



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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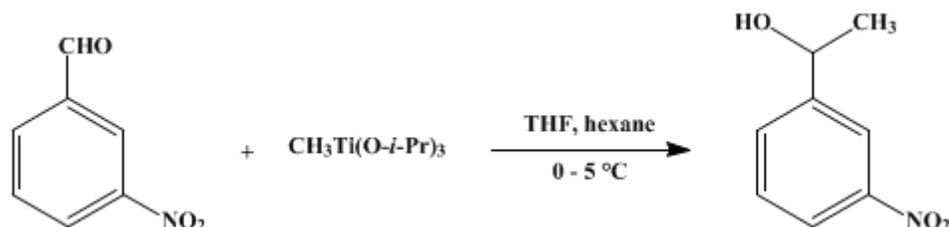
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## 3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRISOPROPOXYTITANIUM TO *m*-NITROBENZALDEHYDE

[Benzenemethanol,  $\alpha$ -methyl-3-nitro-]



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Checked by Cheryl A. Martin and K. Barry Sharpless.

### 1. Procedure

A dry, 500-mL, three-necked flask equipped with pressure-equalizing 100-mL dropping funnel, argon inlet, and magnetic stirrer is evacuated and flushed with argon (three cycles). The flask is charged with 16.0 mL (57.7 mmol) of tetraisopropyl orthotitanate (Note 1) via a plastic syringe and hypodermic needle and 2.1 mL (19.2 mmol) of titanium tetrachloride is added over 5 min, with gentle cooling of the flask in an ice-water bath to give a viscous oil (Note 2). After the addition of 70 mL of tetrahydrofuran (Note 3), the clear solution is stirred at room temperature for 30 min. The dropping funnel is charged with 62 mL (77 mmol, 1.24 M in hexane) of methyllithium (Note 4), which is added to the cooled (ice bath) tetrahydrofuran solution over a period of 25–30 min. During the addition the resulting suspension changes from orange to bright yellow. After the mixture has stirred at ice-bath temperature for 1 hr, a solution of 10.6 g (70 mmol) 3-nitrobenzaldehyde (Note 5) in 60 mL of tetrahydrofuran (Note 3) is added from the dropping funnel within 20–25 min at the same temperature. The mixture is stirred at 0–5°C for 1 hr and then 60 mL of 2 N hydrochloric acid is added. The organic phase is separated in a separatory funnel and the aqueous phase is extracted with three 150-mL portions of diethyl ether. The combined organic phases are washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. After filtration the solution is concentrated on a rotary evaporator and dried at 0.1 mm for 1 hr. The residue, 11.0–11.1 g (94–95%) of an orange-brown viscous oil, sometimes solidifies on standing (mp 55–60°C); the purity of the crude product is at least 95% (estimated by <sup>1</sup>H NMR). The product can be purified by short-path distillation at 120–125°C (0.15 mm) to give 9.9–10.4 g (85–89%) of a yellow oil, which solidifies on standing at room temperature or at –30°C in a freezer, mp 60.5–62.0°C (lit.<sup>2</sup> mp 62°C) (Note 6).

### 2. Notes

- Commercial tetraisopropyl orthotitanate [Ti(O-*i*-Pr)<sub>4</sub>] (Dynamit Nobel) and titanium tetrachloride (Fluka pract.) can be used without further purification. The checkers obtained Ti(O-*i*-Pr)<sub>4</sub> from Aldrich Chemical Company, Inc. and titanium tetrachloride from Fluka. Distillation of Ti(O-*i*-Pr)<sub>4</sub> did not improve the results.
- If the mixture is overcooled, the resulting chlorotris(isopropoxy)titanium partially solidifies.
- Tetrahydrofuran was distilled from potassium/benzophenone immediately before use.
- The methyllithium solution was obtained from Metallgesellschaft, Frankfurt. The checkers used methyllithium (Aldrich Chemical Company, Inc.), salt-free 1.4 M in ethyl ether, with no significant difference observed in the reaction.
- 3-Nitrobenzaldehyde is Fluka purum, used without further purification. The checkers obtained it from Aldrich Chemical Company, Inc.
- The product obtained after distillation can be recrystallized from benzene/petroleum ether (3:2, v : v)

to give pale-yellow crystals (91–95% from distilled product) with a melting point of 61–63°C. Attempts by the checkers to crystallize the crude reaction mixture were unsuccessful.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.54 (d, 3 H,  $J = 6.5$ ,  $\text{CH}_3$ ), 2.3 (br, 1 H, OH), 5.00 (q,  $J = 6.5$ , O-C-H), 7.5–7.7 (m, 2 H, arom. H), 8.0–8.25 (m, 2 H, arom. H); IR (KBr)  $\text{cm}^{-1}$ : 3260 (br, m), 2990 (m), 1580 (m), 1525 (s), 1340 (s), 1205 (m), 1170 (m), 810 (m), 740 (m), 690 (m).

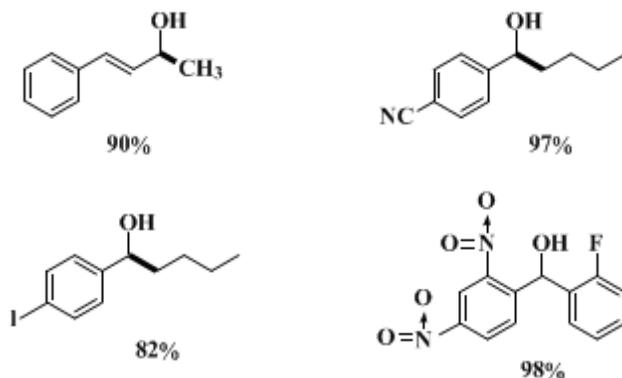
### 3. Discussion

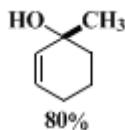
The addition of nucleophilic organometallic compounds (usually RLi or RMgX) to a carbonyl group—a key step in numerous syntheses—is not always straightforward. The addition reaction is complicated by the fact that aldehydes, ketones, and esters are not well differentiated; that other electrophilic functional groups, such as cyano, nitro, halo, and trialkylstannyl may interfere; and that proton abstraction or one electron-transfer processes rather than addition occur. For example, the addition of methyl lithium or methylmagnesium iodide to 3-nitrobenzaldehyde under the same conditions used with  $\text{CH}_3\text{Ti}(\text{OCH}(\text{CH}_3)_2)_3$  (this procedure) leads to a complex mixture of products with formation of only 10–30% of 3'-nitro-1-phenylethanol.<sup>3</sup> In many cases these complications can be remedied by using derivatives of titanium and zirconium, compounds that have become increasingly important in organic syntheses during the past decade. Several review articles discuss different aspects.<sup>3</sup>

The nucleophilic titanium and zirconium reagents are readily available by simple transmetallation of the organolithium or Grignard reagents with  $(\text{RO})_3\text{TiCl}$ ,  $(\text{RO})_3\text{ZrCl}$ , or  $(\text{R}_2\text{N})_3\text{TiX}$ . The trialkoxychloro compounds are prepared by mixing the inexpensive, industrially available, titanates,  $\text{Ti}(\text{OR})_4$ , or zirconates,  $\text{Zr}(\text{OR})_4$ , with the appropriate amount of  $\text{TiCl}_4$  or  $\text{ZrCl}_4$ . In contrast to compounds of most other heavy metals, few toxic effects of  $\text{Ti}(\text{OR})_4$  and  $\text{Zr}(\text{OR})_4$  are known, partly because they are very rapidly hydrolyzed by water and the resulting oxide-hydrates are insoluble ( $\text{TiO}_2$  is a white pigment). Some of the reagents,  $\text{RTi}(\text{OR}')_3$ , can be isolated without difficulty. Thus,  $\text{CH}_3\text{Ti}(\text{O}-i\text{-Pr})_3$  can be obtained as a bright-yellow oil that distills without decomposition at 50°C/0.001 mm.<sup>4</sup>

The organotitanium and -zirconium compounds, for the most part generated in situ, react highly selectively with carbonyl compounds. For example,  $\text{CH}_3\text{Ti}(\text{O}-i\text{-Pr})_3$  reacts five orders of magnitude faster with benzaldehyde than with acetophenone at room temperature.<sup>5</sup> Reagents of the type  $\text{RTi}(\text{O}-i\text{-Pr})_3$  add smoothly to nitro- (see this procedure), iodo-, or cyanosubstituted benzaldehydes, and the reactions may be performed in chlorinated solvents or in acetonitrile (for some examples, see Table I). The zirconium analogs have particularly low basicity and add in high yield to  $\alpha$ - and  $\beta$ -tetralones.<sup>6</sup> The inclusion of chiral OR\* groups gives enantioselective reagents (up to  $\geq 98\%$  ee).<sup>7,8,9</sup> Allylic  $(\text{RO})_3\text{Ti}$  derivatives react diastereoselectively only at the more highly substituted carbon atom with aldehydes and even with unsymmetric ketones.<sup>8,9,10</sup> Titanates can be used as mild catalysts for the transesterification of compounds containing acid- or base-labile functional groups.<sup>11</sup>

TABLE I  
SOME PRODUCTS OF ORGANOTITANIUM  
TRIIISOPROPOXIDES [ $\text{RTi}(\text{O}i\text{Pr})_3$ ] WITH FUNCTIONALIZED  
CARBONYL COMPOUNDS<sup>3,a</sup>





<sup>a</sup>The bonds formed during the reaction are drawn bold.

## References and Notes

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## Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

3'-NITRO-1-PHENYLETHANOL

tetraisopropyl orthotitanate [Ti(O-i-Pr)<sub>4</sub>] (Dynamit Nobel)

CH<sub>3</sub>Ti(OCH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>

CH<sub>3</sub>Ti(O-i-Pr)<sub>3</sub>

Ti(O-i-Pr)<sub>4</sub>

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl ether,  
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

Acetophenone (98-86-2)

carbon (7782-42-5)

Benzophenone (119-61-9)

potassium (7440-09-7)

methylmagnesium iodide (917-64-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methylithium (917-54-4)

titanium tetrachloride (7550-45-0)

zirconium

argon (7440-37-1)

titanium (7440-32-6)

Methyltriisopropoxytitanium (18006-13-8)

Benzenemethanol,  $\alpha$ -methyl-3-nitro- (5400-78-2)

tetraisopropyl orthotitanate (546-68-9)

3-nitrobenzaldehyde,  
m-Nitrobenzaldehyde (99-61-6)

chlorotriisopropoxytitanium