[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Carbonylation of Alcohols with Nickel Carbonyl Catalyst[1]

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Ever since Fischer[4] proposed the direct combination of carbon monoxide and methanol to form acetic acid in the formulation of Synthol from carbon monoxide and hydrogen, workers in the field have tried to prepare acids by similar reactions. Carpenter,[5] Singh and Krase,[6] Hardy,[7] Loder,[8] Larson,[9] and Simons and Werner[10] synthesized acids using alcohols or olefins with carbon monoxide and acid type catalysts. In Germany Reppe[11] developed a synthesis of acids from acetylenic and olefinic compounds using nickel carbonyl and carbon monoxide, and stated that when alcohols were heated at 250–300° under 200–300 atm. pressure in the presence of carbon monoxide, nickel, and iodine (or copper iodide), good yields of acids were obtained.

$$\mathrm{ROH} + \mathrm{CO} \xrightarrow[\mathrm{I_2(CuI)}]{\mathrm{Ni}} \mathrm{RCOOH}$$

Apart from the merits of the process for commercial utilization, the Reppe reaction is obviously of considerable potential value in organic syntheses. We are interested in working out the best conditions for carrying out the reaction in standard equipment in the laboratory and determining the identity and homogeneity of the product formed, the types of alcohols that could be carbonylated, and the effect the structure of the alcohol used had on the nature of the product formed.

The available details of Reppe's process were meager and incomplete at the time the project was begun in this Laboratory. All attempts to duplicate his work failed until it was found that in order to obtain a yield of acid, both nickel chloride and hydrochloric acid were needed as catalysts. After a considerable number of experiments, conditions were found under which the reaction proceeded well with fifteen alcohols. The optimum conditions found can best be described by a typical experiment: octanol-2 (41 g.), water (15 g.), nickel carbonyl (17 g.), nickel chloride hexahydrate (5 g.), and 3 ml. of concentrated hydrochloric acid were placed in the glass liner of a 190 ml. capacity silver-lined steel bomb, and carbon monoxide at a pressure of 900 p.s.i. was introduced. The bomb was heated in an upright stationary position at 300° for fifteen hours during which time the hot pressure dropped from 4200 p.s.i. to 4000 p.s.i. The cold pressure at the completion of the reaction was 2000 p.s.i. The gases were released through a bunsen burner and burned to destroy any volatile nickel complexes present. The contents were extracted with ether and the aqueous layer discarded. The ether was removed in a vented hood, the residue was neutralized with 10% sodium hydroxide solution, and the resulting mixture was reextracted with ether. Distillation of the ether layer yielded no neutral components. The aqueous layer was reacidified and the acid fraction distilled under reduced pressure. The yield of 2-methyloctanoic acid was 76%.

If any one of the reagents or catalysts used in this experiment was omitted, the reaction was unsuccessful. The water and nickel carbonyl were used in excess, whereas nickel chloride and hydrochloric acid were used in catalytic quantities. An increase in the amount of each of the last two named catalysts did not increase the yield of acid obtained. A temperature of 275° was found to be necessary for the carbonylation of secondary and tertiary alcohols, and 300° for primary alcohols. Below 275° only unreacted alcohol or olefins formed by its dehydration were recovered. The higher temperature was used in most reactions, however, because nickel carbonyl decomposed above 275° and the bomb contents were then less dangerous to handle. Due to the corrosive nature of the catalyst used and products formed, a silver lining for the bomb was found to be essential. When brass, steel or copper was used, the lining was quickly corroded to such an extent that the bomb leaked.

The first report[11] on Reppe's work indicated that a mixture of acids was obtained by the addition of carbon monoxide and water to alkene $\mathrm{RCH{=}CH_2}$, *i. e.*, $\mathrm{RCH_2CH_2COOH}$ and $\mathrm{RCH(CH_3)COOH}$. A later report[12] indicated that the branched acid was predominantly formed. With the alcohols we found that in every reaction in which the alcohol used was pure and not prone to rearrangement, the product was homogeneous and was the *branched* acid; in no case was a straight chain acid produced as Reppe claimed. A possible course of the reaction is the dehydration of the alcohol to an olefin, which then undergoes carbonylation to the branched acid. Reasonable evidence for this mechanism is the fact that both octanol-1 and octanol-2, which dehydrate to the same olefin, yield the same acid, 2-methyloctanoic, in this reaction.

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(2) Deceased August 10, 1949.

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(4) Fischer, *Ind. Eng. Chem.*, **17**, 576 (1925).

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$$C_6H_{13}CH_2CH_2OH \text{ or } C_6H_{13}CHOHCH_3 \xrightarrow{-H_2O}$$

$$C_6H_{13}CH{=}CH_2 \xrightarrow[H_2O]{CO} C_6H_{13}CH(CH_3)COOH$$

As can be seen in Table I, aliphatic primary and secondary alcohols of the same carbon chain length gave the same product, the 2-methylalkanoic acid, but the yields from the secondary alcohols were higher. Thus butanol-1 and butanol-2 yielded 2-methylbutyric acid in 47 and 70%, respectively; heptanol-1 and heptanol-2 gave 2-methylheptanoic acid in 33 and 70%, respectively; and octanol-1 and octanol-2 formed 2-methyloctanoic acid in 30 and 76%, respectively. The reaction of the secondary alcohols at lower temperatures and to produce higher yields of acids appears to be related to the relatively greater ease of their dehydration.

TABLE I

CARBONYLATION OF ALCOHOLS WITH NICKEL CARBONYL AT 300°[a]

| Alcohol | Pressure CO, p. s. i. | Time, hr. | Acid formed | Yield, % |
|---|---|---|---|---|
| Butanol-1 | 850 | 21 | 2-Methylbutyric | 47 |
| Pentanol-1 | 650 | 16 | 2-Methylvaleric | 16 |
| Hexanol-1 | 900 | 13 | 2-Methylhexanoic | 55 |
| Heptanol-1 | 800 | 18 | 2-Methylheptanoic | 33 |
| Octanol-1 | 700 | 18 | 2-Methyloctanoic | 30 |
| 2-Ethylbutanol-1 | 650 | 24 | Diethylmethylacetic | 40 |
| 3-Cyclohexylpropanol-1 | 600 | 23 | 3-Cyclohexyl-2-methylpropanoic | 49 |
| Neopentyl | 650 | 21 | $C_6$ acids | 21 |
| Butanol-2 | 600 | 20 | 2-Methylbutyric | 70 |
| Heptanol-2 | 700 | 22 | 2-Methylheptanoic | 70 |
| Octanol-2 | 825 | 19 | 2-Methyloctanoic | 76 |
| Cyclopentanol[b] | 700 | 22 | Cyclopentanecarboxylic | 84 |
| 4-Methylcyclohexanol-1[b] | 900 | 22 | 4-Methylcyclohexanecarboxylic | 53 |
| β-Decalol[b] | 700 | 17 | Decahydronaphthoic acids | 77 |
| Tertiary amyl[b] | 900 | 23 | Dimethylethyl acetic | 35 |

[a] In all runs 5 g. nickel chloride hexahydrate, 15 g. water, 17 g. nickel carbonyl, 3 ml. concentrated hydrochloric acid, and approximately 0.2 mole of alcohol were used. [b] Run at 275°.

The primary alcohols of higher molecular weight gave lower yields of acids than those of lower molecular weight, whereas all of the secondary alcohols gave approximately the same yield. Substitution of alkyl groups on the second or third carbon atom of a primary alcohol seemed to have little effect on the yield or structure of the resulting acid, as 2-ethylbutanol-1 and 3-cyclohexylpropanol-1 gave a 40% yield of diethylmethylacetic acid and a 49% yield of 3-cyclohexyl-2-methylpropanoic acid, respectively. Neopentyl alcohol gave a mixture of acids, which was not surprising, as it would undergo rearrangement upon dehydration. The resulting mixture of olefins would then form several acids on carbonylation. Tertiary amyl alcohol, the only tertiary alcohol used, gave dimethylethylacetic acid in 35% yield.

Both substituted and unsubstituted secondary alicyclic alcohols were successfully carbonylated in good yields. Cyclopentanol gave cyclopentanecarboxylic acid (the only isomer possible) in 84% yield, and 4-methylcyclohexanol-1 gave 53% yield of 4-methylcyclohexanecarboxylic acid. β-Decalol, which was made by the reduction of β-naphthol and was, therefore, a stereoisomeric mixture, gave a 77% yield of decahydronaphthoic acids.

In view of the well-known variations in reactivity of alcohols, it was not surprising that some alcohols could not be carbonylated. When the alcohol contained an aromatic ring, the only product isolated was the alkylbenzene formed by the hydrogenolysis of the terminal hydroxyl group. Thus, 2-phenylethanol-1, 3-phenylpropanol-1 and 4-phenylbutanol-1 yielded ethyl-, *n*-propyl- and *n*-butylbenzene, respectively. When methyl-β-naphthylcarbinol, which contained the less aromatic naphthalene ring and a secondary alcohol group, was carbonylated a resin was obtained, presumably arising from polymerization of β-vinylnaphthalene, the dehydration product of the alcohol. Glycols yielded monocarboxylic acids, through the carbonylation of one hydroxyl and the hydrogenolysis of the other. Thus, 1,5-pentanediol and 1,6-hexanediol gave 2-methylvaleric and 2-methylhexanoic acids, respectively. The hydrogen required for these hydrogenolyses doubtless results from the water gas equilibrium

$$CO + H_2O \rightleftarrows CO_2 + H_2$$

**Hazards.**—The use of carbon monoxide under pressure with the highly poisonous nickel carbonyl is not without danger. The ill effects of breathing carbon monoxide are so well known that a warning is perhaps unnecessary. Nickel carbonyl is very volatile and *extremely* toxic. First class equipment in good condition and in the hands of a competent operator is essential if accidents are to be avoided. There should be *no* leaks of any kind. *All* operations should be carried out in a hood with rapid ventilation. The residual gas from the reaction vessel which contains carbon monoxide and volatile nickel compounds should be burned in a bunsen burner or slowly vented in the hood.

## Experimental Part

The nickel carbonyl was supplied by The Matheson Co., Inc., of East Rutherford, N. J. Some of the alcohols were obtained from commercial sources, *i. e.*, butanol-1, $n^{25}$D 1.3965, 2-ethylbutanol-1, $n^{25}$D 1.4210, and hexanol-1, $n^{25}$D 1.4175, from Carbide and Carbon Chemicals Corporation; butanol-2, $n^{25}$D 1.3960, from Shell Chemical Company; pentanol-1, $n^{25}$D 1.4080, from Mallinckrodt Chemical Company; heptanol-2, $n^{25}$D 1.4184, octanol-1, $n^{25}$D 1.4284, octanol-2, $n^{25}$D 1.4252, 2-phenylethanol-1, $n^{25}$D

1.5312, and tertiary amyl alcohol, $n^{25}\text{D}$ 1.4061, from Eastman Kodak Company; and 1,5-pentanediol, $n^{25}\text{D}$ 1.4494, from Monsanto Chemical Company. Several alcohols were made by hydrogenation of other compounds over various catalysts; cinnamic aldehyde over copper chromium oxide to 3-phenylpropanol-1,[13] $n^{25}\text{D}$ 1.5346; cyclopentanone over copper chromium oxide to cyclopentanol, $n^{25}\text{D}$ 1.4503; β-naphthol over Raney nickel (W-2) to β-decalol, $n^{25}\text{D}$ 1.5012; diethyl adipate over copper chromium oxide to 1,6-hexanediol, m. p. 40–41°; *p*-cresol over Raney nickel (W-2) to 4-methylcyclohexanol-1, $n^{25}\text{D}$ 1.4555[14]; and 3-phenylpropanol-1 over Raney nickel (W-2) to 3-cyclohexylpropanol-1, $n^{25}\text{D}$ 1.4625.[15] Heptanol-1, $n^{25}\text{D}$ 1.4230, was obtained by the saponification of some available *n*-heptyl acetate. Methyl-β-naphthylcarbinol,[16] m. p. 74–75°, was supplied by Dr. E. E. Burgoyne and was made by the hydrogenation of 2-acetylnaphthalene over copper chromium oxide. 4-Phenylbutanol-1, $n^{25}\text{D}$ 1.5122, was made by the reduction of ethyl β-benzoylpropionate over copper chromium oxide.[17] This ester was prepared from β-benzoylpropionic acid, which was made by the Friedel–Crafts reaction of succinic anhydride and benzene.[18]

**Isolation and Characterization of Products.**—Butanol-1 (20 g.) gave 13 g. (47%) of 2-methylbutyric acid,[19] b. p. 81–88° (19 mm.), $n^{25}\text{D}$ 1.4099; m. p. *p*-bromophenacyl ester 53–54°.[20]

Pentanol-1 (29 g.) gave 21 g. (54%) of 2-methylvaleric acid,[21] b. p. 103–105° (20 mm.), $n^{25}\text{D}$ 1.4121; m. p. amide 79–80°.[21]

Hexanol-1 (32.8 g.) gave 27 g. (70%) of 2-methylhexanoic acid,[22] b. p. 110–112° (20 mm.), $n^{25}\text{D}$ 1.4200; m. p. amide 70–71°.[22]

Heptanol-1 (29 g.) gave 12 g. (33%) of 2-methylheptanoic acid, b. p. 138–140° (25 mm.), $n^{25}\text{D}$ 1.4252; m. p. amide 73–74.5°. Authentic 2-methylheptanoic acid was made by the acetoacetic ester synthesis of Marvel and Hager[23] from ethyl methylamylacetoacetate, b. p. 125–126° (15 mm.), $n^{25}\text{D}$ 1.4245; neut. equiv. 140 (calcd. 144); m. p. of amide 74–75° (m. p. of a mixture of this amide and the amide made from the acid obtained by carbonylation 73–75°).

*Anal.* Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97. Found: C, 67.30; H, 11.63.

Octanol-1 (32.8 g.) gave 12 g. (30%) of 2-methyloctanoic acid[24] b. p. 130–135° (20 mm.), $n^{25}\text{D}$ 1.4302, m. p. of amide 78–79° (did not depress m. p. of an authentic sample of the amide of 2-methyloctanoic acid).

3-Cyclohexylpropanol-1 (25 g.) gave 5 g. of unsaturated compounds b. p. 146–152° (730 mm.), $n^{25}\text{D}$ 1.4363. These constants correspond to those of the several isomeric olefins which would be formed by dehydration of the alcohol, followed by double bond migration. The acid fraction weighed 11 g. (36%), b. p. 114–115° (1 mm.), $n^{25}\text{D}$ 1.4616. Since no derivatives have been reported for either of the possible isomeric acids formed in the reaction, this acid fraction was characterized by terminal methyl group analysis by the procedure of Barthel and LaForge.[25] The methyl group no. was 0.78, which showed the acid to be at least predominantly 3-cyclohexyl-2-methylpropanoic acid.[26]

2-Ethylbutanol-1 (25 g.) gave 13 g. (40%) of diethylmethylacetic acid,[27] b. p. 123–125° (27 mm.), $n^{25}\text{D}$ 1.4212, m. p. of amide 78–79°.

Neopentyl alcohol (25 g.) gave 7 g. (22%) of material corresponding to a $C_6$ acid, b. p. 97–99° (16 mm.), $n^{25}\text{D}$ 1.4188, neut. equiv. 112 (calcd. 116). The amide crystallized in two parts, (a) m. p. 114–115° and (b) m. p. 107–109°. No further characterization was done as these melting points did not approach those of the expected isomers.

Butanol-2 (21 g.) gave 20 g. (70%) of 2-methylbutyric acid,[19] b. p. 81–83° (15 mm.), $n^{25}\text{D}$ 1.4051, m. p. of *p*-bromophenacyl ester 52–54°.

Heptanol-2 (23 g.) gave 19 g. (70%) of 2-methylheptanoic acid, b. p. 140° (30 mm.), $n^{25}\text{D}$ 1.4238, neut. equiv. 141 (calcd. 144), m. p. of amide 73–75° (m. p. of a mixture of this amide and authentic amide of 2-methylheptanoic acid 73–75°).

Cyclopentanol (29 g.) gave 32 g. (84%) of cyclopentanecarboxylic acid,[28] b. p. 118° (23 mm.), $n^{25}\text{D}$ 1.4522, m. p. of amide 176–178°.[28]

4-Methylcyclohexanol-1 (24 g.) gave 5 g. of neutral unsaturated compounds, b. p. 80–105° (740 mm.), $n^{25}\text{D}$ 1.4449, which were thought to be a mixture of methylcyclohexenes. The acid layer yielded 15 g. (53%) of 4-methylcyclohexanecarboxylic acid,[29] b. p. 129–131° (13 mm.), $n^{25}\text{D}$ 1.4569, neut. equiv. 138 (calcd. 142), m. p. of amide 177–179°.[29]

β-Decalol (35 g.) gave 5 g. of neutral unsaturated material, b. p. 83–88° (25 mm.), $n^{25}\text{D}$ 1.4997, which was thought to be a mixture of octalins. The acid residue, which was an oil and weighed 32 g. (77%), yielded a solid and oil fraction when recrystallized from petroleum ether (60–68°). The solid had a m. p. 100–105° and a neut. equiv. of 173 (calcd. 182); m. p. of amide 195–196°, all of which showed the acid to be decahydro-α-naphthoic acid.[30] The oil had a neut. equiv. of 188 and the amide made from it had a m. p. 175–180°. This acidic oil was thought to be a mixture of decahydro-α- and -β-naphthoic acids.

Tertiary amyl alcohol (24.3 g.) gave 8 g. (25%) of dimethylethylacetic acid,[31] b. p. 94–96° (15 mm.), $n^{25}\text{D}$ 1.4127, m. p. of amide 102–103°.[32]

2-Phenylethanol-1 (40 g.) gave 2 g. of tar and 5 g. (12%) of ethylbenzene,[33] b. p. 134–135° (760 mm.), $n^{25}\text{D}$ 1.4935. It was insoluble in water, dilute acid or base, and concentrated sulfuric acid.

3-Phenylpropanol-1 (17 g.) gave a tar and 8 g. (40%) of *n*-propylbenzene,[34] b. p. 157° (749 mm.), $n^{25}\text{D}$ 1.4917.

4-Phenylbutanol-1 (20 g.) gave a tar and 10 g. (40%) of *n*-butylbenzene,[35] b. p. 175–180° (750 mm.), $n^{25}\text{D}$ 1.4922.

Methyl-β-naphthylcarbinol (20 g.) yielded a sticky resin presumed to be the polymer of β-vinylnaphthalene.

1,5-Pentanediol (25 g.) yielded 3 g. (10%) of 2-methylvaleric acid,[21] b. p. 85–88° (10 mm.), $n^{25}\text{D}$ 1.4610, neut. equiv. 118 (calcd. 116), m. p. of amide 77–78°.[21]

1,6-Hexanediol (21 g.) gave 7 g. (30%) of 2-methylhexanoic acid,[22] b. p. 107–110° (16 mm.), $n^{25}\text{D}$ 1.4278, m. p. of amide 67–68°.[22]

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## Summary

1. Fifteen alcohols have been carbonylated to acids containing one additional carbon atom, with carbon monoxide in the presence of nickel carbonyl, nickel chloride, and hydrochloric acid. Secondary aliphatic and alicyclic alcohols were carbonylated in an average yield of 75%, whereas the yields from primary and tertiary alcohols were from 30–60%.

2. The products formed generally were homogeneous and branched chain, *e. g.*, both butanol-1 and butanol-2 yielded 2-methylbutyric acid.

3. Aromatic alcohols were converted to alkylbenzenes and glycols to monocarboxylic acids under conditions that converted aliphatic alcohols to di- and tri-substituted acetic acids.

4. The carbonylation reaction appears to proceed through the dehydration of the alcohol to an olefin, which then is carbonylated to the acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

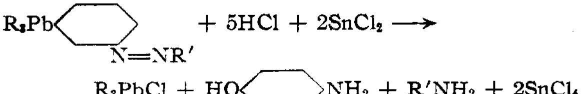
# Organolead Compounds Containing an Azo Linkage

BY HENRY GILMAN AND C. G. STUCKWISCH[1]

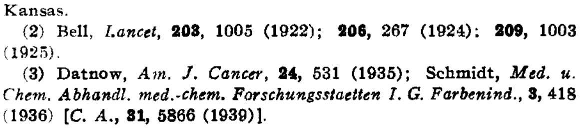
Since its introduction in the chemotherapeutic treatment of cancer by Bell[2] in 1922, lead has attracted more attention than any other metal in this particular field of therapeutics. The toxic side action of the required therapeutic doses has however militated against an extended use of this method of treatment. To circumvent this objection chemists have resorted to the preparation of compounds which contain the lead in highly masked form in complex molecules.[3] Syntheses of organolead compounds containing an azo linkage are described in the present paper.

The diazotization of triphenyl-*p*-aminophenyllead and its subsequent coupling with $\beta$-naphthol have been reported earlier.[4] A more convenient method of preparation of the azo-lead type of compound is the coupling of a diazonium salt with an aminoaryl- or hydroxyaryllead compound. The latter is conveniently prepared from a triaryllead halide and an aminoaryl- or hydroxyaryllithium compound.[5]

$$R_3PbX + R'Li \longrightarrow R_3PbR' + LiX$$



The position of coupling was determined by reductive cleavage with stannous chloride and hydrochloric acid. In each instance coupling took place *ortho* or *para* to the amino or hydroxyl group and *meta* to the lead atom



## Experimental

**General Information.**—The titer of the *n*-butyllithium solutions used in this work was determined by the method of Gilman and Haubein.[6] The amount of $R_3PbCl$ added to the organolithium solutions was equivalent to the amount of the halogen compound used in the interconversion. All melting points are uncorrected.

**Triphenyl-*p*-aminophenyllead.**—Three variations were used for the preparation of triphenyl-*p*-aminophenyllead.

**Method 1.**—This method, which involves adding anhydrous magnesium bromide to the *p*-aminophenyllithium solution, has been described.[4]

**Method 2.**—To 5.67 g. (0.033 mole) of *p*-bromoaniline in 25 ml. of ether was added dropwise 0.1 mole of *n*-butyllithium in 180 ml. of ether. After 60 ml. of the organometallic solution had been added, refluxing ceased and the remaining 120 ml. was added more rapidly. The mixture was stirred for an hour. A yellow, crystalline precipitate of the *p*-N,N-trithioaniline[5b] separated from the solution. The reaction flask was fitted with a stopcock at the bottom, by means of which the solid was filtered from the liquid. To the solid residue remaining in the flask was added 250 ml. of ether and then 10.3 g. (0.022 mole) of triphenyllead chloride. The mixture was stirred for one hour at room temperature and then hydrolyzed with cold, aqueous ammonium chloride. The organic layer was dried over sodium sulfate. Hydrogen chloride was cautiously passed into the dried ether solution, cooled in an ice-bath, to precipitate the hydrochloride of triphenyl-*p*-aminophenyllead. The hydrochloride was converted to the free amine by suspending it in water and adding dilute ammonium hydroxide. The yield of triphenyl-*p*-aminophenyllead thus obtained was 6 g. or 59%. After crystallization from a mixture of benzene and petroleum ether (b. p. 60–68°) the compound melted at 172°. A mixed melting point with the compound obtained by the first method showed no depression.

**Method 3.**—To 5.3 g. (0.031 mole) of *p*-bromoaniline in 30 ml. of ether was added dropwise 0.093 mole of *n*-butyllithium in 200 ml. of ether. The mixture was stirred at room temperature for one hour and was then poured into a suspension of 14.2 g. (0.03 mole) of triphenyllead chloride in ether. After three minutes the mixture was poured into cold water. The ether layer was separated and extracted with dilute hydrochloric acid to remove unreacted *p*-bromoaniline. (Triphenyl-*p*-aminophenyllead is insoluble in dilute hydrochloric acid.) Hydrogen chloride was passed into the dried ether solution to precipitate the hydrochloride of triphenyl-*p*-aminophenyllead. The free amine was obtained as described in Method 2. The yield was 9.5 g. or 60%. In the interconversion of *p*-bromoaniline the *n*-butyllithium solution must be clear, otherwise a gummy precipitate, difficult to work with, will be obtained.

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