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# Regio- and Stereo-selective Oxidation of *gem*-Dimethyl Olefins *via* [2,3]-Sigmatropic Rearrangement of Allyl Amine Oxides

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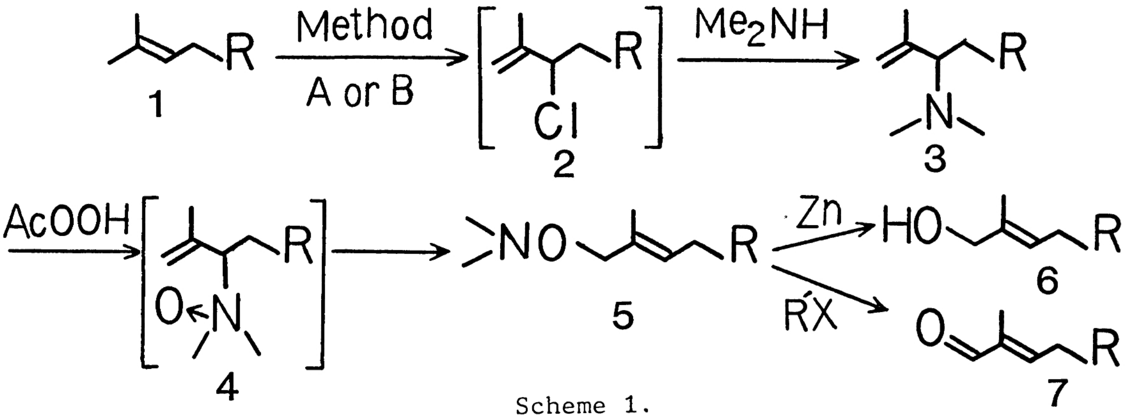
Highly regio- and stereo-selective oxidation sequences are described for the efficient conversion of the *gem*-dimethyl olefin terminus of acyclic terpenes to terminal *trans*-allylic alcohols and *trans*-α,β-unsaturated aldehydes.

Allylic oxidations of *gem*-dimethyl olefins **1** are extremely important for the synthesis of naturally occurring oxygenated isoprenoids. Hence a number of methods have been reported for the synthesis of terminal *trans*-allylic alcohols and α,β-unsaturated aldehydes.$^{1)}$ Here, we report facile, regio- and stereo-selective oxidations of *gem*-dimethyl olefins 1 as shown in Scheme 1.



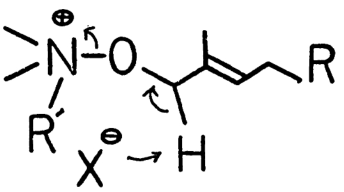
Scheme 1.

Allyl chlorides **2** were prepared by ene-type chlorination$^{2)}$ of olefins **1** using calcium hypochlorite.$^{3)}$ To a stirred mixture of **1** (10 mmol) and calcium hypochlorite (active chlorine 60%; 1.3 g; 11 mmol) in $CH_2Cl_2$ (100 ml) and water (10 ml) were added slowly pieces of dry ice at 10 °C. The mixture was filtered and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude chloride **2** was stirred in 50% aq. dimethylamine (50 ml) and ethanol (17 ml) at room temperature for 3-5 d. The reaction mixture was evaporated *in vacuo* and the residue was extracted with AcOEt. The solvent was evaporated off to give crude product, which was purified by column chromatography on silica gel (elution with 10-50% AcOEt/n-$C_6H_{14}$) to provide the corresponding allylamine **3** in good yield. In case of the chlorination of geraniol (**1d**) the use of $CH_2Cl_2$—sat. aq $Na_2SO_4$ (Method B) as the solvent in stead of $CH_2Cl_2$-$H_2O$ (Method A) described in the original paper[3)] led to fewer amount of by-products, hence resulted in higher yield of **3d**.

Subsequent [2,3]-sigmatropic rearrangement[4)] was carried out by oxidation of allylamines **3** with peracetic acid followed by heating the crude allylamine oxides **4**. Peracetic acid (40%; 1.0 g; 5.5 mmol) was added dropwise to a mixture of **3** (5.0 mmol) and solid $Na_2CO_3$ (0.6 g; 5.5 mmol) in $CH_2Cl_2$ (50 ml) at -50 °C with vigorous stirring. After 30 min the mixture was warmed to room temperature, poured into half-saturated brine and extracted with AcOEt. The combined organic layer was warmed at 40-50 °C for 30 min. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (elution with 5-20% AcOEt/n-$C_6H_{14}$) to provide trans-allyloxy amines **5**, which was not contaminated by the cis-isomer as evidenced by NMR analysis.

The attempted cleavage of nitrogen-oxygen bond of allyloxy amines **5** by $LiAlH_4$ in refluxing THF (24 h)[5)] afforded only a trace of product (as judged by TLC), however, treatment of **5** with excess of zinc dust[6)] cleanly afforded terminal trans-allylic alcohols **6**. A mixture of **5** (1.0 mmol) and Zn dust (0.3 g) in AcOH-$H_2O$ (1:1; 6 ml) was stirred vigorously at room temperature for 1-2 d. The mixture was filtered and extracted with $Et_2O$. The combined organic layer was washed with saturated aqueous $Na_2CO_3$ several times, dried over $MgSO_4$, and concentrated to give the pure alcohol **6** in quantitative yield.

Recently A. Liguori and co-workers reported a ring-opening elimination of isoxazolidines to α,β-enones using trimethyl phosphate.[7)] Therefore, we investigated the N-alkylation of allyloxy amines **5** and the subsequent Hofmann-like elimination of the resulting quaternary ammonium salts **8** to prepare terminal trans-α,β-unsaturated aldehydes **7**. The results are shown in Table 1.

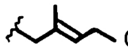
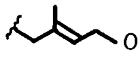
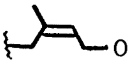
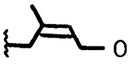
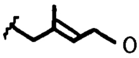
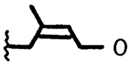
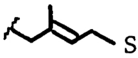


**8**

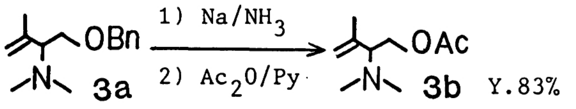
Table 1. Transformation of allyloxy amines 5 to terminal trans-α,β-unsaturated aldehydes 7

| Reagent | Conditions | Yield/% |
|---|---|---|
| $(MeO)_3PO$ | diglyme, refl. | trace |
| MeI | $CHCl_3$, refl., 3 h | quant. |
| $CH_2=CHCH_2Br$ | $CHCl_3$, refl., 3 h | trace |
| | TBAI(5 mol%), $CHCl_3$, refl., 4 h | quant. |
| $PhCH_2Cl$ | TBAI(5 mol%), $CHCl_3$, refl., 4 h | 0 |
| | TBAI(5 mol%), DMF, 100 °C , 4 h | 70 |

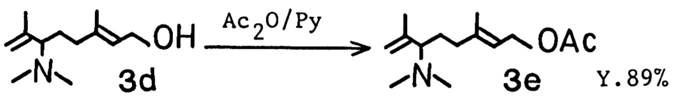
Table 2. Transformation of isoprenoids **1** to allylamines **3**, allyloxy amines **5**, terminal trans-allylic alcohols **6**, and trans-α,β-unsaturated aldehydes **7**

| Isoprenoid **1**<br>R | Method of Chlorination[a] | Yield/%[b] | | | |
|---|---|---|---|---|---|
| | | **3** | **5** | **6** | **7** |
| OBn (**1a**) | A | 77 | 93 | quant. | quant. |
| OAc (**1b**) | - | -- | 86[c] | quant. | quant. |
| OPh (**1c**) | A | 80 | 92 | quant. | quant. |
|  OH (**1d**) | A<br>B | 57<br>73 | -- | -- | -- |
|  OAc (**1e**) | - | --[d] | 86[e] | quant. | quant. |
|  OH (**1f**) | B | 75 | -- | -- | -- |
|  OAc (**1g**) | - | --[d] | 83[f] | quant. | quant. |
|  OBn (**1h**) | A | 70 | 80 | quant. | quant. |
|  OBn (**1i**) | A | 74 | 71 | quant. | quant. |
|  $SO_2$Tol (**1j**) | A | 64[g] | 89 | quant. | quant. |

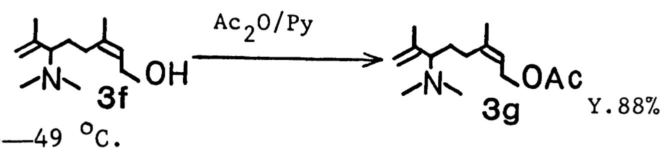
a) Method A: $Ca(OCl)_2$—dry ice, $CH_2Cl_2$—$H_2O$, 10 °C. Method B: $Ca(OCl)_2$—dry ice, $CH_2Cl_2$—$H_2O$ saturated with $Na_2SO_4$, 10 °C. b) All compounds gave satisfactory spectral data. c) Yield from **3b** which was prepared as follows;



d) When acetates **2e** and **2g** were used in amination, deacetylated products **3d** and **3f**, respectively, were obtained. e) Yield from **3e** which was prepared as follows;



f) Yield from **3g** which was prepared as follows;



g) mp 48.5—49 °C.

Treatment of allyloxy amines **5** with N-alkylating reagents such as iodomethane alone or allyl bromide in the presence of tetrabutylammonium iodide (TBAI) cleanly gave the desired aldehydes **7**. A solution of **5** (1.0 mmol) and iodomethane (3 ml) in $CHCl_3$ (6 ml) was refluxed for 3 h. The mixture was poured into water and extracted with $Et_2O$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated to give the pure aldehyde **7** quantitatively.

The versatility of the method for the terminal allylic oxidations mentioned above was demonstrated on the various isoprenoids 1 and results are summarized in Table 2.

We are currently investigating the application to the synthesis of natural products.

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