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Collection
Design and Synthesis of 1-Sulfonyldienes for the Stereoselective Synthesis of Cyclohexenes using Tandem Diels-Alder and Sulfinyl Retro-Ene Reactions

디尔斯-알더 반응 및 레트로-엔 연쇄 반응을 통한 입체선택적 사이클로헥세인 합성을 위한 1-설포닐다이엔의 디자인과 합성

2014 년 2 월

서울대학교 대학원
화학부 유기화학 전공
유 현 정
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이 논문을 이학석사학위논문으로 제출함
2014년 2월

서울대학교 대학원
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유현정의 석사학위논문을 인준함
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위원장 ______________
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<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT .....................................................................................</td>
</tr>
<tr>
<td>INTRODUCTION ..................................................................................</td>
</tr>
<tr>
<td>1. 연구의 배경 ..............................................................................</td>
</tr>
<tr>
<td>2. Sulfonyldiene의 디자인 ...........................................................</td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION ..................................................................</td>
</tr>
<tr>
<td>1. Normal Diels-Alder 반응과 Retro-Ene 반응 ..................................</td>
</tr>
<tr>
<td>1.1 Preparation of substrates .....................................................</td>
</tr>
<tr>
<td>1.2 Normal Diels-Alder 반응 ........................................................</td>
</tr>
<tr>
<td>1.3 Sulfinyl Retro-Ene 반응 ..........................................................</td>
</tr>
<tr>
<td>1.3.1 Model studies .....................................................................</td>
</tr>
<tr>
<td>1.3.2 Sulfone 14 의 Sulfinyl Retro-Ene 반응 ..................................</td>
</tr>
<tr>
<td>2. Inverse Electron Demand Diels-Alder 반응과 Retro-Ene 반응 ..........</td>
</tr>
<tr>
<td>2.1 Preparation of substrates .....................................................</td>
</tr>
<tr>
<td>2.1.1 Sulfonyldiene 2 의 합성 .....................................................</td>
</tr>
<tr>
<td>2.1.2 Sulfonyldiene 3 의 합성 .....................................................</td>
</tr>
<tr>
<td>2.1.3 Sulfinyldiene 4 의 합성 .....................................................</td>
</tr>
<tr>
<td>2.2 Inverse Electron Demand Diels-Alder 반응 ................................</td>
</tr>
<tr>
<td>2.2.1 Sulfonyldiene 2 의 Inverse Electron Demand Diels-Alder 반응 ....</td>
</tr>
<tr>
<td>2.2.2 Sulfonyldiene 3 의 Inverse Electron Demand Diels-Alder 반응 ....</td>
</tr>
<tr>
<td>2.2.3 Sulfinyldiene 4 의 Inverse Electron Demand Diels-Alder 반응 ....</td>
</tr>
</tbody>
</table>
2.3 Sulfone 45의 Sulfinyl Retro-Ene 반응 ................................................. 24

3. 후속 연구 ............................................................................................................. 26

CONCLUSIONS .......................................................................................................... 27

EXPERIMENTAL SECTION ...................................................................................... 28

REFERENCES ............................................................................................................. 47

감사의 글 ..................................................................................................................... 49

SPECTRA .................................................................................................................... 50
ABSTRACT


Keywords: 1-sulfonyldiene, Diels-Alder 반응, Inverse electron demand Diels-Alder 반응, Sulfinyl retro-ene 반응, Allylic sulfinic acid, Cyclohexene

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INTRODUCTION

1. 연구의 배경

1928년 처음 개발된 Diels-Alder 반응은 천연물에서 많이 발견되는 cyclohexene core 를 만드는데 매우 유용한 유기화학 반응이다. 이 반응은 diene 과 dienophile 의 전자적인 에너지 준위가 맞았을 때 반응이 진행되며 intermolecular 그리고 intramolecular [4+2] cycloaddition 과정에서 regioselectivity 와 stereoselectivity 를 조절할 수 있다는 측면에서 중요한 의미를 지니며 많은 연구가 진행되어 왔다. 의약, 천연물 및 다양한 유기분자들의 합성에 탁월한 효용을 지닌 Diels-Alder 반응은 다른 반응들과 직렬 혹은 병렬로 수행했을 때 더 광범위한 응용성을 지닌 새로운 반응이 개발될 수 있다 (Scheme 1).

Scheme 1. Cyclohexene core의 합성

Cyclohexene 을 합성하기 위해 많은 유기화학자들은 A와 같은 역합성을 생각한다. 그러나 cycloaddition 반응은 diene과 dienophile의 에너지 준위가 맞아야 진행될 수 있으므로 전자적 조건이 맞지 않는 경우 수행이 불가능한 경우가 많다. 이런 경우 B와 같이 적절한 치환기가 도입된 diene을 이용한 Diels-Alder 반응을 통해 cyclohexene을 먼저 합성한 후 suprafacial 1,5-sigmatropic rearrangement을 통해 이중결합을 이동시킴으로써 원하는 cyclohexene core를 합성할 수 있다.

2005년, Sorensen group에서는 1-hydrizinodiene을 이용하여 Diels-Alder 반응을 수행하고 중간체로 allylic diazene을 생성한 후, suprafacial 1,5-sigmatropic
rearrangement를 통해 이중결합이 이동하는 반응을 개발하였다. 이 반응에서 사용된 1-hydrazinodiene은 전자가 풍부하므로 normal Diels-Alder 반응에 유용한 반응이다 (Scheme 1).

Lee group에서는 Sorensen group의 연구를 확장하여 아래와 같은 특징을 가지는 반응을 개발하기 위한 연구를 시작하였다.

첫째, 1-hydrazinodiene은 normal Diels-Alder 반응에만 활용이 가능하므로, 이를 통상적인 HOMO-LUMO가 뒤바뀐 inverse electron demand Diels-Alder 반응까지 확장시킬 수 있는 반응을 개발하고자 하였다.

d둘째, 1-hydrazinodiene 대신 1-sulfonyldiene을 사용하여 rearrangement 과정에서 N₂ 기체 대신 SO₂ 기체를 발생시키도록 하였다.

셋째, Sorensen group의 반응은 allylic diazene 중간체를 얻기 위한 deprotection 과정이 여러 스텝을 거치기 때문에 이를 보완하기 위하여 deprotection 과정이 간단하며 mild한 조건에서 일어날 수 있는 protecting group을 디자인하였다.

\[
\begin{align*}
\text{Scheme 2. Allylic sulfinic acid의 retro-ene 반응}
\end{align*}
\]

1953년, Wichterle group에서 allylic sulfinic acid를 이용한 retro-ene 반응을 개발하였다. 그 후 1975년 Peterson group에서 개발한 반응은 후속 연구를 통해
concerted mechanism 임이 밝혀졌지만 sulfinyl retro-ene 반응의 유용성은 큰 관심을 받지 못하였다 (Scheme 2). 3-6

이러한 연구들을 기반으로 하여 그 동안 보고된 적이 없는 1-sulfonyldiene C를 디자인하고, 전자적인 특성을 이용하여 normal Diels-Alder 반응 및 inverse electron demand Diels-Alder 반응을 통해 cyclohexene D 합성 가능성을 모색하였다. 그 후 연속적인 deprotection 과 sulfinyl retro-ene 반응을 통해 suprafacial 1,3-chirality transfer 가 진행되어 형성되는 cyclohexene E의 합성법 개발에 관하여 연구하였다 (Scheme 3).

Scheme 3. Proposed reaction
2. Sulfonyldiene 의 디자인

채안한 반응 연구에 필요한 sulfonyldiene 은 다음과 같은 조건을 가지어야 한다.

첫째, 1,3-chirality transfer 를 증명하기 위하여 sulfonyldiene 의 3 번 위치에 치환기가 존재해야 한다.

둘째, 아래와 같은 조건을 가지는 protecting group 을 선택해야 한다.

- Normal Diels-Alder 반응과 inverse electron demand Diels-Alder 반응을 수행 할 때, 부 반응을 일으킬 를 없을 것.
- Diels-Alder 반응 후 mild 한 조건에서 deprotection 하여 allylic sulfinic acid 를 만들 수 있을 것.

위의 조건을 바탕으로 1,3-chirality transfer 확인을 위해 sulfonyldiene 의 3 번 위치에 methyl 치환기를 도입하였다.

Protecting group 으로는 Diels-Alder 반응이 끝난 후 편리한 조건에서 제거 가능한 benzothiazole, N-methylimidazole, thiazole 을 선택하였다. 특히 benzothiazole 의 2 번 위치에 치환된 sulfone 은 NaBH₄ 와 같은 사용이 간편한 시약으로 deprotection 되고, 약산성 조건에서 retro-ene 반응이 일어났다고 보고 되었다.⁶

Normal Diels-Alder 반응을 위한 sulfonyldiene 의 전자가 풍부하도록 4 번 위치에 carbobenzyloxy (Cbz) 보호기를 지닌 절소기를 도입하고 sulfone 에 benzothiazole 에 결합된 sulfonyldiene 1 을 디자인하였다. Inverse electron demand Diels-Alder 반응을
위해서 protecting group 으로 benzothiazole, N-methylimidazole, thiazole 이 각각 치환된 dienes 2,3 및 4 를 디자인하였다. Inverse electron demand Diels-Alder 반응의 경우는 sulfone 작용기가 diene 에 충분히 친전자성을 부여하지 못한다고 판단하여 sulfoxide 에 O-methylation 을 수행한 cation 4′을 만들기 위한 diene 4 를 디자인하였다 (Fig 1).

Fig1. Diels-Alder 반응에 사용할 sulfonyldiene 의 후보군
RESULTS AND DISCUSSION

1. Normal Diels-Alder 반응과 Retro-Ene 반응

Sulfonyldiene에 존재하는 sulfone 치환기의 전전자성 정도를 예상하기 어려웠기 때문에 먼저 전자가 풍부하도록 sulfone 치환기 이외에 4 번 위치에 carbobenzyloxy (Cbz) 보호기를 지닌 질소기를 도입한 sulfonyldiene 1을 합성하여 Normal Diels-Alder 반응을 수행하고, 연속적으로 sulfinyl retro-ene 반응을 수행할 수 있는지 여부를 검토하였다.

1.1 Preparation of substrates

Sulfonyldiene 1의 합성은 먼저 acid 7을 준비하여 butadiene carbamate 8을 만든 후, sulfenylation 과정을 통해 sulfide를 도입하고, S-oxidation 시켜 완성할 수 있었다 (Scheme 4). Ethyl but-2-ynoate (5)에 vinyl cuprate의 1,4-addition을 통해 ester 6을 한 스태프에 얻을 수 있었다.21 이 때 E:Z = 3:1의 비율로 ester를 얻을 수 있었다. Vinyl Grignard 시약으로부터 cuprate를 준비할 때, CuI는 THF에 잘 녹지 않아서 cosolvent로 dimethylsulfide를 1/12 첨가하였다. Ester 6은 column chromatography를 수행하면 decomposition이 되는 것을 확인하여 곧바로 acid 7로 만들어 보관하였다. Acid 7은 benzylalcohol 존재하에 Curtius rearrangement를 수행하여 carbamate 8을 75%의 수율로 얻었다.22 Carbamate 8은 in-situ 반응으로 2-mercaptobenothiazole 과
sulfurylchloride 를 proton sponge 존재 하에 합성한 생성물과 반응시켜 sulfenyldiene 9 를 40%의 수율로 얻을 수 있었다. Sulfenyldiene 9 의 S-oxidation 을 통해 sulfonyldiene 1 을 59%의 수율로 얻을 수 있었다.

Scheme 4. Sulfonyldiene 1 의 합성
1.2 Normal Diels-Alder 반응

Sulfonyldiene 1 은 전자가 부족한 일련의 dienophiles 인 but-3-en-2-one (10), methyl acrylate (11), dimethyl malate (12), acrolein (13) 등과 Diels-Alder 반응을 수행하였다 (Table 1).

![Chemical structure diagram]

**Table 1. Sulfonyldiene 1과 Normal Diels-Alder 반응**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Condition</th>
<th>Lewis Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Toluene, 40 °C, 3 d</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>Toluene, 80 °C, 3 d</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>Toluene, 40 °C, 5 d</td>
<td>AlCl₃ (10 eq.)</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>Toluene, 80 °C, 3 d</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>Toluene, 25 °C, 3 d</td>
<td>-</td>
<td>1:14 = 30:70⁰</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>Toluene, 25 °C, 3 d</td>
<td>ZnCl₂ (1 eq.)</td>
<td>1:14 = 30:70⁰</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>Toluene, 25 °C, 2 h</td>
<td>ZnCl₂ (10 eq.)</td>
<td>1:14 = 0:100⁰</td>
</tr>
</tbody>
</table>

[a] The ratios were determined by NMR spectroscopy data. The mixture of products could not be separated by column chromatography.
11

1.3 Sulfinyl Retro-Ene 반응

1.3.1 Model studies

Diels-Alder adduct 14 를 이용하여 sulfinyl retro-ene 반응을 수행하기에 앞서 model study 를 통하여 반응 조건을 탐색하였다 (Scheme 5).
모델 연구에 사용할 화합물 18의 합성을 위해 farnesol (15)와 2-mercaptobenzothiazole (50)의 Mitsunobu 반응을 통해 allylic sulfide 16을 99%의 수율로 합성하였다. S-oxidation 반응을 통해 73%의 수율로 sulfone 17을 얻었다.

Scheme 5. Sulfinyl Retro-Ene reaction model study

Deprotection과 rearrangement를 one-pot 과정으로 진행시키기 위한 반응 조건을 찾고자 다음과 같은 실험을 수행하였다 (Table 2).
Table 2. Deprotection / Rearrangement of the reaction products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotection</th>
<th>Rearrangement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>0.9 M aq. Tartaric acid DCM, reflux</td>
<td>19 (62%)</td>
</tr>
<tr>
<td></td>
<td>EtOH/THF, 25 °C, 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>2 N HCl, overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td>EtOH/THF, 25 °C, 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄</td>
<td>0.9 M aq. Tartaric acid DCM, reflux</td>
<td>19 (21%)</td>
</tr>
<tr>
<td></td>
<td>THF, 25 °C, 4 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NaBH₄ utilization of sulfone 17 in deprotection reaction was found to form benzothiazole by TLC detection. However, when aqueous 0.9 M tartaric acid was added to the reaction mixture and the solvent was changed to DCM, rearrangement occurred successfully at 62% yield to give triene 19 (Entry 1).

Rearrangement as one-pot reaction was attempted with 2 N HCl addition to the reaction mixture without changing the solvent, but no reaction occurred (Entry 2).

Deprotection in the presence of protic solvent was attempted at 25 °C, but the reaction was not successful (Entry 3).

Conclusively, deprotection and rearrangement were successfully performed using protic solvent, aqueous tartaric acid, THF/EtOH 2-phase mixture, and H₂O-DCM. The sulfinyl retroene reaction was successfully performed under these conditions.
1.3.2 Sulfone 14의 Sulfinyl Retro-Ene 반응

앞서 얻은 Diels-Alder adduct 14의 sulfinyl retro-ene 반응을 진행시키기 위해 NaBH₄을 첨가하였으나, 과량의 reductant를 첨가해도 aldehyde만 환원되고 benzothiazole은 deprotection 되지 않는 것을 확인하였다. 따라서 먼저 aldehyde의 환원으로 얻어진 alcohol을 TBS 그룹으로 protection시키고, 분리과정없이 바로 rearrangement를 수행하여 48%의 수율로 rearrangement가 이루어진 21을 얻을 수 있었다 (Scheme 6). 생성물 21은 단일 이성체로 얻어졌으나 업체구조의 규명은 불가능하였다.
2. **Inverse Electron Demand Diels-Alder 반응과 Retro-Ene 반응**

Diels-Alder 및 sulfinyl retro-ene 연쇄 반응의 활용 범위를 넓히기 위하여 전자가 부족한 diene 과 전자가 풍부한 dienophile 사이에 진행되는 inverse electron demand Diels-Alder 반응과 sulfinyl retro-ene 반응을 결합해보기로 하였다.

2.1 **Preparation of substrates**

2.1.1 **Sulfonyldiene 2의 합성**

![Scheme 7. Sulfonyldiene 2의 합성](image)

상용 구매 가능한 2-(methylthio)benzothiazole (22)은 Cr(VI) 시약을 사용한 S-oxidation 반응을 통해 sulfone 23을 89%의 수율로 합성하였다. LDA를 사용하여 sulfone 23은 deprotonation 하고 methacrolein 을 첨가하여 카르보닐 첨가반응을
수행한 후, mesyl protection 과 제거반응을 연속적으로 수행하여 27%의 수율로 sulfonyldiene 2를 합성하였다 (Scheme 7).

2.1.2 Sulfonyldiene 3의 합성

Scheme 8. Sulfonyldiene 3의 합성

상용 구매 가능한 3-butyn-2-one (26) 과 2-mercapto-1-methylimidazole (25) 의 1,4-addition 반응을 통해 enone 27 을 49%의 수율로 합성하고 11, Wittig 반응을 통해 diene 28 을 74%의 수율로 얻었다.16 Mo 산화제를 이용한 S-oxidation 을 통해 sulfonyldiene 3을 97%의 수율로 얻었다 (Scheme 8).14
2.1.3 Sulfinyldiene 4의 합성

![Scheme 9. Sulfinyldiene 4의 합성](image)

상용 구매 가능한 2-methyl-1-buten-3-yne (29) 을 Schwartz’s 시약을 사용하여 hydrozirconation 반응을 수행한 후, thionyl chloride 와 반응시켜 diene 30을 얻고, 2-thiazole Grignard 시약과 반응시켜 10%의 수율로 sulfinyldiene 4를 얻을 수 있었다 (Scheme 9).17-18

2.2 Inverse Electron Demand Diels-Alder 반응

2.2.1 Sulfonyldiene 2의 Inverse Electron Demand Diels-Alder 반응

Sulfonyldiene 2은 다양한 enamine 및 enol과 inverse electron demand Diels-Alder 반응을 수행하였다. 반응시킨 dienophile 중, enamine 32, 33은 직접 합성하여 사용하였다 (Scheme 10, 11).
Scheme 10. Enamine 32의 합성

상용 구매 가능한 oxazoline-2-one (36) 을 산 측매 하에 acetal 과 반응시켜 N,O-acetal 37 을 얻고, 제거 반응을 통해 enamine 32 를 38%의 수율로 합성하였다.

Scheme 11. Enamine 33의 합성

Acyl azide를 상용 구매 가능한 acryl chloride로부터 합성한 후, Curtius rearrangement 반응을 통해 enamine 33을 50%의 수율로 합성하였다. 이때 acyl azide 39 가 상온에서 공기에 매우 민감하여 toluene으로 work-up 을 빠르게 수행하고 다음 반응을 곧바로 진행하여 enamine 33을 얻었다.
가장 전자가 부족할 것이라고 예상되었던 enamine 31 과 32 는 toluene reflux 조건에서도 반응이 전혀 진행되지 않았다 (Entry 1,2). 전자 밀도가 중간 정도로 생각되는 enamine 33 도 반응이 진행되지 않았다 (Entry 3). Butyl vinyl ether (34) 와 반응을 시켰을 때는 6%의 낮은 수율로 Diels-Alder adduct 35 를 얻을 수 있었다 (Entry 4). 그러나 얻어낸 Diels-Alder adduct 35는 그 양이 왜냐 미미하여 다양한 분석이 불가능하였고 $^1$H NMR 스펙트럼을 통하여 반응이 진행되었다는 정도의

Table 3. Sulfonyldiene 2 의 Inverse Electron Demand Diels-Alder 반응

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>Toluene, reflux, 5 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Toluene, reflux, 2 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Toluene, reflux, 2 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Benzene, reflux, 1 d</td>
<td>35 (6%)</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>Xylene, reflux, 1 d</td>
<td>2A</td>
</tr>
</tbody>
</table>

단위: $^\circ$C, 분, %
판단만이 가능하였다.

Diene 2의 열 안정도를 파악하기 위해 xylene을 용매로 하여 다른 반응보다 높은 온도에서 반응을 시킨 결과 self-dimerization한 2A를 얻을 수 있었다(Entry 5).

2.2.2 Sulfonyldiene 3의 Inverse Electron Demand Diels-Alder 반응

Sulfonyldiene 3과 enamine의 inverse electron demand Diels-Alder 반응을 연구하였다. 반응에 사용한 dienophile 중에서 enamine 43은 직접 합성하여 사용하였다(Scheme 12).

Scheme 12. Enamine 43의 합성

상용 구매 가능한 acetophenone (46)과 morpholine (47)을 Ti 촉매 하에 반응시켜 매우 전자가 풍부한 enamine 43을 98%의 수율로 합성하였다.15
Sulfonyldiene 3 is reacted with enamine 40, 41 at each reaction, leading to decomposition (Entry 1, 2), enamine 42 and reaction gives 44 with 79% yield (Entry 3). 6-ring expanded structure of 44 and its formation is proposed in Scheme 13.

### Table 4. Sulfonyldiene 3의 Inverse Electron Demand Diels-Alder 반응

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Toluene, reflux, 1.5 d</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>Toluene, 70 °C, 1 d</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Toluene, 25 °C, 3 d</td>
<td>44 (79%)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>Toluene, 70 °C, 2 d</td>
<td>45 (40%)</td>
</tr>
</tbody>
</table>

![Sulfonyldiene and enamin structures](image-url)
가장 전자가 풍부할 것으로 여겨진 enamine 43 은 sulfonyldiene 3 과의 inverse electron demand Diels-Alder 반응을 통해 단일 이성질체를 생성하였다. NMR 분석을 통해 endo 생성물로 추정되는 Diels-Alder adduct 45 를 40%의 수율로 얻을 수 있었다 (Entry 4).

2.2.3 Sulfinyldiene 4 의 Inverse Electron Demand Diels-Alder 반응

Sulfonyldiene 2, 3 이 예상보다 전전자성이 부족한 것으로 판단되어 sulfinyldiene 4 에 Meerwien salt 를 이용하여 O-methylation 을 유도하여 sulfone 보다 전자가 부족한 diene 을 만들고자 하였다.

Scheme 13. Proposed mechanism for production 44
Scheme 14. Sulfinyldiene 4의 Inverse Electron Demand Diels-Alder 반응

NMR 모니터링을 통해 O-methylation 반응의 결과를 확인하고, dienophile 과 inverse electron demand Diels-Alder 반응을 진행하였다. 메틸화 생성물은 염 상태로서 분리가 불가능하여 TLC 분석을 통해 반응의 완료를 판단하였고, NaOH를 이용하여 hydrolysis를 시킨 결과 48을 80%의 수율로 얻었다.

Sulfinyldiene 4는 thiazole에 heteroatom이 존재하기 때문에 의도한 O-methylation 뿐만 아니라 N-methylation도 가능한 것으로 판단되었다. NMR 모니터링을 통해서는 O- 혹은 N-methylation의 판별이 불가능하였고, hydrolysis 완료 후 분리한 결과 48이 얻어졌다. 따라서 Meerwein salt를 사용할 경우 sulfinyldiene 4의 O-methylation 대신 N-methylation이 진행됨을 확인하여, sulfinyldiene 4는 사용할 수 없다는 결론에 이르렀다.
2.3 Sulfone 45의 Sulfinyl Retro-Ene 반응

Dienes 2, 3, 4의 Inverse electron demand Diels-Alder 반응 중에서 분석이 가능한 결과를 얻은 것은 sulfonyldiene 3을 사용한 경우뿐이었다.

![Sulfone 45](image)

Table 5. Sulfinyl retro-ene reaction with Diels-Alder adduct 45

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotection</th>
<th>Condition</th>
<th>Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>EtOH/THF, 25 °C, 20 h</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>NaBH(OAc)₃</td>
<td>EtOH/THF, 70 °C, 2 d</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>NaOMe</td>
<td>MeOH/THF, 70 °C, 2 d</td>
<td>H₂SO₄</td>
<td>49 (60%)</td>
</tr>
</tbody>
</table>

Diels-Alder adduct 45의 deprotection을 위해 앞서 모델 연구에서 얻어진 반응조건을 적용하였으나 반응이 진행되지 않았다 (Entry 1). Hydride 대신 methoxide를 이용하여 deprotection을 시도하였으나 방향족 생성물인 4-methyl-1-1′-biphenyl (49)을 얻게 되었다 (Entry 3).

Biphenyl 49는 아래와 같이 두 가지 mechanism으로 생성이 가능하다. 첫째, methoxide가 imidazole 그룹을 deprotection 시키고, 산성 조건에서 sulfinyl retro-ene 반응이 수행된다. 연속적으로 산성 조건에서 morpholine 그룹이 좋은 이탈기로
작용하여 방향족화가 진행된다 (Scheme 15). 둘째, morpholine 과 sulfonyl 그룹이 모두 염기 조건에서 이탈기로 작용하여 방향족화가 진행된다 (Scheme 16). 하지만 반응의 중간체를 확인할 수 없었으므로 두 mechanism, 중 어느 방식으로 진행되었는지는 알 수 없었다.

Scheme 15. Proposed mechanism for production 49

Scheme 16. Proposed mechanism for production 49
3. 后续研究

研究初期时建议的 1-sulfonyldiene 是预期的反应性，其反应性比预想的要低，protecting 组合的化合物在使用时的 deprotection 过程中产生了各种问题。为了克服这些问题，选择使用 1-sulfonyldiene 的 S-O acetal protection 组合，替代了 S-sulfonyldiene F。利用后继的研究，进行了后续的研究(Scheme 17)。

![Scheme 17. Sulfonyldiene F 的利用 tandem reaction 的后继研究](image)
CONCLUSIONS

-reported activity from a diverse sulfonyldiene system was utilized to execute normal or inverse electron demand Diels-Alder reactions. After the reaction, the sulfinyl retro-ene reaction was performed continuously to prove the feasibility of sulfonyl diene systems.

Sulfonyl substitution as well as additional electron-rich substituents were introduced into sulfonyldienes to execute Normal Diels-Alder reactions and through benzothiazole to regenerate a sulfinyl retro-ene reaction. The occurrence of this reaction was confirmed.

The combination of reactions was utilized to increase the possibility of sulfonyl diene and sulfinyl diene systems in inverse electron demand Diels-Alder reactions. However, most dienophiles did not react, indicating that sulfonyl substitution alone is insufficient for forming an electron-rich environment and yielding low reactivity.

This research was based on sulfonyldiene use, and protecting groups were substituted to conduct subsequent research. As a result, a new reaction was developed using Diels-Alder reactions and sulfinyl retro-ene reactions in a sequential manner to uniquely synthesize cyclohexene.
EXPERIMENTAL SECTION

General information. Unless otherwise noted, all reactions of substrates preparation were conducted in flame-dried glassware under an argon atmosphere using anhydrous solvent (either distilled or passed through an activated alumina column). Commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using EM Science silica gel 60 F\textsubscript{254} plates and Merck Silica gel 60 F\textsubscript{254} plates and visualized using UV light, anisaldehyde, phosphomolybdic acid, or potassium permanganate. Flash chromatography was performed on EM Science silica gel 60 (0.040-0.063 mm) or Merck silica gel 60 (0.040-0.063 mm) using the indicated solvent system. Melting points are uncorrected and were recorded on a Fisher-Johns melting point apparatus (12-144Q). \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded in CDCl\textsubscript{3}, unless otherwise noted, on a Varian Mercury 300 MHz, a Varian Inova 400 MHz, a Varian Inova 500 MHz, Bruker DPX-300 (300 MHz), Varian/Oxford As-500 (500 MHz) or a Varian Inova 600 MHz spectrometer. Chemical shifts in \textsuperscript{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data for \textsuperscript{1}H NMR were reported as follows chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz) and integration. Data for \textsuperscript{13}C NMR spectra were reported in terms of chemical shift in ppm from the central peak of CDCl\textsubscript{3} (77.23 ppm).
3-methylpenta-2,4-dienoic acid (7)

Vinylmagnesium (0.98 mL, 0.98 mmol) was slowly added to a solution of CuI (93 mg, 0.49 mmol) in THF (4.9 mL) and Me₂S (0.4 mL) at -30 °C under Ar. The mixture was stirred for 30 min at -30 °C. Then ethyl-but-2-ynoate 5 (0.10 mL, 0.89 mmol) was added dropwise. The mixture was stirred for 1 h at -30 °C and then quenched with methanol at the temperature to give 6. A solution of butynoate 6 (274 mg, 1.95 mmol) in THF (9.8 mL) and H₂O (2.8 mL) was added lithium hydroxide (410 mg, 9.77 mmol) and stirred under reflux for overnight. After the reaction was completed, 2N HCl was added and extracted with ether, dried over MgSO₄, filtered and evaporated gave 7 (193 mg, 88%).

(E)-benzyl 2-methylbuta-1,3-dienylcarbamate (8)

To a solution of pentanoic acid 7 (260 mg, 2.32 mmol) in ether (4.6 mL) at 0 °C was added triethylamine (0.36 mL, 2.55 mmol) followed by diphenyl phosphoryl azide (0.55 mL, 2.55 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was cooled to 0 °C, and saturated aqueous NaHCO₃ and ether were added. The aqueous layer was separated and extracted with ether and the combined organic layer
was dried over MgSO₄, filtered and concentrated. Flash column chromatography of the residue with a short column to remove the polar impurity. The acylazide was diluted with dry toluene and was then added dropwise to a vigorous stirred solution of benzyl alcohol and hydroquinone, pyridine in dry toluene while a rapid reflux was maintained. Reflux was continued for an additional 1 h and then the reaction mixture was cooled to room temperature and concentrated. Flash column chromatography on silica gel provided 8 (378 mg, 75%): ¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.28 (m, 5H), 6.63 (t, J = 16.6 Hz, 1H), 6.50 – 6.28 (m, 2H), 5.17 (s, 2H), 5.02 (d, J = 17.2 Hz, 1H), 4.91 (d, J = 10.7 Hz, 1H), 1.67 (s, 3H).

Benzyl (1E,3E)-4-(benzo[d]thiazol-2-ylthio)-2-methylbuta-1,3-dienylcarbamate (9)

To a solution of 2-mercaptobenzothiazole (100 mg, 0.81 mmol) and 2,6-di-t-butyl-2-methylpyridine (216 mg, 1.05 mmol) in anhydrous hexane (4 mL) was added dropwise sulfonyl chloride (0.08 mL, 0.97 mmol) at 0 ºC. The reaction was warmed to r.t. after 30 min and stirred at the temperature for 1 h. After removal of hexane and excess sulfonyl chloride in vacuo, (133 mg, 78%) was prepared. Sulfonyl chloride should be used
immediately without purification. Dropwise addition of sulphenyl chloride to 2-methyl-1,3-butadiene-1-carbamate 8 (278 mg, 1.28 mmol) at -78 °C and followed by warming to room temperature and stirred for 30 min at room temperature. DIPEA (0.67 mL, 3.84 mmol) was added and stirred for 30 min at room temperature. After a completion of reaction, the mixture was diluted with ethyl acetate and quenched with ethanol. The combined organic layer was washed with brine and dried over MgSO₄. Flash column chromatography on silica gel provided 9 (200 mg, 40%): ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.44 – 7.35 (m, 7H), 6.79 (dd, J = 23.7, 13.2 Hz, 2H), 6.52 (d, J = 10.8 Hz, 1H), 6.43 – 6.39 (m, 1H), 5.20 (s, 2H), 1.81 (s, 3H).

Benzyl (1E,3E)-4-(benzo[d]thiazol-2-ylsulfonyl)-2-methylbuta-1,3-dienylcarbamate (1)

To a solution of sulfide 9 (50 mg, 0.13 mmol) in methanol (0.65 mL) at 0 °C was added Na₂WO₄ 2H₂O (4 mg, 0.013 mmol) followed by 30% aqueous H₂O₂ (1.3 mL, 0.03 mmol). The reaction mixture was allowed to room temperature and stirred for 8 h. The reaction mixture was then diluted with DCM and a solution of 10% aqueous NaHSO₃ was
added. The biphasic mixture was stirred for 15 min and the layer was separated. The aqueous layer was separated and extracted with DCM and the combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated to gave 1 (32 mg, 59%): $^1$H NMR (500 MHz, CDCl$_3$) δ 8.18 (d, $J = 8.2$ Hz, 1H), 7.97 (d, $J = 7.9$ Hz, 1H), 7.62 – 7.51 (m, 3H), 7.44 – 7.19 (m, 6H), 7.04 – 6.85 (m, 1H), 6.35 (d, $J = 14.7$ Hz, 1H), 5.21 (s, 2H), 1.69 (s, 3H).

Benzyl 4-(benzo[d]thiazol-2-ylsulfonyl)-6-formyl-2-methylcyclohex-2-enylcarbamate (14)

Acrolein (0.04 mL, 0.54 mmol) was added to a solution of sulfonyl diene 1 (15 mg, 0.04 mmol) in toluene (0.08 mL). After then, zinc chloride (0.54 mL, 0.54 mmol) was slowly added to the solution. The mixture was stirred for 2 h at room temperature. After the reaction was completed, saturated NH$_4$Cl was added for quenching and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated to give 14. This Diels-Alder adduct was sensitive to silica gel so used immediately for next step.
2-((2E,6E)-3,7,11-trimethyldoca-2,6,10-trienylthio)benzo[d]thiazole (16)

2-mercaptobenzothiazole 50 (650 mg, 3.89 mmol) and triphenylphosphine (1067 mg, 4.07 mmol) were added to a solution of farnesol 15 (800 mg, 3.60 mmol) in THF (15 mL), then an ice bath was placed and diisopropyl azodicarboxylate (0.77 mL, 3.89 mmol) was added. After finishing the addition, stirring was continued under this condition for 30 min. After the reaction completed, the solvent was evaporated. Flash column chromatography on silica gel provided 16 (1.1 g, 99%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.87 (d, \(J = 8.2\) Hz, 1H), 7.76 (d, \(J = 8.0\) Hz, 1H), 7.44 – 7.39 (m, 1H), 7.31 – 7.27 (m, 1H), 5.42 (t, \(J = 8.4\) Hz, 1H), 5.07 (d, \(J = 6.8\) Hz, 2H), 4.02 (d, \(J = 7.8\) Hz, 2H), 2.13 – 2.00 (m, 6H), 1.98 – 1.92 (m, 2H), 1.77 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H).

2-((2E,6E)-3,7,11-trimethyldoca-2,6,10-trienylsulfonyl)benzo[d]thiazole (17)

To a solution of sulfide 16 (167 mg, 0.45 mmol) in methanol (2.25 mL) at 0 °C was added Na\(_2\)WO\(_4\) 2H\(_2\)O (15 mg, 0.04 mmol) followed by 30% aqueous H\(_2\)O\(_2\) (0.3 mL, 4.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then diluted with DCM and a solution of 10% aqueous NaHSO\(_3\) was added. The biphasic mixture was stirred for 15 min and the layers were
separated. The aqueous layer was extracted with DCM and the combined organic phase was washed with brine, dried over MgSO$_4$, filtered and concentrated. Flash column chromatography on silica gel provided 17 (133 mg, 73%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.22 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 6.7$ Hz, 1H), 7.62 (ddd, $J = 15.2$, 8.2, 5.3, 1.2 Hz, 2H), 5.31 – 5.19 (m, 1H), 5.10 – 4.94 (m, 2H), 4.24 (d, $J = 7.9$ Hz, 2H), 2.03 – 1.86 (m, 8H), 1.67 (s, 3H), 1.60-1.51 (m, 9H).

(E)-3,7,11-trimethyldodeca-1,6,10-triene (19)

Sodium borohydride (27 mg, 0.72 mmol) was added to a solution of 17 in THF (3.3 mL) and ethanol (3.3 mL) at room temperature. After 30 min, the solvent was evaporated. The mixture was brought to reflux after adding DCM, and 0.9 M aqueous tartaric acid (3.1 mL, 2.8 mmol) was added dropwise. After 30 min, the reaction mixture was cooled and extracted with DCM. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. Flash column chromatography on silica gel provided 19 (42 mg, 62%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.77 – 5.60 (m, 1H), 5.10 (q, $J = 6.7$ Hz, 2H), 4.98 – 4.89 (m, 2H), 2.17 – 2.10 (m, 1H), 2.09 – 1.91 (m, 6H), 1.68 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.38 – 1.22 (m, 2H), 0.99 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 145.00, 135.09, 131.49, 124.80, 124.64, 112.73, 40.00, 37.58, 36.97, 26.94, 25.96, 25.86, 20.42, 17.93, 16.22.
benzyl 4-(benzo[d]thiazol-2-ylsulfonyl)-6-((tert-butyldimethylsilyloxy)methyl)-2-methylcyclohex-2-enylcarbamate (20)

Sodium borohydride (3 mg, 0.08 mmol) was added to a solution of Diels-Alder adduct 14 (18 mg, 0.04 mmol) in THF (0.7 mL) and ethanol (0.7 mL) at room temperature. After stirring 2 h, the solvent was evaporated. Then the alcohol was dissolved in DMF (0.02 mL) and t-butyldimethylsilyl chloride (8 mg, 0.05 mmol) followed by imidazole (7 mg, 0.10 mmol) was added. The solution was stirred for 2 h, poured into the water and extracted with DCM to give 20. It is used for next step without purification.: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, $J = 8.3$ Hz, 1H), 8.00 (d, $J = 8.2$ Hz, 1H), 7.56 (t, $J = 7.7$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 1H), 7.40 – 7.32 (m, 5H), 5.67 (s, 1H), 5.08 (q, $J = 12.3$ Hz, 2H), 4.89 (d, $J = 9.9$ Hz, 1H), 4.34 (s, 1H), 4.22 (d, $J = 10.0$ Hz, 1H), 3.76 (d, $J = 8.2$ Hz, 1H), 3.44 – 3.38 (m, 1H), 2.27 (dd, $J = 18.0$, 10.1 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.78 (s, 3H), 0.79 (s, 9H), 0.01 – -0.04 (m, 6H).
benzyl 6-((tert-butyldimethylsilyloxy)methyl)-2-methylcyclohex-3-enylcarbamate (21)

Sodium borohydride (2 mg, 0.053 mmol) was added to a solution of 20 in THF (0.09 mL) and ethanol (0.09 mL) at room temperature. After 30 min, the solvent was evaporated. The mixture was brought to reflux after adding DCM, and 0.9 M aqueous tartaric acid (0.08 mL, 0.09 mmol) was added dropwise. After 30 min, the reaction mixture was cooled and extracted with DCM. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. Flash column chromatography on silica gel provided 21 (1.7 mg, 48%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 – 7.28 (m, 5H), 5.68 (d, $J = 8.8$ Hz, 1H), 5.57 (d, $J = 11.2$ Hz, 1H), 5.50 (d, $J = 10.5$ Hz, 1H), 5.11 – 5.06 (m, 2H), 3.80 – 3.74 (m, 1H), 3.73 – 3.68 (m, 1H), 3.52 (dd, $J = 10.2$, 6.0 Hz, 1H), 2.29 – 2.11 (m, 3H), 1.78 – 1.67 (m, 1H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.08 – 0.01 (m, 6H).

2-(methylsulfonyl)benzothiazole (23)

Periodic acid (2640 mg, 12 mmol) was dissolved in acetonitrile (33 mL) by vigorous stirring at room temperature for 1 h. Then, chromium oxide (55 mg, 10 mol%) was added
to the solution. The mixture was stirred at room temperature for 5 min to give a clear orange solution. The H$_3$I$_6$/CrO$_3$ solution was added dropwise over a period of 45 min to a solution of 2-(methylthio)benzothiazole 22 (1000 mg, 5.5 mmol) in ethyl acetate (70 mL) at -35 °C. After the addition was completed, the reaction mixture was stirred at -35 °C for 10 min. The reaction was quenched by addition of saturated Na$_2$SO$_3$ solution. The resulting mixture was collected by washed with brine and dried over MgSO$_4$ to gave the title compound 23 (1048 mg, 89%): $^1$H (500MHz, CDCl$_3$) δ 8.24 – 8.19 (m, 1H), 8.05 – 8.01 (m, 1H), 7.63 (dddd, J = 15.2, 8.4, 7.2, 1.3 Hz, 2H), 3.42 (s, 3H).

![Chemical structure](image)

**(E)-2-(3-methylbuta-1,3-dienylsulfonyl)benzothiazole (2)**

Diisopropylamine (0.4 mL, 2.8 mmol) in THF (4.7 mL) was stirred at r.t. n-BuLi (1.1mL, 2.0 M in hexane) was added to the solution at -78 °C and stirred for 10 min at the temperature. The mixture was warmed to 0 °C and stirred for 10 min then cooled back to -78 °C. Sulfone 23 (500 mg, 2.3 mmol) in THF was added dropwise to the prepared LDA solution at -78 °C and stirred for 1 h. Methacrolein was added rapidly at -78 °C and stirred for 1.5 h. Pyridine (0.2 mL, 2.3 mmol) was added and stirred for 10 min. Mesyl chloride (0.36 mL, 4.7 mmol) was added and stirred for 2 h at -78 °C. The reaction mixture was quenched with HCl and extracted with DCM and dried over Na$_2$SO$_4$ to gave
the diene 2 (279 mg, 27%): $^1$H (500 MHz, CDCl$_3$) δ 8.20 (d, $J$ = 8.3 Hz, 1H), 8.00 (d, $J$ = 7.8 Hz, 1H), 7.65 – 7.51 (m, 3H), 6.63 (d, $J$ = 15.1 Hz, 1H), 5.57 (d, $J$ = 10.9 Hz, 2H), 1.89 (s, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 167.23, 153.12, 149.32, 139.00, 137.15, 129.26, 128.17, 127.83, 125.65, 125.07, 122.55, 18.24.

\[
\begin{align*}
\text{(E)-4-(1-methyl-1H-imidazol-2-ylthio)but-3-en-2-one (27)}
\end{align*}
\]

To a suspension of 2-mercapto-1-methylimidazole 25 (200 mg, 1.75 mmol) in acetonitrile (13.5 ml) was added triethylamine (0.87 ml, 6.3 mmol), and then a 3-butyln-2-one 26 (238 mg, 3.5 mmol) was added dropwise. The mixture was stirred for 3.5 h at room temperature and solvent was evaporated. Flash column chromatography on silica gel provided 27 (187 mg, 49%): $^1$H (500 MHz, CDCl$_3$) δ 7.58 (d, $J$ = 15.4 Hz, 1H), 7.20 (d, $J$ = 1.2 Hz, 1H), 7.09 (d, $J$ = 1.2 Hz, 1H), 5.92 (d, $J$ = 15.4 Hz, 1H), 3.69 (s, 3H), 2.21 (s, 3H); $^{13}$C (500 MHz, CDCl$_3$) δ 194.98, 143.44, 131.02, 126.98, 124.42, 33.93, 27.63.
(E)-1-methyl-2-(3-methylbuta-1,3-dienylthio)-1H-imidazole (28)

To a suspension of methyl triphenylphosphonium bromide (6.3 g, 17.6 mmol) in THF (59 mL) was added t-BuOK (1.5 g, 13.1 mmol) at 0 °C. Then, sulfide 27 (795 mg, 4.36 mmol) was added to the mixture and stirred for 30 min at 0 °C. After the reaction was completed, the mixture was quenched with H₂O, extracted with ethyl acetate, and the combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated. The resulting crude product was purified by flash column chromatography to give the desired product 28 (548 mg, 74%) as white solid: ¹H (500MHz, CDCl₃) δ 7.13 (s, 1H), 7.02 (s, 1H), 6.31 – 6.29 (m, 2H), 4.92 (d, J = 22.7 Hz, 2H), 3.67 (s, 3H), 1.84 (s, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 140.90, 133.88, 130.11, 123.40, 121.22, 116.64, 33.79, 18.67.

(E)-1-methyl-2-(3-methylbuta-1,3-dienylsulfonyl)-1H-imidazole (3)

Thiodiene 28 (765 mg, 4.24 mmol) in ethanol (71 mL) was added to a solution of (NH₄)₆MoO₂₄·4H₂O (10789 mg, 8.49 mmol) in hydrogen peroxide (10 mL) at 0 °C.
The reaction mixture was stirred for 1.5 h at room temperature. After the reaction was completed, the mixture was quenched with H$_2$O, extracted with DCM, washed with brine, and the combined organic layers were dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated. The resulting crude product was purified by flash column chromatography to give the desired product 3 (870 mg, 97%): $^1$H (500MHz, CDCl$_3$) δ 7.41 (d, $J = 15.2$ Hz, 1H), 7.16 (d, $J = 0.9$ Hz, 1H), 7.01 (d, $J = 0.6$ Hz, 1H), 6.58 (d, $J = 15.2$ Hz, 1H), 5.52 (d, $J = 7.8$ Hz, 2H), 3.98 (s, 3H), 1.91 (s, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 146.89, 138.99, 129.74, 128.22, 126.33, 125.89, 35.42, 18.35.

![Chemical structure](image)

**Anhydrous LiCl (108.5 mg, 2.56 mmol) was prepared under Ar and isopropylmagnesium chloride (1.16 mL, 2.56 mmol) was added dropwise at room temperature. After the completion of addition, the reaction mixture was stirred for 7 h, and 2-bromothiazole (0.19 mL, 2.11 mmol) was added dropwise. The Mg/Br exchange was completed after 30 min at room temperature. To a solution of ZrCp$_2$HCl (300 mg, 1.16 mmol) in THF (2.32 mL) was added a solution of 29 (0.14 mL, 1.51 mmol) in THF (3.78 mL) at 0 ºC. The mixture was warmed to room temperature and stirred for 1 h and then cooled to -10 ºC and thionyl chloride (0.11 mL, 1.51 mmol) was added and stirred 10 min at room temperature. Prepared solution of Grignard reagent was cannulated to the**
solution of sulfinyl chloride at -10 °C and stirred for 4 h at room temperature. After a completion of reaction, the mixture was diluted with ethyl acetate and the organic layer was washed with brine and dried over MgSO₄. Flash column chromatography on silica gel provided 4 (21 mg, 10%): ¹H NMR (500 MHz, CD₂Cl₂) δ 7.94 (d, J = 3.1 Hz, 1H), 7.68 (d, J = 3.1 Hz, 1H), 7.13 (d, J = 15.3 Hz, 1H), 6.57 (d, J = 15.3 Hz, 1H), 5.42 – 5.25 (m, 2H), 1.88 (s, 3H); ¹³C NMR (500 MHz, CD₂Cl₂) δ 145.07, 140.59, 139.79, 132.35, 132.12, 124.21, 124.09, 18.43.

3-vinyl oxazolidin-2-one (32)

A mixture of oxazolidin-2-one 36 (500 mg, 5.7 mmol), acetaldehyde diethyl acetal (8 mL, 56 mmol) and D,L-camphorsulfonic acid (67 mg, 5 mol%) was heated for 15 h at 55 °C. After cooling to room temperature, aqueous NaHCO₃ was added and the reaction mixture was extracted with ether. The organic layer was washed with brine and dried over MgSO₄. Removal of solvent yielded crude N,O-acetal used without purification. To a cooled solution of crude N,O-acetal (0 °C) in anhydrous DCM under N₂ was added dropwisely distilled triethylamine (1.0 mL) and trimethylsilyl triflate (1.0 mL, 7.3 mmol). After slow return to room temperature and stirring for 16 h, the mixture was filtered on basic alumina to give 32 (247 mg, 38%): ¹H (500MHz, CDCl₃) δ 6.82 (dd, J = 15.9, 9.0
Hz, 1H), 4.52 – 4.39 (m, 3H), 4.33 (dd, J = 15.8, 1.2 Hz, 1H), 3.74 (dd, J = 8.9, 7.4 Hz, 2H); \(^{13}\)C (500MHz, CDCl\(_3\)) δ 155.57, 129.78, 93.61, 62.54, 42.03.

Benzyl vinylcarbamate (33)

Sodium azide (1.0 g, 15.47 mmol) was dissolved in distilled water (6.4 mL) and cooled to 0 °C. Acryloyl chloride 38 (0.89 ml, 11.05 mmol) was dissolved in dry toluene (2.8 mL) and dropwise into the cold sodium azide solution. The reaction mixture was stirred for 3 h at 0 °C. After the reaction was completed, the mixture was extracted with small amount of toluene and the combined organic layers were dried with anhydrous Na\(_2\)SO\(_4\) and filtered gave 39. Acryloyl azide 39 in toluene was added dropwise to a stirred and heated (110 °C) mixture of benzyl alcohol (2.66 mL, 25.64 mmol), hydroquinone (97.3 mg, 0.88 mmol) and pyridine (0.11 mL, 1.33 mmol). The solution was stirred for 2 h at 110 °C. After the reaction was completed, the mixture was extracted with ethyl acetate and dried with anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The resulting crude product was purified by flash column chromatography to give the desired product 33 (1.8 g, 50%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.42 – 7.32 (m, 5H), 6.76 – 6.66 (m, 1H), 6.45 (s, 1H), 5.15 (s, 2H), 4.48 (d, J = 15.7 Hz, 1H), 4.30 (d, J = 8.7 Hz, 1H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) δ 153.98, 136.18, 130.15, 128.83, 128.59, 128.48, 93.76, 67.39.
2-(6-butoxy-3-methylcyclohex-2-enylsulfonyl)benzothiazole (35)

A mixture of diene 2 (80 mg, 0.18 mmol) and butyl vinyl ether 34 (0.24 mL, 1.83 mmol) in benzene (3.6 mL) was refluxed for 25 h. After a completion of reaction, the mixture was diluted with ethyl acetate and the organic layer was washed with brine and dried over MgSO₄. Flash column chromatography on silica gel provided 35 (4 mg, 6%): ¹H (500MHz, CDCl₃) δ 8.24 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.67 – 7.54 (m, 2H), 5.53 (s, 1H), 4.43 (s, 1H), 4.11 – 4.06 (m, 1H), 3.39 – 3.34 (m, 1H), 3.29 – 3.22 (m, 1H), 2.09 – 2.02 (m, 2H), 1.81 (s, 3H), 1.78 – 1.72 (m, 2H), 1.12 – 1.02 (m, 4H), 0.67 (t, J = 7.1 Hz, 3H).

4-(1-phenylvinyl)morpholine (43)

To a N₂ filled two neck flask equipped with a reflux condenser and a magnetic stirrer was added anhydrous hexane (125 mL), acetophenone 46 (1.5 g, 12.5 mmol) and morpholine 47 (5.0 g, 57.4 mmol) at 0 °C. The TiCl₄ (8.75 mL, 8.75 mmol) in anhydrous hexane (5 mL) was added dropwise over 40 min. The reaction mixture was stirred under reflux for 3.5 h. After the reaction was completed, solvent was evaporated in vacuo to
obtain a yellow oily product 43 (2.3 g, 98%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.49 – 7.43 (m, 2H), 7.36 – 7.30 (m, 3H), 4.33 (s, 1H), 4.19 (s, 1H), 3.78 – 3.76 (m, 4H), 2.90 – 2.78 (m, 4H).

(Z)-2-(2-methyl-4-(1-methyl-1H-imidazol-2-ylsulfonyl)but-2-enyl)cyclopentanone (44)

A mixture of diene 3 (37 mg, 0.17 mmol) and 1-pyrrolidino-1-cyclopentene (239 mg, 1.74 mmol) in toluene (0.17 mL) was stirred for 3 h at room temperature. After a completion of reaction, the mixture was diluted with ethyl acetate and the organic layer was washed with brine and dried over MgSO\(_4\). Flash column chromatography on silica gel provided 44 (40 mg, 79%): \(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.16 (s, 1H), 7.02 (s, 1H), 5.27 (t, \(J = 7.7\) Hz, 1H), 4.15 (d, \(J = 7.9\) Hz, 2H), 3.94 (s, 3H), 2.55 (dd, \(J = 13.9, 2.7\) Hz, 1H), 2.32 (dd, \(J = 18.6, 8.0\) Hz, 1H), 2.26 – 2.06 (m, 3H), 2.03 – 1.89 (m, 2H), 1.82 – 1.72 (m, 1H), 1.56 (s, 3H), 1.48 – 1.27 (m, 1H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 220.53, 145.88, 141.77, 129.58, 125.88, 110.58, 55.31, 47.49, 40.02, 38.14, 35.37, 29.43, 20.73, 16.54.
4-(4-methyl-2-(1-methyl-1H-imidazol-2-ylsulfonyl)-1-phenylcyclohex-3-enyl)morpholine (45)

A mixture of diene 3 (100 mg, 0.47 mmol) and enamine 43 (893 mg, 4.71 mmol) in toluene (0.59 mL) was heated at 70 °C for 48 h. After a completion of reaction, the mixture was diluted with ethyl acetate and the organic layer was washed with brine and dried over MgSO₄. Flash column chromatography on silica gel provided 45 (66 mg, 40%): ¹H NMR (500 MHz, CDCl₃) δ 7.08-7.09 (m, 5H), 7.07 (d, J = 1.0, 1H), 6.50 (d, J = 0.5, 1H), 5.64-5.64 (m, 1H), 5.01 (d, J = 5.0, 1H), 3.56-3.54 (m, 2H), 3.45-3.43 (m, 2H), 3.16 (s, 3H), 3.02-2.97 (m, 1H), 2.50-2.48(m, 2H), 2.37-2.33 (m, 4H), 2.24-2.10 (m, 2H), 1.91 (s, 3H).

3-methylthiazol-2(3H)-one (48)

NMR tube was charged with diene 4 (21 mg, 0.11 mmol) and CD₂Cl₂ then Me₃OBF₄ (16 mg, 0.11 mmol) was added. Methylation was completed within 16 h which was monitored by NMR spectroscopy provide methylated product. Styrene was added to the solution in NMR tube and the reaction was completed after 24 h at room temperature. 0.2
\( \text{NaN} \text{OH (0.65 ml, 0.13 mmol) was added for quenching and stirring for 30 min. The mixture was diluted with DCM and the organic layer was washed with brine and dried over MgSO}_4 \). Flash column chromatography on silica gel provided 48 (10 mg, 80%): \(^1\text{H}\) (500MHz, CDCl\(_3\)) \( \delta 6.54 \text{ (d, } J = 5.3 \text{ Hz, 1H)}, \ 6.12 \text{ (d, } J = 5.3 \text{ Hz, 1H)}, \ 3.34 \text{ (s, 3H)}. \)

4-methylbiphenyl (49)

Sodium (6.9 mg, 0.3 mmol) was dissolved in absolute ethanol (0.23 mL) at room temperature under strict anhydrous condition, and then a solution of 45 (25 mg, 0.06 mmol) in anhydrous THF (0.1 mL) was added dropwise to give an anhydrous yellow suspension. The reaction mixture was gently heated to give at 70 °C for 20 h. Then sulfuric acid (0.02 mL, 0.30 mmol) was dropped to the solution of sulfinate dissolving in MeOH/THF and stirred for 3.5 h at 70 °C. After a completion of reaction, the mixture was diluted with ethyl acetate and the organic layer was washed with brine and dried over Na\(_2\)SO\(_4\). Flash column chromatography on silica gel provided 49 (6 mg, 60%): \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \( \delta 7.61 - 7.48 \text{ (m, 4H)}, \ 7.46 - 7.30 \text{ (m, 4H)}, \ 7.26-7.25 \text{ (m, 1H)}, \ 2.40 \text{ (s, 3H)}. \)
REFERENCES


감사의 글

2008년 추운 겨울, 교수님과 실험실 동료들에게 어색하게 인사를 드리고 1번 라인에 자리와 환영을 뒤로 간 경험이 생생하면서, 어느덧 이렇게 긴 시간이 지났습니다. 많은 분들의 도움이 있었기에 2년이라는 길고도 짧은 시간을 잘 보낼 수 있었습니다. 석사 과정 동안 유기화학 지식 및 소양을 쌓았을 뿐 아니라 좋은 사람들을 만나고 추억을 만들 수 있었기에 의미 있고 행복한 시간이었습니다.

먼저 지도교수님인 이철범 교수님, 유기 화학자로서 늘 열정과 도움을 보내주시고 부족한 점이 많은 저를 세심하게 지도해주신 점 감사드립니다.

제가 시작한 연구를 훌륭하게 마무리하여 이렇게 감사의 글을 쓸 수 있도록 고생해준 진이와 호윤이에게 깊은 감사를 전합니다.

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마지막으로 항상 제 건에서 응원하고 지지해주시는 사랑하는 부모님과 동생에게 감사를 드리며 글을 마칩니다.
SPECTRA
$^{1}$$\text{H NMR (500 MHz, CDCl}_3\text{) of 8}$

$^{1}$$\text{H NMR (500 MHz, CDCl}_3\text{) of 9}$
$^1$H NMR (500 MHz, CDCl$_3$) of 1

$^1$H NMR (500 MHz, CDCl$_3$) of 16
$^1$H NMR (500 MHz, CDCl$_3$) of 17

$^1$H NMR (500 MHz, CDCl$_3$) of 19
$^{13}$C NMR (500 MHz, CDCl$_3$) of 19

$^1$H NMR (500 MHz, CDCl$_3$) of 20
$^1$H NMR (500 MHz, CDCl$_3$) of 21

$^1$H NMR (500 MHz, CDCl$_3$) of 23
$\text{H NMR (500 MHz, CDCl}_3\text{) of 2}$

$\text{C NMR (500 MHz, CDCl}_3\text{) of 2}$
$^1$H NMR (500 MHz, CDCl$_3$) of 27

$^{13}$C NMR (500 MHz, CDCl$_3$) of 27
$^1$H NMR (500 MHz, CDCl$_3$) of 28

$^{13}$C NMR (500 MHz, CDCl$_3$) of 28
$^1$H NMR (500 MHz, CDCl$_3$) of 3

$^{13}$C NMR (500 MHz, CDCl$_3$) of 3
$^1$H NMR (500 MHz, CD$_2$Cl$_2$) of 4

$^{13}$C NMR (500 MHz, CD$_2$Cl$_2$) of 4
$\text{H NMR (500 MHz, CDCl}_3\text{) of 32}$

$\text{13C NMR (500 MHz, CDCl}_3\text{) of 32}$
$^1$H NMR (500 MHz, CDCl$_3$) of 33

$^{13}$C NMR (500 MHz, CDCl$_3$) of 33
$^{1}H$ NMR (500 MHz, CDCl$_3$) of 35

$^{1}H$ NMR (500 MHz, CDCl$_3$) of 43
$^1$H NMR (500 MHz, CD$_2$Cl$_2$) of 44

$^{13}$C NMR (500 MHz, CDCl$_3$) of 44
$^1$H NMR (500 MHz, CDCl$_3$) of 45

$^1$H NMR (500 MHz, CDCl$_3$) of 48
H NMR (500 MHz, CDCl$_3$) of 49

$^1$H NMR (500 MHz, CDCl$_3$) of 49