

Alkylation-Reduction of Carbonyl Systems. II. A Convenient Synthesis of Aromatic Hydrocarbons by the Alkylation-Reduction of Aromatic Ketones and Aldehydes¹

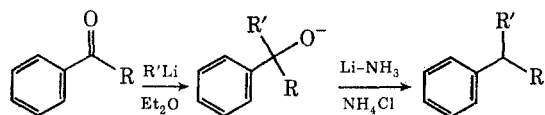
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Aromatic hydrocarbons are prepared from aromatic ketones and aldehydes by alkylation with an organolithium reagent followed by lithium-ammonia reduction in the same reaction vessel without isolation of intermediates. Methylation-reduction yielded *p*-*tert*-butylethylbenzene from *p*-*tert*-butylbenzaldehyde, *p*-ethylisopropylbenzene from *p*-isopropylbenzaldehyde, 1-methylindan from 1-indanone, 1,1,3-trimethylindan from 3,3-dimethylindanone and 5-chloro-3,3-dimethylindanone, 1,1,3,4,5,6,7-heptamethylindan from 3,3,4,5,6,7-hexamethylindanone, 1-methyltetralin from 1-tetralone, 1,1-diphenylethane from benzophenone, 9-methylxanthene from xanthone, 9-methylfluorene from fluorenone, and 2,4-diphenylpentane from dibenzoylmethane. Butylation-reduction yielded *p*-*tert*-butylpentylbenzene from *p*-*tert*-butylbenzaldehyde, *p*-isopropylpentylbenzene from *p*-isopropylbenzaldehyde, 1-butylindan from 1-indanone, 1-butyltetralin from 1-tetralone, and 1,1-diphenylpentane from benzophenone. Phenylation-reduction yielded *p*-*tert*-butylbenzylbenzene from *p*-*tert*-butylbenzaldehyde, *p*-isopropylbenzylbenzene from *p*-isopropylbenzaldehyde, 1-phenylindan from 1-indanone, 1-phenyltetralin from 1-tetralone, triphenylmethane from benzophenone, and 9-phenylfluorene from fluorenone.

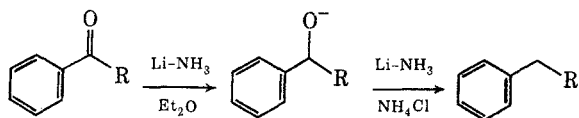
Recently we introduced the concept of tandem alkylation-reduction of aromatic ketones and aldehydes to aromatic hydrocarbons.³ At that time we demonstrated the feasibility of the procedure, which involves the lithium-ammonia reduction of a benzyl alkoxide generated *in situ* by alkylation, with a few methylation-reduction examples. We now wish to report our completed study in this area which includes the alkyla-



tion-reduction of a reasonable sampling of aromatic ketones and aldehydes using phenyllithium, *n*-butyllithium, and methyllithium as illustrative alkylating agents.

The advantages of the method over such classics as the alkylation-dehydration-catalytic reduction procedure are that the entire sequence is carried out in the same reaction vessel without isolation or purification of intermediates, the procedure consumes only a few hours, and the isolated yield of the aromatic hydrocarbon is in most cases excellent.⁴

The basis for this work evolved from the results of some of our earlier studies on the lithium-ammonia reduction of aromatic ketones to aromatic hydrocarbons.⁵ It was demonstrated that aromatic ketones are reduced to benzyl alkoxides in lithium-ammonia solutions and the benzyl alkoxides were protonated and reduced to the corresponding aromatic hydrocarbons during the ammonium chloride quench.⁶ It



(1) This investigation was supported in part by Research Grant CA12984 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Taken in part from the Master of Science Thesis of S. D. L. submitted to The Graduate School, Rutgers University.

(3) Part I: S. S. Hall and S. D. Lipsky, *J. Chem. Soc., Chem. Commun.*, 1242 (1971).

(4) As a matter of fact, the purity of some of the ether extracts made further purification steps unproductive.

(5) (a) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971); (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971).

(6) For a discussion of the possible mechanism see ref 5a.

seemed reasonable to assume that a benzyl alkoxide, generated by other methods, such as alkylation of an aromatic carbonyl compound, should also be reduced to an aromatic hydrocarbon when subjected to this metal-ammonia procedure. The potential advantages of such a sequence were immediately obvious.

The general procedure is to generate the benzyl alkoxide in a metal-ammonia reaction vessel⁷ by the addition of the aromatic ketone or aldehyde to the organolithium reagent in ether. Ammonia is subsequently distilled into the vessel, followed by the addition of lithium wire; and then the resulting mixture is cautiously quenched with ammonium chloride.

The organolithium reagents used were commercial methyllithium (ether), *n*-butyllithium (hexane), phenyllithium (ether-benzene); and phenyllithium (ether) and *n*-butyllithium (ether) generated *in situ* from the corresponding bromides and lithium foil. All the organolithium reagents that were generated in ether or are commercially available in ether were extremely satisfactory; however, slight modifications had to be made for those in hexane or benzene. In these cases a mixture of alkylated aromatic hydrocarbon and alkylated benzyl alcohol resulted when the normal amount of lithium (3 equiv) was used in the reduction step. However, this problem was overcome by the use of excess lithium (6 equiv) and vigorous stirring during the quench step. Evidently the slight amount of hexane in the commercial *n*-butyllithium and the benzene in the commercial phenyllithium results in a two-phase system.⁸

Table I is a listing of aromatic ketones and aldehydes that have been alkylated-reduced to aromatic hydrocarbons by this method. All products gave satisfactory spectral and analytical data and, in some cases, were compared with authentic samples. Minor products are observed when the alkylation step or the reduction step is incomplete. The former yields unalkylated aromatic hydrocarbon,^{5a} which is removed by distillation, and the latter yields alkylated benzyl alcohol, which is conveniently removed by column

(7) For a useful general discussion of metal-ammonia experimental techniques see R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, pp 98-105.

(8) In the latter case there is also the possibility that the benzene is being reduced, and thereby consuming some of the lithium.

TABLE I
 ALKYLATION-REDUCTION OF AROMATIC KETONES AND ALDEHYDES

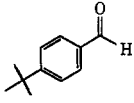
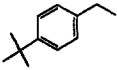
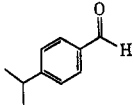
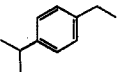
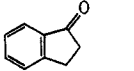
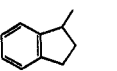
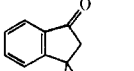
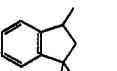
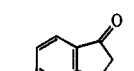
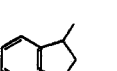
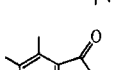
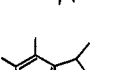
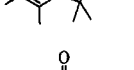
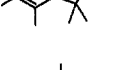
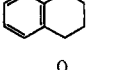
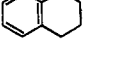
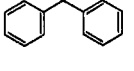
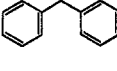
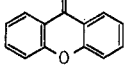
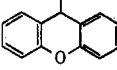
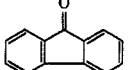
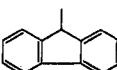
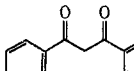
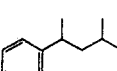
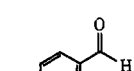
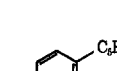
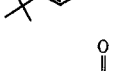

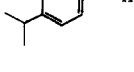
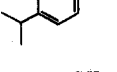
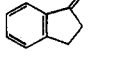
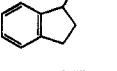
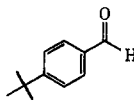
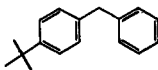
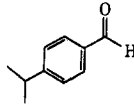
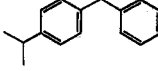
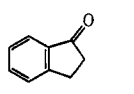
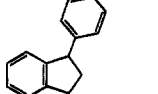
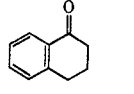
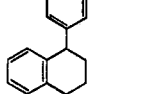
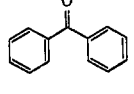
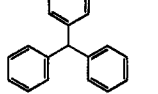
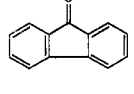
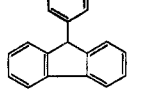
Aromatic carbonyl compound	Registry no.	Organo- lithium reagent	Alkylation- reduction Product	Registry no.	% yield		Minor product (s) ^a		Comments
					Analytical ^a	Isolated ^b	Unalkylated aromatic hydrocarbon	Alkylated benzyl alcohol	
	34032-41-2	MeLi		7364-19-4	100	94			<i>c</i>
	122-03-2	MeLi		4218-48-8	100	95			<i>c</i>
	83-33-0	MeLi		767-58-8	100	95			<i>c</i>
	26465-81-6	MeLi		2613-76-5	85	81	15		<i>c</i>
	30428-23-0	MeLi		38857-68-0	90	85	10		<i>d</i>
	30427-98-6	MeLi		38857-69-1	73	68	27		<i>c</i>
	529-34-0	MeLi		1559-81-5	80	78	20		<i>c</i>
	119-61-9	MeLi		612-00-0	100	95			<i>c</i>
	90-47-1	MeLi		38731-93-0	90	65	10		<i>e</i>
	486-25-9	MeLi		2523-37-7	73	67	13		<i>c, f</i>
	120-46-7	MeLi		1145-23-9	87	79		13	<i>g</i>
		BuLi		38857-73-7	78	66	22		<i>h, i</i>
		BuLi		38857-74-8	90	86	10		<i>h</i>
		BuLi		38857-75-9	90	89	10		<i>h, j</i>
		BuLi		38857-76-0	78	76	22		<i>k</i>
		BuLi		1726-12-1	77	70	23		<i>h, l</i>

TABLE I (Continued)

Aromatic carbonyl compound	Registry no.	Organo-lithium reagent	Alkylation-reduction Product	Registry no.	% yield		Minor product (s) ^a		Comments
					Analytical ^a	Isolated ^b	Unalkylated aromatic hydrocarbon	Alkylated benzyl alcohol	
		PhLi		16251-99-3	96	93	4		<i>h</i>
		PhLi		886-58-8	90	88	10		<i>m, n</i>
		PhLi		26461-03-0	100	97			<i>h</i>
		PhLi		3018-20-0	82	80		18	<i>h</i>
		PhLi		519-73-3	100	97			<i>m</i>
		PhLi		789-24-2	98	93	2		<i>h</i>

^a Analyzed by glpc using a 6 ft × 0.25 in. 10% Apiezon L on Chromosorb W (60-80, AW-DMCS) column in a flame detector instrument at a 40-ml/min flow rate. All samples were injected at a reasonable temperature, followed by a 10-min post-injection interval, and then programmed at 10°/min to 290° and held at limit for 0.5 hr. ^b Isolated from an aluminum oxide column by eluting with petroleum ether. ^c Reaction conditions are those described in the Experimental Section for the methylation-reduction of benzophenone (synthesis of 1,1-diphenylethane) using commercial MeLi and 3 equiv of lithium. ^d Five equivalents of lithium was used for the reduction sequence because of the presence of chlorine. ^e Because of the insolubility of this ketone in ether, a solution of the ketone in 20 ml of THF was added to 2 equiv of MeLi in 10 ml of THF. ^f Plus an unidentified product (14%). ^g In this experiment 2.5 mmol of ketone was used. ^h The organolithium reagent was generated *in situ* in ether from *n*-butyl bromide or bromobenzene and 3 equiv of lithium was used for the reduction. See phenylation-reduction of indanone (synthesis of 1-phenylindane) in Experimental Section. ⁱ When commercial *n*-BuLi and 3 equiv of lithium were used *p*-*tert*-butylpentylbenzene (5%) and 1-(4'-*tert*-butylphenyl)pentanol (95%) were formed. ^j When commercial *n*-BuLi and 6 equiv of lithium were used 1-butylindane (73%) and indane (27%) were formed. ^k Commercial *n*-BuLi and 6 equiv of lithium were used. See phenylation-reduction of benzophenone (synthesis of triphenylmethane) in Experimental Section. ^l When commercial *n*-BuLi and 3 equiv of lithium were used 1,1-diphenylpentane (12%), 1,1-diphenylpentanol (68%), and benzophenol (20%) were formed. ^m Commercial phenyllithium (ether-benzene) and 6 equiv of lithium were used. See phenylation-reduction of benzophenone (synthesis of triphenylmethane) in Experimental Section. ⁿ When commercial phenyllithium and 3 equiv of lithium were used *p*-isopropylbenzylbenzene (56%), *p*-isopropylphenylphenylcarbinol (30%), and *p*-isopropyltoluene (14%) were formed.

chromatography. Since excess organolithium reagent was used the incomplete alkylation suggests that some enolization or reduction of the carbonyl compound may have occurred during the alkylation step.⁹ Incomplete reduction seems to result when the intermediate benzyl alkoxide is splattered on the walls of the reaction vessel and is not in solution during the quench.

Experimental Section¹⁰

Alkylation-Reduction General Comments.—The entire reaction sequence was performed under a prepurified nitrogen

(9) J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

(10) Spectral measurements were determined with the following instruments: ir, Beckman Model IR-10; nmr, Varian Associates Model A-60; mass spectra, Perkin-Elmer Model 270 with a Varian Associates Model 620/i computer attachment. Gas chromatographic analyses (glpc) were performed on a Hewlett-Packard Model 5750 research chromatograph (flame detector) using a 6 ft × 0.25 in. 10% Apiezon L on 60-80 Chromosorb W (AW, DMCS) column. Separations and purifications were attained on absorption alumina (80-200 mesh) columns using petroleum ether (bp 38-58°). Further purification, when necessary, was accomplished by flash or short-path distillation.

atmosphere which is connected by a T tube to the assembly and an oil bubbler. All glassware was oven-dried, cooled to room temperature in a large box desiccator, and then quickly assembled. The commercial organolithium reagents, methyl-lithium (5.1% in ether), *n*-butyllithium (15.1% in hexane), and phenyllithium (19.7% in ether-benzene), were obtained from Foote Mineral Co. Anhydrous ether was used directly from freshly opened containers. Anhydrous ammonia was distilled into the reaction vessel. Lithium wire (0.125 in., 0.01% Na, Ventron Corp.) was wiped free of oil and rinsed in petroleum ether (bp 38-58°) just prior to use. All alkylated aromatic hydrocarbon products gave satisfactory spectral and analytical data, and in some cases were compared with authentic samples. Three alkylation-reductions are described to illustrate the general methods. The first, 1,1-diphenylethane, exemplifies the procedure using an organolithium reagent commercially available in ethyl ether. The second, 1-phenylindane, demonstrates the use of an organolithium reagent which is generated *in situ* in ether. The last, triphenylmethane, uses an organolithium reagent which is commercially available in solvents other than ether.

1,1-Diphenylethane.—To a stirred ethereal solution of methyl-lithium (7.5 mmol, 4.8 ml of a 5.1% ether solution diluted with 10 ml of ether) was slowly added a solution of 0.908 g (5 mmol) of benzophenone in 10 ml of ether in a metal-ammonia reaction

vessel.⁷ After 1 hr 25 ml of ammonia was distilled into the mixture; this was then followed by the addition of 105 mg of lithium wire (15 mg atoms, six pieces). After 15 min the dark-blue color was discharged by the rather cautious addition (*ca.* 5 min) of ammonium chloride¹¹ (*ca.* 1.5 g) and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et₂O, the organic layer was dried, concentrated, and analyzed by glpc. After chromatography (alumina, petroleum ether) a colorless liquid (0.86 g, 95%) was isolated which was identical with an authentic sample of 1,1-diphenylethane.¹²

1-Phenylindan.—Into a metal-ammonia reaction vessel⁷ containing 210 mg of lithium wire (30 mg-atoms, 12 pieces which had been hammered to a foil) in 10 ml of ether was slowly added a solution of 1.18 g (7.5 mmol) of bromobenzene in 7 ml of ether. After 1 hr a solution of 658 mg (5 mmol) of 1-indanone in 8 ml of ether was slowly added and the mixture was stirred for an additional 1 hr. Ammonia (*ca.* 25 ml) was distilled into the mixture and, once the dark-blue color of the mixture was established, *ca.* 1.6 g of ammonium chloride was cautiously added¹¹ (*ca.* 4 min) to discharge the blue color and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and ether, the organic phase was dried, concentrated, and analyzed (glpc). Following chromatography (alumina, petroleum ether) white crystalline material (935 mg,

(11) The ammonium chloride was most conveniently introduced by attaching a glass tube filled with the salt to a side arm with tygon tubing. When the ammonium chloride is to be added the tube is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and the vigorous stirring should be momentarily stopped to avoid an eruption.

(12) J. S. Reichert and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **45**, 3090 (1923).

97%) was isolated and compared with an authentic sample prepared by a classical procedure.¹³

Triphenylmethane.—To a solution of 7.2 mmol of phenyllithium (4.5 ml of a 19.7% ether-benzene solution) in 10 ml of ether in a metal-ammonia reaction vessel⁷ was added, dropwise and with stirring, 908 mg (5 mmol) of benzophenone in 10 ml of ether. After 1 hr *ca.* 25 ml of ammonia was distilled into the mixture and then 210 mg of lithium wire (30 mg-atoms, 12 pieces) was quickly added. After 15 min *ca.* 2.9 g of ammonium chloride was cautiously added¹¹ (*ca.* 4 min) to discharge the dark-blue color and the ammonia was allowed to evaporate. The residue was partitioned between ether and aqueous NaCl, and the ethereal layer was dried, concentrated, and analyzed (glpc). Chromatography (alumina, petroleum ether) yielded 1.22 g (97%) of a white crystalline compound which was identical with a commercial sample of triphenylmethane.

Registry No.—MeLi, 917-54-4; BuLi, 109-72-8; PhLi, 591-51-5.

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(13) This is a good example of what we called a classic procedure (alkylation-dehydration-catalytic reduction) earlier in the discussion. The alcohol 1-phenylindanol, prepared by the phenylation of 1-indanone using a Grignard reagent, was dehydrated by distillation from KHSO₄, and the resulting olefin 1-phenylindene was hydrogenated over Raney nickel. See Pl. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

Alkylation-Reduction of Carbonyl Systems. III. The Selective Synthesis of Aromatic Hydrocarbons and Alcohols by the Alkylation-Reduction of Benzylidene Carbonyl Compounds

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Lithium-ammonia reduction of benzylidene benzyl alkoxides, generated *in situ* by alkylation of benzylidene ketones and aldehydes, yields aromatic hydrocarbons when quenched with ammonium chloride and alcohols when quenched with sodium benzoate. The following examples are cited. Phenylation-reduction of benzylidene acetophenone yields 1,1,3-triphenylpropane and 1,1,3-triphenylpropanol, respectively; benzylidene acetone yields 1,3-diphenylbutane and 1,3-diphenyl-3-butanol, respectively; benzylidene propanal yields 1,3-diphenyl-2-methylpropane and 1,3-diphenyl-2-methylpropanol, respectively; benzylidene acetaldehyde yields 1,3-diphenylpropane and 1,3-diphenylpropanol, respectively. Methylation-reduction of benzylidene acetophenone yields 1,3-diphenylbutane and 1,3-diphenyl-3-butanol, respectively; and benzylidene acetone yields 1-phenyl-3-methyl-3-butanol with either quenching agent since the intermediate alkoxide is not benzylic. Mechanistic implications are discussed.

Recently we introduced the concept of tandem alkylation-reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons by the lithium-ammonia reduction of benzyl alkoxides generated *in situ* by alkylation.¹ In addition this laboratory has demonstrated the mechanistic and selective synthetic utility of using ammonium chloride *vis-à-vis* sodium benzoate as quenching agents in metal-ammonia reductions.² We now wish to report our first example of the combination of these two procedures for the selective synthesis of aromatic

hydrocarbons and alcohols by the alkylation-reduction of benzylidene ketones and aldehydes. It is a method which is characterized by its simplicity, selectivity, and excellent isolated yield of the desired product. In addition the mechanistic implications are obvious.

The general procedure is to generate a benzylidene benzyl alkoxide in a metal-ammonia reaction vessel³ by the addition of the benzylidene ketone or aldehyde to the organolithium reagent in ether. Ammonia is subsequently distilled into the vessel, followed by the addition of lithium wire; and then the resulting dark-blue mixture is cautiously quenched.

The sequence is outlined in Scheme I using two examples. Alkylation of benzylideneacetophenone (1)

(1) (a) Part I: S. S. Hall and S. D. Lipsky, *J. Chem. Soc., Chem. Commun.*, 1242 (1971). (b) Part II: S. S. Hall and S. D. Lipsky, *J. Org. Chem.*, **38**, 1735 (1973). (c) S. S. Hall and S. D. Lipsky, submitted for publication in "Organic Syntheses."

(2) (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).

(3) For a useful general discussion of metal-ammonia experimental techniques see R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, pp 98-105.