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O.N. Chupakhin on his 70th Anniversary

## Condensation of Ketones in the Presence of Titanium Alkoxides

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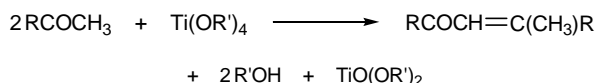
Received January 23, 2004

**Abstract**—Titanium alkoxides promote successful condensation of aromatic and aliphatic ketones provided that the liberated alcohol is selectively removed from the reaction mixture.

Self-condensation of carbonyl compounds is a well known process; however, special reagents are necessary to ensure high yields of the products, especially from aromatic ketones. Ketones undergo condensation by the action of polyphosphoric acid, but in the condensation of acetophenone the yield does not exceed 27% [1]. Ion-exchange resin can be used instead of polyphosphoric acid [2]. Some organo-metallic compounds, e.g., dialkylboron acetates [3], promote condensation of ketones; in such a way, 1,3-diphenyl-2-buten-1-one (dyprone) was obtained in 72% yield. Aluminum *tert*-butoxide ensures condensation of acetophenone in 77–82% yield [4]. Acetone reacts with titanium alkoxides at room temperature to afford a titanium derivative of diacetone alcohol, while on heating, a mixture of di- and triacetone alcohols and 4-methyl-3-penten-2-one is formed [5]. Numerous published data on this topic were reviewed in [6].

In the present work we examined the condensation of aromatic and aliphatic ketones by the action of titanium alkoxides (Scheme 1).

Scheme 1.



To simplify the reaction scheme, the resulting polytitanate is shown as titanoxane. The reaction occurs at elevated temperature, and the yield of the corresponding ketone self-condensation product

(R = Ar) does not change in the series of unbranched alkoxides (R' = Et, Pr, Bu) and is 38–39%; however, the yield sharply falls down in going to branched alkoxides in the series R' = Et, *i*-Pr, *t*-Bu (39, 3, and 0%, respectively). Partial replacement of the alkoxy groups in titanium alkoxide by chlorine also leads to reduced yield: 39, 28, and 23% for mono-, di-, and trichloro ethoxy derivatives, respectively. In the presence of water (i.e., with the use of polytitanate) the yield decreases to 28% (0.5 mol of water per mole of the alkoxide). The same results are obtained when the amount of titanium alkoxide is reduced to 0.5, 0.25, and 0.1 mol/mol: 38, 25, and 7%, respectively. Variation of the solvent polarity and its boiling point insignificantly affects the product yield (38, 41, 43, and 38% for benzene, toluene, xylene, and acetonitrile, respectively). No reaction occurs in alcohol: the yield is about 0%. Increase in the reaction time leads to only slight increase in the yield (38, 48, and 48% in 3, 6, and 10 h, respectively), and we failed to raise it appreciably.

We have found that the yield of the condensation product can be increased to a considerable extent when the liberating alcohol is selectively removed from the reaction mixture. For this purpose, the reaction was carried out in a nonpolar solvent (a saturated hydrocarbon) in a flask equipped with a Dean–Stark trap which was filled by half with a polar solvent as extractant (e.g., water, sulfuric or phosphoric acid, or glycol). A small funnel with a long spout was inserted into the trap in such a way that the distillate dropped

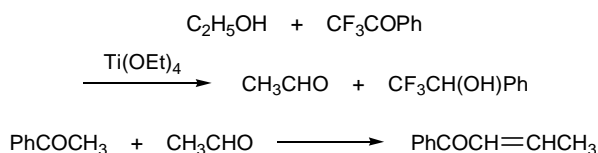
Condensation of aromatic ketones  $\text{ArCOCH}_3$  in the presence of titanium ethoxide

| Ar                                    | Solvent   | Extractant                                     | Reaction time, min | Yield, % |
|---------------------------------------|-----------|--|--------------------|----------|
| $\text{C}_6\text{H}_5$                | Heptane   | 95% $\text{H}_2\text{SO}_4$                    | 60                 | 83       |
| $\text{C}_6\text{H}_5$                | Heptane   | $\text{H}_2\text{O}$                           | 60                 | 72       |
| $\text{C}_6\text{H}_5$                | Octane    | $\text{H}_2\text{O}$                           | 45                 | 87       |
| $\text{C}_6\text{H}_5$                | Isooctane | $(\text{CH}_2\text{OH})_2$                     | 50                 | 86       |
| 4- $\text{CH}_3\text{C}_6\text{H}_4$  | Heptane   | 85% $\text{H}_3\text{PO}_4$                    | 60                 | 70       |
| 4- $\text{CH}_3\text{OC}_6\text{H}_4$ | Heptane   | $\text{H}_2\text{O}$                           | 60                 | 60       |
| 4- $\text{ClC}_6\text{H}_4$           | Heptane   | $\text{H}_2\text{O}$                           | 60                 | 61       |
| 2-Thienyl                             | Heptane   | $\text{HOCH}(\text{CH}_3)\text{CH}_2\text{OH}$ | 50                 | 62       |

into the funnel and then slowly passed through a layer of the extractant, where the alcohol was absorbed and alcohol-free solvent returned into the reaction mixture. More polar ethanol was absorbed best. Under these conditions, the reaction time was no longer than 1 h, and the yields were fairly high. The results are summarized in table.

By mixed condensation of acetophenone with benzaldehyde or benzophenone we obtained chalcone and  $\alpha$ -phenylchalcone in 85 and 2% yield, respectively. Mixed condensation of acetophenone with trifluoroacetophenone in the presence of titanium ethoxide afforded ethylideneacetophenone and dypnone as the major products; in addition,  $\alpha$ -phenyltrifluoroethanol was detected (the products were identified by GLC). These data indicate simultaneous occurrence of the Oppenauer reaction, followed by condensation of the resulting acetaldehyde with acetophenone and self-condensation of the latter (Scheme 2).

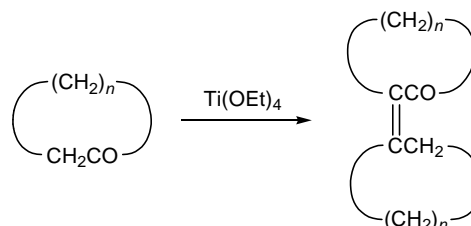
**Scheme 2.**



We also examined self-condensation of cyclopentanone, cyclohexanone, and cyclooctanone and mixed condensation of cyclopentanone with cyclohexanone in the presence of titanium ethoxide (Scheme 3). The yields of the condensation products were 96, 94, 0, and 83%, respectively. In the mixed condensation, the product ratio cyclopentanone–cyclopentanone:cyclohexanone–cyclopentanone : cyclohexanone–cyclohexanone was 22:26:52. It is seen that cyclooctanone fails to undergo self-condensation; it gives rise to the

corresponding enolate with liberation of ethanol, and the initial compound can be recovered by acidification.

**Scheme 3.**



Thus the use of titanium ethoxide promotes condensation of aromatic and aliphatic ketones in high yield provided that the liberated alcohol is selectively removed from the reaction mixture.

## EXPERIMENTAL

The purity of products and their composition were analyzed by GLC using an LKhM-8MD chromatograph equipped with a thermal conductivity detector and a 2-m $\times$ 3-mm column packed with 5% of Carbowax on Chromaton AW-HMDS; carrier gas helium. The products were identified using authentic samples.

A mixture of 24 g (0.2 mol) of acetophenone and 24.08 g (0.1 mol) of ethyl orthotitanate in 30 ml of heptane was heated under reflux with or without removal of the liberated alcohol (see above). Sulfuric acid ( $d = 1.84$ ), 10 ml, was used to absorb the alcohol. When the reaction was complete, the mixture was cooled to room temperature, 20 ml of acetonitrile was added, and the bottom layer was separated and treated with 2 ml of hydrochloric acid ( $d = 1.1$ ). The mixture was heated to the boiling point and cooled, the solution was separated from the precipitate by decanting, the solvent was distilled off, and the residue was subjected

to fractional distillation under reduced pressure. Yield of dypnone 18.4 g (83%), bp 138–140°C (1 mm) [7].

The other reactions were carried out in a similar way; the products were identified by comparing their physical constants with those reported in the literature.

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