Comparison of Amino Acid-Catalyzed Reaction Options for the Knoevenagel Condensation.

by

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Dedication

This thesis is dedicated to my aunt, my uncle, and my grandmother who have always reminded me I could do whatever I set my mind to.

Acknowledgements

I would like to thank my thesis director, Dr. Scott Handy, who has mentored me in organic synthesis for over a year and has taught me organic chemistry for two. His guidance has been crucial to my development as a student, researcher, and chemist.

Additionally, I would like to thank the Undergraduate Research Center directed by Dr. Jaime Burriss for funding my research projects and for its community of researchers on campus that has always encouraged me.

Abstract

The Knoevenagel condensation reaction is a classic condensation reaction that is frequently utilized in the production of fluorescent probes important to biological and disease research. Piperidine is the most common catalyst, although a few reports have used amino acids, particularly glycine. Amino acid catalysts are less toxic than piperidine, can efficiently catalyze condensations without need for isolation separation, or purification, and will not interfere with photophysical or biological studies. The amino acid-catalyzed option has been examined more closely, with a focus on glycine, histidine, arginine, or prolinate. Reaction rates and product yields have been compared across several reactions. The presence of histidine resulted in faster reaction rates across several reactions as compared with the presence of glycine, while prolinate best catalyzed reactions using less acidic active methylene compounds.

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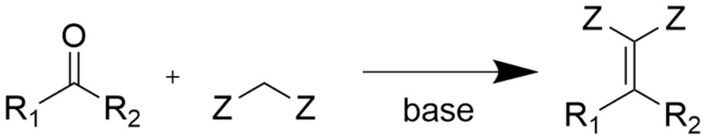


Figure 1. General Scheme of Knoevenagel Condensation.

The Knoevenagel condensation is a reaction widely used in industry for the synthesis of chemical intermediates for polymers, pharmaceuticals, cosmetics, and perfumes.[1] This reaction forms α,β-unsaturated compounds from active methylene compounds (AMC) and carbonyl compounds in the presence of a basic catalyst. [1] In active methylene compounds, the methylene group is acidic due to its location between two electron-withdrawing groups (represented by Z) and is reactive with the basic catalyst. The basic catalyst that is used to promote this reaction is typically piperidine or pyrrolidine dissolved in a volatile organic solvent.[2] The generally accepted mechanism seen in Figure 2 begins with the catalyst enolizing the AMC and enabling it to react with the carbonyl compound and undergo condensation to form the unsaturated product.

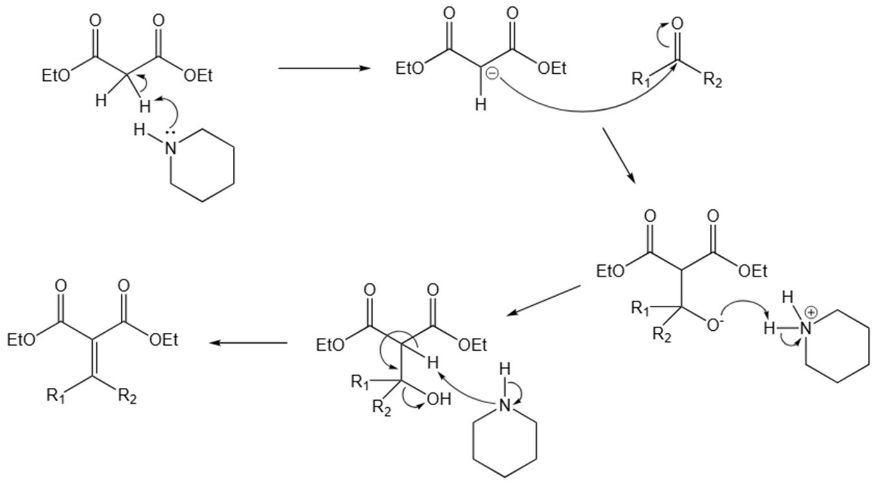


Figure 2. General Mechanism of Knoevenagel Condensation

Beyond piperidine, amino acids have emerged as promising catalysts for this reaction because they are less toxic, less volatile, and more reusable as compared to traditional conditions.[3] Notably, one study has shown that amino acids can function as more effective catalysts in the Knoevenagel condensation than some organic solvents. [3] Several studies have employed modified amino acid catalysts such as nanomaterial-supported systems and metal complexes, as well as amino acid-derived ionic liquids. [4-15] In all these studies, application has been limited to specific families of AMCs, without attempts at application across a broad range of substrates. In addition, there has yet to be any investigation comparing the usage of amino acid catalysts in the synthesis of multiple compounds. Furthermore, amino acid catalysis is particularly favorable for its potential to enable the efficient synthesis of fluorescent probes without the need for isolation, separation, or purification of products for fluorescence testing because, unlike traditional catalysts, most amino acids do not exhibit fluorescence or otherwise interfere with photophysical studies.

Fluorophores are chemicals that exhibit fluorescent properties. Some fluorophores can act as fluorescent probes, organic compounds that fluorescently signal changes in their chemical environment. Moreover, there are an array of fluorescent probes able to detect various chemical factors such as the presence of large biomolecules like proteins, the presence of metal cations, and changes in the pH of a solution.[16] Fluorescent probes are used in, as well as crucial to, biological research focused on medicine and disease during key components of research processes such as drug delivery and live cell imaging due to their high sensitivity, non-invasiveness, and quick response time as a chemical tool.[17]

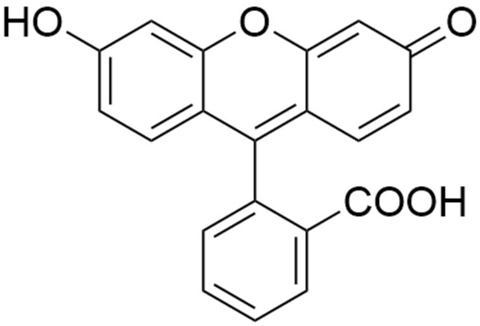


Figure 3. Structure of Fluorescein.

One example of a common pH-sensitive fluorescent probe is Fluorescein (Figure 3). Fluorescein is a chemical often used in ophthalmology for vision testing but can also be used in biomedical research to rapidly visualize biomolecules of interest and associated biological processes.[18] From its structure, key characteristics of typical fluorophore structure can be observed, most notably a highly conjugated, polyaromatic structure with an electron push/pull system propagated by electron-withdrawing groups on one side and electron-donating groups on the other side. These key structural components enable fluorophores to absorb and emit light within the visible spectrum.

In this project, the goal was to develop conditions that would be broad in scope and applicable to a wide range of active methylene compounds, compare catalytic efficiency between amino acids such as glycine and histidine, and employ a simple, inexpensive, and non-toxic catalyst for the efficient synthesis of potential fluorophores.

Results and Discussion

To investigate the catalytic efficiency of glycine compared to histidine, various active methylene compounds (AMC) were reacted with 4-dimethylaminobenzaldehyde in DMSO and in the presence of catalytic (10 mol%) quantities of 1.0M or 0.25M aqueous solutions of glycine or histidine respectively. All reactions were performed at 0.5 mmol scale. Both reaction options were worked up by quenching with water and then filtration of the product when one reaction in the pair appeared to be complete.

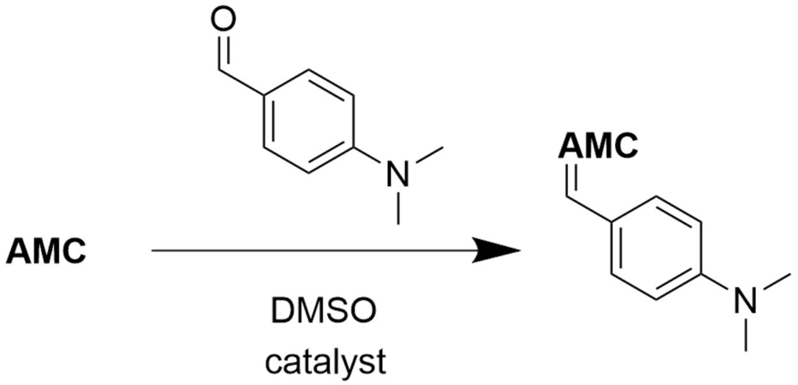


Figure 4. Condensation Reaction Scheme.

Entry	AMC	Time	Glycine Yield	Histidine Yield
1	Malononitrile	1.5h	52%	62%
2	Meldrum's Acid	2.5h	49%	70%
3	1,3-Indanedione	6h	48%	73%
4	Barbituric Acid	1.5h	78%	87%
5	Dimedone	24h	41%	66%

a: The isolated products contain 5-25% unreacted aldehyde.

b: The isolated products contain no unreacted aldehyde.

Table 1. Glycine and Histidine Comparison.

As can be seen in Table 1, the histidine reactions were always faster and resulted in higher yields of the condensation product, likely due to reaction completion. Allowing the glycine-catalyzed reaction conditions to run for a longer time did enable similar product yield once the starting aldehyde was completely consumed.

Figure 5. Structures of Glycine and Histidine in Zwitterionic Form.

Considering the accepted standard mechanism for the Knoevenagel condensation, the improved activity of histidine is logical, given that its zwitterionic form retains a mildly basic imidazole group, while glycine has no such functionality and would be comparably poorly basic or acidic in its zwitterionic form. Since catalysts for the Knoevenagel condensation are generally considered to serve as bases to convert the active methylene compound into a more reactive enolate, improved basicity would logically increase the rate of the reaction. At the same time, attributing the difference in activity to only basicity is inadequate. Indeed, amino acid catalysis of organic reactions has been shown to be attributable to a range of properties, including enolate formation, enhancing the rate of enolization, activation of the electrophilic carbonyl compound via iminium ion formation, or some combination of all of these. [19-21]

Still, the improved conversion with a more basic amino acid provides evidence that enolate formation or at least base-catalyzed enolization is important. Further, all the active methylene compounds in Table 1 are reasonably acidic with pKas around 7 to 8 for meldrum’s acid, 1,3-indanedione, and barbituric acid and around 11 for malononitrile and dimedone. [22-26] As the study was extended to less reactive active methylene compounds, such as benzofuranone, 1-indanone, and 1,2-dimethylpyridinium iodide, reactions did not proceed to completion with either amino acid, even after several days. [27-29] Given the significantly lower acidity of these active methylene compounds, there was a clear limitation to more acidic and more enolizable substrates employing histidine as the catalyst.

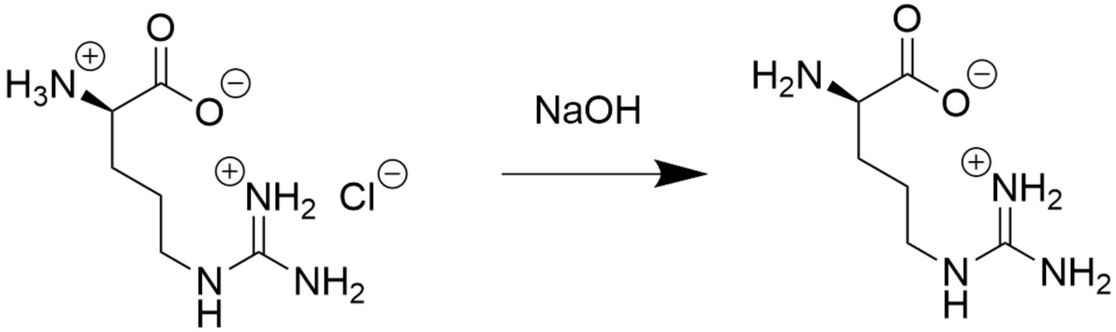


Figure 6. Neutralization of Arginine Hydrochloride

Assuming the basicity of the amino acid catalyst was important for the success of these condensations, arginine was employed. The guanidinium moiety stabilized by resonance on arginine is more basic and would likely act as a better catalyst than the imidazole group with its localized charge on histidine. The commercially available arginine hydrochloride was first neutralized with one equivalent of sodium hydroxide and the resulting solution was added as the catalyst for reactions in DMSO.

Entry	AMC	Time	Yield
1	Benzofuranone	2 days	50%
2	Cyclic malononitrile	5 days	48%
3	Benzothiophenone	5 days	47%
4	1-Indanone	5 days	NR
5	1,2-dimethylpyridinium iodide	5 days	NR

Table 2. Arginine-Catalyzed Reactions.

Not surprisingly, a significant increase in reactivity and expansion of reaction scope was noted. As before, all condensations in Table 2 were run with dimethylamino benzaldehyde. More moderately acidic compounds were able to be condensed, though only with extended reaction times and modest yields. Even then, poorly acidic compounds such as 1-indanone and 1,2-dimethylpyridinium iodide failed to react.

Returning to the various roles that the amino acid catalyst might play in the reaction as well as the form of the amino acid in solution, arginine presumably would exist still in a zwitterionic form, but with the more basic guanidine moiety protonated and the less basic primary amine as a free amine. While this is a stronger base than the imidazole present in histidine, it is also capable of forming imines with the aldehyde. In addition, while iminium ion catalysis has been well documented across chemistry, it is possible that, in this case, it could be preventing or at least slowing the rate of enolization of the active methylene compounds. [19-21] In that case, an amino acid that would not form stable, neutral imines could be a better catalyst. The amino acid that fits this criterion is proline, but as its salt instead of its neutral, zwitterionic form. This salt form closely resembles pyrrolidine, a traditional and successful catalyst for Knoevenagel condensation.

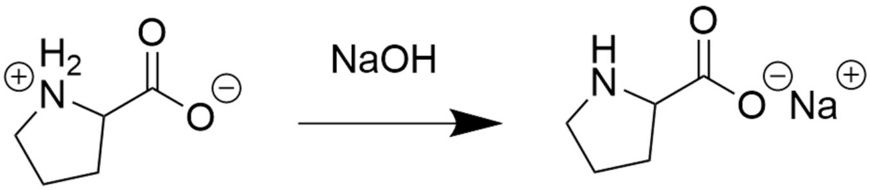


Figure 7. Neutralization of Proline

To explore prolinate, commercially available proline was reacted with one equivalent of sodium hydroxide to form sodium prolinate in water. The resultant solution was then used as a catalyst for reactions between active methylene compounds and dimethylaminobenzaldehyde in DMSO.

Entry	AMC	Conditions/Time	Yield
1	Benzofuranone	RT/2 days	56%
2	Indanemalononitrile	RT/2 days	25%
3	Indanemalononitrile	40°C/2 days	28%
4	1,2-dimethylpyridinium iodide	40°C/24h	47%
5	Thiohydantoin	RT/24h	NR
6	Thiohydantoin	40°C/24h	81%
7	Rhodanine	RT/3 days	87%
8	Rhodanine	40°C/24h	74%
9	Cyclic malononitrile	40°C/24h	72%

Table 3. Prolinate-Catalyzed Reactions.

Figure 8. Structures of Indanemalononitrile (Left) and Cyclic Malononitrile (Right).

Once again, an increase in reactivity and expansion in reaction scope was observed. 1,2-dimethylpyridinium iodide which had failed to react before had now formed product in modest yield while other previously examined compounds such as benzofuranone and cyclic malononitrile experienced increases in product yield. It should also be noted that an increase in temperature for reactions allowed thiohydantoin to react where it had not at room temperature and generally decreased the total reaction time for other active methylene compounds.

In conclusion, comparisons of each amino-catalyzed option for the Knoevenagel condensation have shown that increased basicity of the catalyst has generally resulted in improved catalytic efficiency, likely due to improved enolization of the AMC. Although, sodium prolinate displayed significantly improved catalytic efficiency compared to neutralized arginine hydrochloride despite similar basicity. This difference in efficiency may be due to stable imine formation between the aldehyde and arginine hindering condensation while prolinate would, in contrast, form unstable iminium ions. Also, this prolinate-catalyzed option was generally improved by higher reaction temperatures.

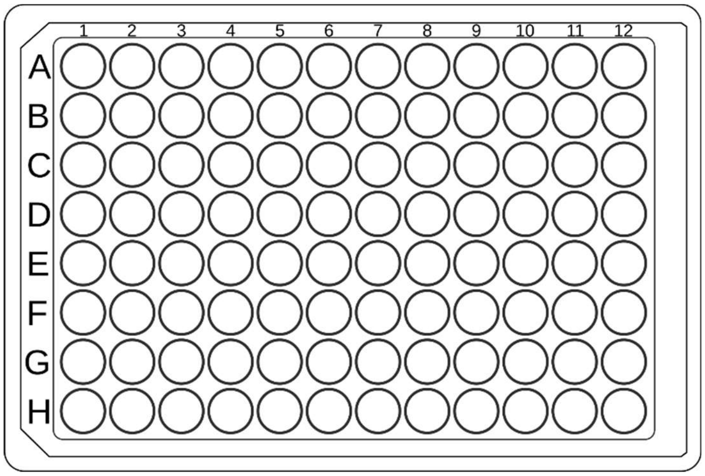


Figure 9. Diagram of UV/Vis Plate.

With this prolinate-catalyzed option, the screening of condensation products for fluorescent properties has been conducted. The prolinate catalyst, which does not exhibit any fluorescence, can be added to a reaction mixture of AMC and aldehyde within the well of a UV/Vis plate to produce potential fluorophores without the need for isolation, separation, or purification. This has enabled rapid fluorescence testing of dozens of novel compounds in response to a variety of chemical factors, with a particular focus on pH.

Experimental

General Experimental

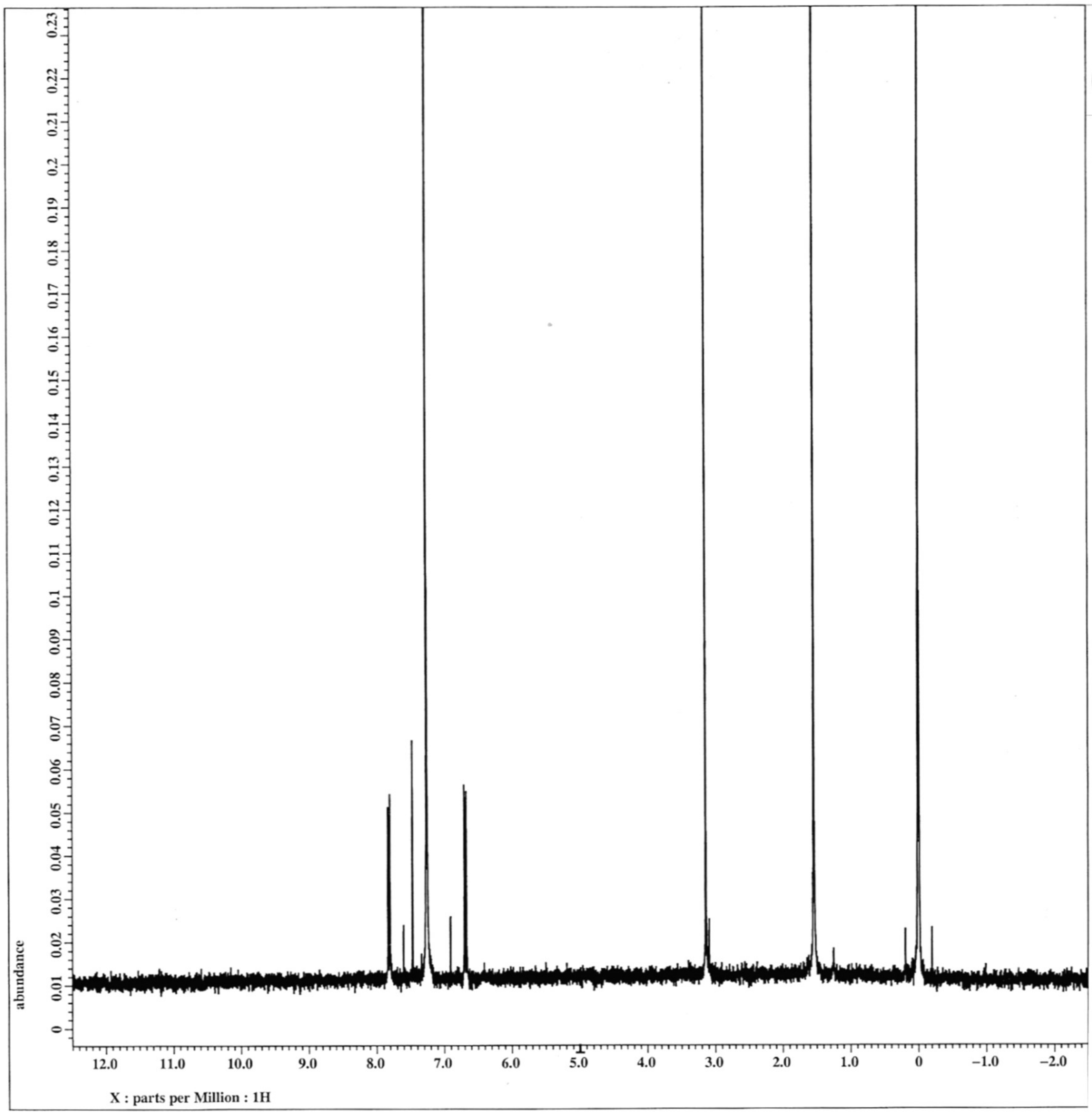
All ^{1}H NMR spectra were recorded on a JEOL AS 300MHz NMR with $CDCl_3$ as the solvent. All chemical shifts are reported in ppm with TMS as the standard. All reagents were ACS grade.

General Procedure for Knoevenagel Condensation Reactions

To a solution of 0.073 g (0.5 mmol) of 4-(dimethylamino)benzaldehyde in 1 mL of DMSO and the indicated catalyst of 0.05 mL of 1.0M glycine in water, 0.2 mL of 0.25M histidine in water, 0.05 mL of 1.0M arginine hydrochloride in water and 0.05 mL of 1.0M sodium hydroxide in water, or 0.05 mL of 1.0M sodium prolinate in water, 0.5 mmol of the active methylene compound indicated was added. The reaction was stirred at room temperature or 40°C for the time specified. Then, the reaction solution was diluted with water to precipitate the product, which was filtered. The resulting solid was left to dry.

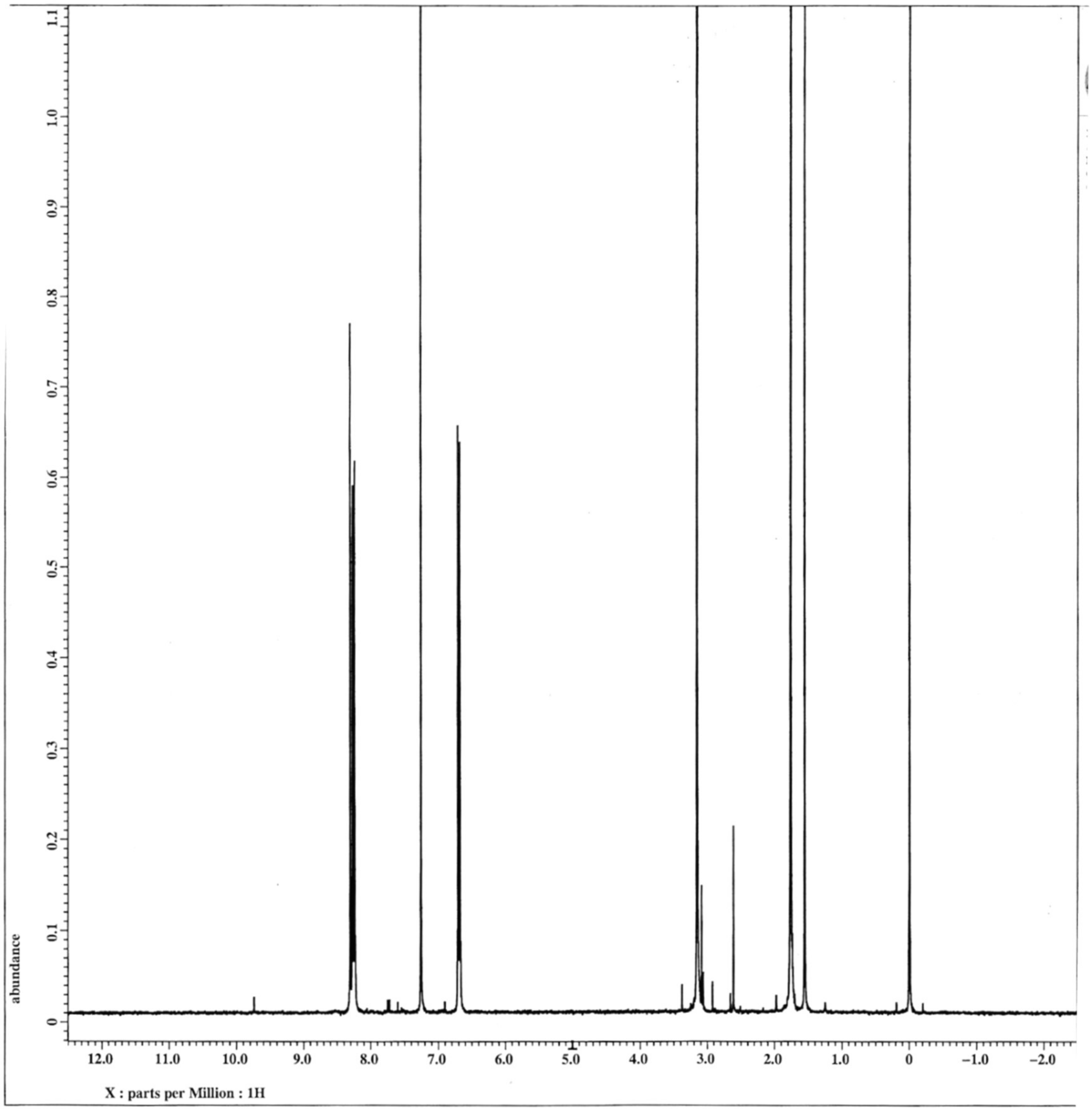
2-(4-(Dimethylamino)benzylidene)malononitrile (Table 1, Entry 1)

0.033g (0.5 mmol) of malononitrile as the active methylene compound and histidine as the catalyst resulted in 0.061g (62%) of the product as an orange solid. ^{1}H NMR (300MHz, CDCl$_3$) δ 7.81 (d, J=9Hz, 2H), 7.47 (s, 1H), 6.69 (d, J=7.2Hz, 2H), 3.09 (s, 6H).



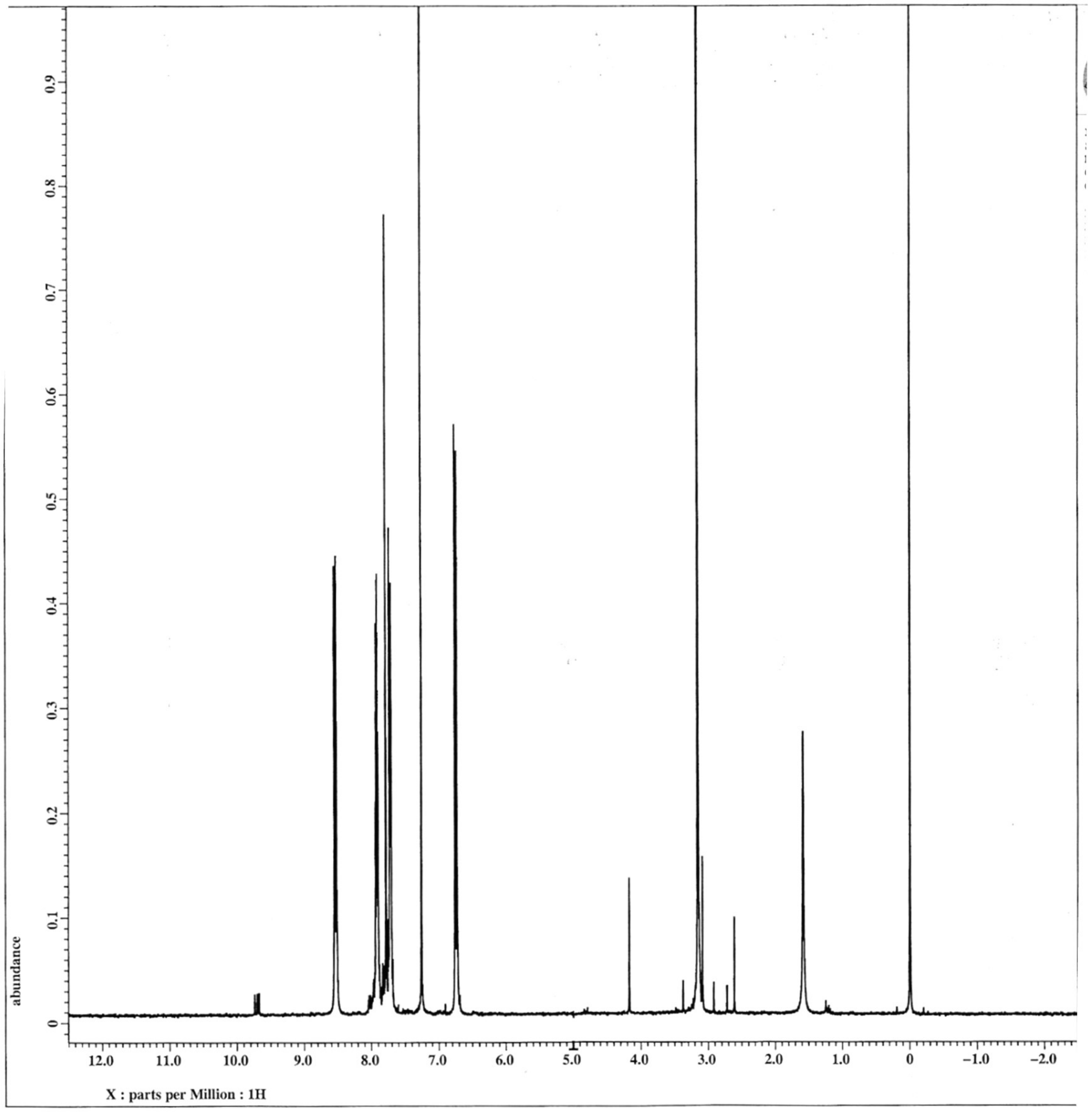
5-(4-Dimethylamino-benzylidene)-2,2-dimethyl-(1,3)dioxane-4,6-dione (Table 1, Entry 2)

0.072g (0.5 mmol) of meldrum's acid as the active methylene compound and histidine as the catalyst resulted in 0.097g (70%) of the product as an orange solid. ^{1}H NMR (300MHz, CDCl$_3$) δ 8.31 (s, 1H), 8.25 (d, J=9.3Hz, 2H), 6.70 (d, J=9.3Hz, 2H), 3.09 (s, 6H), 1.72 (s, 6H).



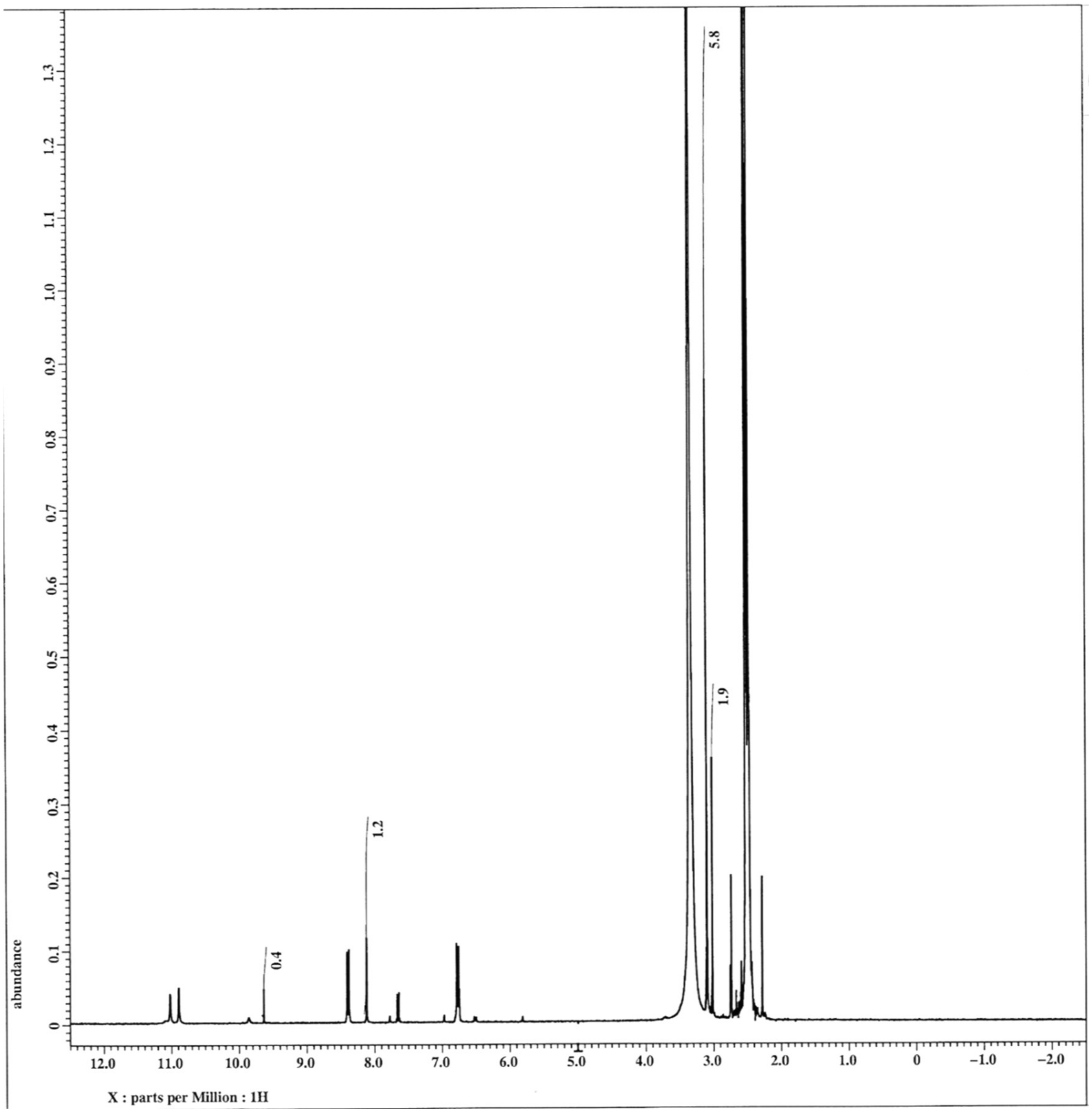
2-(4-(Dimethylamino)benzylidene)-1H-indene-1,3(2H)-dione (Table 1, Entry 3)

0.073g (0.5 mmol) of 1,3-indanedione as the active methylene compound and histidine as the catalyst resulted in 0.102g (73%) of the product as a red solid. ^{1}H NMR (300MHz, CDCl$_3$) δ 8.54 (d, J=9Hz, 2H), 7.92 (d, J=3.6Hz, 2H), 7.79 (s, 1H), 7.72 (d, J=1.8Hz, 2H), 6.75 (d, J=9.6Hz, 2H), 3.09 (s, 6H).



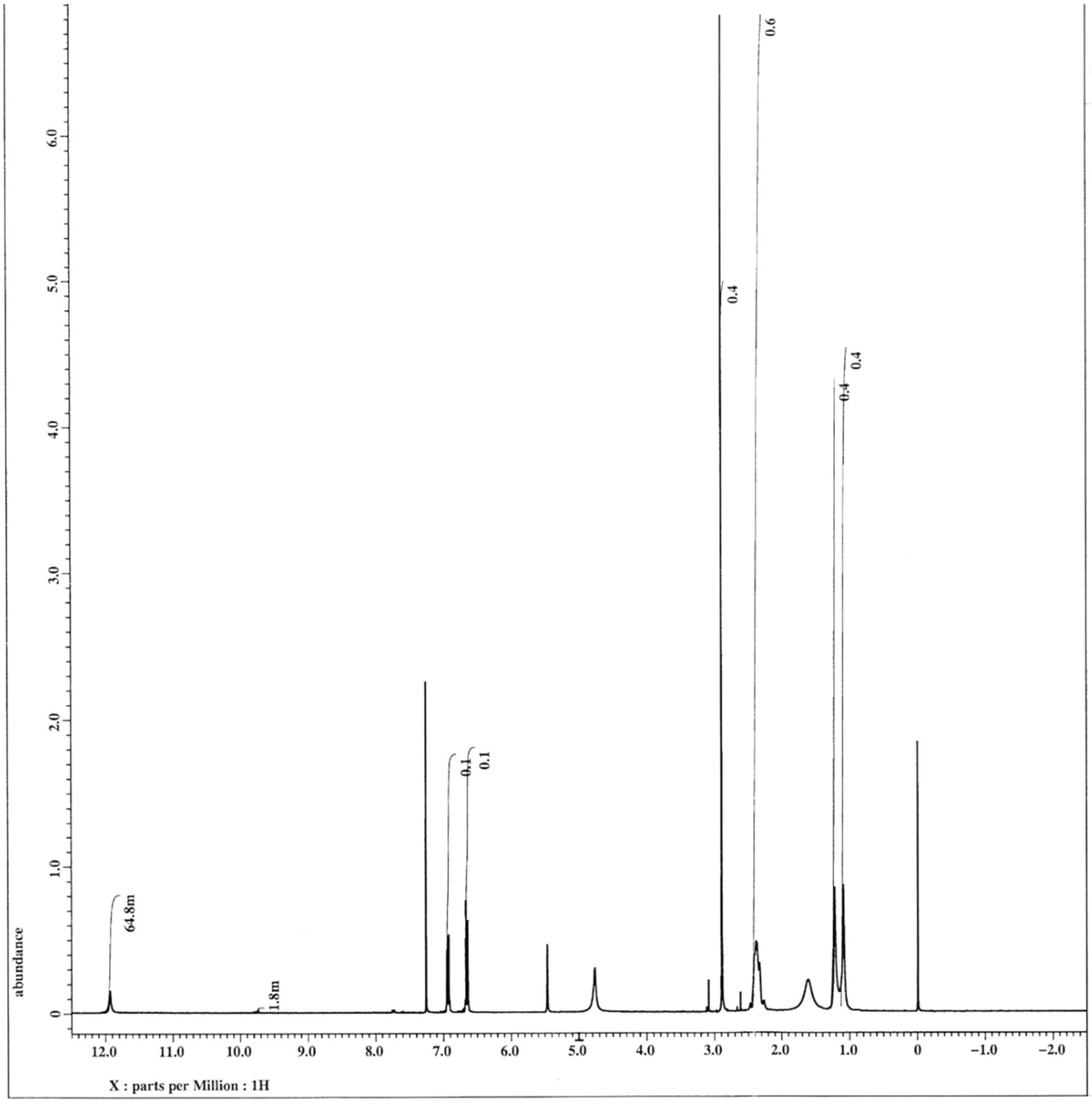
5-((4-(Dimethylamino)phenyl)methylidene)-1,3-diazinane-2,4,6-trione (Table 1, Entry 4)

0.064g (0.5 mmol) of barbituric acid as the active methylene compound and histidine as the catalyst resulted in 0.113g (87%) of the product as a red solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 11.02 (s, 2H), 8.39 (d, J=9.3Hz, 2Hz), 8.12 (s, 1H), 6.76 (d, J=8.7Hz, 2H), 3.09 (s, 6H).



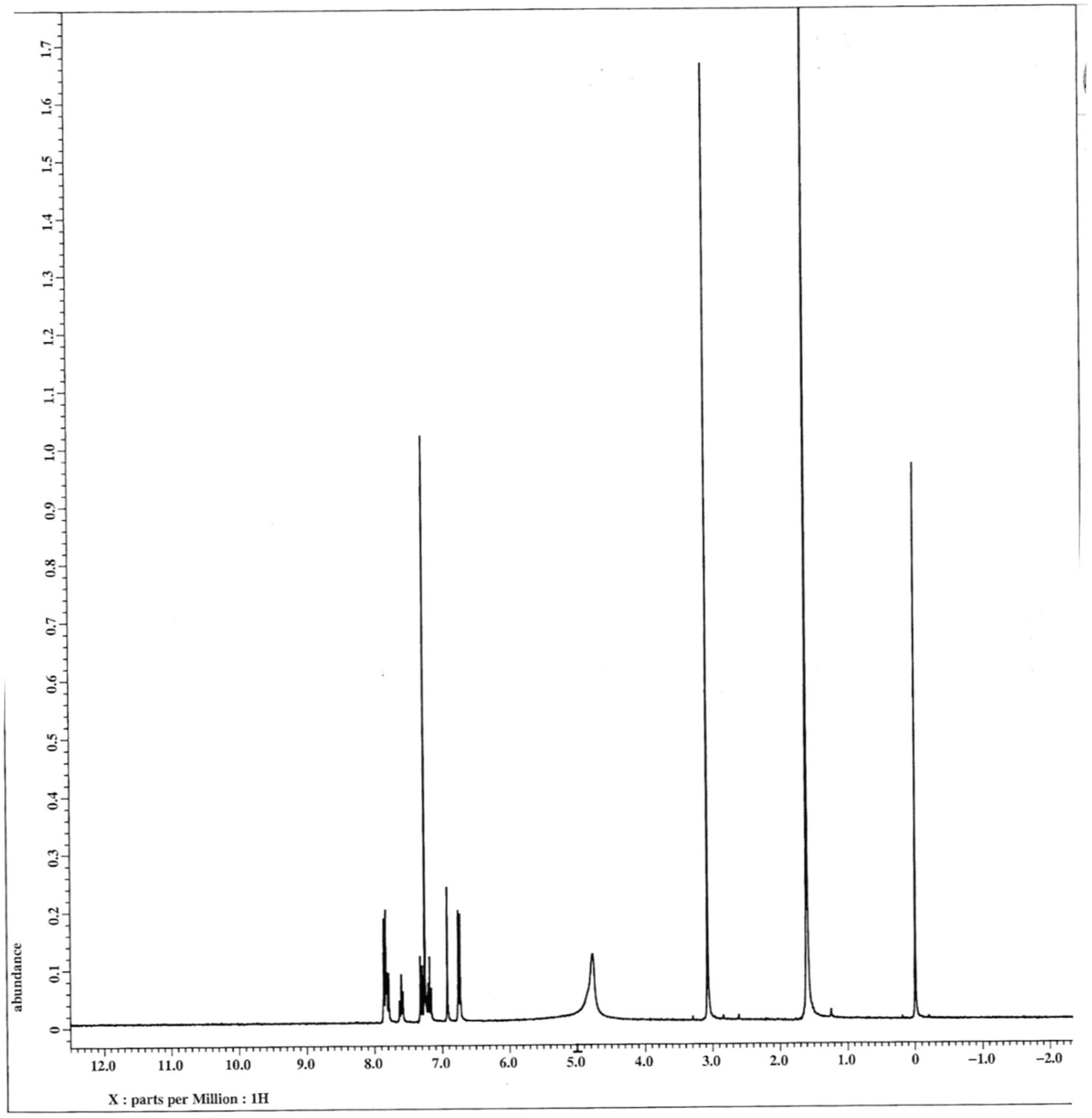
2-(4-(Dimethylamino)benzylidene)-5,5-dimethylcyclohexane-1,3-dione (Table 1, Entry 5)

0.070g (0.5 mmol) of dimedone as the active methylene compound and histidine as the catalyst resulted in 0.090g (66%) of the product as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 6.94 (d, J=8.7Hz, 2H), 6.68 (d, J=8.4Hz, 2H), 5.46 (s, 1H), 2.89 (s, 6H), 2.37 (s, 4H), 1.10 (s, 6H).



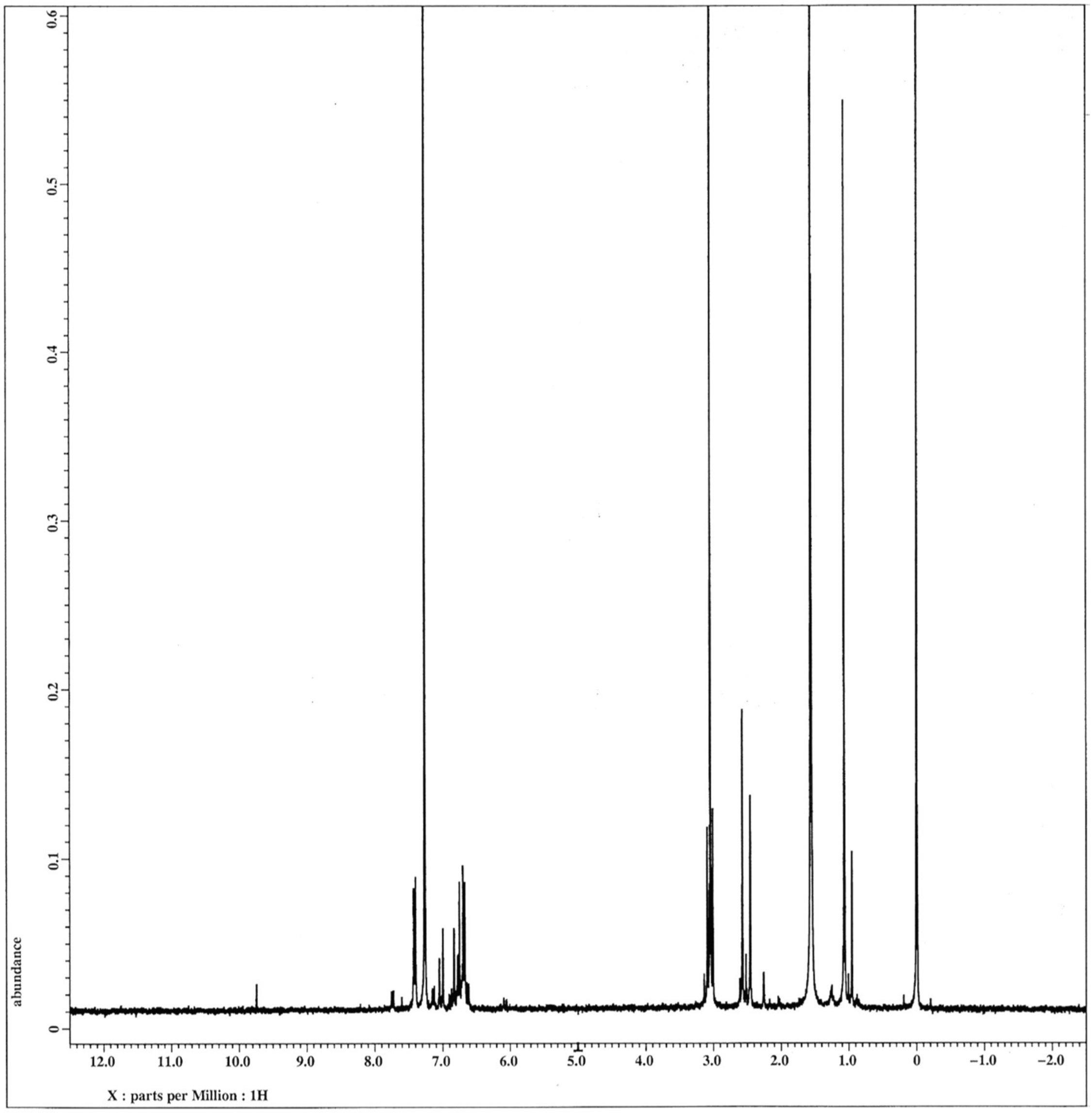
2-((4-(Dimethylamino)phenyl)methylidene)-1-benzofuran-3-one (Table 2, Entry 1)

0.067g (0.5mmol) of benzofuranone as the active methylene compound and arginine as the catalyst resulted in 0.063g (50%) of the product as a red solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.83 (d, J=9.3Hz, 2H), 7.31 (d, J=8.7Hz, 2H), 7.19 (t, J=7.5Hz, 2H), 6.93 (s, 1H), 6.75 (d, J=8.1Hz, 2H), 3.09 (s, 6H).



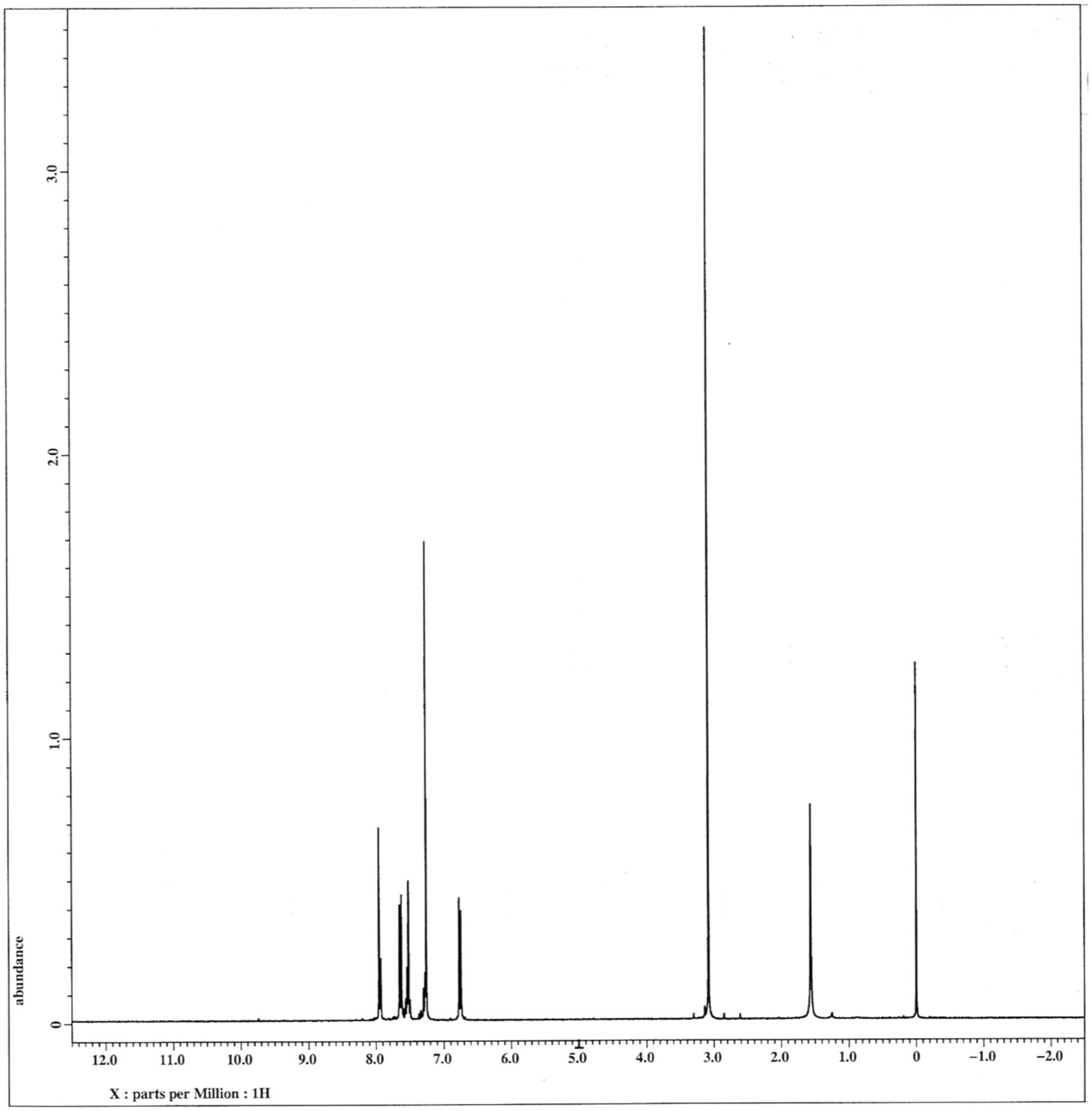
2-(3-(2-(4-(Dimethylamino)phenyl)vinyl)-5,5-dimethyl-2-cyclohexen-1-ylidene)malononitrile (Table 2, Entry 2)

0.079g (0.5mmol) of cyclic malononitrile as the active methylene compound and arginine as the catalyst resulted in 0.076g (48%) of the product as a purple solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.41 (d, J=8.7Hz, 2H), 7.02 (dd, J=18Hz, 2H), 6.75 (d, J=9Hz, 2H), 3.09 (s, 6H), 3.0 (s, 6H), 2.57 (s, 1H), 2.45 (s, 1H), 0.95 (s, 1H).



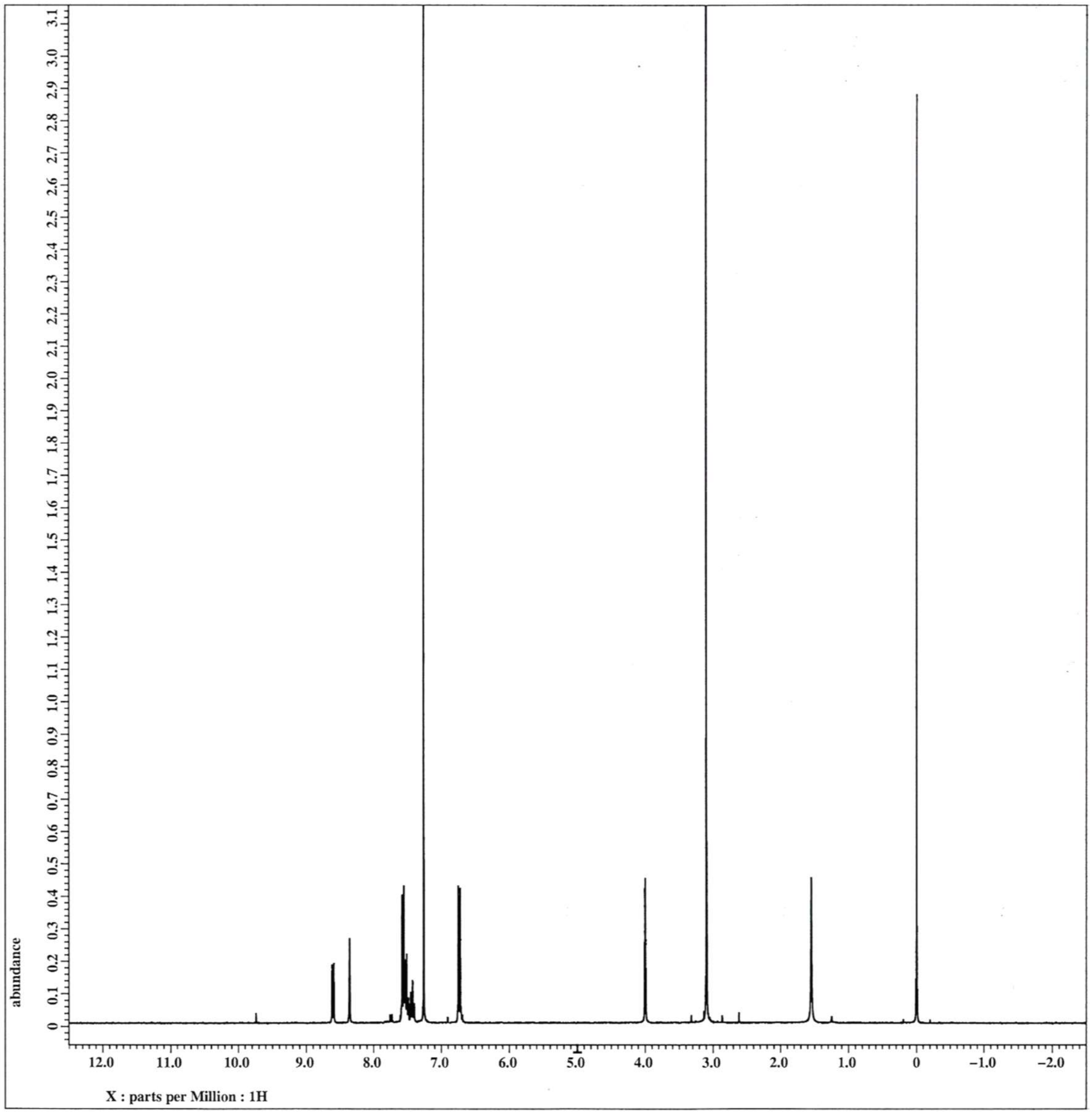
2-((4-(Dimethylamino)phenyl)methylidene)-1-benzothiophen-3-one (Table 2, Entry 3)

0.073 (0.5mmol) of benzothiophenone as the active methylene compound and arginine as the catalyst resulted in 0.064g (47%) of the product as a red solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.95 (dd, J=9Hz, 2H), 7.64 (d, J=9.3Hz, 2H), 7.55 (dt, J=8.7Hz, 2H), 6.76 (d, J=8.7Hz, 2H), 3.08 (s, 6H).



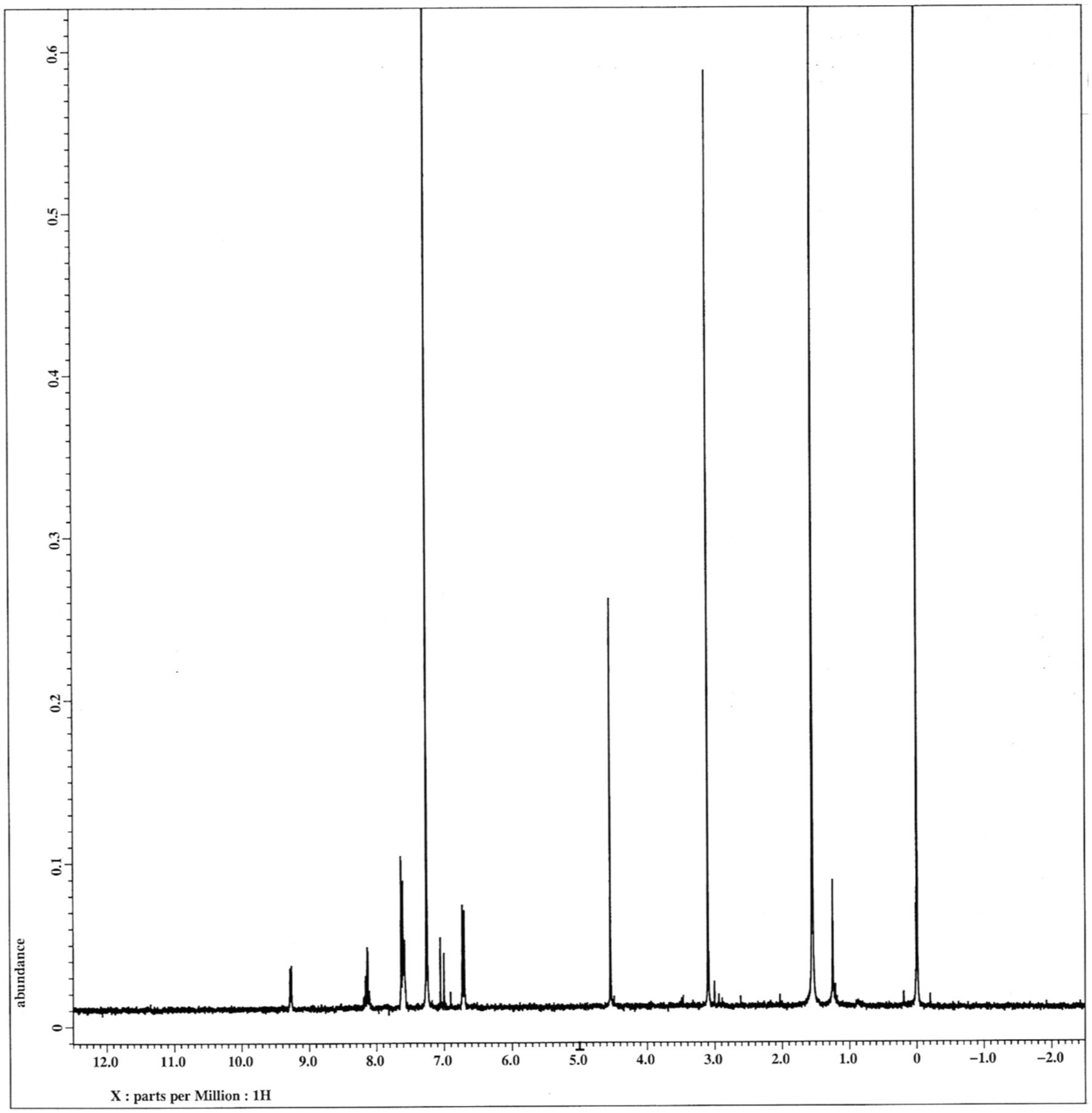
2-((2E)-2-((4-(dimethylamino)phenyl)methylidene)-3H-inden-1-ylidene)propanedinitrile (Table 3, Entry 3)

0.090g (0.5mmol) of indanemalononitrile as the active methylene compound and sodium prolinate as the catalyst resulted in 0.044g (28%) of the product as a black solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.74 (d, J=9.3Hz, 2H), 7.58-7.48 (m, J=7.8Hz, 4H), 6.74 (d, J=9Hz, 2H), 4.02 (s, 1H), 3.09 (s, 6H).



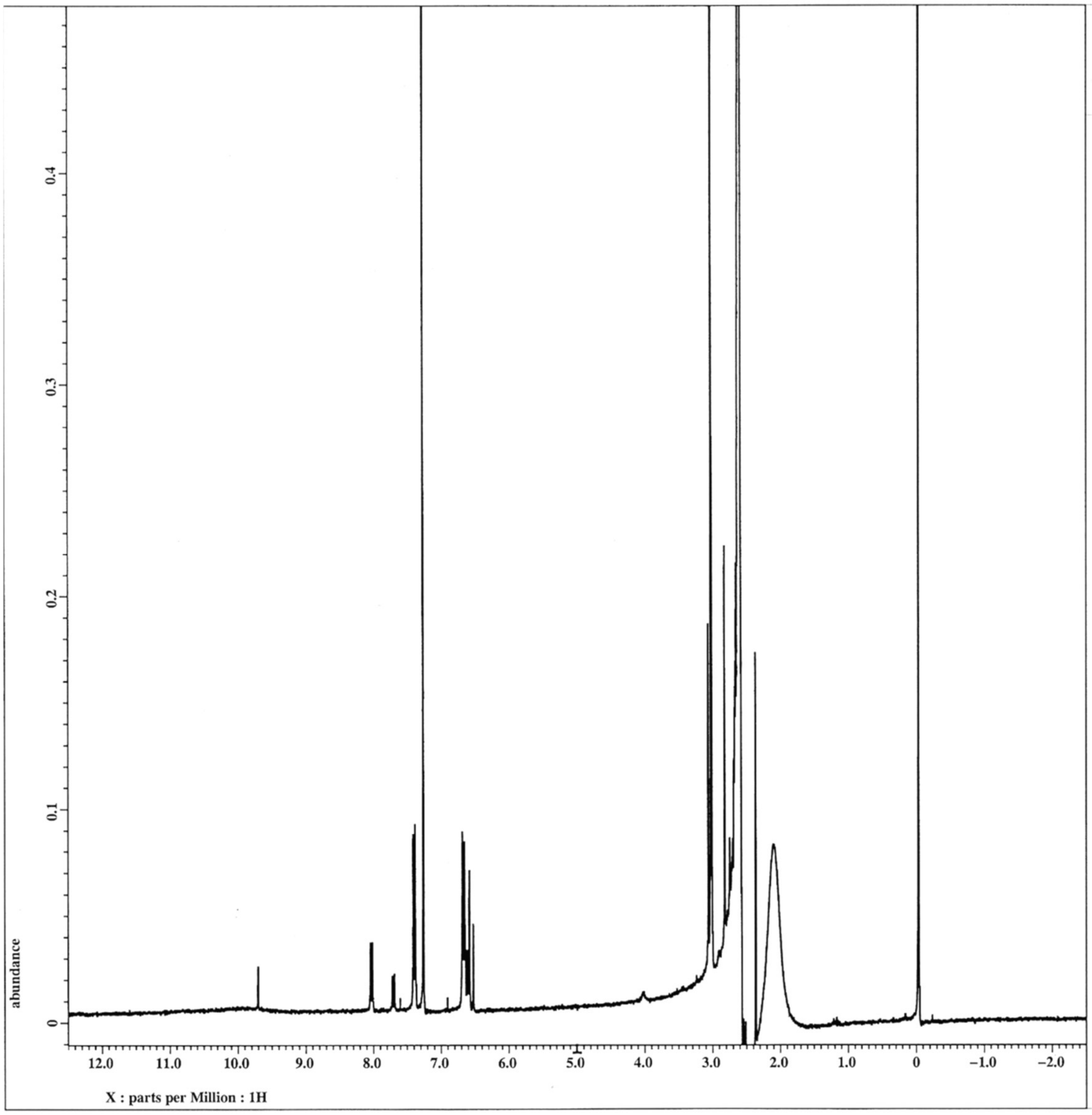
1-Methyl-2-((E)-4-(dimethylamino)styryl)pyridinium iodide (Table 3, Entry 4)

0.118g (0.5mmol) of 1,2-dimethylpyridinium iodide as the active methylene compound and sodium prolinate as the catalyst resulted in 0.086g (47%) of the product as a red solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 9.27 (d, J=6.6Hz, 1H), 8.20-8.10 (m, J=9Hz, 3H), 7.60 (d, J=7.5Hz, 2H), 7.03 (dd, J=18Hz, 2H), 6.72 (d, J=8.7Hz, 2H), 4.52 (s, 3H), 3.09 (s, 6H).



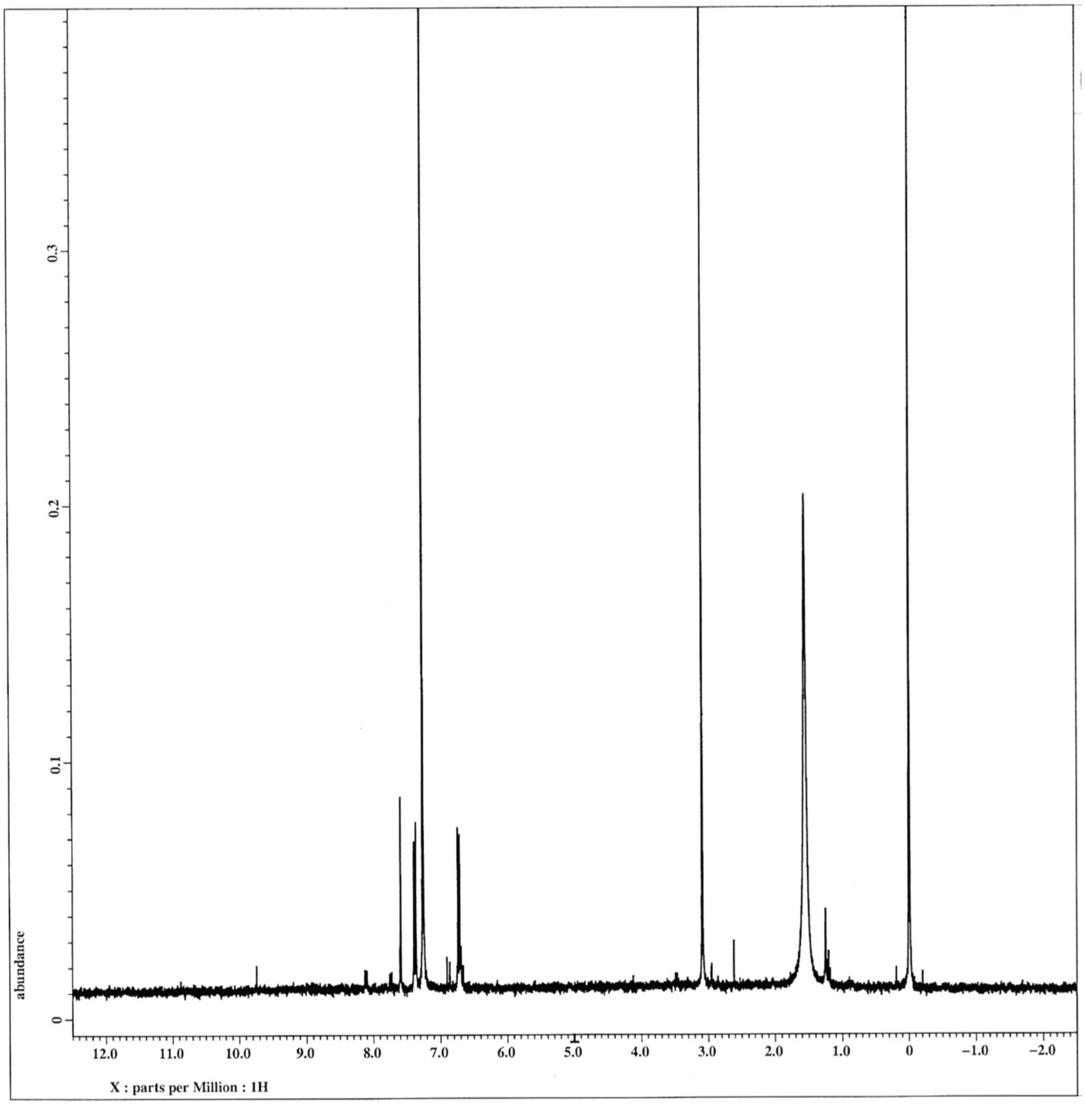
5-(4-Dimethylamino-benzylidene)-2-thioxo-imidazolidin-4-one (Table 3, Entry 5)

0.058g (0.5mmol) of thiohydantoin as the active methylene compound and sodium prolinate as the catalyst resulted in 0.098g (81%) of the product as an orange solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.70 (d, J=9Hz, 2H), 6.67 (d, J=9.9Hz, 2H), 6.61 (s, 1H), 6.58 (s, 1H), 6.52 (s, 1H), 3.06 (s, 6H).



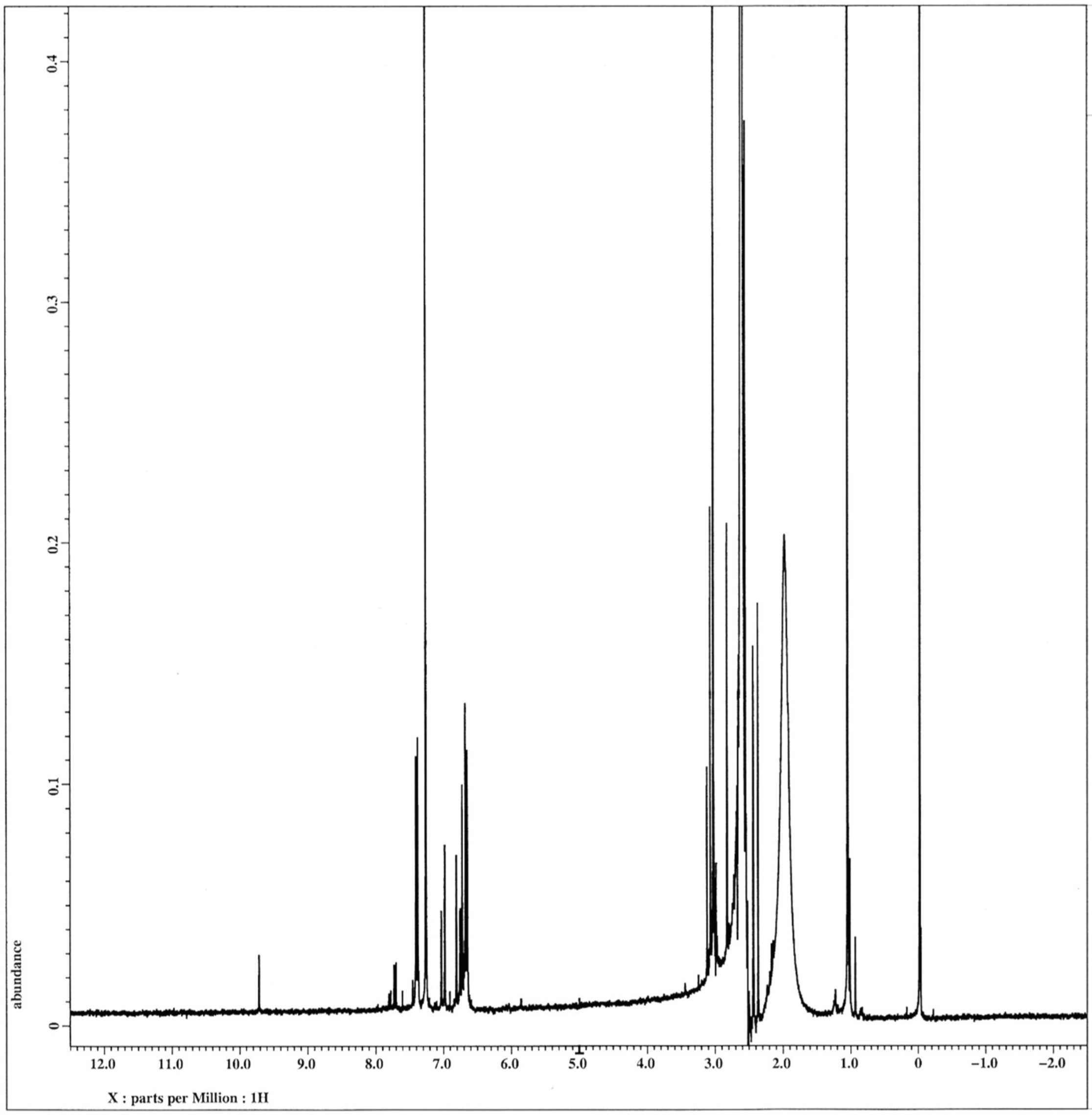
5-(4-Dimethylaminobenzylidene)rhodanine (Table 3, Entry 8)

0.067g (0.5mmol) of rhodanine as the active methylene compound and sodium prolinate as the catalyst resulted in 0.093g (74%) of the product as a red solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.74 (d, J=9Hz, 2H), 7.59 (s, 1H), 6.73 (d, J=8.7Hz, 2H), 6.69 (s, 1H), 3.09 (s, 6H).



2-(3-(2-(4-(Dimethylamino)phenyl)vinyl)-5,5-dimethyl-2-cyclohexen-1-ylidene)malononitrile (Table 3, Entry 9)

0.093g (0.5mmol) of 5,5-dimethyl-2-cyclohexen-1-ylidenepropanedinitrile as the active methylene compound and sodium prolinate as the catalyst resulted in 0.115g (72%) of the product as a purple solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.72 (d, J=8.7Hz, 2H), 7.39 (s, 1H), 7.01 (dd, J=15Hz, 2H), 6.72 (d, J=9Hz, 2H), 3.07 (s, 6H), 2.43 (s, 6H), 2.35 (s, 4H).



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