we applied normal conditions (Method A) and found the best results for the preparation of: **6a-c** and **6f-h** using room temperature and a molar ratio of 1:3 equivalents for **4** to **5**, respectively without any solvent, **6d,e** and **6i,j** using reflux in ethanol and equimolar amounts of **4** and **5**.

Table 1

4-Alkylamino-6-methyl-2(1*H*)-pyridone 3-carbaldehydes **3** and **4**.

Compound	R^1	R^2	m.p. °C	Yield (%)	Solvent for recrystallization
3a	H	$CH_2C_6H_5$	225-226 (dec.)	78	MeOH
3b	H	$CH_2CH_2C_6H_5$	200-203 (dec.)	70	MeOH
4a	CH_3	$CH_2C_6H_5$	116-118	78	MeOH
4b	CH_3	$CH_2CH_2C_6H_5$	130-131	89	MeOH

Table 2

Reaction Conditions, Yields, and Some Physical Data for Novel 1,6-Naphthyridines **6a-j**.

Compound	R^2	R^3	m.p. °C/solvent	Reaction time & Yield (%) Method A	Method B
6a	$CH_2C_6H_5$	$COOCH_3$	207-209 MeOH	48 hours [a] (74)	3 minutes [a] (77)
6b	$CH_2C_6H_5$	$COOC_2H_5$	186-188 MeOH	48 hours [a] (29)	3 minutes [a] (80)
6c	$CH_2C_6H_5$	$COOCH(CH_3)_2$	185-186 MeOH	48 hours [a] (67)	3 minutes [a] (82)
6d	$CH_2C_6H_5$	p-C_6H_4-NO_2	201-202 EtOH	20 hours [b] (40)	6 minutes [c] (65)
6e	$CH_2C_6H_5$	$CONH_2$	> 250 EtOH	13 hours [b] (59)	6 minutes [c] (75)
6f	$CH_2CH_2C_6H_5$	$COOCH_3$	175-177 MeOH	48 hours [a] (72)	3 minutes [a] (76)
6g	$CH_2CH_2C_6H_5$	$COOC_2H_5$	168-170 MeOH	48 hours [a] (59)	3 minutes [a] (71)
6h	$CH_2CH_2C_6H_5$	$COOCH(CH_3)_2$	178-179 MeOH	48 hours [a] (68)	3 minutes [a] (79)
6i	$CH_2CH_2C_6H_5$	p-C_6H_4-NO_2	191-192 EtOH	20 hours [b] (24)	6 minutes [c] (56)
6j	$CH_2CH_2C_6H_5$	$CONH_2$	> 250 EtOH	13 hours [b] (51)	6 minutes [c] (59)

[a] At room temperature without any solvent. [b] Reflux in ethanol (normal conditions). [c] Ethanol was used as solvent in this cases.

Table 3

^{1}H-NMR Data (300 mz in $CDCl_3$) of **3**, **4**, and **6** Prepared [a]

Compound	Chemical Shifts (δ), J (Hz)
3a [b]	2.13 (s, 3H, 6-CH_3), 4.96 (s, 2H, C***H***$_2C_6H_5$), 5.85 (s, 1H, H-3), 6.30 (s, 1H, H-5), 7.18-7.34 (m, 5H arom.), 8.67 (s, 1H, CHO), 11.29 (br.s, 1H, 1-NH)
3b	2.38 (s, 3H, 6-CH_3), 2.87 (t, 2H, J = 7.8 Hz, C***H***$_2C_6H_5$), 3.98 (t, 2H, J = 7.9 Hz, N-CH_2), 5.88 (s, 1H, H-3), 6.34 (s, 1H, H-5), 7.20-7.37 (m, 5H arom.), 8.68 (s, 1H, CHO), 13.28 (br.s, 1H, 1-NH)
4a	2.19 (s, 3H, 6-CH_3), 3.40 (s, 3H, N-CH_3), 4.48 (d, 2H, J = 6.0 Hz, C***H***$_2C_6H_5$), 5.63 (s, 1H, H-5), 7.25-7.38 (m, 5H arom.), 10.22 (s, 1H, CHO), 10.52 (br.t., 1H, 4-NH)
4b	2.27 (s, 3H, 6-CH_3), 2.93 (t, 2H, J = 7.2 Hz, C***H***$_2C_6H_5$), 3.39 (s, 3H, N-CH_3), 3.48 (t, 2H, J = 7.1 Hz, N-CH_2), 5.58 (s, 1H, H-5), 7.21-7.35 (m, 5H arom.), 10.14 (br.t., 1H, 4-NH), 10.20 (s, 1H, CHO)
6a	2.25 (s, 3H, 7-CH_3), 3.48 (s, 3H, N-CH_3), 3.87 (s, 3H, COOC***H***$_3$), 5.52 (s, 2H, C***H***$_2C_6H_5$), 5.88 (s, 1H, H-8), 7.19-7.34 (m, 5H arom.), 8.70 (s, 1H, H-4), 9.35 (br.s., 1H, 2-NH)
6b	1.38 (t, 3H, J = 7.1 Hz, $COOCH_2$C***H***$_3$), 2.29 (s, 3H, 7-CH_3), 3.48 (s, 3H, N-CH_3), 4.33 (q, 2H, J = 7.2 Hz, COOC***H***$_2CH_3$), 5.52 (s, 2H, C***H***$_2C_6H_5$), 5.88 (s, 1H, H-8), 7.19-7.34 (m, 5H arom.), 8.71 (s, 1H, H-4), 9.35 (br.s., 1H, 2-NH)
6c	1.33 (d, 6H, J = 6.3 Hz, 2xCH_3 CH(C***H***$_3$)$_2$), 2.26 (s, 3H, 7-CH_3), 3.49 (s, 3H, N-CH_3), 5.24 (septet, 1H, J = 6.3 Hz, C***H***$(CH_3)_2$), 5.52 (s, 2H, C***H***$_2C_6H_5$), 5.88 (s, 1H, H-8), 7.19-7.34 (m, 5H arom.), 8.67 (s, 1H, H-4), 9.34 (br.s., 1H, 2-NH)
6d	2.25 (s, 3H, 7-CH_3), 3.41 (s, 3H, N-CH_3), 5.54 (s, 2H, C***H***$_2C_6H_5$), 5.96 (s, 1H, H-8), 7.23-7.38 (m, 5H arom.), 7.65 (d, 2H$_a$, J = 8.7 Hz), 7.77 (s, 1H, H-4), 8.30 (d, 2H$_b$, J=8.7 Hz)
6e [b]	2.34 (s, 3H, 7-CH_3), 2.51 (s, 3H, N-CH_3), 5.44 (s, 2H, C***H***$_2C_6H_5$), 6.22 (s, 1H, H-8), 7.19-7.35 (m, 5H arom.), 8.07 (s, 1H, H-4), 9.03 (br.s., 1H, 2-NH)
6f	2.27 (s, 3H, 7-CH_3), 2.94 (t, 2H, J=7.4 Hz, C***H***$_2C_6H_5$) 3.39 (s, 3H, N-CH_3), 3.87 (s, 3H, COOC***H***$_3$), 4.41 (br.t., 2H, N-CH_2), 5.96 (s, 1H, H-8), 7.22-7.33 (m, 5H arom.), 8.65 (s, 1H, H-4), 9.32 (br. s., 1H, 2-N-H)
6g	1.36 (t, 3H, J = 7.2 Hz, $COOCH_2$C***H***$_3$), 2.34 (s, 3H, 7-CH_3), 3.01 (t, 2H, J=7.7 Hz, C***H***$_2C_6H_5$), 3.44 (s, 3H, N-CH_3), 4.27 (q, 2H, J = 7.1 Hz, COOC***H***$_2CH_3$), 4.42 (br. t., 2H, N-CH_2), 5.83 (s, 1H, H-8), 7.21-7.34 (m, 5H arom.), 8.67 (s, 1H, H-4), 9.36 (br.s., 1H, 2-NH)

Table 3 (continued)

Compound	Chemical Shifts (δ), J (Hz)
6h	1.35 (d, 6H, J = 6.3 Hz, 2xCH_3 CH(CH_3)$_2$), 2.37 (s, 3H, 7-CH_3), 3.03 (t, 2H, J=8.0 Hz, $CH_2C_6H_5$), 3.48 (s, 3H, N-CH_3), 4.42 (br. t., 2H, N-CH_2), 5.22 (septet, 1H, J = 6.3 Hz, $CH(CH_3)_2$), 5.84 (s, 1H, H-8), 7.20-7.34 (m, 5H arom.), 8.64 (s, 1H, H-4), 9.39 (br.s., 1H, 2-NH)
6i	2.39 (s, 3H, 7-CH_3), 3.04 (t, 2H, J=7.8 Hz, $CH_2C_6H_5$), 3.49 (s, 3H, N-CH_3), 4.42 (br. t., 2H, N-CH_2), 5.98 (s, 1H, H-8), 7.26-7.33 (m, 5H arom.), 7.61 (d, $2H_a$, J=8.7 Hz), 7.69 (s, 1H, H-4), 8.31 (d, $2H_b$, J=8.7 Hz)
6j [b]	2.44 (s, 3H, 7-CH_3), 2.89 (t, 2H, J=7.9 Hz, $CH_2C_6H_5$), 3.39 (s, 3H, N-CH_3), 4.33 (br. t., 2H, N-CH_2), 6.36 (s, 1H, H-8), 7.23-7.38 (m, 5H arom.), 7.99 (s, 1H, H-4), 9.02 (br.s., 1H, 2-NH)

[a] All new compounds afforded elemental analysis within ± 0.4 % for C, H, and N. [b] The DMSO-d_6 was used in these cases as a solvent

Table 4

Analytical Data of **3**, **4**, and **6** Prepared

Compound	Molecular Formula (Molecular Weight)	Analysis Calcd./Found C	H	N
3a	$C_{14}H_{14}N_2O_2$	69.41	5.82	11.56
	242.3	69.23	5.71	11.41
3b	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93
	256.3	69.95	6.36	10.80
4a	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93
	256.3	70.05	6.18	10.84
4b	$C_{16}H_{18}N_2O_2$	71.09	6.71	10.36
	270.3	70.88	6.63	10.49
6a	$C_{19}H_{19}N_3O_3$	67.64	5.68	12.46
	337.4	67.55	5.59	12.35
6b	$C_{20}H_{21}N_3O_3$	68.36	6.02	11.96
	351.4	68.07	6.11	11.82
6c	$C_{21}H_{23}N_3O_3$	69.02	6.34	11.50
	365.4	68.82	6.22	11.58
6d	$C_{23}H_{20}N_4O_3$	68.99	5.03	13.99
	400.4	68.77	5.11	13.87
6e	$C_{18}H_{18}N_4O_2$	67.07	5.63	17.38
	322.3	66.89	5.54	17.24
6f	$C_{20}H_{21}N_3O_3$	68.36	6.02	11.96
	351.4	68.19	5.91	11.79
6g	$C_{21}H_{23}N_3O_3$	69.02	6.34	11.50
	365.4	68.82	6.23	11.41
6h	$C_{22}H_{25}N_3O_3$	69.64	6.64	11.07
	379.4	69.41	6.56	11.15
6i	$C_{24}H_{22}N_4O_3$	69.55	5.35	13.52
	414.4	69.29	5.25	13.42
6j	$C_{19}H_{20}N_4O_2$	67.84	5.99	16.66
	336.3	67.59	5.88	16.57

Microwave irradiation was carried out in an ordinary domestic microwave oven at 800 Watt reducing the reaction time dramatically (Method B, Table 2). The formation of **6** was monitored by TLC in preliminary tests the microwave oven being stopped at 1 minute intervals to get the reaction times indicated in Table 2. The experimental results showed that the rate of reaction depended on the Watt recorded. In order to find the best conditions for Method B, we performed experiments at 100, 250, 440, and 600 Watt settings and found mixtures of the starting compound and the product. On the other hand, longer irradiation time caused decomposition products.

The 1,6-naphthyridines **6** are relatively stable towards hydrolysis. For example, no change of the starting compounds was registered after heating **6i** with conc. hydrochloric acid or with 10% sulphuric acid at 100 °C or refluxing it with KOH in EtOH for 1 hour.

In conclusion, the present procedure for the preparation of 2-imino-1,6(6*H*)-naphthyridin-5-ones **6** has high advantages over the existing methods and will make a useful and important addition to present methodologies. The main advantage of this new method is the dramatical reduction of the reaction time.

EXPERIMENTAL

All reactions were performed using starting material and solvents as obtained without further purification. The ^{1}H nmr spectra were recorded on a Bruker instrument ARX 300 at 300 K. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Coupling constants (J) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols s(singlet), d(doublet), t(triplet), q(quartet), quint(quintet), m(multiplet), br (broad signal). IR spectra were recorded as KBr pellets on a Perkin Elmer PC1600 FT IR instrument; IR absorption bands are given as wavenumbers in cm^{-1}. Elemental analyses were performed with a Heraeus CHN-analyzer at the Institute of Inorganic Chemistry at the University of Kiel. TLC monitoring was carried out by using precoated aluminium sheets, 0.2 mm of silica gel Merck GF_{254}, eluted by hexane/chloroform/acetic acid (5:5:2, v:v) for compounds **3**, **4** and chloroform/acetone/methanol (3:3:1, v/v) for compounds **6**.

Formyl Derivatives **3** and **4** of 4-Alkylamino-6-methyl-2(1*H*)-pyridones **1** and **2**.

The Vilsmeier formylation was performed using a procedure described in the literature [1]. The physical data are given in Table 1, the spectral data in Table 3 and the analytical cata in Table 4.

1,6-Dialkyl-1,2-dihydro-2-imino-1,6(6*H*)-naphthyridin-5-ones **6a-j**.

General Procedure.

Method A.

A mixture of the corresponding 3-carbaldehyde **4** (1 mmol), the CH-acidic nitrile **5** (3 mmol) and 1 drop of piperidine was

allowed to stay at 20 °C for 48 hours (TLC monitoring). Using *p*-nitrobenzylcyanide (**5d**) or cyanacetic acid amide (**5e**), equimolar amounts of the reactants (1 mmol) were solved in ethanol (3 ml). After addition of 1 drop of piperidine the reaction mixture was refluxed for 13-20 hours under stirring. The separated crystals were filtered and washed with 50% methanol. Yields and solvents for recrystallisation are shown in Table 2.

Method B.

The reaction mixtures were prepared as described above and placed into a 15 ml pressure tube (ALDRICH, with threaded type A plug, length 10.2 cm and additionally provided with a teflon ring). Then the reaction tube was placed in the center of an 800 ml beaker which was filled with vermiculite, a polymeric material for covering hazardous compounds in packages. After irradiation in an ordinary domestic microwave oven (Panasonic NN-5206 with rotating plate) for the period shown in Table 2, the reaction mixture was cooled. In preliminary tests the microwave oven was stopped at 1 minute intervals to get the reaction time for the production of **6**. The exact temperature of the reaction mixture was not measured because the beaker was filled with vermiculite so that the thermometer could not be seen. Work-up, isolation, and purification of **6** was performed identically to the procedure given above. Yields, melting points, and solvents for recrystallisation are given in Table 2, the spectral data in Table 3, and the analytical data in Table 4.

Acknowledgements.

The autors would like to thank to the DAAD, *NATO Science Fellowship program* for supporting the present work.

REFERENCES AND NOTES

* To whom all correspondence should be addressed. Fax +49/0431/8801352, E-mail: dheber@pharmazie.uni-kiel.de.

[1] I. C. Ivanov, E. V. Stoyanov, P. S. Denkova and V. S. Dimitrov, *Liebigs Ann./Recueil*, 1777 (1997).

[2] For further information about antituberculosis tests: TAACF program; E-mail: taacf1@sri.org Fax: (internat.) +205/581-2870 (USA).

[3] D. M. P. Mingos and D. R. Baghurst, *Chem. Soc. Rev.* **20**, 1 (1991).

[4] R. J. Giguere, Organic Synthesis: Theory and Application; Ed. by JAI Press Inc., Vol. **1** (1989).

[5] R. A. Abramovitch and A. Bulman, *Synlett*, 795 (1992).

[6] S. Caddick, *Tetrahedron*, **51**, 10403 (1995).

[7] J. H. Clark, Catalysis of Organic Reactions by Supported Inorganic Reactions; Ed. by VCH: New York, 1994.

[8] D. Subhas Bose and B. Jayalakshmi, *J. Org. Chem.*, **64**, 1713 (1999).

[9] D. Heber and E. V. Stoyanov, *Synlett*, 1747 (1999).