# Microwave-assisted, solvent-free, three-component synthesis of 2,4,6-triarylpyridines from benign components

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2,4,6-Triarylpyridine derivatives were synthesised by the reaction of guanidine with an acetophenone and a chalcone. These reactions were carried out as economical one-pot reactions under green conditions: no catalyst and solvent free.

**Keywords**: pyridine, one-pot synthesis, solvent-free conditions, microwave-assisted synthesis

One-pot multicomponent reactions (MCRs) have become a practical tool for atom economic and benign synthesis by virtue of their convergence, productivity, facile execution, and generation of highly diverse and complex products from easily available starting materials.[1] Green chemistry emphasises the need for environmentally clean synthesis, which involves improvement in selectivity, high atom efficiency, elimination of hazardous reagents, and easy separation with recovery and reuse of reagents.[2] Compared with conventional heating, reactions promoted by microwave irradiation (MWI) have shown an environmental friendly nature, greater selectivity, and enhanced reaction rate. Therefore, the MWI-mediated multicomponent reaction has constituted an especially attractive synthetic strategy for rapid and efficient library generation.[3]

Pyridines are common substructures in natural products, pharmaceuticals, and functional materials.[4] In particular, 2,4,6-triarylpyridines represent an important class of biologically active molecules and are prominent building blocks in supramolecular chemistry.[5]

These significant prevalences of pyridine scaffolds with diverse functionalities and substituents have stimulated the need for elegant and efficient ways to make these heterocycles. So far, the most common synthetic strategies for the preparation of pyridines with a 2,4,6-triaryl substitution pattern (Kröhnke pyridines) include: (1) the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of $NH_4OAc$,[6] (2) reaction of *N*-phosphinylethanimines with aldehydes,[7] (3) reaction of ketoketene dithioacetals with methyl ketones in the presence of $NH_4OAc$,[8] (4) solvent-free reaction between acetophenones, benzaldehydes, and $NH_4OAc$ in the presence of sodium hydroxide,[9] (5) addition of lithiated β-enaminophosphonates to chalcones,[10] and (6) the one-pot reaction of acetophenones, benzaldehydes, and $NH_4OAc$ without catalyst under microwave irradiation.[11]

In order to achieve this goal, MCRs are one of the first choices, since their attractive attribute is the inherent formation of several bonds to construct complex molecules in one operation, ideally without isolation of intermediates.[12] These highly step-economical reactions are particularly appealing in the context of target-oriented synthesis. They also come with the promise of novelty in terms of process and compound-related intellectual property.[13]

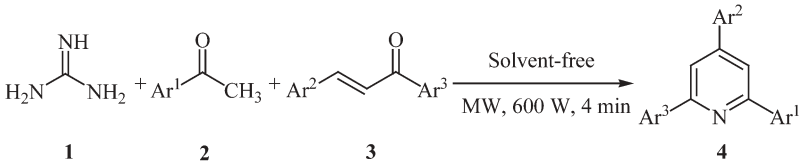
In view of the chemical and pharmacological importance of the Kröhnke pyridines, we have focused on introducing a new facile and efficient synthesis of these pyridines. In this context, and as a part of a research project dealing with the design and synthesis of biologically active organic structures,[14] we report a simple one-pot, three-component reaction between a guanidine, an acetophenone and a chalcone under microwave irradiation and solvent free conditions leading to Kröhnke pyridine derivatives **4** (Scheme 1). We have focused on environmental-friendly features of the employed components and feasibility of the reaction conditions.

## Results and discussion

A mixture of guanidine **1**, various acetophenones **2** and chalcones **3** were irradiated in a microwave oven at 600 W for 4 minutes under solvent-free conditions to produce the corresponding pyridines **4** in 92–98% yields (Table 1).

All the reactions went to completion within 4 min. $^1$H NMR analysis of the reaction mixtures clearly indicated the formation of the corresponding 2,4,6-triarylpyridines **4a–m** in good to excellent yields. All products were characterised by $^1$H and $^{13}$C NMR spectroscopy and by comparison of their spectral data and melting point values with those of the authentic samples reported in the literature.

Although we have not yet established the mechanism of this reaction in an experimental manner, a mechanistic rationalisation for this reaction is provided in Scheme 2. The first step involves condensation of guanidine (**1**) and acetophenone (**2**) to form enamine unit **5**. Then the chalcone is attacked by intermediate **5** leading to adduct **6**, which in turn isomerises to intermediate **7**. Cyclisation of **7** leads, via **8**, to intermediate **9**, which then tautomerises to dihydropyridine **10**. This then finally undergoes autoxidation under the reaction conditions to afford the 2,4,6-triarylpyridines **4**.




**Scheme 1**

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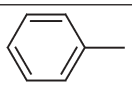
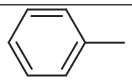
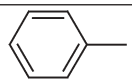
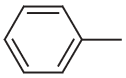
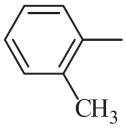
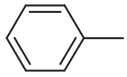
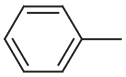
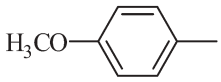
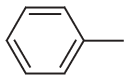
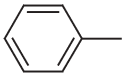
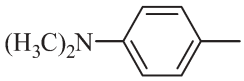
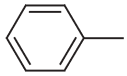
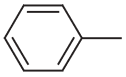
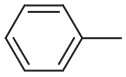
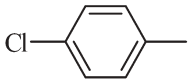
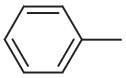
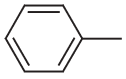
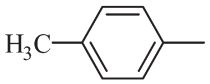
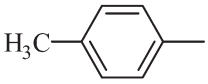
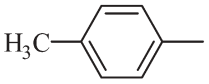
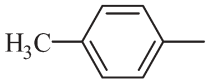
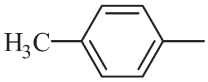
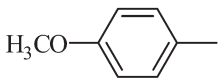
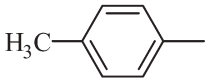
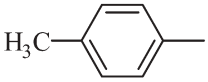
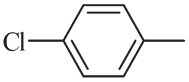
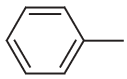
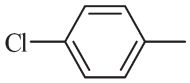
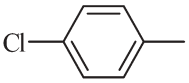
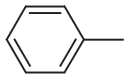
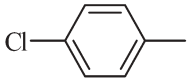
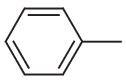
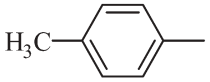
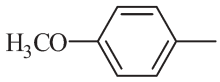
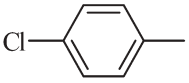
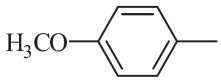
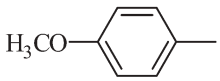
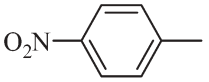
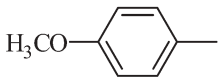
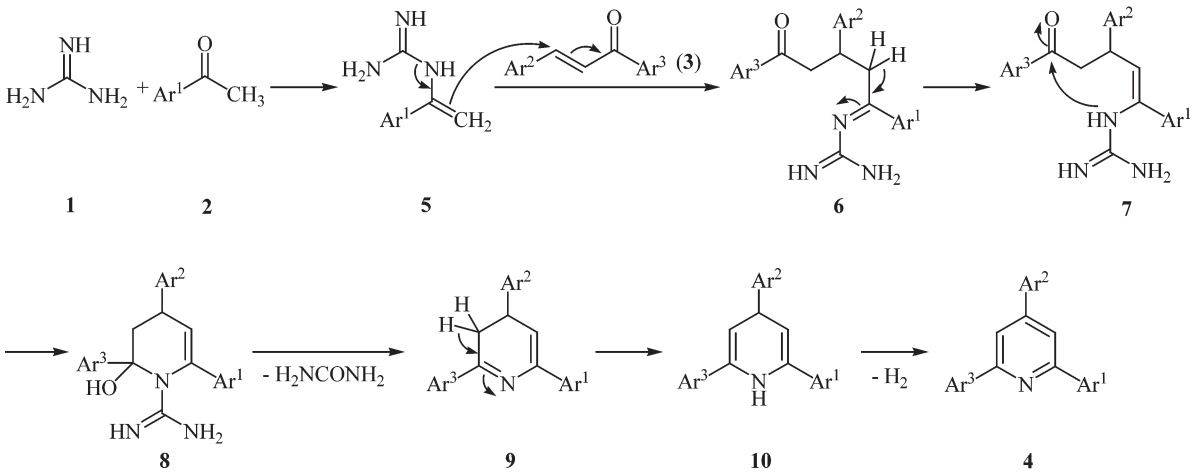
**Table 1** One-pot three-component synthesis of 2,4,6-triarylpyridines **4a–m**

| 4 | $Ar^1$ | $Ar^2$ | $Ar^3$ | Yield/%[a] | M.p./°C (lit.) |
|---|---|---|---|---|---|
| **a** |  |  |  | 98 | 135–136 (136–137)[15] |
| **b** |  |  |  | 98 | 121–122 (122–123)[7] |
| **c** |  |  |  | 95 | 100–102 (99–100)[15] |
| **d** |  |  |  | 96 | 139–140 (138)[16] |
| **e** |  |  |  | 97 | 126–127 (125–127)[17] |
| **f** |  |  |  | 93 | 124 (124–125)[18] |
| **g** |  |  |  | 91 | 177–179 (178–180)[17] |
| **h** |  |  |  | 96 | 156–158 (156–157.5)[15] |
| **i** |  |  |  | 92 | 119–21 (120–122)[18] |
| **j** |  |  |  | 97 | 139–140 (140–142)[19] |
| **k** |  |  |  | 93 | 153–155 (152–154)[20] |
| **l** |  |  |  | 98 | 114–116 (113.8–115)[21] |
| **m** |  |  |  | 94 | 143–145 (143.1–144.7)[11] |



**Scheme 2**

## Conclusion

In summary, the reaction between guanidine, an acetophenone and a chalcone provides a simple one-pot entry into the microwave-assisted synthesis of 2,4,6-triarylpyridines of potential synthetic and pharmaceutical interest. In this work, guanidine was applied as an alternative and environmental friendly source of ammonia. Solvent-free conditions, short reaction times, excellent yields of the products and use of simple starting materials are the key advantages of this method. The simplicity of the present procedure makes it an interesting alternative to complex multi-step approaches.

## Experimental

Chemicals were obtained from Merck and Aldrich chemical companies. Reactions were monitored by TLC using silica-coated plates. All of the products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were recorded on a Jasco IR-680 spectrophotometer. $^{1}$H NMR spectra were achieved with a Bruker-Arance AQS 500.1 MHz. The $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker-Avance spectrometer operating at 125.8 MHz. The experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis.

*Preparation of 2,4,6-triphenylpyridine (***4a***); general procedure*

A mixture of 1,3-diphenyl-2-propen-1-one (0.21 g, 1 mmol), acetophenone (0.12 g, 1 mmol), and guanidine (0.118 g, 2 mmol) was irradiated in a microwave oven for four minutes at 600 W under solvent-free conditions. TLC showed completion of the reaction. After cooling to room temperature, the solid residue was recrystallised from absolute ethanol. The product **4a** was obtained in 98% yield as colourless crystals, m.p. 135–136 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1577, 1555, 1517, 1480, 1352, 1254, 1066, 1021, 730, 679; $^{1}$H NMR (500.1 MHz, $CDCl_3$): δ 7.35–7.61 (9H, m, 9CH), 7.74 (2H, d, $J$ = 8.1 Hz, 2CH), 7.88 (2H, s, 2CH), 8.20 (4H, d, $J$ = 8.1 Hz, 4CH). $^{13}$C NMR (125.8 MHz, CDCl3): δ 117.15, 126.97, 128.00, and 128.81 (4CH), 129.00 (C), 129.10 and 129.17 (2CH), 138.98 (C), 139.58 (CH), 150.20 and 157.39 (2C) MS, *m/z* (%): 307 ($M^+$).

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## References

1 I. Ugi, A. Dombling and B. Werner, *J. Heterocycl. Chem*., 2000, **37**, 647.
2 R.A. Sheldon, *J. Mol. Catal. A.*, 1996, **107**, 75.
3 P. Lidstrom, J. Tierney and B. Wathey, *Tetrahedron*, 2001, **57**, 9225.
4 G.D. Henry, *Tetrahedron*, 2004, **60**, 6043.
5 R.K.R. Jetti, A. Nagia, F. Xue and T.C.W. Mark, *Chem. Commun*., 2001, 919.
6 R.A. Abramovitch, J.M. Beckert, P. Chinnasamy, H. Xiaohua, W. Pennington and A.R.V. Sanjivamurthy, *Heterocycles*, 1989, **28**, 623.
7 T. Kobayashi, H. Kakiuchi and H. Kato, *Bull. Chem. Soc. Jpn*., 1991, **64**, 392.
8 A.R. Katritzky, J.M. Aurrecoechea, K.K. Quian, E. Anna and G.J. Palenik, *Heterocycles*, 1987, **25**, 387.
9 F. Kröhnke and W. Zecher, *Angew. Chem. Int. Ed.*, 1962, **1**, 626.
10 F. Kröhnke, *Synthesis*, 1976, 1.
11 S. Tu, T. Li, F. Shi, F. Fang, S. Zhu, X. Wei and Z. Zong, *Chem. Lett.*, 2005, **34**, 732.
12 L.F. Tietze, *Chem. Rev*., 1996, **96**, 115.
13 A. Dömling, *Chem. Rev.*, 2006, **106**, 17.
14 M.M. Mojtahedi, M.S. Abaee and M. Eghtedari, *App. Organometal. Chem*., 2008, **22**, 529.
15 R. Lombard and J.P. Stephan, *Bull. Soc. Chim. Fr.*, 1958, 1458.
16 G.N. Dorofeenko and S.V. Krivum, *Zh. Obshch. Khim.*, 1964, **34**, 105.
17 R.S. Tewari and A.K. Dubey, *Indian J. Chem. Sect. B.*, 1980, **19**, 153.
18 F. Palacios, A.M.O. de Retana and J. Oyarzabal, *Tetrahedron Lett.*, 1996, **37**, 4577.
19 X.Q. Huang, H.X. Li, J.X. Wang and X.F. Jia, *Chin. Chem. Lett.*, 2005, **16**, 607.
20 A.R. Katritzky, A.A.A. Abdel-Fattah and D.O. Tymoshenko, *Synthesis*, 1999, 2114.
21 M. Borthakur, M. Dutta, G. Shyamalee and R.C. Boruah, *Synlett*, 2008, 3125.