One-pot Solvent and Catalyst-free Synthesis of Functionalized 1,8-Naphthyridines and Quinolines by Microwave Irradiation

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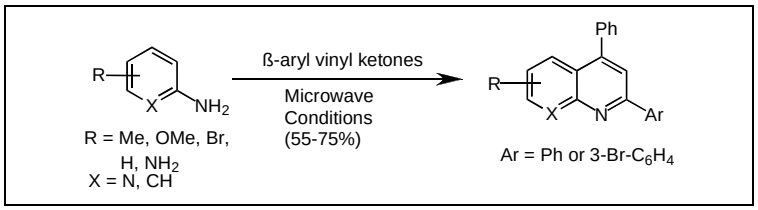

A series of functionalized, aryl substituted naphthyridines and quinolines has been synthesized by microwave-assisted one-pot two-component synthesis under solvent-free conditions in good yields by the reaction of a variety of aryl or heteroaryl amines and aryl vinyl ketones. A combinatorial type approach for a one-step microwave reaction has been developed where a ring-closing condensation is followed by a spontaneous aromatization to afford the functionalized aryl substituted 1,8-naphthyridines and quinolines.

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INTRODUCTION

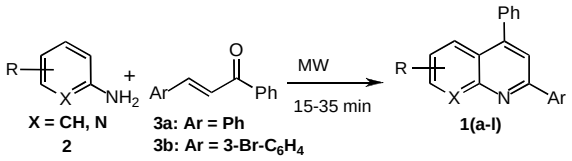
The compounds containing quinoline and naphthyridine systems are of great importance due to their broad spectrum of biological activities. Many of them are useful as antibacterial, antimalarial and potent anticancer compounds. Quinolines and their derivatives are of immense interest for their presence in many natural products [1] and drugs [2]. Substituted 1,8-naphthyridine compounds are also used as antihypertensives, antiarrhythmics, herbicide safeners and also as immunostimulants and antitumor agents [3]. Besides this, 2,7-difunctionalized-1,8-naphthyridines are used as important binding units in the molecular design of synthetic receptors [4] for the recognition of different biologically important substrates. The other important role of the naphthyridine system is in the field of bioinorganic and coordination chemistry where it is used for the synthesis of different ligands for metal ion coordination [5].

In our continuing search for the new synthetic methodologies [6] using microwave technique, we disclose here the development of a mild synthesis of substituted naphthyridines and quinolines under microwave irradiation. Quinoline based compounds were synthesized by many groups by using different Lewis acid catalyzed solid supported reactions [7] whereas the synthesis of naphthyridine based compounds [8] is less studied under microwave condition. Generally the synthesis of naphthyridine based compounds requires very drastic condition in conventional procedure [9]. Now-a-days microwave assisted organic reactions [10] draw tremendous attention of the scientific community all over the world for its excellent impact on ecology, easy work-up and time saving nature.

RESULTS AND DISCUSSION

Here we have performed the microwave-assisted condensation reaction of aryl or heteroaryl amines with β-aryl vinyl ketones for the synthesis of naphthyridine and quinoline heterocycles (Scheme I). Thus various substituted anilines and β-aryl vinyl ketones were subjected to microwave irradiation without any solid support for the synthesis of corresponding quinolines in good yields (Table 1). This method was successfully employed in the case of substituted heterocyclic amines by which 2,4,6-substituted 1,8-naphthyridines were synthesized in good yield (Table 1). To our knowledge, there is no precedent of this new synthesis of naphthyridines under such mild condition.

Scheme I



Synthesis of quinolines and naphthyridines from β-aryl vinyl ketones with aromatic and heteroaromatic amines respectively (for R, X and Ar see Table 1).

We have recently demonstrated the synthesis of 2,7-functionalized 1,8-naphthyridines [11]. However, a one-pot access to 2, 4, 6 or 7 substitued 1,8-naphthyridines is difficult. Therefore, this procedure offers a good scope of putting different aryl, alkyl and other functionalities with proper choice of aminopyridines and β-aryl vinyl ketones. Thus, reactions of suitably substituted 2-aminopyridines with β-aryl vinyl ketones afforded 7-methyl- (Table 1,

entries 5 and 6), 6-bromo- (Table 1, entries 7 and 8), and 7-amino (Table 1, entries 11 and 12) naphthyridines in good yields.

On the basis of the known chemistry of the β-aryl vinyl ketones and substituted aminopyridines, the following mechanism is proposed for the synthesis of functionalized 1,8-naphthyridines and quinolines (Scheme II). Initially the Michael addition probably occurred through amine group to the β position of the β-aryl vinyl ketones, followed by subsequent cyclization and aromatization under microwave heating to provide naphthyridines. The involvement of the Michael intermediate in this reaction process is strongly supported by the results of the reaction between amine **2f** (entry 6) and β-aryl vinyl ketone **3b** in which we isolated **4a** as determined by the spectroscopic studies (See experimental section).

This mechanistic proposal is further supported for the synthesis of quinolines. Irradiation of amine **2d** and β-aryl vinyl ketone **3b** (entry 4) produced similar Michael intermediate **4b** (See experimental section for characterization details of this intermediate), and thus confirmed our initial hypothesis.

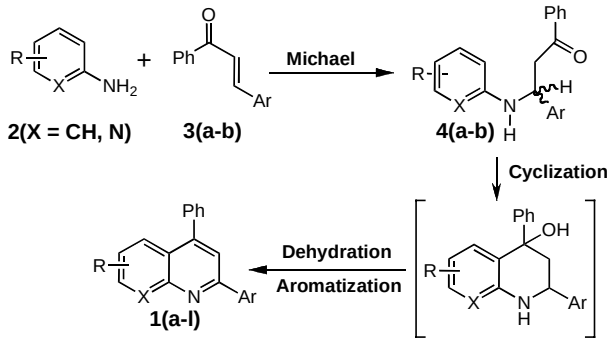
This type of cyclization and aromatization in the presence of air under microwave heating is not unprecedented [7a] for the quinolines.

Table 1
Microwave-expedited Two-component Synthesis of Quinolines and 1,8-Naphthyridines

Entry	Amine (**2**)	β-aryl vinyl ketones (**3a & 3b**)	MW condition (Watt, min)	Products (**1**)	Yield (%)[a]
1.	**2a:** R = 2-Me, X = CH	**3a**	450, 30	**1a:** Ar=Ph	55
2.	**2b:** R = 2-Me, X = CH	**3b**	450, 35	**1b:** Ar=3-Br-C_6H_4	60
3.	**2c:** R = 4-OMe, X = CH	**3a**	450, 35	**1c:** Ar =Ph	62
4.	**2d:** R = 4-OMe, X = CH	**3b**	450, 35	**1d:** Ar=3-Br-C_6H_4	65
5.	**2e:** R = 6-Me, X = N	**3a**	450, 30	**1e:** Ar =Ph	51
6.	**2f:** R = 6-Me, X = N	**3b**	450, 30	**1f:** Ar =3-Br-C_6H_4	55
7.	**2g:** R = 5-Br, X = N	**3a**	450, 25	**1g:** Ar=Ph	70
8.	**2h:** R = 5-Br, X = N	**3b**	450, 20	**1h:** Ar =3-Br-C_6H_4	68
9.	**2i:** R = H, X = N	**3a**	450, 20	**1i:** Ar =Ph	67
10.	**2j:** R = H, X = N	**3b**	450, 20	**1j:** Ar =3-Br-C_6H_4	73
11.	**2k:** R = 6-NH_2, X = N	**3a**	450, 15	**1k:** Ar =Ph	70
12.	**2l:** R = 6-NH_2, X = N	**3b**	450, 15	**1l:** Ar =3-Br-C_6H_4	75

[a]Isolated yields are of chromatographically obtained pure material.

Scheme II



Probable mechanism for the synthesis of substituted quinolenes/1,8-naphthyridines from substituted aromatic/heteroaromatic amines and β-aryl vinyl ketones.

All the quinolines and naphthyridine products were characterized by spectroscopic studies.

One interesting aspect of this type of reaction is that less microwave energy is required when the heteroaromatic ring contains extra amine group (Table 1, entries k, l), which makes the steps for C-C bond formation, cyclization as well as aromatization easier.

In summary, our present method is an operationally simple, efficient and eco-friendly clean synthesis of aryl substituted functionalized fused heterocycles containing one or two N-atoms. So this one-pot approach is developed to be an alternate way for the synthesis of quinolines and 1,8-naphthyridines from aromatic/ heteroaromatic amines and β-aryl vinyl ketones under solvent and catalyst free conditions. The course of reaction is studied with the help of two intermediates of both 1,8-naphthyridine and quinoline system. To our knowledge, this constitutes a new synthesis of naphthyridines under mild condition.

EXPERIMENTAL

A general and representative reaction procedure for the synthesis of 1,8-naphthyridines/quinolines using β-aryl vinyl

ketone. A thoroughly ground mixture of 2,6-diaminopyridine (**2l**) (recrystallized)(109 mg, 1.0 mmol) and β-aryl vinyl ketone (**3b**) (287 mg, 1.0 mmol) was taken in an open-mouth conical flask and irradiated at 450 W with a domestic microwave oven (BPL 800G) for an optimum time of 15 min (Scheme 1, Table 1). The solid residue was washed with water and extracted with EtOAc(20 mL x 4) which was concentrated under reduced pressure to obtain the crude product. This crude product was purified using silica gel (100-200 mesh) column chromatography (20% EtOAc in petroleum ether), which afforded compound **1l** as a light yellow coloured solid (75%).

All compounds gave satisfactory spectral data. Selected physical data for compounds **1l** and **1d**.

7-(3-Bromo-phenyl)-5-phenyl-[1,8]naphthyridin-2-ylamine (**1l**). Off white solid. mp: 243-246 °C; ir (KBr): 3470, 3051, 1644, 1564, 1357, 771, 705 cm^{-1}; ^1H nmr (DMSO-d_6, 500 MHz): δ 8.46(t, 1H, *J* = 1.7 Hz), 8.25(d, 1H, *J* = 8.0 Hz), 7.81(d, 1H, *J* = 9.0 Hz), 7.23(s, 1H), 7.64(d, 1H, *J* = 7.5 Hz), 7.55(d, 4H, *J* = 4.3 Hz), 7.53-7.50(m, 1H), 7.45(t, 1H, *J* = 7.9 Hz), 6.91(bs, 2H), 6.81(d, 1H, *J* = 9.0 Hz); ^{13}C nmr (DMSO-d_6, 125 MHz): δ 161.78, 157.95, 156.08, 150.30, 142.17, 138.23, 135.66, 132.90, 131.71, 130.63, 130.38, 129.54, 129.41, 126.96, 123.18, 115.38, 114.87, 114.58; ms (ESI): m/z 378.1(M^++2, 100), 376.1(M^+, 94.7); *Anal.* Calcd. for $C_{20}H_{14}BrN_3$: C, 63.85; H, 3.75; N, 11.17. Found: C 63.91; H, 3.71; N, 11.12.

2-(3-Bromo-phenyl)-6-methoxy-4-phenyl-quinoline (**1d**). mp: 110-112 °C; ir (KBr): 1623, 1589, 1253, 1224, 689 cm^{-1}; ^1H nmr ($CDCl_3$, 500 MHz): δ 8.15(d, 1H, *J* = 1.7 Hz), 8.14(d, 2H, *J* = 3.8 Hz), 7.74(s, 2H), 7.64(d, 1H, *J* = 7.9 Hz), 7.51(t, 1H, *J* = 7.4 Hz), 7.50(d, 2H, *J* = 7.6 Hz), 7.46-7.39(m, 3H), 7.11(d, 1H, *J* = 2.4 Hz), 3.82(s, 3H); ^{13}C nmr ($CDCl_3$, 125 MHz): δ 158.41, 155.01, 146.49, 145.31, 143.35, 141.19, 139.92, 132.71, 132.15, 131.83, 130.61, 129.52, 129.25, 128.42, 127.70, 123.25, 122.41, 119.96, 103.72, 55.92; ms (ESI): m/z 390.1(M^+, 94), 391(M^++1, 26), 392(M^++2, 100), 393(M^++3, 24); *Anal.* Calcd. for $C_{22}H_{16}BrNO$: C, 67.71; H, 4.13; N, 3.59. Found: C, 67.75; H, 4.10; N, 3.54.

3-(3-Bromo-phenyl)-3-(6-methyl-pyridin-2-ylamino)-1-phenyl-propan-1-one (**4a**): (X = N, R = 6-Me, Ar = 3-Br-C_6H_4): A thoroughly ground mixture of 2-amino-6-methylpyridine (**2b**) (108 mg, 1.0 mmol) and (**3b**) (287 mg, 1.0 mmol) was taken in an open-mouth conical flask and irradiated at 450 W with a domestic microwave oven (BPL 800G) for an optimum time of 30 min (Scheme 1, Table 1). The solid residue was washed with water and extracted with CH_2Cl_2 (20 mL x 4), which was concentrated under reduced pressure to obtain the crude product. This crude product was purified using silica gel (100-200 mesh) column chromatography (7% EtOAc in petroleum ether), which afforded compound **1f** (215 mg, 55%) and **4a** (71 mg, 18 %) as sticky light yellow semisolid; ir (KBr): 3408, 1683, 1597, 1461, 779, 689 cm^{-1}; ^1H nmr ($CDCl_3$, 500 MHz): δ 7.92(d, 2H, *J* = 8.3 Hz), 7.59(t, 1H, *J* = 1.7 Hz), 7.45(d, 1H, *J* = 8.0 Hz), 7.44(t, 1H, *J* = 7.8 Hz), 7.36(d, 1H, *J* = 8.5 Hz), 7.35(t, 1H, *J* = 8.2 Hz), 7.25(t, 1H, *J* = 7.8 Hz), 7.17(t, 1H, *J* = 7.8 Hz), 6.44(d, 1H, *J* = 7.3 Hz), 6.12(d, 1H, *J* = 8.3 Hz), 5.33(q, 1H, *J* = 12.8 Hz, in D_2O, t, 1H, *J* = 6.2 Hz), 5.20(d, 1H, *J* = 6.7 Hz, 1H- D_2O exchangeable), 3.62(dd, 1H, *J* = 16.6 Hz), 3.41(dd, 1H, *J* = 16.6 Hz), 2.34(s, 3H). ^{13}C nmr ($CDCl_3$, 125 MHz): δ 197.76, 157.47, 157.34, 145.59, 138.33, 137.04, 133.86, 130.88, 130.67, 130.13, 129.10, 128.60, 125.71, 123.25, 113.44, 104.33, 52.69, 46.14, 24.66; ms (ESI): m/z 397 (M^++2, 92.6), 395 (M^+, 90.7), 277(100), 275(92.5); *Anal.* Calcd. for $C_{21}H_{19}BrN_2O$: C, 63.81; H, 4.84; N, 7.09. Found: C, 63.78; H, 4.86; N, 7.14.

3-(3-Bromo-phenyl)-3-(4-methoxy-phenylamino)-1-phenyl-propan-1-one (**4b**). (X = CH, R = 4-OMe, Ar = 3-Br-C_6H_4): Reddish brown solid; Yield 15%; mp: 84-86 °C; ir (KBr): 3465, 1676, 1636, 1595, 1512, 1238, 683 cm^{-1}; ^1H nmr ($CDCl_3$, 500 MHz): δ 7.90(d, 2H, *J* = 7.9 Hz), 7.59(t, 1H, *J* = 1.7 Hz), 7.56(d, 1H, *J* = 7.4 Hz), 7.46(d, 1H, *J* = 7.9 Hz), 7.45(t, 1H, *J* = 7.8 Hz), 7.35(t, 2H, *J* = 6.5 Hz), 7.18(t, 1H, *J* = 7.8 Hz), 6.69(d, 2H, *J* = 8.9 Hz), 6.50(d, 2H, *J* = 8.9 Hz), 4.87(q, 1H, *J* = 7.6 Hz), 4.23(bs, 1H, 1H-D_2O exchangeable), 3.39(s, 3H), 3.44(dd, 1H, *J* = 16.4 Hz), 3.38(dd, 1H, *J* = 16.4 Hz). ^{13}C nmr ($CDCl_3$, 125 MHz): δ 198.28, 152.99, 146.33, 141.27, 137.01, 133.95, 130.88, 130.8, 129.96, 129.16, 128.97, 128.59, 125.63, 123.67, 115.84, 115.19, 56.11, 55.69, 46.70. ms (ESI): m/z 412.0(M^++2, 10), 410(M^+, 8), 292(100), 290(78), 124(48). *Anal.* Calcd. for $C_{22}H_{20}BrNO_2$: C, 64.40; H, 4.91; N, 3.41. Found: C, 64.49; H, 4.89; N, 3.34.

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REFERENCES AND NOTES

[1] (a) Morimoto, Y.; Oda, K.; Matsuda, F.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chem. Lett*. **1988**, *17*, 909; (b) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Synlett* **1991**, 202; (c) Isobe, M.; Nishikawa, T.; Yamamoto, N.; Sukiyama, T.; Ino, A.; Okita, T. *J. Heterocycl. Chem*. **1992**, *29*, 619; (d) Michael, J. P. *Nat. Prod. Rep*. **1997**, *14*, 605 and references cited therein.

[2] (a) Markees, D. G.; Dewey, V. C.; Kidder, G. W. *J. Med. Chem*. **1970**, *13*, 324; (b) Alhaider, A. A.; Abdelkader, M. A.; Lien, E. J. *J. Med. Chem*. **1985**, *28*, 1394; (c) Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *J. Med. Chem*. **1988**, *31*, 1031.

[3] (a) Tomcufcik, A. S.; Meyer, W. E.; Marsico, J. W. *Eur. Pat. Appl.* EP 446604, **1991**; *US Appl*. 494387, **1990**; [*Chem. Abstr*. **1992**, *116*, 235628p]. (b) Saupe, T.; Schaefer, P.; Meyer, N.; Wuerzer, B.; Westphalen, K.O. *Ger. Offen*. DE 3907937, **1990;** [*Chem. Abstr*. **1991**, *114*, 81808s]. (c) Cotrel, C.; Guyon, C.; Roussel, G.; Taurand, G. *Eur. Pat. Appl.* EP 208621, **1987**; *FR Appl*. 85/10619, **1985**; [*Chem. Abstr*. **1987**, *107*, 39780g]. (d) Tsuzuki, Y.; Tomita, K.; Sato, Y.; Kashimoto, S.; Chiba, K. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 3189; (e) Mahesh, R.; Perumal, R. V.; Pandi, P. V. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 5179.

[4] (a) Goswami, S. P.; Mukherjee, R. *Tetrahedron Lett*. **1997**, *38*, 1619; (b) Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757; (c) Goswami, S. P.; Ghosh, K.; Mukherjee, R. *Tetrahedron* **2001**, *57*, 4987; (d) Hamilton, A. D.; Pant, N. *J. Chem. Soc. Chem. Commun*. **1988**, 765; (e) Alvarez-Rua, C.; Garcý-Granda, S.; Goswami, S. P.; Mukherjee, R.; Dey, S.; Claramunt, R. M.; Marý, M. D. S.; Rozas, I.; Jagerovic, N.; Alkorta, I.; Elguero, J. *New. J. Chem.* **2004**, *28*, 700; (f) Li, X.-Q.; Jia, M.-X.; Wang, X.-Z.; Jiang, X.-K.; Li, Z.-T.; Chenand, G.-J.; Yu, Y.-H. *Tetrahedron* **2005,** *61*, 9600; (g) Nakatani, K.; Horie, S.; Murase, T.; Hagihara, S.; Saitoa, I. *Bioorg. Med. Chem*. **2003**, *11*, 2347; (h) Peng, T.; Murase, T.; Goto, Y.; Kobori, A.; Nakatani, K. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 259; (i) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc*. **2005**, *127*, 810.

[5] (a) He, C.; Lippard, S. J. *J. Am. Chem. Soc*. **2000**, *122*, 184; (b) He, C.; Lippard, S. J. *Tetrahedron* **2000**, *56*, 8245; (c) Maekawa, M.; Munakata, M.; Kitagawa, S.; Kuroda-Sowa, T.; Suenaga, Y.; Yamamoto, M. *Inorg. Chim. Acta*. **1998**, *271*, 129.

[6] (a) Goswami, S. P.; Adak, A. K. *Tetrahedron Lett.* **2002**, *43*, 8371; (b) Goswami, S. P.; Adak, A. K. *Synth. Commun.* **2003**, *33,* 475; (c) Goswami, S. P.; Dey, S.; Jana, S.; Adak, A. K. *Chem. Lett.* **2004**, *33,* 916; (d) Goswami, S. P.; Jana, S.; Dey, S.; Adak, A. K. *Aust. J. Chem.* **2007**, *60*, 120.

[7] (a) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531; (b) Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, *5*, 3061; (c) Yadav, J. S.; Subba Reddy, B. V.; Sunitha, V.; Srinivasa Reddy, K.; Ramakrishna, K. V. S. *Tetrahedron Lett.* **2004**, *45,* 7947; (d) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E.; Verdecchia, M. *Synlett* **2006**, 3218; (e) Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synlett* **2006**, 2947; (f) Tu, S.; Zhang, Y.; Zhang, J.; Jiang, B.; Jia, R.; Zhang, J.; Ji, S. *Synlett* **2006**, 2785; (g) Devi, I.; Baruah, B.; Bhuyan, P. J. *Synlett* **2006**, 2593.

[8] (a) Springfield, S. A.; Marcantonio, K.; Ceglia, S.; Albaneze-Walker, J.; Dormer, P. G.; Nelson, T. D.; Murry, J. A. *J. Org. Chem.* **2003**, *68*, 4598; (b) Mitsos, C. A.; Zografos, A. L.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2003**, *68*, 4567; (c) Wang, Y. D.; Boschelli, D. H.; Johnson, S.; Honores, E. *Tetrahedron* **2004**, *60*, 2937. (d) Mogilaiah, K.; Uma Rani, J.; Sakram, B.; Reddy, N. V. *J. Heterocycl. Chem.* **2006**, *43*, 485; (e) Zhichkin, P.; Beer, C. M. C.; Rennells, W. M.; Fairfax, D. J. *Synlett* **2006**, 379.

[9] Chandler, C. J.; Deady, L. W.; Reiss, J. A.; Tzimos, V. *J. Heterocycl. Chem.* **1982**, *19*, 1017.

[10] For recent book and reviews on microwave-assisted organic reactions: (a) Hayes, B. L. *Mircowave Synthesis: Chemistry at the Speed of Light,* CEM publishing, Mattaws, NC, 2002, p 28105; (b) Wathey, B.; Tierney, J.; Lidstrom, P.; Westman, J. *Drug Disc. Today* **2002**, *7*, 373; (c) Kappe, C. O. *Angew Chem. Int. Ed. Engl.* **2004**, *43*, 6250; (d) For a recent review on the synthesis of heterocyclic compounds under microwave irradiation; see: Xu, Y.; Guo, Q. *Heterocycles* **2004**, *63*, 903.

[11] Goswami, S. P.; Mukherjee, R.; Mukherjee, R.; Jana, S.; Maity, A. C.; Adak, A. K. *Molecules* **2005**, *10*, 929.

[12] Loh, T. -P.; Wei, L. –L. *Synlett* **1998**, 975.

[13] Ogata, Y.; Kawasaki, A.; Suyama, S. *Tetrahedron* **1969,** *25,* 1361.