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A facile synthesis of 2,3-disubstituted-6-arylpyridines from enaminones using montmorillonite K10 as solid acid support

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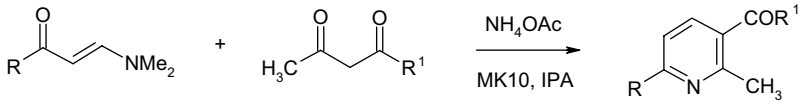
Abstract—A facile synthesis of 2,3-disubstituted-6-arylpyridines from enaminones using montmorillonite K10 as solid acid support is reported herein.

Substituted pyridines have become increasingly important because of the diverse types of biological activities they exhibit.[1] A number of substituted pyridines such as 6-aryl-2-methylnicotinates are also useful as building blocks in the synthesis of pyridine fused ring systems.[2] Enaminoketones are versatile and readily available intermediates and play an important role in the synthesis of a number of heterocyclic compounds.[3] 6-Aryl-2-methylnicotinates can be synthesized by the reaction of a 3-aminocrotonate with acetophenone Mannich base hydrochlorides in refluxing ethanol for 12 h,[4] with acetylenic ketones at higher temperatures[5] and with oxazolidines possessing a CH_2-EWG at C-2 in refluxing acetonitrile in the presence of acetic acid.[6] These pyridines can also be prepared by the reaction of enaminoketones with β-dicarbonyl compounds in the presence of ammonium acetate in refluxing acetic acid.[7] However, these methods are limited by the use of expensive and commercially unavailable reagents, long reaction times, acidic conditions and tedious end product isolation procedures.

Recently, the use of solid acid catalysts, such as clays has gained importance in organic synthesis, because they are easy to handle, are noncorrosive, selective and inexpensive.[8] In view of the limitations involved in the synthesis of 6-aryl-2,3-disubstituted pyridines, the growing importance of solid acid supports as ecofriendly reagents[9] and our continued interest in the synthesis of heterocycles,[10] we report herein the synthesis of substituted pyridines using montmorillonite K10 as a solid acid support (Scheme 1).

The reaction of enaminoketones **1** with ethyl acetoacetate **2** and ammonium acetate in refluxing isopropanol in the presence of K10 clay afforded the corresponding pyridine derivatives **3** in good yields.[11] Thus the condensation reaction of enaminoketone with ethyl acetoacetate takes place in totally acetic acid free conditions[7] and in heterogeneous media. The generality of the present method is evident from the reaction of a variety of enaminoketones with **2** to give different 6-aryl-substituted 2-methylnicotinates **3**. 3-Acetylpyridine **4** was



1 **2** **3** $R^1 = OC_2H_5$ **4** $R^1 = CH_3$

Scheme 1.

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Table 1. Physical data of the 6-aryl-2,3-disubstituted pyridines prepared[12]

Entry	R	Mp °C	(Lit. °C)	Yield %
3a	C_6H_5	44–46	(46–47)[4] (Oil)[6]	76
3b	4-ClC_6H_4	74–75	(76)[7]	79
3c	4-BrC_6H_4	72–74	—	81
3d	4-FC_6H_4	62–63	—	82
3e	4-$CH_3C_6H_4$	53–54	(55)[7]	78
3f	4-$CH_3OC_6H_4$	65–67	(68)[7]	77
3g	4-$CH_3SC_6H_4$	59–61	—	75
3h	4-$NO_2C_6H_4$	71–73	—	83
3i	2,4-$Cl_2C_6H_3$	65–67	—	73
3j	2-Thienyl	58–60	—	71
4	C_6H_5	110–112	—	75

obtained when enaminoketone **1a** was reacted with acetylacetone using the same procedure. To study the role of the clay, the reaction was also carried out in its absence, however, the reaction took 24 h for completion compared to refluxing for 2–4 h in the presence of clay or in acetic acid. The structures of compounds **3** and **4** were determined based on ^{1}H NMR spectra and by comparison of physical data with known compounds (Table 1). The reusability of the catalyst was also studied by reusing the clay after filtering and drying. The yields were not effected in the second cycle.

In conclusion, we have reported a facile synthesis of 2,3-disubstituted-6-arylpyridines in isopropanol under acetic acid free conditions, demonstrating the use of montmorillonite K10 as a heterogeneous acid catalyst. The present procedure has the advantages of simple experimental and product isolation procedures coupled with high purity and yields.

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11. *Typical experimental procedure:* a mixture of an aminoketone **1** (0.01 mol), ethyl acetoacetate (0.012 mol), ammonium acetate (2 g), montmorillonite K10 (0.5 g) in isopropanol (10 mL) was stirred at reflux for 2–4 h. After completion of the reaction as indicated by TLC, the catalyst was filtered off. The solvent was evaporated in vacuo and the residual solid was recrystallized from methanol to give pure **3** as a crystalline solid. 3-Acetylpyridine **4** was also prepared in a similar manner using acetylacetone in place of ethyl acetoacetate.
12. All new products were characterized by ^{1}H NMR.
    Ethyl (2-methyl-6-4′-bromophenyl)nicotinate-**3c**. Yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (t, 3H, J = 7.2 Hz), 2.91 (s, 3H), 4.37 (q, 2H, J = 7.1 Hz), 7.41 (d, 2H, J = 7.3 Hz), 7.58 (d, 1H, J = 7.2 Hz), 7.96 (d, 2H, J = 7.2 Hz), 8.25 (d, 1H, J = 8.0 Hz). Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.25; H, 4.37; N, 4.37. Found: C, 56.37; H, 4.49; N, 4.53.
    Ethyl (2-methyl-6-4′-fluorophenyl)nicotinate-**3d**. Yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.4 Hz), 2.92 (s, 3H), 4.41 (q, 2H, J = 7.3 Hz), 7.42 (d, 2H, J = 7.8 Hz), 7.56 (d, 1H, J = 7.9 Hz), 7.98 (d, 2H, J = 7.8 Hz), 8.24 (d, 1H, J = 8.0 Hz). Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.40; N, 5.40. Found: C, 69.62; H, 5.26; N, 5.73.
    Ethyl (2-methyl-6-4′-methylthiophenyl)nicotinate-**3g**. Light orange solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.4 Hz), 2.52 (s, 3H), 2.89 (s, 3H), 4.38 (q, 2H, J = 7.3 Hz), 7.34 (d, 2H, J = 7.4 Hz), 7.57 (d, 1H, J = 7.3 Hz), 8.01 (d, 2H, J = 7.2 Hz), 8.23 (d, 1H, J = 8.0 Hz). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.89; H, 5.92; N, 4.87. Found: C, 67.01; H, 6.23; N, 4.63.
    Ethyl (2-methyl-6-4′-nitrophenyl)nicotinate-**3h**. Yellow crystalline solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (t, 3H, J = 7.4 Hz), 2.93 (s, 3H), 4.36 (d, 2H, J = 7.4 Hz), 7.69 (d, 1H, J = 7.3 Hz), 8.26–8.36 (m, 5H). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.90; N, 9.79. Found: C, 63.04; H, 5.06; N, 9.62.
    Ethyl (2-methyl-6-2′,4′-dichlorophenyl)nicotinate-**3i**. Light cream solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.4 Hz), 2.91 (s, 3H), 4.38 (q, 2H, J = 7.3 Hz), 7.41–7.80 (m, 4H), 8.25 (d, 1H, J = 8.0 Hz). Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.06; H, 4.19; N, 4.51. Found: C, 58.21; H, 4.36; N, 4.67.
    Ethyl (2-methyl-6-thien-2-yl)nicotinate-**3j**. Pale yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H,J = 7.4 Hz), 2.86 (s, 3H), 4.37 (q, 2H, J = 7.4 Hz), 7.12 (dd, 1H, J = 3.4, 1.5 Hz), 7.50 (dd, 1H, J = 4.8, 1.5 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.65 (dd, 1H, J = 5.5, 1.5 Hz), 8.21 (d, 1H, J = 8.0 Hz). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.15; H, 5.26; N, 5.66. Found: C, 63.28; H, 5.31; N, 5.74.
    1-(2-Methyl-6-phenylpyridin-3-yl)ethanone-**4**. Yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 3H), 2.84 (s, 3H), 7.46 (m, 3H), 7.66 (d, 1H, J = 7.4 Hz), 8.07 (m, 3H). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.62; H, 6.16; N, 6.63. Found: C, 79.69; H, 6.34; N, 6.84.