Synthesis of a highly functionalized thiohydantoin derivative from Vilsmeier–Haack reaction

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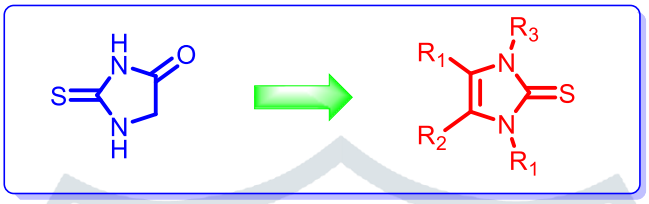
Abstract:



Highly functionalized thiohydantoin derivatives were achieved by an efficient Vilsmeier-Haack reaction of 2-thiohydantoin and propargylation of the corresponding product. The products were obtained in good yields with ease which were further characterized by NMR, IR and ESI-HRMS spectroscopy.

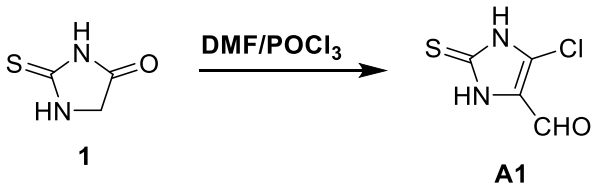
Keywords: Propargylation, Vilsmeier-Haack, 2-thiohydantoin, Chloroformylation, DMF

Introduction

2-thiohydantoin scaffold is one among the diversely active moiety that potentially act as anticarcinogenic, antimutagenic, antiviral, human immunodeficiency virus, tuberculosis and antimicrobial agents.[1-8] Thiohydantoins are sulfur analogs of hydantoin (2,4-imidazolidinediones) with one of the carbonyl group being replaced as thiocarbonyl group. Many reviews on the chemistry of hydantoins including thiohydantoins have been published based on its considerable biological activities in various fields. Henceforth, development of novel approaches for the preparation of 2-thiohydantoin fused heterocycles are of immense potential and many synthetic routes are known in literature till date. The Vilsmeier-Haack reagent is an efficient mild reagent used for the formylation of reactive aromatic and heteroaromatic substrates. It's used as a most versatile synthetic tool for the construction of many heavily functionalized heterocyclic compounds. Moved by these results we report a simple protocol for the synthesis of chloroformyl derivatives of 2-thiohydantoin (**Scheme 1**).

Results and discussions

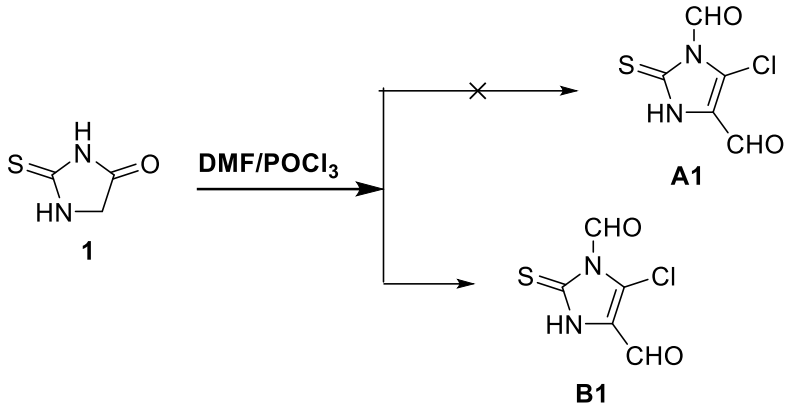
A Vilsmeier-Haack reaction with 2-thiohydantoin (**1**) was proposed to achieve the desired chloroformyl derivative of 2-thiohydantoin (**Scheme 1**).



Scheme 1. Synthesis of chloroformyl derivative of 2-thiohydantoin.

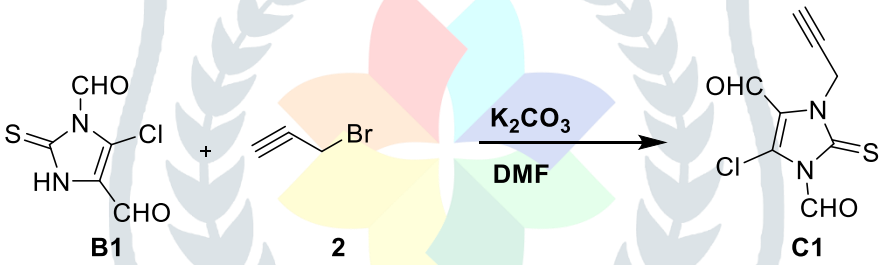
We initiated the reaction by adding two equivalence of dimethylformaide (DMF) and 3 equivalence of phosphorous oxychloride ($POCl_3$) to form the Vilsmeier adduct. Then, 2-thiohydantoin (**1**) (1 equivalence) was added to the formed adduct which was refluxed at 75 °C over 8 hours. After cooling to ambient temperature it was poured into ice. But, the reaction failed to give the desired product (**Scheme 1**). After many trails it was decided to increase the formation of the Vilsmeier adduct to achieve the product and the DMF/$POCl_3$ was added in 3:7 ratio with 2-thiohydantoin (**1**) in one equivalence. Later, the reaction mixture

was left standing in ice for 2 hours. A brown needle like precipitate started to appear which on collection by filteration and further purification and subsequent characterization by NMR led to be scaffold **B1** (**Scheme 2**) instead of product **A1**. Notable changes in the yield of the products were not observed even on repeating the reaction and increasing the equivalence of the adduct didn't increase the yield too. The reaction condition was optimised as mentioned above.



Scheme 2. Synthesis of 5-chloro-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde **B1**.

Based on the above results it is understood that excess of Vilsmeier adduct in the reaction made the reaction to cause the N- formylation along with the chlorformylation of the 2-thiohydantoin (**1**). Encouraged by this result, we tried to increase the functional groups on this dreivative. Hence, we did proporgylation of the **B1** derivative under room temperature with propargylbromide (**2**) in DMF (**Scheme 3**) and this reaction yielded **C1** in good amount.



Scheme 3. Synthesis of 5-chloro-3-(prop-2-yn-1-yl)-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde **C1**.

Conclusion

Thus, we have synthesized a highly functionalized thiohydantoin derivartive with an aldehyde functional group to make the incorporation of the thiohydantion easy into other heterocycles to enrich their biological activity.

Experimental Section

All reactions required normal experimental conditions. The required chemicals were procured from Sigma Aldrich, Avra synthesis and utilized as such. DMSO-d_6 was procured from Sigma Aldrich. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra for the synthesized molecules were recorded at room temperature on a Bruker 400 MHz spectrometer using the internal standard tetramethylsilane (TMS, $\delta = 0$). Mass spectra for the synthesized molecules were recorded on an Agilent 1200 LC/MS-6110 mass spectrometer.

5-chloro-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde (B1)

A round-bottomed flask containing 0.3 ml (3mmol) of DMF was set at ice cold temperature. To that was added 0.7 ml (7 mmol) of $POCl_3$ dropwise with constant stirring. 117 mg of 2-thiohydantoin (**1**) was added (1 mmol) into RBF then later shifted to reflux at 75 ^{0}C for about 8 hours. Then the reaction mixture was poured into ice. The resulting brown needle like crystals was collected and washed with water to yield 70% of product. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 9.89 (s, 1H), 8.59 (s, 1H) ppm; **^{13}C NMR** (100 MHz, DMSO-d_6) 182.4, 161.0, 153.1, 142.1, 130.4 δ ppm. HRMS (ESI) Calcd for $C_5H_3ClN_2O_2S$ $[M + H]^+$ 190.9574 amu, obs 190.9574 amu.

5-chloro-3-(prop-2-yn-1-yl)-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde (C1)

Into a RB flask was added 190 mg of **B1** was added in DMF (1 mmol) along with 0.1 ml (1.5 mmol) of propargylbromide (**2**), and 278 mg K_2CO_3 (2 mmol). This was left to stir at room temperature for 12 hours and then reaction mixture was poured into crushed ice. A white precipitate resulted which was collected and washed with water to yield 85 % of product. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.89 (s, 1H), 4.9 (d, 2H), 3.0 (s, 1H) ppm; **^{13}C NMR** (100 MHz, DMSO-d_6) δ 182.0, 163.1, 152.6, 141.4, 131.3, 77.9, 75.4, 36.3 ppm. HRMS (ESI) Calcd for $C_8H_5ClN_2O_2S$ $[M + H]^+$ 228.9760 amu, obs 228.9760 amu.

Acknowledgement

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Supplementary data

Fig S1: ^{1}H, ^{13}C spectrum of 5-chloro-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde **(B1)**

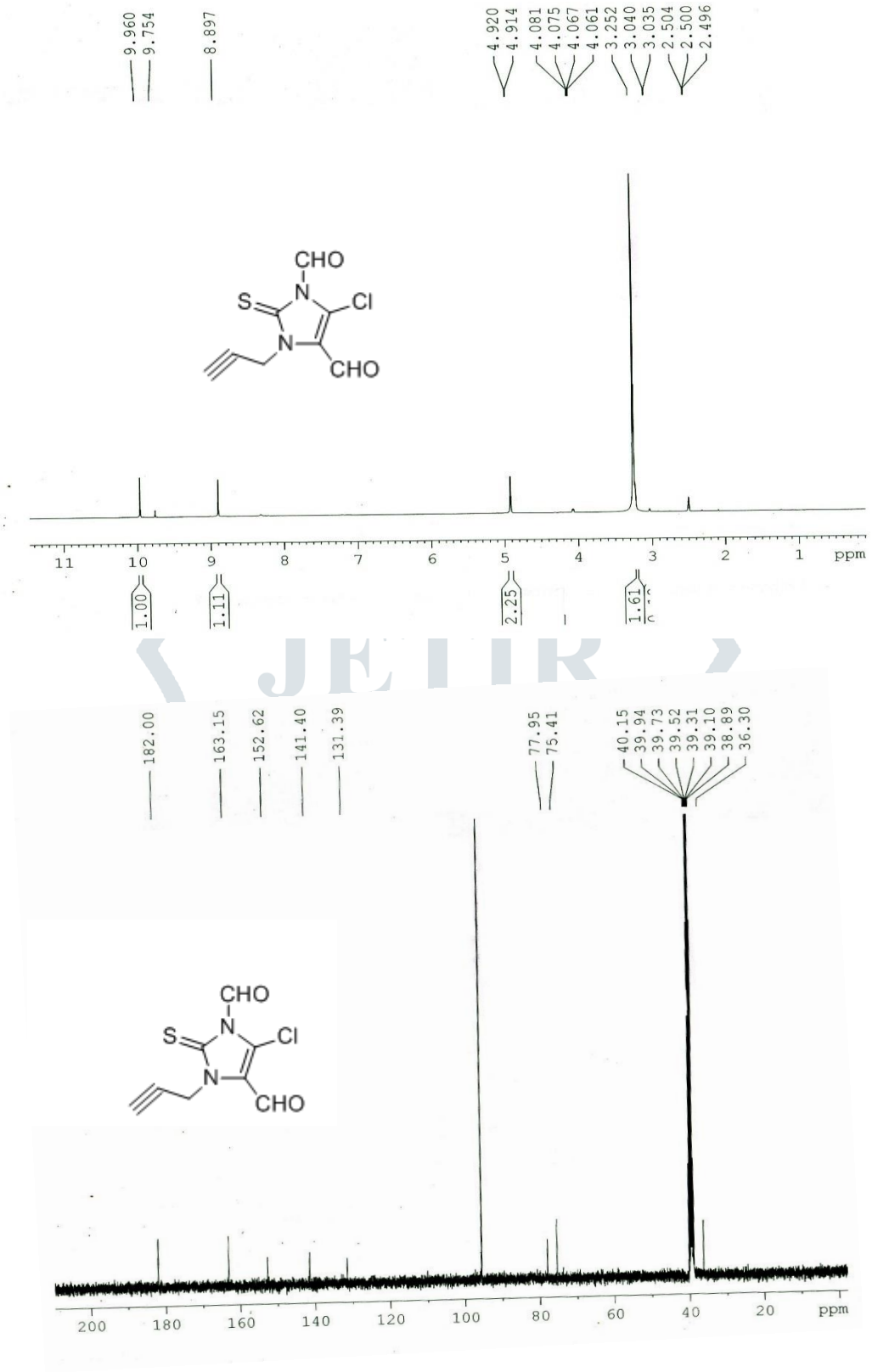

Fig S2: ^{1}H, ^{13}C spectrum of 5-chloro-3-(prop-2-yn-1-yl)-2-thioxo-2,3-dihydro-1H-imidazole-1,4-dicarbaldehyde **(C1)**