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Synthesis of 1, 4, 5-trisubstituted - 1,2,3-triazole Derivatives

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ABSTRACT: The reaction of β-keto esters or acetylacetone with sodium azide in the system K_2CO_3/DMSO proved to be a convenient method of synthesis of tri-substituted-1,2,3-triazoles. The synthesis of 1,2,3-triazoles via conversion of 2-chloro-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide to azides by treatment with sodium azide in the presence of DBU and THF, followed by cyclization of azides with active methylene ketones.

KEYWORDS:2-amine-5-phenyl-1,3,4-oxadiazole, DBU, β-ketoester, sodium azide.

I. INTRODUCTION

Interest in 1H-1,2,3-triazole derivatives is largely determined by biological activity of compounds containing an 1H-1,2,3-triazole fragment. In particular, some 1,2,3-triazole derivatives have been found to exhibit antitumor activity, and structure–activity relations have been derived, which make it possible to optimize the search for more active compounds.

The reactions of azides with β-keto esters are chemo selective. However, we recently found that the ester group of β-keto esters can compete with the keto group in the reaction with azides. In particular, study of the Dimroth reaction of aryl azides with alkyl 3-R-3-oxopropanoates in methanol in the presence of sodium methoxide showed that in some cases the products were stable N-aryl-3-R-2-diazo-3-oxopropanamides resulting from attack of the azido group on the ester fragment. The highest yields of such diazo compounds were obtained when R = isopropyl, cyclopropyl, or diethoxymethyl group and aryl azide contained an electron-withdrawing substituent, and the main factor determining the yield of diazo compounds was the system base–solvent.

II. EXPERIMENTATION

All chemical reagents and solvents were procured from Acros, Fisher scientific and Sigma-Aldrich etc., which were directly used as such without any purification. All the reactions were carried out under inert conditions. Isolated the products through crystallization, precipitation techniques and purify the products through column chromatography. Calculate percentage of yields based on pure products. Silica gel (100-200 mesh) is used as solid phase for column chromatography. Precoated silica aluminum sheets were used for TLC. Identify the product on TLC plate by using Iodine or UV cabinet. NMR spectrum was recorded on 400 MHz Bruker by using solvents CDCl 3 or DMSO-d 6 , Mass spectrum on Apex, IR spectrum on Bruker. Melting Points were determined for the compounds and are uncorrected.

The reaction of 2-amino-5-phenyl-1,3,4-oxadiazole and chloroacetyl chloride was carried out in the presence of catalytic amount of DBU. We were pleased to observe that use of 1.2 mmol of DBU for 6 mmol of 2-amino-5-phenyl-1,3,4-oxadiazole significantly increases the rate of reaction and yield of the product at room temperatures. 2-amino-5-phenyl-1,3,4-oxadiazole underwent one-pot reaction to produce the corresponding amides in 75-95% isolated yield. In a typical reaction, 2-amino-5-phenyl-1,3,4-oxadiazole (6 mmol) was dissolved in THF (5 ml) and then DBU (1.2 mmol) was added. The reaction mixture was placed on the freezing mixture of ice and salt & mechanically stirred for 15 min. Further, the chloroacetyl chloride (6.1 mmol) was added from dropping funnel at such rate that the temperature does not rise beyond 5oC. The reaction mixture was further stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into cold water. The compound was precipitated out which was filtered and washed with water. The precipitate was dried and recrystallized using ethanol. The product, 2-chloro-N-(5-phenyl-1,3,4- oxadiazol-2-yl)acetamide was obtained as a solid powder in 86% yield.

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In this work we studied the reaction of β-keto esters with sodium azide. Nucleophilic substitution of the chlorine atom in by azido group and cyclization of ethyl acetoacetate with the resulting azide without isolation of the latter gave compound in 57% yield.As shown below, sodium azide is convenient precursor to 1,4,5-trisubstituted 1,2,3-triazoles in the system K_2CO_3/DMSO. Herein, we report the results of our study of the reaction of sodium azide with a series of β-keto esters containing ethyl, methyl, and trifluoromethyl substituents.

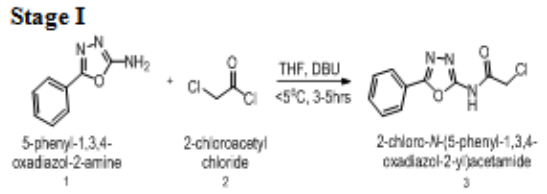

Fig1: synthesis of 2-chloro-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide

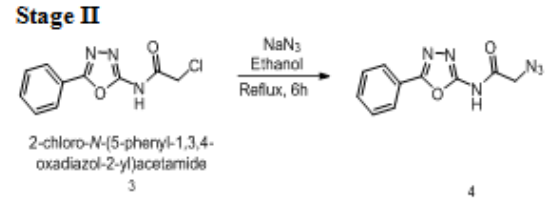

Fig2: synthesis of 2-azido-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide

Fig3: Generalized structure of 1,2,3-triazole derivatives

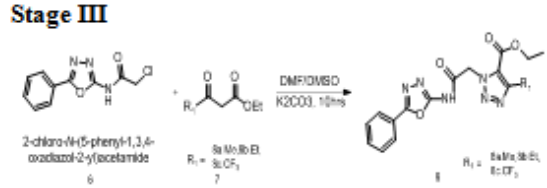

Fig3: synthesis of 1,2,3-triazole derivatives

III. RESULTS AND DISCUSSION

In a 50 mL round bottom flask, substituted 2-amino-5-phenyl-1,3,4-oxadiazole (6 mmol) was dissolved in THF (7 ml). To this solution, DBU (1.6 mmol) was added. The reaction mixture was placed on freezing mixture of ice and salt & mechanically stirred for 30 min. To this reaction mixture, chloroacetyl chloride (6.1 mmol) was added from dropping funnel at such rate that the temperature does not rise beyond 5°C. After allchloroacetyl chloride was added to the reaction mixture, it was stirred for 3-6 h at rt. The progress of reaction was monitored by TLC (Hexane: EtOAc; 7:3). After completion, the reaction mixture was poured into cold water. The compound was precipitated out. This was filtered and washed with water. The precipitate was dried and recrystallized by using ethanol as solvent. The product was obtained as solid powder.

Azide Synthesis (general procedure): A solution of sodium azide in 5 mL of water was added to a solution of the corresponding halogen derivative (1mmol) in 10 mL of methanol, and the mixture was refluxed for 4–5 h. The mixture was evaporated under reduced pressure, and the residue was extracted with methylene chloride. Evaporation of the extract under reduced pressure gave pure azide.

One-pot synthesis of 1,2,3-triazole-4-carboxylates derivatives (general procedure): 2-azido-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide (10mmol), was added in 12 mL of DMSO. The suspension was stirred at room temperature for 4 h, 5 g of potassium carbonate and 16 mmol of ethyl acetoacetate were added, and the mixture was stirred at 55–60°C for 10 h. It was then cooled to 5°C, 20 mL of water was added, and the mixture was extracted with 30 mL of methylene chloride. The extract was dried over sodium sulfate, and the solvent was evaporated

Synthesis of 2-chloro-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide(3):
Colorless solid, Yield 62-78%, Melting point 370.15^{0}c
^{1}H NMR (400 MHz,) δ: 11.49 (1H, s)7.80 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.25-7.24 (1H, m), 6.09 (2H, m).
^{13} C NMR (101 MHz, DMSO): 164.32, 157.80, 142.16, 130.81, 129.68, 125.48, 124.86, 60.90
IR (neat): 686, 722, 849, 1025, 1140, 1264, 1327, 1442, 1572, 1657, 3354
Mass (m/z): 235.03 (M+Z)
Elemental Analysis: C, 50.54; H, 3.39; Cl, 14.92; N, 17.68; O, 13.46.
Synthesis of 2-azido-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide(4):
Colorless liquid, Yield 62-78%.

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^{1}H NMR (400 MHz,) δ: 11.49 (1H, s)7.80 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.25-7.24 (1H, m), 6.09 (2H, m).
^{13} C NMR (101 MHz, DMSO): 164.32, 157.80, 139.12, 130.81, 129.68, 125.48, 124.86, 65.78.
Mass (m/z): 245.18(M+Z).
Elemental Analysis: C, 49.18; H, 3.30; N, 34.41; O, 13.10.

Synthesis of ethyl 4-methyl-1-(2-oxo-2-((5-phenyl-1,3,4-oxadiazol-2-yl)amino)ethyl)-1H-1,2,3-triazole-5-carboxylate (8a):
Yellow liquid, yield 56-60%, Melting point 42-45^{0}c.
^{1}H NMR (400 MHz,) δ 12.01 (1H, s), 7.80 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.25-7.24 (1H, m), 6.09 (3H, m), 5.18-5.10 (2H, m), 2.26 (3H, s), 1.06-0.97 (2H, m).
^{13} C NMR (101 MHz, DMSO): 173.60, 164.32, 157.80, 144.14, 130.81, 129.68, 125.48, 124.86, 61.97, 13.82, 10.63.
Mass (m/z): 357.15 (M+Z).
Elemental Analysis: C, 53.93; H, 4.53; N, 23.58; O, 17.96.

Synthesis of ethyl 4-ethyl-1-(2-oxo-2-((5-phenyl-1,3,4-oxadiazol-2-yl)amino)ethyl)-1H-1,2,3-triazole-5-carboxylate(8b):
Yellow liquid, Yield 52-55%, Melting point 53-52^{0}c
^{1}H NMR (400 MHz,)δ: 12.12 (1H, s), 7.80 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.25-7.24 (1H, m), 6.09 (3H, m), 5.18-5.10 (2H, m), 4.12-3.96 (2H, m) 2.15 (2H, s), 1.11-0.87(6H, m).
^{13} C NMR (101 MHz, DMSO): 175.40, 164.32, 157.80, 144.14, 130.81, 129.68, 125.48, 124.86, 62.97, 13.82, 12.95, 11.68.
Mass (m/z): 371.16 (M+Z).
Elemental Analysis: C, 55.13; H, 4.90; N, 22.69; O, 17.28.

Synthesis of ethyl 1-(2-oxo-2-((5-phenyl-1,3,4-oxadiazol-2-yl)amino)ethyl)-4-(trifluoromethyl)-1H-1,2,3-triazole-5-carboxylate(8C):
White liquid, Yield 42-45%, Melting point 58 - 59^{0}c.
^{1}H NMR (400 MHz) δ: 14.54 (1H, s), 7.80 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.25-7.24 (1H, m), 6.09 (3H, m), 5.18-5.10 (2H, m), 1.07 – 0.98 (3H, m).
^{13} C NMR (101 MHz, DMSO): 180.90, 164.32, 157.80, 149.28, 130.81, 129.68, 125.48, 124.86, 65.13, 13.82.
Mass (m/z): 411.16(M+Z).
Elemental Analysis: C, 46.84; H, 3.19; F, 13.89; N, 20.48; O, 15.60.

IV. CONCLUSION

In summary, the azido group in organic substrates are effectively served in the synthesis of various heterocycles through different mechanistic steps, such as one-pot reactions, nucleophilic additions (such as Aza-Michael addition), cycloaddition reactions (such as [3+2] cycloaddition), mixed addition/cyclization/oxygen, and insertionreactions of C-H amination. The selectivity of the chosen catalyst plays an important role in the chemoselectivityfavoring C−H and C-N bonds, as it can beseen that organic azideshave been used in the synthesis of various types of natural products producing good to excellent yields.

SOME OF THE ADVANAGES FROM THE ABOVE RESULTS

a) using DBU gives highest yield of chloroacetamide derivatives.
b) we get highest yield without column chromatography
c)operation simplicity
d)mild experimental condition

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