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Short communication

The synthesis and photophysical studies of pyridinyl-1,2,4-triazine derivatives and use as a fluorescent sensor for ferric salts

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ABSTRACT

A simple method is described for the efficient synthesis of bisaryl-3-pyridinyl-1,2,4-triazine derivatives via condensation of cinnamils with pyridine carboxtrisamidrazone in methanol under both conventional heating and microwave irradiation in high yield (85–66%). Photophysical analysis revealed that the derivatives displayed good fluorescent properties and bisaryl-3-pyrazine-1,2,4-triazine derivatives selectively bound Fe(III) ions.

1. Introduction

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive synthetic targets over many years and they are found in various natural products. Substituted 1,2,4-triazines represent an important class of nitrogen containing heterocycles. 1,2,4-Triazines and their derivatives occupy a pivotal position in modern medicinal chemistry because of their high potential for biological activity [1]. Thus, the 1,2,4-triazine ring is a prominent structural motif found in numerous natural and synthetic biologically active compounds. For example well-known antiviral drug azaribine is structurally based on the 1,2,4-triazine scaffold [1,2]. In addition, certain azanucleosides, for example, 6-azacytosine and 6-azauracil, bearing the 1,2,4-triazine heterocycle, have displayed an impressive array of biological activities such as antimicrobial [3], antiviral [4], anti-inflammatory [5] and antimalarial.[6] activities. Furthermore, 6-azaisocytosine (3-amino-1,2,4-triazin-5(2H)-one), an isosteric isomer of 6-azacytosine and 6-azauracil, is a great biological interest due to its resistance to deaminase [7].

The 1,2,4-triazine core is a versatile synthetic platform to access a wide range of condensed heterocyclic ring systems *via* intramolecular Diels–Alder reactions with a vast array of dienophiles. In addition, the triazine ring system is a key component of commercial dyes, herbicides, insecticides and more recently, pharmaceutical compositions [8]. As our efforts are directed at an iterative analog library approach to support nascent medicinal chemistry programs, this latter application for the triazine scaffold attracted our attention.

Fluorescent property is the ultimate tool for the identification of chromosomes and ultra fast DNA sequencing by showing different colours with each DNA base pairs *via* fluorescence resonance energy transfer [9,10]. Many nitrogen containing heterocyclic compounds have displayed photoluminescence and electroluminescence properties. Compounds with fused 1,2,4-triazine aromatic rings are used as raw material for organic light-emitting devices, light emitting cells and optoelectronic devices [11–13].

The wide-ranging biological activity associated with 1,2,4-triazine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest. Various methods for the preparation of these compounds have been reported. However these methods suffer from tedious synthetic routes, longer reaction time, drastic reaction conditions, as well as narrow substrate scope [14–17]. To the best of our knowledge, there have been very few reports for the synthesis of 1,2,4-triazine derivatives in literature [18–21]. As part of our ongoing research on the development of novel synthetic routes for the synthesis of biologically active heterocyclic compounds and use

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of green chemical techniques in organic synthesis [22–24], herein, we report a simple and facile one pot procedure for the synthesis of 1,2,4-triazine derivatives under reflux condition.

2. Experimental

2.1. General

All the substituted aldehydes, biacetyl, and all the substituted cyanopyridines were purchased from Aldrich Chemicals. Piperidine and other reagents were purchased from S. D. Fine. Chem. India Limited. Methanol was distilled with Mg/I_2 under nitrogen and stored over 3A° molecular sieves. IR measurements were done as KBr pellets for solids using Perkin Elmer Spectrum RXI FT-IR. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard with JEOL 500 MHz and Bruker 300 MHz high resolution NMR spectrometer respectively. Multiplicities were abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Mass spectra were recorded using Electron Spray Ionization method with Thermo Finnigan mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN. The electronic spectral measurements were carried out in Perkin–Elmer Lambda 35 double beam spectrometer at room temperature. The steady state emission spectra were recorded on Hitachi 650–40 spectrofluorometer at room temperature. Time-resolved fluorescence measurements were determined using picosecond laser excited Horibajobinyvon time correlated single photon counting spectrofluorometer. The excitation source was a tunable Ti-sapphire laser (Tsunami, Spectrometer, USA) with a pulse width of <2 ps and repetition rate of 82 MHz, Ar–*H*. The sample was excited at its corresponding wavelength and the emission was monitored between 400 to 600 nm using a MCP-PMT detector. Decay traces were deconvulated using a non-linear least-squares analysis using IBH software.

2.2. General procedure for the synthesis of bisaryl-3-pyridinyl-1,2,4-triazine derivatives (**3a**–**l**)

Method: A

A mixture of cinnamil (1.0 mmol) and pyridine carboxtrisamidrazone (1.0 mmol) in methanol (30 mL) was refluxed for the appropriate time as described in Table 1. After completion of the reaction, as indicated by TLC, the precipitated solid was filtered, washed with water and dried. The obtained crude solid was purified further by recrystalization with ethanol.

Method: B

A mixture of cinnamil (1.0 mmol) and pyridine carboxtrisamidrazone (1.0 mmol) in methanol (2 mL) was irradiated in a microwave oven (BPL BMG 800 TS model) at 80 W for the appropriate time displayed in Table 1. After completion of the reaction, as indicated by TLC, the precipitated solid was filtered, washed with water and then dried. The obtained crude product was recrystallized with ethanol.

2.2.1. **3a**. 5,6-bis[(E)-2-phenylvinyl]-3-pyridin-2-yl-1,2,4-triazine (Table 1 entry 1)

Yellow solid; mp 72–74 °C; R_f 0.80 (40% AcOEt/Petroleum ether); IR (KBr): 1072, 1365, 1484, 1623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.43 (m, 8H, –Ar–*H*), 7.45 (d, 1H, J = 8.4 Hz, –Ar–*H*), 7.50 (s, 1H, –Ar–*H*), 7.67–7.70 (m, 3H, –Ar–*H*), 7.91–7.94 (m, 1H, –Ar–*H*), 8.13 (d, 1H, –Ar–*H*), 8.39 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.69 (d, 1H, J = 7.6 Hz, –Ar–*H*), 8.89 (d, 1H, J = 3.8 Hz, –Ar–*H*); ^{13}C NMR (75 MHz, DMSO-d_6): 118.5, 119.4, 127.8, 128.3, 129.0, 129.1, 129.7, 130.5, 135.3, 135.9, 139.2, 143.2, 144.6, 145.6, 145.9, 148.8, 151.4, 152.6, 159.1; MS (EI): m/z 363.27 [$M^+ + H^+$]; $C_{24}H_{18}N_4$. Anal. Calcd for $C_{24}H_{18}N_4$. C 79.54 H 5.01 N 15.46. Found: C 79.49 H 5.03 N 15.49.

2.2.2. **3b**. 5,6-bis[(E)-2-(4-methylphenyl)vinyl]-3-pyridin-2-yl-1,2,4-triazine (Table 1, entry 2)

Yellow solid; mp 168–170 °C; R_f 0.83 (40% AcOEt/Petroleum ether); IR (KBr): 1065, 1180, 1363, 1400, 1481, 1623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H, Ar–C*H*$_3$), 2.41 (s, 3H, Ar–C*H*$_3$), 7.22–7.26 (m, 4H, –Ar–*H*), 7.30–7.39 (m, 2H, –Ar–*H*), 7.54–7.60 (m, 2H, –Ar–*H*), 8.10 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.30 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.43 (d, 1H, J = 6.1 Hz, –Ar–*H*), 8.82 (d, 1H, J = 4.6 Hz, –Ar–*H*); ^{13}C NMR (75 MHz, DMSO-d_6): 21.4, 21.5, 117.9, 118.8, 124.0, 125.1, 127.7, 128.2, 129.6, 129.7, 132.9, 133.4, 137.0, 138.3, 139.7, 140.7, 142.6, 150.3, 151.4, 152.2, 153.4, 160.3; MS (EI): m/z 391.20 [$M^+ + H^+$]; Anal. Calcd for $C_{26}H_{22}N_4$. C 79.97 H 5.68 N 14.35. Found: C 79.87 H 5.66 N 14.29.

2.2.3. **3c**. 5,6-bis[(E)-2-(4-methoxyphenyl)vinyl]-3-pyridin-2-yl-1,2,4-triazine (Table 1, entry 3)

Yellow solid; mp 62–64 °C; R_f 0.64 (40% AcOEt/Petroleum ether); IR (KBr): 822, 1026, 1171, 1278, 1301, 1508, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 6H, Ar–OC*H*$_3$), 6.92 (d, 5H, J = 9.2 Hz, –Ar–*H*), 7.22–7.30 (m, 2H, –Ar–*H*), 7.59 (d, 2H, J = 16.1 Hz, –Ar–*H*), 7.63 (d, 2H, J = 16.1 Hz), 8.09 (d, 1H, J = 16.1 Hz, –Ar–*H*), 8.30 (d, 1H, J = 16.1 Hz, –Ar–*H*), 8.71 (d, 1H, J = 2.3 Hz, –Ar–*H*), 8.81 (d, 1H, J = 2.3 Hz, –Ar–*H*), 8.84 (d, 1H, J = 1.6 Hz, –Ar–*H*); ^{13}C NMR (75 MHz, DMSO-d_6): 55.3, 55.4, 117.2, 117.6, 123.8, 125.0, 127.2, 128.4, 129.0, 129.2, 129.5, 129.9, 130.8, 136.4, 137.0, 137.7, 142.0, 147.4, 150.2, 151.3, 152.1, 155.5, 160.7; MS (EI): m/z 423.27 [$M^+ + H^+$]; Anal. Calcd for $C_{26}H_{22}N_4O_2$. C 73.92 H 5.25 N 13.26. Found: C 73.84 H 5.23 N 13.23.

2.2.4. **3d**. 5,6-bis[(E)-2-(3,4-dimethoxyphenyl)vinyl]-3-pyridin-2-yl-1,2,4-triazine (Table 1, entry 4)

Yellow solid; mp 180–182 °C; R_f 0.35 (40% AcOEt/Petroleum ether); IR (KBr): 963, 1019, 1140, 1260, 1511, 1624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.90 (s, 6H, Ar–OC*H*$_3$), 3.92 (s, 3H, Ar–OC*H*$_3$), 3.93 (s, 3H, Ar–OC*H*$_3$), 6.88 (d, 2H, J = 8.4 Hz, –Ar–*H*), 7.15–7.23 (m, 4H, –Ar–*H*), 7.25–7.31 (m, 2H, –Ar–*H*), 7.41–7.43 (m, 1H, –Ar–*H*), 7.87–7.90 (m, 1H, –Ar–*H*), 8.02 (d, 1H, J = 16.2 Hz, –Ar–*H*), 8.29 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.65 (d, 1H, = 7.6 Hz, –Ar–*H*), 8.87 (d, 1H, J = 4.6 Hz, –Ar–*H*); ^{13}C NMR (75 MHz, DMSO-d_6): 55.9, 56.0, 110.2, 110.7, 111.3, 117.1, 117.8, 121.5, 122.2, 123.9, 125.0, 128.7, 129.3, 137.0, 138.0, 142.3, 149.2, 150.2, 150.5, 151.1, 151.3, 152.1, 153.4, 160.0; MS (EI): m/z 483.20 [$M^+ + H^+$]; Anal. Calcd for $C_{28}H_{26}N_4O_4$. C 69.70 H 5.43 N 11.61. Found: C 69.81 H 5.45 N 11.57.

2.2.5. **3e**. 5,6-bis[(E)-1-napthylvinyl]-3-pyridin-2-yl-1,2,4-triazine (Table 1, entry 5)

Yellow solid; mp 68–70 °C; R_f 0.82 (40% AcOEt/Petroleum ether); IR (KBr): 1024, 1251, 1395, 1465, 1621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.88–6.93 (m, 6H, –Ar–*H*), 7.22–7. 32 (m, 4H, –Ar–*H*), 7.41–7.43 (m, 1H, –Ar–*H*), 7.56–7.64 (m, 5H, –Ar–*H*), 7.76 (d, 1H, J = 16.1 Hz), 7.86–7.88 (m, 1H, –Ar–*H*), 8.05 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.33 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.64 (d, 1H, J = 15.3 Hz, –Ar–*H*), 8.86 (d, 1H, J = 3.6 Hz, –Ar–*H*); ^{13}C NMR (75 MHz, DMSO-d_6): 121.0, 121.8, 122.1, 123.4, 123.7, 124.5, 125.3, 125.6, 126.3, 126.4, 126.9, 127.1, 128.7, 128.9, 130.0, 130.8, 132.9, 133.8, 136.0, 139.7, 150.7; MS (EI): m/z 463.27 [$M^+ + H^+$]; $C_{32}H_{22}N_4$.