Organic Syntheses

A Publication
of Reliable Methods
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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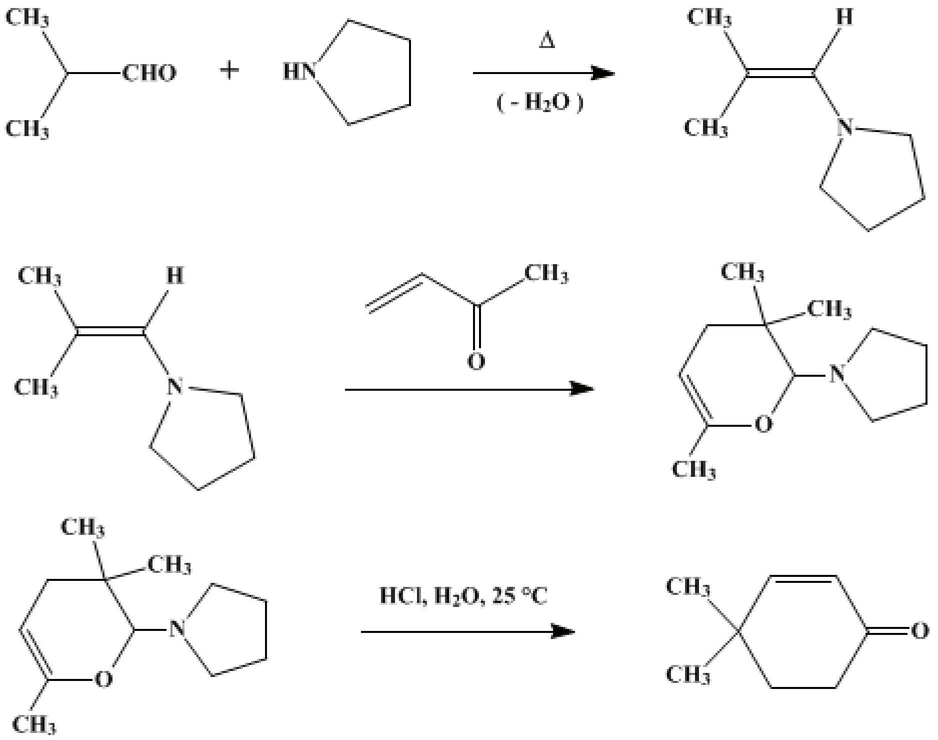
4,4-DIMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 4,4-dimethyl-]



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1. Procedure

A. *1-(2-Methylpropenyl)pyrrolidine.* A 200-ml., three-necked flask is equipped with a magnetic stirring bar, a heating mantle, a pressure-equalizing dropping funnel, a glass stopper, and a continuous water separator (a Dean-Stark trap, (Note 1)) fitted with a condenser and a nitrogen inlet tube. The reaction vessel is flushed with nitrogen, and 61.5 g. (0.853 mole) of isobutyraldehyde (Note 2) is added to the reaction flask. An additional amount of isobutyraldehyde (Note 2) is added to the continuous water separator, filling the water-collecting trap. A static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction and distillation. To the reaction flask is added, dropwise and with stirring over 5 minutes, 60.6 g. (0.852 mole) of pyrrolidine (Note 3). After addition is complete, the dropping funnel is replaced with a glass stopper and the reaction mixture is refluxed with stirring for 3.5 hours during which time about 15 ml. (0.83 mole) of water collects in the water separator (Note 4). The water separator and condenser are replaced with a distillation head, and the reaction mixture is distilled under reduced pressure, yielding 99.1–100.7 g. (94–95%) of the enamine as a colorless liquid, b.p. 92–106° (115–118 mm.), n_D^{25} 1.4708–1.4738 (Note 5).

B. *4,4-Dimethyl-2-cyclohexen-1-one.* A dry, 1-l., three-necked flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, a nitrogen inlet tube, and an ice-water cooling bath. The apparatus is flushed with nitrogen, and a static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction. 1-(2-Methylpropenyl)pyrrolidine (62.6 g., 0.501 mole) is added to the reaction flask before 42.1 g. (0.601 mole) of methyl vinyl ketone (Note 6) is added, dropwise with stirring and cooling, over 5 minutes. After the resulting mixture has been stirred with cooling for 10 minutes, the ice bath is removed and stirring at room temperature is continued for 4 hours (Note 7). The reaction mixture is again cooled with an ice-water bath, and 250 ml. of 8 *M* hydrochloric acid is added, dropwise and with stirring (Note 8). After addition is complete, the mixture is stirred with cooling for 10 minutes, then stirred at room temperature for 14 hours (Note 9). The resulting brown reaction mixture is extracted with two 300-ml. portions of diethyl ether. The residual aqueous phase is neutralized by the cautious addition of 150–155 g. of solid sodium hydrogen carbonate and extracted with two 400-ml. portions of ether. The combined ethereal extracts (Note 10) are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residual liquid is distilled under reduced pressure, yielding 44.2–53.0 g. (71–85%) of 4,4-dimethyl-2-cyclohexen-1-one as a colorless liquid, b.p. 73–74° (14 mm.), n_D^{25} 1.4699–1.4726 (Note 11).

2. Notes

1. An illustration of a continuous water separator is provided in *Org. Synth.*, **Coll. Vol. 3**, 502 (1955).
2. The checkers employed isobutyraldehyde from Eastman Organic Chemicals. The aldehyde, b.p. 62–63°, was freshly distilled from a few milligrams of *p*-toluenesulfonic acid.
3. The pyrrolidine, obtained from Aldrich Chemical Company, Inc., was redistilled before use; b.p. 88–89°.
4. The water should not be drained from the water separator during the course of the reaction.
5. The enamine has IR absorption (pure liquid) at 1676 cm.$^{-1}$ (enamine C=C).
6. Methyl vinyl ketone (b.p. 35–36° at 140 mm.), obtained from Aldrich Chemical Company, Inc., was distilled immediately before use.
7. The use of solvents such as anhydrous ether or benzene is not only unnecessary but also undesirable, since yields are decreased by their presence. For best results the Diels-Alder adduct, which has been characterized by Opitz and Holtmann,[2] should not be isolated for the subsequent hydrolysis and cyclization.
8. The hydrolysis product, 2,2-dimethyl-5-oxo-hexanal, can be isolated if desired by stirring the Diels-Alder adduct with either 50% acetic acid or 2 *M* hydrochloric acid followed by extraction with ether and distillation,[3] b.p. 92–94° (20 mm.).
9. Cyclization can also be accomplished by the use of an ion exchange resin.[4] On a 0.1-mole scale, 110 ml. of 1 *M* hydrochloric acid and 70 ml. of wet Amberlite 1R-120 resin (acidified with hydrochloric acid) are added to the Diels-Alder adduct, and the mixture is refluxed for 24 hours. The mixture is cooled and washed with four portions of ether. The ether extract is dried over anhydrous magnesium sulfate and distilled, separating 9.7–10.8 g. (78–87%) of 4,4-dimethyl-2-cyclohexen-1-one; b.p. 73–74° (14 mm.).
10. Washing the ethereal extract with either dilute acid, aqueous sodium hydrogen carbonate, or saturated brine only decreased the yield of product and is, therefore, omitted. An acid-catalyzed reaction of methyl vinyl ketone with isobutyraldehyde gives the product in 71% yield.[5]
11. The product exhibits a single peak (retention time 5.7 minutes) on a 4-m. GC column packed with silicone fluid QF_1 on Chromosorb P and heated to 191°. This material has the following spectral characteristics: IR (CCl_4) 1675 (conjugated C=O) and 1623 cm.$^{-1}$ (conjugated C=C); UV (95% C_2H_5OH) max 224 (10,600) and 321 nm (34); ^{1}H NMR (CCl_4), δ 1.17 (s, 6H, 2CH_3), 1.7–2.6 (m, 4H, 2CH_2), 5.71 (d, J = 10 Hz., 1H, vinyl C*H*), and 6.65 (d of t, J = 10 and 1.5 Hz., 1H, vinyl C*H*); *m/e* (rel. int.), 124(M$^+$, 49), 96(83), 82(100), 81(56), 68(25), 67(42), 53(22), 43(21), 41(25), and 39(25).

3. Discussion

The procedure described is essentially that of Opitz and Holtmann.[2] The yield has been increased from 27% to 85% by making changes as indicated in (Note 7) and (Note 10). 4,4-Dimethyl-2-cyclohexen-1-one has also been prepared by Michael addition of methyl vinyl ketone to isobutyraldehyde followed by ring formation in basic media with yields of 25%,[6] 35%,[7] and 43%.[8] This procedure has general utility in preparing 4-substituted or 4,4-disubstituted cyclohexen-2-ones and, as such, constitutes a useful substitute for the Robinson annelation reactions.[9,10] Unlike the latter, the alkylation step in this procedure does not require strongly basic conditions. Consequently, side reactions such as aldol condensation of the carbonyl compounds and polymerization of methyl vinyl ketone are avoided. Moreover, since the location of the double bond in the enamines is controlled by the amines used,[11] it may be possible to direct the alkylation to either side of a given carbonyl group making this procedure potentially very versatile. Similar reactions using acrolein and enamines of cyclic ketones have been utilized for the synthesis of bicyclo[n.3.1] systems.[9,12]

References and Notes

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

brine

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

Acrolein (107-02-8)

sodium hydrogen carbonate (144-55-8)

Salt (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

magnesium sulfate (7487-88-9)

isobutyraldehyde (78-84-2)

pyrrolidine (123-75-1)

methyl vinyl ketone (78-94-4)

p-toluenesulfonic acid (104-15-4)

4,4-Dimethyl-2-cyclohexen-1-one,
2-Cyclohexen-1-one, 4,4-dimethyl- (1073-13-8)

1-(2-Methylpropenyl)pyrrolidine (2403-57-8)

2,2-dimethyl-5-oxo-hexanal (13544-11-1)