The Microwave Assisted Nucleophilic Substitution of 4-Hydroxy-6-methyl-2(1*H*)-pyridones

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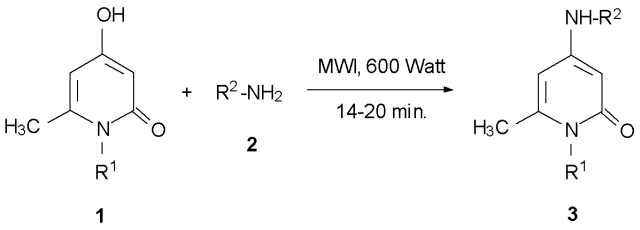
Abstract: The condensation of 4-hydroxy-6-methyl-2(1*H*)-pyridones **1** with araliphatic amino compounds **2** gives rise to the 4-alkylamino-6-methyl-2(1*H*)-pyridones **3**. Irradiation using an ordinary domestic microwave oven provides a fast and simple method for their preparation. However, under the conditions used, aliphatic and aromatic amines gave no reaction.

Key words: 4-alkylamino-6-methyl-2(1*H*)-pyridones, microwave irradiation, condensation

In a recent paper[1] one of us described the synthesis of 2-imino-1,6(6*H*)-naphthyridin-5-ones with interesting antituberculosis activity. The reaction sequence involved the Vilsmeier formylation of 1-alkyl-4-alkylamino-6-methyl-2(1*H*)-pyridones **3** followed by condensation of the corresponding heterocyclic carbaldehydes with methylene active nitriles under Knoevenagel reaction conditions. The preparation of the pyridones **3j,k** described previously by Castillo *et al.*[2] requested long reaction times starting from 4-hydroxy-6-methyl-2-pyrone and the yields and the molar equivalents were not reported in this paper. Other authors[3,4] reported the preparation of compounds **3a** and **3b** using drastic reaction conditions (reflux in benzylamine under nitrogen for 72 hours). In a previous paper[5] on the preparation of 4-hydroxy- and 4-alkylamino-2(1*H*)-pyridones we established that the reaction time requested in a boiling solution of the amine ranges from 2 to 5 hours for the preparation of **3h-k**.

In order to save the 2-imino character of novel 1,6-naphthyridines synthesized for the determination of structure-activity relationships of these heterocyclic compounds, we needed a facile method for the preparation of the starting 4-alkylamino-6-methyl-2(1*H*)-pyridones **3**. In our research work on amino acids we applied successfully microwave irradiation which has been used to enhance a great number of classical organic reactions.[6-8] Thus, in a typical procedure the nucleophilic substitution of the hydroxy group of 4-hydroxy-6-methyl-2(1*H*)-pyridones **1** was carried out using an excess of amine **2** (ratio **1** : **2** = 1 : 4.5) without any solvent under microwave irradiation for a short of time (Scheme 1). It is noteworthy to mention that the starting 4-hydroxypyridones **1** were isolated after 20 minutes at 100, 240 and 440 W so that no reaction had taken place under these conditions. When switching to 600 W the process was accomplished after 14 - 20 minutes and the reaction mixture had changed from suspension to solution (Table 1). Shorter irradiation times gave always mixtures of starting compounds **1** and products **3**. The pressure reaction tube used for these experiments must be provided with a teflon ring to close the tube and to permit longer irradiation at 600 W. 4-Hydroxy-6-methyl-2(1*H*)-pyridone (R^1=H) did not react with 1-phenylethylamine neither did 1-ethyl-4-hydroxy-6-methyl-2(1*H*)-pyridone with all used amines under the reaction conditions used. Irradiation time for each experiment was determined by tlc-control with pre-coated plates of silica gel every 2 minutes.



Scheme 1

Table 1 Nucleophilic Substitution of 4-Hydroxy-6-methyl-2(1*H*)-pyridones **1** with Araliphatic Amino Compounds **2** to Give 4-Amino-6-methyl-2(1*H*)-pyridones **3**

Product	R^1	R^2	Yield (%)	Reaction time[a] (in min.)
3a	H	$CH_2C_6H_5$	79	14
3b	CH_3	$CH_2C_6H_5$	69	16
3c	H	$CH_2CH_2C_6H_5$	90	14
3d	CH_3	$CH_2CH_2C_6H_5$	80	16
3e	CH_3	$CH(CH_3)C_6H_5$	78	18
3f	$CH_2C_6H_5$	$CH(CH_3)C_6H_5$	60	16
3g	$CH_2CH_2C_6H_5$	$CH(CH_3)C_6H_5$	81	20
3h	$CH_2C_6H_5$	$CH_2C_6H_5$	89	15
3i	$CH_2CH_2C_6H_5$	$CH_2CH_2C_6H_5$	84	15
3j	$CH_2C_6H_5$	$CH_2CH_2C_6H_5$	91	15
3k	$CH_2CH_2C_6H_5$	$CH_2C_6H_5$	82	15

[a] at 600 Watt
All new compounds gave satisfactory microanalyses: C, H, N ±0.40,

In order to establish the general behaviour of this reaction under microwave conditions, several types of amino compounds were studied. The following amines did not give any reaction under the conditions described above: ali-

phatic primary amino compounds such as allylamine, propylamine, 2-hydroxyethylamine, and *N*,*N*-dibutylethylene diamine as well as methylamine and ethylamine as water solution and the aromatic amines aniline, p-toluidine, *N*-methylaniline, 4-hydroxyaniline, and 4-aminopyridine and the secondary aliphatic amines piperidine and diisobutylamine.

Structural assignment of **3(c-j)** was made on the basis of spectral data (^{1}H NMR).

In conclusion, the present procedure for the amination of 4-hydroxy-2(1*H*)-pyridone **3** has some advantages over the existing methods and will make a useful and important addition to present methodologies. The main advantages of this new method are short reaction times and excellent yields.

Acknowledgement

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References and Notes

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(9) **General procedure:** A mixture of 1 mmol of the corresponding 4-hydroxy-2(1*H*)-pyridone **3** and 4.5 mmol of benzyl-, 1-phenylethyl- or 2-phenylethylamine **2** was filled 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 rotate plate) for the period shown in Table 1, the reaction mixture was cooled. Adding ice-cold ethyl acetate the separated solid was collected by filtration and washed twice with ethyl acetate to give tlc pure compounds. The compounds were recrystallized from MeOH, EtOH, or 2-PrOH. TLC monitoring: precoated aluminium sheets, 0.2 mm layer of silicagel Merck GF_{254}, eluted by methylene chloride/acetone/methanol (3:2:1, v/v); detection by Fluotest® Universal (λ = 254/366 nm).
^{1}H-NMR spectroscopic data of some of 4-alkylamino-2(1*H*) -pyridones **3** (300 MHz): **3a** (DMSO-d_6): δ = 2.01 (s, 3H, 6-CH_3), 4.20 (d, 2H, J= 5.8 Hz, C***H***$_2$C$_6$H$_5$), 4.89 (s, 1H, H-3), 5.52 (s, 1H, H-5), 6.96 (t, 1H, J = 6.8 Hz, 4-N-H), 7.22-7.36 (m, 5H arom.), 10.43 (s, 1H, 1-N-H).
3b ($CDCl_3$): δ = 2.23 (s, 3H, 6- CH_3), 3.40 (s, 3H, N-CH_3), 4.26 (d, 2H, J = 5.5 Hz, C***H***$_2$C$_6$H$_5$), 4.40 (br.t, 1H, N-H), 5,52 (s, 2H, H-3 and H-5), 7.26-7.36 (5H arom.).
3c (DMSO-d_6): δ = 2.21 (s, 3H, 6-CH_3), 2.79 (t, 2H, J = 7.1 Hz, C***H***$_2$C$_6$H$_5$), 3.19 (t, 2H, J = 7.5 Hz, N-C***H***$_2$), 4.85 (s, 1H, H-3), 5.48 (s, 1H, H-5), 6.45 (t, 1H, J = 5.3 Hz, N***H***-CH_2), 7.17-7.32 (5H arom.), 10.39 (s, 1H, 1-N-H).
3d ($CDCl_3$): δ = 2.22 (s, 3H, 6-CH_3), 2.88 (t, 2H, J = 6.9 Hz, C***H***$_2$C$_6$H$_5$), 3.23 (t, 2H, J = 7.1 Hz, N- C***H***$_2$), 3.41 (s, 3H, N-CH_3), 4.04 (br.t., 1H, N-H), 5.41 (s, 1H, H-3), 5.53 (s, 1H, H-5), 7.17-7.34 (m, 5H arom.).
3e (DMSO-d_6): δ = 1.38 (d, 3H, J = 6.8 Hz, C***H***$_3$-CH), 2.17 (s, 3H, 6-CH_3), 3.23 (s, 3H, N-CH_3), 4.41 (p, 1H, J = 6.8 Hz, C***H***-CH_3), 4.89 (s, 1H, H-3), 5.66 (s, 1H, H-5), 6.80 (d, 1H, J = 6.8 Hz, 4-N-H), 7.30-7.34 (m, 5H arom.).
3f (DMSO-d_6): δ = 1.86 (d, 3H, J = 6.7 Hz, C**H**$_3$-CH), 2.16 (s, 3H, 6-CH_3), 4.48 (p, 1H, J = 6.9 Hz, C***H***-CH_3), 5.09 (s, 2H, C***H***$_2$C$_6$H$_5$), 5.15 (q, 1H, J = 16 Hz, H-3), 5.71 (s, 1H, H-5), 7.03 (d, 1H, J = 6.8 Hz, N***H***-CH), 7.20-7.34 (m, 10H arom.).
3g (DMSO-d_6): δ = 1.38 (d, 3H, J = 6.8 Hz, C***H***$_3$-CH), 2.04 (s, 3H, 6- CH_3), 2.75 (t, 2H, J = 7.6 Hz, C***H***$_2$C$_6$H$_5$), 3.89 (t, 2H, J = 7.9 Hz, N-C***H***$_2$), 4.43 (p, 1H, J = 6.8 Hz, C***H***- CH_3), 4.93 (s, 1H, H-3), 5.62 (s, 1H, H-5), 6.84 (t, 1H, J = 6.8 Hz, 4-N-H), 7.10-7.33 (m, 10H arom.).

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