One-Pot and Stereospecific Synthesis of cis-1,2-Diazides via Mitsunobu Reaction of Epoxides

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Abstract: Mitsunobu reaction of epoxides using hydrazoic acid, diethylazodicarboxylate, and triphenylphosphine as reagents gave the corresponding cis-1,2-diazides in moderate yield. Application of similar reaction conditions to trans-diols furnished the corresponding trans-1,2-diazides.

Key words: Mitsunobu reaction, cis-1,2-diazides, trans-1,2-diazides, epoxides, trans-1,2-diols

Azides are versatile functional groups for many purposes in organic synthesis. 1,2-Diazides are especially important precursors for the synthesis of 1,2-diamines, which are otherwise difficult to obtain. So far, many procedures have been developed for the preparation of 1,2-diazides starting from alkenes. Minisci et al. described radical oxidation-reduction processes using sodium azide, iron(II) salts and peroxides by which two azido groups are introduced to a double bond of olefin. Hugl and Zbiral used Pb(IV) salts to convert alkenes to 1,2-diazides, and 1,3-dienes to 1,4-diazides. Schafer electrochemically converted olefins to 1,2-diazides by oxidative addition of the azide to olefins. Mn(III) salts have been used to convert olefins to 1,2-diazides. Moriarty and Khasrowskahi have synthesized vicinal diazides from alkenes by using iodosylbenzene.

However, few papers appear in the literature for stereospecific conversion of olefins to 1,2-diazides. Magnus et al. described a diastereoselective synthesis of certain trans-1,2-diazides from trisopropylsilylenol ethers by the treatment of iodosylbenzene and trimethylsilylazide. Only Sasaki et al. has reported stereospecific formation of some cis-1,2-diazides from the corresponding alkenes by the reaction of iodine azide and sodium azide by a one-pot reaction. The most common method for introducing vicinal diazides has been via a series of standard S_N2 displacements utilizing highly nucleophilic azide anion.

In this paper, we describe a convenient method for stereospecific synthesis of cis-1,2-diazides using Mitsunobu reaction.

Mitsunobu reaction, useful to convert alcohols to many functional groups, has been used for many syntheses over thirteen years. An important aspect of this reaction is that it proceeds by an S_N2 mechanism. From this aspect, Mitsunobu reaction was used to synthesize cis-1,2-diazidocyclohexane from trans-2-azidocyclohexanol by Zbiral and Hugl.

However, the preparation of trans-2-azidoalcohols from epoxides requires additional S_N2 displacement with NaN_3. Trimethylsilyl azide can also be used for this conversion by which O-silylated derivative of 2-azidoalcohols are obtained. We propose that direct application of Mitsunobu reaction to epoxides can produce cis-1,2-diazides considering mechanistic aspects: (i) the first step: ring-opening of epoxides via S_N2 mechanism to afford trans-2-azidocycloalkanols; (ii) the second step: Mitsunobu reaction of trans-2-azidocycloalkanols to give cis-1,2-diazides (Scheme 1).

Scheme 1

For this purpose, epoxides 1–7 prepared from the corresponding cycloalkenes were treated with the Mitsunobu reagents, triphenylphosphine, diethyl azodicarboxylate, hydrazoic acid, to give cis-1,2-diazides 8–14 in moderate yields ranging from 50–85% (Scheme 2 and Table 1).

Scheme 2

As seen in Table 1, the reactions proceed in stereospecific manner to form cis-1,2-diazides without any side product. ^1H and ^13C NMR spectra of the azides are in good agreement with the structures. Again, characteristic IR absorption bands of azide functional groups were observed for all products.

The unsymmetrical structure of 12 and cis-configuration were determined by means of NMR data. The observed coupling constant between H_1 and H_2 in 12 is 3.4 Hz which is in good agreement with the reported value (~ 4 Hz) of the similar cis-1,2 functionalised-1,2,3,4-tetrahydronaphthalene systems. Unfortunately, ^1H NMR values of the corresponding diazide compounds are not reported except for cis-1,2-diazidocyclohexane (9) by trans-1,2-di-
azidocyclohexane (23), cis-1,2-diazido-1,2,3,4-tetrahydronaphthalene (12), and trans-2,3-diazido-1,2,3,4-tetrahydronaphthalene (25). 

\(^1\)H NMR spectral data for cis-diazides 9 and 12 are in good agreement with the reported ones in the literature. Besides, to establish exactly stereochemistry of the other structures, we decided to synthesize trans-1,2-diazides from trans-1,2-diols via Mitsunobu reaction. Skarzewski and Gupta showed stereospecific transformations of vicinal trans-diols in five-membered heterocyclic system derived from tartaric acid to the corresponding trans-1,2-diazides via Mitsunobu reaction. We assumed that Mitsunobu reaction of cyclic trans-1,2-diols 15–21 also proceeded by an in situ azidation, generating trans-1,2-diazides 22–28. Indeed, most of experiments occurred stereospecifically in good yields as shown in Scheme 3 and Table 2.

As seen in Table 2, Mitsunobu reaction of trans-1,2-diols proceeded to give the corresponding trans-1,2-diazides as the main product. This reaction occurred in better total yields and faster than the epoxides. The formation of naphthalene (29) from 1,2,3,4-tetrahydronaphthalene-2,3-diol (18) and the formation of 4-azido-1,2-dihydronaphthalene (30) from 1,2,3,4-tetrahydronaphthalene-1,2-diol (19) may be explained by dehydration via E1 mechanism. In some literature examples, the formation of epoxides from trans-diols is possible.

Considering this aspect, most probably the formation of cis-1,2-diazides 9 and 10 occurs through epoxides (Scheme 3). 

All 

\(^1\)H and \(^1\)C NMR spectral data for both cis- and trans-1,2-diazides are given in Table 3 for comparison. As expected and seen in Table 3, all \(^1\)H NMR and \(^1\)C NMR data of cis- and trans-1,2-diazide diastereomers are different from each other.

Considering the toxicity of benzene we also used toluene instead of benzene for transformation of epoxides 2, 7 and trans-diols 16, 21 to the corresponding diazides. These reactions occurred in similar yields with azidation in benzene.

In conclusion, this study shows the possibility of one-pot and stereospecific preparation of cis-1,2-diazides from epoxides and some trans-1,2-diazides from trans-1,2-diols via Mitsunobu reaction.

IR spectra were obtained by using on a Mattson 1000 FT-IR spectrophotometer. The \(^1\)H and \(^1\)C NMR spectra were recorded on 200 (50) MHz Varian spectrometers. Column chromatography experiments were performed on silica gel 60 (70–230 mesh ASTM). TLC was carried out on Merck 0.2 mm silica gel, 60 F254 analytical aluminum plates. Starting materials cyclopentene, cyclohexene, 1,4-cyclohexadiene and 1,5-cyclooctadiene are commercially available. Cycloheptene from cycloheptanol, 1,4-dihydronaphthalene from naphthalene were prepared as previously reported. 1,2-dihydronaphthalene was prepared from 1,4-dihydronaphthalene by refluxing with t-BuOK in THF using slightly modified literature procedure. Preparation of HN₃ in benzene and determination of molarity were made according to literature. CAUTION! Hydrazoic acid causes eye irritation, cough, headache, fall in blood pres-
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Sure, weakness, palpitation, ataxia and collapse. All experiments should be handled in an efficient fume hood behind a protection shield. Benzene is also a carcinogenic material. Therefore, toluene may be also used instead of benzene. Due to the instability of diazides, they all must be kept in a refrigerator after synthesis.

Epoxide \(\text{4}\) was prepared from the corresponding alkene by the treatment with MCPBA and refluxing in CHCl\(_3\), following a general epoxidation procedure.\(^{20}\) Epoxides \(\text{1, 2, and 6}\) were prepared in CH\(_2\)Cl\(_2\) by a similar procedure but at r.t. Epoxides \(\text{3, 5, 7}\) were prepared again by a similar procedure in CH\(_2\)Cl\(_2\) at 0 °C.

**Table 2 **Mitsunobu Reaction Products of trans-1,2-Diols

<table>
<thead>
<tr>
<th>trans-Diol</th>
<th>Product</th>
<th>Side Product</th>
<th>Reaction Time (h)(^{a})</th>
<th>Total Yield (%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{15})</td>
<td>(\text{22})</td>
<td>–</td>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>(\text{16})</td>
<td>(\text{23})</td>
<td>(\text{9})</td>
<td>12</td>
<td>74 (ratio of (\text{23:9} = 4:1))(^{c})</td>
</tr>
<tr>
<td>(\text{17})</td>
<td>(\text{24})</td>
<td>(\text{10})</td>
<td>12</td>
<td>67 (ratio of (\text{24:10} = 3:1))(^{c})</td>
</tr>
<tr>
<td>(\text{18})</td>
<td>(\text{25})</td>
<td>(\text{29})</td>
<td>12</td>
<td>84 (ratio of (\text{25:29} = 8:1))(^{d})</td>
</tr>
<tr>
<td>(\text{19})</td>
<td>(\text{26})</td>
<td>(\text{30})</td>
<td>12</td>
<td>84 (ratio of (\text{26:30} = 3:1))(^{d})</td>
</tr>
<tr>
<td>(\text{20})</td>
<td>(\text{27})</td>
<td>–</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>(\text{21})</td>
<td>(\text{28})</td>
<td>–</td>
<td>12</td>
<td>58</td>
</tr>
</tbody>
</table>

\(^{a}\) Progress of the reaction was checked by TLC.
\(^{b}\) Isolated yields.
\(^{c}\) Ratios determined by NMR spectra.
\(^{d}\) Ratios determined according to isolated amounts by column chromatography.

\[\text{13}^1\text{C NMR (50 MHz): } \delta = 133.6, 131.2, 128.5, 53.5, 31.8.\]

\[\text{Cycloheptene Oxide (6)}^{33}\]
\[\text{1H NMR (200 MHz): } \delta = 3.00 (m, 2 H), 1.96–1.73 (m, 4 H), 1.61–1.27 (m, 4 H), 1.19–1.04 (m, 2 H).\]

\[\text{13}^1\text{C NMR (50 MHz): } \delta = 57.8, 33.0, 31.0, 26.4.\]

**Mitsunobu Reaction of Epoxides: Typical Procedure**

To a magnetically stirred solution of PPh\(_3\) (4.00 g, 15.3 mmol) in anhyd benzene (30 mL), a soln of DEAD (2.55 g, 14.7 mmol) in anhyd benzene (10 mL) was added dropwise under N\(_2\) atm at 10 °C. To the resulting mixture, azidoic acid (15.3 mmol, 8.5 mL, 1.8 M) in benzene, and cyclohexene oxide (\(\text{2}^{18}\)) (0.60 g, 6.1 mmol) was added respectively and stirred for 20 min at the same temperature. The mixture was refluxed for 35 h and then cooled to r.t. The solvent was evaporated (35 °C), the residue was dissolved in hexane–Et\(_2\)O, 2:3 and left in a refrigerator overnight. The precipitate was filtered off. Chromatography of the filtrate on silica gel column using hexane–Et\(_2\)O–CHCl\(_3\), 100:3:3 as an eluent afforded cis-1,2-diazidocyclohexane (\(\text{9}\)) (60%).
Table 3  NMR Spectral Data for cis- and trans-1,2-Diazides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>(^1)H NMR (200 MHz), (\delta, J) (Hz)</th>
<th>(^{13})C NMR (50 MHz), (\delta, J) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-(8)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.81 (m, 2 H), 2.20–1.50 (m, 6 H)</td>
<td>66.5, 30.0, 22.0</td>
</tr>
<tr>
<td>trans-(22)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.74 (m, 2 H), 2.10–1.96 (m, 2 H), 1.85–1.63 (m, 4 H)</td>
<td>68.9, 31.3, 22.9</td>
</tr>
<tr>
<td>cis-(9)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.61 (quasi d, 2 H, (J = 7.7)), 1.92–1.25 (m, 8 H)</td>
<td>63.4, 29.4, 23.7</td>
</tr>
<tr>
<td>trans-(23)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.17 (m, 2 H), 2.20–1.18 (m, 8 H)</td>
<td>66.5, 32.6, 25.8</td>
</tr>
<tr>
<td>cis-(10)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>5.62 (m, 2 H), 3.79 (quasi t, 2 H, (J = 5.3)), 2.38 (m, 4 H)</td>
<td>123.7, 58.9, 28.2</td>
</tr>
<tr>
<td>trans-(24)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>5.59 (m, 2 H), 3.54 (m, 2 H), 2.53 (A part of AB system, br d, 2 H, (J = 17.5)), 2.13 (B part of AB system, dm, 2 H, (J = 17.5))</td>
<td>124.1, 61.1, 30.4</td>
</tr>
<tr>
<td>cis-(11)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>7.21–7.10 (AA’BB’ system, 4 H), 3.99 (quasi t, 2 H, (J = 5.6)), 3.12 (m, 4 H)</td>
<td>133.6, 131.0, 128.8, 61.3, 33.7</td>
</tr>
<tr>
<td>trans-(25)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>7.23–7.10 (AA’BB’ system, 4 H), 3.75 (m, 2 H), 3.24 (A part of AB system, dd, 2 H, (J = 16.9, 4.0)), 2.90 (B part of AB system, dd, 2 H, (J = 16.9, 9.6))</td>
<td>133.5, 130.0, 128.2, 62.7, 35.0</td>
</tr>
<tr>
<td>cis-(12)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>7.38–7.17 (m, 4 H), 4.65 (br d, 1 H, (J = 3.4)), 3.80 (dt, 1 H, (J = 11.1, 3.4)), 3.15–2.81 (m, 2 H), 2.35–2.00 (m, 2 H)</td>
<td>137.4, 133.8, 131.6, 131.3, 131.1, 128.6, 64.6, 61.7, 29.4, 24.9</td>
</tr>
<tr>
<td>trans-(26)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>7.43–7.15 (m, 4 H), 4.46 (d, 1 H, (J = 6.9)), 3.89 (ddd, 1 H, (J = 9.8, 6.9, 3.2)), 2.94 (m, 2 H), 2.24 (A part of AB system, ddt, 1 H, (J = 14.1, 5.9, 3.2)), 2.00 (B part of AB system, m, 1 H)</td>
<td>137.0, 132.9, 130.4, 130.3, 129.9, 128.1, 64.9, 62.9, 27.3, 26.5</td>
</tr>
<tr>
<td>cis-(13)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.70 (quasi d, 2 H, (J = 9.2)), 1.99–1.40 (m, 10 H)</td>
<td>66.9, 30.8, 28.3, 24.7</td>
</tr>
<tr>
<td>trans-(27)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>3.38 (m, 2 H), 1.96–1.42 (m, 10 H)</td>
<td>69.7, 32.4, 29.6, 25.3</td>
</tr>
<tr>
<td>cis-(14)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>5.66 (m, 2 H), 3.82 (quasi t, 2 H, (J = 4.1)), 2.56 (m, 2 H), 2.20–1.65 (m, 6 H)</td>
<td>131.5, 66.4, 32.3, 24.3</td>
</tr>
<tr>
<td>trans-(28)</td>
<td><img src="cis-1,2-Diazidocyclohexane" alt="" title="9" /></td>
<td>5.59 (m, 2 H), 3.65 (m, 2 H), 2.60–2.05 (m, 6 H), 1.80 (m, 2 H)</td>
<td>130.5, 67.5, 32.2, 25.7</td>
</tr>
</tbody>
</table>

**cis-1,2-Diazidocyclohexane (9)**
Colorless oil [lit.\(\beta^\Phi\) bp 80 °C/0.5 mm Hg]
IR: 2953, 2876, 2110, 1472, 1370, 1319, 1268 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 9 are given in Table 3.

** cis-1,2-Diazidocyclopentane (8)**
Colorless oil [lit.\(\beta^\Phi\) bp 47–50 °C/0.5 mm Hg].
IR: 2978, 2876, 2136, 1472, 1446, 1344, 1268 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 8 are given in Table 3.

** cis-4,5-Diazidocyclohexene (10)**
Colorless oil.
IR: 3020, 2890, 2880, 2110, 1656, 1446, 1270 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 10 are given in Table 3.

** cis-2,3-Diazido-1,2,3,4-tetrahydronaphthalene (11)**
Colorless oil.
IR: 3080, 3029, 2953, 2851, 2110, 1600, 1497, 1446, 1370, 1268 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 11 are given in Table 3.

** cis-1,2-Diazido-1,2,3,4-tetrahydronaphthalene (12)**
Colorless oil.
IR: 3080, 3029, 2950, 2851, 2136, 1600, 1523, 1446, 1370, 1268 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 12 are given in Table 3.

** cis-1,2-Diazidocycloheptane (13)**
Yellow oil.
IR: 2978, 2876, 2136, 1472, 1395, 1344, 1293 cm\(^{-1}\).
\(^1\)H and \(^{13}\)C NMR data of 13 are given in Table 3.
cis-5,6-Diazidocyclooctene (14)\(^9\)
Yellowish oil.
IR: 3029, 2953, 2876, 2110, 1472, 1446, 1370, 1344, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 14 are given in Table 3.

Mitsunobu Reaction of trans-1,2-Diols: Typical Procedure
To a magnetically stirred soln of PPh\(_3\) (5.60 g, 21.4 mmol) in anhyd benzene, then azidoic acid (21.37 mmol, 11.87 mL, 1.8 M) in anhyd THF (15 mL) was added dropwise under nitrogen atm at 10 °C. To the resulting mixture azidoic acid (21.37 mmol, 11.87 mL, 1.8 M) in anhyd benzene, then trans-cyclohexene-1,2-diol 16 (1.00 g, 8.6 mmol) was added and stirred for 40 min at the same temperature followed by stirring at r.t. for 8–12 h. The solvent was evaporated.

Chromatography of the filtrate on silica gel column using hexane–Et\(_2\)O–CHCl\(_3\), 100:3:3 as an eluent afforded (74\%).

trans-1,2-Diazidocyclohexane\(^{13}\) (23)
Colorless oil.
IR: 3029, 2953, 2876, 2110, 1472, 1370, 1319, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 23 are given in Table 3.

trans-1,2-Diazidocyclopentane (22)
Colorless oil.
IR: 3029, 2953, 2876, 2110, 1472, 1370, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 22 are given in Table 3.

trans-4,5-Diazidocyclohexene (24)
Colorless oil.
IR: 3055, 2927, 2851, 2110, 1676, 1446, 1370, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 24 are given in Table 3.

trans-2,3-Diazido-1,2,3,4-tetrahydronaphthalene (25)
Colorless crystal.
Mp 50–52 °C, solidified. [lit.\(^{36}\) mp 55 °C from MeOH, lit.\(^{14}\) colorless oil].
IR: 3080, 3055, 2953, 2902, 2851, 2110, 1523, 1472, 1446, 1370, 1319, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 25 are given in Table 3.

trans-1,2-Diazido-1,2,3,4-tetrahydronaphthalene (26)
Colorless oil [lit.\(^{18}\) bp 68–82 °C/0.35 mm Hg].
IR: 3080, 3029, 2953, 2876, 2136, 1625, 1497, 1472, 1370, 1319, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 26 are given in Table 3.

trans-1,2-Diazidocycloheptane (27)
Yellow oil.
IR: 2953, 2876, 2110, 1472, 1370, 1319, 1268 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 27 are given in Table 3.

trans-5,6-Diazidocyclooctene (28)
Yellowish oil.
IR: 3029, 2953, 2927, 2876, 2120, 1497, 1472, 1446, 1370, 1344, 1293 cm\(^{-1}\).

\(^1\)H and \(^{13}\)C NMR data of 28 are given in Table 3.

4-Azido-1,2-dihydronaphthalene (30)\(^{36}\)
IR: 3080, 3029, 2953, 2902, 2136, 1651, 1497, 1446, 1345, 1293, 1063 cm\(^{-1}\).

\(^1\)H NMR: \(\delta = 7.39\) (m, 1 H), 7.27–7.14 (m, 3 H), 5.74 (t, J = 4.8 Hz), 2.85 (t, J = 7.9 Hz), 2.47 (dt, J = 4.8, 7.9 Hz).

\(^1\)C NMR: \(\delta = 137.6, 137.3, 131.7, 129.5, 128.7, 128.5, 126.3, 113.0, 29.1, 24.0.

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References
(16) See ref. 10b especially pp 375.
(27) See ref. 22 pp 100.
(31) See ref. 22 pp 161.
(34) See Ref. 17 pp. 446.