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Working with Hazardous Chemicals

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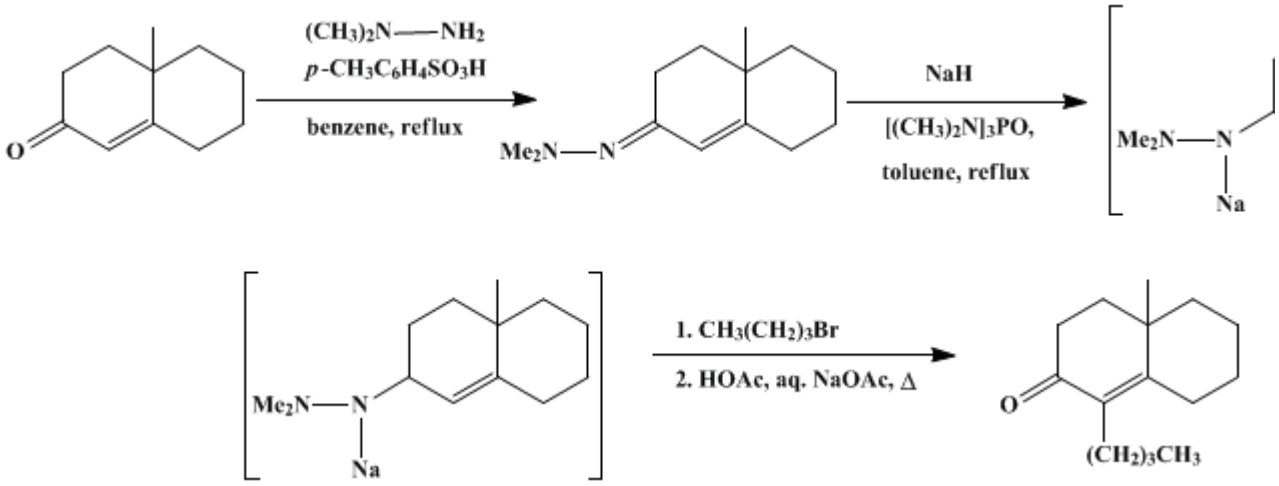
MONOALKYLATION OF α,β-UNSATURATED KETONES *via* METALLOENAMINES: 1-BUTYL-10-METHYL-Δ$^{1(9)}$-2-OCTALONE

[2(3*H*)-Naphthalenone, 1-butyl-4,4a,5,6,7,8-hexahydro-4a-methyl-]



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1. Procedure

Caution! Hexamethylphosphoric triamide vapors have been reported to cause cancer in rats.[3] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. 10-*Methyl*-Δ$^{1(9)}$-2-*octalone* N,N-*dimethylhydrazone.* A 250-ml., round-bottomed flask equipped with a magnetic stirring bar and a Dean-Stark trap is maintained under a dry nitrogen atmosphere (Note 1) and charged with 7.4 g. (0.045 mole) of 10-methyl-Δ$^{1(9)}$-2-octalone (Note 2), 9.0 g. (0.15 mole) of *N,N*-dimethylhydrazine, 150 ml. of dry benzene, and 0.02 g. of *p*-toluenesulfonic acid. This mixture is refluxed for 10–14 hours, after which time no additional water separates. Benzene and excess *N,N*-dimethylhydrazine are removed by simple distillation, and the residue is distilled under reduced pressure, giving 8.1 g. (87%) of the dimethylhydrazone as a pale-yellow liquid, b.p. 94–98° (0.2 mm.) (Note 3), (Note 4).

B. *1-Butyl-10-methyl-Δ$^{1(9)}$-2-octalone.* A 250-ml., three-necked flask equipped with a magnetic stirring bar, a reflux condenser, a 50-ml., pressure-equalizing funnel, and a rubber septum is charged with 1.4 g. (0.032–0.035 mole) of 55–60% sodium hydride dispersion in mineral oil and put under a dry nitrogen atmosphere. The mineral oil is removed by washing the sodium hydride three or four times with 5-ml. portions of dry toluene (Note 5). A solution of 6.12 g. (0.0297 mole) of 10-methyl-Δ$^{1(9)}$-2-octalone *N,N*-dimethylhydrazone in 100 ml. of dry toluene is placed in the flask, and 10 ml. of dry hexamethylphosphoric triamide is added. The rubber septum is replaced with a glass stopper. The solution is warmed with an oil bath to reflux the toluene; hydrogen evolution is observed. Reflux is maintained for 14–16 hours, during which time the solution becomes dark brown. The solution is then

cooled to −10° and 4.5 g. (0.033 mole) of 1-bromobutane in 10 ml. of dry toluene is slowly added. The solution is warmed to 60° and maintained at that temperature for 4–5 hours. An abundant precipitate of sodium bromide is formed. The solution is cooled to 0°, and an acetate-buffer solution (Note 6) is added. The mixture is refluxed for 4–5 hours to complete the hydrolysis before it is cooled and decanted. The aqueous phase is extracted three times with 25-ml. portions of diethyl ether. The combined organic layers are successively washed with three 80- to 100-ml. portions of 10% hydrochloric acid, three 50-ml. portions of saturated sodium hydrogen carbonate, two 50-ml. portions of saturated sodium chloride, and then dried over sodium sulfate. The solvents are removed by rotary evaporation (Note 7). The residue is distilled under high vacuum using a short column. After a small forerun, 4.3–4.7 g. (65–72%) of pure 1-butyl-10-methyl-$\Delta^{1(9)}$-2-octalone, b.p. 84–92° (0.2 mm.), is obtained (Note 8).

2. Notes

1. A positive pressure of nitrogen is maintained using a mercury bubbler.
2. 10-Methyl-$\Delta^{1(9)}$-2-octalone, which can be prepared from 4-(diethylamino)-2-butanone, 2-methylcyclohexanone, and sodium,[4] has b.p. 65–70° (0.1 mm.) and n_D^{20} 1.523. IR (neat) cm.$^{-1}$: 1610, 1670; ^{1}H NMR (CCl_4), δ (assignment): 1.25 (CH_3), 5.6 (C*H*).
3. The hydrazone should be stored under dry nitrogen at −10°.
4. ^{1}H NMR (CCl_4), δ (multiplicity, assignment): 1.15 (s, CCH_3), 2.35 [s, $N(CH_3)_2$], 6.35 (40%) and 5.70 (60%) (s, C*H* of diastereomeric hydrazones); IR (neat) cm.$^{-1}$: 1620, 1580; n_D^{20} 1.505.
5. A 5-ml. portion of dry toluene is introduced into the flask with a syringe, and sodium hydride dispersion is stirred for 1 minute before 4 ml. of the supernatant toluene is carefully removed from the flask with a syringe.
6. The buffer solution is prepared by dissolving 20 g. of anhydrous sodium acetate in a mixture of 40 ml. of acetic acid and 40 ml. of water.
7. At this point the submitters reported 7.07 g. of crude product; GC analysis on an SE-30 column at 200° showed 1–3% of 10-methyl-$\Delta^{1(9)}$-2-octalone and 85% of the desired alkylated product.
8. ^{1}H NMR (CCl_4), δ (multiplicity, assignment): 0.9 (t, CH_2CH_3), 1.2 (s, CCH_3); IR (neat) cm.$^{-1}$: 1660, 1600; n_D^{25} = 1.511.

3. Discussion

Alkylations of enamines of α,β-unsaturated ketones with alkyl halides often give very poor yields of *C*-alkylated products because of competing *N*-alkylation.[5,6] In the type of transformation illustrated here, direct alkylations of enamines are completely unsuccessful, even in cases where hindered enamines[7] are used. Generally, the metalloenamine method[8] can be applied with good success to the problem of monoalkylation of α,β-unsaturated ketones.[9]

Metalloenamines can be formed from *N,N*-dimethylhydrazones, as illustrated here, or from *N*-cyclohexylimines. Various strong bases have been used, including *n*-butyllithium, lithium diisopropylamide, sodium hydride, and lithium bis(trimethylsilyl) amide. The nature and sometimes the stoichiometry of the strong base used can be important. Poor yields of alkylated compounds are obtained with Grignard reagents, and in the case of *n*-butyllithium, excess base can result in the formation of significant amounts of kinetically controlled alkylation products (*e.g.*, alkylation at C-3 of 10-methyl-$\Delta^{1(9)}$-2-octalone). In the cases of octalones and steroid compounds (cholestenone, testosterone benzoate) it has been found that sodium hydride and lithium diisopropylamide gave the best yields of the desired alkylated compounds.[9]

References and Notes

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

1-Butyl-10-methyl-$\Delta^{1(9)}$-2-octalone

10-Methyl-$\Delta^{1(9)}$-2-octalone N,N-dimethylhydrazone

10-methyl-$\Delta^{1(9)}$-2-octalone

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

1-bromobutane (109-65-9)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

4-(diethylamino)-2-butanone (3299-38-5)

Cholestenone

N,N-dimethylhydrazine (57-14-7)

n-butyllithium (109-72-8)

sodium hydride (7646-69-7)

2-methylcyclohexanone (583-60-8)

hexamethylphosphoric triamide (680-31-9)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

lithium bis(trimethylsilyl) amide (4039-32-1)

testosterone benzoate

2(3H)-Naphthalenone, 1-butyl-4,4a,5,6,7,8-hexahydro-4a-methyl- (66252-93-5)