# The synthesis of 2-(1,2,3-triazol-2-yl)-1,8-naphthyridines under microwave irradiation

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An efficient and convenient method is described for the synthesis of 3-aryl-2-(4,5-dimethyl-2*H*-1,2,3-triazol-2-yl)-1,8-naphthyridines (**4**) from α-acetylacetaldoxime 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) in the presence of acetic anhydride and DMF using basic alumina as solid support under microwave irradiation.

**Keywords:** 1,2,3-triazoles, 1,8-naphthyridines, α-acetylacetaldoxime, hydrazones

1,8-Naphthyridine derivatives constitute an important class of compounds possessing diverse biological activities.[1-3] The synthesis of 1,2,3-triazoles has been studied by several researchers owing to their remarkable biological activities.[4-6] Though various methods for the synthesis of these compounds are known,[7-10] some involve long reaction times and high reaction temperatures, and even then may produce low yields. Therefore the development of further convenient and efficient methods for the preparation of 1,2,3-triazoles is of practical importance.

Microwave-assisted organic reactions have attracted considerable attention in organic synthesis because of their simplicity, greater selectivity, and rapidity in operation, for the synthesis of a variety of organic compounds.[11-13] In view of this, and in continuation of our work on microwave assisted organic transformations of 1,8-naphthyridine derivatives,[14-17] we now describe a convenient, efficient, inexpensive and high yielding protocol for the synthesis of 2-triazolyl-1,8-naphthyridines under microwave irradiation using basic alumina as solid support. The synthetic approach is outlined in Scheme 1.

Condensation of 3-aryl-2-hydrazino-1,8-naphthyridines[18] (**1**) with α-acetylacetaldoxime (**2**) in the presence of a catalytic amount of DMF under microwave irradiation afforded α-acetylacetaldoxime 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) in excellent yields. With a plethora of coordinating sites, these compounds **3** may form interesting metal complexes. Such aspects and the possibility of these compounds acting as host molecules under suitable conditions would be worthy of probing.

Cyclodehydration of **3** with a mixture of acetic anhydride and DMF[19] under microwave irradiation using basic alumina as solid support furnished the respective 3-aryl-2-(4,5-dimethyltriazol-2-yl)-1,8-naphthyridines (**4**) in very good yields. The reaction is fairly general, facile and efficient and is devoid of by-products. The products that are obtained do not require purification. The experimental procedure is very simple. In a typical case, a mixture of **3a**, acetic anhydride and DMF, deposited on basic alumina, was exposed to microwave irradiation at 450 watts intermittently at 30 s intervals for 4.0 min. The reaction mixture was allowed to cool to room temperature and extracted with methanol. After work-up 3-phenyl-2-(4,5-dimethyltriazol-2-yl)-1,8-naphthyridine (**4a**) was obtained in 90% yield. The reaction is of general applicability and the various 2-triazolyl-1,8-naphthyridines synthesised are given in Table 1.

The structures of the compounds **3** and **4** were determined by IR, $^1$H NMR and mass spectroscopy. To the best of our knowledge this is the first report on the synthesis of 1,2,3-triazoles under microwave irradiation using basic alumina as solid support.

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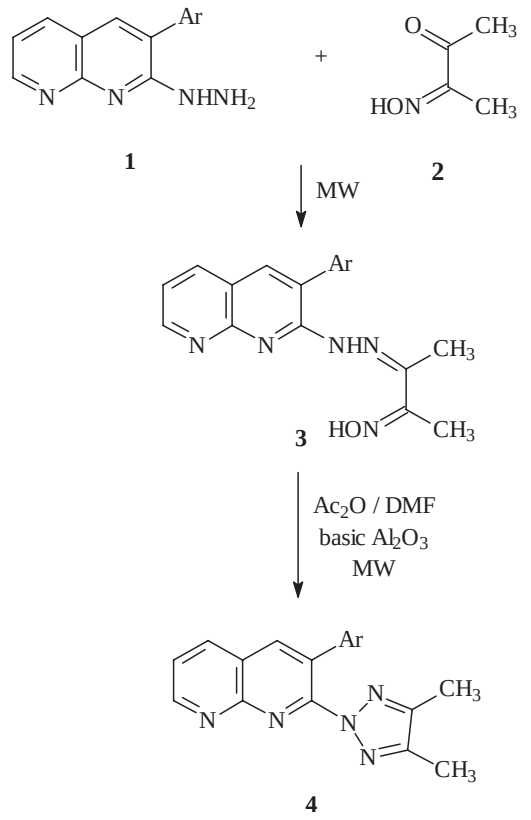


Ar: see Table 1

**Scheme 1**

In conclusion: we have devised a simple and efficient method for the synthesis of 1,2,3-triazoles under microwave irradiation. The mild conditions, good yields, high purity, short reaction time and easy work-up are some of the major advantages of this method. Study of the biological activity of the compounds **4** is in progress and will be reported in future publications.

## Experimental

Melting points were recorded on a Cintex melting point apparatus. IR spectra in KBr were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer $^1$H NMR spectra were obtained on samples in $CDCl_3$ with a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded in EI mode on a Finnigan MAT 8230 GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyser. Purity of the compounds was checked using precoated TLC plates (Merk 60F-254). Irradiation was carried out in a domestic microwave oven (BPL 800 G, 2450 MHz). 3-Aryl-2-hydrazino-1,8-naphthyridines (**1**) were prepared according to the literature method.[19] The α-aceetylacetaldoxime (**2**) was purchased from Aldrich Chemical Company.

*α-Acetylacetaldoxime 3-aryl-1,8-naphthyridin-2-ylhydrazones* (**3**), *general procedure:* A mixture of 1 (0.01 mole), α-acetylacetaldox-

**Table 1** Physical and analytical data of α-acetylacetaldoxime 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) and 3-aryl-2-(4,5-dimethyl-2*H*-1,2,3-triazol-2-yl)-1,8-naphthyridines (**4**)

| Compd | Ar | Reaction time/min | Yield % [m.p. °C] | Mol. formula | Microanalysis calculated [found] % | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **3a** | $C_6H_5$ | 1.5 | 94 [230–232] | $C_{18}H_{17}N_5O$ | 67.71 [67.88] | 5.33 [5.37] | 21.94 [21.86] |
| **3b** | *p*-$CH_3OC_6H_4$ | 2.0 | 96 [225–227] | $C_{19}H_{19}N_5O_2$ | 65.33 [65.48] | 5.44 [5.48] | 20.06 [20.15] |
| **3c** | *o*-$ClC_6H_4$ | 1.5 | 95 [220–222] | $C_{18}H_{16}ClN_5O$ | 61.10 [61.29] | 4.53 [4.58] | 19.80 [19.88] |
| **3d** | *m*-$ClC_6H_4$ | 2.0 | 94 [241–242] | $C_{18}H_{16}ClN_5O$ | 61.10 [61.10] | 4.53 [4.57] | 19.80 [19.86] |
| **3e** | *p*-$ClC_6H_4$ | 1.5 | 98 [184–185] | $C_{18}H_{16}ClN_5O$ | 61.10 [61.28] | 4.53 [4.56] | 19.80 [19.87] |
| **3f** | *p*-$NO_2C_6H_4$ | 2.0 | 95 [240–242] | $C_{18}H_{16}N_6O_3$ | 59.34 [59.48] | 4.40 [4.45] | 23.08 [23.15] |
| **4a** | $C_6H_5$ | 4.0 | 90 [190–192] | $C_{18}H_{16}N_5$ | 71.76 [71.92] | 4.98 [4.94] | 23.26 [23.34] |
| **4b** | *p*-$CH_3OC_6H_4$ | 5.0 | 89 [195–196] | $C_{19}H_{17}N_5O$ | 68.88 [68.75] | 5.14 [5.18] | 21.15 [21.08] |
| **4c** | *o*-$ClC_6H_4$ | 4.5 | 88 [150–152] | $C_{18}H_{14}ClN_5$ | 64.38 [64.53] | 4.17 [4.20] | 20.86 [20.95] |
| **4d** | *m*-$ClC_6H_4$ | 4.5 | 87 [260–262] | $C_{18}H_{14}ClN_5$ | 64.38 [64.52] | 4.17 [4.22] | 20.86 [20.94] |
| **4e** | *p*-$ClC_6H_4$ | 5.0 | 92 [225–226] | $C_{18}H_{14}ClN_5$ | 64.38 [64.38] | 4.17 [4.21] | 20.86 [20.96] |
| **4f** | *p*-$NO_2C_6H_4$ | 6.0 | 86 [230–232] | $C_{18}H_{14}N_6O_2$ | 62.43 [62.60] | 4.05 [4.09] | 24.28 [24.21] |

ime (**2**) (0.01 mole) and DMF (5 drops) was exposed to microwaves at 150 watts intermittently at 30 s intervals for the specified time (Table 1). On completion of the reaction, as monitored by TLC, the mixture was digested with cold water. The precipitate thus obtained was filtered, washed with water and recrystallised from ethanol to afford **3**.

*3-Phenyl derivative* (**3a**)**:** IR (KBr): 3350 (OH), 3190 (NH), 1620 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.17 (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$), 7.72 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.33 (m, 1H, $C_7$–H), 8.80 (brs, 1H, OH), 9.91 (s, 1H, NH), 7.00–7.43 (m, 5H, Ar–H); MS: *m/z* 319 ($M^+$, 100).

*3-(p-Methoxyphenyl) derivative* (**3b**)**:** IR (KBr): 3345 (OH), 3198 (NH), 1615 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.18 (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 7.68 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.32 (m, 1H, $C_7$–H), 9.11 (brs, 1H, OH), 9.93 (s, 1H, NH), 6.98–7.29 (m, 4H, Ar–H); MS: *m/z* 349 ($M^+$, 100).

*3-(o-Chlorophenyl) derivative* (**3c**)**:** IR (KBr): 3345 (OH), 3186 (NH), 1622 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.02 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 7.67 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.33 (m, 1H, $C_7$–H), 9.20 (brs, 1H, OH), 9.72 (s, 1H, NH), 6.98–7.48 (m, 4H, Ar–H); MS: *m/z* 353 ($M^+$, 100).

*3-(m-Chlorophenyl) derivative* (**3d**)**:** IR (KBr): 3318 (OH), 3150 (NH), 1621 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.15 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_3$), 7.79 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.32 (m, 1H, $C_7$–H), 9.91 (brs, 1H, OH), 10.44 (s, 1H, NH), 7.05–7.37 (m, 4H, Ar–H); MS: *m/z* 353 ($M^+$, 100).

*3-(p-Chlorophenyl) derivative* (**3e**)**:** IR (KBr): 3347 (OH), 3172 (NH), 1620 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.17 (s, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 7.69 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.31 (m, 1H, $C_7$–H), 9.31 (brs, 1H, OH), 9.97 (s, 1H, NH), 7.00–7.41 (m, 4H, Ar–H); MS: *m/z* 353 ($M^+$, 100).

*3-(p-Nitrophenyl) derivative* (**3f**)**:** IR (KBr): 3325 (OH), 3180 (NH), 1618 $cm^{-1}$ (C=N); $^1H$ NMR: δ 2.20 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 7.83 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.42 (m, 1H, $C_7$–H), 9.72 (brs, 1H, OH), 10.23 (s, 1H, NH), 7.02–7.52 (m, 4H, Ar–H); MS: *m/z* 364 ($M^+$, 100).

*3-Aryl-2-(4,5-dimethyl-1,2,3-triazol-2-yl)-1,8-naphthyridines* (**4**), *general procedure:* Basic alumina (5 g) was added to the mixture of **3** (0.01 mole), acetic anhydride (3 ml) and DMF (1 ml) at room temperature. The mixture was thoroughly mixed and adsorbed material was dried in air and irradiated in microwave oven at 450 watts intermittently at 30 s intervals for the specified time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was cooled, the product was extracted by simple washing and filtration with methanol (5 × 5 ml). Dilution of methanol with ice-cold water gave the product, which was filtered, washed with water and recrystallised from ethanol to give **4**.

*3-Phenyl derivative* (**4a**): IR (KBr): 1610 $cm^{-1}$ (C=N); $^1H$ NMR: δ 3.28 (s, 6H, 2 × $CH_3$), 8.07 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.69 (m, 1H, $C_7$–H), 7.23–7.58 (m, 5H, Ar–H); MS: *m/z* 301 ($M^+$, 9).

*3-(p-Methoxyphenyl) derivative* (**4b**): IR (KBr): 1608 $cm^{-1}$ (C=N); $^1H$ NMR: δ 3.26 (s, 6H, 2 × $CH_3$), 3.88 (s, 3H, $OCH_3$), 8.02 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.72 (m, 1H, $C_7$–H), 7.04–7.41 (m, 4H, Ar–H); MS: *m/z* 331 ($M^+$, 12).

*3-(o-Chlorophenyl) derivative* (**4c**): IR (KBr): 1605 $cm^{-1}$ (C=N); $^1H$ NMR: δ 3.28 (s, 6H, 2 × $CH_3$), 8.25 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.75 (m, 1H, $C_7$–H), 6.97–7.63 (m, 4H, Ar–H); MS: *m/z* 335 ($M^+$, 8).

*3-(m-Chlorophenyl) derivative* (**4d**): IR (KBr): 1602 $cm^{-1}$ (C=N); $^1H$ NMR: δ 3.29 (s, 6H, 2 × $CH_3$), 8.16 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.72 (m, 1H, $C_7$–H), 7.22–7.60 (m, 4H, Ar–H); MS: *m/z* 335 ($M^+$, 10).

*3-(p-Chlorophenyl) derivative* (**4e**): IR (KBr): 1606 $cm^{-1}$ (C=N); $^1H$ NMR: δ 3.27 (s, 6H, 2 × $CH_3$), 8.22 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.78 (m, 1H, $C_7$–H), 7.08–7.53 (m, 4H, Ar–H); MS: *m/z* 335 ($M^+$, 15).

*3-(p-Nitrophenyl) derivative* (**4f**): IR (KBr): 1609 $cm^{-1}$ (C=N). $^1H$ NMR: δ 3.29 (s, 6H, 2 × $CH_3$), 8.26 (m, 3H, $C_4$–H, $C_5$–H, $C_6$–H), 8.86 (m, 1H, $C_7$–H), 7.12–7.69 (m, 4H, Ar–H); MS: *m/z* 346 ($M^+$, 6).

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