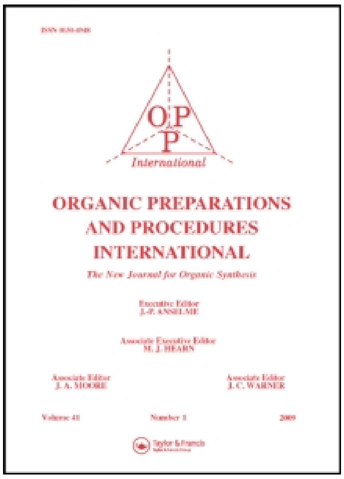

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SELECTIVE REDUCTION OF α,β-UNSATURATED ALDEHYDES AND KETONES TO ALLYLIC ALCOHOLS WITH DIISOBUTYLALKOXYALANES

Submitted by
(12/14/95)

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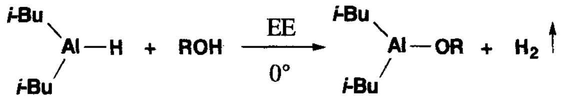
Very recently, we reported that diisobutylchloroalane (DIBAL-Cl) is a highly selective reducing agent for the reduction of enals and enones to the corresponding allylic alcohols,[1] and for the reduction of aldehyde or ketone groups in the presence of many other readily reducible functional groups.[2] We attributed such a high selectivity to the cyclic mechanism in which the β-hydride of the isobutyl group is shifted to the carbonyl carbon of the substrate:[1,2] the reduction is very similar to a Meerwein-Ponndorf-Verley type process.[3] These unique reactions led us to extend our investigation to the alkoxy derivatives of diisobutylaluminum hydride (DIBAL-H) as a reducing agent. In the course of exploring the reducing action of diisobutylalkoxyalanes (DIBAL-OR), we observed that the reagents are much milder than DIBAL-Cl and effectively reduce aldehydes and ketones under mild conditions. Herein we report the application of these newly synthesized reagents, DIBAL-OR, for the selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols. The reagents are conveniently prepared by a simple reaction between DIBAL-H and the corresponding alcohols in ethyl ether (EE) solution (Eq 1).



$$(i\text{-Bu})_2\text{Al—H} + \text{ROH} \xrightarrow[0^\circ]{\text{EE}} (i\text{-Bu})_2\text{Al—OR} + \text{H}_2\uparrow \qquad (1)$$

R = Et; DIBAL-OEt, R = *i*-Pr; DIBAL-O^{i}Pr, R = *t*-Bu; DIBAL-O^{t}Bu

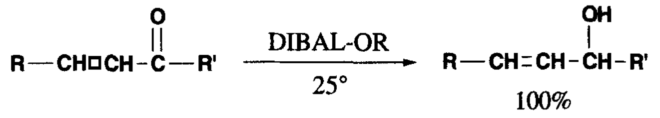
The relative reactivities of DIBAL-OR toward some representative aldehydes and ketones are presented in Table 1. In general, all the alkoxy derivatives examined appear to be much milder than DIBAL-Cl. The relative reactivity of DIBAL-OR is in the order of DIBAL-OEt ≥ DIBAL-O^{i}Pr > DIBAL-O^{t}Bu. Apparently, such a reactivity order arises from the size of the alkoxy substituent. The

TABLE 1. Reduction of Representative Aldehydes and Ketones with DIBAL-OR[a]

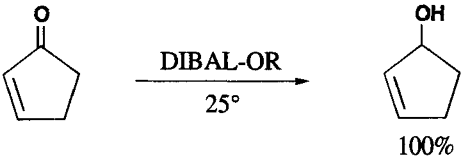
Compound	Time (hrs)	Yield (%)[b] DIBAL-OEt	DIBAL-O^{i}Pr	DIBAL-O^{t}Bu
1-Butanal	1	96	95	90
	3	100	99	95
	6		100	99
	12			100
Benzaldehyde	0.5	98	96	91
	1	100	98	95
	3		100	98
	6			100
2-Butanone	24	90	83	65
	48	100	99	90
	72		100	100
Acetophenone	24	95	90	75
	48	100	100	90
				100

a) In ethyl ether at 25°; 10% excess reagent was utilized. Reaction mixtures were *ca.* 1 M in substrates. b) Determined by GC using internal standard.

reductions of enals and enones were carried out by the addition of two equivalents of DIBAL-OR to the carbonyl compounds in EE at 25° and the products were analyzed by GC (Table 2). Reduction of simple conjugated aldehydes, such as crotonaldehyde, 2-hexenal and cinnamaldehyde, afforded entirely the corresponding allylic alcohols, resulting only from 1,2-reduction. In the case of acyclic enones, such as, 3-penten-2-one, benzalacetone and chalcone, the reaction also proceeded cleanly in a 1,2-sense to give the corresponding allylic alcohols in essentially quantitative yields at 25°. 2-Cyclohexenone was readily reduced to 2-cyclohexenol in a quantitative yield. Even 2-cyclopentenone, known for its susceptibility to undergo conjugate reduction, was cleanly converted to the desired 2-cyclopentenol in a quantitative yield. Similarly, isophorone was also readily reduced to 3,5,5-trimethyl-2-cyclohexen-1-ol.



$$R{-}CH\square CH{-}\overset{\overset{\large O}{\|}}{C}{-}R' \xrightarrow[25°]{\text{DIBAL-OR}} R{-}CH{=}CH{-}\overset{\overset{\large OH}{|}}{CH}{-}R' \quad 100\%$$



The results summarized in Table 2 clearly reveal that the reagents are ideal for the selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols, even though some hindered ketones require longer reaction times for completion. The selectivity reaches 100%. Furthermore, DIBAL-OR is extremely mild. Various representative functional groups, such as esters, lactones, amides, nitriles and even acid chlorides, the most susceptible functional group, are compatible. In addition, by appropriate introduction of alkoxy groups to DIBAL-H it should be possible to adjust the reducing power of the reagents and hence increase its selectivity when necessary. This represents an additional advantage of the reagents over those of previous reagents.[4-10]

EXPERIMENTAL SECTION

All glassware used were dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out using standard techniques for handling air-sensitive materials.[11] All chemicals were commercial products of the highest purity which were purified further by standard methods before use. Ethyl ether (EE) was dried over sodiun-benzophenone ketyl and distilled. Diisobutylaluminum hydride (DIBAL-H) was purchased from the Aldrich Chemical Company. GC analyses were performed on a Donam DS 6200 FID chromatograph equipped with a Youngin D520 B computing integrator, using a 10% Carbowax 20 M capillary column (25 m). All GC yields were determined with use of a suitable internal standard and authentic mixtures. ^{1}H NMR spectra were recorded on a Varian EM-360 A instrument. ^{27}Al NMR spectra were recorded on a Bruker AMX-300 spectrometer, and chemical shifts are with reference to $[Al(H_2O)_6]^{3+}$.

Preparation of Diisobutylalkoxyalanes (DIBAL-OR) in EE.- The following procedure for the preparation of DIBAL-OEt is illustrative. To an oven-dried, 250-mL flask with a side-arm and a reflux condenser leading to a mercury bubbler were added 35.6 mL of DIBAL-H (28.4 g, 200 mmol) and 30 mL of EE. It was cooled to 0°, and 12.3 mL of ethyl alcohol (9.7 g, 210 mmol) was added dropwise with vigorous stirring. After the hydrogen evolution ceased, the solution of DIBAL-OEt was diluted with EE to 2 M using a mass cylinder. The ^{27}Al NMR spectrum of the solution showed a broad singlet at δ 152 ppm.

DIBAL-O^{i}Pr and DIBAL-O^{t}Bu were also prepared by the identical procedure described above and the ^{27}Al NMR spectra showed a broad singlet at δ 160 and 164 ppm, respectively.

Reduction of α,β-Unsaturated Carbonyl Compounds to Allylic Alcohols.- The following procedure for the reduction of crotonaldehyde with DIBAL-OEt is representative. An oven-dried, 25-mL flask equipped with a side-arm fitted with a rubber septum, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was charged with 5 mL of a stock solution of DIBAL-OEt (2 M, 10 mmol) and 0.60 mL of *n*-tridecane (2.5 mmol) as an internal standard. The solution was maintained at 25° in a water bath. To this solution was added 0.42 mL of freshly-distilled crotonaldehyde (0.35 g, 5 mmol) with stirring, and the reaction mixture was stirred at that temperature. At the appropriate reaction time, an aliquot was withdrawn and hydrolyzed with 3 N HCl. The aqueous layer was then saturated with potassium carbonate and the ether layer was dried over magnesium sulfate.

TABLE 2. Reduction of α,β-Unsaturated Aldehydes and Ketones with DIBAL-OR[a,b]

Compound	Time (hrs)	DIBAL-OEt		DIBAL-O^{i}Pr		DIBAL-O^{t}Bu	
		Product ratio (1,2 : 1,4)	Yield (%)	Product ratio (1,2 : 1,4)	Yield (%)	Product ratio (1,2 : 1,4)	Yield (%)
Crotonaldehyde	3	100 : 0	97	100 : 0	95	100 : 0	84
	6	100 : 0	100(78)	100 : 0	99	100 : 0	90
	12			100 : 0	100	100 : 0	95
	24					100 : 0	100
2-Hexenal	6	100 : 0	94	100 : 0	90	100 : 0	85
	12	100 : 0	98	100 : 0	97	100 : 0	89
	24	100 : 0	100(76)	100 : 0	100	100 : 0	92
	48					100 : 0	95
	72					100 : 0	100
Cinnamaldehyde	6	100 : 0	99	100 : 0	99	100 : 0	93
	12	100 : 0	100	100 : 0	100	100 : 0	97
	24					100 : 0	99
	48					100 : 0	100
3-Penten-2-one	6	100 : 0	98	100 : 0	96	100 : 0	93
	24	100 : 0	100	100 : 0	100	100 : 0	97
	72					100 : 0	100
Benzalacetone	24	100 : 0	84	100 : 0	86	100 : 0	60
	72	100 : 0	100	100 : 0	94	100 : 0	72
	120			100 : 0	100	100 : 0	87
	240					100 : 0	>99.9
Chalcone	72	100 : 0	78	100 : 0	65	100 : 0	43
	120	100 : 0	91	100 : 0	84	100 : 0	64
	168	100 : 0	100	100 : 0	90	100 : 0	77
	240			100 : 0	>99.9	100 : 0	86, 100[c]
2-Cyclopenten-1-one	24	100 : 0	96	100 : 0	89	100 : 0	74
	72	100 : 0	100(80)	100 : 0	96	100 : 0	82
	120			100 : 0	100	100 : 0	91
	240					100 : 0	100
2-Cyclohexen-1-one	6	100 : 0	87	100 : 0	79	100 : 0	70
	24	100 : 0	>99.9	100 : 0	92	100 : 0	87
	72			100 : 0	100	100 : 0	96
	120					100 : 0	>99.9
Isophorone	24	100 : 0	92	100 : 0	88	100 : 0	55
	72	100 : 0	100	100 : 0	93	100 : 0	69
	120			100 : 0	>99.9	100 : 0	84
	240					100 : 0	100

a) In ethyl ether at 25°. Two equivalents of reagent were utilized. Reaction mixtures were *ca.* 1 M in substrates. b) Determined by GC using internal standard. Numbers in parentheses indicate isolated yields. c) Four equivalents of reagent were utilized.

Gas chromatographic analysis showed the presence of crotyl alcohol as a sole product in yields of 97% at 3 hr and 100% at 6 hrs.

In a large scale reaction, crotonaldehyde (2.80 g, 40 mmol) was treated with DIBAL-OEt (80 mmol) for 6 hrs at 25°. Workup as described above, followed by distillation provided crotyl alcohol in 78% yield: bp. 121-123° / 758 mmHg. GC analysis showed > 99% purity and ^{1}H NMR spectrum was identical to that of an authentic sample.

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