Oxidative Rearrangement of Imidazoles with Oxaziridinium Salt

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Abstract

The objective of the project was to develop an alternative to dimethyldioxirane and oxaziridine for the rearrangement of imidazoles to imidazolones which would allow the assembly of biologically active complex molecules such as palauámine, styloguanidine and axinellamine. Towards this end, oxaziridinium salt and chloroimidazoles were synthesized and tested.

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Introduction

The family of oroidin-derived alkaloids is a diverse group of marine natural products that results from different modes of functionalization and cyclization of the parent heterocycle. Some of the most complex members in the family include palau'amine, styloguanidine, konbu'acidin A and axinellamine A (Fig. 1).

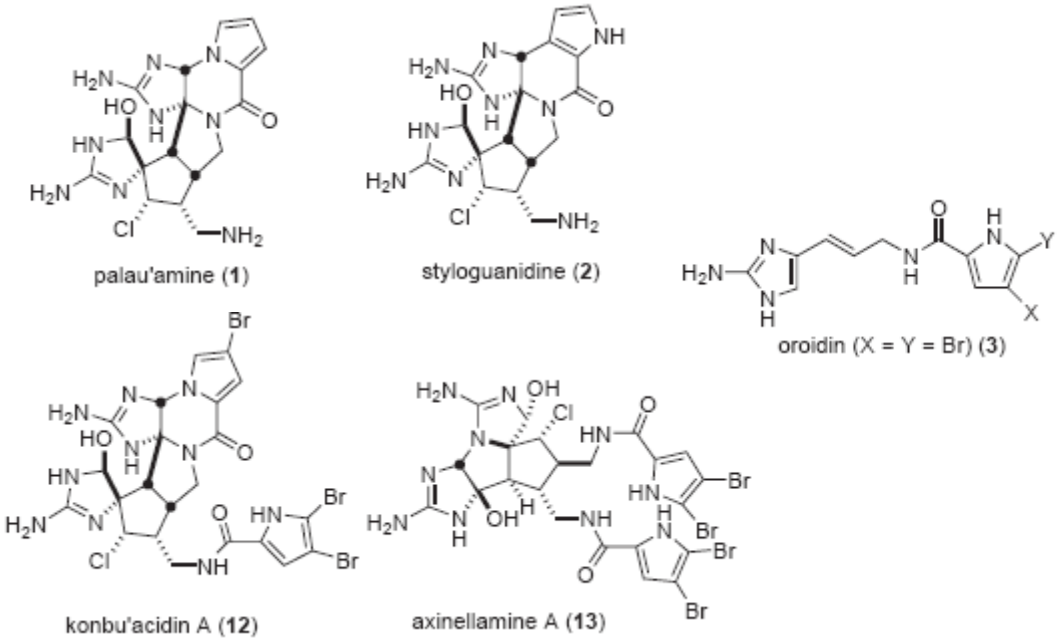


Figure 1

Though these molecules differ slightly in structure, all are derived from the dimerization of two molecules of oroidin. In addition, each contains one spirofused cyclopentylimidazole system (Fig. 2). These molecules are attractive synthetic targets due to their structural complexity and potentially useful biological activity. An example is palau'amine, a very antibiotic, antifungal, cytotoxic, and immunosuppressive alkaloid compound.

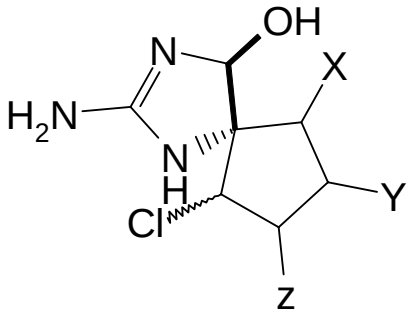
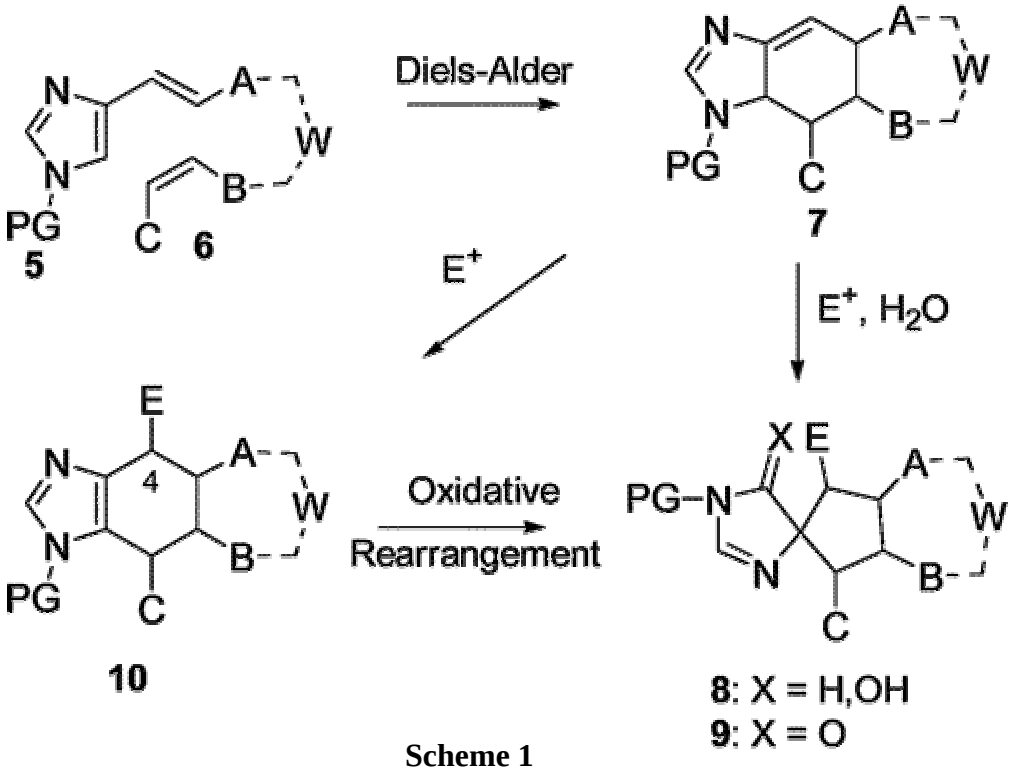


Figure 2

The most challenging feature of these molecules[1] is the construction of hexasubstituted chlorocyclopentane ring system. Dr. Lovely's research group relied on a biomimetic approach, i.e. the rearrangement of cyclohexylfused imidazoles to spiro imidazolones proposed by Kinnel *et al*, for assembling this part of the target molecules. The precursors have been made by Diels-Alder reaction of 4-vinylimidazoles, and their rearrangement was affected using dimethyldioxirane. The Diels- Alder reaction of vinyl imidazole produces an enamine which can be transformed to chloro compound by the reaction of chloronium ion source (Scheme 1). Oxidative rearrangement of this obtained chloro substrates should give access to the 5-5 spirofused compounds that are part of highly complex natural products.

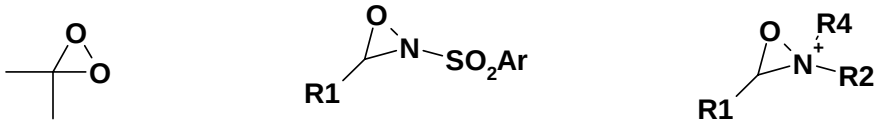


Scheme 1

Earlier Dr. Lovely's group identified dimethyldioxirane and N-sulfonyloxaziridine as oxidants for the above oxidative rearrangement of imidazoles to imidazolones[2]. Dimethyldioxirane was the initial compound used for oxidation, yet it possess its own drawbacks such as instability due to a three-member ring containing two oxygens, which prevents it from being stored for long periods of time. It must be made when needed and the reactions require strict conditions, causing it to be inconvenient and expensive.

These drawbacks have been taken care of by switching to oxaziridines, which are more stable and reactive due to a weak N-O bond in the strained ring. Although oxaziridines achieved their desired purpose in lab, there is still evident need for a better reagent. One improvement to existing methodology was to identify cost effective N-

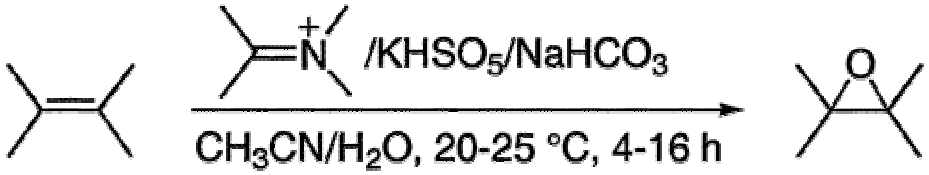
sulfonyloxazirdines, which afford greater selectivity for oxidations than other oxidants do (Fig. 3).



DMDO **N-Sulfonyloxaziridine** **Oxaziridinium**

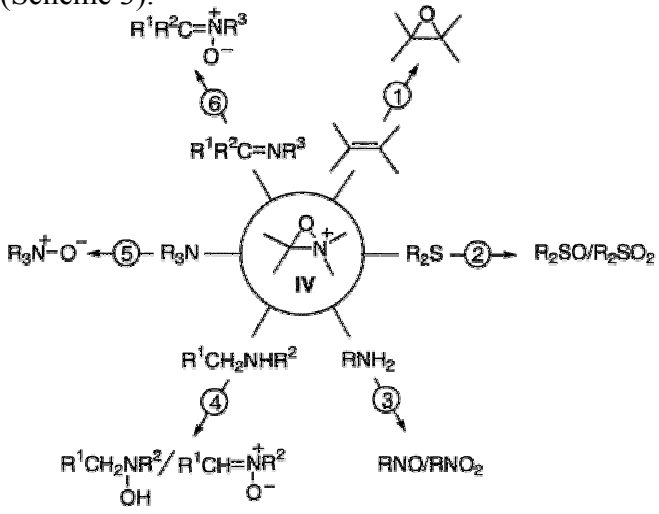
Figure 3

Another improvement was to look for other oxidants such as oxaziridinium. Oxaziridinium salts are prepared through oxidation of iminium salts with peracids or monoperoxysulfate (Scheme 2). Their oxidizing capability comes from the strongly electrophilic oxidizing atom that can be transmitted to many substrates. Oxaziridinium salts can be involved in catalytic as well as stoichiometric oxidations, enabling the efficient oxidation of unfunctionalized alkenes to epoxides. Thus, there has been an interest in using iminium and oxaziridinium salts as catalysts in oxidation reactions. Tetraphenylphosphonium monoperoxysulfate (TPPP) has been used in these reactions to eliminate the use of both water and a base.



Scheme 2

In addition, it provides greater scope for monitoring and analyzing the reaction, through NMR spectroscopy (Scheme 3).



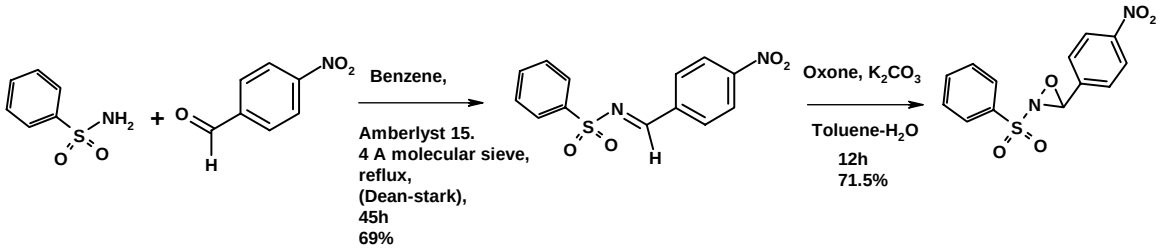
Scheme 3

Results and Discussion

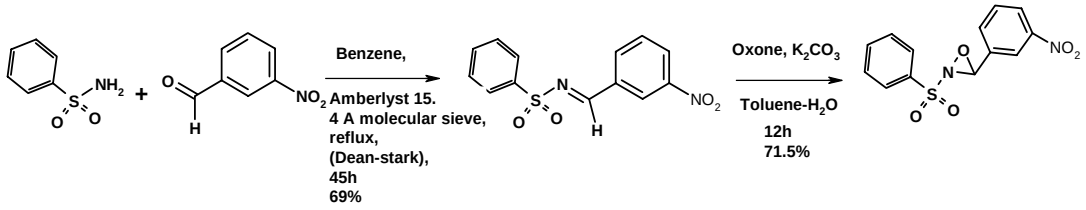
Dr. Lovely and his research group used expensive 4-nitrobenzaldehyde in the preparation of oxaziridines. Thus, 3- nitrobenzaldehyde was used instead, since it is more cost effective and easy to scale up the preparation of the oxaziridine (Scheme 4). Sulfonimines of nitrobenzaldehydes were conveniently prepared by heating an aromatic sulfonamide with an equivalent amount of the aldehyde at 130 °C. The imino proton appears in the 'H NMR at δ 8.9-9.1. The 'H NMR spectra of these compounds are characterized by a sharp singlet appearing in the region δ 5.4-5.6, and these are attributed to the 3-H proton. The oxaziridine obtained from 3-nitrobenzaldehyde was found to be comparable in its reactivity to that of 4-nitrobenaldehde derived oxaziridine.

Oxaziridinium reagent:
In dichloromethane, oxaziridinium salt efficiently transfers oxygen to unfunctionalized double-bonds, as shown in Table 1. Like peracids, oxaziridinium salt effects oxygen transfer in a stereospecific manner. Under identical conditions, the reaction time is shorter with oxaziridinium salt compared to meta-chloroperbenzoic acid.

3-(4-nitrophenyl)-2-(phenylsulfonyl) Oxaziridine

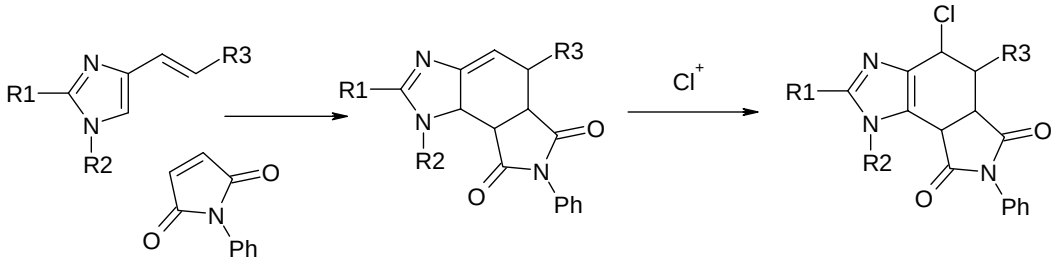


3-(3-nitrophenyl)-2-(phenylsulfonyl) Oxaziridine



Scheme 4

Preparation of chloro substrates for rearrangement:
The Diels Alder reaction was performed to produce enamines from vinyl imidazoles. The resulting enamines were then chlorinated with a chlorionium ion source, such as NCS, NCP, and chloramine- T as shown in Scheme 5. Among these three, NCP was found to be the reagent of choice. Chloramine-T did not work at room temperature in the initial trials and warrants further research. These reactions were carried out in NMR tubes. These substrates will be used for further oxidative rearrangements (Scheme 6).



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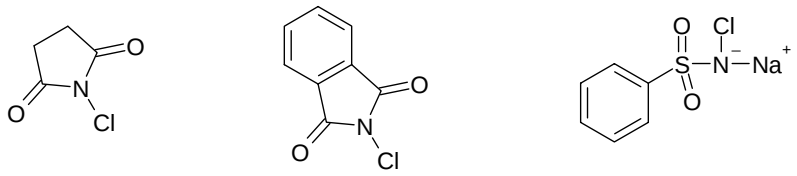
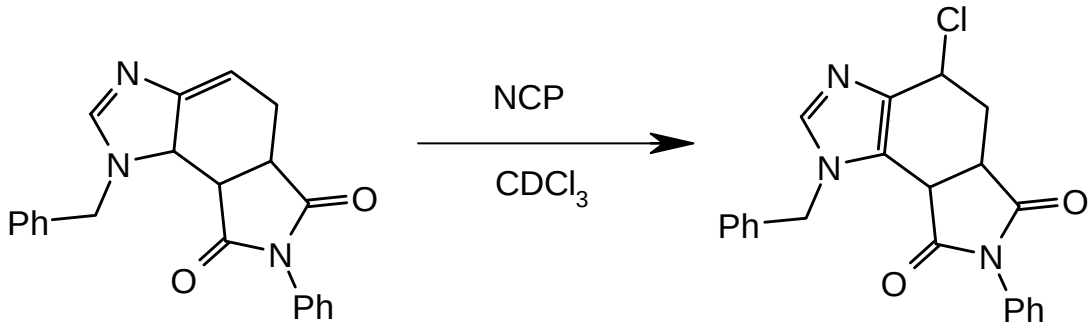
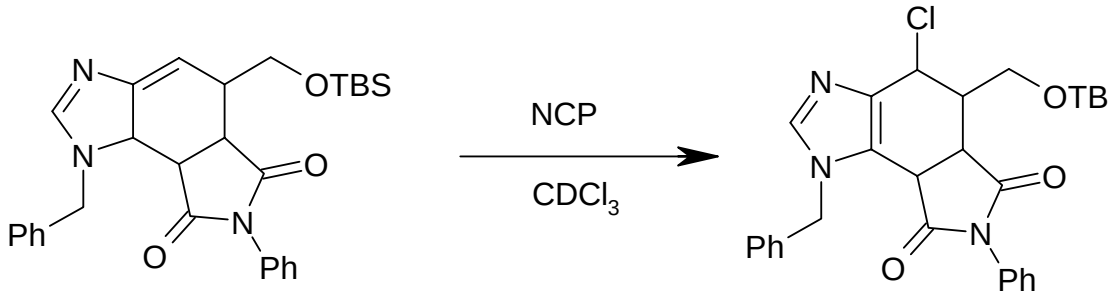


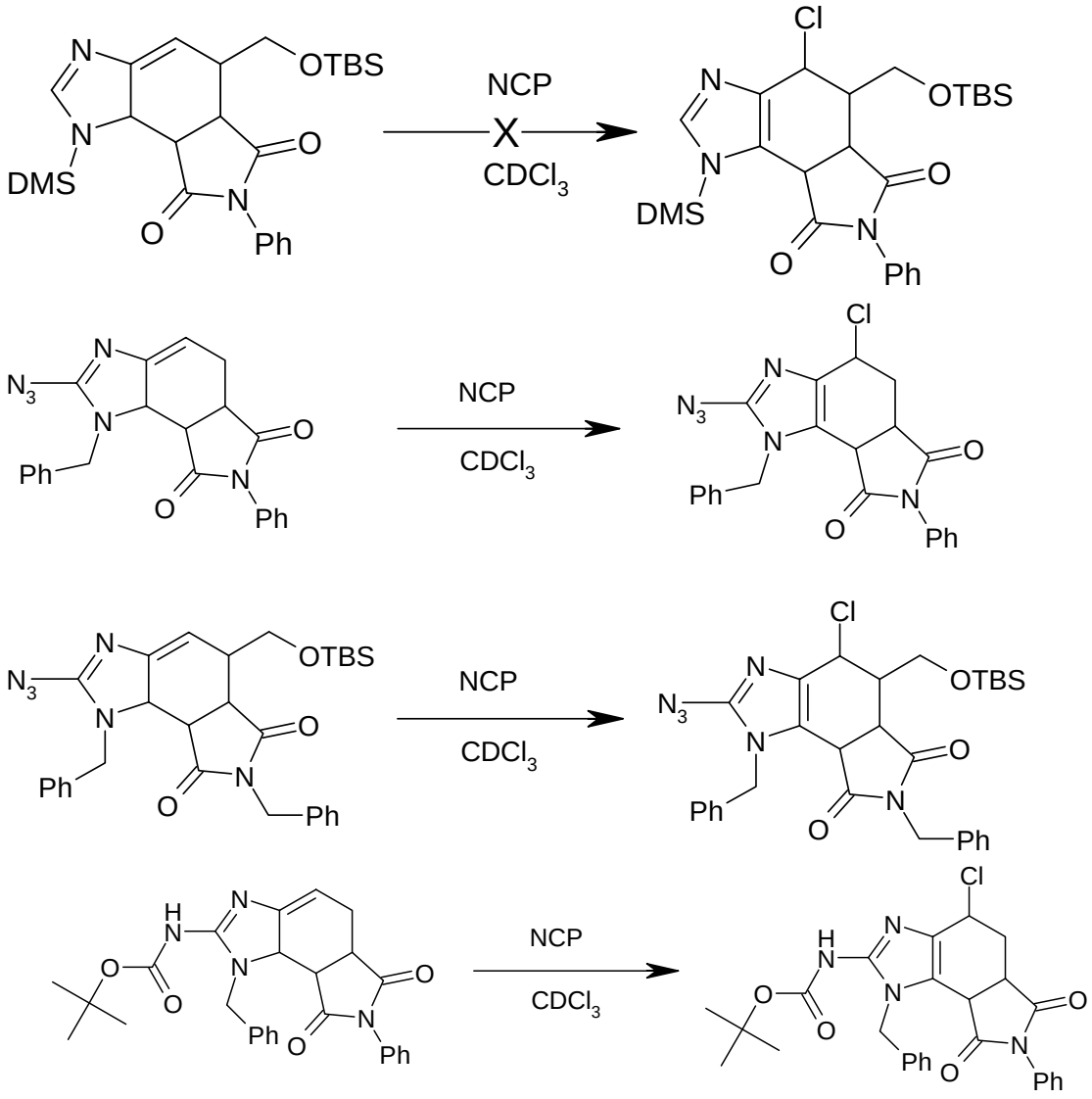
NCS NCP chloramine-T

Scheme 5

Enamine: Chloro:



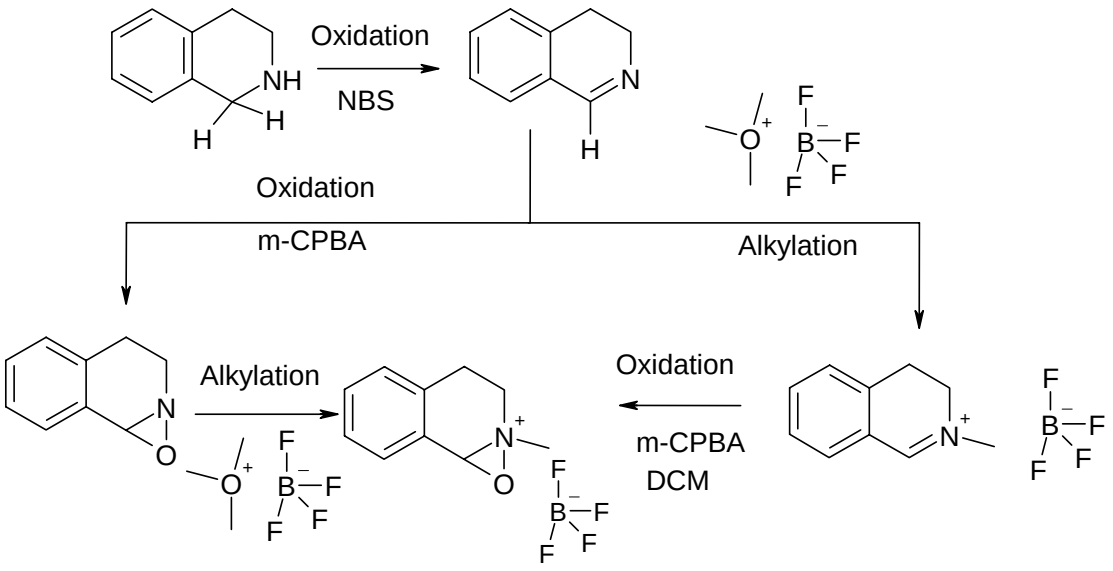




Scheme 6

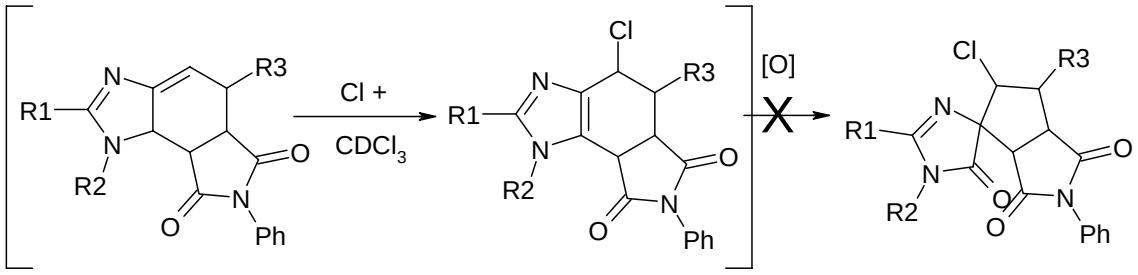
Preparation of Oxaziridinium:

Oxaziridinium salt was made according to literature procedure[3] as shown in the scheme below (Scheme 7).



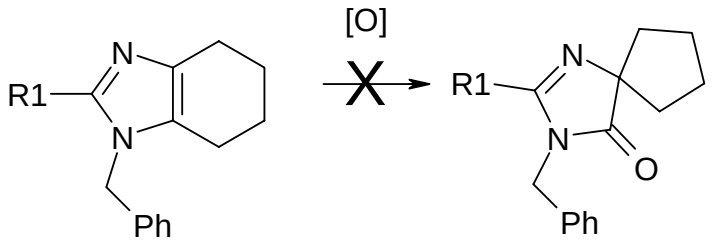
Scheme 7

Reaction of Imidazoles with Oxaziridinium Salt:
Attempts to purify chloro compounds were futile. The chloro substrates were found to be unstable on the column and could not be purified, so the reaction mixture as obtained from chlorination was treated with oxaziridine salt solution in DCM. The reaction was carried out in NMR tubes, monitored by NMR, and resulted in the formation of a complex mixture. However, the chloro compound did not oxidize when reacted with the oxaziridinium salt (Scheme 8).



Scheme 8

At this stage we decided to try the oxidative rearrangement of substrates devoid of chloro substituents as they are stable compared to the later ones. Again, the rearrangements were carried out in an NMR tube and reaction progress was monitored by NMR (Scheme 9). Even the compounds devoid of Chloro substituents did not undergo oxidative rearrangement with “oxaziridinium salt” solution in DCM.



Scheme 9

Oxaziridinium salts did not yield the desired imidazolones from imidazoles. Even initial attempts to carry out the *in situ* tetraphenylphosponium-peroxymonosulfate mediated iminium ion catalyzed oxidation[4] did not bring out the oxidative rearrangement of imidazole substrates (scheme 9). It is necessary to mention that only one oxaziridine salt was tried as a solution in dichloromethane, which contains m-CPBA impurities. This research is in progress to probe in to the other factors that influence the outcome of the organic transformations.

Conclusions

1. Inexpensive Oxaziridine was prepared and tested to be reactive for the rearrangement of imdiazoles to imidazolones.
2. Efficient method for chlorination of DA products was developed using N-chlorophthalimide.
3. Oxaziridinium salt was prepared and tested for its efficacy toward the oxidative rearrangement of imdiazoles to imdazolones.

Experimental

General Procedure for preparation of Sulfonimines:
In a 500mL, single-necked, round-bottom flask equipped with a Dean- Stark separator, condenser, and nirogen inlet were placed 7.85 g (0.1 mol) of benzenesulfonamide, 7.55 g (0.1 mol) of 3- or 4-nitrobenzaldehyde, 12.5 g of 4-A powdered molecular sieves, and 0.2 g of Amberlyst 15 ion-exchange resin in 250 mL of toluene. The reaction mixture was heated at reflux until all of the water has separated (24 h), and carefully filtered while the solution was hot. The residue was washed with an additional 100 mL of toluene and the filtrates were combined. The solvent was removed on the rotatory evaporator to give a yellow solid which was washed with 100 mL of n-pentane to give of *N-(*3 or 4 Nitrobenzylidene)benzenesulfonamide**.**

General Procedure for Oxidation of Sulfonimines.
In 250-mL three-necked flask, equipped with a mechanical stirrer and a 50-mL addition funnel, were placed 13.78 mmol of the appropriate sulfonimines **2a** in 160 mL of toluene and 16 g of K_2C0_3 (3.5 equiv based on potassium peroxymonosulfate) in 50 mL of water. The reaction was stirred vigorously and a solution of 10 g (21 mmol) of Oxone in 50 mL of water was added dropwise over 15 min. The reaction mixture was stirred until all of the sulfonimine had been consumed. The reaction progress was determined by removing

1-mL aliquots from the organic solvent, evaporating it in vacuo below 40 OC, and determining the ratio of sulfonimine (6 8.7-9.2) to oxaziridine (6 5.4-6.0) by NMR. When the reaction was complete the aqueous layer was separated and washed once with 25 mL of toluene. The combined toluene extracts were washed with 25 mL of aqueous 10% sodium sulfite and dried over anhydrous Na_2SO_4 and the solvent was evaporated on an efficient rotary evaporator keeping the bath temperature below 40^o C. The resulting viscous oil was triturated with a few milliliters of n-pentane to afford the pure oxaziridines as determined.

General Procedure for Chlorination of Enamines:
In an NMR tube were placed 1 mL of $CDC1_3$, 20 mg of 1-Methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole, approximately 2eq chlorinating agent and The H^1 NMR was taken at regular time intervals to monitor the reaction progress.

Oxidation of 1,2,3,4-tetrahydroisoquinoline
To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (10.0 g, 75.2 mmol) in CH_2Cl_2(200 mL) was added N-bromosuccinimide (14.7 g, 82.7 mmol) portionwise over 20 min. After the addition was complete, the mixture was stirred until TLC ($CHCl_3$,:MeOH = 9:l) indicated that the starting material was consumed (30 min). Sodium hydroxide (50 mL of a 30% aqueous solution) was added, and stirring was continued for 1 h at 25^oC. The organic layer was separated and washed with water (100 mL), and the product was extracted with 10% HCl (2 **x** 100 mL). The combined acidic extracts were washed with CH_2Cl_2 (100 mL) and made basic with concentrated ammonia (pH 9). The liberated oil was extracted with CH_2Cl_2 (3 x 100 mL), dried (Na_2S0_4), and evaporated in vacuo to afford a light yellow oil which was distilled [60-65 ^{o}C (1 mmHg to give 9.26 g (94%) of colorless oil: 'H NMR ($CDC1_3$,) 6 8.33 (t, *J* = 2.1 Hz, 1 H, C=N), 7.1-7.4 (m, 4 H, ArH), 3.76 (td, *J* = 7.8 Hz and *J* = 2.1 Hz, 2 H, CH_2CH_2N), 2.74 (t, *J* = 7.8 Hz, 2 H, CH,CH,N)

Formation of Iminium salt :
Meerwin's salt (Tetrafluoroborate) (0.83 g, 564 mmol) was added to a solution 0.725 g (5.62 mmol) of dihydroisoquinoline in 25 ml of methylene chloride at 0^oC. The medium becomes homogeneous after few minutes upon stirring . After one hour 100 mL of ethanol was added and concentrated under vacuum until formation of a precipitate was seen. It was left at rt for few hrs to complete the solid formation and the precipitate was filtered to give 1.134 g (87%) of white crystals of tetrafluoroborate iminium salt which was characterized by ^{1} H NMR in CD_2Cl_2 9.12 (1H),

Preparation of a dichoromethane solution of oxaziridinium salt: A dichloromethane solution of oxaziridinium salt can be prepared by peracid (meta-chloroperbenzoic oxidation of the corresponding iminium salt in the presence of 0.1 eq. of sodium hydrogencarbonate . After filtration of the acid generated by the reaction, this solution was used for oxygen transfer reactions.

Works Cited

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2. Du, Hongwang; He, Yong; Sivappa, Rasapalli; Lovely, Carl J. New methods of Imidazole functionalization - from Imidazole to marine alkaloids. *Synlett* **2006**, 965-992.

3. Lusinchi, Xavier; Hanquet, Gilles. Oxygen transfer reactions from an oxaziridine tetrafluoroborate salt to olefins. *Tetrahedron* **1997**, *53*, 13727-13738 and references cited there in.

4. Page, Philip C. Bulman; Barros, David; Buckley, Benjamin R.; Ardakani, Adel; Marples, Brian A Organocatalysis of Asymmetric Epoxidation Mediated by Iminium Salts under Nonaqueous Conditions. *Journal of Organic Chemistry* **2004**, *69*, 3595-3597.

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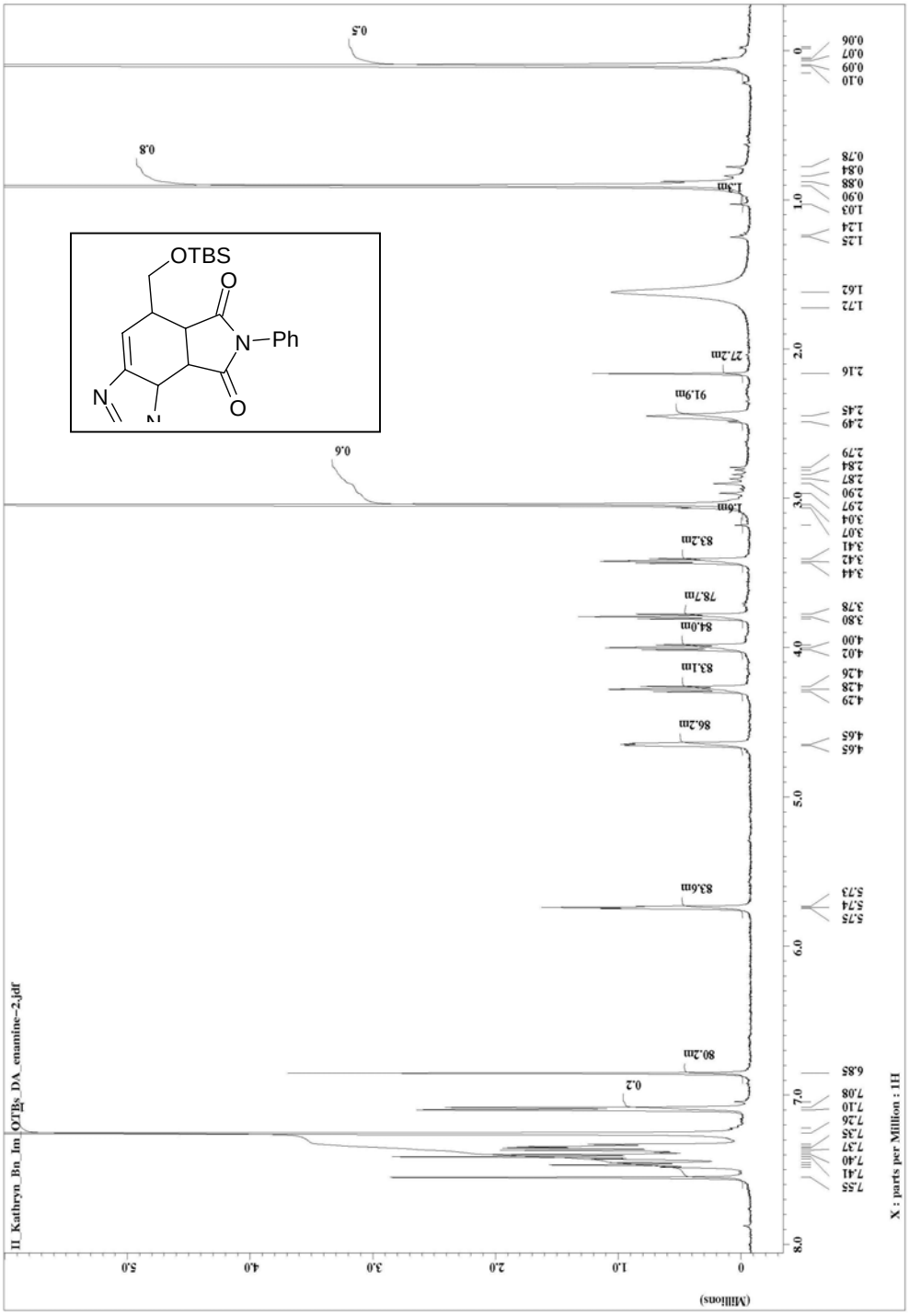
Appendices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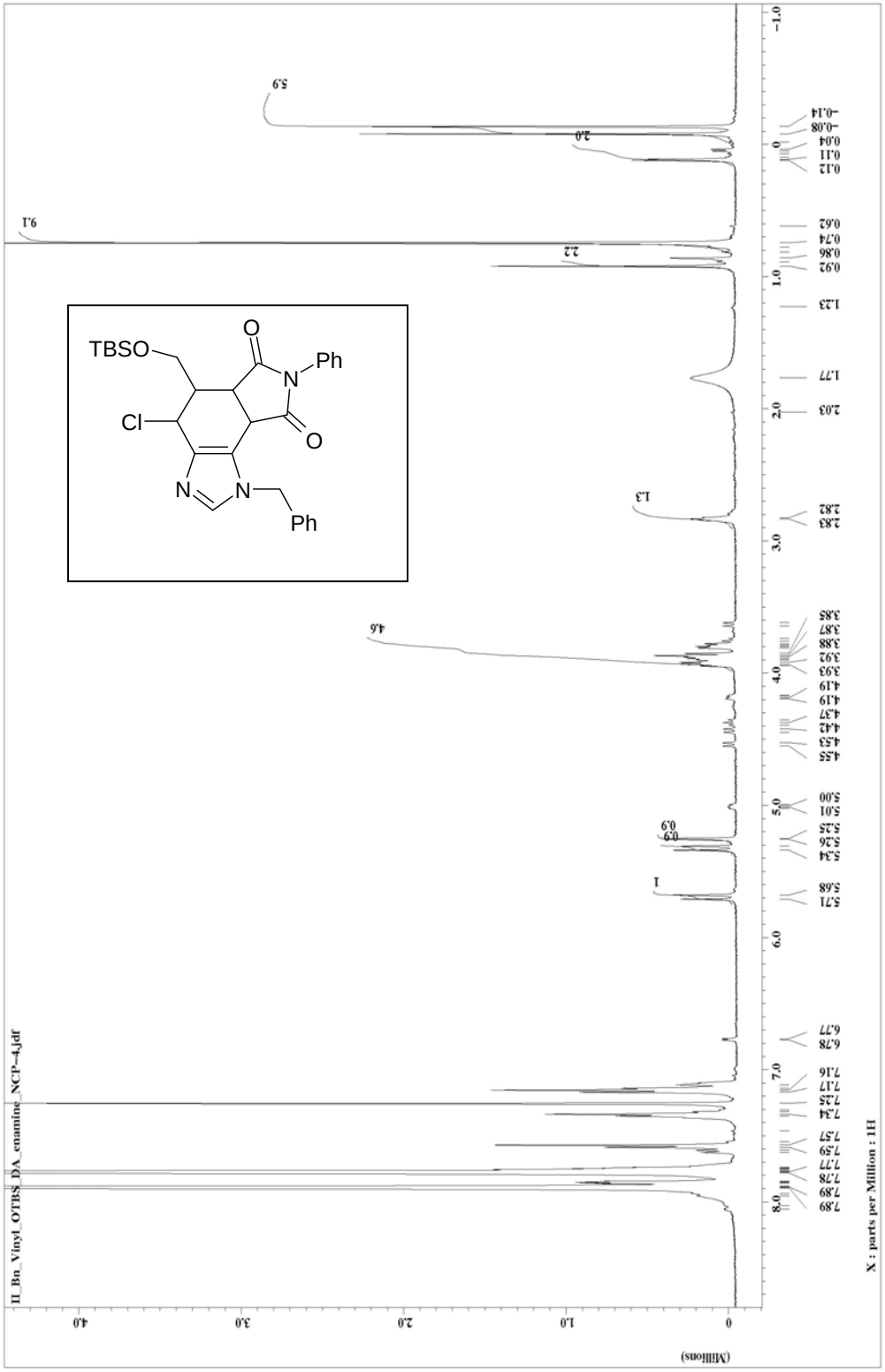
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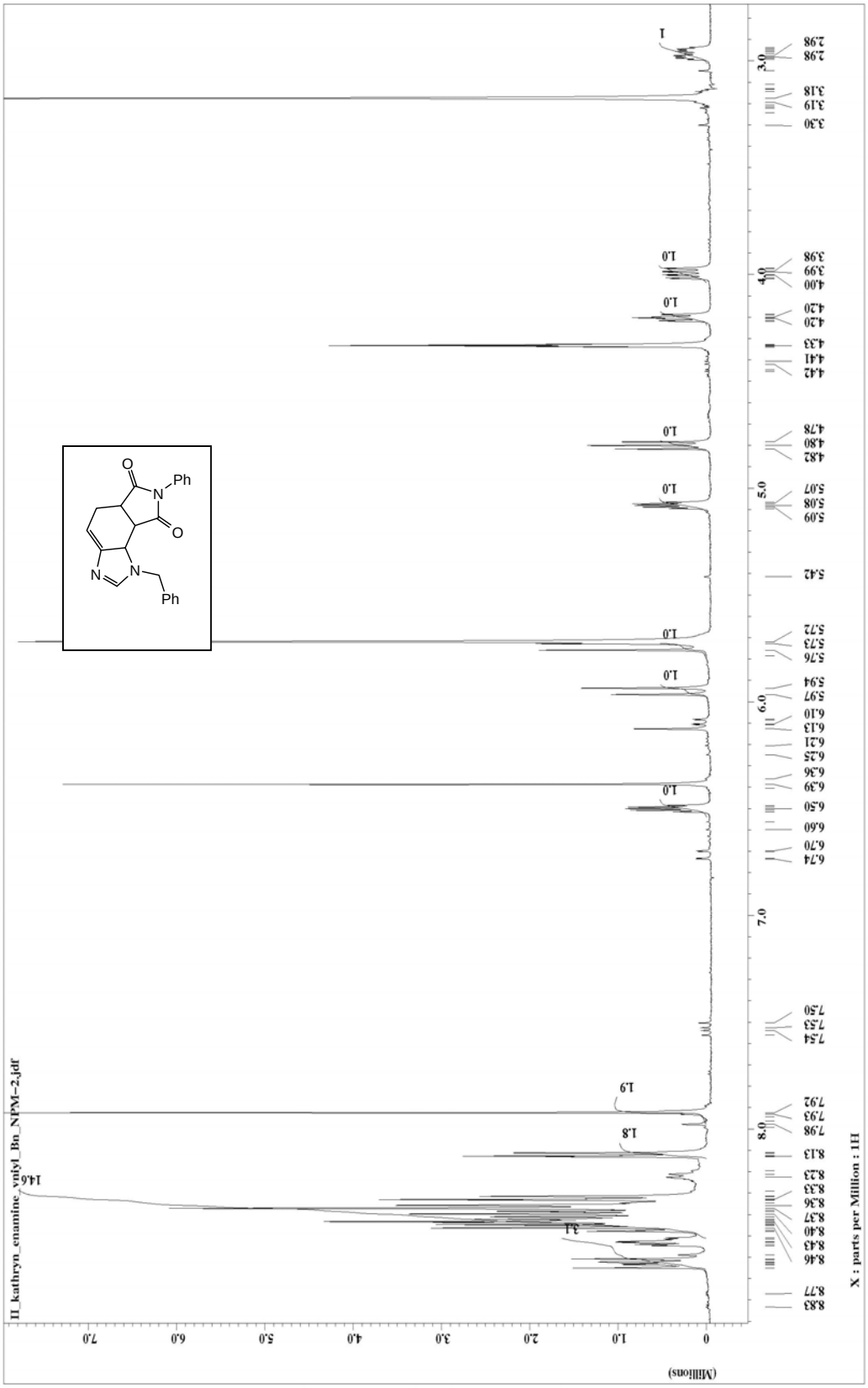
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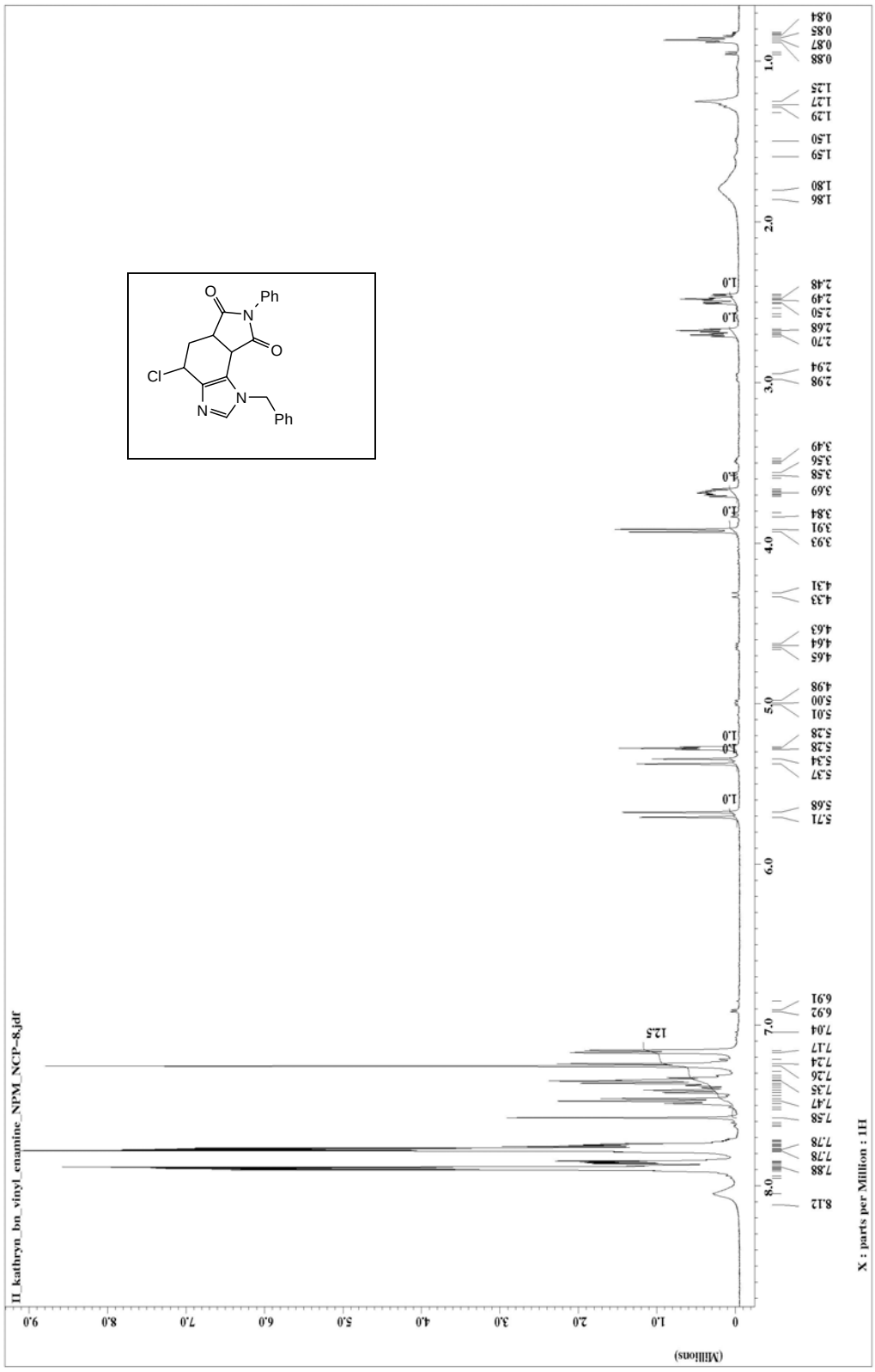
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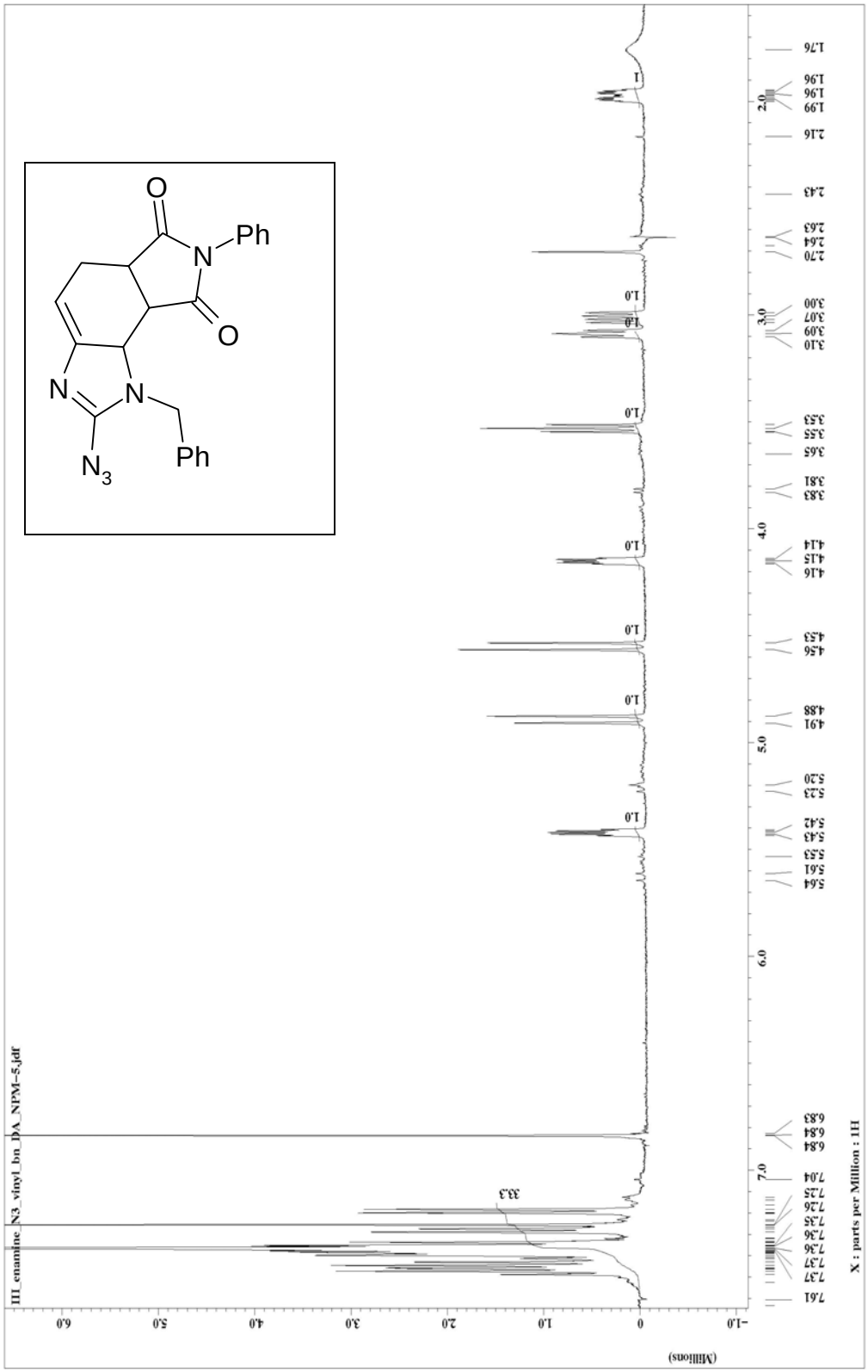
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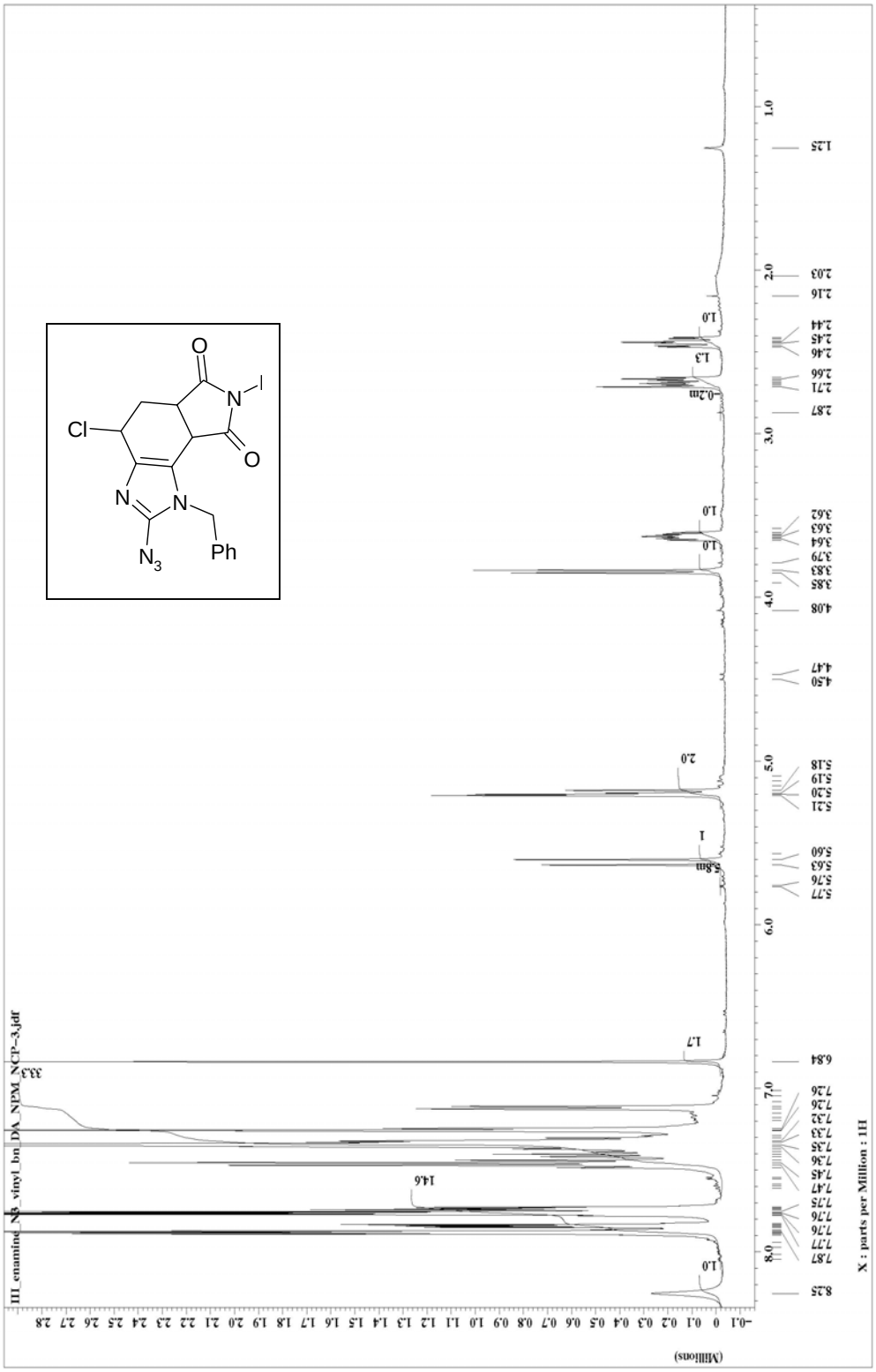
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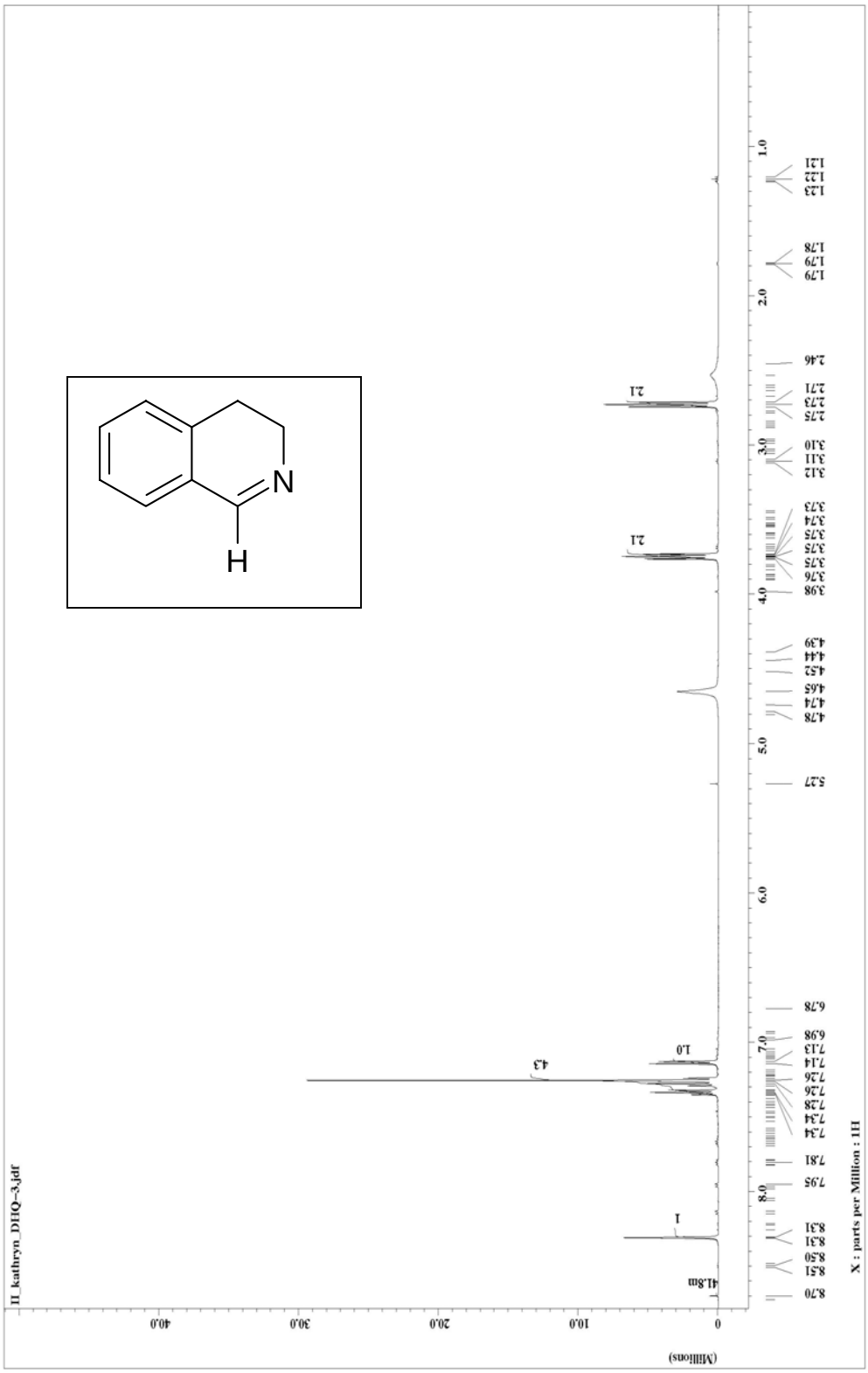
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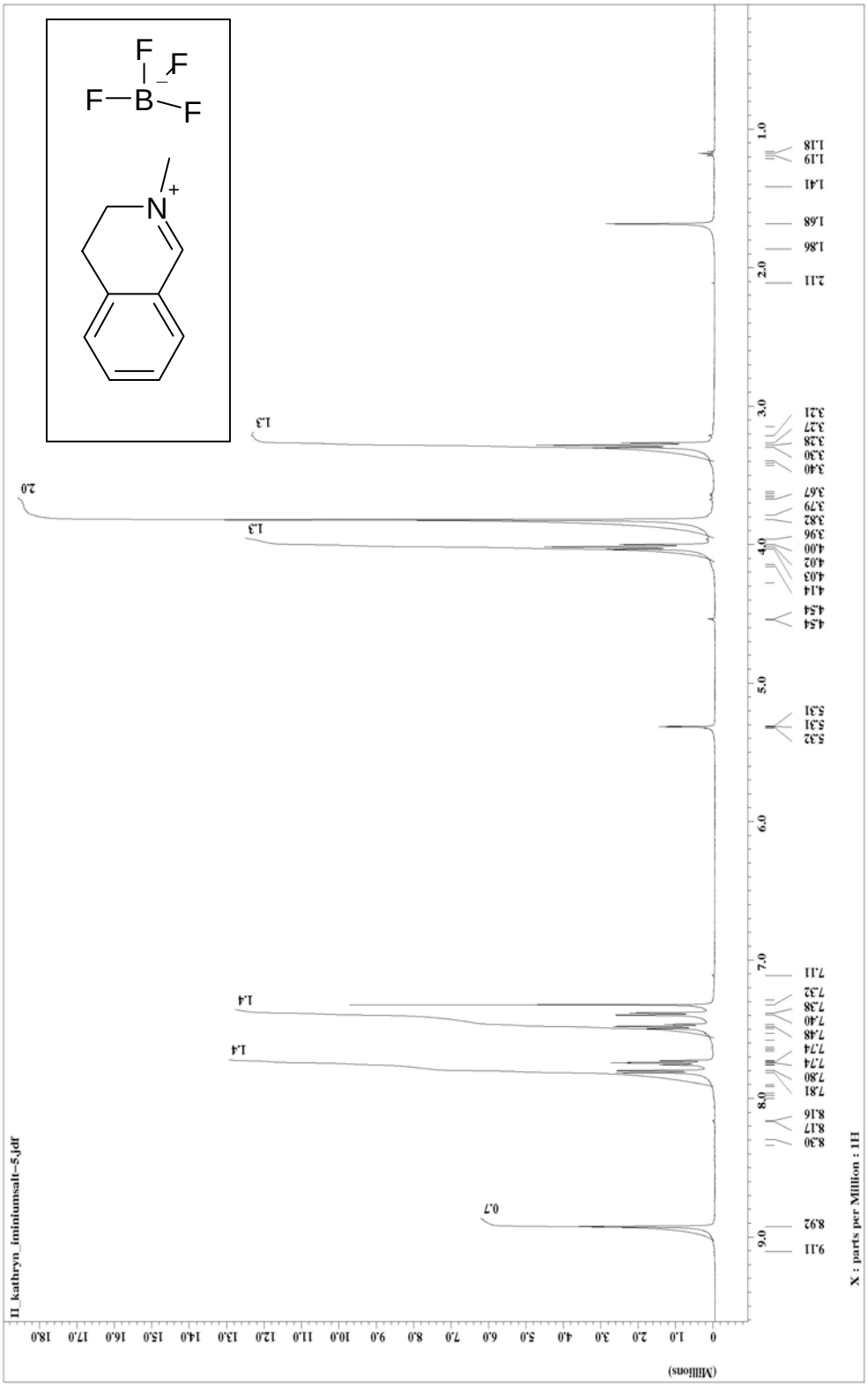
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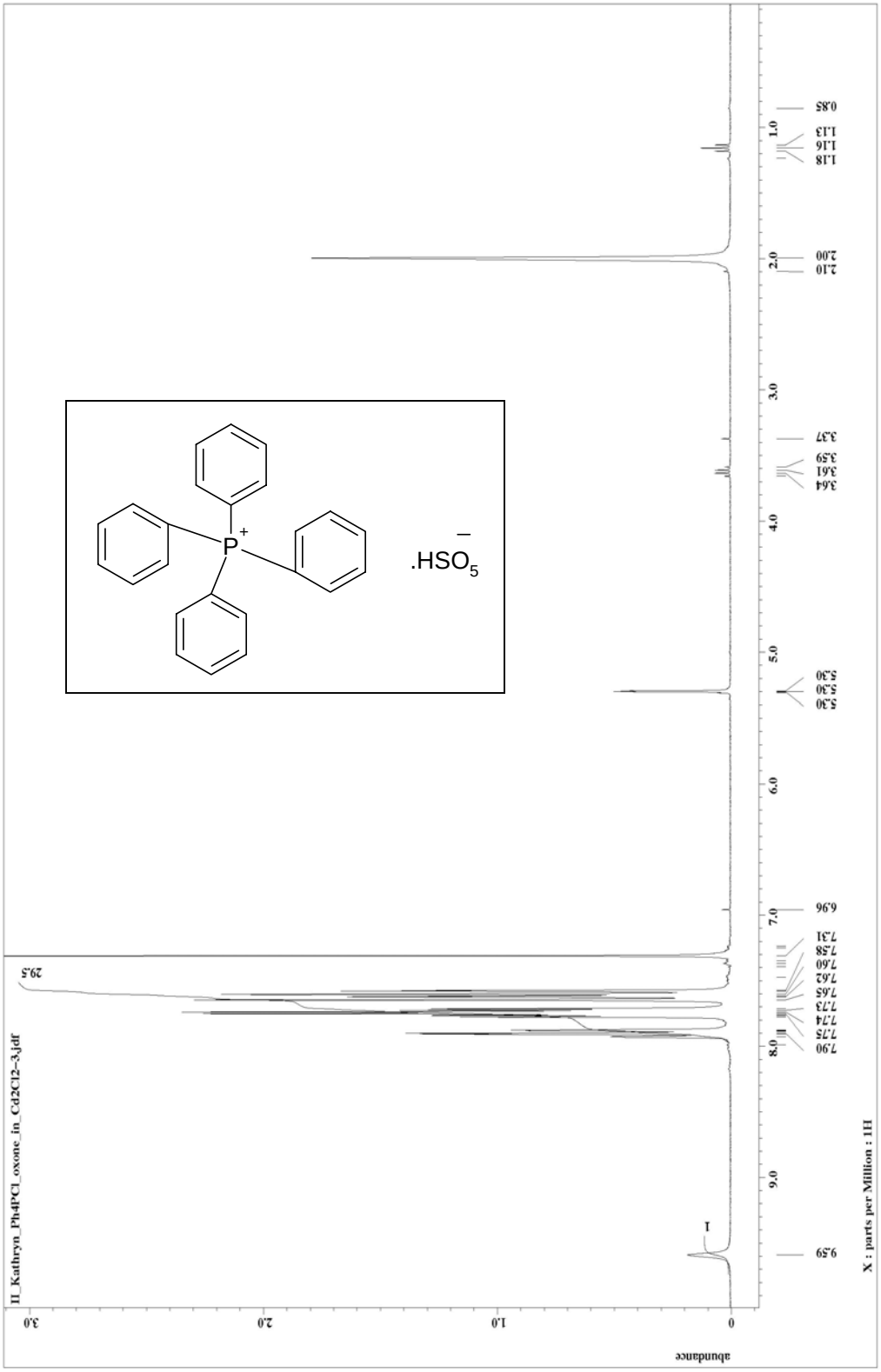
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