Reaction of Lithium Alkyls with Aldehydes and Ketones. A General Study

JERRY D. BUHLER[1]

Richard B. Wetherill Laboratory, Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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The maximum yield of addition product from *n*-butyllithium and representative aldehydes and ketones is obtained by adding a hexane or ether solution of the carbonyl compound to the lithium reagent at −78°. In most cases under these conditions, products resulting from reduction or condensation of the aldehyde or ketone are insignificant, while enolization gives rise to moderate amounts of the starting carbonyl reagent upon hydrolysis. In the case of nonenolizable aldehydes and ketones, quantitative yields of alcohols are obtained. *tert*-Butyllithium reacts similarly to *n*-butyllithium, but because of increased amounts of enolization, somewhat lower yields of secondary and tertiary alcohols are obtained.

In connection with work in progress in this laboratory dealing with the preparation of organolithium reagents from trialkylboranes *via* organomercurials,[2] the feasibility of analyzing for LiR by treating the lithium alkyls with a carbonyl compound and analyzing the resulting secondary or tertiary alcohol was considered. This would require a quantitative reaction between the lithium reagent and the ketone or aldehyde in order to be useful. However, a search of the literature proved fruitless in finding data on such a reaction. No general study of alkyllithium additions to carbonyl reagents could be found which reported all products and yields. Nearly all examples in the literature involved only specific compounds and usually reported only isolated yields of the major product. This was somewhat surprising, not only because of the wide use of lithium alkyls in organic synthesis, but also because of the large number of similar studies reported on the corresponding Grignard reactions. For this reason, a brief study of the reaction of *n*-butyl- and *tert*-butyllithium with various aldehydes and ketones was undertaken, being careful to determine all products and their yields. Efforts were made to determine the conditions which would maximize the yield of the desired addition product.

Results

The lithium alkyls used were *n*-butyl- and *tert*-butyllithium. They were chosen because they are frequently used, they are commercially available, and they represent extreme examples of various lithium reagents (*i.e.*, primary *vs.* tertiary, unhindered *vs.* sterically hindered). Various typical aldehydes and ketones were used. The reaction products resulting from addition, reduction, and enolization were determined (Chart I).

The first efforts were aimed at maximizing the yields of the addition product. For this purpose, *n*-butyllithium and 3-pentanone were chosen as typical examples. The results of this study are given in Table I.

Once the optimum reaction conditions were determined, *n*-butyllithium was treated with various aldehydes and ketones using three standard sets of conditions. The results of these reactions are given in Table II.

Finally, *tert*-butyllithium was treated under the same conditions (1.0 *M* hexane solution of carbonyl added to *t*-BuLi at −78°) with several of the same aldehydes and ketones, and the results were compared with those from *n*-butyllithium. These results are given in Table III.

CHART I

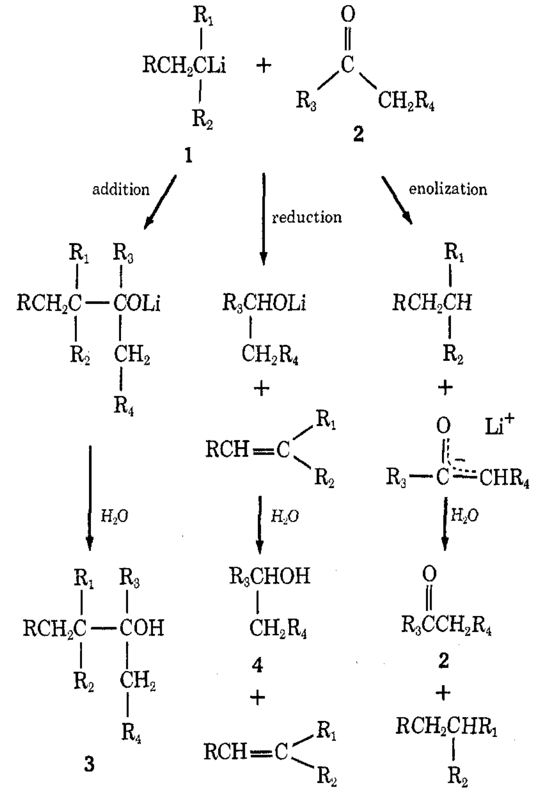

TABLE I

REACTION OF *n*-BUTYLLITHIUM WITH 3-PENTANONE

Solvent	Addition temp, °C	Ketone form[a]	Yield,[b] %			
			Et_2C-(Bu)OH (addn)	Et_2-CHOH (redn)	Et_2-C=O (enol)	Mass balance
Hexane	0	Neat	82	Tr	18	100
Hexane	0	Neat[c]	66	0	30	96
THF[d]	0	Neat	73	0	16	89
Et_2O	0	Neat	83	0	12	95
Hexane	−30	Neat	82	Tr	15	97
Hexane	RT → 50°	Neat	81	Tr	18	99
Hexane	0	Neat[e]	83	Tr	14	97
Hexane	0	2.0 *M* Hexane soln	85	Tr	12	97
Hexane	−78	2.0 *M* Hexane soln	84	0	14	98

[a] Ketone added to *n*-BuLi in all cases except as noted. [b] Determined by glc analysis. [c] Inverse addition, *n*-BuLi to ketone. [d] Tetrahydrofuran. [e] 100% excess *n*-BuLi used.

Discussion

Table I shows that, in the reaction of *n*-butyllithium with 3-pentanone, the greatest possible yield of addition product is obtained by adding a solution of the

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[1] Procter and Gamble Fellow, 1971–1972.

[2] J. D. Buhler and H. C. Brown, *J. Organometal. Chem.*, **40**, 265 (1972).

TABLE II

REACTION OF *n*-BUTYLLITHIUM WITH REPRESENTATIVE ALDEHYDES AND KETONES

Ketone	Conditions[a]	Yield,[b] % RR'C(Bu)OH (addn)	RR'CHOH (redn)	RCOR' (enol)	Mass balance
Acetone	A	53	0	28	81
Acetone	B	67	0	19	86
Acetone	C	80	0	16	96
3-Pentanone	A	82	Tr	18	100
3-Pentanone	B	85	Tr	12	97
3-Pentanone	C	84	0	14	98
Cyclohexanone	A	75	Tr	19	94
Cyclohexanone	B	82	Tr	13	95
Cyclohexanone	C	89	0	9	98
Cyclopentanone	A	44	0	27	71
Cyclopentanone	B	63	0	18	81
Cyclopentanone	C	75	0	18	93
Norcamphor[c]	B	76	Tr	12	88
Norcamphor	C	81	Tr	9	90
Acetophenone	A	67	2–3	27	97
Acetophenone	B	73	2	22	97
Acetophenone	C	81	1–2	20	102
Benzophenone	B[d]	64	23	Tr	87
Benzophenone	C[d]	73	26	Tr	99
Di-*tert*-butyl ketone	C	101	0	Tr	101
Camphenilone[e]	C	98	0	0	98
Nortricyclanone	C	95	0	0	95
Benzaldehyde	C	100	0	0	100

[a] Conditions: A, neat carbonyl reagent added to *n*-BuLi at 0°; B, 1.0 *M* hexane solution of carbonyl compound added to *n*-BuLi at 0°; C, as in B, except at −78°. [b] Determined by glc analysis. [c] 2-Norbornanone. [d] 0.40 *M* hexane solution. [e] 3,3-Dimethyl-2-norbornanone.

TABLE III

REACTION OF *tert*-BUTYLLITHIUM WITH REPRESENTATIVE ALDEHYDES AND KETONES

Ketone	Yield,[a] % RR'C(*t*-Bu)OH (addn)	RR'CHOH (redn)	RCOR' (enol)	Mass balance
3-Pentanone	66	3	27	96
3-Pentanone[b]	70	3	27	100
3-Pentanone[c]	61	3	35	99
Cyclohexanone	53	0	44	97
Norcamphor[d]	40	0	38	78
Nortricyclanone	102	0	0	102
Acetophenone	52	7	31	90
Benzaldehyde	63	2	3	68

[a] Determined by glc analysis. [b] 10% excess *t*-BuLi used [c] Inverse addition, *t*-BuLi added to ketone. [d] 2-Norbornanone.

carbonyl compound (preferably in hexane or ether) to the alkyllithium at −78°, then stirring at room temperature. [Although 3-pentanone does not show any difference between reaction at 0 and −78°, other ketones (Table II) do show a considerable variation with −78° being significantly preferred in all cases.]

That the residual ketone found in all cases was not due to incomplete reaction is shown in the two reactions (entries 6 and 7, Table I) in which the reaction temperature was increased to 50° and 100% excess *n*-BuLi was used, respectively. No increase in yields or decrease in the amount of remaining 3-pentanone occurred in either case. Further, experiments in which several reaction mixtures were methanolized after various reaction times at −78° showed that the reaction of *t*-BuLi with 3-pentanone was over in less than 5 min at −78° and gave essentially the same product distribution as that given in entry 1, Table III. This data indicates that enolization is taking place. That is, a rapid metalation reaction leading to the enolate anion of the carbonyl compound along with butane appears to compete with addition, even at −78°. Hydrolysis then regenerates the carbonyl compound. Finally, enolization is also indicated by the fact that quantitative yields of addition product were obtained when *n*-BuLi was treated with nonenolizable aldehydes and ketones such as benzaldehyde, nortricyclanone, di-*tert*-butyl ketone, and camphenilone (Table II).

Table II confirms the results of Table I in that −78° is the preferred reaction temperature in nearly all cases. At this temperature, reduction and enolization are minimized, thus giving rise to higher yields of addition product. Condensation reactions also appear to be minimized, since the highest mass balances are obtained at −78°. The outstanding feature revealed by this data is the clean reactions observed. In all cases except acetophenone and benzophenone, the addition product was contaminated only with the starting carbonyl reagent (resulting from enolization to the enolate anion prior to hydrolysis), with no significant reduction or condensation products observed. Even in the case of acetophenone, less than 3% of the reduction product was found. Thus, when nonenolizable ketones were used, the one competing side reaction (enolization) was no longer possible and quantitative yields of addition products were obtained, except with benzophenone.

Benzophenone was the only case in which significant amounts of reduction were observed. This is possibly due to the slower reaction of this ketone, since it was observed in a separate experiment that the reaction was only 75% complete in 5 min at −78° while the previously mentioned *t*-BuLi addition to diethyl ketone was complete in less than 5 min at the same temperature.

Thus, in reactions with *n*-butyllithium at −78°, aldehydes and ketones which can enolize can be expected to give rise to alcohol yields of 75–90% with the sole impurity being in nearly all cases the starting carbonyl reagent. With nonenolizable ketones and aldehydes, quantitative yields of alcohols can be obtained. (The aromatic carbonyls appear to be the exceptions to this statement.) Remarkably, this is true of even highly hindered ketones such as di-*tert*-butyl ketone and camphenilone, both of which gave quantitative yields of addition product. These carbonyls can thus serve as reagents for the analysis of this type of lithium reagent.

With *tert*-butyllithium yields of addition products are somewhat lower (Table III), but still quite impressive. For example, a 53% yield of 1-*tert*-butyl-1-cyclohexanol from cyclohexanone is quite respectable when compared with the poor yield of addition product obtained with *tert*-butylmagnesium chloride[3] and the 7% obtained with *tert*-butylsodium.[4] With nonenolizable ketones, such as nortricyclanone, quantitative yields were obtained as with *n*-alkyllithiums. However, benzaldehyde gave only a 63% yield of addition product with a correspondingly low mass balance. The reason for this is not known at the present; again the aromatic carbonyl reagents give anomalous behavior. Thus, even

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(3) L. Bateman and H. P. Loch, *J. Chem. Soc.*, 600 (1944).

(4) P. D. Bartlett and A. Schneider, *J. Amer. Chem. Soc.*, **67**, 141 (1945).

TABLE IV

PHYSICAL PROPERTIES OF ALCOHOL PRODUCTS[r]

Alcohol	Bp, °C (mm)	n^{20}_{D} or mp, °C
2-Methyl-2-hexanol	67–68.5 (35) [68.5 (35)][a]	1.4175 (1.4176)[b]
3-Ethyl-3-heptanol	72 (9.8) [70–72 (11)][c]	1.4364 (1.4360)[c]
1-Butyl-1-cyclohexanol	89–92 (8.2) [88–91 (7)][d]	1.4648 (1.4648)[d]
1-Butyl-1-cyclopentanol	95–98 (15) [99 (20)][e]	1.4576 (n^{19}_{D} 1.4562)[f]
2-Butyl-2-norbornanol[s]	76 (19)	1.4820
2-Phenyl-2-hexanol	100–104 (4) [120 (10)][g]	1.5112 (1.5091)[h]
1,1-Diphenyl-1-pentanol	136–138 (0.08) [134–135 (1.5)][i]	1.5673 (1.5680)[j]
2,2-Dimethyl-3-(2-methyl-2-propyl)-3-heptanol	103–104 (8.1) [121.5–123 (24)][k]	1.4548 (1.4540)[k]
3,3-Dimethyl-2-butyl-2-norbornanol[t]	89 (1.8)	1.4843
1-Phenyl-1-pentanol	82–84 (0.95) [100–104 (3)][l]	1.5095 (1.5078)[l]
3-Butyl-3-nortricyclanol[u]	83–84 (3.0)	1.4866
2,2-Dimethyl-3-ethyl-3-pentanol	76–77 (28) [84 (40)][m]	1.4429 (1.4429)[m]
1-(2-Methyl-2-propyl)-1-cyclohexanol	93–94 (18) [80 (13)][n]	44–49 (49–50)[n]
2-(2-Methyl-2-propyl)-2-norbornanol[v]		66–67
3-(2-Methyl-2-propyl)-3-nortricyclanol[w]		61.0–61.5
3,3-Dimethyl-2-phenyl-2-butanol	82–84 (2.1) [95.5 (4.5)][o]	1.5145 (n^{25}_{D} 1.5142)[p]
2,2-Dimethyl-1-phenyl-1-propanol	93 (5.0) [97 (7)][q]	1.5122

[a] *J. Inst. Petr.*, **34**, 351 (1948). [b] F. C. Whitmore and H. M. Woodburn, *J. Amer. Chem. Soc.*, **55**, 361 (1933). [c] J. B. Conant and A. H. Blatt, *ibid.*, **51**, 1227 (1929). [d] F. K. Signaigo and P. L. Cramer, *ibid.*, **55**, 3326 (1933). [e] C. R. McLellan and W. R. Edwards, Jr., *ibid.*, **66**, 409 (1944). [f] N. Zelinsky and S. Namjetkin, *Ber.*, **35**, 2683 (1902). [g] H. Gilman and R. N. Meals, *J. Org. Chem.*, **8**, 126 (1943). [h] J. B. Conant and G. H. Carlson, *J. Amer. Chem. Soc.*, **54**, 4048 (1932). [i] K. W. Wilson, J. D. Roberts, and W. G. Young, *ibid.*, **72**, 218 (1950). [j] M. S. Eventova, P. P. Borisov, and M. V. Chistyakova, *Vestn. Mosk. Univ.*, **3**, 185 (1957). [k] A. D. Petrov, E. B. Sokolova, and C. L. Kao, *Zh. Obshch. Khim.*, **30**, 1107 (1960). [l] V. N. Ipatieff and V. Haensch, *J. Amer. Chem. Soc.*, **64**, 520 (1942). [m] F. C. Whitmore and W. S. Forster, *ibid.*, **64**, 2966 (1942). [n] L. Bateman and H. P. Koch, *J. Chem. Soc.*, 600 (1944). [o] G. A. Olah, M. B. Comisarow, and C. J. Kim, *J. Amer. Chem. Soc.*, **91**, 1458 (1969). [p] B. B. Corson, H. E. Tiefenthal, G. R. Atwood, W. J. Heintzelman, and W. L. Reilly, *J. Org. Chem.*, **21**, 584 (1956). [q] R. H. Baker and H. Adkins, *J. Amer. Chem. Soc.*, **62**, 3305 (1940). [r] Satisfactory analytical data were reported for all new compounds listed in the table. [s] Registry no., 37710-44-4. [t] Registry no., 37710-45-5. [u] Registry no., 37710-46-6. [v] Registry no., 37710-47-7. [w] Registry no., 37710-48-8.

sterically hindered *tert*-butyllithium gives reasonable yields of addition products with carbonyl compounds with no significant reduction or condensation. In most cases, alkyllithiums appear to be the preferred reagents for alkylation of a carbonyl group with a tertiary alkyl group.

Experimental Section

Materials.—THF was distilled from $LiAlH_4$ under nitrogen. Et_2O was Mallinckrodt anhydrous grade used directly. Hexane was stirred for several days over concentrated H_2SO_4, washed with aqueous K_2CO_3 and water, dried over CaH_2, and distilled under nitrogen.

n-Butyllithium in hexane and *tert*-butyllithium in pentane were purchased from Alfa Inorganics, stored at 0°, and standardized in benzene by the method of Watson and Eastham[5] using 2-butanol in xylene as titrant with 2,2′-biquinoline as indicator (2.24 and 1.11 *M*, respectively). Total base was determined by hydrolysis with 5 *M* H_2O in THF followed by titration with standard H_2SO_4 to a bromothymol blue end point (2.34 and 1.13 *M*, respectively).

Acetone (Mallinckrodt Spectral Grade), cyclopentanone (Matheson Coleman and Bell Reagent Grade), norcamphor (Aldrich Reagent Grade), acetophenone (Baker Reagent Grade), and di-*tert*-butyl ketone (Chemical Samples, 98%) were commercial products and were used without further purification. 3-Pentanone, cyclohexanone, benzophenone, camphenilone (98% pure), and benzaldehyde were commercial products which were purified by distillation under nitrogen. Nortricyclanone was prepared by the method of Hall:[6] bp 78.5–79.5 (24 mm); n^{25}_{D} 1.4873; 98% pure by glc analysis [lit.[6] bp 78–79° (24 mm); n^{25}_{D} 1.4878]. All ketones and aldehydes were shown to be 100% pure by glc analysis except in the cases stated otherwise above.

General.—All glassware was dried in an oven at 140° and flushed with dry nitrogen during cooling. Glc analyses were performed on a 6 ft × 0.25 in. Carbowax 20M column with Chromosorb W as stationary phase. Various straight-chain saturated hydrocarbons (Phillips, 99%) were used as internal standards.

General Procedure for Alkyllithium Reactions.—In a standard reaction, 4.45 ml of 2.24 *M* *n*-BuLi (10.0 mmol) and 5.0 ml of hexane (or 9.0 ml of 1.11 *M* *t*-BuLi in pentane) were syringed into a 25-ml flask at −78°, followed by the appropriate internal standard; 10.0 ml of 1.0 *M* ketone or aldehyde in hexane was then syringed in dropwise at −78°. After addition, the reaction was allowed to warm to room temperature and stirred for 1 hr, after which it was hydrolyzed with aqueous K_2CO_3, and the organic layer was dried ($MgSO_4$) and analyzed by glc.

All products were isolated from larger scale reactions (50 mmol) and compared with literature data. Consistent ir and nmr spectra were obtained in all cases. Satisfactory combustion analyses (±0.3%, C, H) were obtained for all new compounds. Table IV gives the physical properties of all alcohols prepared.

Registry No.—*n*-Butyllithium, 109-72-8; 3-pentanone, 96-22-0; acetone, 67-64-1; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; norcamphor, 497-38-1; acetophenone, 98-86-2; benzophenone, 119-61-9; di-*tert*-butyl ketone, 815-24-7; camphenilone, 13211-15-9; nortricyclanone, 695-04-5; benzaldehyde, 100-52-7.

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(5) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(6) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **82**, 1209 (1960).