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Original article

Synthesis of new 4,6-diaryl-2-(arylthio)nicotinonitriles in Triton X-100 aqueous micellar media

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ABSTRACT

In this communication, we report four component condensations of acetophenone, arylaldehydes, arylthiol, and malononitrile in the presence of Triton X-100 (5 mol%) aqueous micelles. This reaction led to the formation of 4,6-diaryl-2-(arylthio)nicotinonitrile new derivatives in good yields. The FT-IR, ^{19}F NMR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis confirm the structure of compounds.

1. Introduction

The pyridine ring is a core structure presenting in a number of pharmaceuticals and natural products [1–3]. Pyridine derivatives and their nucleoside analogs showed strong cytotoxicity against several human cancer cell [4], antimycobacterial activities [5], and have been used for enrichment of cereals [6], and for regulation of arterial pressure [7] and cholesterol levels in blood [8]. In addition, some of polysubstituted pyridines are used as non-linear optical materials [9], the ability of chelating agent to complex various metal ions [10], Luminescent agents and building block for supramolecular chemistry [11] and has fluorescent liquid crystals [12]. Numerous methods are reported for the construction of pyridines by varying substitution pattern around the ring. A very common approach for the synthesis of pyridines is the condensation of 1,5-diketone with ammonia followed by nitric acid oxidation [13]. The reaction of β-aminoenones with malononitrile furnishing pyridones is known [14]. The reaction of α,β-unsaturated ketones and malononitrile in the presence of ammonium acetate has been reported [15]. Thiopyridines such as 2-amino-3,5-dicyano-6-sulfanylpyridines and corresponding 1,4-dihydropyridines have been prepared [16] from the reaction of an aldehyde, malononitrile, and a thiol. The synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitriles *via* a three-component condensation reaction with various aldehydes, arylthiols and malononitrile is reported using catalytic $ZrOCl_2{\cdot}8H_2O/NaNH_2$ in $[bmim]BF_4$ under ultrasound irradiation at room temperature [17]. A series of 2-*p*-tolylthiopyridine derivatives was directly synthesized *via* three-component reactions of chalcones, malononitrile, and 4-methylbenzenethiol catalyzed by Et_3N in DMF under microwave irradiation [18]. Cyclotrimerization of a nitrile and two alkynes in the presence of cobalt (II) catalysts [19] is an alternative approach for the construction of highly functionalized pyridines. We report here a highly efficient procedure for the preparation of 4,6-diaryl-2-(arylthio)nicotinonitriles *via* one-pot four component reaction between aromatic aldehydes, acetophenone, malononitrile and thiols using non-ionic surfactant catalyst in water (Scheme 1). Triton X-100 (TR) is one of the most commonly used detergents in biochemistry as solublizer with a wide range of applications to biological systems [20]. Solublization of lipid membranes triggered by Triton X-100 is a well-described phenomenon. It is also used as an emulsifier, and complexing agent in both aqueous and non-aqueous media. Non-ionic surfactants have the tendency to adsorb at interfaces and to form micelles beyond their critical micelle concentration (CMC) similar to the ionic surfactants [21]. However; the advantage of non-ionic surfactants (Triton X-100) is the absence of the electrical double layer as formed by the ionic surfactants. Consequently, non-ionic surfactants are desirable model adsorbents for interfacial processes. Therefore, we decided to exploit these properties of non-ionic surfactant for organic reaction.

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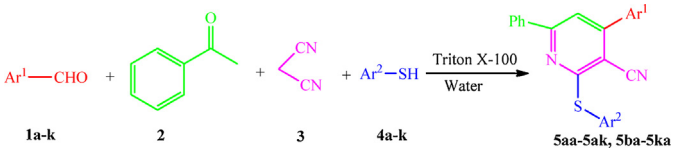

Scheme 1. Synthesis of 2-(arylthio)nicotinonitriles in Triton X-100 aqueous micellar media.

2. Experimental

Aldehydes were distilled before use and all chemicals used were reagent grade and were used as received without further purification. Melting points were determined using a Linkman HF591 heating stage, used in conjunction with a TC92 controller, and re uncorrected. NMR spectra were recorded using either a Brucker DRX500 machine at room temperature. ^{1}H NMR and ^{13}C NMR spectra were measured using DMSO-d_6 as solvent and chemical shifts were measured relatives to residual solvent or $CFCl_3$ as an internal standard for 19FNMR and are expressed in δ. Mass spectra were obtained using a Micro Mass LCT machine in ES or EI mode. Infrared spectra were measured on a Perkin Elmer Paragon 100 FT-IR spectrometer. All Analytical thin layer chromatography was performed with E. Merck silica gel 60F254 aluminum sheets and was visualized with UV light.

A mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), with thiolphenol (1 mmol) were taken in a mixture of Triton X-100 (5 mol%) and water (2 mL) in a round bottomed flask. The resulting mixture was vigorously stirred at room temperature until completion of the reaction as monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was poured onto crushed ice (70 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified by column chromatography on silica gel (60–120 mesh, ethyl acetate/hexane, 1:3) to afford pure products. Structures of the all the products were confirmed by analytical and spectral data. Some selected data are listed below, and others please see the Supporting information.

4,6-Diphenyl-2-(phenylthio)nicotinonitrile (**5aa**): White powder; 335 mg (92%); mp 235 °C; IR (KBr, cm^{-1}): ν 3105, 2212, 1578, 1523, 1453, 1382, 1092, 973, 866, 745, 729; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.69 (d, 2H, J = 7.5 Hz, ArH), 7.97 (d, 2H, J = 8.0 Hz, ArH), 7.84–7.65 (m, 3H, ArH), 7.54–7.46 (m, 3H, ArH), 7.40–7.32 (m, 2H, ArH), 7.30–7.25 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.21, 160.21, 159.23, 139.54, 138.25, 137.65, 136.58, 135.74, 134.65, 133.85, 132.11, 131.11, 130.14, 129.44, 128.33, 126.47, 125.75, 124.12, 123.22, 122.12, 121.41, 117.14, 112.76, 101.34; MS (EI) m/z (%): 364 (M$^+$, 20), 255 (85); HRMS (EI) Found: M$^+$, 364.1010. $C_{24}H_{16}N_2S$ requires M$^+$, 364.1011; Anal. Calcd. for $C_{24}H_{16}N_2S$: C, 79.09; H, 4.42; N, 7.69; S, 8.80; Found: C, 79.12; H, 4.38; N, 7.61; S, 8.72.

2-((4-Fluorophenyl)thio)-4,6-diphenylnicotinonitrile (**5ad**): White powder; 363 mg (95%); mp 247 °C; IR (KBr, cm^{-1}): ν 3095, 2199, 1625, 1510, 1451, 810, 735, 726; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.66 (d, 2H, J = 8.0 Hz, ArH), 8.09 (d, 2H, J = 8.0 Hz, ArH), 7.77–7.64 (m, 3H, ArH), 7.60–7.49 (m, 3H, ArH), 7.45–7.21 (m, 2H, ArH), 7.12–7.02 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.05, 160.40, 159.64, 140.05, 139.92, 138.04, 135.07 (d, $^1J_{CF}$ = 253.58 Hz), 136.05, 135.14, 133.90, 132.17, 131.74, 130.12, 129.32, 128.45, 126.47, 125.24, 124.89, 123.33, 122.12, 122.94, 120.47, 116.74, 111.74, 100.15; ^{19}F NMR (DMSO-d_6, 470 MHz): −71.82; MS (EI), m/z (%): 382 (M$^+$, 15), 292 (65); HRMS (EI) Found: M$^+$, 382.0912. $C_{24}H_{15}FN_2S$ requires M$^+$, 382.0489; Anal Calcd. for $C_{24}H_{15}FN_2S$: C, 75.37; H, 3.95; N, 7.32; S, 8.38. Found: C, 75.41; H, 3.92; N, 7.43; S, 8.31.

2-((2-Fluorophenyl)thio)-4,6-diphenylnicotinonitrile (**5ae**): White powder; 344 mg (90%); mp 251 °C; IR (KBr, cm^{-1}): ν 3089, 2201, 1635, 1525, 1485, 820, 725, 735; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, 2H, J = 8.0 Hz, ArH), 8.02 (d, 2H, J = 8.0 Hz, ArH), 7.41–7.39 (m, 3H, ArH), 7.35–7.30 (m, 3H, ArH), 7.25–7.21 (m, 2H, ArH), 7.19–7.10 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.14, 160.48, 159.54, 140.35, 139.32, 138.34, 136.65 (d, $^1J_{CF}$ = 252.18 Hz), 135.15, 134.18, 133.25, 132.17, 131.74, 130.56, 128.32, 128.35, 126.69, 125.25, 124.42, 123.22, 122.54, 122.68, 120.57, 117.54, 115.41, 101.21; ^{19}F NMR (DMSO-d_6, 470 MHz): −69.81; MS (EI), m/z (%): 382 (M$^+$, 15), 292 (65); HRMS (EI) Found: M$^+$, 382.0602. $C_{24}H_{15}FN_2S$ requires M$^+$, 382.0903; Anal Calcd. for $C_{24}H_{15}FN_2S$: C, 75.37; H, 3.95; N, 7.32; S, 8.38. Found: C, 75.41; H, 3.89; N, 7.43; S, 8.21.

4,6-Diphenyl-2-((4-(trifluoromethyl)phenyl)thio)nicotinonitrile (**5aj**): White powder; 345 mg (80%); mp 246 °C; IR (KBr, cm^{-1}): ν 3079, 2989, 2239, 1641, 1565, 1454, 1105, 845, 717, 715; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.72 (d, 2H, J = 8.0 Hz, ArH), 8.12 (d, 2H, J = 8.0 Hz, ArH), 8.10–7.98 (m, 2H, ArH), 7.93 (d, 1H, J = 8.0 Hz, ArH), 7.84–7.52 (m, 3H, ArH), 7.50–7.31 (m, 2H, ArH), 4.16 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.26, 160.45, 159.12, 140.14, 139.14, 138.14, 136.58, 135.17, 134.02, 134.63, 134.96, 132.50, 132.90, 131.18, 130.17, 128.31, 126.45, 126.89 (q, J = 283.5 Hz, CF_3), 125.45, 122.43, 121.48, 120.09. 116.25, 115.54, 103.34; ^{19}F NMR (DMSO-d_6, 470 MHz): −43.25; MS (EI), m/z (%): 432 (M$^+$, 5), 286 (65); HRMS (EI) Found: M$^+$, 432.0912. $C_{25}H_{15}F_3N_2S$ requires M$^+$, 439.0901; Anal Calcd. for $C_{25}H_{15}F_3N_2S$: C, 69.43; H, 3.50; N, 6.48; S, 7.41. Found: C, 69.52; H, 3.41; N, 6.51; S, 7.36.

2-(Naphthalen-2-ylthio)-4,6-diphenylnicotinonitrile (**5ak**): White powder; 393 mg (95%); mp 253 °C; IR (KBr, cm^{-1}): ν 3102,3054, 2247, 1643, 1558, 1448, 827, 728, 713; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.89 (2H, d, J = 7.5 Hz, ArH), 8.45 (d, 2H, J = 7.5 Hz, ArH), 7.89–7.78 (m, 2H, ArH), 7.70 (d, 1H, J = 8.0 Hz, ArH), 7.65–7.55 (m, 4H, ArH), 7.50–7.42 (m, 2H, ArH), 7.40–7.25 (m, 3H, ArH); 7.20–7.08 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.65, 161.58, 159.45, 140.12, 139.23, 139.92, 138.88, 136.65, 134.88, 134.93, 133.12, 133.85, 132.65, 130.01, 130.19, 129.41, 127.30, 126.14, 124.89, 122.43, 121.65, 120.89, 117.32, 116.54, 100.95, 100.05; ^{19}F NMR (DMSO-d_6, 470 MHz): −74.25; MS (EI), m/z (%): 414 (M$^+$, 7), 285 (85); HRMS (EI) Found: M$^+$, 414.1209. $C_{28}H_{18}N_2S$ requires M$^+$, 414.1220; Anal Calcd. for $C_{28}H_{18}N_2S$: C, 81.13; H, 4.38; N, 6.76; S, 7.74. Found: C, 81.21; H, 4.45; N, 6.85; S, 7.85.

6-(4-Fluorophenyl)-4-phenyl-2-(phenylthio)nicotinonitrile (**5ha**): White powder; 343 mg (90%); mp 250 °C; IR (KBr, cm^{-1}): ν 3082, 2212, 1668, 1553, 1452, 821, 714, 708; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.81 (q, 1H, J = 7.4 Hz, $^4J_{HF}$ = 2.0 Hz, ArH), 7.78 (s, 2H, ArH), 7.56 (d, 2H, J = 7.5 Hz, ArH), 7.48–7.38 (m, 4H, ArH), 7.34–7.24 (m, 3H, ArH), 7.20–7.03 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 180.19, 160.32, 159.62, 140.14, 139.19, 138.36, 137.12, 136.01, 135.24 (d, $^1J_{CF}$ = 250.41 Hz), 134.12, 133.10, 132.15, 131.21, 130.05, 129.03, 124.36, 123.09, 122.43, 121.14, 120.08, 120.45, 120.89. 113.19, 101.34; ^{19}F NMR (DMSO-d_6, 470 MHz): −73.44; MS (EI), m/z (%): 382 (M$^+$, 11), 305 (51); HRMS (EI) Found: M$^+$, 382.0910. $C_{24}H_{15}FN_2S$ requires M$^+$, 382.0911; Anal Calcd. for $C_{24}H_{15}FN_2S$: C, 75.37; H, 3.95; N, 7.32; S, 8.38. Found: C, 75.56; H, 4.02; N, 7.46; S, 8.42.

6-(Naphthalen-2-yl)-4-phenyl-2-(phenylthio)nicotinonitrile (**5ka**): White powder; 372 mg (90%); mp 268 °C; IR (KBr, cm^{-1}): ν 3089, 2241, 1661, 1525, 1450, 826, 729, 716 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.91 (s, 1 H, ArH), 8.56 (d, 2H, J = 7.5 Hz, ArH), 8.15 (dd, 2H, J = 7.5 Hz, J = 2.5 Hz, ArH), 7.82 (d, 2H, J = 7.5 Hz, ArH), 7.71–7.56 (m, 5H, ArH), 7.46–7.30 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 182.32, 160.23, 159.86, 141.21, 140.69, 139.22, 138.34, 137.46, 135.04, 133.09, 133.15, 132.85, 131.30,