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Synthesis of Mixed Heterocycles from Terephtalic Acid †

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Abstract: The mixed heterocycles of the type Triazole, Thiadiazole, Oxazoles are very interesting chemical compounds in scientific research because of their potential of application in different fields, for this reason their synthesis has become a very important subject. Our work aims to synthesize a new series of mixed heterocycles from terephthalic acid, which can be easily converted to monoalkyl terephthalate with good yields, via a two-step procedure. Treatment of monoalkyl terephthalate with $SOCl_2$ provides methyl terephthalaoyl chloride, which reacts with thiosemicarbazide to give methyl 4-(2-carbamothioylhydrazine-1-carbonyl)benzoate, which is then used to synthesize the 1,2,4-triazole and 1,3,4-thiadiazole heterocycles.

Keywords: Terephtalic acid ; 1,2,4-triazole ; 1,3,4-thiadiazole ; mixed heterocycles

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1. Introduction

Particular attention has recently been paid to the synthesis of heterocyclic compounds with a broad spectrum of biological activity, including antibacterial, antifungal and other properties.

The 1,2,4-triazole and 1,3,4-thiadiazole ring system has attracted a lot of attention to this class of heterocycles as many of them possess biological activities.[1]

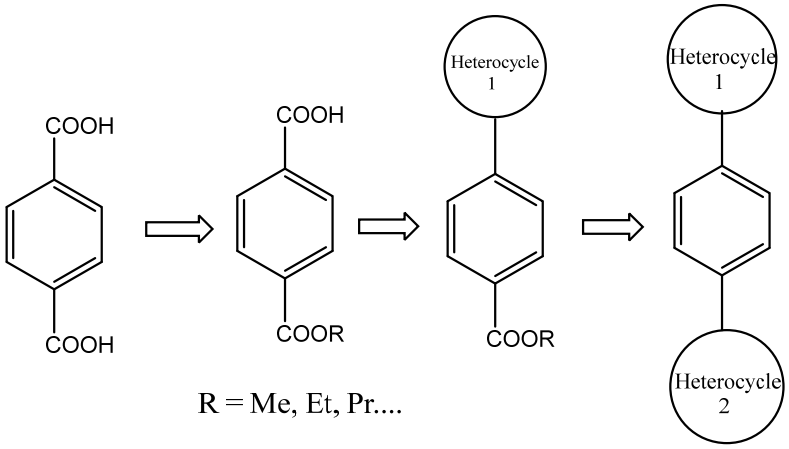
For example, some of the 1,2,4-Triazole derivatives were reported to possess anti-inflammatory [2], antiviral [3], analgesic [4], antimicrobial [5–7], anticonvulsant [8] and antidepressant activity [9]

In this context we report the synthesis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives from terephthalic acid converted to monoalkyl terephthalate, a procedure already described in the literature.

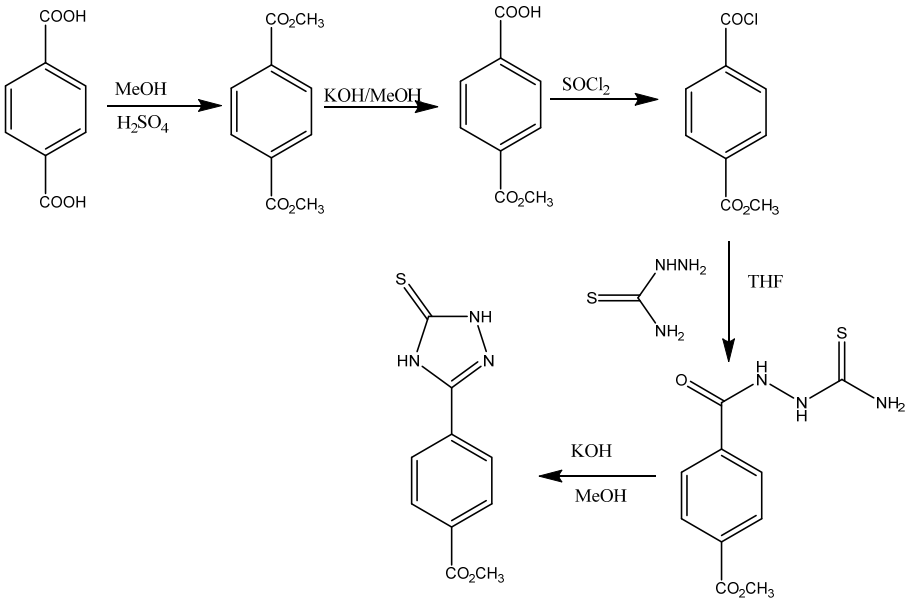
2. Results and Discussion

Our aim is to synthesise a new series of mixed heterocycles from terephthalic acid using simple and rapid strategies.

Terephthalic acid can be easily converted into the corresponding monoalkyl tereph thalate in high yield using a two-step procedure.The first step: esterification of the acid in methanol with a catalytic amount of acid. yields exceed 90% [10]. The second step: preparation of terephthalic acid monoester from an easy-to-perform hydrolysis, using a solution of potassium hydroxide in the corresponding alcohol.[11] Triazole was synthesised by forming methyl terephthaloyl chloride, prepared from monoalkyl terephthalate and thionyl chloride. The yield was excellent and ranged from 95% to 98% [10]. The method used consisted of reacting methyl terephthaloyl chloride with thiosemicarbazide in THF. the product obtained was treated with a solution of freshly prepared sodium methalonic methylate to give the 1,2,4-triazole (schema 2) [10].



Scheme 1.: representing the synthesis strategy for mixed heterocycles.



Scheme 2. Synthetic pathway for the preparation of methyl 4-(5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzoate.

3. Conclusions

In the present studies, we opted for the study of mixed nitrogen heterocycles. more particularly the derivatives of the 1.2.4 Triazole family because of their chemical and biological importance. in perspective we will focus on the study of mixed heterocycles by finding new synthesis routes from a diacid, namely terephthalic acid. The originality of our work consists of synthesizing different mixed heterocyles same molecule which is terephthalic acid

4. Experimental

4.1. Synthesis of Dimethylterephthalate

Terephthalic acid (7 g, 0.04 mol), methanol (150 mL) and H2SO4 (5 mL) were heated under reflux for 4 h. Solid NaHCO3 was added to neutralise the acid to pH 7 and filtered. The filtrate was evaporated to dryness under vacuum to give colourless crystalline dimethyl terephthalate (8,64g, 97%). M.p.140 °C (lit. 141–142 °C).[10].

4.2. Synthesis of Monoalkyl Terephthalate

To the starting diester (5 mmol, 0.97), 30 mL of methanol,and the mixture was heated for 15 min. Potassium hydroxide (1 eq, 0.28g) was poured into the solution, and then the mixture was heated for 3.5 h underreflux. The mixture was cooled, and the alcohol was evaported.The resulting crude product was dissolved in water and extracted with di chloromethane. The aqueous layer was acidified with concentrated hydrochloric acid. The precipitate was then filtered to give a white solid (0.82g, 60%). M.p. 226 °C (lit. 130 °C)[11].

4.3. Synthesis of Methyl Terephthaloyl Chloride

Monoalkyl terephtalate (0.50 g, 0.01 mol) and thionyl chloride (15 mL) were heated under reflux for 5 h until the acid was dissolved completely, after the completion of the reaction (verified by TLC analysis). Excess reagent was removed under vacuum to give the methyl terephthalaoyl chloride as white solid (0.54g,92%). M.p. 62 °C

4.4. Synthesis of methyl 4-(2-carbamothioylhydrazine-1-carbonyl)benzoate

Methyl terephthalaoyl chloride (2 g, 0.01 mol), THF (30 mL) and thiosemicarbazide (1 g, mol) was added over a period of 15 min with an aid of stirring at room temperature. Stirring continued at room temperature for 24 h when the colour of the solution changed to green. The aqueous solution of sodium bicarbonate 3% (100 mL) was added dropwise while stirring to give a solid precipitate. Filtered to give white solid(1,34g, 51%). M.p.266 °C ν_{max} 3259,16 (NH), 1671.89 (CO), 1630 (CN) and 1300 (C=S).

4.5. Synthesis of methyl 4-(5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzoate

methyl 4-(2-carbamothioylhydrazine-1-carbonyl)benzoate (0.1 g) was added to freshly prepared sodium methoxide in methanol (Na 0.15 g, 0.006mol, 10 mL of methanol) was added thereto and heated to reflux. for 8 h. The solvent was removed in vacuo, water (20 mL) was added carefully and the mixture was acidified with hydrochloric acid. The precipitate formed is filtered to give a solid which recrystallized from methanol to give a white solid (0.04g, 59,70%), M.p.270 °C ν_{max} 3129.46 (NH), 1697.05 (C=O), 1588.27 (C=N) and 1416 (C=S).

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Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

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