Selective Hydrogenation of Alkene in (3-Trifluoromethyl) Phenyl diazirine Photophor with Wilkinson’s Catalyst for Photoaffinity Labeling

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Selective hydrogenation of carbon–carbon double bond in the presence of nitrogen–nitrogen double bond in (3-trifluoromethyl) phenyldiazirine achieved with Wilkinson’s catalyst.

Key words photoaffinity labeling; diazirine; hydrogenation; Wilkinson’s catalyst

Photoaffinity labeling is a powerful method in the study of biological structures and functions. 1,2) It is suitable for the analysis of biological interactions because it is based on the affinity of the ligand moiety. Various photophors, such as phenyldiazirine, arylazide and benzophenone, were used. Comparative irradiation studies of these three photophors in living cells suggested that a carbene precursor, (3-trifluoromethyl) phenyldiazirine, is the most promising, 3–6) but complicated synthesis of the diazirinyl three-membered ring prevented the application of the photophor. Post-functional synthesis of TPD derivatives is one of problems to be solved. 7–10) It is well known that catalytic transfer hydrogenation followed by Wittig reaction is a useful method for general purpose carbon elongation, but the synthetic route does not apply for diazirinyl compounds, because it was reported that the diazirinyl nitrogen–nitrogen double bond was not tolerated under a hydrogen atmosphere in the presence of Pd–C for more than 1 h. 11,12) Although the selective hydrogenation of alkene in diazirinyl and other photophors containing photo ligand in the presence of Pd/C was reported very recently, the hydrogenation of diazirinyl derivatives is low yield compared with other photophors due to the presence of the homogenous N=N double bond. 13) Furthermore, the applications of the method were not reported.

Wilkinson’s catalyst (RhCl(PPh3)3) was used as a homogenous catalyst for alkene hydrogenation. The catalyst seems suitable for catalytic hydrogenation in diazirinyl compounds, because we have already established that the triphenylphosphine moiety does not affect diazirinyl compounds and it was reported as a selective carbon–carbon double bond over a heterogeneous multiple bond (nitro, carboxylic acid, and ester). 14) We will describe selective hydrogenation of the carbon–carbon double bond in the presence of a nitrogen–nitrogen double bond in diazirinyl moiety with Wilkinson’s catalyst.

Diazirinyl cinnamyl derivatives were prepared from aldehydes 1 15,16) and 2 17) with corresponding Wittig reagents in moderate yield (Fig. 1). The reaction afforded predominantly trans isomer calculated by 1H-NMR signals. Ethyl esters 3a 15) and 4a 18) were hydrolyzed with aqueous sodium hydroxide to afford cinnamic acid derivatives Selective hydrogenation of diazirinyl compounds with Wilkinson’s catalyst was examined in THF-tert-butanol or methanol in a similar manner as described in the reference (Fig. 2). Little difference was observed between these two solvents. The results gave the hydrogenated proportion of the reaction mixture, which was directly monitored by 1H-NMR in CD3OD. Table 1 shows the degree of hydrogenation of typical compound 3a with various amounts of Wilkinson’s catalyst at room temperature. Although slightly larger amounts of the catalyst than in

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<th>Wilkinson’s catalyst (mol%)</th>
<th>Remaining starting material 3a</th>
<th>Conversion product 5a</th>
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<tr>
<td>4</td>
<td>87</td>
<td>13</td>
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<tr>
<td>8</td>
<td>70</td>
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<td>12</td>
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<td>25</td>
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Proportions were judged by 1H-NMR in CD3OD.

Fig. 1. Synthesis of Unsaturated Diazirinyl Compounds with Wittig Reactions

Each yield and trans : cis ratio from 1H-NMR are indicated in parentheses.

Fig. 2. Selective Hydrogenation of Diazirinyl Cinnamyl Derivatives with Wilkinson’s Catalyst

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previous reports was needed, the carbon–carbon double bond was reduced by NMR analysis over 25 mol% catalyst. No temperature dependence was observed in this reaction.

Table 2 shows correlations between reaction time and hydrogenation. The reaction was not completed within 5 h. No saturated or unsaturated alcohol was detected in the reaction mixture from cinnamic esters by NMR analysis. These products have characteristic UV adsorption ($
\lambda_{\text{max}}$ ca. 350 nm), $^{13}$C-NMR (for CF$_3$ 125 ppm, $\delta$, J = 274 Hz, for diazirinyl quaternary carbon 40 ppm, q, $\delta$, J$_{CF}$ = 40 Hz) and $^{19}$F-NMR signals ($\delta$ 65 ppm). These results indicated that the reduction proceeded selectively for the carbon–carbon double bond over the nitrogen–nitrogen and carboxyl double bond. Methoxy substituent at ortho position of the carbon–carbon double bond did not interfere with the hydrogenation.

Carboxylic acid derivatives (3b, 4b) were reduced in a similar manner as described above without alcohols. The $\alpha$,$\beta$-unsaturated nitriles (3c, 4c) afforded the desired diazirinyl saturated nitriles (5c, 6c, IR ca. 2200 cm$^{-1}$).

Cinnamaldehyde derivatives afforded saturated aldehyde (5d, 6d) and saturated alcohol (5e, 6e). The ratio of saturated aldehyde and saturated alcohol was constant over 12 h incubation (Fig. 3). The results indicated that saturated aldehyde was not reduced to saturated alcohol.

Recent progress of mass spectrometers suggested the application of a stable isotope for photoaffinity labeling. The hydrogenation of diazirinyl compounds could also introduce deuterium with commercially available deuterium gas (D$_2$, 99.8% atom D) in the presence of Wilkinson’s catalyst in a similar manner described above. No serious H-D exchange reaction was detected during the reaction (Fig. 4).

It was reported that microwave-assisted catalytic transfer hydrogenation in the presence of Wilkinson’s catalyst is more effective, but the diazirinyl moiety does not tolerate microwave conditions, because of the high temperature. Hydrogenation at 1 atm at room temperature was a better method for this purpose. Furthermore we found that hydrogenation of 4a with Pd/C (5%) in methanol strongly promoted decou-
Typical Experiment for Hydrogenation of Diazirinyl Compounds
The unsaturated diazirinyl compound and Wilkinson's reagent (25 mol%) were dissolved in CH2OH. The reaction mixture was stirred at room temperature for 10 h under hydrogen atmosphere and subjected to silica column chromatography (CH2Cl2:n-hexane = 1:1) to afford pure material.

**Ethyl 3-(4-(3-(Trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoic Acid (5b)**

1H-NMR (CDCl3): δ 7.23 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 9.2 Hz), 2.97 (2H, t, J = 7.7 Hz), 2.63 (2H, t, J = 7.4 Hz), 1.22 (3H, t, J = 7.2 Hz), 1.15 (6H), FAB-MS m/z: 287.1012 (Calcd for C11H12F3N2O2: 287.1007).

**Ethyl 3-(4-(3-(Trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoic Acid (5c)**

1H-NMR (CDCl3): δ 7.28 (2H, d, J = 8.6 Hz), 7.18 (2H, d, J = 7.7 Hz), 2.97 (2H, t, J = 7.7 Hz), 1.22 (3H, t, J = 7.5 Hz), 1.15 (6H), FAB-MS m/z: 243.0755 (Calcd for C11H10F3N2O: 243.0745).

**Ethyl 3-(4-(3-(Trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoic Acid (5d)**

1H-NMR (CDCl3): δ 7.28 (2H, d, J = 8.6 Hz), 7.24 (2H, d, J = 7.7 Hz), 2.97 (2H, t, J = 7.4 Hz), 2.60 (2H, t, J = 7.1 Hz), 1.22 (3H, t, J = 7.2 Hz), 1.15 (6H), FAB-MS m/z: 243.0755 (Calcd for C11H10F3N2O: 243.0745).

**Ethyl 3-(4-(3-(Trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoic Acid (5e)**

1H-NMR (CDCl3): δ 7.28 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 9.2 Hz), 2.98 (2H, t, J = 7.7 Hz), 1.22 (3H, t, J = 7.2 Hz), 1.15 (6H), FAB-MS m/z: 243.0755 (Calcd for C11H10F3N2O: 243.0745).

**Ethyl 3-(4-(3-(Trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoic Acid (5f)**

1H-NMR (CDCl3): δ 7.23 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 9.2 Hz), 2.97 (2H, t, J = 7.7 Hz), 2.69 (2H, t, J = 7.4 Hz), 1.22 (3H, t, J = 7.2 Hz), 1.15 (6H), FAB-MS m/z: 243.0755 (Calcd for C11H10F3N2O: 243.0745).

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