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Remarkable O_2-Effect in 1,4-Additions of Diethylzinc to 6-Acyloxy-2*H*-pyran-3(6*H*)-ones and 6-Alkoxy-2*H*-pyran-3(6*H*)-ones

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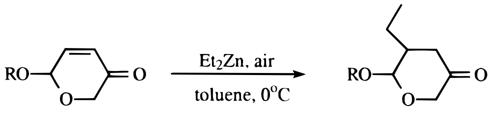
ABSTRACT



1 **2**

Under the influence of air, a facile 1,4-addition of diethylzinc to acyloxypyranones and alkoxypyranones 1 takes place. Reaction of diethylzinc with molecular oxygen provides EtOOZnEt, which catalyzes the addition of diethylzinc.

Conjugate addition of organozinc derivatives to α,*β*-unsaturated systems comprises a useful strategy for C−C bond formation.[1] Due to the low reactivity of dialkylzinc reagents, these reactions usually involve transmetalation or Lewis acid catalysis. Recently, considerable interest has been devoted to the development of chiral catalysts in order to perform asymmetric conjugate additions of dialkylzinc reagents.[2]

Herein we wish to report the unexpected discovery of 1,4-additions of Et_2Zn to pyranones **1** initiated by molecular oxygen, unaided by the presence of any ligand or metal catalyst. Until now, conjugate additions of carbon nucleophiles to pyranone systems have only been accomplished using Grignard reagents and organolithium-based cuprates.[3]

Although it was previously found that the autoxidation products of Et_2Zn can initiate the polymerization of alkenes or facilitate cyclopropanation by a radical mechanism,[4] the combination of dialkylzinc and oxygen has found only limited use in synthetic organic chemistry. It was established that α,*β*-unsaturated ketones undergo nucleophilic epoxidation with alkylperoxyzinc species, which are formed during the autoxidation of dialkylzincs.[5] Asymmetric epoxidations of enones with oxygen and diethylzinc have been described by Enders.[6] In these reactions (*R*,*R*)-*N*-methylpseudoephedrine is used as chiral ligand, which reacts with Et_2Zn followed by a reaction with O_2, to give EtOOZnOR* as the actual epoxidizing agent.

Recently it was shown that diethylzinc in the presence of oxygen can be used to promote tin-mediated radical reactions.[7] Oxygen-induced additions of diethylzinc to the C═N double bond in glyoxylic acid derivatives has also been

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[1] Knochel, P.; Almene Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

[2] (a) Feringa, B. L.; de Vries A. H. M. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press Inc.: 1995; Vol. 1, p 151. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; Vries, A. H. M. de *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (c) Soai, K.; Shibata, T. In *Organozinc Reagents, a practical approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: 1998; pp 245−261 (d) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283.

[3] (a) Paulsen, H.; Koebernick, W.; Koebernick, H. *Tetrahedron Lett.* **1976**, 2297. (b) Paulsen, H.; Koebernick, W. *Carbohydr. Res.* **1977**, *56*, 53.

[4] See, for example: Rousseau, G.; Slougi, N. *J. Am. Chem. Soc*. **1984**, *106*, 7283.

[5] (a) Yamamoto, K.; Yamamoto, N. *Chem. Lett*. **1989**, 1149. (b) Shi, M.; Itoh, N.; Masaki, Y *J. Chem. Res., Synop.* **1995**, *8*, 304.

[6] (a) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1725. (b) Enders, D.; Kramps, L. *Liebigs Ann./Recueil* **1997**, 1101. (c) Enders, D.; Kramps, L.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3959.

[7] Ruy, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.

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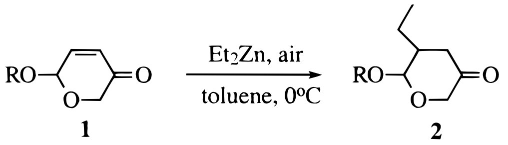
reported.[8] Addition of alkyl halides in this radical chain reaction leads to incorporation of the alkyl groups instead of the ethyl group. This variation can also be applied to cyclohexenone. Without the use of alkyl halides, 1,4-addition of Et_2Zn to cyclohexenone was observed,[8] an observation in conflict with the findings of Yamamoto.[5a]

We found that on reaction of diethylzinc with acyloxypyranones and alkoxypyranones in toluene under the influence of air, the 1,4-adducts are readily formed (Scheme 1).

Scheme 1. 1,4-Addition of Diethylzinc to 6-Acyloxy- and 6-Alkoxypyranones



R = -$COCH_3$, -$COCH_2CH_3$, -$COCH(CH_3)_2$,
-CH_3, -pantholactone

When Et_2Zn (1.2 equiv) was added to acetoxypyranone under oxygen free conditions, no reaction took place. This is illustrated in Figure 1. During the first 10 min, the reaction mixture is kept under an argon atmosphere, under which condition no conversion can be measured.[9] After 10.5 min, the mixture is exposed to the air. From that point the reaction starts rapidly and proceeds until completeness in about 85 min.

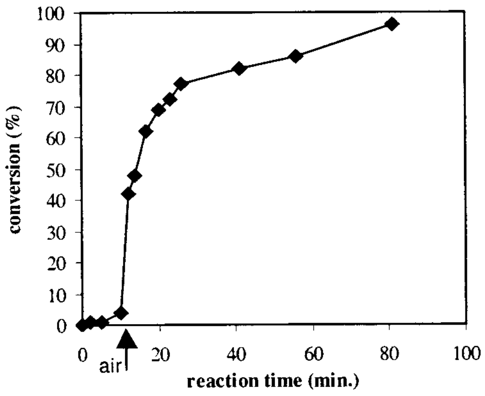


Figure 1. Influence of air on 1,4-addition of Et_2Zn to acetoxypyranone.

The 1,4-addition of Et_2Zn was performed with several pyranones as listed in Table 1.[10] In these examples the amount of Et_2Zn was increased to 1.5 equiv to get a faster and complete reaction. The method developed here is applicable to acyloxypyranones (**1a**, **1b**, **1c**) as well as alkoxypyranones (**1d** and **1e**). In all cases only the 1,4-adducts were formed, which were isolated in 62−76% yield. No other products, such as the epoxide, could be detected.[11] When the reactions are complete, they have to be stopped, since otherwise undesired polymerization takes place. As judged from the coupling constants in the ^1H NMR spectra, the additions take place trans-stereoselectively with respect to the substituent at the 6-position.

Table 1. Air-Induced 1,4-Additions of Diethylzinc to Pyranones

starting material	R	reaction time (h)[a]	product	yield (%)[b]
1a	−$COCH_3$	1	**2a**	71
1b	−$COCH_2CH_3$	1	**2b**	62
1c	−$COCH(CH_3)_2$	1	**2c**	68
1d	−CH_3	1	**2d**	70
1e	−pantholactone	2	**2e**	76

[a] Reactions were monitored by GC using a Hewlett-Packard 5890 GC, equipped with a 30.0 m × 250 μm × 1.00 μm capillary column coated with dimethylpolysiloxane. Small aliquots (0.1 mL) were taken from the reaction mixture, quenched with 1 mL of saturated NH_4Cl solution, extracted with 2 mL of diethyl ether, and dried over $MgSO_4$. [b] Isolated yields.

The 1,4-additions even take place with a very small amount of oxygen. If the toluene is exposed to air before use, a fast reaction takes place even though the mixture is kept under argon during the subsequent reaction.

When Et_2Zn reacts with oxygen, it is known that first EtZnOOEt is formed, which oxidizes further to EtOOZnOOEt.[12] To determine whether EtZnOOEt or EtOOZnOOEt or another autoxidation product of Et_2Zn is responsible for the 1,4-addition, some reactions with EtZnOOtBu and EtOOZnOOEt were carried out.

EtOOZnOOEt was prepared in situ by following a literature procedure of treating Et_2Zn with an excess of oxygen at room temperature.[12] On reaction with acetoxypyranone after 2 h, only starting material was observed in the reaction mixture as determined by GC analysis.

The reaction of Et_2Zn with t-BuOOH at 0 °C afforded EtZnOOtBu. When only 10% (relative to Et_2Zn) of t-BuOOH was used, the 1,4-addition product was formed exclusively after the addition of methoxypyranone **1d**. Then the amount of t-BuOOH was increased to 50% and 100%, respectively. During the reaction with methoxypyranone, in the first case a second product was formed (GC analysis) in addition to

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(8) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189.

(9) Quenching of the samples also has to take place under oxygen free conditions, to prevent a fast reaction at the moment of quenching.

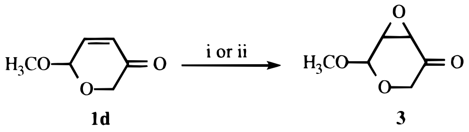
(10) **Typical experimental procedure:** 200 mg of acetoxypyranone **1a** (1.28 mmol) was dissolved in 10 mL of freshly distilled toluene under an argon atmosphere and cooled with an ice bath. Then 1.5 equiv of Et_2Zn (1.92 mmol, 1.1 M in toluene) was added and the argon inlet was replaced by a $CaCl_2$ tube. After completion of the reaction, the mixture was quenched with 10 mL of a saturated NH_4Cl solution and extracted three times with 25 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude product was obtained as an oil, which could be purified by chromatography (silica, hexanes:EtOAc 2:1), to give 203 mg of **2a** as a yellow oil (71%).

(11) All new compounds exhibit spectral (^1H NMR, ^{13}C NMR, and mass) data consistent with the assigned structures.

(12) (a) Abraham, M. H. *J. Chem. Soc.* **1960**, 4130. (b) Sosnovsky, J.; Brown, J. H. *Chem. Rev.* **1966**, *66*, 529.

the 1,4-adduct. In the latter case only the second product was observed. This unknown compound was shown to be the epoxidation product **3** of methoxypyranone as could be proven by independent epoxidation of methoxypyranone with H_2O_2/NaOH (Scheme 2). The t-BuOOZnEt-mediated epoxidation of pyranone **1** is in accordance with previously reported epoxidations of enones using in situ prepared alkylperoxyzinc species.[5]

Scheme 2. Epoxidation of Methoxypyranone

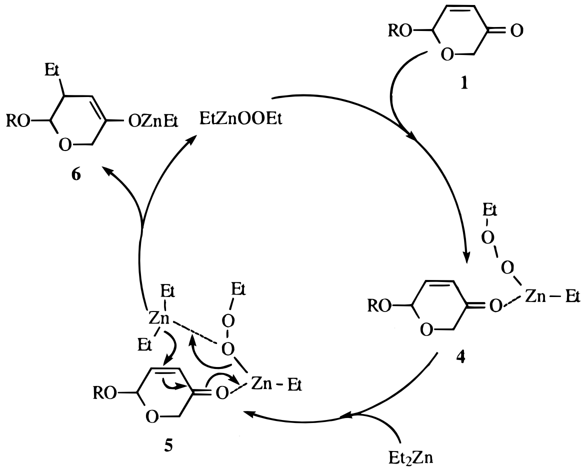


i) t-BuOOZnEt, ii) H_2O_2/NaOH

The last question that remains is whether EtZnOEt or EtZnO-t-Bu, which might be formed by the reduction of EtZnOO-t-Bu with Et_2Zn, plays a role in the 1,4-addition. Therefore, Et_2Zn was allowed to react with t-BuOH to form EtZnO-t-Bu. When methoxypyranone was added to this mixture, no conversion took place.

From these experiments it is clear that EtZnOOEt either catalyzes the addition of Et_2Zn to the pyranones or alternatively initiates the formation of ethyl radicals and acts subsequently as a chain transfer agent. In the first mechanistic pathway, depicted in Scheme 3, it is proposed that EtZnOOEt coordinates to the pyranone (structure **4**) and then activates a molecule of Et_2Zn to give a 1,4-addition. In this step the original Zn−oxygen bond is broken and a new Zn−oxygen bond is formed, resulting in enolate **6** and the free catalyst. In the second mechanistic pathway that can be envisioned for the Et_2Zn addition in the presence of O_2, EtZnOOEt is able to initiate the formation of an ethyl radical. Addition of the ethyl radical to the enone, activated by Et_2Zn, leads to the 1,4-adduct with generation of a new ethyl radical. In this case, Et_2Zn acts as both a Lewis acid and a chain transfer agent, as recently proposed for Et_2Zn additions to imines.[8] When there is no more free Et_2Zn present in the reaction mixture, EtZnOOEt reacts with the enone to form the epoxide. Which of the two mechanisms proposed here is operating in the 1,4-addition to pyranones awaits further detailed mechanistic studies.

Scheme 3. Proposed Mechanism of Air-Induced 1,4-Addition of Et_2Zn to Pyranones **1**



We have shown here that it is possible to perform selective and efficient 1,4-additions of Et_2Zn to pyranones under the influence of air. A small amount of air is sufficient for these reactions to occur. Ongoing efforts will show whether this strategy is also suitable for other activated α,β-unsaturated systems. This finding may also have implications for some of the numerous other asymmetric addition reactions of Et_2Zn studied. Small traces of O_2 can form EtZnOOEt that might catalyze the nonstereoselective carbon−carbon formation, resulting in lower enantiomeric excesses as anticipated on the basis of the chiral catalyst employed. Therefore, it is recommended to scrutinize the effect of traces of O_2 in enantioselective catalysis employing diorganozinc reagents.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2a**−**2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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