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USE OF t-BUTYLLITHIUM AS A REDUCING AGENT

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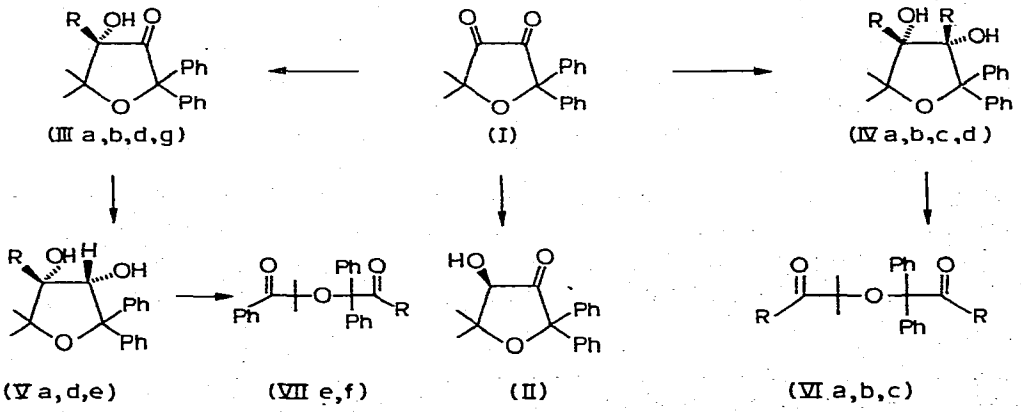
Summary

Details of the first reported use of an alkyllithium reagent for the reduction of a C=O bond are presented.

We wish to report the use of an alkyllithium reagent for the 1,2-reduction of a carbonyl moiety. Treatment of the non-enolizable α-dione I [1] with an equivalent of t-butyllithium afforded ketoalcohol II in a 46% yield (based on recovered starting material the yield would be 94%). With the exception of the starting dione I, no other compound could be isolated from the reaction mixture (Scheme 1).

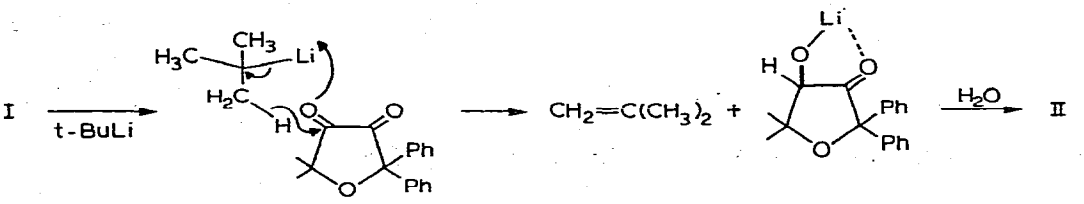
SCHEME 1



a, R = Ph; b, R = Me; c, R = n-Bu; d, R = i-Pr; e, R = H; f, R = OH; g, R = *p*-FC_6H_4-CH_2

Reaction of dione I with i-PrMgBr [2] gave a 2/1 mixture of monoadduct IIId and reduction product II, respectively, whereas exposure of I to an excess of n-BuLi, another potential lithio-reducing agent with a β-hydrogen, led only

to the diadduct IVc. The following transition state could be postulated to explain the transformation of I into II*.



With PhLi one could selectively prepare the monoadduct IIIa or diadduct IVa by simply controlling the amount of lithio reagent, even at a temperature of 0°C. Using MeLi the authors were unable to prepare the monoadduct IIIb, isolating only diadduct IVb.

The *cis* stereochemical assignments for IVa, IVb and IVc were based on IR dilution data, which suggested intramolecular hydrogen bonding [3] and on the PMR spectra, all of which exhibited one exchangeable and one non-exchangeable hydroxyl proton. On examination of Dreiding models, it would appear that intramolecular hydrogen bonding is only possible if the vicinal hydroxyls are *cis* to one another. Oxidative cleavage of these vicinal diols to the corresponding dione ethers VIa, VIb and VIc helped to confirm the gross structural assignments. The use of activated MnO_2 in the transformation of IVb to VIb again suggests the *cis* configuration. Activated MnO_2 is known [4] to only cleave *cis* vicinal diols and analogous *trans* compounds with a flexible arrangement of hydroxyl groups. Most *trans* diols are thus unreactive toward MnO_2.

The structural assignment for monoadduct IIIa was based on the PMR spectrum. An upfield shift of one of the methyl signals can be explained on examination of the Dreiding models only when the phenyl group is introduced on the furan ring α to the geminal dimethyl moiety. The PMR spectra of IIId and IIIg do not exhibit such a shift, whereas the methyl α to the geminal diphenyl grouping of compound IVa is of the proper stereochemistry to be shielded and is indeed shifted upfield. Transformation of IIIa to VIIf, which involved reduction to diol Va, followed by oxidative cleavage to ketoaldehyde VIIe and finally oxidation to the keto acid VIIf, further confirms the 1,2-relationship of methyls and phenyl on the furan ring.

Spectral evidence provided the data necessary for the stereochemical assignments of the reduction products, diols Va, Vd and Ve. The IR dilution studies of all three compounds suggested intramolecular hydrogen bonding [3]. The vicinal methine protons of Ve exhibited a PMR coupling constant of 8 Hz,

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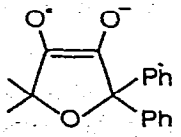
* A referee has suggested that reduced product II could be attributable to the tendency of 1,2-diketones to abstract an electron from a variety of strong bases forming a stable semidione anion radical (i) with subsequent protonation and disproportionation.



(i)

TABLE 1

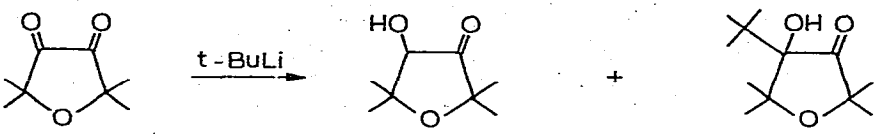
ANALYSES, STRUCTURAL AND SPECTRAL DATA OF THE OBTAINED COMPOUNDS

Exp. No.	Starting material	Product	Reagent	Yield (%) [a]	M.p. (b.p.) [b]	Partial spectral data	
						IR (cm^{-1})	NMR (δ, ppm)
1	I	II	t-BuLi	46 [3]	94.5-5.5	3540, 1768	0.96 (s, 3H), 1.60 (s, 3H), 4.23 (s, 1H)
2	I	IIIa	PhLi	83 [c]	oil	3550, 1760	0.83 (s, 3H), 1.40 (s, 3H)
3	I	IIId	i-PrMgBr	60	83-4.5	3530, 1760	0.43 (d, *J* 6Hz 3H), 0.95 (d, *J* 6Hz, 3H) 1.06 (s, 3H), 1.54 (s, 3H), 2.07 (m, 1H)
		and II		32			
4	I	IIIg	p-$FC_6H_4CH_2MgBr$	40	148-149	3530, 1764	1.03 (s, 3H), 1.62 (s, 3H), 2.88 (s, 2H)
		and (p-$FC_6H_4CH_2)_2$		54	83-84	1510	2.92 (s, 4H) 6.8-7.1 (m, 8H)
5	I	IVa	2PhLi	78	160-161.5	3540s [d]	1.52 (s, 3H), 1.64 (s, 3H), 2.37 (s, 1H) [e]
6	I	IVb	2MeLi	64	oil	3570s [d]	1.15 (s, 3H), 1.45 (m, 9H) 2.00 (s, 1H) [e]
7	I	IVc	2n-BuLi	58	oil	3570s [d]	0.90 (t, *J* 5Hz, 6H), 1.52 (s, 6H), 1.85 (s, 1H) [e]
8	IIIa	Va	$LiAlH_4$	94	131.5-133	3560s [d]	1.37 (s, 6H), 5.25 (d, *J* 5Hz, 1H) [f]
9	IIId	Vd	$LiAlH_4$	66	124-125.5	3565s [d]	0.94 (d, *J* 6Hz, 3H), 1.10 (d, *J* 6Hz, 3H), 1.34 (s, 3H), 1.52 (s, 3H), 2.32 (m, 1H), 4.73 (d, *J* 3Hz, 1H) [f]
10	II	Ve	$NaBH_4$	50	140.5-142	3590s [d]	1.00 (s, 3H), 1.41 (s, 3H), 3.70 (d, *J* 8Hz, 1H), 4.63 (d, *J* 8Hz, 1H)
11	IVa	VIa	$Pb(OAc)_4$	74	141.5-143	1680	1.50 (s, 6H)
12	IVb	VIb	MnO_2	84	(145-7/0.1 mm Hg) [g]	1712	1.24 (s, 6H), 2.14 (s, 3H), 2.22 (s, 3H)
13	IVc	VIc	$Pb(OAc)_4$	63	(147-53/0.1 mmHg) [g]	1715	1.17 (s, 6H), 2.54 (q, *J* 7Hz, 4H)
14	Va	VIIe	$Pb(OAc)_4$	62	115.5-117.5	1732, 1683	1.60 (s, 6H), 9.74 (s, 1H)
15	VIIe	VIIf	Ag_2O	71	120-125	3510, 1695	0.80-1.60 (m, 6H)

[a] Isolated yields; not optimized. [b] Expressed in °C and (°C/mmHg). [c] Biphenyl was also recovered from the reaction mixture. [d] No shift in frequency upon dilution. [e] Non-exchangeable OH. [f] Coalesced into a singlet upon D_2O exchange. [g] Bulb-to-bulb distillation.

indicative of the *cis* configuration [5]. All new structures were assigned on the basis of spectral data and combustion analysis. A summary of the results can be found in Table 1 along with the reagent used in each transformation.

Whereas this case does not represent a general synthetic method for reduction, it is the first use of an alkyllithium reagent for the 1,2-reduction of a carbonyl. Reaction of t-BuLi with the less hindered α-dione VIII provides in addition to a 37% yield of the reduction product IX a 32% yield of monoadduct X. More work involving the application of this unique reduction is in progress.



(VIII) (IX) (X)

Experimental

General comments

Infrared (IR) spectra were recorded on Perkin—Elmer 257 and 457 grating infrared spectrometers and nuclear magnetic resonance (NMR) spectra were recorded using either a Varian T-60 or A-60A spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS; coupling constants (*J*) are given in Hz. Melting points were obtained on a Thomas Hoover capilary melting point apparatus and are uncorrected.

Except where noted solvents were reagent grade and were used as received. The organolithium reagents were obtained from Foote Mineral Co. and Lithium Corporation of America, and used without purther purification. The tetrahydrofuran was dried by storage over 3 Å molecular sieves. Silica gel (0.063-0.2 mm) was used in preparing column chromatograms and analytical thin layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of Silical Gel G with fluorescent indicator. In all workup procedures, the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation. The pertinent spectral data can be found in Table 1.

Preparation of keto alcohol II

This preparation is fully described as an example of the procedure used in the addition of organolithium reagents to α-dione I.

To a cooled, bright red solution of α-dione I (5.60 g, 20 mmol) in dry tetrahydrofuran (80 ml) at —5°C was added dropwise under an atmosphere of nitrogen a 0.8 *M* solution of t-BuLi in pentane (27.5 ml, 22 mmol). After an additional two hours at —5°C the mixture was quenched by the dropwise addition of saturated, aqueous ammonium acetate solution (25 ml). The organic layer was removed, washed with brine, dried and evaporated to give the crude product mixture.

Chromatography over Silica Gel (30/1) eluting first with chloroform (2 l) afforded 2.78 g of the bright red α-dione I (49.7%) as an oil.

Elution with additional chloroform (3 l) provided on evaporation of the solvent, 2.58 g of keto alcohol II (46%) as a white solid. Recrystallization from a minimum of ether gave white needles, m.p. 94.5-95.5°C.

Preparation of α-diol Va

This preparation is described as an example of the lithium aluminum hydride reduction of keto alcohol III.

A solution of keto alcohol IIIa (12.6 g, 0.035 mol) in dry tetrahydrofuran (100 ml) was added dropwise under nitrogen to a suspension of lithium aluminum hydride (3.8 g, 0.1 mol) in dry tetrahydrofuran (200 ml) at —60°C. After two hours at —60°C, the mixture was allowed to warm to room temperature and stirred at room temperature for 15 hours. Saturated ammonium chloride solution was added, and the organic layer separated, washed with brine, dried and evaporated providing an oil. Crystallization from isopropanol at —5°C gave 11.9 g (94%) of white needles, m.p. 131.5-133°C.

Preparation of α-diol Ve

To a chilled solution of keto alcohol II (4.0 g, 14 mmol) in 95% ethanol (40 ml) was added portionwise sodium borohydride (0.76 g, 20 mmol) and the mixture was allowed to warm slowly to room temperature, then dumped in water (100 ml). The resulting solution was extracted throroughly with ether and the combined ether extracts were washed with brine, dried and evaporated to give 2.02 g of white solid (50%).

Recrystallization from ether—hexane gave white needles, m.p. 140.5-142°C.

Preparation of dione VIa

This reaction is fully described as an example of the procedure used in the cleavage of α-diols IV and V with lead tetraacetate.

A mixture of α-diol IVa (6.8 g, 15.6 mmol) and lead tetraacetate (9.5 g, 21.4 mmol) in glacial acetic acid (150 ml) was stirred at room temperature for four days. After filtration and evaporation in vacuo the resulting residue was partitioned between ether and water. The ether layer was washed with 10% sodium bicarbonate solution and brine, dried and evaporated to give a light foam. Recrystallization from ether at —5°C gave 5.04 g (74%) of a white solid, m.p. 141.5-143°C.

In the case of VIc, the crude product was purified by bulb-to-bulb distillation.

Preparation of dione VIb

A mixture of α-diol IVb (10 g, 32 mmol) and activated manganese dioxide (191 g, 2.2 mol) in methylene chloride (400 ml) was stirred overnight at room temperature under nitrogen. Filtration and evaporation of the filtrate provided an oil homogeneous by TLC. Bulb-to-bulb distillation (145-147°C/0.1 mm Hg) gave 8.4 g of a clear yellow oil (84%).

Ketoacid VIIf

To a solution of ketoaldehyde VIIe (2.6 g, 7.3 mmol) in 95% ethanol (200 ml) was added silver nitrate (2.7 g, 15.9 mmol) and the resulting solution was stirred at room temperature while 1 *N* sodium hydroxide (36 mmol) was added dropwise. After stirring for an additional 18 hours at room temperature, the solution was filtered, reduced to 1/2 volume and partitioned between ether—water. The aqueous phase was removed, acidified and extracted thoroughly with

ether. The combined ether extracts were washed with brine, dried and evaporated to give 1.92 g (71%) of a white foam, homogeneous by TLC. Crystallization from a minimum of ether gave a white solid, m.p. 120-125°C.

Acknowledgement

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