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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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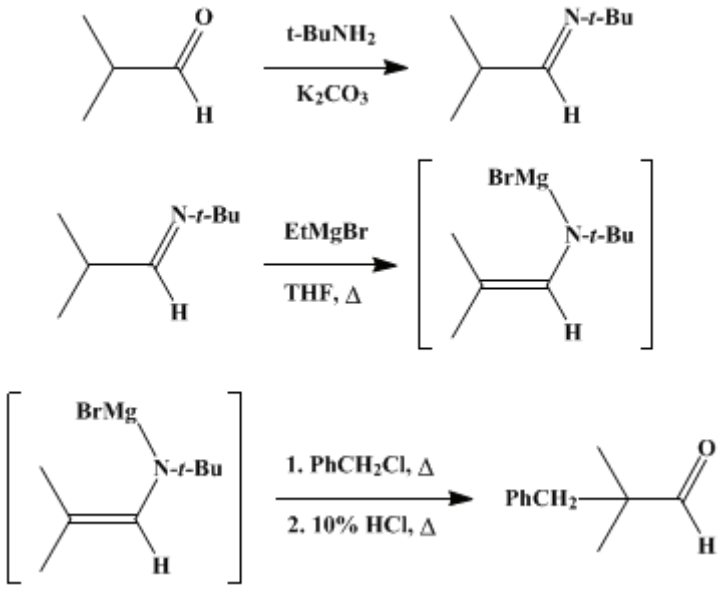
ALKYLATIONS OF ALDEHYDES *via* REACTION OF THE MAGNESIOENAMINE SALT OF AN ALDEHYDE: 2,2-DIMETHYL-3-PHENYLPROPIONALDEHYDE

[Benzenepropanal, α,α-dimethyl-]



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1. Procedure

A. N-(2-*Methylpropylidene*)-tert-*butylamine*. A 100-ml., three-necked, round-bottom flask equipped with a condenser, a nitrogen inlet tube, a 50-ml. dropping funnel, and a magnetic stirring bar is evacuated through a mercury bubbler, flamed dry, and flushed with nitrogen three times. The flask is charged with 36.0 g. (0.500 mole) of *tert*-butylamine (Note 1), and 36.5 g. (0.501 mole) of isobutyraldehyde (Note 1) is placed in the dropping funnel. Half of the isobutyraldehyde is added slowly through the dropping funnel before the remaining half-volume is added rapidly. The milky solution is allowed to stand at room temperature for 1 hour; the water layer is then pipeted out, and excess anhydrous potassium carbonate is added. Filtration and distillation of this reaction mixture gives 32.0 g. (50%) of *N*-(2-methylpropylidene)-*tert*-butylamine, b.p. 50° (75 mm.) (Note 2).

B. 2,2-*Dimethyl*-3-*Phenylpropionaldehyde*. A 100-ml., three-necked, round-bottom flask equipped with an ether condenser, a nitrogen inlet tube, a 50-ml. Herschberg dropping funnel, and a magnetic stirring bar is evacuated through a mercury bubbler, flamed dry, and flushed with nitrogen three times. The system is left under a slight positive pressure of nitrogen, and all the reactants are added under a stream of nitrogen. A solution of 0.05 mole of ethylmagnesium bromide in 37 ml. of tetrahydrofuran (Note 3) is placed in the flask. A solution of 6.35 g. (0.0567 mole) of *N*-(2-methylpropylidene)-*tert*-butylamine (Note 4) in 5 ml. of tetrahydrofuran (Note 5) is then added from the dropping funnel. The resulting mixture is refluxed for 12–14 hours until 1 mole-equivalent of gas has evolved (Note 6). The reaction mixture is cooled to room temperature; 6.30 g. (0.0498 mole) of benzyl chloride (Note 1) is added from the dropping funnel; and the solution is refluxed for 20 hours, at which time the pH is 9–10 (pHydrion paper). To the cooled solution, which contains a large amount of solid, is added 20–30 ml. of 10% hydrochloric acid. The clear, yellow-brown solution is then refluxed for 2 hours, cooled, saturated with solid sodium chloride, and extracted five times with diethyl ether. The organic extracts are washed once with 25 ml. of 5% hydrochloric acid, then repeatedly with brine until the washings are neutral. The

organic layer is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed at atmospheric pressure through a 12-in. Vigreux column fitted with a partial take-off head. Distillation of the residue (Note 7) through a 20-in. vacuum-jacketed fractionating column affords 5.1–5.4 g. (63–66%) of 2,2-dimethyl-3-phenylpropionaldehyde, b.p. 70–73° (1.5 mm.) (Note 8).

2. Notes

1. These reagents were obtained from Eastman Organic Chemicals, but not distilled prior to use.
2. The checkers found that the yield could be improved (37–38 g., 58–60%) if the reaction mixture was allowed to remain over anhydrous potassium carbonate for 8–12 hours.
3. Ethylmagnesium bromide was prepared in dry tetrahydrofuran and stored no longer than 1 week in a 250-ml. tube fitted with a 3-way vacuum stopcock and a dropping buret. The solution is decanted into the buret, and the correct volume is transferred to the reaction flask with positive nitrogen pressure. The tetrahydrofuran was purified by distillation from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973), for warning regarding the purification of tetrahydrofuran.
4. The aldimine is freshly distilled [b.p. 50° (75 mm.)] prior to use.
5. A vigorous reaction may result. At this stage of the reaction, control is maintained with an ice–water bath.
6. The volume of gas evolved is estimated with an inverted cylinder filled with water attached by rubber tubing to the outlet of the mercury bubbler.
7. GC analysis at 155° on a 5 ft. 5% SE-30 column shows only 2,2-dimethyl-3-phenylpropionaldehyde and solvent.
8. The IR spectrum ($CHCl_3$) showed absorption at 2705, 1725, and 1605 cm^{-1}. The 2,4-dinitrophenylhydrazone, recrystallized from ethanol–ethyl acetate as long, yellow-orange needles, melted at 150–152° (reported[3] 154–155°).

3. Discussion

This procedure illustrates the mono-alkylation of α-substituted aldehydes by the metalloenamine method.[4] The preparation of the aldimine has been adapted from the procedure of Tiollais[5] and is useful in the preparation of aldimines from low-boiling components. The readily prepared aldimine is treated with an alkyl Grignard reagent generating the magnesioenamine halide salt, which can be alkylated with a variety of alkylating agents at the α-position. The yields are high, monoalkylation is the exclusive reaction, and there is no rearrangement when using an allylic halide. The general method is applicable to the alkylation of ketones *via* the magnesium bromide salts of the corresponding ketimines (Table I).

TABLE I
REACTION OF VARIOUS ALDIMINE AND KETIMINE MAGNESIUM BROMIDE SALTS WITH ALKYLATING AGENTS IN TETRAHYDROFURAN

Imine	Halide	Yield, %				
N-(2-methylpropylidene)-*tert*-butylamine	*n*-butyl iodide	65				
N-(heptylidene)-*tert*-butylamine	*n*-butyl iodide	47				
N-(propylidene)-*tert*-butylamine	*n*-butyl bromide	60				
	n-butyl iodide	78	2-iodopropane	61	benzyl chloride	60
N-(cyclohexylidene) cyclohexylamine	*N*-(cyclopentylidene) cyclohexylamine	*n*-butyl iodide	72			
	N-(cycloheptylidene) cyclohexylamine	*n*-butyl iodide	75			

In a variation of this method, metalloenamines have been generated from the aldimine and lithium

diisopropylamide in ether and alkylated in a limited number of cases.[6] A further variation, using lithium dialkylamides in hexamethylphosphoric triamide, has been shown by Cuvigny and Normant[7] to give good yields of alkylated aldehydes. However, secondary alkyl halides fail to react, giving the dehydrohalogenation product instead. Another approach, that of Meyers and co-workers,[8] involves the alkylation of the lithio salt of 2-methyldihydro-1,3-oxazines, but suffers from the necessity of carrying out several low-temperature steps and a pH-controlled borohydride reduction.

References and Notes

1. Department of Chemistry, Columbia University, New York, New York 10027.
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3. G. Opitz, H. Heilmann, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 36 (1961).
4. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
5. R. Tiollais, *Bull. Soc. Chim. Fr.*, **14**, 708 (1947).
6. G. Wittig, H.-D. Frommeld, and P. Suchanek, *Angew. Chem. Int. Ed. Engl.*, **2**, 683 (1963); G. Wittig and H.-D. Frommeld, *Chem. Ber.*, **97**, 3548 (1964).
7. Th. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).
8. A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.*, **91**, 763 (1969).

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

2,4-dinitrophenylhydrazone

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium chloride (7647-14-5)

n-butyl bromide (109-65-9)

nitrogen (7727-37-9)

acetate

benzyl chloride (100-44-7)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

2-iodopropane (75-30-9)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexamethylphosphoric triamide (680-31-9)

lithium diisopropylamide (4111-54-0)

borohydride (16971-29-2)

2,2-Dimethyl-3-phenylpropionaldehyde,
Benzenepropanal, α,α-dimethyl- (1009-62-7)

n-Butyl iodide (542-69-8)

tert-Butylamine (75-64-9)

N-(2-Methylpropylidene)-tert-butylamine (6852-60-4)

N-(heptylidene)-tert-butylamine

N-(propylidene)-tert-butylamine

N-(cyclohexylidene)cyclohexylamine

N-(cyclopentylidene)cyclohexylamine

N-(cycloheptylidene)cyclohexylamine