Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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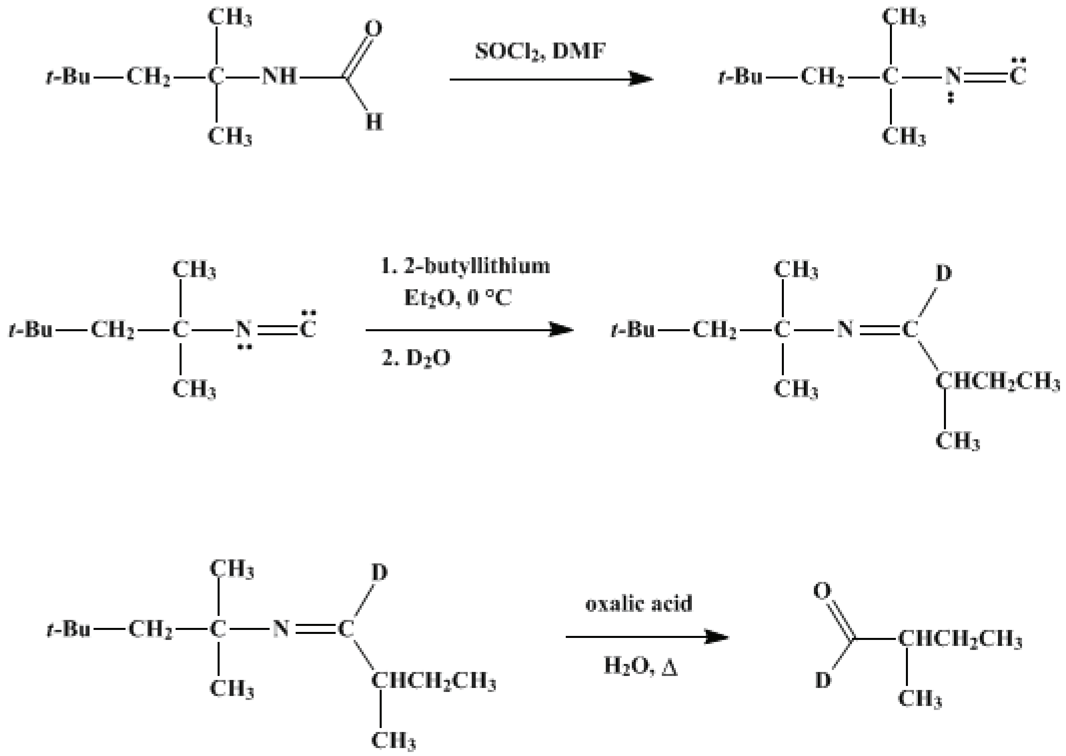
Organic Syntheses, Coll. Vol. 6, p.751 (1988); Vol. 51, p.31 (1971).

1-*d*-ALDEHYDES FROM ORGANOMETALLIC REAGENTS: 2-METHYLBUTANAL-1-*d*

[Butanal-1-*d*, 2-methyl-]



Submitted by G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky[1].
Checked by Frank E. Herkes and Richard E. Benson.

1. Procedure

A. 1,1,3,3-*Tetramethylbutyl isonitrile.* A 3-l., three-necked, round-bottomed flask fitted with a Hershberg stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen-inlet tube is flamed dry under a nitrogen atmosphere and allowed to cool. The nitrogen-inlet tube is replaced with a low-temperature thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. To the flask are added 118 g. (0.752 mole) of *N*-(1,1,3,3-tetramethylbutyl)formamide (Note 1) and 1500 ml. of *N,N*-dimethylformamide (Note 2). The addition funnel is charged with a premixed (Note 3) solution of 89 g. (55 ml., 0.75 mole) of thionyl chloride and 250 ml. of *N,N*-dimethylformamide. The flask is immersed in an acetone–dry ice bath, and moderately fast stirring is started. When the temperature of the flask reaches −50°, the solution in the funnel is added at a rate such that the temperature ranges between −55° and −50° (about 10 minutes are required for the addition). After the addition is complete, the bath is removed momentarily, allowing the reaction temperature to rise to −35°. The bath is then replaced, and 159 g. (1.50 mole) of dry sodium carbonate (Note 4) is added directly to the mixture (Note 5). After the addition the bath is removed, and the flask contents are stirred for an additional 6 hours at room temperature (Note 6). The reaction mixture (Note 7) is poured into a 6-l. Erlenmeyer flask containing 3 l. of ice water (Note 8). The reaction flask is rinsed with 300 ml. of pentane and sufficient water to dissolve the inorganic material that may be present (Note 9). The washings are added to the Erlenmeyer flask. The mixture is stirred vigorously for 5 minutes, and the layers are separated. The upper layer is washed twice with 100-ml. portions of water and dried over anhydrous sodium sulfate. The solution is filtered, and the pentane is removed by distillation. The crude product is distilled through a 1.5 × 15 cm. Vigreux column; the fraction collected at 55.5–56.6° (11 cm.), yields 86–90 g. (82–87%) of 1,1,3,3-tetramethylbutyl isonitrile, n_D 1.4178, d^{25} 0.7944. The compound shows strong absorption in the IR (CCl_4) at 2130 cm.$^{-1}$ attributable to the isonitrile function. The ^1H NMR spectrum (neat, external tetramethylsilane reference) shows peaks at δ 1.08 (s, 9H, $C(CH_3)_3$), 1.43 (t, $J_{^{14}\text{N-H}}$ = 2 Hz., 6H, $C(CH_3)_2$), and 1.58 (t, $J_{^{14}\text{N-H}}$ = 2.3 Hz., 2H, CH_2).

B. N-(2-*Methylbutylidene*-1-*d*)-1,1,3,3-*tetramethylbutylamine* (Note 10). A 1-l., three-necked, round-bottomed flask fitted with a Teflon paddle stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen-inlet tube is flamed dry under a nitrogen atmosphere and allowed to cool. The nitrogen-inlet tube is replaced with a thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. A solution of 27.8 g. (35.1 ml., 0.200 mole) of 1,1,3,3-tetramethylbutyl isonitrile in 300 ml. of anhydrous diethyl ether is added to the flask. The flask is cooled to 0° with an ice–salt bath, and 0.2 mole of 2-butyllithium in hexane (Note 11) is transferred to the addition funnel with a syringe. The alkyllithium solution is added to the stirred (Note 12) solution at such a rate that the temperature never exceeds 5°. After the addition is complete, the mixture is stirred for 15 minutes as the temperature slowly drops to −5°, and 8 ml. (0.4 mole) of deuterium oxide (Note 13) is injected rapidly into the reaction mixture (Note 14). The ice bath is removed; the mixture is stirred for 30 minutes and filtered through a Büchner funnel into a 1-l., round-bottomed flask. The reaction flask is rinsed with pentane, and the rinse is added to the flask. After evaporation of the solvent, 33.7–34.9 g. (85–88%) of the aldimine is collected by distillation through a 1.5 × 15 cm. Vigreux column, b.p. 52.5–54° (1.5 mm.), $n_D^{24.5}$ 1.4321. The IR spectrum (neat) shows strong absorption at 1663 cm.$^{-1}$, attributable to the isonitrile function.

C. 2-*Methylbutanal*-1-*d*. A 1-l., three-necked, round-bottomed flask is equipped with a dropping funnel, a gas-inlet tube for steam, and a Dean-Stark trap attached to a condenser through which acetone cooled to −15° is circulated (Note 15). A solution of 50.4 g. (0.400 mole) of oxalic acid dihydrate in 200 ml. of water is added to the flask and heated at reflux. Steam is introduced into the flask, and when it begins to condense in the Dean-Stark trap, the aldimine from part B is added dropwise from the funnel. The aldehyde and water collect in the trap, and the water layer is periodically removed. After the distillation of the aldehyde is complete, the product is drained from the trap; the water layer is separated and discarded. The oil is washed with three 25-ml. portions of saturated sodium chloride and dried over anhydrous calcium sulfate. The crude aldehyde is decanted from the drying agent and distilled through a short Vigreux column, giving 13.0–13.3 g. (87–88%) of high-quality 2-methylbutanal-1-*d*, b.p. 92–93°, n_D^{30} 1.3896 (Note 16). The IR spectrum (neat) shows strong adsorption at 1721 cm.$^{-1}$ attributable to the carbonyl function.

2. Notes

1. *N*-(1,1,3,3-tetramethylbutyl)formamide is prepared in 86–90% yield by refluxing 194 g. (1.50 moles) of 1,1,3,3-tetramethylbutylamine with 138 g. (3.00 moles) of formic acid in 400 ml. of toluene. Azeotropic distillation using a Dean-Stark trap gradually removes all water and excess formic acid. The toluene is removed by distillation at atmospheric pressure, and the product is distilled at reduced pressure, b.p. 76–77° (1 mm.), n_D^{25} 1.4521, yielding 203–214 g. (86–90%).
2. Industrial grade *N,N*-dimethylformamide is purified by distillation, first at atmospheric pressure to remove most of the water in the initial small fraction, and then by distillation at reduced pressure from barium oxide, b.p. 63° (30 mm.).
3. A temperature rise of about 30° is observed.
4. Commercial anhydrous sodium carbonate is dried in a vacuum oven at 130° for 1 hour.
5. The checkers used a solid addition funnel and added the sodium carbonate under nitrogen over a 10-minute period.
6. The mixture can be left stirring overnight since isonitrile is stable to the reaction conditions. Alternatively, a hot-water bath can be used, with very fast stirring, to heat the mixture quickly to 35°. The bath is then removed, and after 1 hour of additional stirring, the mixture is ready for the workup procedure.
7. *Isonitriles are presumed to be toxic*, and it is recommended that the workup procedure be performed in a hood. Unlike most isonitriles, however, 1,1,3,3-tetramethylbutyl isonitrile (TMBI) is not malodorous. It has a sweetish pine odor, which becomes unpleasant only after continued inhalation.
8. The addition of the reaction mixture to water is exothermic.

9. The inorganic salts are not always soluble in the amount of water specified.

10. This procedure uses the commercially available 2-butyllithium reagent. The submitters state that the corresponding Grignard reagent may also be used. A 300-ml., three-necked, round-bottomed flask is fitted with an addition funnel, a reflux condenser, a magnetic stirring bar, and a nitrogen-inlet tube. Magnesium turnings (3.65 g., 0.150 mole) and 80 ml. of anhydrous tetrahydrofuran (Note 17) are added to the flask, and a nitrogen atmosphere is maintained. 2-Bromobutane (20.6 g., 0.150 mole), 0.25 ml. of 1,2-dibromoethane, and 70 ml. of tetrahydrofuran are placed in the addition funnel. Stirring is begun, and the solution is added dropwise at a rate which sustains refluxing. After the addition is complete, the solution is stirred until room temperature is reached. The amount of Grignard reagent prepared is determined (Note 18). To this Grignard solution is added 14.2 g. (0.102 mole) of 1,1,3,3-tetramethylbutyl isonitrile (Note 19). After stirring for 4–6 hours (Note 20), the solution is cooled in an ice bath to 0°. To the rapidly stirred solution (Note 21) is injected 6.0 ml. (0.30 mole) of deuterium oxide (Note 13). The ice bath is removed, and the mixture is stirred for 10 minutes before 50 ml. of water is added (Note 22). The contents of the reaction flask are decanted into a 1-l. separatory funnel containing 200 ml. of ether. The aqueous layer is separated, and the ether layer is washed with 100 ml. of saturated sodium chloride. The magnesium salts remaining in the reaction vessel are washed twice with 100-ml. portions of ether. The ether extracts are washed with 100 ml. of saturated sodium chloride. The combined ether solutions are dried over anhydrous sodium sulfate and evaporated with a rotary evaporator, giving the crude aldimine. Distillation (see Part B) yields 13.7 g. (67%) of the pure aldimine. Hydrolysis and steam distillation (as described in Note 15) yield 5.85 g. (65%, overall) of the aldehyde (Note 23).

11. The commercially available organolithium reagent is titrated with benzoic acid, using triphenylmethane as an indicator according to the procedure of Eppley and Dixon.[2] The checkers used product available from Alfa Inorganics, Inc.

12. During the addition of the alkyllithium the mixture becomes gelatinous. As this happens, the stirring rate is increased to ensure thorough mixing.

13. Deuterium oxide having an isotopic purity of >99% was used. The product available from Columbia Organic Chemicals Company, Inc., was used by the checkers.

14. The stirring should be very rapid at this point or frothing will occur. The flask temperature will reach 30° during deuteriolysis. It is important that the temperature of the ice–salt bath remains at −10° to −15°.

15. The submitters recommend the following procedure for steam distillation of low-boiling aldehydes. A 500-ml., three-necked flask is fitted with two addition funnels, one of which has a double-bore stopcock for external drainage. This addition funnel is fitted with a cold finger (−5°) and an inlet tube leading to a bubbler and a nitrogen source. The aldimine is placed in the other addition funnel. While the aldimine is added dropwise to the refluxing oxalic acid solution, the distillate passes up the equalizing pressure tube of the collecting funnel and is condensed by the cold finger. The water layer is periodically drained back into the flask. After distillation, the aldehyde is washed with saturated sodium chloride, then drained from the funnel through the external tube.

16. The submitters found that GC analysis of the undistilled aldehyde, conducted on a column packed with 16% LS-40 on Chromosorb P/AW at 100°, indicated a purity of 98.6%. ^{1}H NMR (CCl_4) analysis indicated an isotopic purity of 97.9% (trace of impurity at δ 9.60 due to C*H*O. If the crude aldimine is hydrolyzed, the aldehyde is obtained in 96% overall yield; however, the purity is only 94% by GC analysis. The checkers found no detectable impurity by GC in the distilled aldehyde, and the NMR spectrum indicated very high isotopic purity.

17. Alkyl magnesium halides form intermediates with tetramethylbutyl isonitrile which are not very soluble in ether. If it is necessary to prepare the Grignard reagent in ether, the ether should either be diluted with tetrahydrofuran or replaced by tetrahydrofuran. See the warning note in *Org. Synth.*, **Coll. Vol. 5**, 976 (1973), for purification of tetrahydrofuran.

18. The molarity is determined[3] by adding an excess of standardized acid and back-titrating with base. The moles of Grignard reagent present are determined based on a volume of 150 ml. When ether is used to prepare the Grignard reagent, an actual measurement of the volume is necessary. This can be done conveniently by transferring the solution back into the addition funnel with a large graduated syringe. The Grignard reagent content averages 0.102 mole.

19. The molar amount of 1,1,3,3-tetramethylbutyl isonitrile used is equivalent to the Grignard reagent content.

20. After 4 hours, periodic aliquots are taken and worked up. The disappearance of the isonitrile absorption at 2130 cm.$^{-1}$ and the appearance of the imine absorption at 1665 cm.$^{-1}$ are used for analysis. Usually within 6 hours the isonitrile peak vanishes or remains at a very low constant intensity indicative of completion of the reaction.

21. The sudden quenching with deuterium oxide minimizes the exchange between the 1-metalloaldimine and the active hydrogen at the C-2 position of the already-deuteriated aldimine. Performing the reaction in refluxing tetrahydrofuran produces an exchange (approximately 10%) with incorporation of deuterium in the C-2 position. If only the 1-H-aldehyde is desired, 50 ml. of water is added dropwise.

22. Saturated ammonium chloride solution slowly hydrolyzes the aldimine to the aldehyde, which, in this case, is undesirable.

23. NMR analysis shows that deuterium incorporation at the C-1 position is 95.3% and at C-2, 5%.

3. Discussion

This reaction illustrates a general procedure for the preparation of 1-*d*-aldehydes from aliphatic and alicyclic[4] Grignard[5] and lithium[6] reagents. The use of the lithium reagent is normally preferred because of higher yields and greater isotopic purity if the 1-*d*-aldehyde is desired. For the synthesis of aromatic aldehydes, the use of the lithium reagent is specifically preferred since aromatic Grignard reagents react poorly with 1,1,3,3-tetramethylbutyl isonitrile. The aldehydes prepared by this method are illustrated in Table I.

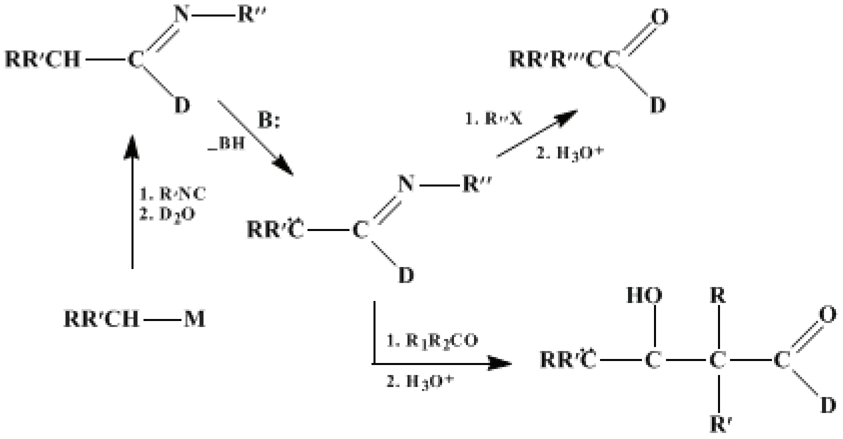


TABLE I

ALDEHYDES FROM 1,1,3,3-TETRAMETHYLBUTYL ISONITRILE AND ORGANOMETALLIC REAGENTS

Organometallic Reagent	Aldehyde, % Yield
n-Butyllithium	93[a]
Phenyllithium	55[a]
2-Butylmagnesium bromide	67 (96[b,c])
tert-Butylmagnesium bromide	48[b]
n-Hexylmagnesium bromide	62[b]
2-Phenylethylmagnesium bromide	63 (80[b,c])
Cyclopentylmagnesium bromide	66 (89[b,c])

[a] Reference 6.

[b] Reference 5.

[c] Percent deuterium at C-1 as determined by NMR.

The intermediate aldimines can also be alkylated[7] or used as condensing agents[8] by removal of the α-hydrogen atom. The metalloaldimine is a useful intermediate for the preparation of α-keto acids, acyloins, β-hydroxy ketones, and silyl ketones.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

1,1,3,3-tetramethylbutyl isonitrile (TMBI)

Benzyl and vinyllithium

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

2-Bromobutane (78-76-2)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

barium oxide

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

calcium sulfate (7778-18-9)

acetone (67-64-1)

toluene (108-88-3)

1,2-dibromoethane (106-93-4)

Pentane (109-66-0)

Triphenylmethane (519-73-3)

Phenyllithium (591-51-5)

lithium (7439-93-2)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

oxalic acid dihydrate (6153-56-6)

1,1,3,3-tetramethylbutylamine (107-45-9)

deuterium oxide (7789-20-0)

deuterium (7782-39-0)

1,1,3,3-tetramethylbutyl isonitrile (14542-93-9)

2-butyllithium (598-30-1)

tetramethylbutyl isonitrile

2-Butylmagnesium bromide

2-Phenylethylmagnesium bromide

Cyclopentylmagnesium bromide

2-METHYLBUTANAL-1-d,
Butanal-1-d, 2-methyl- (25132-57-4)

N-(1,1,3,3-tetramethylbutyl)formamide (10151-02-7)

tert-Butylmagnesium bromide

n-Hexylmagnesium bromide (3761-92-0)

N-(2-Methylbutylidene-1-d)-1,1,3,3-tetramethylbutylamine (34668-70-7)