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Catalyst-Free One-Pot Four-Component Synthesis of 3-(Imino)-pyrrolo[2,1-*a*]isoquinolines in Glycerol: Two Different Products through Two Different Purification Methods

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A one-pot four component synthesis of 3-(imino)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile derivatives *via* a catalyst-free reaction between aryl aldehydes, malononitrile, isoquinoline and isocyanides was successfully conducted in glycerol as a benign, nontoxic and biodegradable promoting reaction medium. The progress of the reaction with two different common purification methods were investigated. Moreover, synthesized products were examined as the chemical sensors for the detection of a wide range of metal ions and it was successful for the detection of Co^{2+} ions.

Keywords: Multicomponent synthesis, In column chromatography reaction, Glycerol, Sustainable reaction medium, Isocyanide

INTRODUCTION

Column chromatography is one of the most useful and practicable analytical tools for the separation and purification of organic mixtures. Although this method is widely used as an analytical technique, there are some reports on using this technique as a reaction medium as well as a separation tool [1,2], named on-column reaction chromatography. In fact, the chemical reaction takes place inside the column of chromatography.

Among various kinds of nitrogen-containing heterocyclic compounds, highly-functionalized quinolines and isoquinolines have attracted much attention due to the diverse biological activities [3]. Moreover, it has been investigated that highly cyano substituted heterocyclic compounds display remarkable solvatochromic and photochromic properties [4]. These polycyano heterocycles have also optical emission properties enabling them to be used as chemical sensors [5]. Recently, a new one-pot four component reaction between aryl aldehydes, malononitrile, isoquinoline and isocyanides has been introduced by Aminkhani *et al.* for the synthesis of 3-(imino)-2,3-dihydropyrrolo [2, 1-*a*] isoquinoline-1,1(10*bH*)-dicarbonitrile derivatives in CH_2Cl_2 at room temperature [6]. Unfortunately this method suffers from some drawbacks such as very long reaction times (48-72 h) and application of a toxic halogenated organic solvent (CH_2Cl_2). So, there still exists a demand for devising new more efficient and more environmentally benign methods for the synthesis of titled compounds in shorter reaction times using more eco-friendly reaction conditions.

Glycerol is a by-product of biodiesel synthesis. It is an inflammable, nonvolatile, highly nontoxic (LD_{50} = 12600 mg Kg^{-1} (oral rat)), very cheap and biodegradable liquid with a unique solubility profile. It is miscible with water providing a facile work up procedure for the separation of organic compounds from the reaction medium with a simple extraction. More recently the effectiveness of glycerol as a promoting medium for the activation of electrophiles has been demonstrated [7]. All of these unique properties encouraged us to use the glycerol as a benign

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and eco-friendly promoting reaction medium for this reaction.

Recently, a few research groups have reported synthesis of novel heterocyclic compounds through the reaction of isocyanides and Knoevenagel adduct with the third chemical substances *via* three or four component reactions [8]. Subsequently, Maghsoodlou and Li in two separate works reported a three-component condensation reaction between aza-polycyclic aromatic hydrocarbons, isocyanides and arylidenemalononitriles [9]. Interestingly, they obtained two different chemical structures with different numbers of cyano groups. This work was not considered seriously due to the lack of characterization data and an ambiguous expression [10]. The literature background and our general interest to isocyanide-based multicomponent reactions [11,12] encouraged us to more investigate this reaction. With scrutiny into these reports, it is inferred that the path of the reaction was changed through the silica gel column chromatography, so, it can be considered that an on-column reaction chromatography has been occurred. Therefore, we designed a conceptual framework for specifying the path of the reaction with two different separation methods. Moreover, we herein report a facile, catalyst-free, one-pot four-component synthesis of 3-(imino)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitriles (5a-n) in glycerol as a nontoxic, biodegradable and very cheap promoting reaction medium (Scheme 1).

EXPERIMENTAL

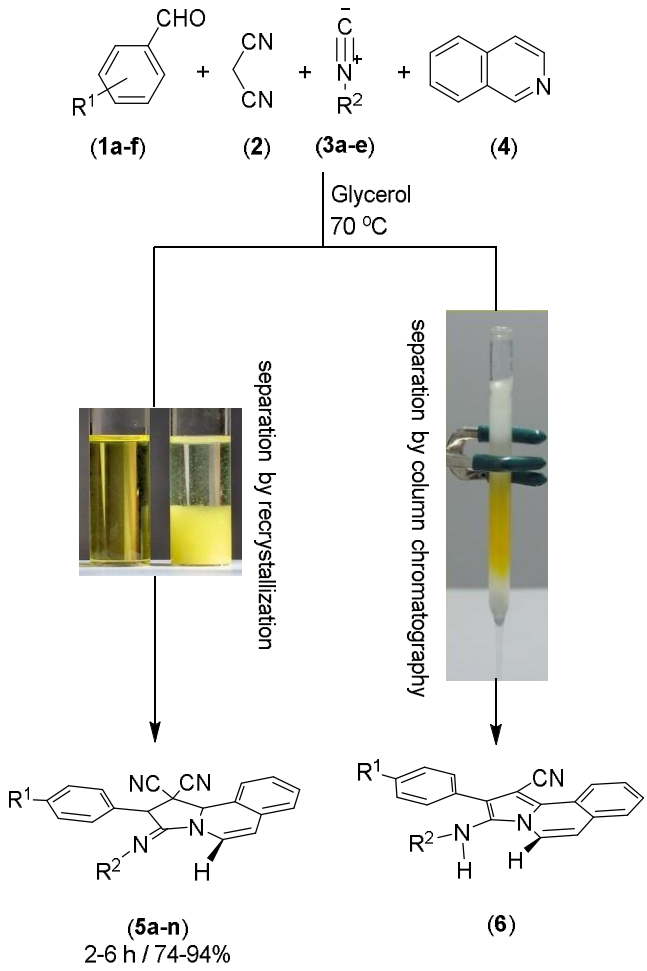
Chemicals and Apparatus

All reagents and solvents were purchased from Merck, Fluka or Aldrich companies and used without further purification. Melting points were determined in capillary tubes in an Electrothermal 9100 apparatus and uncorrected. The progress of the reaction and the purity of compounds were monitored by TLC on analytical silica gel plates (Merck 60 F250). All IR spectra were obtained with a PerkinElmer Spectrum RXI FT-IR apparatus. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX-300 FT-NMR spectrometer. Chemical shifts are given as δ values against tetramethylsilane as an internal standard and *J* values are given in Hz. The microanalysis was performed on a Perkin-Elmer 240-B microanalyzer.

General procedure for the synthesis of 3-(imino)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitriles in glycerol. In a 25 ml round-bottom flask connected to a condenser, a solution of malononitrile (1 mmol, 0.066 g), aryl aldehydes (1 mmol), isocyanides (1 mmol) and isoquinoline (1 mmol, 0.129 g, 0.11 ml) in 5 ml of glycerol was magnetically stirred at 70 °C for an appropriate time (Table 2) and the progress of the reaction was monitored by TLC (EtOAC: *n*-Hexane 2:1 v/v). After completion of the reaction, warm water (10 ml) was added, glycerol dissolved in the water and the insoluble crude products were isolated by simple filtration, washed with distill water (5 ml, 2 times) and recrystallized from boiling EtOH/H_2O 1:1 v/v (10 ml) to afford the pure products (5a-n) in good to excellent yields.

(3*E*)-3-(cyclohexylimino)-2,3-dihydro-2-phenylpyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5a) [6]. Purple solid: m. p.: 125-129 °C. IR (KBr, cm^{-1}): 3028, 2927, 2855, 2206, 1674, 1408, 1349, 1312, 779. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.72-1.88 (10H, m, 5CH_2 of cyclohexyl), 2.94 (1H, s, CH of cyclohexyl), 4.79 (1H, s, CH-N), 5.68 (1H, s, CH-Ar), 5.86 (1H, CH-N), 7.00-7.91 (10H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.3, 24.6, 25.4, 34.0, 34.9, 43.6, 53.6, 59.8, 62.2, 77.2, 107.3, 123.2, 123.6, 125.8, 127.6, 128.8, 129.6, 130.0, 131.1, 132.6. Anal. Calcd. for $C_{26}H_{24}N_4$: C, 79.56; H, 6.16; N, 14.27; found C, 79.59; H, 6.12; N, 14.30. MS (*m/z*): 392.3 (M^+).

(3*E*)-3-(cyclohexylimino)-2,3-dihydro-2-(4-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5b) [6]. Orange solid: m. p.: 135-139 °C. IR (KBr, cm^{-1}): 3074, 2929, 2854, 2201, 1666, 1598, 1522, 1343, 1106, 853, 792. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.72-1.88 (10H, m, 5CH_2 of cyclohexyl), 2.71 (1H, s, CH of cyclohexyl), 4.60 (1H, s, CH-N), 5.59 (1H, s, CH-Ar), 6.49 (1H, CH-N), 7.05-8.45 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.7, 25.4, 33.9, 57.2, 77.2, 113.7, 118.3, 119.8, 120.5, 123.0, 124.1, 124.5, 124.6, 127.3, 128.3, 128.4, 128.5, 128.8, 129.5, 139.6, 146.8. Anal. Calcd for $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.01; found C, 71.34; H, 5.34; N, 16.03. MS (*m/z*): 437.2 (M^+).



Scheme 1. One-pot four-component synthesis of novel highly cyano substituted isoquinoline derivatives and the dependence of the final products on the purification method

(3*E*)-2-(4-chlorophenyl)-3-(cyclohexylimino)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5c) [6]. Purple solid: m. p.: 149-153 °C. IR (KBr, cm^{-1}): 3098, 2927, 2852, 2199, 1723, 1656, 1594, 1565, 1493, 1379, 1093, 797. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.89-1.92 (10H, m, $5CH_2$ of cyclohexyl), 2.72-2.76 (1H, d, J = 12.0 Hz, CH of cyclohexyl), 3.81 (1H, s, CH-N), 5.98 (1H, s, CH-Ar), 6.24 (1H, s, CH-N), 7.01-8.89 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.7, 25.3, 25.5, 33.8, 57.1, 73.3, 77.2, 113.1, 120.7, 120.9, 122.9, 127.2, 127.8, 128.3, 128.8, 129.0, 129.1, 130.2, 131.0, 131.1, 166.7. Anal. Calcd. for $C_{26}H_{23}ClN_4$: C, 73.14; H, 5.43; N, 13.12; found C, 73.16; H, 5.47; N, 13.08. MS (*m/z*): 426.3 (M^+).

(3*E*)-3-(cyclohexylimino)-2,3-dihydro-2-(3-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5d). Yellow solid: m. p.: 142-145 °C. IR (KBr, cm^{-1}): 3084, 2927, 2854, 2196, 1674, 1529, 1348, 1096, 896, 798. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.90-1.79 (10H, m, $5CH_2$ of cyclohexyl), 2.77 (1H, s, CH of cyclohexyl), 4.92 (1H, s, CH-Ar), 5.90-5.93 (1H, d, J = 9.0 Hz, CH-N), 6.37 (1H, s, CH-N), 7.33-8.91 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.7, 25.4, 33.9, 57.3, 60.1, 77.2, 81.5, 113.6, 118.3, 119.8, 120.6, 122.2, 123.0, 123.5, 124.5, 127.3, 128.2, 128.4, 128.5, 129.9, 134.3, 135.0, 148.4. Anal. Calcd. for $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.01; found C, 71.32; H, 5.36; N, 15.98. MS (*m/z*): 437.1 (M^+).

(3*E*)-3-(cyclohexylimino)-2-(4-fluorophenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5e) [6]. Pale pink solid: m. p.: 130-134 °C. IR (KBr, cm^{-1}): 3076, 3035, 2928, 2855, 2229, 1670, 1598, 1507, 1408, 1307, 1235, 840, 770. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.03-1.56 (10H, m, $5CH_2$ of cyclohexyl), 2.80-2.89 (1H, m, CH of cyclohexyl), 4.71 (1H, s, CH-N), 5.54 (1H, s, CH-Ar), 5.74-5.79 (1H, d, J = 15.0 Hz, CH-N), 7.02-7.91 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.3, 25.4, 34.9, 52.7, 59.8, 62.1, 77.2, 107.5, 116.7, 117.0, 117.3, 123.1, 123.5, 125.9, 127.7, 129.7, 130.7, 133.3, 133.4, 149.1, 158.2. Anal. Calcd. for $C_{26}H_{23}FN_4$: C, 76.08; H, 5.65; N, 13.56; found C, 76.03; H, 5.69; N, 13.54. MS (*m/z*): 410.1 (M^+).

(3*E*)-3-(cyclohexylimino)-2,3-dihydro-2-(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5f). Brown solid: m. p.: 110-113 °C. IR (KBr, cm^{-1}): 3010, 2897, 2843, 2219, 1666, 1402, 1357, 1308, 771. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.91-1.68 (10H, m, $5CH_2$ of cyclohexyl), 3.06 (1H, s, CH of cyclohexyl), 4.67 (1H, s, CH-N), 5.46 (1H, s, CH-Ar), 6.40 (1H, CH-N), 7.09-7.40 (10H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.8, 24.4, 32.6, 47.8, 54.7, 55.4, 63.9, 111.2, 114.1, 115.9, 125.6, 127.0, 127.4, 127.9, 130.1, 130.7, 131.0, 131.8, 132.1, 149.1, 158.7. Anal. Calcd. for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20; N, 13.26; found C, 76.71; H, 6.22; N, 13.28. MS (*m/z*): 422.1 (M^+).

(3*E*)-3-(tert-butylimino)-2,3-dihydro-2-(4-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5g) [6]. Light orange solid: m. p.: 125-129 °C. IR (KBr, cm^{-1}): 3079, 2970, 2926, 2204, 1677, 1580, 1512, 1456, 1387, 1192, 853, 775. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.02 (9H, s, $3CH_3$), 4.82 (1H, s, CH-N), 5.43 (1H, s, CH-Ar), 6.52-6.55 (1H, d, J = 9.0 Hz, CH-N), 7.04-8.29 (9H, m, H_{arom}). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ (ppm) = 30.8, 31.5, 53.9, 60.4, 77.2, 107.6, 123.2, 123.4, 124.4, 124.7, 124.8, 125.9, 126.0, 127.4, 127.7, 129.8, 130.3, 130.4, 132.5. Anal. Calcd. for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02; found C, 70.12; H, 5.10; N, 17.00. MS (*m/z*): 411.3 (M^+).

(3*E*)-3-(tert-butylimino)-2-(4-chlorophenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5h) [6]. Light purple solid: m. p.: 140-143 °C. IR (KBr, cm^{-1}): 2929, 2853, 2219, 1674, 1573, 1513, 1455, 1314, 1127, 884, 776. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.94 (9H, s, $3CH_3$), 4.52-4.55 (1H, d, J = 9.0 Hz, CH-N), 5.50 (1H, s, CH-Ar), 7.03 (1H, s, CH-N), 7.31-8.23 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 30.0, 56.3, 77.2, 112.6, 118.5, 121.6, 123.0, 124.3, 127.1, 128.0, 128.2, 129.00, 129.08, 129.1, 129.9, 130.5, 130.6. Anal. Calcd. for $C_{24}H_{21}ClN_4$: C, 71.90; H, 5.28; N, 13.98; found C, 71.88; H, 5.31; N, 13.95. MS (*m/z*): 400.1 (M^+).

(3*E*)-2,3-dihydro-2-(4-nitrophenyl)-3-(tosylmethylimino)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5i). Dark brown solid: m. p.: 155-157 °C. IR (KBr, cm^{-1}): 3059, 2908, 2837, 2213, 1627, 1579, 1528, 1392, 1189, 1125, 834, 785. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.41 (3H, s, CH_3), 4.65 (1H, s, CH-N), 4.68-4.70 (1H, d, J = 4.9 Hz, H of CH_2), 4.96-5.00 (1H, d, J = 4.9 Hz, H of CH_2), 5.31 (1H, s, CH-Ar), 6.42 (1H, CH-N), 7.15-8.23 (13H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 21.6, 47.8, 73.0, 76.1, 111.4, 115.6, 125.3, 125.7, 126.8, 127.0, 127.6, 127.9, 129.3, 129.5, 130.6, 131.0, 131.8, 133.4, 136.6, 144.7, 147.7, 162.8. Anal. Calcd. for $C_{28}H_{21}N_5O_4S$: C, 64.23; H, 4.04; N, 13.38; found C, 64.29; H, 4.01; N, 13.35. MS (*m/z*): 523.2 (M^+)

(3*E*)-2-(4-chlorophenyl)-2,3-dihydro-3-(tosylmethylimino)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5j). Light brown solid: m. p.: 147-149 °C. IR (KBr, cm^{-1}): 3087, 2938, 2873, 2178, 1742, 1676, 1582, 1586, 1469, 1370, 1048, 783. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.43 (3H, s, CH_3), 4.67 (1H, s, CH-N), 4.72-4.77 (1H, d, J = 4.9 Hz, H of CH_2), 4.95-5.00 (1H, d, J = 4.9 Hz, H of CH_2), 5.18 (1H, s, CH-Ar), 6.49 (1H, CH-N), 7.14- 7.79 (13H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 21.5, 47.8, 73.1, 76.1, 111.4, 115.6, 125.3, 125.7, 126.8, 127.0, 127.6, 127.9, 129.3, 129.5, 130.6, 131.1, 131.9, 133.3, 136.6, 144.7, 147.4, 162.6. Anal. Calcd. for $C_{28}H_{21}ClN_4O_2S$: C, 65.56; H, 4.13; N, 10.92; found C, 65.53; H, 4.17; N, 10.90. MS (*m/z*): 512.2 (M^+).

(3*E*)-2,3-dihydro-3-(isopropylimino)-2-phenylpyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5k). Light purple solid: m. p.: 134-139 °C. IR (KBr, cm^{-1}): 3021, 2913, 2802, 2212, 1636, 1522, 1357, 1078, 875, 769. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.94-0.96 (6H, d, J = 5.0 Hz, $2CH_3$), 3.81-3.92 (1H, m, CH-$(CH_3)_2$), 4.70 (1H, s, CH-Ar), 5.69 (1H, s, CH-N), 6.41 (1H, s, CH-N), 7.15-8.27 (10H, m, H_{arom}). ^{13}C NMR (75 MHZ, $CDCl_3$): δ (ppm) = 23.7, 47.9,

51.3, 63.7, 111.4, 115.7, 125.5, 126.9, 127.0, 127.6, 127.8, 128.3, 129.1, 130.5, 131.0, 131.9, 135.1, 148.2. Anal. Calcd. for $C_{23}H_{20}N_4$: C, 78.38; H, 5.72; N, 15.90; found C, 78.32; H, 5.75; N, 15.93. MS (*m/z*): 352.1 (M^+).

(3*E*)-2,3-dihydro-3-(isopropylimino)-2-(4-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5l). Light orange solid: m. p.: 148-151 °C. IR (KBr, cm^{-1}): 3081, 2973, 2921, 2197, 1679, 1559, 1509, 1447, 1391, 1184, 863, 782. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.89-0.91 (6H, d, J = 5.0 Hz, $2CH_3$), 3.80-3.92 (1H, m, CH-$(CH_3)_2$), 4.66 (1H, s, CH-Ar), 5.68 (1H, s, CH-N), 6.43 (1H, s, CH-N), 7.17-8.27 (9H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 23.7, 47.9, 51.3, 63.9, 111.1, 115.5, 125.2, 125.5, 126.7, 127.0, 127.6, 127.8, 130.4, 131.1, 131.9, 136.4, 147.6, 148.3. Anal. Calcd. for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62; found C, 69.56; H, 4.86; N, 17.59. MS (*m/z*): 397.1 (M^+).

(3*E*)-2,3-dihydro-2-phenyl-3-(phenylimino)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5m). Pale pink solid: m. p.: 142-145 °C. IR (KBr, cm^{-1}): 2921, 2847, 2205, 1665, 1578, 1507, 1459, 1321, 1115, 874, 774. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.73 (1H, s, CH-N), 5.47 (1H, s, CH-Ar), 6.50 (1H, s, CH-N), 7.04-7.65 (15H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 47.9, 63.1, 77.2, 111.4, 115.7, 120.6, 123.6, 125.5, 126.9, 127.0, 127.6, 127.8, 128.3, 128.8, 129.1, 130.5, 131.0, 131.9, 135.1, 148.0, 158.8. Anal. Calcd. for $C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50; found C, 80.83; H, 4.67; N, 14.55. MS (*m/z*): 386.1 (M^+).

(3*E*)-2,3-dihydro-2-(4-nitrophenyl)-3-(phenylimino)pyrrolo[2,1-*a*]isoquinoline-1,1(10*bH*)-dicarbonitrile (5n). Dark orange solid: m. p.: 149-154 °C. IR (KBr, cm^{-1}): 3035, 2921, 2819, 2221, 1616, 1568, 1528, 1388, 1194, 1158, 840, 773. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.56 (1H, s, CH-N), 5.14 (1H, s, CH-Ar), 6.47 (1H, s, CH-N), 7.04-8.25 (14H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 47.7, 63.1, 77.2, 111.5, 115.7, 120.6, 123.6, 125.2, 125.5, 126.7, 127.3, 127.6, 127.8, 128.8, 130.3, 131.3, 131.9, 136.4, 147.6, 148.0, 158.5. Anal. Calcd. for $C_{26}H_{17}N_5O_2$: C, 72.38; H, 3.97; N, 16.23; found C, 72.43; H, 3.99; N, 16.18. MS (*m/z*): 431.1 (M^+).

3-(cyclohexylamino)-2-(4-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (6a). Dark orange solid: m. p.: 150-153 °C. IR (KBr, cm^{-1}): 2970, 2810, 2228, 1610, 1560, 1520, 1385, 1193, 1155, 843, 779. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.334-1.923 (m, 10H, $5CH_2$ of cyclohexyl), 3.588 (m, 1H, CH of cyclohexyl), 7.055 (s, 1H, NH), 7.073-8.391 (m, 9H, Harom), 8.909 (s, 1H, CH-N). Anal. Calcd. for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65; found C, 73.01; H, 5.49; N, 13.92. MS (*m/z*): 410.2 (M^+).

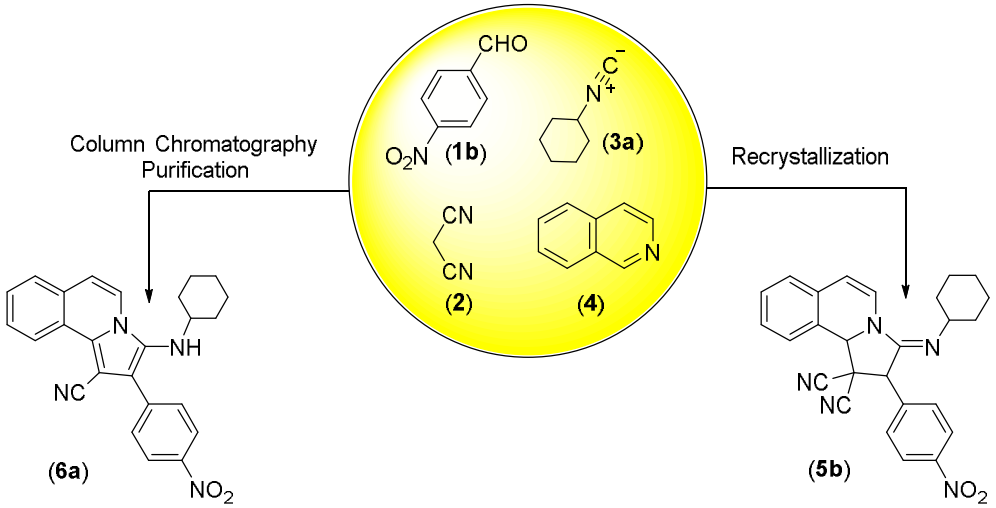
2-Phenyl-3-(phenylamino)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (6b). Pale orange solid: m. p.: 161-164 °C. IR (KBr, cm^{-1}): 2953, 2890, 2225, 1618, 1566, 1521, 1385, 1198, 1150, 840, 773. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.02-7.06 (m, 1H, NH), 7.31-8.19 (m, 15H, H_{arom}), 8.98 (d, J = 7.5 Hz, 1H, CH-N). Anal. Calcd. for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69; found C, 88.60; H, 4.59; N, 11.84. MS (*m/z*): 359.2 (M^+).

RESULTS AND DISCUSSIONS

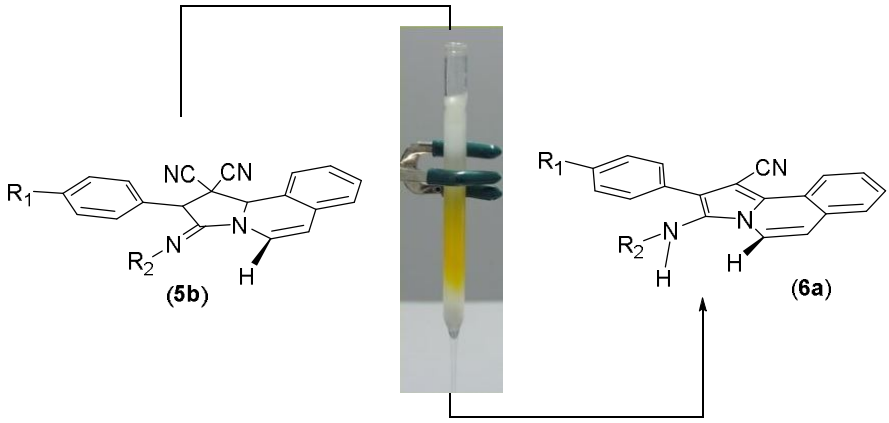
Initially, the one-pot condensation of 4-nitrobenzaldehyde (1b, 1 mmol, 0.151 g), malononitrile (2, 1 mmol, 0.066 g), isoquinoline (4, 1 mmol, 0.129 g) and cyclohexyl isocyanide (3a, 1 mmol, 0.109 g) was selected as a model reaction (Scheme 2) and the reaction time and yield were investigated in different solvents without catalyst at various temperatures and two different separation methods were considered for the purification of products. The reaction yield, time and chemical structure of product were monitored in each run. The obtained results are summarized in Table 1.

As shown in Table 1, the chemical structure of the product is strongly dependent to the applied purification method. In fact, on-column reaction chromatography took place inside the SiO_2 column during the purification process. The elimination of HCN was occurred followed with a [1,3]-H shift. Although the products were obtained in different solvents at various temperatures, the best results were obtained in glycerol at 70 °C for both chemical structures (5b) and (6a) after using different separation methods. It is worth mentioning that the compound (5b) was transformed to compound (6a) after passing through the SiO_2 column (Scheme 3).

The distinction between two structures of (5b) and (6a) was simply determined by ^{1}H NMR spectroscopy



Scheme 2. The one-pot condensation reaction of 4-nitrobenzaldehyde (1b, 1 mmol, 0.151 g), malononitrile (2, 1 mmol, 0.066 g), isoquinoline (4, 1 mmol, 0.129 g) and cyclohexyl isocyanide (3a, 1 mmol, 0.109 g) under various reaction conditions with different separation methods



Scheme 3. Transformation of (5b) to (6) after passing from the SiO_2 column

technique. The ^{1}H NMR spectrum of (5b) exhibited three distinct singlet signals in δ 4.62, 5.6 and 6.44 ppm related to three separate hydrogens (Fig. 1a), while the signal of connected hydrogen to C-2 in product (6a) appeared in δ 8.91 ppm (Fig. 1b).

Moreover, structures of (5b) and (6a) were deduced from IR, ^{13}C NMR, and elemental analysis (see supporting information). In addition, the mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. This displacement of signal for C2-H can be attributed to aromatization of *N*-heterocyclic cycle of isoquinoline in compound (6a) due to the elimination of HCN on the SiO_2 column *vs.* the nonaromatic corresponding cycle in compound (5b). This peak of down field movement is attributed to the anisotropy effect of aromatic compounds in the external magnetic fields (Fig. 2).

These exciting results encouraged us to explore and establish the generality and efficiency of this concept for a diversity-oriented synthesis of a library of novel

Table 1. The One-pot Condensation Reaction of 4-Nitrobenzaldehyde (1b, 1 mmol, 0.151 g), Malononitrile (2, 1 mmol, 0.066 g), Isoquinoline (4, 1 mmol, 0.129 g) and Cyclohexyl Isocyanide (3a, 1 mmol, 0.109 g) under Various Reaction Conditions with Different Separation Methods

Entry	Solvent (5 ml)	Temp. (°C)	Time (h)	Separation method	Yield (%)[a]	
					(5b)	(6a)
1	CH_2Cl_2	Reflux	12	Recrystallization	59	-
				Column chromatography	-	62
2	$CHCl_3$	Reflux	12	Recrystallization	55	-
				Column chromatography	-	60
3	CH_3CN	70	8	Recrystallization	81	-
				Column chromatography	-	88
4	Toluene	70	8	Recrystallization	85	-
				Column chromatography	-	91
5	EtOH	Reflux	12	Recrystallization	80	-
				Column chromatography	-	84
6	MeOH	Reflux	12	Recrystallization	80	-
				Column chromatography	-	80
7	H_2O	70	12	Recrystallization	45	-
				Column chromatography	-	51
8	Glycerol	r.t.	12	Recrystallization	30	-
				Column chromatography	-	33
9	Glycerol	40	7	Recrystallization	79	-
				Column chromatography	-	83
10	Glycerol	50	5	Recrystallization	81	-
				Column chromatography	-	83
11	Glycerol	60	3.5	Recrystallization	85	-
				Column chromatography	-	89
12	Glycerol	70	2.5	Recrystallization	91	-
				Column chromatography	-	92
13	Glycerol	80	2.5	Recrystallization	90	-
				Column chromatography	-	92
14	Glycerol	90	2.5	Recrystallization	91	-
				Column chromatography	-	92
15	-	70	12	Recrystallization	66	-
				Column chromatography	-	74

[a]Isolated yield.

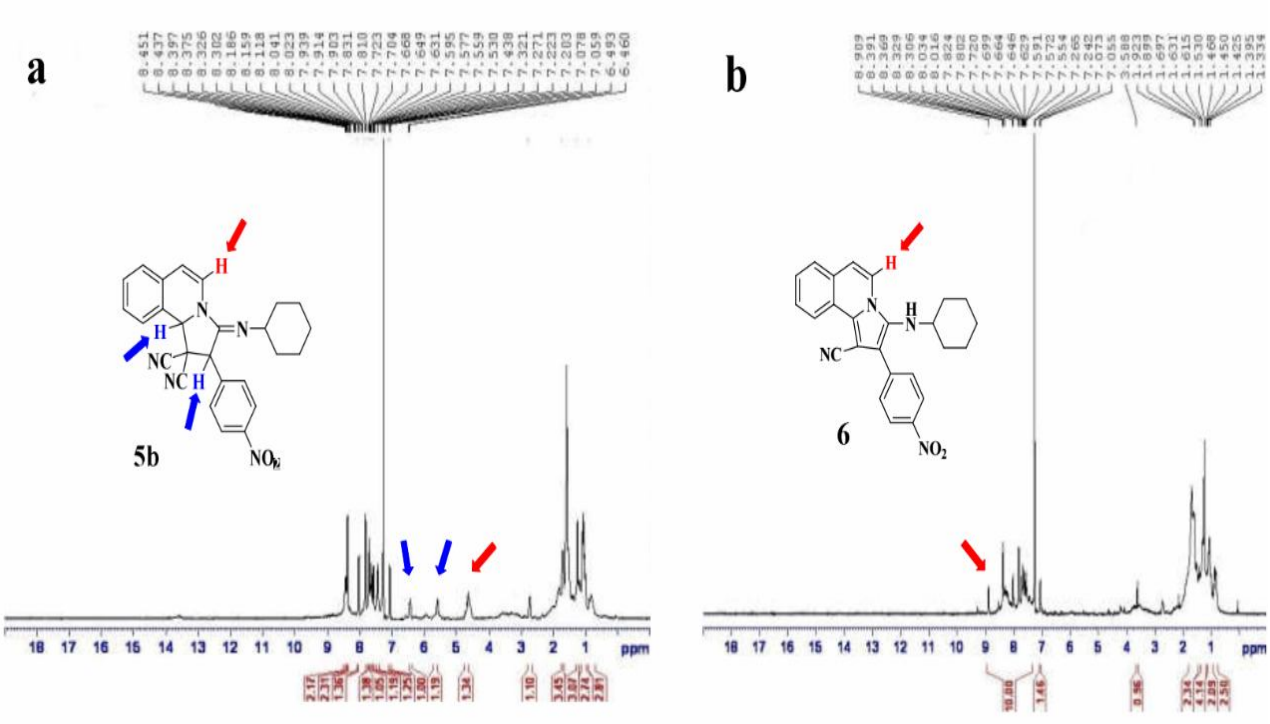


Fig. 1. ^{1}H NMR spectra of products (5b) (a) and (6a) (b).

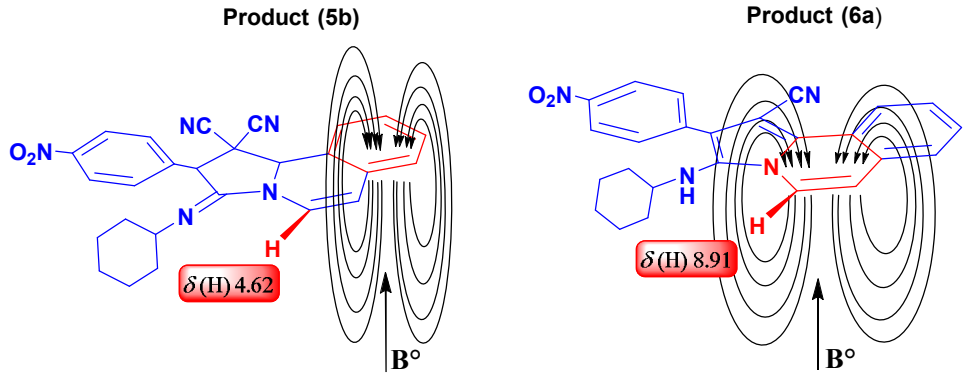


Fig. 2. The shielding of C_2-H (red hydrogen) in product (5b) (purified by recrystallization), the deshielding of C_2-H (red hydrogen) in product (6a) (purified by column chromatography) due to the anisotropy effect of aromatic *N*-heterocycle in the presence of external magnetic field B°.

highly substituted cyano functionalized isoquinolines. In this regard a variety of aryl aldehydes (1a-f), malononiitrile (2), isocyanides (3a-e) and isoquinoline (4) were examined under optimized conditions, and crude products were recrystallized from EtOH/H_2O (1:1 v/v) to afford pure products in good to excellent yields (Scheme 1). The obtained results are summarized in Table 2.

All reactions proceeded efficiently, and the desired products were obtained in good to excellent yields. As

Table 2. The One-pot Four-component Condensation of Aryl aldehydes (1a-f, 1 mmol), Malononitrile (2, 1 mmol), Isocyanides (3a-e, 1 mmol) and Isoquinoline (4, 1 mmol) in Glycerol (5 ml) at 70 °C Purified with Recrystallization

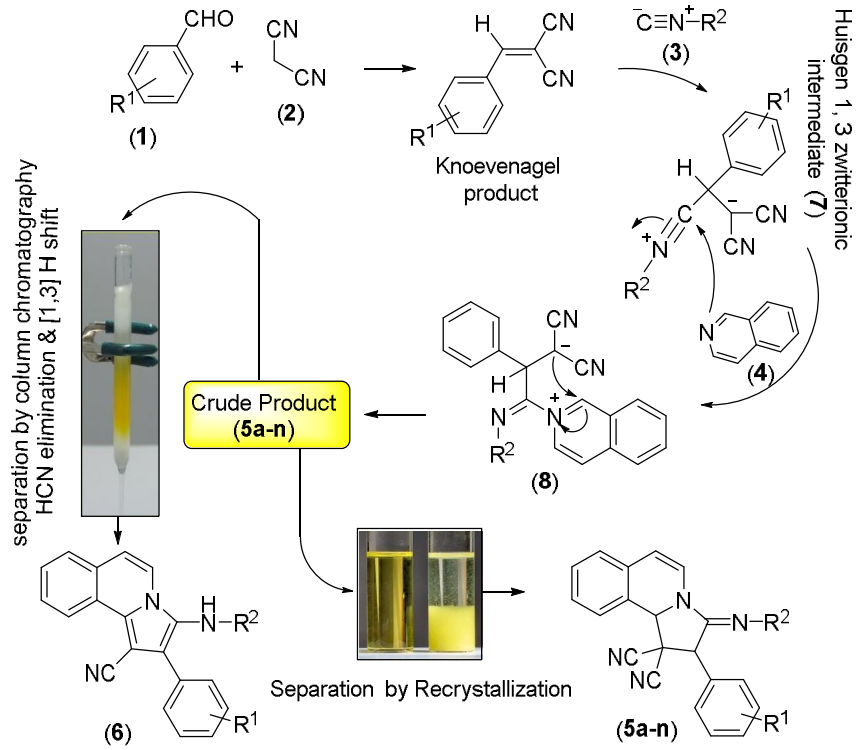
Entry	Product	R^1	R^2	Time (h)	Yield (%)[a]
1	5a	H (1a)	Cyclohexyl (3a)	5	76
2	5b	4-NO_2 (1b)	Cyclohexyl (3a)	2.5	91
3	5c	4-Cl (1c)	Cyclohexyl (3a)	3	87
4	5d	3-NO_2 (1d)	Cyclohexyl (3a)	3	89
5	5e	4-F (1e)	Cyclohexyl (3a)	2	94
6	5f	4-OMe (1f)	Cyclohexyl (3a)	6	74
7	5g	4-NO_2 (1b)	*t*-Butyl (3b)	3	84
8	5h	4-Cl (1c)	*t*-Butyl (3b)	4	81
9	5i	4-NO_2 (1b)	*p*-Toluene sulfonyl methyl (3c)	3	80
10	5j	4-Cl (1c)	*p*-Toluene sulfonyl methyl (3c)	3.5	78
11	5k	H (1a)	Isopropyl (3d)	4	80
12	5l	3-NO_2 (1d)	Isopropyl (3d)	3.5	87
13	5m	H (1a)	Phenyl (3e)	3.5	82
14	5n	3-NO_2 (1d)	Phenyl (3e)	3	89

[a]Isolated yield.

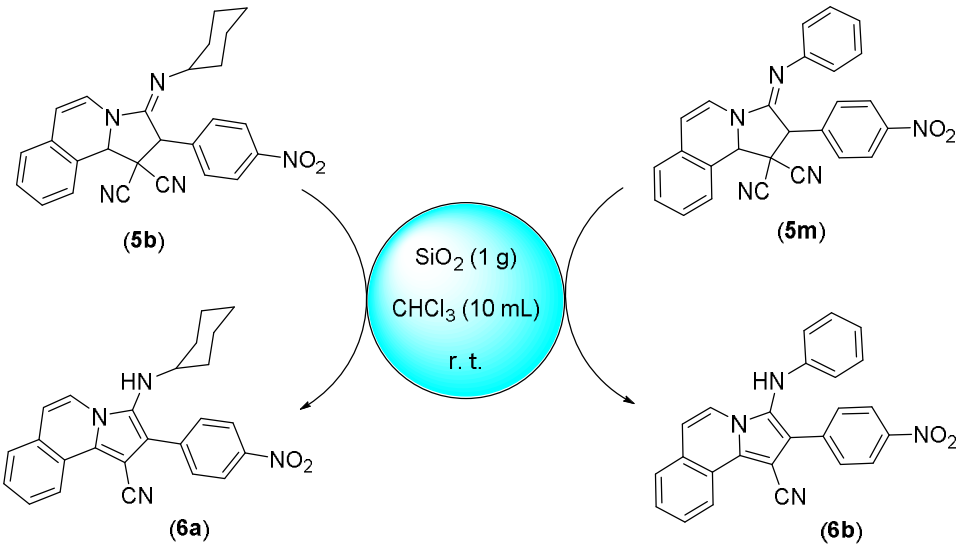
shown in Table 2, aryl aldehydes with electron-withdrawing groups (Table 2; entries 2, 4, 5, 9, 12 and 14) reacted faster with higher yields in comparison with those that have electron-releasing groups (Table 2, entry 6). In another study, ethyl cyanoacetate was applied instead of malononitrile in the model reaction under optimized reaction conditions, and unfortunately, a mixture of starting materials and unknown products was obtained even after a long time (12 h). It may be due to the lower reactivity of ethyl cyanoacetate as well as different nature of CO_2Et functional group.

With obtained results in hand and according to previous reports [13], it is inferred that the reaction initiates with a Knoevenagel condensation reaction of aldehydes (1) and malononitrile (2) (Step 1) following with the formation of a Huisgen 1,3-zwitterionic intermediate (7) *via* a Michael addition of isocyanides (3) to the Knoevenagel product (Step 2). The third step was occurred by nucleophilic attack of nitrogen atom of isoquinoline (4) to the intermediate (7) to afford intermediate (8). Finally, desired products (5a-n) or (6) were obtained depending on which separation method is used (Scheme 4).

The presence of reactive -OH groups in the structure of glycerol plays a major role in its promoting activity for the Knoevenagel condensation of aldehydes (1) with highly active C-H acidic malononitrile (2). Besides, it may be speculated that the polar amphoteric hydroxyl groups of the glycerol facilitate the interaction of weak acidic and basic components due to the stabilization of the corresponding transition states and



Scheme 4. The proposed mechanism for one-pot four-component condensation of aryl aldehydes (1), malononitrile (2), isocyanides (3) and isoquinoline (4) in toluene at reflux conditions



Scheme 5. Treatment of compounds (5b, 1 mmol) and (5m, 1 mmol) with column SiO_2 (1 g) in $CHCl_3$ (10 ml) at room temperature for 10 min

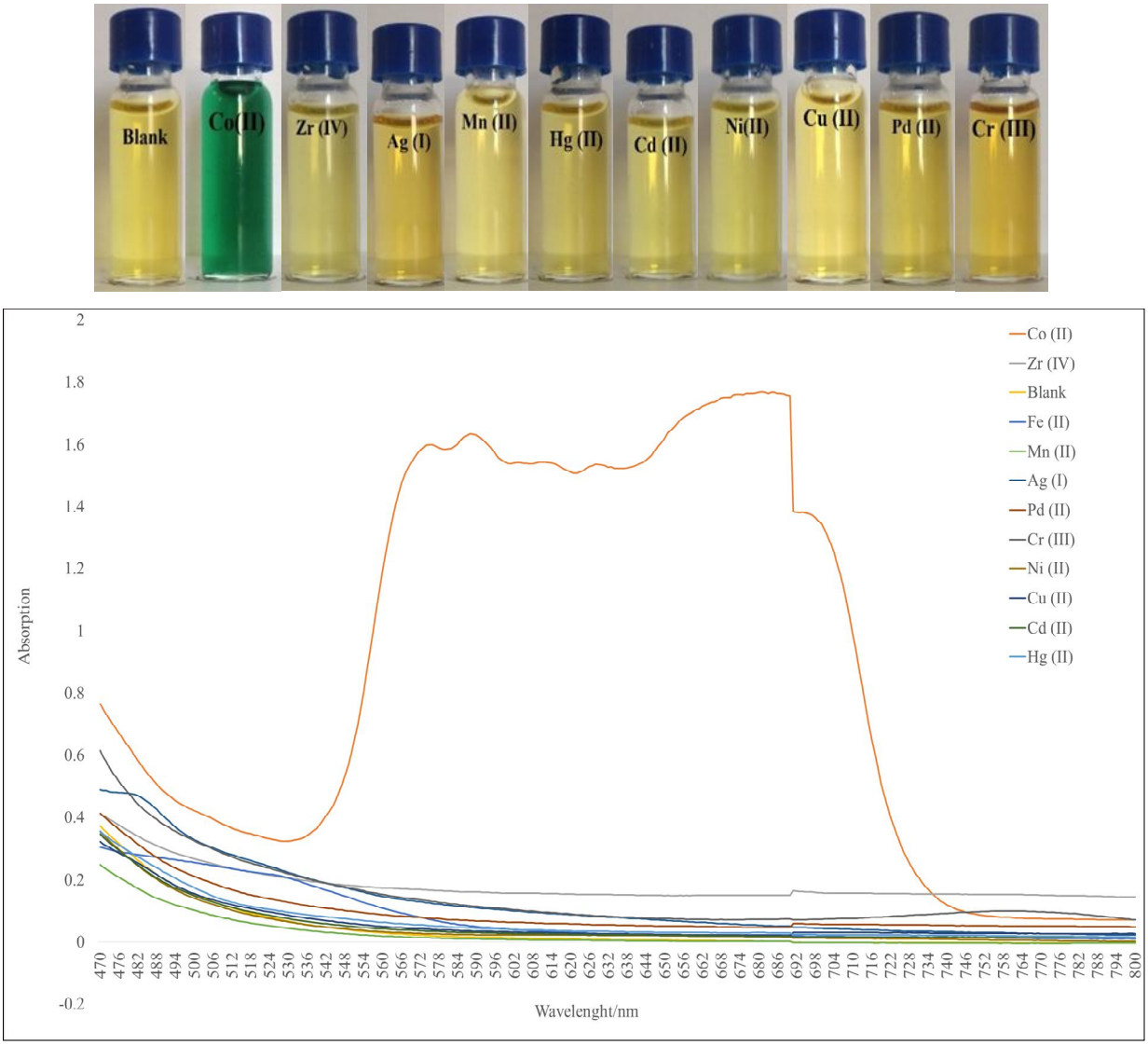


Fig. 3. The visual appearance of the 10 µM solution of (5b) in H_2O:CH_3CN 9:1 v/v in the presence of various metal ions and their UV-Vis spectrum.

intermediates by hydrogen bonding. Moreover, polar interactions between glycerol as a polar solvent and intermediates (7) and (8) stabilize these intermediates and facilitate their formations.

In order to study the role of column SiO_2 on the transformation of products (5) to (6), products (5b) and (5m) were synthesized and purified (recrystallization method) and were separately treated (1 mmol of each products) with column SiO_2 (1 g) in $CHCl_3$ (10 ml) and mixtures obtained were stirred magnetically at room temperature for 10 min in a round-bottom flask. The column SiO_2 was separated by centrifugation, $CHCl_3$ was evaporated under reduced pressure and crude solids were washed with water (5 ml, 2 times) and dried at vacuum at room temperature. The ^{1}H NMR study of both products approve the formation of compounds (6a) and (6b) *via* the treatment of (5b) and (5m) with SiO_2, respectively (Scheme 5).

The applicability of our method at large scales was examined with the conduction of the model reaction in the scale of 10 mmol under the optimized reaction conditions and unfortunately only a mixture of starting materials and unknown products was obtained even after a long time (12 h).

In another attempt, selective detection of metal ions was explored due to their importance in biological and environmental issues. For this investigation, the photo-physical behaviour of compound (5b) in the presence of various metal ions (10 μM, 3 equivalent) in aqueous solution of acetonitrile (H_2O:CH_3CN 9:1 v/v) through UV-Vis spectroscopy were examined. Interestingly, among the various salts of metal solutions of Co(II), Zr(IV), Ag(I), Mn(II), Hg(II), Cd(II), Ni(II), Cu(II), Pd(II) and Cr(III), adduct (5b) and Co^{2+} showed strong selectivity with an evident colour change from yellow to green. This absorption band of (5b)-Co^{2+} in the visible region clearly showed the metal dependent behaviour of (5b) as a chemical sensor for the detection of Co^{2+} (Fig. 3). It can be attributed to the proper coordination of compound (5b) as a multi-dental ligand to the cobalt ions.

CONCLUSIONS

Glycerol as a nontoxic, biodegradable, very cheap promoting reaction medium was successfully applied for the synthesis of 3-(imino)-2,3-dihydropyrrol[2,1-*a*] isoquinoline-1,1(10*bH*)-dicarbonitrile derivatives *via* a catalyst-free reaction between aryl aldehydes, malononitrile, isoquinoline and isocyanides. Presented method avoids the use of hazardous catalysts or solvents. Moreover, in comparison with the previously reported method, the reaction times were obviously decreased from 42-72 h to 2.5-4 h. Additionally, the progress of the reaction during two different common separation methods were investigated. The exploration shows that the on-column reaction chromatography occurs inside the silica gel column when the column chromatography is used as a purification method. It was found that the HCN elimination and a tautomerization occur in the presence of SiO_2 during the purification process with column chromatography. Furthermore, the photo-physical properties of synthesized compounds were studied and it was found that some of synthesized compounds such as (5b) can be used for the preparation of a selective Co^{2+} sensor.

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