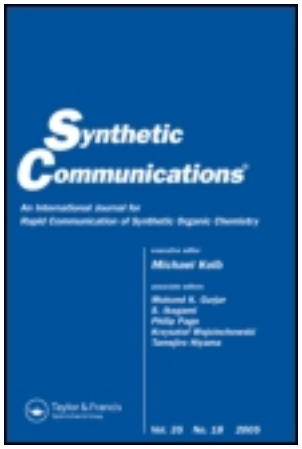

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MAGNESIUM METHOXIDE–ASSISTED SYNTHESIS OF 2,4,6-TRIARYL PYRIDINES

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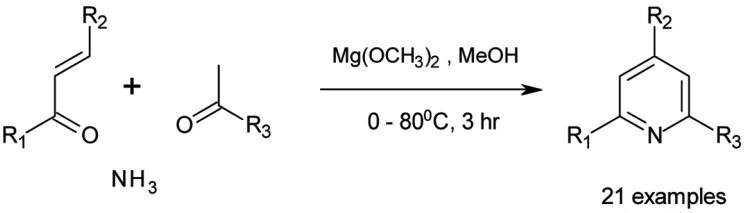
GRAPHICAL ABSTRACT



Abstract *A new three-component reaction of chalcones, ketones, and ammonia assisted by magnesium methoxide is described. The corresponding 2,4,6-triaryl pyridines (Kröhnke pyridines) are formed in fair to good yields (34–76%) within 3 h. The method also provides a facile way to synthesize 2(6)-difluoromethyl pyridines via an interesting mechanism.*

Keywords Condensation; heterocycle; multicomponent reaction; pyridine

INTRODUCTION

Nitrogen heterocycles are significant in the living world. Among them, pyridine is one of the most important ring systems because it is at the core of many biologically active compounds. It is widely used in medicinal chemistry as an antimalarial, anaesthetic, anticonvulsant, and antitumor agent and also in agrochemicals as fungicide, insecticide, and herbicide.[1] Aryl-substituted pyridines are particularly fascinating because of their biological activities and their application in material science.[2] Since Kröhnke's first report have of the synthesis of 2,4,6-triarylpyridines,[3] many other reports have appeared in literature over the years on the synthesis of arylsubstituted pyridines.[4,5] The previously reported methods involve the condensation of 1,5-diketones with ammonia[5a] or the activation of methyl ketone as N-phenacylpyridinium salts,[5d,e] α-ketoketenedithioacetal,[5f] N-phosphinylethanimines,[5g] lithiated β-enaminophosphonates.[5h] These multistep processes suffered from various drawbacks such as harsh

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reaction conditions, tedious workup procedure, long reaction time, and poor yield with occurrence of side products. Besides the procedures discussed previously, some other methods,[6] though quite simple, also suffered from various other shortcomings, including giving rise to only symmetrically substituted pyridines, requiring microwave condition, or being limited to synthesis of only aryl-substituted pyridines. As a result, a short, simple, and versatile route for the synthesis of substituted pyridinesis still a topic of research.[7]. From our literature search we did not find any simple method of preparing Kröhnke pyridines using an enone and a ketone.

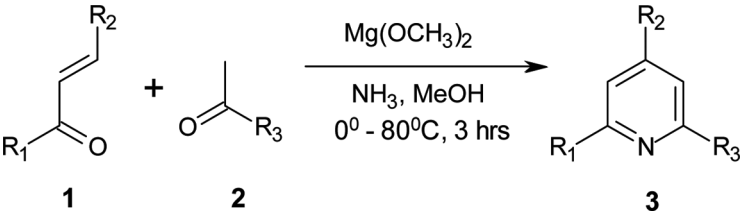
To overcome the limitations mentioned, we were looking for some simple reaction condition for the synthesis of 2,4,6-trisubstituted pyridines from an enone and a ketone in presence of ammonia. Kumar et al.[8] used bismuth(III) nitrate-alumina as catalyst in their solid-phase synthesis of 2,4,6-triarylpyridines from benzylidene acetophenones. The limitations of that method were that it resulted in either symmetrically substituted pyridines or a mixture of products and required a high temperature. Recently, use of nanoparticles of magnesium oxide was reported,[9] in a reaction of malononitrile, aryl aldehydes, and thiols to synthesize highly substituted pyridines. Ley et al.[10] demonstrated the use of magnesium nitride (Mg_3N_2), a commercially available reagent, as a surrogate for ammonia when used in protic media. Their work inspired us to explore this reagent for the synthesis of Kröhnke pyridines. We were curious to see the effect of this in situ–generated magnesium salt in the course of a reaction between a chalcone and a ketone.

RESULTS AND DISCUSSION

Herein, we report a magnesium methoxide–assisted one-pot synthesis of 2,4,6-trisubstituted, mainly triaryl pyridines by the reaction of an enone, a ketone, and ammonia in methanol (Scheme 1).

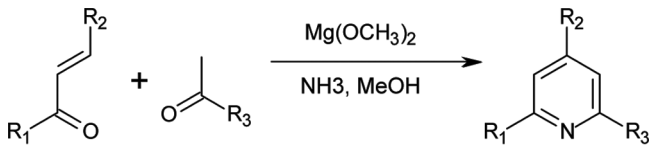
We studied the effect of various enones[11] and ketones in the synthesis of substituted pyridines. The results are summarized in Table 1. The reaction worked well with various aryl or heteroaryl substituents on the chalcone. We also cited examples when R_1 was *t*-butyl or trifluoromethyl or benzylidene group. Generally, reaction with all types of ketone (acyclic, cyclic, aryl, or heteroaryl) worked satisfactorily. In the case when R_1 was an alkyl group, the reaction ended up with a tarry mass from which nothing could be isolated, and when R_2 was an aliphatic substituent, we recovered the corresponding starting enone.

For this reaction the presence of magnesium ion was essential. When reaction was carried out without any magnesium salt, we isolated only a 1:1 mixture [based



Scheme 1. Synthesis of 2,4,6-trisubstituted pyridines.

Table 1. Magnesium methoxide–assisted three-component reaction of chalcones, ketones, and ammonia

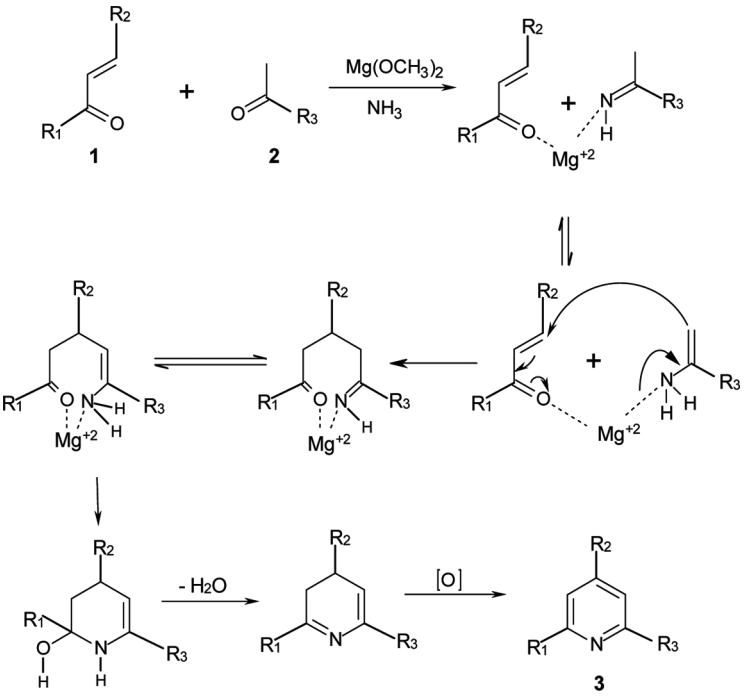


1 2 3

	Enone					
Entry	R_1	R_2	Ketone	Product	Yield %	Mp (°C)
1	Ph	2-Thienyl	1-(4-Pyridyl)ethanone	**3a**	64	140–142
2	Ph	2-Thienyl	Cyclohexanone	**3b**[a]	60	64–65
3	Ph	2-Thienyl	1,2-diPhenylethanone	**3c**[a]	38	164–165
4	Ph	2-Thienyl	1-Cyclopropylethanone	**3d**	34	67–69
5	Ph	Pyridin-3-yl	Cyclohexanone	**3e**[a]	50	82–83
6	Ph	2-Furyl	1-(Pyridin-4′-yl)ethanone	**3f**	60	132–134
7	Ph	2-Furyl	Cyclohexanone	**3g**[a]	50	65–67
8	Ph	Pyridin-3-yl	1-(Pyridin-4′-yl)ethanone	**3h**	50	202–204
9	Ph	Pyridin-3-yl	Cyclopentanone	**3i**	76	Gummy mass
10	Benzylidinyl	Phenyl	Cyclopentanone	**3j**	45	Gummy mass
11	2-Thenyl	2-Thienyl	1-(Pyridin-4′-yl)ethanone	**3k**	48	118–120
12	Thiazol-2-yl	3-BrC_6H_4	Cyclopentanone	**3l**	60	109–110
13	Pyridin-3-yl	3-Thienyl	1-(Furan-2′-yl)ethanone	**3m**	57	125–126
14	Pyridin-3-yl	3-Thienyl	1-(Pyridin-4′-yl)ethanone	**3n**	45	180–181
15	^{t}Bu	Ph	Cyclopentanone	**3o**	50	73–74
16	2-ClC_6H_4	3-Thienyl	1-(Pyridin-4′-yl)ethanone	**3p**	53	119–120
17	4-$OMeC_6H_4$	2-Thienyl	Cyclopentanone	**3q**	68	106–107

[a]Initial isolated product contained ~1:1 mixture of pyridine and dihydropyridine derivative (LCMS). The dihydropyridine derivative could never be isolated in pure form, but on keeping in air for 4–5 h, it underwent oxidation to yield the pyridine derivative only.

on liquid chromatography–mass spectrometry (LCMS) analysis] of the starting enone and the corresponding enamine of the ketone. The same reaction mixture afforded the desired pyridine when magnesium methoxide was added externally, so we assumed that the reaction was initiated by polarization of the carbonyl group of the enone assisted by magnesium ion, which was also perhaps simultaneously bound to the nitrogen atom of the enamine,[12] making it more nucleophilic. Thus the Michael reaction at the first step was facilitated by the two components in close proximity to each other (Scheme 2). Subsequent ring cyclization/dehydration/aromatization gave rise to the desired pyridine. Though the magnesium ion was initiating the Michael addition, it was required in more than the stoichiometric amount; otherwise the reaction was incomplete. Use of other metal salts such as magnesium bromide, magnesium hydroxide, and ferric chloride also produced the desired product, but in poor yields (10–20%), and magnesium methoxide was found to be the best. Like some of the reported methods,[2a,4e,5b] we did not require any activating group at the α-position of the ketone for facilitating the initial Michael attack. Generally we used dry methanol (from commercial source), but when the reaction

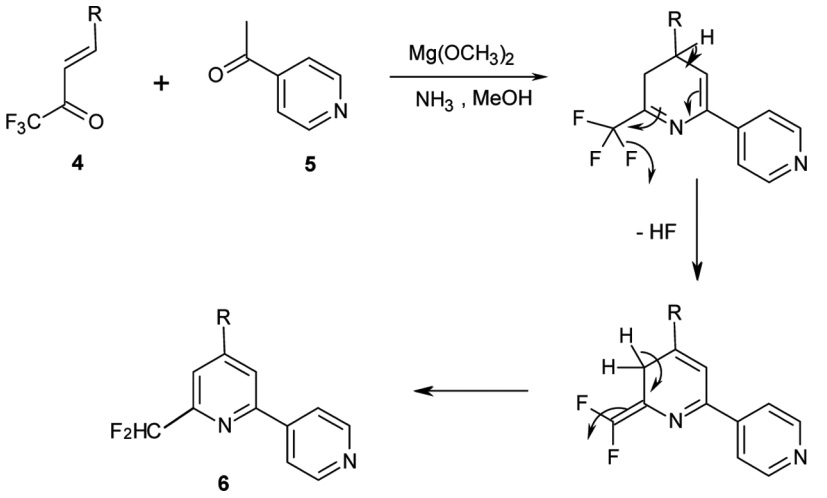


Scheme 2. Plausible mechanism for the magnesium methoxide–assisted synthesis of 2,4,6-trisubstituted pyridines.

was carried out using moist (1% moisture) methanol, the yield dropped by ~5–10%. Thus by this method varieties of 2,4,6-trisubstituted pyridines could be synthesized conveniently.

When R_1 was atrifluoromethyl group, instead of isolating the expected 2(6)-trifluoromethyl pyridine derivative, we isolated the corresponding difluoromethyl derivative as the exclusive or the major product. As reported by Shen et al.,[13] and in our case also, under the basic condition dehydrofluorination took place from the dihydropyridine intermediate (Scheme 3) and finally gave rise to the difluoromethyl derivative as the product. [In some cases the ring aromatization competed with the dehydrofluorination and resulted in some amount of trifluoro derivatives (Table 2)]. This was a very important observation, as this process also provided a facile method of synthesis of difluoromethyl substituted pyridines, which are not easy to prepare and are well known for their biological activities.[14] However, the same reaction did not work when the trifluoromethyl group was at R_2 or R_3 position. In those cases we recovered the starting enones. The advantages of our procedure over that reported by Shen et al. was that dehydrofluorination took place in the same pot without using any additional base and it was more flexible for synthesizing 2(6)-difluoromethyl-substituted pyridines of choice. The results are summarized in Table 2.

However, magnesium nitride is known for its hazardous properties.[10,15] We carried out all experiments safely using 1.3 mmol of the reagent, and for safety

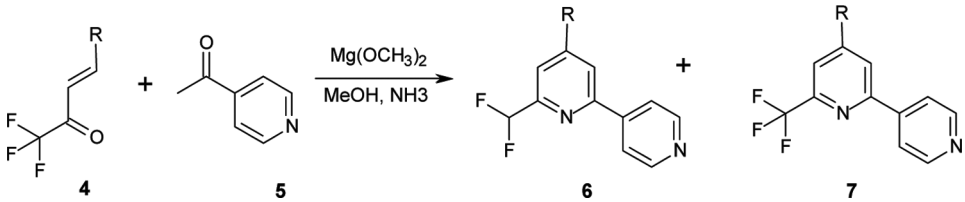


Scheme 3. Plausible mechanism for the formation of 2(6)-difluoromethyl pyridines.

reason any reaction using this reagent in the laboratory should not be scaled up beyond the scale mentioned in the experimental section. We also developed an alternative method B to avoid the use of magnesium nitride. In the alternative method the different components of the reaction were mixed together, in the same proportions as described in method A, in a reaction vial under the same reaction condition. The desired products were obtained in comparable yield.

In summary, we have developed a new, simple, and one pot synthesis of 2,4,6-triaryl pyridines, assisted by magnesium methoxide, from enones, ketones, and ammonia. This process also provided a facile way of synthesizing 2(6)-difluoromethyl substituted pyridines starting from corresponding trifluoromethyl substituted enones in single pot, without using any additional base.

Table 2. Magnesium methoxide–assisted synthesis of 2(6)-difluoromethyl pyridines



Entry	Enone R	Product	Yield %	Melting point (°C)	Product	Yield %	Melting point (°C)
1	2- Thienyl	**6a**	55	114–115	–	0	—
2	3-Pyridyl	**6b**	40	143–144	**7b**	0	—
3	2-Furyl	**6c**	45	93–94	**7c**	10	124–125
4	Ph	**6d**	55	113–114	**7d**	10	109–110

EXPERIMENTAL

Unless otherwise mentioned, all chemicals and solvents were procured from commercial sources and were used directly without any purification. Magnesium nitride of 99.9% purity was procured from M/S Aldrich Chemicals. All reactions were carried out using magnesium nitride safely and without any incident in the scale mentioned in method A. All yields reported are isolated yields. The products were characterized by their melting points and spectral and analytical data. Melting points were recorded in an Opti Melt machine from Stanford Research System in open capillaries and are uncorrected. NMR spectra were taken in $CDCl_3$ solution [in one case (**3a**) in dimethylsulfoxide, DMSO-d^6] at ambient temperature in a 400-MHz multinuclear Bruker machine, and the chemical shift values are mentioned in δ. Purities of all the products were ≥96% and were checked by high-performance liquid chromatography (HPLC) in an Agilent-1200 series machine. They were also cross-checked by LC-MS on a Surveyor HPLC with MSQ on a Thermo machine and by high-resolution mass spectrometry (HRMS) on Agilent 6520 Q-TOF and on LTQ Orbitrap Velos (Thermo Scientific) instruments respectively. All experiments were carried out using ~0.5 and ~2.5 mmol of the chalcones in methods A and B respectively unless otherwise mentioned.

Typical Experimental Procedure (Preparation of Compound 3i) Method A (Using Magnesium Nitride)

Magnesium nitride (0.131 g, 1.3 mmol) was added to a stirred solution of 1-phenyl-3-(pyridin-3′-yl)propenone (0.110 g, 0.53 mmol) and cyclopentanone (0.044 g, 0.52 mmol) in dry methanol (3 mL) at 0 °C in a 2–5 mL microwave reaction vial in a single portion. The vial was sealed immediately, kept in ice bath under stirring for 1 h, and then allowed to warm at room temperature slowly in a water bath during another 1 h. The reaction mixture was then placed in a preheated oil bath at 80 °C under stirring for 3 h. After allowing the reaction mixture to cool to room temperature, the vial was opened carefully. The content was diluted with ethyl acetate (15 mL) and water (15 mL), and the layers were separated. The aqueous layer was neutralized with 3 N hydrochloric acid and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by a filtration column with mixture of ethylacetate:hexane (3:7) to give rise to the product (0.109 g, brown gummy mass) in 76% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12–2.19 (m, 2H), 3.02–3.06 (m, 2H), 3.14–3.18 (m, 2 H), 7.25–7.51 (m, 5H), 7.81–7.86 (m, 1H), 7.99 (d, 2H, $J = 1.2$ Hz), 8.65 (dd, 1H, $J = 4.8$, 1.2 Hz), 8.79 (d, 1H, $J = 2.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 28.5, 32.8, 115.9, 121.6, 125.1, 126.7, 126.8, 131.3, 132.8, 133.5, 137.7, 140.5, 147.1, 147.4, 154.9, 165.1. HRMS: $(M + H)^+$, cal. for $C_{19}H_{17}N_2$ 273.1386; found 273.1387.

Method B (Using Freshly Prepared Magnesium Methoxide)

Freshly prepared magnesium methoxide (0.498 g, 5.8 mmol) was added to a stirred solution of 1-phenyl-3-(pyridin-3′-yl)propenone (0.500 g, 2.4 mmol) and cyclopentanone (0.193 g, 2.3 mmol) in methanol (12 mL), saturated with ammonia

gas, in a 10–20 mL microwave vial. The vial was sealed immediately and was placed in a preheated oil bath at 80 °C for 3 h. After allowing the reaction mixture to cool at room temperature, the vial was opened carefully. The content was diluted with ethyl acetate (50 mL) and water (30 mL), and the layers were separated. The aqueous layer was neutralized with 3 N hydrochloric acid, and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by passing through a filtration column (ethylacetate:hexane) to give rise to the product **3i** (0.487 g, brown gummy mass) in 74.94% yield.

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