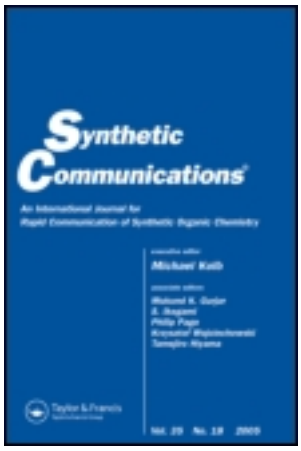

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SYNTHESIS OF HIGHLY SUBSTITUTED 1,6-NAPHTHYRIDINES: A REINVESTIGATION

Eva Veverková [a] , Marika Nosková [a] & Štefan Toma [b]

[a] Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Bratislava, SK-842 15, Slovakia

[b] Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Bratislava, SK-842 15, Slovakia

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SYNTHESIS OF HIGHLY SUBSTITUTED 1,6-NAPHTHYRIDINES: A REINVESTIGATION

Eva Veverková,* Marika Nosková, and Štefan Toma†

Department of Organic Chemistry,
Faculty of Natural Sciences, Comenius University,
SK-842 15 Bratislava, Slovakia

ABSTRACT

A reinvestigation of the recently described method of synthesis of highly substituted 1,6-naphthyridines was carried out. It was found out that the reaction of chalcones with malononitrile catalysed by pyrrolidine afforded the mixture of four products both when thermal as well as microwave heating was used. The claimed[1] 1,6-naphthyridines formation were exceptions.

Key Words: Microwaves; 1,6-Naphthyridines; Reinvestigation

INTRODUCTION

The 1,6-naphthyridines are interesting substance from the view of their biological properties. Murugan et al. have disclosed very recently in this

*E-mail: veverkova@fns.uniba.sk
†Corresponding author. Fax: 421-2-60296-690; E-mail: toma@fns.uniba.sk

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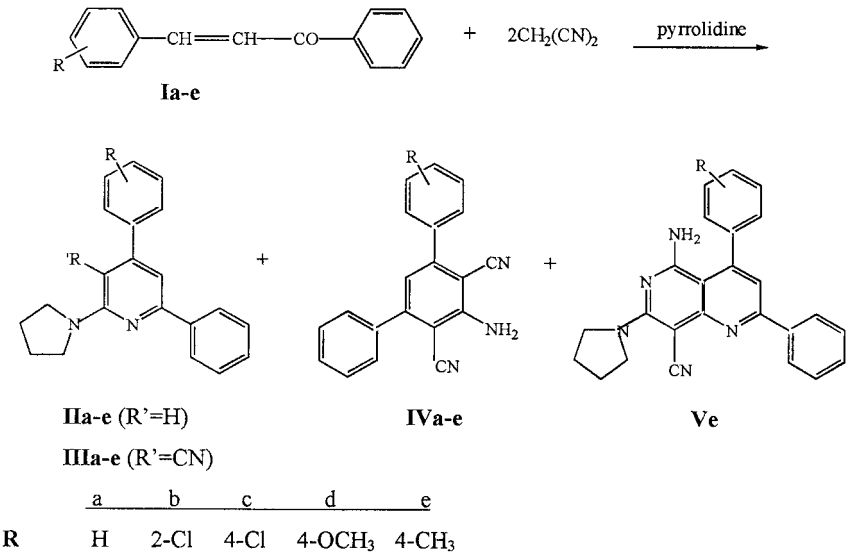
Journal[1] an interesting one-step method of their synthesis, by just refluxing of ethanolic solution of chalcones with malononitrile using pyrrolidine as the catalyst. They observed formation of the desired 1,6-naphthyridines, as the single products, in 60–76% yield after 25 h refluxing of the reaction mixture. It is well known that the reaction time of many heterogeneous as well as homogeneous reactions can be considerably shortened when microwave heating is applied to the reaction mixture.[2–7] We decided therefore to check if microwave effects would be observed in the synthesis of 1,6-naphthyridines.

RESULTS AND DISCUSSION

We started our experiments using unsubstituted chalcone as the reagent and ethanol as the solvent. After 2 min of the microwave irradiation only one highly substituted benzene derivative (**IVa**) in 68% yield, but no 1,6-naphthyridine irradiation was isolated from the reaction mixture. (Scheme 1, R = H). It is well known that ethanol is not a good solvent for microwave reactions, therefore we decided to perform the reaction in chlorobenzene as the solvent as well as the solvent free reaction. Two products were isolated from the reaction carried out in chlorobenzene (reaction time 5 min, $T_{fin} = 125^{\circ}C$) one being 3-cyano-2-(pyrrolidine-1-yl)-4,6-diphenylpyrridine



Scheme 1.

(**IIIa**, 56%) and the other one 1-amino-2,6-dicyano-4,5-diphenylbenzene (**IVa**, 25%). From the solvent free reaction were isolated 33% of 2-(pyrrolidine-1-yl)-4,6-diphenylpyrridine (**IIa**), 18% of **IIIa** and 18% **IVa**.

In order to see if these unusual results are not caused by microwave irradiation we decided to repeat exactly the procedure described by Murugan et al., that is using thermal heating of the reaction mixture in ethanol for 25 h. To our surprise the result was similar as in the solvent-free reaction under microwave irradiation. Compounds **IIa** (7%), **IIIa** (38%) and **IVa** (27%) were isolated but no 1,6-naphthyridine was isolated. The experiments with substituted chalcones were carried out to check if these results can be influenced by substituents on the benzene ring of chalcone.

From the data given in the Table 1 similar results were observed with different chalcones,and observed product/substituent dependence is difficult

Table 1. Microwave Assisted Reaction of Chalcones Ia–e with Malonodinitrile and Pyrrolidine, $P = 120$ W

Comp.	React. Condition*	React. Time [min : sec]	T_{fin} [°C]	Isolated Yields [%] II	III	IV	V
a	A	2 : 00	72	–	–	68	–
	B	5 : 00	125	–	56	25	–
	C	2 : 00	132	33	18	18	–
	D	25	78	7	38	27	–
b	A	2 : 30	70	–	17	43	–
	B	5 : 00	115	–	54	23	–
	C	2 : 30	164	18	40	18	–
c	A	2 : 00	72	18	33	30	–
	B	5 : 00	116	–	52	21	–
	C	2 : 40	186	42	11	18	–
	D	25	78	12	17	43	–
d	A	2 : 00	71	–	17	–	–
	B	5 : 00	121	–	23	6	–
	C	2 : 00	178	19	11	25	–
	D	25	78	–	28	–	–
e	A	3 : 00	64	–	–	74	–
	B	5 : 00	105	–	65	7	–
	C	2 : 20	122	14	23	50	10
	D	25	78	–	42	47	9

*A-ethanol, B-chlorbenzene, C-free solvent, D-thermal heating (time in hour).

to rationalize. On the other hand we can conclude that microwave heating in chlorobenzene or at solvent-free conditions prefer the pyridine ring formation over the benzene ring formation (**IV**). Small amount of 1,6-naphthyridine derivative (**Ve**) was isolated only in the reaction with p-methyl derivative of chalcone. We made also an unsuccessful attempt on the 1,6-naphthyridine synthesis in which a 10 molar excess of malononitrile was used.

It is of interest to note that Victory et al.[8,9] made a thorough investigation of the reaction of chalcone with malononitrile in anhydrous ethanol using piperidine as the catalyst. They never isolated 1,6-naphthyridine derivative, only benzene derivative **III** and 3-benzoyl-4-hydroxy-2,4,5-triphenyl-1,1-cyclohexanecarbonitrile. They isolated pyridine derivatives[8] only in experiments when sodium alkoxide was used as the catalyst. We can assume therefore that the results we achieved in ethanole (conditions A,D) could be modified by traces of sodium ethoxide which could be found in ethanol distilled from sodium.

The fact that we could repeat results described by Murugan et al.[1] and the described procedure for 1,6-naphthyridine synthesis simply prompted us to write to Professor Ramakrishnan and ask him if there was not something omitted from the experimental procedure. His answer was negative and he sent us a detailed procedure in which was stated that they have used lime distilled ethanol. We have used both 96% ethanol as well as very dry ethanol pre-distiled from lime and then dried by natrium, but the results were the same: negative. The possible explanation for the very different results of Professor Ramakrishnan and ours could be that some special, not specified salt (catalyst) could be extracted into ethanol from the Indian lime.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were measured on Varian Gemini 2000 instrument, working frequency 300 MHz and 75 MHz respectively. $CDCl_3$ was used as the solvent and tetramethylsilane as an internal standard. Microanalysis were carried out on a Carlo Erba Strumenstacione Milano CHN analyser, model 1106. Melting point were determined on a Kofler apparatus and are not corrected. All microwave experiments were carried out in the SYNTHEWAVE 402, PROLABO reactor.

General Procedure for the Microwave Experiments

A mixture of 3-aryl-1-fenyl propenone **Ia–e** (0.005 mol), malononitrile (0.6 g, 0.01 mol) and pyrrolidine (0.84 mL, 0.01 mol) in solvent (40 mL) was

irradiated in the microwave reactor (120 W input power). After removing the solvent under reduced pressure, the residue was chromatographed over a silica gel column. Using hexane–ethyl acetate mixture (5 : 1) as eluent was obtained the products **II** and **III**, with hexane–ethyl acetate (3 : 1) was obtained the product **IV** and with ethyl acetate was obtained the product **V**. The reaction conditions (solvent or solvent-free), the reaction time and the yields are given in Table 1 (reaction condition A,B,C).

General Procedure for Reactions Under Thermal Heating

A mixture of 3-aryl-1-fenyl propenone **I** (0.005 mol), malononitrile (0.6 g, 0.01 mol) and pyrrolidine (0.84 mL, 0.01 mol) in ethanole (40 mL) was refluxed for 25 h. After removing the solvent under reduced pressure, the residue was chromatographed over a silica gel column. Using hexane–ethyl acetate mixture (5 : 1) as eluent was obtained the products **II** and **III**, with hexane–ethyl acetate (3 : 1) was obtained the product **IV** and with ethyl acetate was obtained the product **V**. The yields are given in Table (reaction conditions D).

2,4-Diphenyl-6-pyrrolidin-1-yl-pyridine (IIa): m.p. 158–159°C (Ref. [10] 161–162°C); spectroscopic and analytical data are in agreement with the reported ones.[10]

4-(2-Chlorphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine (IIb): m.p. 143–144°C; ^{1}H NMR ($CDCl_3$) δ 2.03 and 3.60 (2t, 8H), 6.36 (d, 1H), 7.08 (d, 1H), 7.29–7.49 (m, 7H), 8.06–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.84, 49.24, 104.95, 110.49, 124.15, 124.66, 127.04, 129.00, 129.15, 129.25, 131.54, 134.72, 137.04, 141.51, 150.53, 156.17, 158.14. Anal. Calcd. for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37; Cl, 10.58. Found: C, 74.83; H, 5.73; N, 8.38; Cl 10.23.

4-(4-Chlorphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine (IIc): m.p. 159–161°C; ^{1}H NMR ($CDCl_3$) δ 2.05 and 3.62 (2t, 8H), 6.44 (d, 1H), 7.17 (d, 1H), 7.43–7.47 (m, 7H), 7.61 (d, 2H), 8.06–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.83, 47.06, 102.97, 106.77, 127.12, 128.63, 128.69, 128.79, 129.21, 134.67, 139.00, 140.41, 149.32, 156.39, 157.93. Anal. Calcd. for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37; Cl, 10.58. Found: C, 74.81; H, 5.76; N, 8.38; Cl 10.21.

4-(4-Methoxyphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine (IId): m.p. 143–144°C; ^{1}H NMR ($CDCl_3$) δ 2.04 and 3.63 (2t, 8H), 3.87 (s, 3H), 6.46 (d, 1H), 7.01 (d, 2H), 7.20 (d, 1H), 7.37–7.47 (m, 3H), 7.63 (d, 2H), 8.08–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.52, 49.43, 55.15, 105.78, 110.48, 111.45, 124.05, 126.27, 128.98, 131.23, 136.85, 137.95, 146.75,

153.42, 158.79, 159.85. Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.06; H, 6.73; N, 8.50.

4-(4-Methylphenyl)-2-phenyl-6-(pyrrolidin-1-yl) pyridine (IIe): m.p. 122–124°C; ^{1}H NMR ($CDCl_3$) δ 2.04 and 3.62 (2t, 8H), 2.42 (s, 3H), 6.49 (d, 1H), 7.13 (d, 2H), 7.22 (d, 1H), 7.38–7.48 (m, 3H), 7.58 (d, 2H), 8.08–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.21, 25.62, 46.84, 102.86, 106.88, 116.92, 126.99, 128.39, 128.84, 129.75, 137.46, 138.35, 140.49, 150.27, 155.92, 157.81. Anal. Calcd. for $C_{22}H_{22}N_2$: C, 84.02; H, 7.05; N, 8.91. Found: C, 83.98; H, 6.97; N, 8.93.

2,4-Diphenyl-6-pyrrolidin-1-yl-pyridine-5-carbonitrile (IIIa): m.p. 133°C; ^{1}H NMR ($CDCl_3$) δ 2.04 and 3.94 (2t, 8H), 7.11 (s, 1H), 7.45–7.50 (m, 7H), 7.51–7.58 (m, 2H), 8.05–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.84, 47.09, 102.85, 105.72, 126.05, 126.33, 126.55, 127.16, 129.01, 135.73, 139.82, 147.42, 154.43, 157.90. Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 80.54; H, 5.09; N, 12.54.

4-(2-Chlorphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine-5-carbonitrile (IIIb): m.p. 175–176°C; ^{1}H NMR ($CDCl_3$) δ 2.04 and 3.94 (2t, 8H), 7.03 (s, 1H), 7.36–7.54 (m, 7H), 8.05–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.65, 49.25, 88.69, 109.57, 118.35, 126.92, 128.65, 129.99, 130.05, 130.25, 130.39, 132.50, 137.08, 138.19, 157.25, 158.14. Anal. Calcd. for $C_{22}H_{18}ClN_3$: C, 73.43; H, 5.04; N, 11.68; Cl, 9.85. Found: C, 72.91; H, 5.04; N, 11.49; Cl, 9.74.

4-(4-Chlorphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine-5-carbonitrile (IIIc): m.p. 168–169°C; ^{1}H NMR ($CDCl_3$) δ 2.04 and 3.93 (2t, 8H), 7.06 (s, 1H), 7.45–7.54 (m, 7H), 8.06–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.69, 49.48, 86.95, 109.06, 118.99, 127.12, 130.11, 135.57, 136.47, 138.18, 156.29, 158.12, 158.37. Anal. Calcd. for $C_{22}H_{18}ClN_3$: C, 73.43; H, 5.04; N, 11.68; Cl, 9.85. Found: C, 72.91; H, 5.03; N, 11.47; Cl 9.70.

4-(4-Methoxyphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine-5-carbonitrile (IIId): m.p. 179–181°C; ^{1}H NMR ($CDCl_3$) δ 2.03 and 3.92 (2t, 8H), 3.04 (s, 3H), 7.02 (d, 2H), 7.09 (s, 1H), 7.44–7.46 (m, 3H), 7.56 (d, 2H), 8.06–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.96, 49.74, 55.61, 87.23, 109.48, 114.33, 115.12, 127.51, 128.86, 130.12, 130.31, 130.50, 138.71, 157.41, 158.27, 158.72, 160.85. Anal. Calcd. for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 78.06; H, 6.21; N, 11.99.

4-(4-Methylphenyl)-2-phenyl-6-pyrrolidin-1-yl-pyridine-5-carbonitrile (IIIe): m.p. 156°C; ^{1}H NMR ($CDCl_3$) δ 2.03 and 3.93 (2t, 8H), 2.43 (s, 3H), 7.09 (s, 1H), 7.31 (d, 2H), 7.44–7.47 (m, 3H), 7.49 (d, 2H), 8.06–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.37, 24.71, 87.24, 109.29, 119.35, 127.26, 128.54, 128.63, 128.84, 129.34, 129.92, 135.13, 138.39, 139.44, 157.58, 158.04, 158.29. Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.39; H, 6.24; N, 12.38. Found: C, 81.09; H, 6.21; N, 12.65.

2-Amino-4,6-diphenylbenzene-1,3-carbodinitrile (IVa): m.p. 223–224°C (Ref. [8], 223–224°C), spectroscopic and analytical data are in agreement with the reported ones.[9]

2-Amino-4-(2-chlorphenyl)-6-phenylbenzene-1,3-carbodinitrile (IVb): m.p. 208–211°C (Ref. [11], 213–215°C), analytical data are in agreement with the reported ones.[11] ^{1}H NMR ($CDCl_3$) δ 5.39 (s, 2H), 6.84 (s, 1H), 7.35–7.61 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 94.92, 95.42, 115.79, 120.91, 122.74, 127.33, 128.75, 129.53, 129.77, 134.72, 135.05, 137.79, 140.01, 140.14, 151.73, 152.13, 153.92.

2-Amino-4-(4-chlorphenyl)-6-phenylbenzene-1,3-carbodinitrile (IVc): m.p. 249–251°C (Ref. [11], 250–251°C), analytical data are in agreement with the reported ones.[11] ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2H), 6.86 (s, 1H), 7.47–7.59 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 94.72, 95.28, 115.75, 119.88, 128.38, 128.98, 129.24, 129.75, 129.85, 135.76, 136.11, 137.24, 148.75, 150.32, 153.16.

2-Amino-4-(4-methoxyphenyl)-6-phenylbenzene-1,3-carbodinitrile (IVd): m.p. 176–179°C (Ref. [11], 178–179°C), analytical data are in agreement with the reported ones.[11] ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 5.36 (s, 2H), 6.88 (s, 1H), 7.02 (d, 2H), 7.49–7.59 (m, 7H), ^{13}C NMR ($CDCl_3$) δ 55.42, 94.95, 96.16, 111.32, 114.79, 122.45, 123.75, 126.33, 133.15, 133.96, 134.02, 136.92, 152.08, 154.25, 155.78, 159.63.

2-Amino-4-(4-methylphenyl)-6-phenylbenzene-1,3-carbodinitrile (IVe): m.p. 202–203°C (Ref. [11], 207°C), analytical data are in agreement with the reported ones.[11] ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 5.36 (s, 2H), 6.89 (s, 1H), 7.31 (d, 2H), 7.48–7.59 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 21.55, 95.01, 95.19, 116.22, 116.31, 120.29, 128.57, 128.66, 129.15, 129.88, 129.90, 134.83, 137.79, 140.23, 150.26, 150.42, 153.44.

5-Amino-4-(4-methylphenyl)-2-phenyl-7-(pyrrolidin-1-yl)-1,6-naphthyridine-8-carbonitrile (Ve): m.p. 249–250°C, ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 4H), 2.47 (s, 3H), 3.87 (t, 4H), 4.96 (s, 2H), 7.31–7.49 (m, 8H), 8.27–8.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.36, 25.52, 49.04, 103.71, 116.87, 120.24, 127.72, 128.32, 128.76, 129.79, 130.17, 136.53, 138.05, 139.27, 148.93, 156.88, 157.72, 157.91, 159.44. Anal. Calcd. for $C_{26}H_{23}N_5$: C, 77.01; H, 5.72; N, 17.27. Found: C, 76.83; H, 5.58; N, 17.48.

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NOTE ADDED IN PROOF

Authors of the paper in reference 1 made an unfair command. After an exchange of letters, they have published in this journal a paper "A Facile One Pot Synthesis of *m*-Terphenyl and Biaryl Derivatives" (Synth. Commun. 2001, 31, 3497). They are using the same procedure as described in reference 1, receiving different products, but they did not mention that their results described in 1 are not correct. They did not even mention this previous paper in the references.

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