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Lead Catalysis of a Thiocarbonyl Reduction Using Zinc Dust

Marvin M. Hansen* and John L. Grutsch, Jr.

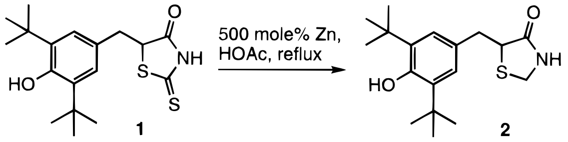
Chemical Process Research and Development Division, Lilly Research Laboratories,
A Division of Eli Lilly and Company, Indianapolis, Indiana 46285-4813

Abstract:

A catalytic amount of lead is necessary to promote the reduction of a 2-thioxo-4-thiazolidinone to the corresponding 4-thiazolidinone with zinc dust. If sufficient lead ($>$1000 ppm) is not contained in the commercially supplied zinc dust, a catalytic amount of lead dust or a lead salt may be added to consistently obtain the desired reactivity. Addition of larger amounts ($>$2 mol %) of lead salts or other metal salts results in a decrease in reactivity. Thallium(I) chloride is also a useful additive for increasing the reactivity of commercial zinc dust which does not contain lead. Identification of the catalytic role of lead allowed development of a robust process for the synthesis of 4-thiazolidinones.

Introduction

Zinc is an inexpensive and readily available metal which has found wide use in the preparation of organometallic compounds[1] and as a reducing agent[2] in organic synthesis. Activation of zinc is often necessary to achieve increased reactivity or more reproducible results.[3] Despite the availability of these techniques, however, variable reactivity presents a major challenge to the process chemist charged with development of a robust process utilizing zinc dust. Recently, Takai and co-workers reported that the level of lead present in commercial zinc dust dramatically impacts the zinc reactivity. In the Wittig-type olefination using $RCHX_2-TiCl_4-Zn$, a catalytic amount of lead (0.04−0.07 mol %) was crucial to obtaining acceptable yields.[4] Surprisingly, for the Simmons−Smith cyclopropanation or conversion of alkyl iodides to alkylzinc reagents, the same levels of lead inhibited the reaction.[5] The conversion of 2-thioxo-4-thiazolidinones to 4-thiazolidinones using zinc dust in acetic acid was recently reported (see eq 1).[6] As noted in that communication, zinc dust from one commercial source was not effective in this reductive thiocarbonyl removal. We now report that catalytic levels of lead are critical to the effectiveness of the zinc dust used in this thiocarbonyl removal reaction. In addition, lead metal or lead salts may be added to unreactive zinc dust to consistently achieve the desired reactivity. The result is a reliable process for conversion of 2-thioxo-4-thiazolidinones to 4-thiazolidinones using zinc dust.



(1)

Results and Discussion

Reduction of the 2-thioxo-4-thiazolidinone **1** to the corresponding 4-thiazolidinone **2** was chosen as the test reaction for comparing various lots of zinc dust.[6] Reactions were carried out by adding 500 mol % of zinc dust to a 0.8 M solution of compound **1** in acetic acid at reflux.[7] Figure 1 shows the percent remaining substrate **1** as a function of time for six commercial lots of 325 mesh zinc dust.[8] Lead levels in the commercial zinc lots were determined by inductively coupled plasma atomic emission spectroscopy.[9] A correlation between reactivity and lead content was observed. Lots that contained more than 1000 ppm of lead all displayed acceptable reactivity, and reactions were complete within 4 h. The lots with low lead contamination, including lot 3 reported in our initial communication,[6] provided slow conversion to the desired product.[10] Both lots 1 and 6 were purchased from the same supplier, and no data regarding variation in the zinc dust quality was provided.

By analogy with the results reported by Takai and coworkers,[4] a catalytic amount of lead powder or lead(II) chloride could be added to the ineffective zinc dust to duplicate the reactivity of the effective zinc lots. Figure 2 shows that addition of 0.05−200 mol % of lead powder to lot 1 zinc dust ($<$0.001% Pb) dramatically increased the reaction rate. The rate obtained by addition of 0.05% lead was less than that observed using commercial zinc dust containing a similar amount of lead. Better dispersion of the lead throughout the commercial zinc dust is likely

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* E-mail: MMH@Lilly.com.

(1) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188. (b) Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980.

(2) Hudlicky, M. *Reductions in Organic Synthesis*; Wiley: New York, 1984.

(3) (a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203−2212. (b) Rieke, R. D. *Science* **1989**, *246*, 1260−1264. (c) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453. (d) Durant, A.; Delplancke, J.; Winand, R.; Reisse, J. *Tetrahedron Lett.* **1995**, *36*, 4257−4260. (e) A Zn−Pb couple has been reported for removal of the TROC protecting group; see: Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833−2835.

(4) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.

(5) Takai, K.; Kakiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671−2673.

(6) Hansen, M. M.; Harkness, A. R. *Tetrahedron Lett.* **1994**, *35*, 6971−6974.

(7) Excess zinc dust is required to minimize the formation of dimeric byproducts; see ref 6.

(8) Initial studies showed that washing the zinc with aqueous HCl did not affect the reaction rate. Acetic acid at reflux may remove the zinc oxide coating.

(9) All ICP analyses reported in this paper were conducted by Thiokol Corporation, P.O. Box 707, Brigham City, UT 84302-0707. A full metal screen was conducted on zinc dust lot 4 with the following results: lead, 1476 ppm; aluminum, 195 ppm; iron, 148 ppm; cadmium, 53 ppm; tin, 43 ppm; copper, 32 ppm; calcium, 32 ppm; and barium, 3 ppm.

(10) Ultrahigh-purity zinc (99.9998%) from Aldrich was unreactive, with $>$97% compound **1** remaining after 4 h.

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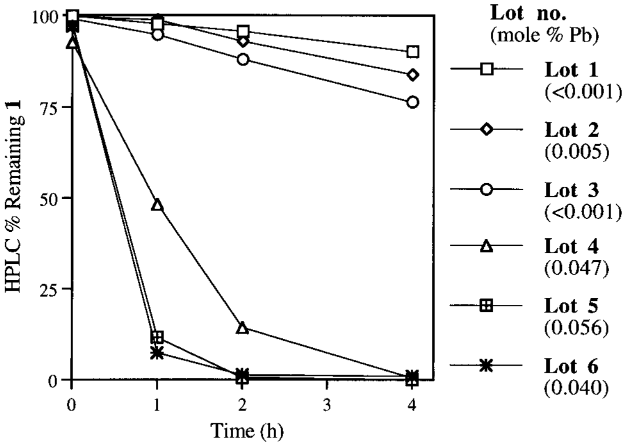

Figure 1. **Reduction of 1 with commercial zinc dust: effect of lead content.**

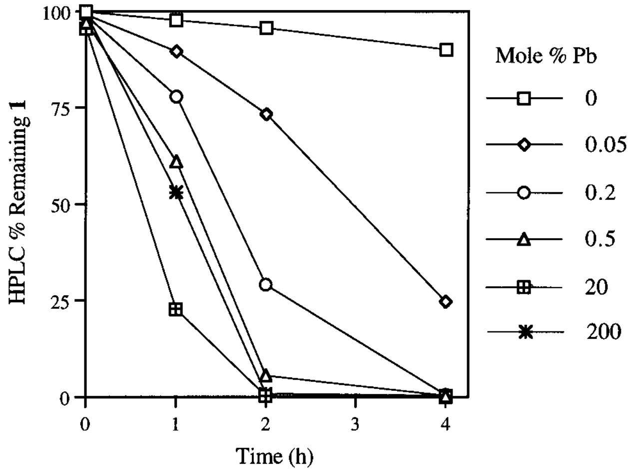

Figure 2. **Reduction of 1 with lot 1 zinc dust and lead.**

responsible for the higher catalytic efficiency. Increasing amounts of lead increased the rate until a plateau was reached at 0.5% added lead. The rate obtained by adding between 0.5 and 200 mol % of lead was comparable to the rate observed using the best commercial lots of zinc dust. Demonstration that any amount of lead between 0.5 and 200% gives a comparable reaction rate is of practical benefit to the process chemist. It is not necessary to determine whether a given zinc dust lot contains lead, because addition of 0.5 mol % lead will provide the desired reactivity regardless of the initial lead level. A control experiment showed that 500 mol % of lead powder alone does not convert **1** to **2**. Therefore, a mechanism where lead is the active reductant and zinc serves only to recycle lead(II) back to lead(0) is unlikely.[11]

Lead(II) chloride was also a useful catalyst at low levels (0.1 or 0.5 mol %); however, addition of 2 or 5 mol % of $PbCl_2$ to the lead-free zinc did not increase the rate significantly (see Figure 3). The best conversion rates obtained using $PbCl_2$ were lower than those obtained using lead powder as the additive. We considered the possibility that chloride may inhibit the reduction process. A similar inhibitory effect was observed using 5 mol % of $PbBr_2$ (87% conversion at 4 h) and PbI_2 (47% conversion at 4 h). The effect of halide additives was further probed by conducting the reaction using lot 5 zinc dust (0.056 mol % Pb) in the presence of the following chloride sources: aqueous HCl, $ZnCl_2$, $MgCl_2$, *n*-Bu_4NCl, or NaCl. At low levels (0.5 mol %), none of these additives changed the reaction rate. However, 5 mol % of $ZnCl_2$ or $MgCl_2$ dramatically inhibited the reaction, while the other additives had little impact on the rate (see Figure 4). Because not all chloride sources inhibit the reaction, chloride is not directly involved in interfering with the electron transfer process required for reduction. Rather, $ZnCl_2$ and $MgCl_2$ may inhibit the reaction by coating the zinc surface and disrupting the interaction of substrate with the zinc. In a similar manner, $PbCl_2$ at sufficient levels could adhere to the zinc surface and block interaction with the substrate.

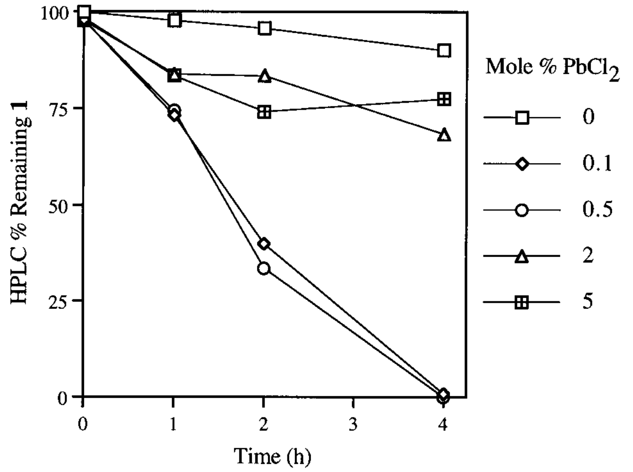

Figure 3. **Reduction of 1 with lot 1 zinc dust and $PbCl_2$.**

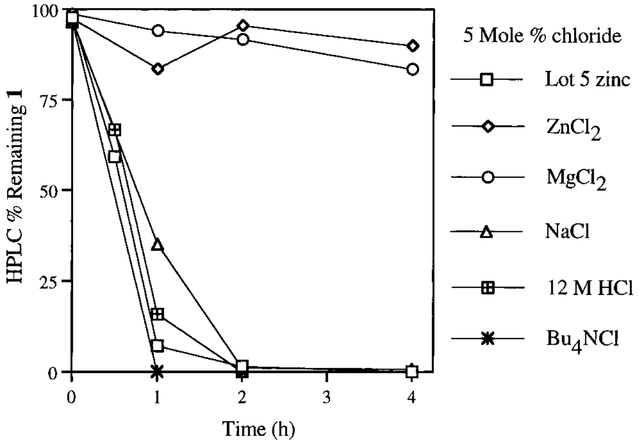

Figure 4. **Reduction of 1 with lot 5 zinc dust and a chloride source.**

Reduction of lead(II) chloride to lead under the reaction conditions is expected,[12] and black particles with an appearance similar to that of lead dust were observed in the reaction mixtures after 1−2 h. In a reaction where 5 mol % of lead(II) acetate (see below) was used rather than $PbCl_2$, it was possible to isolate these black particles by decanting the

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(11) Such a recycle mechanism has been proposed to explain nickel catalysis of the addition of vinylic halides and triflates to aldehydes in the presence of chromium(II); see: (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050.

(12) Standard reduction potential, $E°$ (Zn^{2+}) = −0.763 V, $E°$ (Pb^{2+}) = −0.126 V.

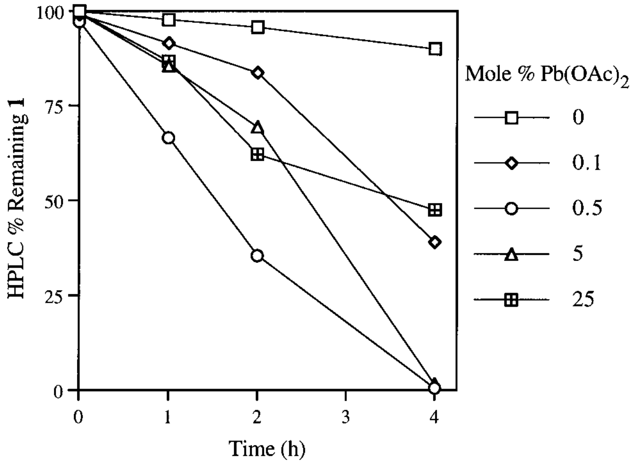

Figure 5. **Reduction of 1 with lot 1 zinc dust and Pb(OAc)$_2$.**

reaction mixture. Analysis of this black solid by inductively coupled plasma atomic emission spectroscopy showed 30% lead and 65% zinc, consistent with the formation of a mixed lead−zinc aggregate. It is likely that the Pb(OAc)$_2$ was reduced to lead early in the reaction to form small particle size lead powder.[13] Formation of visible black pieces occurred only after the lead coagulated with some zinc to form larger particles.

Coating of the zinc surface by an added salt is also likely with non-halide salts, and we have found similar behavior using lead(II) acetate (see Figure 5). Relative to PbCl$_2$, 0.1 mol % of Pb(OAc)$_2$ had a moderate effect on the reaction rate. The optimal amount of Pb(OAc)$_2$ was 0.5 mol %, where it had an effect comparable to that of 0.5 mol % of PbCl$_2$. Higher levels of Pb(OAc)$_2$ were less deleterious than comparable amounts of PbCl$_2$, yet the rate was still slowed relative to the rate for 0.5 mol % of Pb(OAc)$_2$. Coating of the zinc surface by Pb(OAc)$_2$, or more likely by Zn(OAc)$_2$ formed directly on the zinc surface by reaction of Pb(OAc)$_2$ with zinc, is a likely explanation for the observed inhibition.

We surveyed other metals to determine if the reaction rate acceleration was unique to lead. In order to avoid possible halide effects, the following commercially available metal powders were screened as additives: bismuth, copper, nickel, tin, aluminum, and iron. Mercury(II) chloride was also investgated. Reactions were run using 0.1 or 0.5 mol % of each metal or salt and lot 1 zinc dust (<0.001% Pb). No significant catalysis was observed with these metals: 73−96% of compound **1** remained at 4 h. More promising results were obtained when thallium(I) chloride was investigated (see Figure 6). With 0.05 or 0.1% TlCl the reaction went to near completion over 4 h. Use of 0.5 or 2 mol % of TlCl afforded slower reaction rates, presumably due to the salt inhibition effect discussed above.

Although the mechanism of the accelerating effect of lead on this zinc-mediated thiocarbonyl removal reaction is unknown, identification of thallium as a second catalyst adds a second option for the design of mechanism elucidation experiments. A metal capable of a single electron transfer may be critical to the reduction process. We briefly investigated the effect of lead on the well-known zinc reduction of aromatic nitro groups and found that lead inhibited this reaction.[14] These results, along with those of Takai and co-workers,[4,5] show that lead may have a significant activating or deactivating influence on the course of a number of different organic transformations.

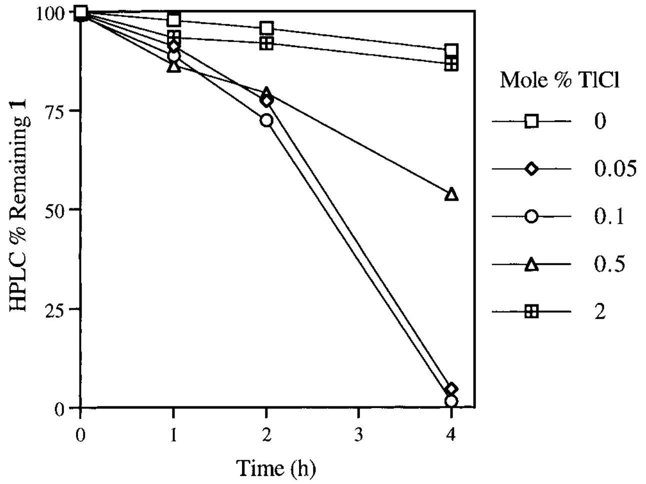

Figure 6. **Reduction of 1 with lot 1 zinc dust and TlCl.**

The present study was critical to the development of a robust process for conversion of 2-thioxo-4-thiazolidinone **1** to the corresponding 4-thiazolidinone **2** using zinc dust. Zinc dust from a variety of commercial sources is acceptable if 0.5 mol % of lead powder is added to the reaction mixture. In addition, the deleterious effect of some metal salts on the course of a zinc reaction was identified for the first time. Further study of the impact of trace metal contamination and the presence of metal salts on the course of other processes that utilize zinc is warranted.

Experimental Section

The commercial lots of zinc dust compared in Figure 1 were purchased from the following suppliers. Lot 1 was purchased from Aldrich Chemical Company in 1995 (Aldrich Lot 04415CF). Lot 6 was purchased from Aldrich in 1991 (Aldrich Lot 10008TW). Lot 3 was purchased from the Aldrich affiliate in the United Kingdom in 1991. Two grades of zinc dust were purchased from Southern Zinc. Lots 4 and 5 were sold as Superfine-5, which normally contains about 0.05 mol % of Pb. Superfine-5 zinc dust was used to prepare compound **2** on pilot plant scale. Lot 2 was sold as Superfine-5L, which normally contains <0.015 mol % of Pb. Lead powder (325 mesh, 99+%) and the other additives were purchased from Aldrich.

General Zinc Reduction Procedure. To 10.0 g (28.5 mmol) of **1** in 36 mL of HOAc at reflux was added 9.30 g (142 mmol) of zinc dust. For reactions in which a metal or metal salt additive was added,[15] the additive was premixed with the zinc dust immediately prior to addition to the reaction mixture. The well-agitated reaction mixture was heated at reflux, and conversion to **2** was monitored by HPLC

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(13) In analogy to the formation of Rieke type metals; see ref 3b.

(14) Treatment of a 4-substituted nitrobenzene derivative in ethanol/acetic acid with 600 mol % of lot 1 zinc dust (no Pb) resulted in complete conversion to the aniline over 10 min. With 0.5 mol % of lead dust as an additive, 90 min was required for complete conversion.

(15) For entry 5 of Figure 4, 12 M HCl was added to the reaction mixture immediately prior to addition of the zinc dust.

using a Zorbax Rx-C8 column. The percent remaining starting material at 1, 2, and 4 h is presented in Figures 1−6. Addition of **1** to zinc dust in portions as recommended in ref 6 was not employed as this would have complicated relative reaction rate comparisons. In the present study, compound **2** was not isolated; however, details on the preparation and isolation of compound **2** are provided in ref 6.

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