An Efficient Improve for the Kröhnke Reaction: One-pot Synthesis of 2,4,6-Triarylpyridines Using Raw Materials under Microwave Irradiation

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A series of 2,4,6-triarylpyridines have been prepared by the one-pot reaction of aldehydes with aromatic ketones in the presence of ammonium acetate under microwave irradiation without catalyst. This method has the advantage of easier workup, shorter reaction time, higher yield, and environment-friendly.

Kröhnke type pyridines[1] and substituted phenylpyridines[2,3] are useful intermediates in the synthesis of drugs, agrochemicals, herbicides, insecticides, desiccants, surfactant agents, and antiinflammartory agents.[4,5] They are widely used as ligands in coordination complex preparation. Triarylpyridines are prominent building blockers in supramolecular chemistry with their π-stacking ability, directional H-bonding and coordination. Hence, their synthesis has received much attention.

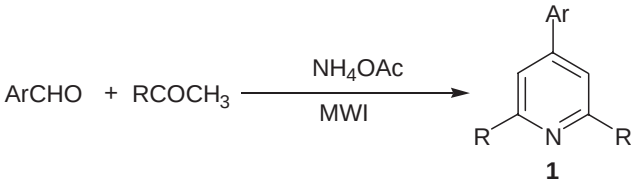
Traditionally, triarylpyridines are synthesized using the Kröhnke approach[1] by the reaction of pyridium salts with an unsaturated ketone, which started from the preparation of pyridium salts and involved the release of pyridium halide in the last step. And many articles adopting the method to synthesize 2,4,6-triarylpyridines have been described.[6–12] However, these methods coupled with the fact that the pyridinium halide and α,β-unsaturated ketone often have to be synthesized first. So it was an expensive, time consumming protocol and did harm to the enviroment. Since then, some new methods for the synthesis of 2,4,6-triarylpyridines have also been reported. One employed the reaction of β-enaminophosphonates with chalcones in tetrahydrofuran catalized by butyllithium.[13] Gareth reported the synthesis of triarylpyridines in the presence of sodium hydroxide using a multistep solid-phase reaction.[14]

Green chemistry is an environmental, health, and safe strategy that emphasizes pollution prevention and application of chemical process to reduce or eliminate the use and generation of hazardous substance.

We investigated that microwave irradiation could assist this reaction, and streamlined the usual multistep procedure to a single step, cut it use of poisonous catalyst and eliminated the generation of poisonous pyridium halide. In our previous paper, we have reported the synthesis of heterocyclic compounds under microwave irradiation.[15] In this paper, we would like to report the one-pot synthesis of 2,4,6-triarylpyridines using raw materials under microwave irradiation without catalyst.

Under microwave irradiation, the reaction of an aldehyde with an aromatic ketone in the presence of ammonium acetate completed within 6 min and yielded **1a**–**1x** in 80–96% yields (Scheme 1).[16] While in traditional heating mode (110 °C), the reaction time is 2 h and the yields are 70–78%, which indicates this reaction can be promoted by microwave irradiation.

The results (Table 1) show that a wide range of aromatic aldehydes and aromatic or heteroaromatic ketones can take part in this reaction. This method is simple and easy work up.



Scheme 1.

All these products were characterized by IR and ^{1}H NMR analysis, and their melting points were identical to those of the known compounds reported in the literature. Meanwhile, the structure of the compound **1s** was established on the basis of spectroscopic data and conformed by X-ray diffraction study

Table 1. The synthesis of triarylpyridine **1**

Entry	Ar	R	Yield/%	Mp (°C).Lit.
1a	4-ClC_6H_4	3-$O_2NC_6H_4$	92	285.6–286.6
1b	4-ClC_6H_4	4-$CH_3C_6H_4$	90	200.6–202
1c	4-ClC_6H_4	2-ClC_6H_4	91	155.8–156
1d	4-ClC_6H_4	4-FC_6H_4	92	209.4–210.1
1e	4-ClC_6H_4	4-$CH_3OC_6H_4$	91	113.8–115.0
1f	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	95	176.4–177.0
1g	4-$O_2NC_6H_4$	4-$CH_3OC_6H_4$	90	143.1–144.7
1h	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	91	>300
1i	4-$CH_3OC_6H_4$	2,4-$Cl_2C_6H_3$	89	161.0–161.8
1j	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	92	156.8–157.9 (156–157.5)[18]
1k	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	92	136–137 (135)[19]
1l	2-ClC_6H_4	2-ClC_6H_4	89	146.5–147.3
1m	2-ClC_6H_4	2,4-$Cl_2C_6H_3$	89	201.2–201.6
1n	4-BrC_6H_4	2,4-$Cl_2C_6H_3$	92	177.9–178.2
1o	4-BrC_6H_4	4-$CH_3OC_6H_4$	92	163.9–165
1p	C_6H_5	2,4-$Cl_2C_6H_3$	88	160.1–161
1q	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	91	203.9–204.8
1r	3,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	90	152.9–154.8
1s	3-indole	4-$CH_3OC_6H_4$	89	232.0–233.0
1t	2,4-$Cl_2C_6H_3$	2-pyridyl	84	158.4–159.3
1u	4-$CH_3OC_6H_4$	2-pyridyl	81	167–168 (171–172)[20]
1v	4-BrC_6H_4	2-pyridyl	89	154–156 (158–160)[20]
1w	4-$CH_3C_6H_4$	2-pyridyl	80	166–167 (166–167)[20]
1x	C_6H_5	2-pyridyl	80	210.8–211.6 (206–207)[20]

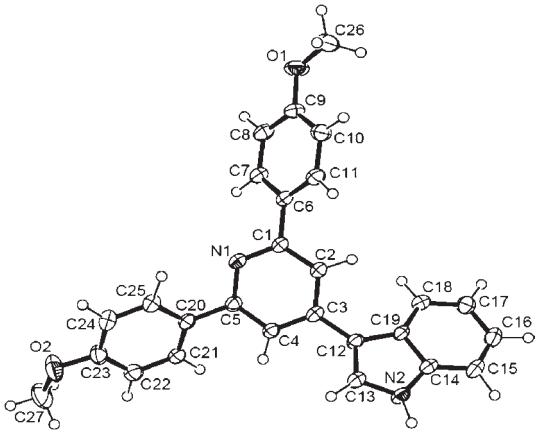


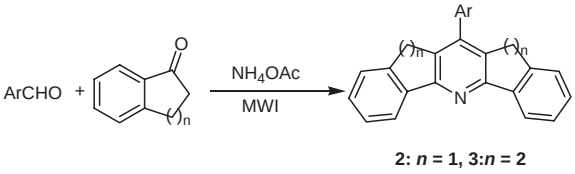
Figure 1. X-ray structures of **1s**.

(Figure 1).[17]

However, when using aldehyde and two different ketones as the starting material, we obtained mixture including two different chalcone, which are primary products, and a little amount of unsymmetrical triarylpyridine.

This method is applied to aromatic and heteroaromatic ketones. Furthermore, this versatile method is also suitable for the synthesis of 1-indenone and α-tetralone. 11-aryl-10*H*,12*H*-diindeno[1,2-b:2′,1′-e]pyridine **2** and 7-aryl-5,6,8,9-tetrahydrodibenzo[*c*,*h*]acridine **3** were obtained with good yields (Scheme 2). The results are listed in Table 2.

Here, we disclose a facile method to synthesize a wide range of symmetrical triarylpyridines. This methodology is superior to the reported methods from the view of green chemistry. The significance of our approach relates to the elimination of toxic starting materials, as well as its simplicity and avoiding the release of any hazardous products. In summary, this procedure is simple, environment-friendly.



Scheme 2.

Table 2. The synthesis of **2**, **3**

Entry	Ar	Yield/%	Mp (°C).Lit.
2a	C_6H_5	93	>300 (298)[1]
2b	4-OH-3-$CH_3OC_6H_3$	92	>300
2c	4-ClC_6H_4	95	>300
2d	3,4-$OCH_2OC_6H_3$	93	>300
2e	4-BrC_6H_4	96	>300
2f	4-$CH_3OC_6H_4$	93	251.8–252.2
2g	3,4-$Cl_2C_6H_3$	94	>300
2h	3-indole	90	>300
3a	4-OH-3-$CH_3OC_6H_3$	91	292.0–292.8
3b	3,4-$Cl_2C_6H_3$	90	147.6–148.9
3c	C_6H_5	90	167.5–168.9
3d	4-$CH_3OC_6H_4$	92	183.6–184.4
3e	3,4-$OCH_2OC_6H_3$	93	193.0–195.6
3f	4-ClC_6H_4	95	260.0–262.0
3g	4-BrC_6H_4	95	279.6–280.0

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References and Notes

1 F. Kröhnke, *Synthesis*, **1976**, 1.
2 F. Neve, A. Grispini, and S. Campagna, *Inorg. Chem.*, **36**, 6150 (1997).
3 B. Olenyuk, J. A. Whiteford, A. Frechtenkötter, and P. J. Stang, *Nature*, **398**, 796 (1999).
4 S. Shimizu, N. Abe, N. Goto, T. Niwa, and A. Iguchi, Jpn. Patent, JP 01261367A (1998).
5 S. Peter, H. Gerhard, H. Elisabeth, K. Ralf, K. Hartmann, H. Albercht, G. Norbert, W. Helmut, W. Karl-Otto, and M. Uif, U. S. Patent, US 5 733850 (1998).
6 R. S. Tewari and N. K. Mishra, *Croat. Chem. Acta*, **54**, 241 (1981).
7 R. S. Tewari and A. K. Dubey, *J. Chem. Eng. Data*, **25**, 91 (1980).
8 N. K. Mishra, K. S. Mishra, and H. C. Srivastara, *Indian J. Agric. Chem.*, **21**, 91 (1988).
9 R. K. Singhal and N. K. Mishra, *Indian J. Chem., Sect. B*, **24B**, 1079 (1985).
10 T. Kobayashi and M. Nitta, *Chem. Lett.*, **1986**, 1549.
11 S. Sukhwal and B. L. Verma, *Indian J. Heterocycl. Chem.*, **31**, 287 (1994).
12 A. S. Kiselyor, *Tetrahedron Lett.*, **36**, 9297 (1995).
13 P. Francisco, M. Ana, R. Ochoa, and O. Julen, *Tetrahedron Lett.*, **37**, 4577 (1996).
14 W. V. C. Gareth and L. R. Collin, *Chem. Commun.*, **2000**, 2199.
15 S. Tu, C. Miao, F. Fang, F. Youjian, T. Li, Q. Zhuang, X. Zhang, S. Zhu, and D. Shi, *Bioorg. Med. Chem. Lett.*, **14**, 1533 (2004).
16 A Typical procedure for triarylpyridine: A dry flask (25 mL) was charged with a solution of the appropriate aldehyde (2 mmol), aromatic ketone (4 mmol), NH_4OAc (2 mmol) in a microwave oven. The flask was then connected with refluxing equipment. After irradiation for 5–9 min (irradiation sequences were interrupted with a cooling perios in between), the reaction mixture was cooled and the crude solid precipitated from the solution was filtered and washed with 95% ethanol to afford the products. Analytical data of compound **1j**: IR (neat): 3038, 1609, 1598, 1580, 1543, 820 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.39 (6H, s, 2 CH_3), 3.85 (3H, s, OCH_3), 7.11 (2H, d, $J = 8.0$ Hz, ArH), 7.35 (2H, d, $J = 8.0$ Hz, ArH), 8.01 (2H, d, $J = 8.0$ Hz, ArH), 8.08 (2H, s, Pyridine–CH), 8.21 (2H, d, $J = 8.0$ Hz, ArH). compound **1s**: IR (neat): 3135, 3105, 3061, 3008, 2829, 1599, 1512, 1458, 1421, 1342, 1299, 1244, 1171, 1103, 1033, 880, 801, 753 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.86 (6H, s, $2OCH_3$), 7.10–7.12 (4H, m, ArH), 7.22–7.24 (2H, m, ArH), 7.51–7.58 (2H, m, ArH), 8.08 (2H, s, Pyridine–CH), 8.08–8.11 (1H, m, Indole–CH), 8.24–8.27 (4H, m, Indole–CH), 11.75 (1H, s, Indole–NH). Compound **2f**: IR (neat): 3041, 1612, 1560, 1517, 858, 831, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.88 (3H, s, OCH_3), 3.96 (4H, s, $2CH_2$), 7.14 (2H, d, $J = 8.0$ Hz, ArH), 7.42–7.52 (4H, m, ArH), 7.63 (2H, d, $J = 7.2$ Hz, ArH), 7.76 (2H, d, $J = 8.0$ Hz, ArH), 8.11 (2H, d, $J = 7.2$ Hz, ArH). Compound **3a**: IR (neat): 3446, 3028, 1594, 1542, 1511, 766, 750, 736 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 2.60–2.87 (8H, m, $4CH_2$), 3.81 (3H, s, OCH_3), 6.68 (1H, d, $J = 8.4$ Hz, ArH), 6.84 (s, 1H, ArH), 6.92 (1H, d, $J = 8.4$ Hz, ArH), 7.27–7.42 (6H, m, ArH), 8.42 (2H, d, ArH), 9.17 (1H, s, OH).
17 Crystal data for **1s**: Empirical formula $C_{27}H_{22}N_2O_2$, $M_r = 406.47$, $T = 193(2)$ K, Triclinic, space group $P\bar{1}$, $a = 8.7438(13)$ Å, $b = 16.341(2)$ Å, $c = 16.460(2)$ Å, $\alpha = 68.442(11)^\circ$, $\beta = 76.059(12)^\circ$, $\gamma = 75.827(12)^\circ$, $V = 2090.7(5)$ Å^3, $Z = 4$, $D_{calcd} = 1.291$ Mg/cm^3, λ(Mo Kα) = 0.71073 Å, $\mu = 0.082$ mm^{-1}, $F(000) = 856$, $3.05^\circ < \theta < 27.48^\circ$, $R = 0.0741$, $wR = 0.1445$, $S = 1.160$, Largest diff. Peak and hole: 0.248 and -0.207 e/Å^3.
18 R. Lombard and J. P. Stephan, *Bull. Soc. Chim. Fr.*, **1958**, 1458.
19 G. N. Dorofeenko, E. P. Olekhnovich, and L. I. Laukhina, *Zh. Org. Khim.*, **7**, 1296 (1971).
20 T. Mutai, J. D. Cheon, S. Arita, and K. Araki, *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1045.

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