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Novel three-component cyclocondensation reaction by use of a bis-reagent: New synthesis of diethyl 4,4-(1,4-phenylene) bis(6-methyl-2-oxo(thioxo)-1,2,3,6-tetrahydropyrimidine-5-carboxylates (biginelli reaction)

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ABSTRACT

The one-pot, three-component (Biginelli reaction) cyclocondensation reaction of ethyl acetoacetate, terephthalaldehyde and urea in the ratio of 2: 1: 2 in absolute ethanol solvent in the presence of dodecyl benzene sulfonic acid (DBSA) as catalyst leads to the formation of the title compound in a good yield. © 2010 Trade Science Inc. - INDIA

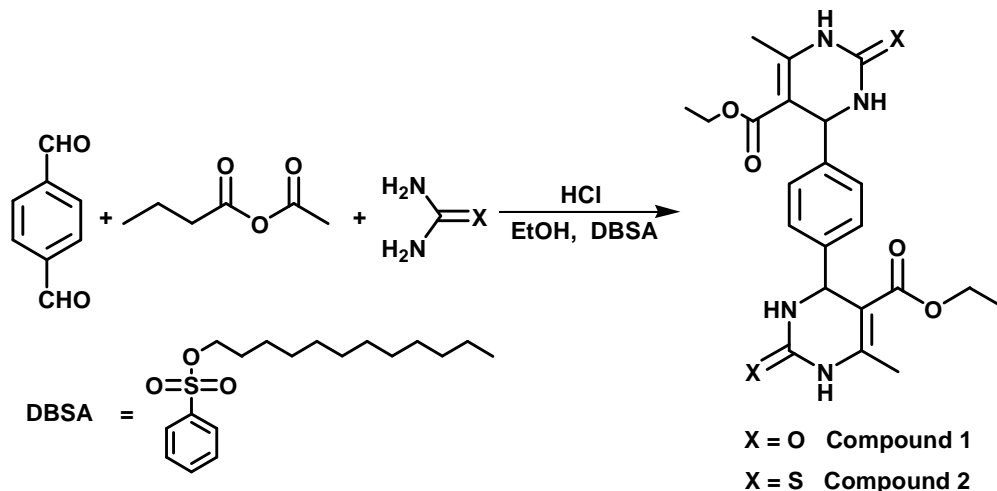
KEYWORDS

Biginelli reaction;
Cyclocondensation;
Terephthalaldehyde;
Bis-reagent;
Multicomponent.

INTRODUCTION

Multicomponent reactions (MCR_s) are of increasing importance in organic and medicinal chemistry. In such reactions, three or more reactants come together in a single reaction vessel to form new products that

contain portions of all the components. In 1893 Biginelli reported the first synthesis of dihydropyrimidine by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea. The increasing interest in dihydropyrimidine scaffolds (DHPM_s) (also known as Biginelli compounds) is mainly due to their therapeutic



Scheme 1

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and pharmacological properties. They have been found to exhibit a wide spectrum of biological effects including antiviral, antitumour, antibacterial and anti-inflammatory activities. While searching for new extensions of the Biginelli reaction^[1-5], we have recently found that the reaction of ethyl acetoacetate, terephthalaldehyde and urea in the ratio of 2: 1: 2 in absolute ethanol as solvent in the presence of HCl as catalysis leads to the formation of the title compound (Scheme 1). When the condensation was performed with reflux in ethanol in presence of HCl for 10 hr, the bis-pyrimidines were not obtained in a good yield. We also performed the reaction in ethanol in the presence of HCl and dodecyl benzene sulfonic acid (DBSA). In this case, the isolated product (bis-pyrimidine) was obtained in a good yield. It seems that dodecyl benzene sulfonic acid has two roles: 1) It acts as a surfactant to dissolve starting materials in EtOH and 2) It acts as an acidic catalyst to activate carbonyl group^[6,7].

In the ¹H-NMR spectrum, the compound (1) showed one singlet signal from protons in the phenylene fragment, one broadened singlet from two NH protons at about δ 8.23 ppm, one broadened doublet from two NH protons at about δ 8.67 ppm and a doublet at δ 5.19 ppm ($^3J_{\text{NH-CH}} = 3$ Hz) from the 4-H protons. In addition, signals from protons in the ester ethoxy groups were present.

Diethy-4,4'-(1,4-phenylene) bis (6-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate) (1)

The reaction mixture containing ethylacetoacetate (0.26g, 2 mmol), terephthalaldehyde (0.134g, 1mmol), urea (0.12g, 2 mmol), two drops of concentrated HCl and a catalytic amount of dodecyl benzene sulfonic acid in EtOH (20 ml) was heated at 80°C for 10 hr. The solvent removed under reduced pressure. The residue was washed with chloroform (10mlit). Recrystallization from methanol-ether (1: 3) gave com-

pound (1): m.p.: 292-293°C. FT-IR (KBr): 3332, 3226, 3100, 1700, 1680, 1339, 1265 (cm⁻¹). ¹H-NMR (DMSO-d₆) δ : 4.18 (4H, q, J = 7.5 Hz, CH₂), 2.4 (6H, s, CH₃), 1.03 (6H, t, J = 7.5 Hz, CH₃), 5.19 (2H, d, J = 3 Hz, CH), 7.36 (4H, s, Ph), 8.23 (1H, br.s, NH), 8.67 (1H, br.d, J = 3 Hz, NH) ppm. Anal. Calcd. for C₂₂H₂₆N₄O₆: C, 59.71; H, 5.92; N, 12.66; O, 21.69. Found: C, 58.98; H, 5.89; N, 12.62; O, 21.65.

Diethy-4,4'-(1,4-phenylene) bis(6-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate) (2)

This compound was synthesized in a similar way from (0.26g, 2mmol) of ethylacetoacetate, (0.134g, 1 mmol) of terephthalaldehyde and (0.152g, 2 mmol) of thiourea. m.p.: 310-311°C. FT- IR (KBr): 3389, 3322, 3110, 1690, 1530, 1250 (cm⁻¹). ¹H-NMR (DMSO-d₆) δ : 4.1 (4H, q, J = 7.3 Hz, CH₂), 2.35 (6H, s, CH₃), 1.02 (6H, t, J = 7.3 Hz, CH₃), 5.23 (2H, d, J = 3 Hz, CH), 7.16 (4H, s, Ph), 9.21 (1H, br.s, NH), 10.11 (1H, br.d, J = 3 Hz, NH) ppm. Anal. Calcd. For C₂₂H₂₆N₄O₄S₂ (474.6029): C, 55.67; H, 5.52; N, 11.8; O, 13.48. Found: C, 55.20; H, 5.47; N, 11.69; O, 13.33.

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