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International journal of Advanced Biological and Biomedical Research

Volume 1, Issue 11, 2013: 1364-1367

Synthesis of 2-Amino-4hydroxy-1H-pyrrole-3-carbonitrile from Glycine under Microwave Irradiation

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ABSTRACT

Reaction of Glycin with Malononitrile afforded respective Pyrrole. Pyrrole is one of the heterocyclic compounds with very important biological activities. Heterocycles are extremely important because of their wide range of applications that goes from their use as pharmaceuticals and agrochemicals to dyestuffs and additives. In this view, it was proposed to synthesize pyrrole-3-carbonitrile derivative. An efficient one-step protocol has been developed to make new molecules of this family. An expeditious synthesis of derivatives pyrrole has been developed by reacting Malononitrile and Glycine derivatives using a microwave. The structures of synthesized were assigned on the basis of IR and 1H NMR spectroscopy data.

Keywords: Glycine, Malononitrile, Pyrrole.

1. INTRODUCTION

N-Heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores (Gribble *et al.*, 1996). In these heterocycles, the pyrrole ring is one of the most fundamental. Pyrrole derivatives are considerable attention of synthetic importance and extensively used in drug discovery (Toja *et al.*, 1987) and pharmacological activity such as anti-inflammatory (Joseph *et al.*, 1985), cytotoxicity (Dannhardt *et al.*, 2000; Khanna *et al*., 1997), *in vitro* cytotoxic activity against solid tumour models (Burnham *et al*., 1998; Gupton *et al*., 1999), treatment of hyperlipidemias (Justin *et al*., 2004), antitumour agents (Krowicki *et al.*, 1998). The pyrrole containing heterocyclic derivatives have been reported in synthetic and effective biological importance (Almerico *et al*., 1998; Carpio *et al*., 1982)**.** Pyrrole derivatives have biological activity such as COX-1/COX-2 inhibitors (Dannhar *et al.*, 2000) and cytotoxic activity against a variety of marine and human tumor models (Evans *et al.*, 2003). The reaction of Malenonitrile with Glycine in the presence of piperidine was carried out, and the results were reported (Scheme *1)*.

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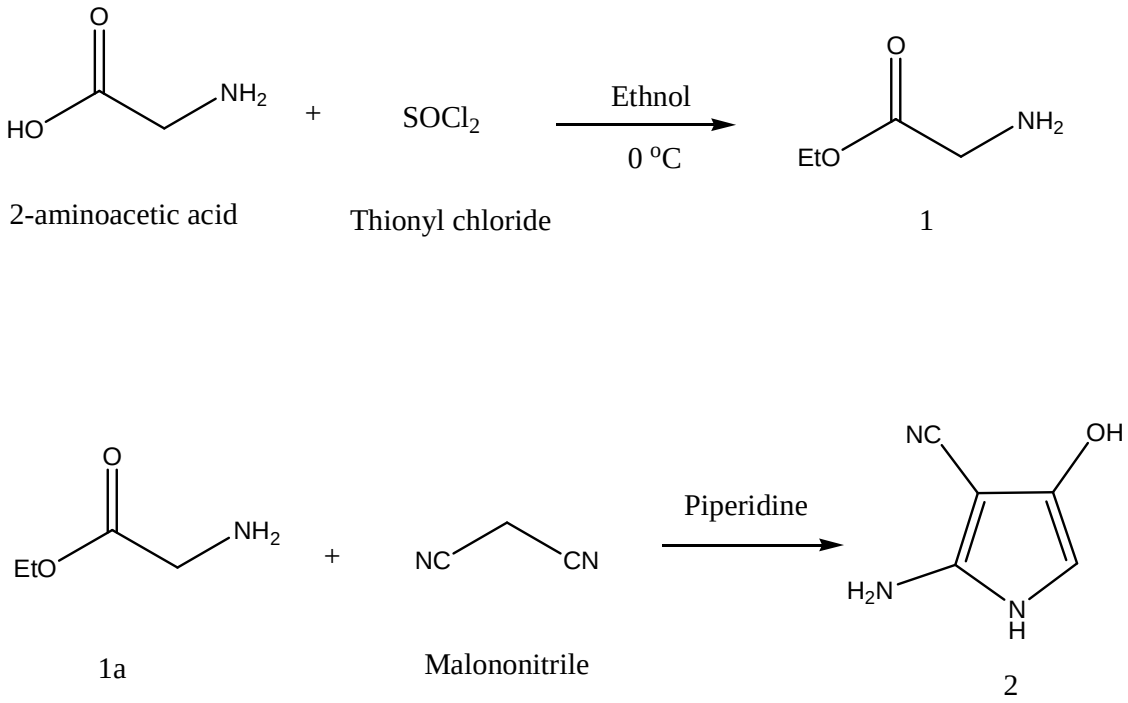

Figure 1. One-pot preparation ethyl 2-aminoacetate from glycine and reaction of malononitrile.

2. MATERIALS AND METHODS

2.1. General Procedure

Glycine, Ethanol, malononitrile, Thionyl chloride, Piperidine were obtained from Merck Chemical Company and used without further purification. IR spectra were recorded using KBr pellets on a Bruker IR spectrophotometer. 1H and 13C NMR spectra were recorded on a Bruker 400 Avance instrument (at 400 and 100 MHz, respectively) with DMSO and CDCl3 as solvent and TMS as internal reference.

2.2. Preparation of 1 product

Glycin (4.5gm, 6m mol) was dissolved in 10ml ethanol and the solution was cooled to 5ºC. An excess thionyl chloride (2.5ml) was added dropwise with continuous stirring, during which the temperature of the reaction mixture was kept below 10ºC. The mixture was then refluxed for more than 4hrs. The hydrochloride form of the product precipitated after slow addition of diethylether with stiring. The salt was collected by suction filtration, washed with diethylether and dried in vacuo. The product is white crystalline; 78.62 % of chemical yield; m.p 185 ^{o}C.

2.3. Preparation of Compound 2

A mixture of compound 1 (2.00 mmol), Malononitrile (2.00 mol), and 3 drops of piperidine was heated in the microwave oven at 360 W for 8 minute. The combination produced was filtered off and then washed thoroughly with a mixture of 1:1 hexane-ethylacetate.

3. RESULTS AND DISCUSSION

Compound **2** were prepared from reaction of compound **1** and Malononitrile under microwave irradiation. The main step in this reaction is NH_2 attack to CN group. The hydrogens between the two CN groups are acidic enough, can attack the carbonyl group of Glycine and the ester group is removed. The proposed structures of 1and 2 products were supported by their spectroscopic data, such as IR, 1H NMR and 13C NMR spectra. For example, IR spectrum of **1** shows one peak for carbonyl groups. The carbonyl group reveals a strong band at 1748 cm^{-1}.

4. Spectral Data

Ethyl 2-aminoacetate.

White powder, yield 78.62%, m.p. = 185 ^{0}C, IR (KBr) (νmax, cm^{-1}): 1748, 2929 and 3343
^{1}H NMR: δ 1.22 (3H, $^2J_{HH}$ = 16 Hz), 3.71 (2H, s, CH_2), 4.17 (2H, $^2J_{HH}$ =24 Hz), 8.51(NH_2).
^{13}C NMR: δ 13.9, 44.2, 61.3, 168.1.

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White powder, yield 62.24%, m.p. = 192 ^{0}C, IR (KBr) (νmax, cm^{-1}): 2254, 2950, 3164, 3355, and 3409.
^{1}H NMR: δ 5.01(OH), 7.34 (1H, s, arom), 8.16 (s, 2H, NH_2), 8.82 (s, 1H, NH).
^{13}C NMR: δ 108.21, 109.56, 116.35, 118.24, 119.32.

5. CONCLUSION

The reaction of compound **1** with Maleonitrile under microwave irradiation give compound **2**. The main step in this reaction is NH_2 attack to CN group. The hydrogens between the two CN groups are acidic enough, can attack the carbonyl group of Glycine and the ester group is ejected. Compounds 1 and 2 were obtained with good yield.

ACKNOWLEDGMENT

The authors are grateful to Islamic Azad University, Kerman Branch for financial assistance of this work.

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