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A CONVENIENT PROCEDURE FOR THE PREPARATION OF REACTIVE ZINC FOR THE REFORMATSKY REACTION

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ABSTRACT

A reactive zinc powder is obtained by addition of $ZnCl_2$ to a lithium dispersion suspended in ether. Reformatsky Reactions with the zinc powder are described.

The classical procedure for conducting the Reformatsky Reaction [1] uses granular zinc to condense α-bromoesters with aldehydes or ketones and is a model of simplicity and convenience. However, the yield of β-hydroxyester is often modest, due, in part, to the extended reaction times or elevated temperatures required. Reike[2] introduced the use of reactive zinc powders, prepared originally by reduction of zinc salts with

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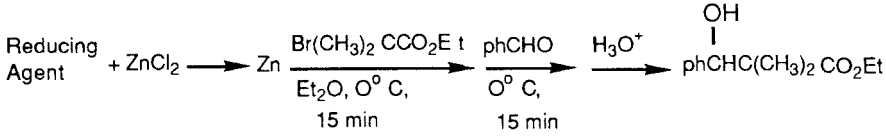
potassium metal. Subsequent procedures using sodium naphthalide [3] or lithium metal with catalytic amounts of napthalene[4] in place of potassium have produced even more reactive zinc. Excellent yields of β-hydroxyesters have been reported with all of these procedures, but each suffers from the extended time required to either prepare or react the reducing agent. We have found that a commercially available dispersion of lithium in mineral oil reacts directly with $ZnCl_2$ in ether at room temperature and produces a particularly reactive form of zinc. The preparation is routinely completed in 15 minutes and can be made even more convenient by the use of commercially available solutions of anhydrous $ZnCl_2$ in ether.

The reactivity of zinc prepared by the lithium dispersion procedure was compared to that of zinc prepared by two other published procedures in a two-stage Reformatsky Reaction.



Lithium dispersion 95%
(Et_2O, 15 min, 25°C)

Lithium rod, napthalene[4]. 69%
(Et_2O, 18 hrs, 25°C)

Sodium Naphthalide[3]. 42%
(THF, 15 min, 25°C)

A more dramatic difference among the procedures was observed when the three forms of zinc were prepared as above but the reactions with bromoester and benzaldehyde were conducted at -78°C (15 min each step). Under these conditions, the lithium dispersion procedure gave a 56% yield of β-hydroxyester while the other two procedures gave less than 10% yields. The only previous report of a successful Reformatsky Reaction as -78°C utilized laminated zinc/silver-graphite obtained from C_8K and $ZnCl_2$/AgOAc[5].

The success of a two-stage Reformatsky sequence is significant because it allows the preparation of solutions of the intermediate zinc ester enolate for stability or structural studies.[6] We have applied the lithium dispersion procedure to the reaction of the methyl, ethyl, isopropyl and *t*-butyl esters of 2-bromoacetic acid and 2-bromopropanoic acid. In all cases, complete reaction with zinc was observed within 15 min at 0°C. Nearly quantitative formation of the zinc ester enolate was demonstrated by subsequent quenching with benzaldehyde followed by gas chromatographic analysis for the corresponding β-hydroxyester.

Experimental:

The following procedure for the reaction of ethyl α-bromoisobutyrate with benzaldehyde is representative. Lithium dispersion (25 weight % in mineral oil, sodium content ~0.5%) and $ZnCl_2$ (1.0M solution in Et_2O) were purchased from Aldrich Chemical Company. The lithium dispersion (0.0832g, 3 mmol) is weighed directly

into a 10 ml round bottom flask. Et_2O (0.5 ml) is added and the flask immersed in a water bath at 25°C. $ZnCl_2$ in Et_2O (1.5 ml, 1.5 mmol) is added dropwise. After 15 min, the flash is immersed in an ice-water bath, ethyl α-bromoisobutyrate (0.146 ml, 1.0 mmol) is added and the mixture is stirred an additional 15 min. Benzaldehyde (0.101 ml, 1.0 mmol) is added dropwise and after 15 min, the mixture is quenched with 1N aqueous HCl (2 ml). The organic layer is extracted with Et_2O (3 X 2 ml) and the combined organic extracts are examined by gas chromatography to determine the yield of ethyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (0.98 mmol, 98% yield).

References and Notes

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