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DEAD-(cat)$ZnBr_2$ an efficient system for the oxidation of alcohols to carbonyl compounds

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ABSTRACT

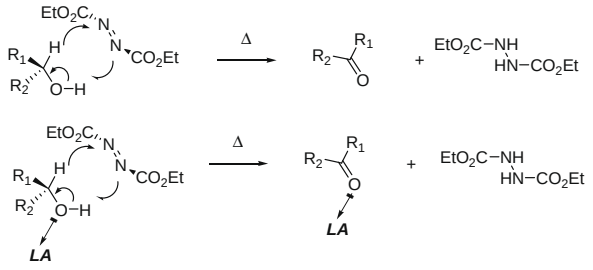
The combination of diethyl azodicarboxylate (DEAD) and a catalytic amount of $ZnBr_2$ is an efficient system for the dehydrogenation of alcohols to the corresponding carbonyl compounds. The scope and limitations of this process have been studied.

Diethyl azodicarboxylate (DEAD) and its congeners are very useful reagents in organic synthesis, especially regarding the Mitsunobu reaction.[1] It is known that DEAD alone can dehydrogenate various types of compounds (alcohols, thiols, hydroxylamines, hydrazines for instance).[2] The oxidation by DEAD, of alcohols to carbonyl compounds, has been first reported on a limited number of examples by the group of Yoneda.[3] This is an interesting reaction affording, as the only byproduct, diethyl hydrazodicarboxylate ($DEADH_2$), which is easily separated by chromatography. Furthermore, this product could be recycled since reoxidation to DEAD has also been reported.[4] However, to the best of our knowledge, this methodology has not been very often used in organic synthesis until now. By analogy with the well-known Meerwein–Pondorf–Verley/Oppenauer reactions,[5] we can propose a simple pericyclic mechanism for this reaction (Scheme 1): a six-membered cyclic transition state could account for the transfer of the two hydrogen atoms onto the azo molecule.[6] Based on this tentative mechanism, it appeared to us that this reaction could be catalyzed by an appropriate Lewis acid (LA). Complexation of the oxygen atom of the alcohol should facilitate the cleavage of the OH bond and the hydrogen transfer. This should contribute to have a faster reaction occurring under milder conditions.

The purpose of this Letter is to demonstrate that the combination of DEAD with catalytic amounts of $ZnBr_2$ indeed gives a simple and efficient process for the oxidation of various types of alcohols under mild reaction conditions.

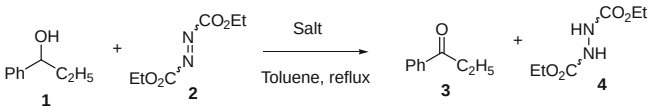
The first stage of this study was to validate this proposal and perform a quick screening of the possible Lewis acids. This was done by using phenyl-1-propanol **1** as a model. As indicated in Table 1, various salts are indeed able to activate this reaction: in refluxing toluene, the oxidation by DEAD alone is complete only after 48 h, while in the presence of 1 equiv of $MgBr_2$ or $CuBr_2$, the reaction is finished after 1 h affording the corresponding ketone in 90% and 84% yields, respectively. Of the different salts attempted, $ZnBr_2$ was found to be the most efficient and the most convenient for the substrate alcohol chosen. With this latter salt, the dehydrogenation of **1** is complete within 30 min.

The next step was to explore the possibility to use this mild Lewis acid salt in a catalytic manner. For that purpose, the same alcohol was used as a reference and the results are reported in Table 2.



Scheme 1. Postulated mechanism for the DEAD-mediated dehydrogenation and our working hypothesis.

Table 1
Screening of the salts used as mild Lewis acids



Entry	Salt (1 equiv)	Time (h)	Ketone **3** (yield) (%)
1	—	48	98
2	$MgBr_2$	1	90
3	$CuBr_2$	1	84
4	$NiBr_2$	2	82
5	$InBr_3$	0.5	94
6	$ZnBr_2$	0.5	96

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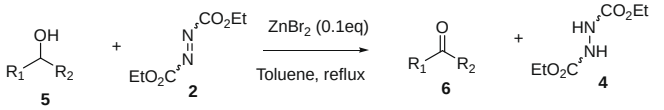
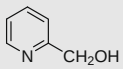
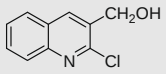
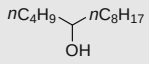
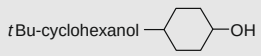
Table 2
Optimization of the amount of catalyst

Entry	$ZnBr_2$ (equiv)	Time (h)	Ketone **3** (yield) (%)
1	—	48	98
2	1	0.5	96
3	0.6	0.5	98
4	0.2	0.75	98
5	0.1	1	96[a]
6	0.05	3	98

[a] Under the same reaction conditions, diisopropyl azodicarboxylate (DIAD) gives the ketone **3** in 92% yield.

Table 3
Extension to various types of alcohols



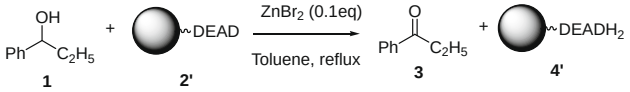
Entry	Alcohol **5**	Time (h)	Carbonyl derivative **6** (yield) (%)
1	$PhCH_2OH$	1.5	90
2	p-NO_2PhCH_2OH	1.5	91
3	p-$MeOPhCH_2OH$	1.5	92
4	t-$BuCH_2OH$	2.5	90
5		2.5	70
6		2	86
7	Ph_2CHOH	1.5	96
8		4	98
9		3.5	98

In fact $ZnBr_2$ is an efficient catalyst since the oxidation of **1** is quantitative even at the level of 5 mol % (entry 6). In the latter case, the reaction duration is 3 h only.[7]

The next step was the extension of this reaction to other alcohols and to check its scope and limitations. For that purpose we selected the following standard reaction conditions: DEAD (1 equiv) with $ZnBr_2$ (10 mol %) in refluxing toluene. The results are reported in Table 3.[8]

Several points are worthy of noted:

- Excellent results are obtained with benzyl alcohol and substituted derivatives with electron-withdrawing, as well as electron-donating groups (entries 1–3). A very good yield is also obtained with a sterically hindered alcohol (entry 4).
- The reaction is compatible with heteroaromatic systems such as pyridine or quinoline derivatives (entries 5 and 6).
- It is possible to use it efficiently as well with diaryl- (entry 7) as well as dialkyl-secondary alcohols (entry 8) or cyclohexyl derivatives (entry 9).
- The reaction is slightly faster on the secondary alcohol **1** as compared to corresponding primary benzyl alcohol: a competition experiment using a 1:1 mixture of these two alcohols affords a 1.4:1 mixture of ketone **3** and benzaldehyde.



Scheme 2. Reaction with DEAD anchored on Merrifield's resin.

- At this stage, this reaction does not work with allylic or propargylic alcohols since it leads to complex mixtures of products but not to the desired carbonyl compounds.[9]

A final attractive possibility is to use DEAD anchored on a support **2′**, since it would offer additional facility for the separation of the byproduct which will be the supported $DEADH_2$ **4′** (Scheme 2).

This reaction works indeed very well. By using 1 equiv of commercially available DEAD supported on Merrifield resin, the reaction is complete in 1.5 h affording the pure ketone **3** in 95% yield after filtration and evaporation of the solvent.[10]

In conclusion, these preliminary results demonstrate that catalytic amounts of $ZnBr_2$ strongly catalyze the DEAD-mediated dehydrogenation of alcohols to carbonyl compounds. Extension of this methodology is under active study in our group.

Acknowledgments

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References and notes

1. For recent reviews on Mitsunobu reaction see: (a) Dembinski, A. *Eur. J. Org. Chem.* **2004**, 2763–2772; (b) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340–1355 and references cited therein.
2. Stoner, E. J. In *Encyclopedia of Organic Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons, 1995; pp 1790–1793.
3. (a) Yoneda, F.; Suzuki, K.; Nitia, Y. *J. Am. Chem. Soc.* **1966**, *88*, 2328–2329; (b) Yoneda, F.; Suzuki, K.; Nitia, Y. *J. Org. Chem.* **1967**, *32*, 727–729.
4. Moriarty, R. M.; Prakash, I.; Penmasta, R. *Synth. Commun.* **1987**, *17*, 409–413.
5. Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons, 2001.
6. This tentative mechanism is based on the simple analogy of the π-system of the azo group with a carbonyl group. Of course, alternative mechanisms could be considered as well. For a new DEAD-mediated dehydrogenation of tertiary amines, see: Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048–14049.
7. The reaction temperature is also important: by reacting **1** with 0.1 equiv of $ZnBr_2$ and 1 equiv of DEAD in toluene, the reaction is not complete after 2 days at 80 °C and the isolated yield in ketone **3** is only 34%.
8. *Representative experimental procedure*: To a solution of alcohol **1** (230 mg, 1.7 mMol) in toluene (2.5 mL) are added DEAD **2** (294 mg, 1.7 mMol) and $ZnBr_2$ (38 mg, 0.17 mMol). The solution is heated under reflux for 0.5 h. After removal of the solvent under reduced pressure, SiO_2 chromatography easily allows separation of the ketone **3** (218 mg, 96% yield) and $DEADH_2$ **4** (287 mg, 96% yield). Compound **3**: R_f = 0.57 (pentane/ether: 9:1). ^1H NMR: (300 Hz, $CDCl_3$) δ (ppm) 7.96–7.25 (m, 5H (H_{Ar})), 3.00 (qd, J = 7.3 Hz, 2H (CH_2)), 1.21 (t, J = 7.3 Hz, 3H(CH_3)) ^{13}C NMR: (75 Hz, $CDCl_3$) δ (ppm) 8.2, 31.7, 127.9, 128.5, 132.9, 136.9, 200.8. **4**: R_f = 0.14 (pentane/ether: 9:1) ^1H NMR (300 Hz, $CDCl_3$) δ (ppm) 6.62 (br, 2H (2NH)), 4.20 (qd, J = 7.1 Hz, 4H ($2CH_2$)), 1.27 (t, J = 7.1 Hz, 6H ($2CH_3$)). ^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm) 14.0, 61.9, 156.4. All other carbonyl derivatives have spectral data in agreement with authentic samples and/or with literature data.
9. It is well established that DEAD reacts in ene-type reactions with allylic derivatives (see Ref. 2). Catalysis of this type of reaction by Lewis acids has been also reported, see for instance: (a) Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261–5263; (b) Aburel, P. S.; Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2344–2349 and references cited therein.
10. Another possibility would be the use of DEAD anchored on a fluorous support since such reagents and their use have been reported recently. See for instance: (a) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807–2810; (b) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855–3864; (c) Chu, Q.; Henry, C.; Curran, D. P. *Org. Lett* **2008**, *10*, 2453–2456. and references cited therein.