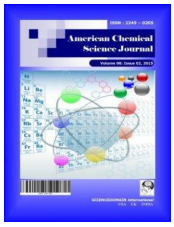

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Regioselectivity in the Multicomponent Reaction of 5-aminopyrazoles, Meldrum's Acid and Triethyl Orthoformate

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Authors' contributions

This work was carried out in collaboration between all authors. Author KUS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AMAH and AMNE managed the analyses of the study. Author MMI managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

A regioselective multicomponent synthesis of pyrazolo[1,5-a]pyrimdines-7(4H)-ones 5 is reported. The reaction proceeded regioselectively via initial Michael addition of exocyclic amino function to the intermediately formed 5-ethoxymethylene Meldrum's acid followed by a ring opening of Meldrum's acid and subsequent ring closure with the ring nitrogen. The regioselectivity of the reaction was confirmed by the isolation and characterization of the Michael adduct.

Keywords: Multicomponent reactions; regioselectivity; pyrazolo [1; 5-a] pyrimdines.

1. INTRODUCTION

Several pyrazolo[1,5-a]pyrimdine derivatives are of considerable interest in fields related to biological and medicinal activities [1-3]. Pyrazolo [1,5-a] pyrimdines possess a broad spectrum in the field of medicinal chemistry as selective cox-2 inhibitors [4], benzodiazepine receptor

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antagonists and estrogen receptor antagonists [5]. Also, as a purine analogous, they possess a wide range of biological activities [6]. Condensed pyrazoles are generally obtained by reaction of amino pyrazoles with 1,3-bifunctional reagents [7].

Multicomponent reactions have attracted a great attention as safe, high yielding, environmentally benign and high diversity protocol for the synthesis of complex molecules utilizing readily available starting materials [8].

3(5)-amino pyrazoles are very attractive scaffold for the study of multicomponent heterocyclization since there is possible diversity to introduce several substituents in the pyrazole ring [9]. In addition, it is well established that 5-aminopyrazoles have non-equivalent nucleophilic reaction centers which can lead to the formation of several different cyclic reaction products [10]. It is worth mentioning that selectivity in multicomponent reactions still unresolved issue whether it is chem- or regioselective or both due to the several possible reaction pathways which resulted in the formation of different reaction products.

The multicomponent reaction of 5-amino pyrazoles, Meldrum's acid and aromatic aldehydes was reported to afford several different of fused pyrazoles. Thus, in an early reported [11], the reaction of the three components in methanol afforded mainly the corresponding 4,5-dihydro-1H-pyrazolo[3,4-b]pyridines. This finding was later supported by other authors. Specifically, those researchers conduct the multicomponent reaction in ethanol at 80ºC in the presence of catalytic amount of L-proline [12]. Very recently [13], a multicomponent, regioselective, synthesis of dihydropyrazolo[1,5-a]pyrimidines is reported via reaction of aminopyrazole CAN508 with meldrum's acid and aldehydes. The reaction proceeds regioselectivity via the initial addition of the exocyclic amino function to arylidine

Meldrum's acid followed by ring opening and recyclization. The structure of the end product was established based on x- ray crystallography [13]. It is worth to mention that, there are only few articles concerning multicomponent reaction of amino pyrazoles, cyclic active methylene compounds, aldehydes or ortho-esters in which the arylidine or ethoxymethylene component react with exocyclic amino function instead of the endocyclic nucleophilic centers [14]. To the best of our knowledge, the isolation and characterization of the formed Micheal adduct has not been reported in literature.

2. EXPERIMENTAL

2.1 Materials and Equipment

All reagents and solvents were commercially available and used without further purification. Melting points were measured on Gallenkamp melting point apparatus and are uncorrected. 1H-NMR (400 MHz) and 13C-NMR (100MHz) spectra were measured on a Bruker DPX instrument with DMSO as solvent and TMS as internal standard. Chemical shifts are expressed as δ in ppm. Coupling constants (J) are given in Hertz (Hz).

2.2 General Procedure for the Synthesis of Copounds 4a-e

A solution of 5-aminopyrazoles (1, 0.01mol), Meldrum's acid (2, 0.01 mol) and triethyl orthoformate (3, 0.01 mol) in 45 dioxane (10 ml) was left at ambient temperature (25ºC) overnight. The solid formed was collected by filtration and crystallized from ethanol to afford analytically pure sample.

Compounds 4a-e were newly synthesized. Compounds 4a: mp 358-360ºC. 1H-NMR (DMSO-d6): 1.69 (s, 6H), 2.58 48 (s, 3H), 7.47 (s, 1H), 7.48-7.58 (m, 2H), 7.96 (d, J = 7.6 Hz, 2H), 8.79 (d, J = 14 Hz, 1H), 12.37 (d, J = 14 Hz, 1H), 13.3 49 (br, S, 1H). 13C-NMR (DMSO-d6): 9.01, 26.58, 88.49, 104.67, 121.68, 124.91, 129.35, 130.52, 137.95, 143.47, 150.26, 50 151.69, 162.46, 163.82.

A solution of 4a-e in dioxane (10 ml) was heated under reflux for 12 hrs. After being cooled to room temperature, the 52 solid product formed was collected by filtration and crystallized from ethanol to afford analytically pure sample of 5a-e. The same products could be obtained via heating under reflux equimolecular amounts of 1a-e, 2 and 3 (0.01 mol) in 54 dioxane for15 hrs. Compound 5a: mp: 258-260ºC. 1H-NMR (DMSO-d6): 2.12 (s, 3H), 6.14 (d, J = 10 Hz, 1H), 6.18 (s, 55 1H), 8.49 (m, 5H), 11.0 (S, 1H). m/z = 253.

3. RESULTS AND DISCUSTION

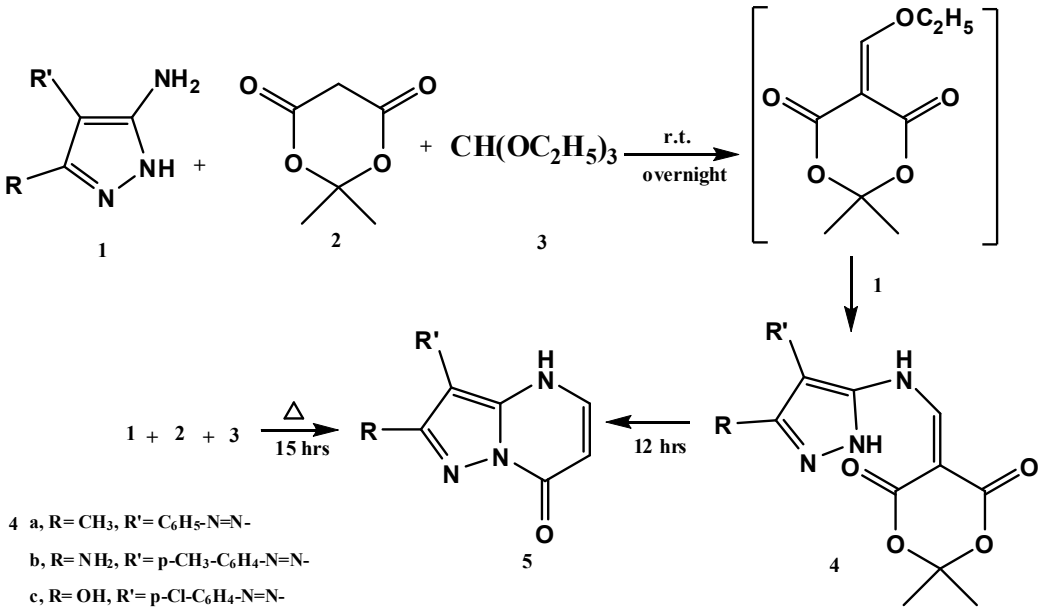
In continuation of our studies in which we perform multicomponent reaction for the

synthesis of fused heterocycles [15-17] we reported herein the results of our investigation concerning the regioselectevitiy in multicomponent reaction 59 of 5-amino pyrazoles 1, Meldrum's acid 2 and triethyl orthoformate 3 in dioxane at ambient and refluxing temperatures.

We began this study by reacting 5-amino pyrazole (1a) and Meldrum's acid (2) with triethyl orthoformate (3) in dioxane at ambient temperature overnight. The precipitate solid product was isolated in 92% yield. The mass spectra of the reaction product showed a molecular ion peak m/z = 355.3 (35%). The 1H-NMR revealed absorption bands at δ = 1.69 (s, 6H), 2.58 (s, 3H), 7.47 (s, 1H), 7.48-7.58 (m, 2H), 7.96 (d, J = 7.6 Hz, 2H), 8.79 (d, J = 7.6 Hz, 2H), 12.37 (d, J = 14 Hz, NH), 13.3 (br, S, 1H, NH). The acyclic intermediate 4a was established as the reaction product and 13C- NMR was in agreement with the proposed structure.

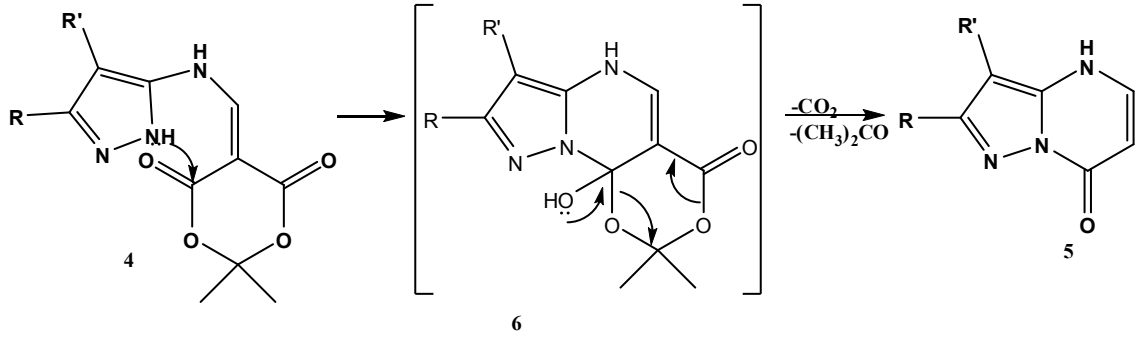
We went on to study the scope of such protocol with several substituted 5-amino pyrazoles, Meldrum's acid and triethyl orthoformate under the same reaction conditions. Thus, reaction of 1b-e, 2 and 3 afforded the corresponding acyclic adducts 4b-e. We have attempted the cyclization of 4a-e via heating under reflux in dioxane for 12 hours. The cyclization occurred smoothly and the corresponding dihydropyrazolo[1,5-a]pyrimidine-7(4H)-one 5a was obtained in excellent yield. The structure proposed for the reaction product was established based on the analytical and spectral data. Compound 5a was also directly obtained via a multicomponent reaction of 1a, 2, 3 in dioxane at reflux for 15 hours (Scheme 1).

Similarly, compounds 5b-e were obtained under the same experimental conditions in high yields. The mechanism for the cyclization of 4a-e was depicted in scheme 2.



Scheme 1: multicomponent synthesis of pyrazolo[1,5-a]pyrimdines-7(4H)-ones

Scheme 1. Multicomponent synthesis of pyrazolo[1,5-a]pyrimdines-7(4H)-ones



Scheme 2: The proposed mechanism for the formation of pyrazolo[1,5-a]pyrimdines

Scheme 2. The proposed mechanism for the formation of pyrazolo*[1; 5-a] pyrimdines*

4. CONCLUSION

In conclusion, we have developed an efficient regioselective synthesis of dihydropyrazolo[1,5-a]pyrimidines via multicomponent reaction of 5-aminopyrazoles, Meldrum's acid and aromatic aldehydes. The regioselectivity of the reaction could be confirmed via isolation and characterization of the acyclic intermediate formed via condensation of exocyclic amino function with ethoxymethylene Meldrum's acid.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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