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'One Pot' Synthesis of 2-Amino-3-cyano-4,6-diarylpyridines under Ultrasonic Irradiation and Grindstone Technology

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A simple facile 'one pot' synthesis of 2-amino-3-cyano-4,6-diarylpyridine derivatives *via* three component reaction of chalcone, malanonitrile and ammonium acetate under ultrasonic irradiation and grindstone technology. All the synthesized compounds have been characterized on the basis of their elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass).

Key Words: 2-Amino-3-cyano-4,6-diarylpyridines, Chalcones, Ultrasonic irradiation, Grindstone technology

Introduction

Pyridine functionalities have been widely studied[1,2] and widely used[3-6] but still generate much interest due to their wide range of application in medicinal chemistry.[7-11] The naturally occurring B_6-vitamins pyridoxine, pyrodoxal, pyridoxamine and codecarbaxylase contain a pyridine nucleus.[12] Pyridine derivatives have been used as herbicides,[13] for enrichment of cereals,[14] for regulation of arterial pressure,[15] and cholesterol levels in blood.[16] Some pyridines constitute an important class of antitumor compounds.[17-18] They also show antibacterial,[19] antifungal,[20] antimyotic[21] and antidepressant[22] activities.

Some bifunctional pyridines are used as non linear optical materials,[23] electrical materials,[24] chelating agents in metal-ligand chemistry,[25] and as fluorescent liquid crystals.[26] Among them, 2-amino-3-cyanopyridines have been identified as IKK-β inhibitors.[27] Besides this, they are important and useful intermediates in preparing variety of heterocyclic compounds.[28-30] Therefore, the synthesis of 2-amino-3-cyano-4,6-diarylpyridines attract much interest in organic chemistry. There are a variety of methods described in literature[31-33] to synthesize similar skeleton. Many precedent methods, however have inevitable drawbacks, for eg., conventional methods used in synthesis of substituted pyridines involve volatile organic solvents and display only moderate to low yields with low atom efficiency.[34] In developing a more versatile route for synthesis of such compounds, and adopting principles of green chemistry, we have extended our studies with new green procedures (ultrasonic irradiation and grinding).

A survey of literature shows that various organic reactions could be accelerated by ultrasonic irradiation with a higher yield, shorter reaction time and milder conditions.[35-36] The pioneering work of Toda *et al.* has shown that many exothermic reactions can be accomplished in high yields by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry'. Reactions are initiated by grinding, with the transfer of very small amounts of energy through friction. It is not only advantageous from the environmental point of view but also offers rate enhancement, less waste products and higher yields.[37]

Results and Discussion

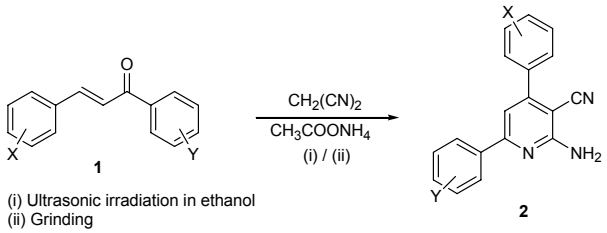
Synthesis. Chalcone, malanonitrile and ammonium acetate were grinded together with pestle and mortar without using any solvent for 15 - 20 minutes. The reaction mixture was left at room temperature overnight which yielded a yellow solid product. But, in ultrasonic irradiation requisite amount of ethanol was used (Scheme 1). Both the above said procedures provided products in good to excellent yields with simple and mild reaction conditions.

The comparative data of both the procedures are tabulated in Table 1. Structures of synthesized compounds were established on the basis of elemental and spectral analyses (IR, ^{1}H NMR, ^{13}C NMR, Mass).

In the IR spectra of chalcone **1,** characteristic absorption band at 1660 cm^{-1} (> C=O) is observed which disappears in the IR spectra of 2-amino-3-cyano-4,6-diarylpyridine derivatives **2**. Besides this, the stretching vibration of -NH_2 group appears as broad band in the region 3440 - 3300 cm^{-1}. Appearance of characteristic peak of -CN group in the region 2250 - 2200 cm^{-1} confirms the formation of desired compounds (**2a-h**).

In the ^{1}H NMR spectra of 2-amino-3-cyano-4,6-diarylpyridine derivatives **2,** a singlet is observed in the region δ 5.60 - 5.94 ppm due to presence of NH_2 group. Aromatic protons are obtained as multiplets in the region δ 6.79 - 8.01 ppm* (*The 5-C-H proton of pyridyl ring is also merged in this region).

In the ^{13}C NMR of 2-amino-3-cyano-4,6-diarylpyridine derivatives **2**, various characteristic peaks at δ 154.06, 157.86, 160.36 ppm are observed. Aromatic region is obtained from δ



(i) Ultrasonic irradiation in ethanol
(ii) Grinding

Scheme 1

Table 1. Synthesis of 2-amino-3-cyano-4,6-diarylpyridines **(2a-h)**

Compound	X	Y	Ultrasonic irradiation		Grinding		mp (°C)
			Time (min)	Yield (%)	Time (min)	Yield (%)	
2a	H	H	22	85	15	82	186
2b	4-Cl	H	23	86	14	85	190
2c	H	4-Cl	24	82	13	86	182
2d	4-OCH_3	4-Br	25	86	14	84	181
2e	H	4-Br	25	84	15	84	175
2f	4-OCH_3	4-Cl	24	80	18	86	177
2g	4-F	4-Br	22	82	14	82	172
2h	4-F	4-Cl	24	86	14	81	181

109.77 - 135.79 ppm.

Final confirmation was obtained from FAB Mass spectra which showed an accurate M^+/M+2 peaks at *m*/*z* 287 (**2a**), 306/308 (**2b**, **2c**), 380/382 (**2d**), 350/352 (**2e**), 336/338 (**2f**), 368/370 (**2g**), 324 (**2h**) that agreed well with their corresponding molecular formulae.

Conclusion

In summary, we have developed two simple, novel and eco-friendly synthetic protocols for the synthesis of 2-amino-3-cyano-4,6-diarylpyridines (**2a-h**) using ultrasonic irradiation and grindstone technology which provides higher yields in shorter reaction time with the simplicity of the procedures.

Experimental

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra (υ_{max} in cm^{-1}) were recorded on FT-IR SHIMADZU-8400S Spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on JEOL-AL 300 spectrophotometer (300 MHz) using $CDCl_3$/DMSO-d_6 as solvents. TMS was taken as internal standard. FAB mass spectra were recorded on JEOL SX-102/DA-6000 (FAB) mass spectrometer/data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas at Central Drug Research Institute (CDRI), Lucknow using m-nitrobenzyl alcohol as matrix.Elentar Vario EL III automatic CHN analyzer was used for elemental analyses. The FAB mass spectra and CHN analyses were recorded at Central Drug Research Institute (CDRI), Lucknow, India. Sonication was performed in a Toshcon model SW 4 cleaner (with a frequency of 37 KHz and operating at maximum power of 150 W). The purity of compounds was checked by TLC using silica gel (60 - 120 mesh) as adsorbent, UV light, or iodine accomplished visualization. All common reagents and solvents were used as obtained from commercial suppliers without further purification. Chalcones (**1**) were prepared by method described in literature.[38]

General procedure for the synthesis of 2-amino-3-cyano-4,6-diarylpyridines (2a-h).

Method (i): Chalcone (**1**) (0.05 mol), malanonitrile (0.05 mol), and ammonium acetate (0.04 mol) were grinded together in a mortar. Then this mixture was transferred into a 250 mL round bottom flask with the addition of ethanol (50 mL). The reaction flask was then placed in the maximum energy area in an ultrasonic cleaning bath (observation of the surface of the reaction solution during vertical adjustment of flask depth shows the optimum position by the point at which maximum surface disturbance occurs). The bath temperature was controlled by addition or removal of water at 30 °C. The progress of the reaction was monitored by TLC using C_6H_6 : EtOAC : 95:5 as solvent system. Sonication was continued until starting reactants disappeared as indicated by TLC. A yellow solid prouduct was obtained within 20 - 25 mins of irradiation (Table 1). After the completion of the reaction, the mixture was poured into crushed ice with constant stirring to obtain a yellow solid mass, which was dried and recrystallized from 95% ethanol.

Method (ii): Chalcone (**1**) (0.05 mol), malanonitrile (0.05 mol), and ammonium acetate (0.04 mol) were grinded together in a mortar with pestle for 13 - 18 mins. The color of the reaction mixture turned light yellow from colorless starting reactants. The progress of the reaction was monitored by TLC using C_6H_6 : EtOAC : 95:5 as solvent system. Then the reaction mixture was left overnight whereby a yellow solid crude product was obtained which was recrystallized from 95% ethanol.

2-Amino-3-cyano-4,6-diphenylpyridine (2a). Yellow solid, Yield: (i) 85%, (ii) 82%, mp 186 °C. IR (cm^{-1}): 3430 and 3310 (NH_2), 3200 (ArH), 2200 (CN), 1625, 1575, 1550, 1510, 1250, 1175, 1025, 820. MS (*m*/*z*) 287. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, NH_2, 2H), 7.22-8.20 (m, ArH, 11H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 109.77, 115.64, 115.92, 128.68, 128.82, 130.31, 135.77, 154.05, 157.85, 160.62.

2-Amino-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (2b). Yellow solid, Yield: (i) 86%, (ii) 85%, mp 190 °C. IR (cm^{-1}): 3500 and 3400 (NH_2), 3245 (ArH), 2205 (CN), 1625, 1575, 1550, 1515, 1255, 1170, 1030, 825. MS (*m*/*z*) 306/308. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (s, NH_2, 2H), 7.18-7.99 (m, ArH, 10H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 108.77, 114.64, 115.91, 128.64, 128.82, 130.33, 135.77, 153.50, 157.42, 160.63.

2-Amino-3-cyano-6-(4-chlorophenyl)-4-phenylpyridine (2c). Yellow solid, Yield: (i) 82%, (ii) 86%, mp 182 °C. IR (cm^{-1}): 3500 and 3410 (NH_2), 3245 (ArH), 2200 (CN), 1630, 1565, 1550, 1511, 1250, 1170, 1025, 820. MS (*m*/*z*) 306/308. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, NH_2, 2H), 6.79-8.00 (m, ArH, 10H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 109.65, 115.61, 114.97, 128.63, 128.81, 131.13, 135.13, 154.00, 157.82, 160.12.

2-Amino-3-cyano-6-(4-bromophenyl)-4-(4-methoxyphenyl)-pyridine (2d). Yellow solid, Yield: (i) 86%, (ii) 84%, mp 181 °C. IR (cm^{-1}): 3435 and 3370 (NH_2), 3200 (ArH), 2975 (OCH_3), 2200 (CN), 1622, 1575, 1550, 1510, 1245, 1180, 1015, 820. MS (*m*/*z*) 380/382. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, OCH_3, 3H), 5.78 (s, NH_2, 2H), 6.95-8.01 (m, ArH, 9H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 61.22, 111.77, 114.64, 115.90, 127.68, 128.72, 130.21, 135.67, 154.15, 157.35, 160.12.

2-Amino-3-cyano-6-(4-bromophenyl)-4-phenylpyridine (2e). Yellow solid, Yield: (i) 84%, (ii) 84%, mp 175 °C. IR (cm^{-1}): 3450 and 3390 (NH_2), 3270 (ArH), 2215 (CN), 1625, 1575, 1570, 1520, 1250, 1170, 1025, 805. MS (*m*/*z*) 350/352. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (s, NH_2, 2H), 6.95-8.01 (m, ArH, 9H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 109.81, 115.44, 115.80, 127.68, 129.81, 130.30, 135.57, 154.05, 157.81, 160.52.

2-Amino-3-cyano-6-(4-chlorophenyl)-4-(4-methoxyphenyl)-pyridine (2f). Yellow solid, Yield: (i) 80%, (ii) 86%, mp 177 °C. IR (cm^{-1}): 3445 and 3380 (NH_2), 3200 (ArH), 2970 (OCH_3), 2200 (CN), 1625, 1575, 1550, 1510, 1250, 1175, 1025, 820. MS (*m*/*z*) 336/338. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, OCH_3, 3H), 5.37 (s, NH_2, 2H), 7.02-8.01 (m, ArH, 9H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 61.17, 109.57, 115.34, 115.72, 127.68, 128.86, 130.33, 135.57, 154.05, 157.84, 161.62.

2-Amino-3-cyano-6-(4-bromophenyl)-4-(4-fluorophenyl)-pyridine (2g). Yellow solid, Yield: (i) 82%, (ii) 82%, mp 172 °C. IR (cm^{-1}): 3470 and 3375 (NH_2), 3260 (ArH), 2200 (CN), 1620, 1575, 1555, 1505, 1260, 1175, 1030, 830. MS (*m*/*z*) 368/370. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, NH_2, 2H), 7.17-7.97 (m, ArH, 9H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 109.87, 115.44, 115.82, 128.68, 128.80, 130.34, 135.65, 154.00, 157.83, 160.61.

2-Amino-3-cyano-6-(4-chlorophenyl)-4-(4-fluorophenyl) pyridine (2h). Yellow solid, Yield: (i) 86%, (ii) 81%, mp 181 °C. IR (cm^{-1}): 3475 and 3380 (NH_2), 3250 (ArH), 2210 (CN), 1625, 1575, 1555, 1511, 1250, 1170, 1025, 825. MS (*m*/*z*) 324/326. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (s, NH_2, 2H), 7.17-7.97 (m, ArH, 9H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 109.77, 115.64, 115.92, 128.68, 128.82, 130.31, 135.79, 154.06, 157.86, 160.63.

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References

1. Krohnke, K. *Synthesis* **1976**, 1.
2. Katritzky, A. R.; Elisseou, E. M.; Patel, R. C.; Plau, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 125.
3. Steenwinkel, P.; James, S. L.; Grove, D. M.; Kooijman, H.; Spek, A. L.; Koten, G. V. *Organometallics* **1997**, *16*, 513.
4. Neve, F.; Campagna, S.; Crispini, A. *Inorg. Chem.* **1997**, *36*, 6150.
5. Cave, G. W. V.; Hallett, J.; Errington, W.; Rourke, J. P. *Angew. Chem.* **1998**, *23*, 3466 (*Angew. Chem., Int. Ed.* **1998**, *37*, 3270).
6. Constable, E. C.; Housecroft, C. E.; Neuburger, M.; Phillips, D.; Raithby, P. R.; Schofield, E.; Sparr, E.; Tocher, D. A.; Zehnder, M.; Zimmermann, Y. *J. Chem. Soc., Dalton Trans*. **2000**, 2219.
7. Cave, G. W. V.; Hardie, M. J.; Roberts, B. A.; Raston, C. L. *Eur. J. Org. Chem*. **2001**, 3227.
8. Constable, E. C.; Housecroft, C. E.; Neuburger, M.; Schneider, A. G.; Springler, B.; Zehnder, M. *Inorg. Chim. Acta* **2000**, *49*, 300.
9. Li, Y.; Liu, Y.; Bu, W.; Guo, J.; Wang, Y. *Chem. Commun*. **2000**, 1551.
10. Rice, C. R.; Ward, M. D.; Nazeeruddin, M. K.; Grazel, M. *New J. Chem.* **2000**, *24*, 651.
11. Cave, G. W. V.; Fanizzi, F. P.; Deeth, R. J.; Errington, W.; Rourke, J. P. *Organometallics* **2000**, *19*, 1801.
12. Konda, S. G.; Khedkar, V. T.; Dawane, B. S. *J. Chem. Pharm. Res.* **2010**, *2*, 187.
13. Temple, C. J.; Rener, G. A.; Waud, W. R.; Noker, P. E. *J. Med. Chem.* **1992**, *35*, 3686.
14. Budgett, C. O.; Woodward, C. F. *J. Am. Chem. Soc*. **1947**, *69*, 2907.
15. Mercier, J.; Gavend, M.; Vanluv, V.; Dessaigne, S. *Congr Unionther Int [CR]* **1963**, *8*, 361.
16. Dorner, G.; Fischer, F. W. *Arezenmittel Forch* **1961**, *11*, 110.
17. Boger, D. L.; Nakahara, S. J. *Org. Chem.* **1991**, *56*, 880.
18. (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (b) Zhang, T. Y.; Stout, J. R.; Keay, J. G.; Seriven, E. F. V.; Toomey, J. E.; Goe, G. L. *Tetrahedron* **1995**, *51*, 13177.
19. Youngdale, G. A. *US Pat*. 4 288 440, 1980; *Chem. Abstr*. **1982**, *96*, 6596.
20. Todd, A. H.; *UK Pat*. 1 203, 149, 1970; *Chem. Abstr*. 73, 120509, 1970.
21. Lohaus, G.; Dittmar, W.; Afric, S. *Pat*. 6 906, 036, 1968; *Chem. Abstr*. 73, 120508, 1970.
22. Gachet, C.; Cattanea, M.; Ohlmann, P.; Lecchi, B.; Cassel, J.; Mannucci, P.; Cazenave, J. P. *Br. J. Haematol.* **1995**, *91*, 434.
23. Wang, H.; Helgeson, R.; Ma, B.; Wudl, F. *J. Org. Chem*. **2000**, *65*, 5862.
24. Kanbara, T.; Kushida, T.; Saito, N.; Kuwajima, I.; Kubota, K.; Yamamoto, T. *Chem. Lett.* **1992**, 583.
25. Meyer, T. J. *Acc. Chem. Res*. **1989**, *22*, 163.
26. Harada, H.; Watanuki, S.; Takuwa, T.; Kawaguchi, K.; Okazaki, T.; Harano, Y.; Saitoh, C. *PCT Int. Appl. WO* **2002**, 006, 237 A1, **2002**, 92.
27. Murata, T.; Shimada, M.; Sakakibara, S.; Yoshino, T.; Kadono, H.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Sakai, K.; Inbe, H.; Takeshita, K.; Niki, T.; Umeda, M.; Bacon, K. B.; Ziegelbauer, K. B.; Lowinger, T. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 913.
28. (a) Shishoo, C. J.; Devani, M. B.; Bhadti, V. S.; Ananthan, S.; Ullas, G. V. *Tetrahedron Lett.* **1983**, *24*, 4611. (b) Doe, K.; Avasthi, K.; Pratap, R.; Bakuni, D. S.; Joshi, M. N. *Indian J. Chem.* **1990**, *29B*, 459.
29. Bhalerao, U. T.; Krishnaiah, A. *Ind. J. Chem.* **1995**, *34B*, 587.
30. Al-Haiza, M. A.; Mostafa1, M. S.; El-Kady, M. Y. *Molecules* **2003**, *8*, 275.
31. Janis, R. A.; Silver, P. J.; Triggle, D. *J. Adv. Drug Res.* **1987**, *16*, 309.
32. Tyndall, D. V.; Nakib, T. A.; Meegan, M. J. *Tetrahedron Lett*. **1988**, *29*, 2703.
33. Al-Arab, M. M. J. *Heterocycl. Chem.* **1989**, *26*, 1665.
34. Cave, G. W. V.; Raston, C. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3258.
35. Luche, J. L. *Synthetic Organic Sonochemistry*; Plenum Press: New York, 1998.
36. Li, J. T.; Yang, W. Z.; Wang, S. X.; Li, S. H.; Li, T. S. *Ultrason. Sonochem*. **2002**, *9*, 237.
37. Pathak, V. N.; Gupta, R.; Varshney, B. *Indian J. Chem. B* **2008**, *47*, 434.
38. Cheng, M. S.; Li, R. S.; Kenyon, G. *Chinese Chemical Letters* **2000**, *11*, 851.