Investigation into the reaction optimization studies for the synthesis of 1,3-Dicyclohexylbarbituric acid

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Abstract: Barbituric acid and its derivatives have biological, industrial and pharmaceutical importance. 1,3-Dicyclohexylbarbituric acid (1,3- DCBA) has antineoplastic properties. In the present work the reaction optimization studies for 1,3-Dicyclohexylbarbituric acid from Malonic acid are carried out by varying different conditions.

Key words: Antineoplastic, Barbituric acid, 1,3-Dicyclohexylbarbituric acid and reaction optimization.

INTRODUCTION

Cancer is one of the most lethal diseases globally. In the quest for new anticancer agents, a range of innovative hybrid molecules has been developed by using barbituric acid derivatives. Barbituric acid is scientifically referred to as pyrimidine-2,4,6-(1H,3H,5H)-trione. It comprises five heteroatoms (three oxygen and two nitrogen) and is commonly recognized as barbiturates [1]. It was first synthesized by Adolf Von Baeyer in 1864 through the reaction of urea and malonic acid [2].

Barbituric acid and its derivatives serve as versatile components in numerous compounds, demonstrating significant utility across biological, industrial, and pharmaceutical domains. Its most used application is being its sedative effects on the central nervous system [3]. The derivatives of Barbituric acid are also favored in medicinal chemistry for their roles as anticonvulsants, sedatives, hypnotics, and anxiolytics.[4]

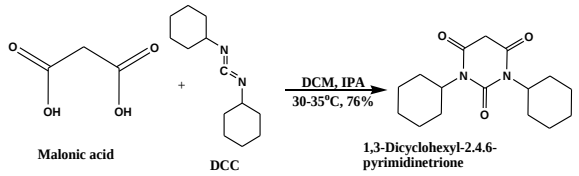
Phenobarbital a derivative of Barbituric acid is used in the management of specific types of epilepsy. It is derived from the original barbital and features two distinct substituents at the C-5 position [2].

The potential for double functionalization at the C-5 position of barbituric acid has facilitated the creation of various spiro-compounds, leading to more rigid structures including nucleotide mimics, inhibitors of matrix metalloproteinases (MMP), and anticancer agents [3-7]. On the other hand the synthesis of fused bicyclic derivatives has resulted in compounds with either antidiabetic [8] or antituberculosis properties [9].

1,3-Dicyclohexylbarbituric acid (1,3-DCBA) is a cytotoxic compound that interacts with DNA and suppresses protein synthesis. Research has demonstrated its efficacy against human carcinoma cells both in vitro and in vivo. As a highly effective antineoplastic agent. Antineoplastic agents or anticancer drugs are a diverse array of therapeutics. While their applications are somewhat limited, they hold significant importance in the cancer treatment. However, these agents can sometimes lead to considerable liver toxicity. Nearly all antineoplastic agents exhibit some level of hepatotoxicity, primarily resulting from direct or intrinsic toxicity [10-11].

In addition to medicinal chemistry, the photophysical characteristics of barbituric acid derivatives have been harnessed for applications in colorimetric and thermal detection, yielding promising dyes and fluorogenic probes [12-13]. The diverse properties of the products derived from barbituric acid have inspired organic chemists to delve into its chemistry [15-18]. Various barbiturate derivatives linked to aryl hydrazone moieties have been explored as urease inhibitors, showcasing their design and synthesis potential. [16-19]

In literature a number of methods for the synthesis of Barbituric acid and its derivatives are available [20-21]. But, in most of the synthesis reactions either the reaction conditions used are not mild or final yield of the product is very low. Therefore, owing to the importance of synthesis of barbituric acid derivatives, the present work aims towards the investigation and optimization of reaction parameters for the synthesis as well as improved yield and quality of 1,3-Dicyclohexylbarbituric acid (1,3-DCBA).



Scheme 12: Synthesis of 1,3-Dicyclohexylbarbituric acid from Malonic acid.

Attempts were made towards the synthesis of 1,3-Dicyclohexylbarbituric acid by reacting Malonic acid with N, N- Dicyclohexylcarbodiimide.

A range of reaction parameters was changed, including the type and amount of solvent (w/v), the reaction temperature (°C), the duration of the reaction (h), and the solvent employed for crystallization.
The data for these reactions are summarized in Table.

Table: Variation of reaction parameters for the synthesis of 1,3-Dicyclohexylbarbituric acid.

S. No.	Solvent used for reaction	Quantity of solvent	Reaction temperature (°C)	Reaction time (h)	Solvent used for crystallization	% Yield
1	THF	10 vol.	20-25	2	Ethanol	71.4
2	DCM	10 vol.	20-25	2	Ethanol	69.4
3	DCM	10 vol.	20-25	2	Methanol	67.6
4	DCM	10 vol.	20-25	2	Isopropyl alcohol	70.3
5	DCM	12 vol.	20-25	2	Ethanol	71.2
6	DCM	12 vol.	20-25	2	Methanol	69.2
7	DCM	12 vol.	20-25	2	Isopropyl alcohol	72.1
8	DCM	16 vol.	10-15	2	Ethanol	71.6
9	DCM	16 vol.	10-15	2	Methanol	70.4
10	DCM	16 vol.	10-15	2	Isopropyl alcohol	70.1
11	DCM	16 vol.	20-25	2	Ethanol	73.2
12	DCM	16 vol.	20-25	2	Methanol	69.4
13	DCM	16 vol.	20-25	2	Isopropyl alcohol	74.4
14	DCM	16 vol.	20-25	0	Ethanol	71.0
15	DCM	16 vol.	20-25	0	Methanol	70.2
16	DCM	16 vol.	20-25	0	Isopropyl alcohol	74.8
17	DCM	16 vol.	20-25	2	Ethanol	73.1
18	DCM	16 vol.	20-25	2	Methanol	71.0
19	DCM	16 vol.	20-25	2	Isopropyl alcohol	75.2
20	DCM	16 vol.	20-25	4	Ethanol	73.2
21	DCM	16 vol.	20-25	4	Methanol	71.2
22	DCM	16 vol.	20-25	4	Isopropyl alcohol	75.1
23	DCM	16 vol.	20-25	8	Ethanol	73.1
24	DCM	16 vol.	20-25	8	Methanol	71.1
25	DCM	16 vol.	20-25	8	Isopropyl alcohol	75.0
26	DCM	16 vol.	30-35	2	Ethanol	74.3
27	DCM	16 vol.	30-35	2	Methanol	73.8
28*	DCM	16 vol.	30-35	2	Isopropyl alcohol	76.5
29	Toluene	15 vol.	20-25	2	Isopropyl alcohol	50.0

EXPERIMENTAL

General: Melting points (°C) (m.p) were taken in open capillaries are uncorrected. Infrared spectra (IR) were recorded using Perkin Elmer Model 1430 spectrophotometer with potassium bromide (KBr) palette. Only principle absorption bands of interest are reported and expressed in cm^{-1}. NMR spectra were recorded using BRUKER AVANCE II 400(500MHz). Chemical shifts are given in ppm relative to tetramethyl silane as an internal standard (δ= 0 ppm) for ^1H NMR spectra.

Preparation of 1,3-Dicyclohexylbarbituric acid from Malonic acid: A solution of N, N-Dicyclohexylcarbodiimide (0.254 g; 1.23 mmol) in anhydrous THF (5 mL) was slowly added dropwise to a cold (0ºC) solution of malonic acid (0.11 g; 61.0 mmol) in anhydrous THF (5 mL). The mixture was stirred at r.t. for 2 h and filtered to give a yellow solid. The yellow solid was taken in ethanol (10 ml) and refluxed for 30 minutes in alcohol. The mixture was then allowed to cool to r.t. and filtered to obtain a pale-yellow solid which was washed with cold ethanol (2 x 5 mL) to give an off white solid 1,3-Dicyclohexyl-2.4.6-pyrimidinetrione (0.510 g, 71.4%), m.p. 200-203ºC.

^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.16 - 1.25 (m, 1 H) 1.29 - 1.38 (m, 2 H) 1.60-1.67 (m, 3H), 1.81 - 1.84 (m, 2 H), 2.20 - 2.29 (m, 2 H), 3.59 (s, 2 H), 4.55 - 4.62 (m, 2 H).

IR (KBr, cm^{-1}): 1743.09 (C=O), 1695.07 (C=O), 1677.77 (C=O), 2932.78 (CH stretching).

Preparation of 1,3-Dicyclohexylbarbituric acid from Malonic acid: A solution of N, N-Dicyclohexylcarbodiimide (0.254 g; 1.23 mmol) in anhydrous dichloromethane (10 mL) was slowly added dropwise to a cold (0ºC) solution of malonic acid (0.11 g; 61.0 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at 20-25ºC for 2 h and filtered to give a yellow solid. The yellow solid was taken in ethanol (10 ml) and refluxed for 30 minutes in alcohol. The mixture was then allowed to cool to r.t. and filtered to obtain a pale-yellow solid which was washed with cold ethanol (2 x 5 mL) to give an off white solid 1,3-Dicyclohexylbarbituric acid (0.495 g, 69.4%), m.p. 200-202ºC.

Preparation of 1,3-Dicyclohexylbarbituric acid from Malonic acid: A solution of N, N-Dicyclohexylcarbodiimide (0.254 g; 1.23 mmol) in anhydrous dichloromethane (16 mL) was slowly added dropwise to a cold (0ºC) solution of malonic acid (0.11 g; 61.0 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at 30-35ºC for 2 h and filtered to give a yellow solid. The yellow solid was taken in ethanol (10 ml) and refluxed for 30 minutes in alcohol. The mixture was then allowed to cool to r.t. and filtered to obtain a pale-yellow solid which was washed with cold isopropyl alcohol (2 x 5 mL) to give an off white solid 1,3-Dicyclohexylbarbituric acid (0.546 g, 76.5%), m.p. 200-204ºC.

Preparation of 1,3-Dicyclohexylbarbituric acid from Malonic acid: A solution of N, N-Dicyclohexylcarbodiimide (0.254 g, 1.23 mmol) in anhydrous toluene (16 mL) was slowly added dropwise to a cold (0ºC) solution of malonic acid (0.11 g, 61.0 mmol) in toluene (5 mL). The mixture was stirred at r.t. for 2 h and filtered to give a yellow solid. The yellow solid was taken in ethanol (10 ml) and refluxed for 30 minutes in alcohol. The mixture was then allowed to cool to r.t. and filtered to obtain a pale-yellow solid which was washed with cold toluene (2 x 5 mL) to give an off white solid 1,3-Dicyclohexyl-2.4.6-pyrimidinetrione (0.357 g, 50%), m.p. 200-203ºC.

RESULTS AND DISCUSSION

In the present investigation, various methodologies were examined for the synthesis of 1,3-Dicyclohexylbarbituric acid, employing Malonic acid as a precursor. A range of reaction parameters was meticulously varied, including the type and quantity of solvent, reaction temperature (°C), reaction duration (h), and the solvent used for crystallization. It was noted that an increase in the polarity of the solvents utilized for crystallization led to a reduction in the yield of the final product. Conversely, an increase in the weight ratio of the solvent resulted in an enhancement of the final product yield. Furthermore, extending the reaction time from 2 hours to 8 hours did not affect the yield of the final product, 1,3-Dicyclohexylbarbituric acid.

CONCLUSION

The results obtained indicate that the optimal solvent for this synthesis is Dichloromethane at a volume by weight ratio of 16 v/w, conducted at a temperature

range of 30-35°C for a duration of 2 hours. Isopropyl alcohol was utilized as the crystallization solvent, resulting in a final yield of 76.5%.

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