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MAGNESIUM AND ZINC-CATALYZED THIOKETALIZATION

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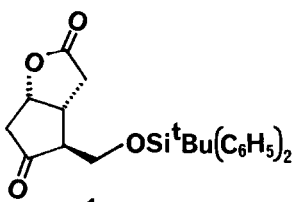
Summary: Reaction of a variety of ketones with ethane-1,2-dithiol to form thioketals proceeds very efficiently and under mild conditions using magnesium or zinc triflates as catalyst.

Prostaglandin D_2 and its metabolites are of interest with the development of diagnostic procedures for the subclassification of allergic states and for the detection of conditions such as systemic mastocytosis.[1] In connection with synthetic studies in this area, we required a procedure for the protection of the ketonic carbonyl function of 1 as the dithioketal 2.



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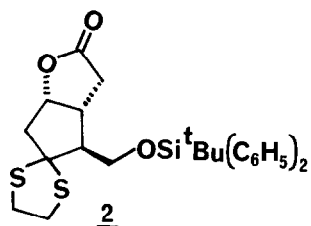

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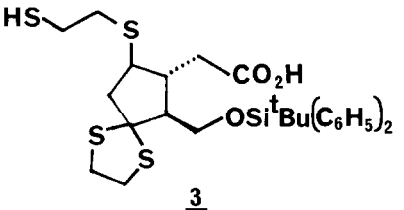
It was found that the conventional methods for thioketalization involving ethane-1,2-dithiol and various protic acids or $BF_3 \cdot Et_2O$ or Zn Hal_2 were totally inoperable with 1, a molecule which is very sensitive to acid-catalyzed β-elimination of the lactone oxygen. Very mild catalysts such as molecular sieves-4A or magnesium sulfate were without effect. The latter, which was tried on the premise that magnesium ion could in principle activate the ketonic function by coordination at oxygen without deactivating the dithiol by complexation, was quite insoluble in aprotic, non-basic solvents (e.g., chloroform), suggesting that poor solubility might have been responsible for the observed lack of catalytic activity. Partly for this reason we decided to study magnesium and zinc triflates, which were expected to be both more soluble and stronger as Lewis acids (versus carbonyl oxygen). The results of this research were sufficiently positive to warrant the broader investigation which is reported herein and which demonstrates that magnesium and zinc triflates are outstanding as promotors of thioketalization.

When a solution of ketone 1, 2 equiv. of ethane-1,2-dithiol, and 1.1 equiv. of zinc triflate in methylene chloride was stirred at 23° for 3.5 hr. and then at reflux for 2 hr., thioketal 2 was produced cleanly and was isolated in > 85% yield after extractive workup and chromatography on silicic acid (elution with 100:3 methylene chloride-ether; R_f values for 1 and 2 on silica gel plates using 2:5 hexane-ether 0.30 and 0.58, respectively). Conversion of 1 to 2 could also be accomplished using 10 equiv. of magnesium triflate and 10 equiv. of ethane-1,2-dithiol in methylene chloride with stirring for 12 hr. at 23° in 75% isolated yield. Formed as a by-product in this reaction was the mercapto acid 3.



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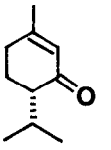

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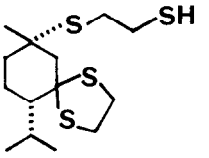

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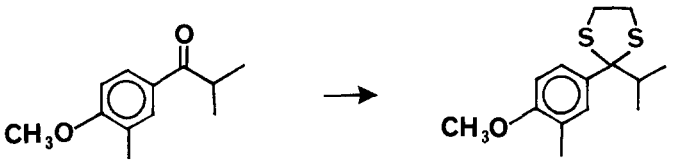
4-t-Butylcyclohexanone was quantitatively converted to the thioketal using 1.2 equiv. of either magnesium or zinc triflate and 1.2 equiv. of ethane-1,2-dithiol in methylene chloride at 23° for 5 min. Menthone under the same conditions with either magnesium or zinc triflates for 2.5 hr. was also converted quantitatively to the ethylene thioketal. Norcamphor in parallel experiments with either metal triflate and 30 min. reaction time gave > 97% of the ethylene thioketal.

Even the highly hindered ketone camphor could be transformed into the ethylene thioketal with 1.2 equiv. of magnesium or zinc triflate and 1.2 equiv. of ethane-1,2-dithiol in 1,2-dichloroethane at reflux for 15 hr. in 99% yield.

The α,β-unsaturated ketone Δ^4-cholesten-3-one was thioketalized in 98% yield using the conditions just described for camphor (reaction time 3.7 hr.) to give a 4:1 mixture of Δ^4- and Δ^5-cholestenone thioketals. However, with zinc triflate as catalyst the thioketal of Δ^4-cholestenone was obtained cleanly. On the other hand, piperitone (4) with zinc triflate and ethane-1,2-dithiol in chloroform at reflux gave mainly the Michael adduct of the thioketal (5) carvone showed a similar tendency.

Reaction of 3,4-diphenyl-2-cyclopentenone with magnesium triflate (1.2 equiv.) and ethane 1,2-dithiol (1.2 equiv.) in chloroform at reflux for 4 hr. gave the ethylene thioketal in 98%

yield. Under the same conditions p-methoxyacetophenone was thioketalized in 97% yield after 24 hr. at reflux; with zinc triflate only a 30 min. reflux period was required to provide the same yield. Similarly, the transformation of 6 to 7 proceeded at reflux in chloroform for 13 hr. in 100% yield using magnesium triflate and required only a 5 hr. reaction period with zinc triflate.



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Magnesium and zinc triflates are readily prepared by the procedures which follow. The method for thioketalization outlined herein is especially promising for sensitive substrates.

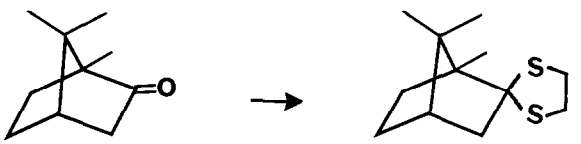
Magnesium triflate $Mg(OTf)_2$. A. Triflic acid (5 ml, 0.056 mol) was added dropwise to a suspension of magnesium carbonate (1.69 g, 0.02 mol) in dry methanol (20 ml) at room temperature. During the addition, carbon dioxide was evolved. The reaction mixture was stirred at 23° for 20 min., then at reflux for 2 hr. The clear solution was cooled to 23° and concentrated under reduced pressure. The resulting white cake was dried at 125° for 2 hr. at 3 Torr. to give 6.3 g of magnesium triflate (98% yield). B. Triflic acid (5 ml, 0.056 mol) was added dropwise to a suspension of magnesium carbonate (1.69 g, 0.02 mol) in dry methylene chloride (50 ml) at 0° and the resulting mixture was stirred at room temperature for 16 hr. The white precipitate was collected, washed with dry methylene chloride (2 x 30 ml), and dried at 125° for 2 hr. at 3 Torr. to give 5.9 g of magnesium triflate (91.5% yield).

Zinc triflate $Zn(OTf)_2$. Zinc triflate was obtained in 98% yield following procedure A for magnesium triflate.

The experimental procedures which follow provide detailed information regarding the use of the thioketalization method with magnesium or zinc triflate.

Dithioketalization of 1 to 2. To a well-stirred mixture of 1,2-ethanedithiol (0.45 ml, 5.4 mmol) and zinc triflate (1.09 g, 3.0 mmol) in methylene chloride (5 ml) was added a solution of the crude ketone 1[2] (1.20 g, 1.68 mmol) in methylene chloride (5 ml) at 23°, and the reaction mixture was stirred for 3.5 hr. at 23° and for 2 hr. at reflux. Water (20 ml)

was added and the resulting mixture was extracted with 1:1 ether-hexane. The extracts were washed first with two 20 ml-portions of dilute hydrochloric acid, then with saturated aqueous sodium bicarbonate, dried (Na_2SO_4) and concentrated *in vacuo* to afford a straw-colored oil. Chromatography over silica gel (40 g) using 100:3 methylene chloride-ether for elution afforded 2 (1.10 g, 85%) as a yellow oil; R_f 0.58 (silica gel, 20:1 methylene chloride-ether); pmr (80 MHz; $CDCl_3$), δ 7.50 (m, 10 H), 4.93 (m, 1 H), 3.98 (d-d, 1 H), 3.70 (d-d, 1 H), 3.3 to 2.1 (m, 10 H), and 1.05 (s, 9 H); IR ($CDCl_3$), 1770, 1520, 1430, 1215, 790, 765, 730, and 670 $cm.^{-1}$; mass spectrum; M^+ -t-Bu at 427.



Camphor Ethanedithioketal. A mixture of camphor (152 mg, 1.0 mmol), 1,2-ethanedithiol (0.10 ml, 1.2 mmol), and zinc triflate (440 mg, 1.2 mmol) in 1,2-dichloroethane (3 ml) was stirred for 15 hr. at reflux, then cooled to 23°. The contents were diluted with hexane (20 ml), washed with three 5 ml-portions of water, dried (Na_2SO_4), and concentrated *in vacuo* to afford a colorless oil. Chromatography over silica gel (10 g) using 1:1 methylene chloride-hexane for elution afforded camphor ethanedithioketal (225 mg, 99%) as a colorless oil; R_f 0.52 (silica gel, 1:1 methylene chloride-hexane); pmr (80 MHz, $CDCl_3$), δ 3.12 (m, 4 H), 2.7 to 1.1 (m, 7 H), 1.03 (s, 6 H), and 0.91 (s, 3 H); IR (liquid film), 1483, 1455, 1380, 1370, and 1277 $cm.^{-1}$; mass spectrum; M^+ at 228.[3,4]

References

1. L. J. Roberts, B. J. Sweetman, R. A. Lewis, K. F. Austen, and J. A. Oates, New Eng. J. Med., 303, 1400 (1980).

2. The ketone 1 was obtained from the corresponding secondary alcohol by oxidation with a solution of 2 equiv. of diisopropylcarbodiimide and 0.5 equiv. of dichloroacetic acid in 1:1 dimethyl sulfoxide - benzene at 23° for 30 min., followed by extractive isolation. Crude 1 (yield > 95%) was used directly for the preparation of 2.

3. For another recently described method of thioketalization (not successful for the case 1 → 2), see D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, J. Am. Chem. Soc., 99, 5009 (1977)

4. This research was assisted financially by a grant from the National Institutes of Health.

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