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Multi-component synthesis of methylene bis isoxazolo[4,5-*b*]-pyridine-*N*-oxides

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Abstract

A three component one-pot protocol was investigated for the synthesis of methylene bis isoxazolo[4,5-*b*]-pyridine-*N*-oxides from commercially available materials.

Keywords: Multi-component synthesis; Knoevenagel condensation; Michael addition; New methodology

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation [1] and are important owing to their synthetic efficiency [2]. In times, where a premium is put on speed, diversity and efficiency in the drug discovery process [3], MCR strategies offer significant advantages over conventional linear-type syntheses. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Various biological applications have been reported for isoxazoles such as antitumor [4], CNS-active [5], analgesic [6], antimicrobial [7] and chemotherapy [8]. Isoxazoles display a wide range of organic reactivities and could be used as an effective means of preparing new molecular scaffolds [9]. Several pyridine-*N*-oxide derivatives were shown to exhibit anti-HIV activity and they are unusual anti-HIV compounds with multiple mechanism of antiviral action [10–12]. Pyridine-*N*-oxides are usually synthesized by the oxidation of pyridine derivatives [13–15] or by ring transformation of isoxazole [16,17]. These reactions require the usage of variety oxidants, drastic conditions, and moreover results in poor yields. Hence, we thought of constructing the pyridine-*N*-oxide ring by interaction of 3,5-dimethyl-4-nitroisoxazole **1** with compounds possessing a methyl ketone or β-diketone moiety in piperidine [18–20]. We could able to achieve the target, because our method produced good yields under mild conditions compared to the existing known methods. In continuation of our earlier work, now, we proposed the synthesis of title compounds.

3,5-Dimethyl-4-nitroisoxazole **1** represents a versatile building block bearing a number of different functionalities which can be selectively reacted to generate molecularly diverse products and we reported many reactions by describing the reactivity of isoxazole **1** [21–24]. Our approach to the development of multi-component one-pot synthesis is based on the creation of building blocks containing several reactive centres which can be selectively

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reacted. Owing to the potential activity of pyridine-*N*-oxides and isoxazoles, we are interested in development of hybrid molecules and in the design of new drugs to accommodate bis-pyridine-*N*-oxide and isoxazole moieties in a single molecular frame work for enhancing biological activity. Inspired by these findings and to develop new synthetic strategies, we could able to perform a multi-component one-pot synthesis on 3,5-dimethyl-4-nitroisoxazole **1** to synthesize the title compounds. As a part of our endeavour to develop diversity-oriented synthesis using poly functional scaffold such as 3,5-dimethyl-4-nitroisoxazole **1**, we now report a new one-pot three-component procedure (actually involving 5 components, MCR-5) which allows the synthesis of title compounds, which may probably possess potential pharmacological activity, from commercially available starting materials.

Considering that, tandem synthesis involving Knoevenagel and Michael reaction in a sequential order have been extensively reported [25], we anticipated that methylene bis isoxazolo[4,5-*b*]pyridine-*N*-oxides could be prepared through a multi-component procedure in which **6** was generated first from **1** and **5** by Knoevenagel condensation and these reacted in situ with **7** through Michael addition and subsequently it undergoes further *in situ* cyclocondensation with 2 moles of **1** to give the title compounds **4**.

1. Experimental

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F254 silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a PerkinElmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shift (δ) is given with tetramethyl silane as an internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and PerkinElmer model 240 analyzers.

To a stirred solution of **1** (1 mmol) in ethanol (10 mL) were added piperidine (0.1 mmol) and an aromatic aldehyde **2** (1 mmol). The reaction mixture was refluxed at 80 °C for 1 h, and acetyl acetone **3** (1 mmol) was added later to the reaction mixture, heating continued at 80 °C for 2 h, and then **1** (2 mmol) was further added to it and heating continued further for 3 h. After completion of the reaction (monitored by TLC) the solid product **4** separated on cooling was filtered and recrystallized from methanol.

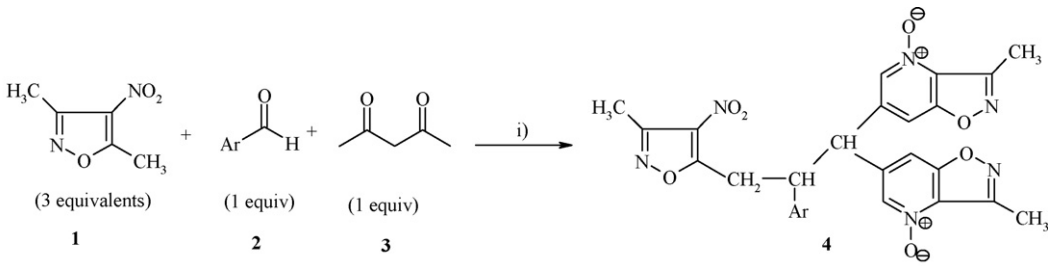
To a solution of Michael adduct **8** (1 mmol) in ethanol (10 mL), catalytic amount of piperidine (0.01 mmol) and 2 equivalents of nitro isoxazole **1** (2 mmol) were added and the contents are refluxed for 3 h. The product separated on cooling was filtered and recrystallized from methanol. The compound **4** obtained in this method was found to be similar to that of a multi-component one-pot synthesis by mps, ^{1}H NMR and mass spectral data.

2. Results and discussion

In a typical experiment, equimolar amounts (1 equivalent) of 3,5-dimethyl-4-nitroisoxazole **1**, aromatic aldehyde **2**, were reacted in the presence of piperidine in ethanol (1 h at 80 °C), and acetyl acetone (1 equiv) was added and the refluxing continued for another 2 h at 80 °C, finally 2 equivalents of **1** was added and the reaction was carried out for another 3 h at 80 °C. The solid that separated on cooling, was filtered and purified by recrystallization from ethanol. Compounds **4a–j**, were isolated in good yields (Scheme 1).

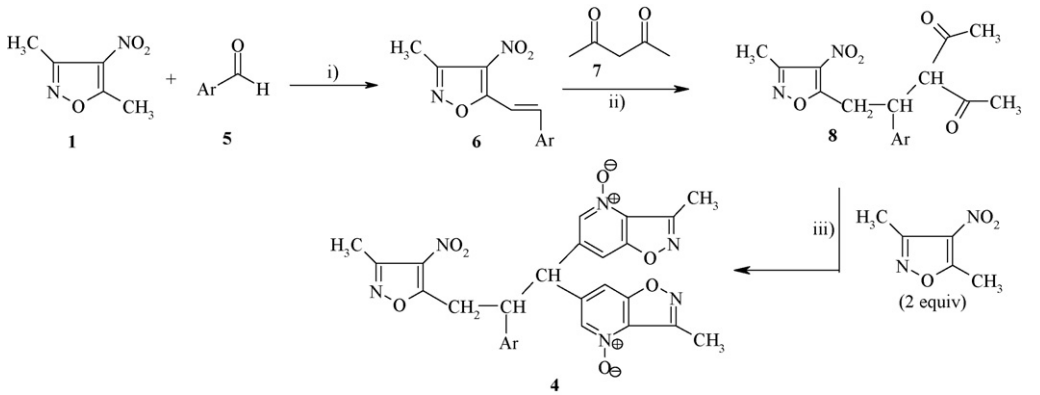
In order to establish the evidence for the formation of **4a–j**, we carried out a step-wise synthesis of compounds **4a–j**, starting from the building block **1**. We reacted 3,5-dimethyl-4-nitroisoxazole **1** (1 mmol) with different aromatic aldehydes (1 mmol) in alcohol under refluxing condition on a hot-water bath for 1 h in presence of catalytic amount of piperidine (0.01 mmol) which led to the formation nitrostyryl isoxazole **6** by Knoevenagel condensation in good yields [26]. Only the 5-methyl group of isoxazole is activated by the nitro group, hence it alone takes part in this regioselective reaction [27]. Compound **6** was later reacted with acetyl acetone **7** in ethanol containing catalytic amount of piperidine for 2 h at 80 °C. This reaction led to the formation of Michael adducts **8** in moderate yields [28]. Finally compound **8** containing two acetyl groups was reacted with 2 equivalents of **1** in ethanol containing catalytic amount of piperidine for 3 h at 80 °C, which resulted in the formation of title compounds **4a–j** (Scheme 2).

The compounds **4a–j**, obtained in a one-pot multi-component synthesis and by a step-wise synthesis were found to be similar by mps, ^{1}H NMR and mass spectra. The structure of newly synthesized methylene bis isoxazolo[4,5-*b*]pyridine-*N*-oxides **4a–j** were established on the basis of IR, ^{1}H NMR and MS spectra and by elemental analyses [29]. The yields in multi-component synthesis are more (80–85%), compared to that of step-wise synthesis (65–75%).



4a-j: Ar = C_6H_5, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3,4-$OCH_2OC_6H_3$, 2-$CH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 2,6-$Cl_2C_6H_3$

Scheme 1. Reagents and conditions: i) ethanol–piperidine, reflux, 6 h.



Scheme 2. Reagents and conditions: i) ethanol–piperidine, reflux, 1 h. ii) Ethanol–piperidine, reflux, 2 h. iii) Ethanol–piperidine, reflux, 3 h.

The different substituents present on benzene ring of aromatic aldehydes did not affect much on the yields of the products **4a–j**.

In conclusion, we reported the multi-component (MCR-5) synthesis of methylene bis isoxazolo[4,5-*b*]-pyridine-*N*-oxides with potential biological activity using inexpensive and commercially available materials in a one-pot reaction. This synthesis benefits from a simple method of purification, which does not require chromatography. This ease of purification compliments the one-pot synthesis, making the technology practical, easy to perform and facile. Moreover, pyridine-*N*-oxides are recently proved to be anti-HIV agents, this study may activate the researchers concerned in this field to explore the pharmacological activity of the compounds.

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(c) Analytical data for compound **8a**: Colourless solid, yield 65%, mp 170 °C, IR (KBr): cm^{-1}; 1705 (C═O), 1600 (C═N), 1520 (NO_2), ^1H NMR (300 MHz, $CDCl_3$): δ 1.8(s, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.6 (m, 2H), 4.1(m, 1H, benzylic-H), 4.3(d, 1H, J = 12 Hz), 6.8–7.2 (m, 5H, Ar–H); MS (EI): m/z 330 [M^+]. Anal. Calcd. for $C_{27}H_{18}N_5O_2$; C, 61.81; H, 5.45; N, 8.48; Found: C, 61.76; H, 5.41; N, 8.45. **8b**: Colourless solid, yield 60%, mp 146 °C, IR (KBr): cm^{-1}; 1709 (C═O), 1600 (C═N), 1575 (NO_2), ^1H NMR (300 MHz, $CDCl_3$): δ 1.7(s, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.1 (m, 1H, benzylic-H), 4.5(d, 1H, J = 12 Hz), 7.1 (d, 2H, Ar–H, J = 7.3 Hz), 7.4 (d, 2H, Ar–H, J = 7.3 Hz); MS (EI): m/z 360 [M^+]. Anal. Calcd. for $C_{18}H_{20}N_2O_6$; C, 60.00; H, 5.55; N, 7.77; Found: C, 60.03; H, 5.49; N, 7.75.
[29] Aanalytical data for compounds: **4a**: pale red crystalline solid, yield 85%, mp 240 °C, IR (KBr): cm^{-1}; 1385 (═N^+–O^-), 1648 (C═N), ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 6H, $2CH_3$), 2.5 (s, 3H, CH_3), 3.8 (m, 2H), 4.2 (m, 1H, benzylic-H), 4.9 (d, 1H, J = 12 Hz), 6.6 (s, 2H, pyridine-H), 6.8–7.2 (m, 5H, Ar–H), 7.5 (s, 2H, pyridine-H); MS (EI): m/z 542 [M^+]. Anal. Calcd. for $C_{27}H_{22}N_6O_7$; C, 59.77; H, 4.05; N, 15.49; Found: C, 59.81; H, 4.02; N, 15.50. **4b**: pale red crystalline solid, yield 82%, mp 221 °C, IR (KBr): cm^{-1}; 1325 (═N^+–O^-), 1659 (C═N), ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 6H, $2CH_3$), 2.5 (s, 3H, CH_3), 3.6 (s, 3H, OCH_3), 3.8 (m, 2H), 4.2 (m, 1H, benzylic-H), 4.8 (d, 1H, J = 12 Hz), 6.6 (s, 2H, pyridine-H), 6.8 (d, 2H, Ar–H, J = 7.5 Hz), 7.2 (d, 2H, Ar–H, J = 7.5 Hz), 7.6 (s, 2H, pyridine-H); MS (EI): m/z 572 [M^+]. Anal. Calcd. for $C_{28}H_{24}N_6O8$; C, 58.74; H, 4.19; N, 14.68; Found: C, 58.77; H, 4.22; N, 14.66. **4c**: pale red crystalline solid, yield 81%, mp 211 °C. **4d**: pale red crystalline solid, yield 82%, mp 202 °C. **4e**: orange crystalline solid, yield 82%, mp 198 °C. **4f**: orange crystalline solid, yield 81%, mp 190 °C. **4 g**: pale red crystalline solid, yield 83%, mp 188 °C. **4 h**: pale red crystalline solid, yield 80%, mp 217 °C. **4i**: pale red crystalline solid, yield 82%, mp 223 °C. **4j**: orange crystalline solid, yield 81%, mp 232 °C.