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Kröhnke pyridines: an efficient solvent-free synthesis of 2,4,6-triarylpyridines

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Abstract—A simple and efficient synthesis of 2,4,6-triarylpyridines is described from a novel reaction between chalcones and ammonium acetate under solvent-free conditions in excellent yields.

Pyridines are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B_6), and pyridine alkaloids.[1] Due to their π-stacking ability, some pyridines are used in supramolecular chemistry.[2] Some examples are used as pharmaceuticals (as antimalarial, vasodilator, anesthetic, anticonvulsant, and antiepileptic), dyes, additives (as antioxidant), agrochemicals (as fungicidal, pesticidal, and herbicidal), veterinary (as anthelmintic, antibacterial, and antiparasitic), and also in qualitative and quantitative analysis.[1,3–6]

So far, the most common synthetic methods for the preparation of pyridine ring systems involve: (i) transformation of another ring, and (ii) cyclizations classified on the basis of the number of ring atoms in each of the components being cyclized: (iia) from six ring atoms by N–C_α, C_α–C_β, or C_β–C_γ bond formation; (iib) by formation of two bonds, from [5+1], [4+2], or [3+3] atom fragments; (iic) by formation of three bonds, from [4+1+1], [3+2+1], or [2+2+2] atom fragments; and (iid) by formation of four bonds, from [3+1+1+1] or [2+2+1+1] atom fragments.[7,8]

Pyridines with a 2,4,6-triaryl substitution pattern (Kröhnke pyridines)[9] have been synthesized using various methods and procedures. Traditionally, these compounds have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of NH_4OAc.[9,10] However, the pyridinium salts and the unsaturated ketones have to be synthesized first, so this method is relatively expensive. More recently, several new improved methods and procedures have been developed for the synthesis of these pyridines: reaction of α-ketoketene dithioacetals with methyl ketones in the presence of NH_4OAc,[11] reaction of *N*-phosphinylethanimines with aldehydes,[12] addition of lithiated β-enaminophosphonates to chalcones,[13] solvent-free reaction between acetophenones, benzaldehydes, and NH_4OAc in the presence of sodium hydroxide,[14] and the one-pot reaction of acetophenones, benzaldehydes, and NH_4OAc without catalyst under microwave irradiation.[15]

Knowing the chemical and pharmacological importance of the Kröhnke pyridines, we have recently focused on introducing a new facile and efficient synthesis of these pyridines. Thus, a range of symmetrical 2,4,6-triarylpyridines **2a**–**s** were synthesized by heating a mixture of 1,3-diaryl-2-propen-1-ones, **1a**–**s**, and NH_4OAc in the presence of a catalytic amount of AcOH at 100 °C for 4 h under solvent-free conditions in 93–98% yields (a new cyclization from [3+2+1] atom fragments). The results are given in Table 1.

The structures of the isolated products, **2a**–**s**, were corroborated by comparison of their mp values, elemental analyses, and their spectral data (mass, IR, high-field

Keywords: 2,4,6-Triarylpyridines; Chalcones; Ammonium acetate; Solvent-free synthesis.
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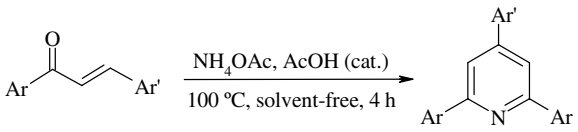
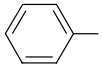
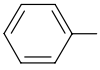
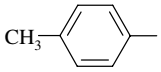
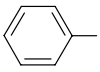
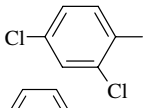
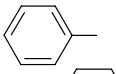
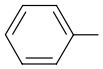
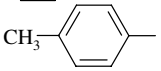
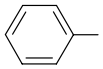
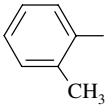
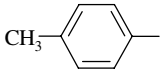
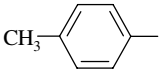
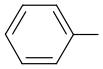
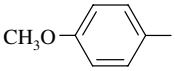
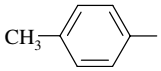
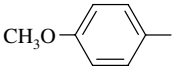
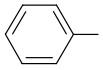
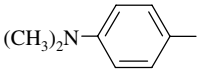
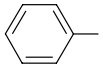
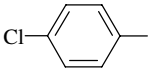
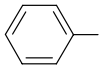
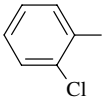
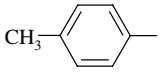
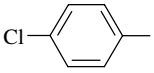
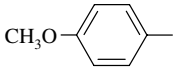
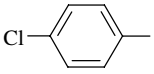
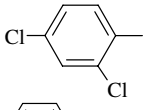
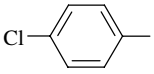
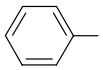
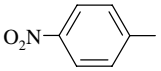
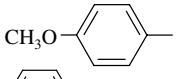
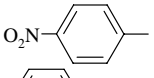
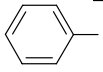
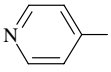
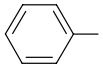
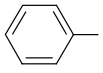
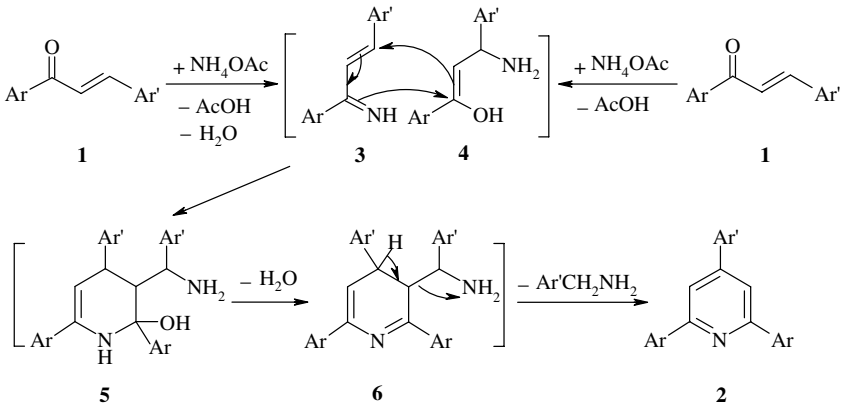
Table 1. Solvent-free synthesis of 2,4,6-triarylpyridines



1a-s **2a-s**

Entry	Ar	Ar′	% Yield[a]	mp (°C) (lit.)
a			97	134–135 (136–137)[16a]
b			97	157–158 (159–160)[16a]
c			94	159–161 (160.1–161)[15]
d			95	123–124 (124.5–125)[12]
e			94	120–122 (122–123)[12]
f			95	178–179 (178–180)[16b]
g			94	100–103 (99–100)[16a]
h			93	155–157 (156–157.5)[16a]
i			93	138–140 (138)[16c]
j			97	125–127 (129–130)[12]
k			93	113–114 (114–115)[12]
l			98	199–201 (200.6–202)[15]
m			97	115–116 (113.8–115)[15]
n			95	175–177 (176.4–177)[15]
o			93	195–197 (202–203)[12]
p			93	143–144 (143.1–144.7)[15]
q			98	187–190
r			96	168–170
s			95	162–163 (165–166)[12]

[a] Isolated yields.



Scheme 1.

^{1}H and ^{13}C NMR spectra) with those of authentic samples.[17]

Mechanistically, it is reasonable to assume that the first step may involve condensation of ammonia with a molecule of chalcone and Michael addition of ammonia to a second chalcone molecule leading to 2,4-diaryl-1-azadiene **3** and the 1:1 adduct, **4**, respectively. Azadiene **3** and adduct **4** probably undergo a formal [4+2] cycloaddition reaction to form tetrahydropyridine intermediate **5**. Dehydration to dihydropyridine intermediate **6** and then oxidative aromatization with removal of the benzyl side chain would yield 2,4,6-triarylpyridine **2**. This oxidative dealkylation has been previously observed.[18] Isolation of benzylamine from the reaction mixture of ammonium acetate and 1,3-diphenyl-2-propen-1-one, **1a**, confirms the proposed mechanism (Scheme 1). A similar reaction pathway has been proposed for the reaction between *N*-(diphenylphosphinyl)-1-ethanimine and aromatic aldehydes in the formation of 2,4,6-triarylpyridines.[12]

In conclusion, we have developed a novel and facile method for the preparation of 2,4,6-triarylpyridines. Solvent-free conditions, excellent yields, and a simplified purification process are the main advantages of this method. This method appears to have a broad scope with respect to variation in the pyridine 2-/or 6- and 4-positions.

Acknowledgement

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17. The procedure for the preparation of 2,4,6-triphenylpyridine **2a** is described as an example: A mixture of 1,3-diphenyl-2-propen-1-one, **1a** (0.42 g, 2 mmol) and ammonium acetate (0.16 g, 2.2 mmol) in the presence of a catalytic amount of acetic acid was stirred at 100 °C for 4 h (progress of the reaction followed by TLC

monitoring). Then the reaction mixture was cooled to room temperature and the crude solid obtained was recrystallized from absolute ethanol. The product **2a** was obtained in 97% yield as colorless crystals, mp 134–135 °C, IR (KBr) (ν_{max}/cm^{-1}): 1575 (shoulder), 1558, 1516, 1483, 1356, 1256, 1065, 1020, 731, 676. MS, *m*/*z* (%): 307 (M^+, 100), 230 (68), 202 (44), 77 (28). Anal. Calcd for $C_{23}H_{17}N$ (307.39): C, 89.87; H, 5.57; N, 4.56. Found: C, 89.5; H, 5.5; N, 4.9. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.40–7.60 (9H, m, 9CH), 7.78 (2H, d, $J = 8.0$ Hz, 2CH), 7.92 (2H, s, 2CH), 8.23 (4H, d, $J = 8.0$ Hz, 4CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 117.18, 127.21, 127.25, and 128.78 (4CH), 129.04 (C), 129.12 and 129.18 (2CH), 139.09 (C), 139.62 (CH), 150.24 and 157.54 (2C). Compound **2q**: Colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.45 (2H, t, $J = 7.4$ Hz, 2CH), 7.51 (4H, t, $J = 7.4$ Hz, 4CH), 7.61 (2H, d, $J = 4.7$ Hz, 2CH), 7.84 (2H, s, 2CH), 8.18 (4H, d, $J = 7.5$ Hz, 4CH), 8.76 (2H, d, $J = 4.7$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 116.58, 121.65, 127.09, 128.78, and 129.37 (5CH), 139.00, 146.49, and 147.31 (3C), 150.52 (CH), 157.91 (C). Compound **2r**: Colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.49 (1H, dd, $J = 3.4$ Hz and $J = 1.6$ Hz, CH), 6.90 (1H, d, $J = 3.4$ Hz, CH), 7.38 (2H, t, $J = 7.4$ Hz, 2CH), 7.45 (4H, t, $J = 7.5$ Hz, 4CH), 7.51 (1H, d, $J = 1.6$ Hz, CH), 7.86 (2H, s, 2CH), 8.13 (4H, d, $J = 7.4$ Hz, 4CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 108.46, 112.07, 112.97, 127.04, 128.64, and 129.05 (6CH), 139.03 and 139.39 (2C), 143.58 (CH), 151.92 and 157.45 (2C).

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