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# COMPOUNDS OF ($i$-PrO)$_3$TiX AS NOVEL REAGENTS FOR REGIOSELECTIVE OXIRANE RING OPENING

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ABSTRACT: Substituted titanium (IV) triisopropoxides [($i$-PrO)$_3$TiX] are highly effective reagents for the regioselective ring opening of 2,3-epoxyalcohols.

The discovery of the asymmetric Sharpless epoxidation of allylic alcohols has attracted much attention to the problem of regioselective oxirane ring opening. The combination of these two reactions provides new paradigms for the synthesis of biologically active compounds.

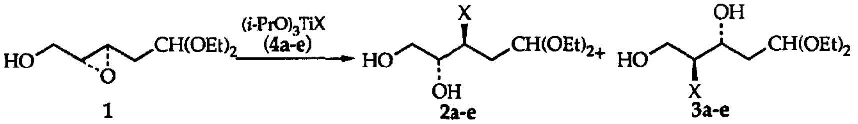
During the course of our research in the field of carbohydrate synthesis, we observed that the regioselective oxirane ring opening of 1,1-diethoxy-3R,4R-epoxypentane-5-ol (**1**)[1] with Ti(O-$i$-Pr)$_4$ - (CH$_3$)$_3$SiOAc afforded the 3-acetoxyacetal (**2a**). Detail mechanistic studies of this reaction by $^{13}$C-NMR showed that the mixing of titanium(IV) isopropoxide and trimethylsilyl acetate affords trimethylsilyl isopropyl ether which infers that the titanium atom preferentially coordinates the acetoxy group. Thus, the oxirane ring cleavage was facilitated by ($i$-PrO)$_3$TiOAc. We proposed generically that compounds of ($i$-PrO)$_3$TiX type may be formed from titanium (IV) isopropoxide and used to catalyze regioselective oxirane ring openings[2]. Our assumption is further supported by reports of oxirane ring cleavages of 2,3-epoxy alcohols by titanium diisopropoxy diazide[3,4], as well as the ring cleavage of unsymmetrically substituted oxiranes by titanium acetylides[5].

We describe in this communication the use of ($i$-PrO)$_3$TiX compounds [*e.g.* ($i$-PrO)$_3$TiCl (**4c**)[6], ($i$-PrO)$_3$TiOCOR (**4a-b**)[7], ($i$-PrO)$_3$TiSCOPh (**4d**), and ($i$-PrO)$_3$TiN$_3$ (**4e**)] for oxirane ring cleavages. All of these reagents are readily obtained from titanium (IV) isopropoxide. Reagent (**4b**) may be obtained from either the corresponding carboxylic acid, anhydride or trimethylsilyl ester[8].

These reagents are highly effective in converting 1,1-diethoxy-3R,4R-epoxypentane-5-ol (**1**) to mixtures of 3- and 4- substituted acetals (**2** and **3**, respectively) with preferential nucleophilic attack at C-3. The initial isomer ratios of (**2**) and (**3**) were determined by means of $^1$H and $^{13}$C-NMR spectroscopy (Table 1) with component isolation by column chromatography and characterization by elemental analysis and NMR.

$$\mathrm{Ti(O\text{-}}i\mathrm{\text{-}Pr)_4 + RX \longrightarrow (}i\mathrm{\text{-}PrO)_3TiX + }i\mathrm{\text{-}PrOR}\quad [\mathrm{R{=}H,\ OAc,\ Si(CH_3)_3}]$$

**4a** X=OAc **4d** X=SCOPh
**4b** X=OTol **4e** X=N$_3$
**4c** X=Cl



In summary, we have described a) a general synthesis of $(i\text{-PrO})_3TiX$ reagents and b) their use in a highly efficient regioselective cleavage of epoxy alcohols. While these reagents are representative of a general class of titanium reagents, they hold promise for use in general oxirane cleavage transformations.

Table 1. Regioselective ring cleavage of
1,1-diethoxy-3R,4R-epoxypentane-5-ol (**1**) with $(i\text{-PrO})_3TiX$[8,9]

| | $(i\text{-PrO})_3TiX$ | Reaction Time (hr.) | solvent | Yield,%[a] | Ratio of (2:3) (**2**) | (**3**) |
|---|---|---|---|---|---|---|
| **4a** | OAc[9b] | 1 | $CHCl_3$ | 95 | >98 | <2 |
| **4b** | OTol | 1 | $CHCl_3$ | 90 | >98 | <2 |
| **4c** | Cl | 1 | $C_6H_6$ | 85 | 85 | 15 |
| **4d** | SCOPh | 1 | $CHCl_3$ | 80 | >98 | <2 |
| **4e** | $N_3$ | 1.5 | $CHCl_3$ | 95 | 92 | 8 |

[a]Total yield of (**2**) and (3) after workup[9]

## References and Notes

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8. a) Tri(isopropoxy)titanium acetate (**4a**) was obtained from $Ti(O\text{-}i\text{-}Pr)_4$ and $(CH_3)_3SiOAc$ (1:1), in dry $CHCl_3$ and used without isolation. Acetic acid or acetic anhydride may be used instead of trimethylsilyl acetate. Tri(isopropoxy)titanium toluate (**4b**) was similarly obtained. **b)** Tri(isopropoxy)titanium chloride (**4c**) was obtained from $Ti(O\text{-}i\text{-}Pr)_4$ and $TiCl_4$ (3:1)[7]or from $Ti(O\text{-}i\text{-}Pr)_4$ and $(CH_3)_3SiCl$, 1:1, in dry $CHCl_3$ and used without isolation. **c)** Tri(isopropoxy)titanium thiobenzoate (**4d**) was obtained from 28.4g (0.1 mol) of $Ti(O\text{-}i\text{-}Pr)_4$ and 13.8g (0.1 mol) of thiobenzoic acid in 100 ml of pentane. After 30 min of stirring, the yellow crystalline solid was collected (28.9g, 80% yield), mp 100-105°C. Anal. Calcd. for $C_{16}H_{26}O_4TiS$: C, 53.04; H, 7.23; Ti, 13.21; S, 8.85. Found: C, 52.56; H, 7.01; Ti, 14.1; S, 9.02. **d)** Tri(isopropoxy)titanium azide (**4e**) was obtained from 28.4g (0.1 mol) of $Ti(O\text{-}i\text{-}Pr)_4$ by the addition of 160 ml of 0.6M $HN_3$ solution in pentane as a green-yellow crystalline solid (19.8g, 68% yield), mp 67-70°. Anal. Calcd.for $C_9H_{21}O_3TiN_3$: C, 40.46; H, 7.92; Ti, 17.92; N, 15.73. Found: C, 39.60; H, 7.73; Ti, 19.03; N, 14.98.

9. a) Epoxy alcohol cleavages were carried out in a 2.5-3.0M solution of epoxy alcohol with 1.5 mol excess of the reagent $(i\text{-PrO})_3TiX$ (4) by stirring at room temperature with silica gel TLC monitoring, (10:1) $CH_3Cl$-$CH_3OH$, detection by heat charring; $R_F$ of epoxy alcohol (1) 0.5, $R_F$ of 3-acetals (2) 0.30-0.37; $R_F$ of 4-acetals (3) 0.44-0.45. The reaction mixtures were quenched with saturated aqueous $NaHCO_3$ (10% v/v) by stirring for 0.5-1h. **b)** Aqueous workup without sodium bicarbonate is preferable to minimize acyl migration.