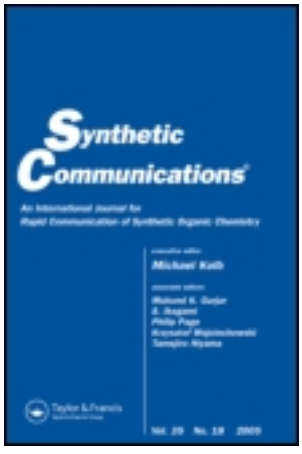

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One-Pot Synthesis of 4,6-Diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles via Three-Component Cyclocondensation under Solvent-Free Conditions

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Abstract: An efficient and facile synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles via three-component cyclocondensation from aromatic aldehydes, aromatic ketones, and 2-cyanoacetamide under solvent-free conditions is described. The mild reaction conditions, simple protocol, and clean reaction make this protocol practical and economically attractive.

Keywords: heating, 2-pyridone, solvent-free condition

In recent years, emphasis in chemistry has shifted to develop environmentally benign routes to a myriad of materials.[1] Green chemistry approaches hold significant potential not only for reduction of by-products, a reduction in the waste produced, and lowering of energy costs but also for the development of new methodologies to achieve previously unobtainable materials, using existing technologies.[2] Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally high ratio of waste/product, are perhaps the most ripe for improvement.[3] Multicomponent

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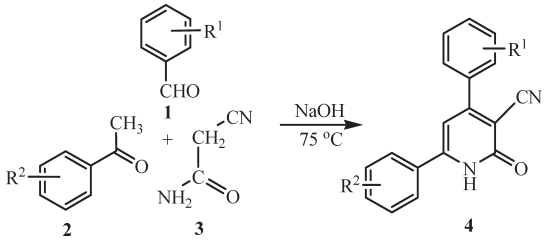
coupling reactions (MCRs) are emerging as useful tools for carbon–carbon and carbon–heteroatom bond-forming reactions and for the synthesis of small druglike molecules with several degrees of structural diversity.[4] Development of new solid-phase (solvent-free) MCRs is the subjects of recent interest in organic synthesis.[5] Solvent-free reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products, and manipulative simplicity.[6] Some solvent-free reactions could be carried out just by heating.[7]

Substituted six-membered lactams, 2-pyridones, and their hydrogenating derivatives have attracted the attention of synthetic organic chemists for many years because these structural features are found in a wide variety of naturally occurring alkaloids.[8] Since compounds with these scaffolds have been shown to exhibit significant pharmacological properties, medicinal chemists often incorporate these motifs in the design of novel biologically active molecules. Development of a general and efficient synthetic strategy that could provide access to a wide range of nitrogen heterocycles with a six-membered lactam core is therefore highly desired. Several novel synthetic methodologies directed toward the preparation of six-membered nitrogen heterocycles have been reported.[9] However, preparations of these reactive intermediates are not always straightforward to carry out because of various drawbacks involved in these reactions, such as long reaction times, low yields, and forced reaction conditions. Especially in these reactions, the organic solvents are needed.[10] Therefore, the development of a simple and efficient method for the preparation of 2-pyridone derivatives is an active area of research, and there is scope for further improvement involving milder reaction conditions and higher product yields. In continuation of our ongoing endeavor to apply solvent-free conditions to the synthesis of organic compounds,[11] we herein describe a practical and simple MCR to prepare 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles by heating starting material under dry conditions. The aromatic aldehydes **1**, aromatic ketones **2**, and 2-cyanoacetamide **3** were mixed together in a flask in the presence of catalyst NaOH. The mixture was heated at 75°C about 30 min, and the reaction could be finished with good yields (Scheme 1). The results of reaction are listed in Table 1. As shown in Table 1, we can see not only that



Scheme 1.

Table 1. Synthesis of 1,2-dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile under solvent-free conditions

Entry	R^1	R^2	Product	Yields
1	4-F	H	**4a**	88
2	4-Cl	H	**4b**	85
3	4-Br	H	**4c**	89
4	2-Cl	H	**4d**	84
5	2,4-Cl_2	H	**4e**	80
6	3,4-Cl_2	H	**4f**	83
7	3,4-$(CH_3O)_2$	H	**4g**	80
8	3,4-OCH_2O	H	**4h**	81
9	4-CH_3	4-CH_3	**4i**	80
10	4-CH_3	4-Br	**4j**	85
11	H	4-CH_3O	**4k**	78
12	H	4-Cl	**4l**	86

all the reactions can be completed smoothly but also that a series of aldehydes or ketones bearing either electron-withdrawing or electron-donating groups perform equally well in the reactions.

In conclusion, we have developed a rapid and highly efficient multicomponent coupling reaction for the synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives via the reaction of different aromatic aldehydes, aromatic ketones, and 2-cyanoacetamide under solvent-free conditions. The advantages of the present method in terms of avoiding toxic organic solvent, ease of manipulation, fast reaction rates, and lower cost should make this protocol a valuable alternative to the existing methods.

EXPERIMENTAL

Melting points were determined on an XT-5 microscopic melting-point apparatus and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer.

General Procedure for the Synthesis of 4,6-Diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles (4)

The mixture of aromatic aldehydes (2 mmol), aromatic ketones (2 mmol), 2-cyanoacetamide (3 mmol), and NaOH (3 mmol) was put in a reaction

flask at 70°C for about 30 min. After completion, the reaction mixture was poured into water and then washed with water thoroughly. The product was filtered, dried, and recrystallized from 95% ethanol.

Spectral Data

4-(4-Fluorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4a**): Mp 270–272°C; IR (KBr, ν, cm^{-1}): 3146 (NH), 2220 (CN), 1643 (CO); ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.80 (1H, s, NH), 7.92 (2H, d, $J = 8.4$ Hz, ArH), 7.83–7.88 (2H, m, ArH), 7.51–7.62 (3H, m, ArH), 7.43 (2H, t, $J = 8.0$ Hz, ArH), 6.87 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{11}FN_2O$: C, 74.47; H 3.82; N, 9.65. Found: C, 74.60; H, 3.63; N, 9.53.

4-(4-Chlorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4b**): Mp 287–288°C (lit.[10d] 311–312°C); IR (KBr, ν, cm^{-1}): 3150 (NH), 2221 (CN), 1644 (CO); ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.73 (1H, s, NH), 8.19 (2H, m, ArH), 8.03–8.07 (3H, m, ArH), 7.88 (2H, m, ArH), 7.75–7.83 (2H, m, ArH), 7.48 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.55; H, 3.52; N, 9.07.

4-(4-Bromophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4c**)**:** Mp 291–293°C; IR (KBr, ν, cm^{-1}): 3141 (NH), 2220 (CN), 1652 (CO); ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.91 (1H, s, NH), 7.89 (2H, m, ArH), 7.82 (2H, d, $J = 8.4$ Hz, ArH), 7.70 (2H, d, $J = 8.4$ Hz, ArH), 7.51–7.56 (3H, dd, $J = 8.4$ Hz, $J = 8.4$ Hz, ArH), 6.80 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{11}BrN_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.48; H, 3.24; N, 7.81.

4-(2-Chlorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4d**): Mp 290–292°C; IR (KBr, ν, cm^{-1}): 3145 (NH), 2222 (CN), 1645 (CO); ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.86 (1H, s, NH), 7.91 (2H, d, $J = 8.0$ Hz, ArH), 7.61–7.66 (4H, m, ArH), 7.43–7.50 (3H, m, ArH), 6.72 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.50; H, 3.45; N, 9.01.

4-(2,4-Dichlorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4e**): Mp 278–280°C; IR (KBr, ν, cm^{-1}): 3141 (NH), 2221 (CN), 1650 (CO); ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.01 (s, 1H, NH), 7.90 (2H, d, $J = 8.0$ Hz, ArH), 7.62–7.67 (2H, m, ArH), 7.53–7.58 (4H, m, ArH), 6.82 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{10}Cl_2N_2O$: C, 63.36; H, 2.95; N, 8.21. Found: C, 63.44; H, 2.75; N, 8.33.

4-(3,4-Dichlorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4f**): Mp > 300°C; IR (KBr, ν, cm^{-1}): 3135 (NH), 2221 (CN), 1656 (CO); ^1H

NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.88 (1H, s, NH), 7.50–7.92 (8H, m, ArH), 6.91 (1H, s, C^5 − H). Anal. calcd. for $C_{18}H_{10}Cl_2N_2O$: C, 63.36; H, 2.95; N, 8.21. Found: C, 63.51; H, 2.70; N, 8.35.

4-(3,4-Dimethoxyphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4g**): Mp 273–275°C; IR (KBr, ν, cm^{-1}): 3138 (NH), 2220 (CN), 1653 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.78 (1H, s, NH), 7.87 (2H, d, $J = 6.0$ Hz, ArH), 7.55 (2H, d, $J = 6.0$ Hz, ArH), 7.36 (2H, d, $J = 8.0$ Hz, ArH), 7.12 (2H, d, $J = 8.0$ Hz, ArH), 6.85 (1H, s, C^5-H), 3.84 (3H, s, OCH_3), 3.38 (3H, s, OCH_3). Anal. calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.40; H, 4.73; N, 8.32.

4-(Benzo[d][1,3]dioxol-5-yl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4h**): Mp 290–291°C; IR (KBr, ν, cm^{-1}): 3165 (NH), 2221 (CN), 1657 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.76 (s, 1H, NH), 7.88–7.91 (2H, m, ArH), 7.54–7.58 (2H, m, ArH), 7.29 (2H, d, $J = 8.0$ Hz, ArH), 7.11 (2H, d, $J = 8.0$ Hz, ArH), 6.76 (1H, s, C^5-H), 6.15 (2H, s, OCH_2O). Anal. calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.02; H, 3.71; N, 8.89.

4,6-Dip-tolyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4i**): Mp 291–293°C (lit.[10b] 290–291°C); IR (KBr, ν, cm^{-1}): 3148 (NH), 2221 (CN), 1629 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.78 (1H, s, NH), 7.80 (2H, d, $J = 8.4$ Hz, ArH), 7.65 (2H, d, $J = 8.4$ Hz, ArH), 7.33–7.43 (4H, m, ArH), 6.75 (1H, s, C^5-H), 2.40 (3H, s, CH_3), 2.38 (3H, s, CH_3). Anal. calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.87; H, 5.43; N, 9.41.

6-(4-Bromophenyl)-2-oxo-4-p-tolyl-1,2-dihydropyridine-3-carbonitrile (**4j**): Mp 297–298°C; IR (KBr, ν, cm^{-1}): 3165 (NH), 2220 (CN), 1661 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.82 (1H, s, NH), 7.88 (2H, m, ArH), 7.75 (2H, d, $J = 8.4$ Hz, ArH), 7.68 (2H, d, $J = 8.4$ Hz, ArH), 7.39 (2H, d, $J = 8.4$ Hz, ArH), 6.86 (1H, s, C^5-H), 3.34 (3H, s, CH_3). Anal. calcd. for $C_{19}H_{13}BrN_2O$: C, 62.48; H, 3.59; N, 7.67. Found: C, 62.37; H, 3.66; N, 7.61.

6-(4-Methoxyphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (**4k**): Mp 252–254°C (lit.[10b] 268–269°C); IR (KBr, ν, cm^{-1}): 3181 (NH), 2219 (CN), 1628 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.72 (1H, s, NH), 7.90 (2H, d, $J = 8.4$ Hz, ArH), 7.70–7.76 (2H, dd, $J = 3.2$ Hz, $J = 3.2$ Hz, ArH), 7.57 (3H, t, $J = 3.2$ Hz, $J = 3.2$ Hz,, ArH), 7.08 (2H, d, $J = 8.4$ Hz, ArH), 6.78 (1H, s, C^5-H), 3.84 (3H, s, OCH_3). Anal. calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.60; H, 4.42; N, 9.35.

6-(4-Chlorophenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (**4l**): Mp 282–283°C (lit.[10b] 294–295°C); IR (KBr, ν, cm^{-1}): 3145 (NH), 2221 (CN), 1638 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.91 (1H, s,

NH), 7.98 (2H, d, $J = 8.4$ Hz, ArH), 7.73–7.95 (2H, m, ArH), 7.58–7.66 (5H, m, ArH), 6.87 (1H, s, C^5-H). Anal. calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.61; H, 3.58; N, 9.00.

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