Synthesis of Some New 3, 5-Bis (substituted) Pyrazoles and Isoxazoles Based on \((N'^1E, N'^3E) - N'^1, N'^3\)-Bis (3, 4, 5-substitutedbenzyldene) Malonohydrazide under Solvothermal Conditions

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ABSTRACT

The new 3,5-(substituted) pyrazoles and isoxazoles were prepared by reaction of \((N'^1E, N'^3E) - N'^1, N'^3\)-bis (3,4,5-substitutedbenzyldene)malonohydrazide with hydrazine hydrate and hydroxylamine hydrochloride respectively under solvothermal conditions involving an ecofriendly method without any environmental pollution, the yield are in the range of 75-96%. The structure of the new compounds were established using elemental analysis, IR, \(^1\)H NMR, \(^13\)C NMR. (Int J Biomed Sci 2010; 6(1):45-48)

Keywords: solvothermal; pyrazoles; isoxazoles

INTRODUCTION

Synthesis of pyrazole and isoxazole derivatives has been a subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as agrochemical industry. Numerous compounds containing pyrazole and isoxazole moieties have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic antibacterial, antiviral, antitumor, antifungal and antidepressant activities (1-13). They are also useful intermediate for many industrial products (14, 15). A lot of synthetic methods for pyrazoles and isoxazoles have been developed. However these methods are usually carried out in organic solvents and many of them reactions require long reaction times, high temperatures, or inconvenient reaction condition for their execution and are often accompanied by tedious chromatographic techniques for purification of the desired products. Recently Rai et al have developed a simple method for the organic synthesis in the presence of a salen metal catalyst. The chemistry of solvothermal reactions involves two major factors namely, high temperature and pressure. “Solvothermal reactions can be defined as reaction in closed system, in the presence of solvent at a temperature higher than its boiling point. Consequently these reactions can be developed in supercritical or in sub critical conditions” (16). Some of the reactions, which proceed at slow rates under normal pressure, can be enhanced by increasing the pressure. This can be achieved by heating the reaction mixture under sealed condition. The development of solvothermal reaction is of interest because they offer the possibility of environmentally benign reaction conditions by reducing the burden of organic solvent disposal. Solvothermal process involves the heterogeneous chemical reaction, which occur at solid-liquid or solid-liquid-gas interfaces under high temperature and high pressure. Rai and Linganna successively used thiourea as thionating agent for (i) the conversion of
1,3,4-oxadiazole to 1,3,4-thiadiazole under solvothermal condition (17) by heating in a sealed tube at 100°C. (ii) the conversion of esters to thioesters under solvothermal condition using More’s autoclave (18). Besides, Rai et al (19) successfully converted aldehyde semicarbazones to bis hydrazones by thermolysis under pressure using ethanol as solvent in a sealed tube. These facts prompted us to apply this technology for the synthesis of 3,5-bis(substituted) pyrazoles and isoxazoles based on cyclocondensation of (N¹,E, N³E)- N¹, N³-bis (3,4,5-substituted benzylidene) malonohydrazide with hydrazine hydrate and hydroxylamine hydrochloride via solvothermal mode (Figure 1).

RESULTS AND DISCUSSION

Synthesis of malonyldihydrazide was prepared by reacting the diethylmalonate (1 mole) with hydrazine hydrate (2 mole) (Figure 2). The desired starting materials (1a-h)
were prepared in high yield by reacting ethanol solution of dihydrazide (1mole) with different benzaldehyde derivatives (2mole). The mixture was refluxed for 1hour and filtered, washed with ethanol and dried over desiccator (Figure 2).

Syntheses of pyrazoles (2a-h) were undertaken first. Thus, when \((N'\text{E}, N'\text{E})-N'\text{N}, N'\text{ bis (3,4,5-substituted enzyldiene)malonohydrazides (1a-h)}\) were reacted with hydrazine hydrate in the absence of solvent under solvothermal condition using More’s autoclave at 100°C for 1hour. Products (2a-h) were obtained in good to excellent yield. In the case of reaction between 1a and hydrazine hydrate the yield is relatively low, this is ascribed to lower reaction activity of compound 1a due to strong electron-withdrawing effect of the nitro groups. Similarly treatment of \((N'\text{E}, N'\text{E})-N', N'\text{ bis (3,4,5-substituted benzylidene) malonohydrazides (1b,d and e)}\) with hydroxylamine hydrochloride under solvothermal condition using More’s autoclave at 150°C for 3hours afforded compounds (3a-c) in good yield. The structures of isolated products were established with the help of spectral and analytical data.

**CONCLUSIONS**

We report the reactions of \((N'\text{E}, N'\text{E})-N', N'\text{ bis (3,4,5-substituted benzylidene) malonohydrazides with hydrazine hydrate and hydroxylamine hydrochloride under solvothermal condition, a variety of pyrazole and isoxazole derivatives have been obtained in high yields.

**Experimental**

All reagents were purchased from commercial sources. 1H NMR (300 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker av300 spectrometer in CDCl₃ or DMSO-d₆ and TMS is used as internal reference. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400 - 4000 cm⁻¹. Elemental analyses were carried out on an Elementor vairo-EL instrument. Melting points are uncorrected. The starting materials were carried out on an Elementor vairo-EL instrument.

**Synthesis of 3, 5-bis(substituted) pyrazoles (2a-h) – General procedure**

A mixture of (1a, 0.01mole) and excess of hydrazine hydrate were taken in autoclave reaction container (Teflon liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 100°C for 1hour. The products after cooling, were extracted into ethylacetate (20mL), washed thoroughly with water. The organic layer was dried over Na₂SO₄, solvent was evaporated and the product obtained as:

**2a: Solid 71% mp 98-100°C. Anal. Calc. for C₃H₄N₂O₆: C, 51.78, H, 3.58, N, 28.42. Found: C, 51.46, H, 3.61, N, 28.08.**

**2b: Solid 81% mp 168-171°C. Anal. Calc. for C₃H₅Cl₂N₂: C, 54.71, H, 3.78, N, 22.52. Found: C, 53.92, H, 3.63, N, 23.01.**

**2c: Solid 91% mp 138-141°C. Anal. Calc. for C₁₇H₂₆N₆O₆: C, 62.62, H, 5.53, N, 23.06. Found: C, 62.44, H, 5.62, N, 22.80.**

**2d: Solid 94% mp 145°C decomposes. Anal. Calc. for C₁₇H₂₆N₆O₆: C, 64.59, H, 6.71, N, 28.70. Found: C, 64.42, H, 6.82, N, 28.50.**

**2e: Solid 89% mp 114-117°C. Anal. Calc. for C₁₇H₂₆N₆O₆: C, 50.72, H, 5.82, N, 17.35. Found: C, 50.92, H, 5.85, N, 16.82.**

**2f: Solid 87% mp 160-164°C. Anal. Calc. for C₁₇H₂₆N₆O₆: C, 59.42, H, 5.70, N, 19.80. Found: C, 59.02, H, 5.85, N, 19.52.**
Synthesis of 3, 5-bis(substituted) isoxazoles (3a-c) – General procedure

A mixture of (1a, 0.01mol) and an equimolar amount of hydroxylamine hydrochloride were taken in autoclave reaction container (Teflon liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 150°C for 3 hours. The products after cooling, were extracted into ethylacetate (20 ml), washed thoroughly with water. The organic layer was dried over Na₂SO₄, solvent was evaporated and the product obtained as:

3a: Solid 80% mp 112-113°C. Anal. Calc. for C₃₅H₂₄Cl₂N₂O₂: C, 64.43, H, 6.44, N, 25.05. Found: C, 64.21, H, 6.53, N, 24.89. H NMR (DMSO-d₆): δ 4.78 (br, 1H, NH), 5.67-6.70 (dd, 4H, Ar), 7.30-7.70 (m, 5H, Ar), 8.75 (s, 1H, -N=CH), 11.30 (br, 1H, NH). C NMR (100 MHz DMSO-d₆): δ 75.89, 84.67, 117.34, 120.08, 130.02, 135.20, 150.51. IR (KBr): ν(cm⁻¹) 3571, 3286, 2952, 1594, 1474.

3b: Solid 75% mp 78-80°C. Anal. Calc. for C₃₅H₂₃Cl₂N₂O₂: C, 56.90, H, 5.61, N, 14.43. Found: C, 56.85, H, 5.75, N, 14.15. H NMR (CDCl₃): δ 3.80 (s, 9H, -OCH₃), 6.70 (s, 1H, C4), 6.90 (s, 2H, Ar), 8.00 (s, 1H, -N=CH). C NMR (100 MHz CDCl₃): δ 55.90, 60.06, 103.58, 128.56, 138.53, 144.42, 147.84, 152.38, and 153.49. IR (KBr): ν(cm⁻¹) 3571, 3286, 2952, 1594, 1474.

3c: Solid 77% mp 92-94°C. Anal. Calc. for C₃₅H₂₂Cl₂N₂O₂: C, 54.56, H, 3.50, N, 18.71. Found: C, 54.43, H, 3.61, N, 18.60. H NMR (CDCl₃): δ 4.10 (br, 1H, NH), 6.80 (s, 1H, C4), 7.90-8.20 (dd, 4H, Ar), 8.70 (s, 1H, -N=CH), 8.90 (s, 1H, -N=CH). C NMR (100 MHz CDCl₃): δ 98.59, 123.96, 127.30, 131.46, 146.79, 147.47, 155.50. IR (KBr): ν(cm⁻¹) 3318, 3108, 2947, 1601, 1335.

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