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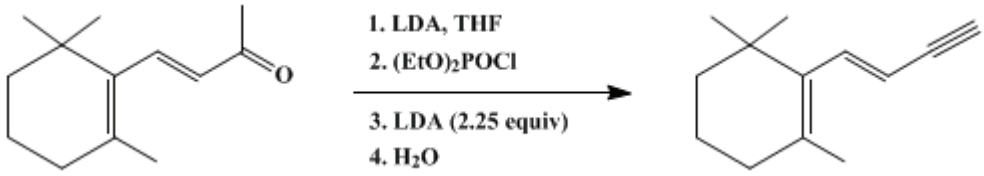
DOI:10.15227/orgsyn.064.0044

Organic Syntheses, Coll. Vol. 7, p.63 (1990); Vol. 64, p.44 (1986).

CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES: (*E*)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE

[Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (*E*)-]



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Checked by Weyton W. Tam and Robert V. Stevens.

1. Procedure

An oven-dried, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen and charged with 100 mL of tetrahydrofuran (THF) (Note 1). To this are added sequentially at 0°C, diisopropylamine (Note 2) (10.6 g, 14,7 mL, 105 mmol) and butyllithium in hexane (Note 3) (2.22 *M*, 47.3 mL, 105 mmol). The reaction mixture is stirred for 30 min and cooled to −78°C. β-Ionone (Note 4) (19.2 g, 20.3 mL, 100 mmol) is slowly added. After stirring the mixture for 1 hr at −78°C, diethyl chlorophosphate (Note 5) (18.1 g, 15.2 mL, 105 mmol) is added, and the reaction mixture is allowed to warm to room temperature over 2–3 hr (reaction mixture A) (Note 6).

Lithium diisopropylamide is prepared in a separate 1-L flask from diisopropylamine (22.8 g, 31.6 mL, 225 mmol), butyllithium in hexane (2.22 *M*, 101 mL, 225 mmol), and THF (200 mL), as described above. To this is added over approximately 45 min at −78°C reaction mixture A prepared above via a 16-G double-ended needle under a slight pressure of nitrogen. The resulting mixture is allowed to warm to room temperature over 2–3 hr and is quenched with water (200 mL) at 0°C. The organic layer is separated, and the aqueous layer is extracted with pentane (3 × 50 mL). The combined organic layer is treated with ice-cold hydrochloric acid (1 *N*, 200 mL), water (2 × 100 mL), and saturated aqueous sodium bicarbonate (100 mL) to pH ≥8 (Note 7). After drying over magnesium sulfate, the volatile compounds are evaporated using a rotary evaporator at ca. 20 mm. The residue is distilled at 0.7 mm to provide (E)-buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene (Note 8) in one fraction boiling at 69–73°C (0.7 mm) (Note 9). The yield by isolation has ranged from 12.5 g (72%) to 14.8 g (85%) (Note 10). The purity of the product by GLC is 98%.

2. Notes

1. Tetrahydrofuran available from Aldrich Chemical Company, Inc. was purified by distillation from sodium and benzophenone.
2. The submitters used diisopropylamine (99%) available from Aldrich Chemical Company, Inc. without further purification.
3. The submitters used butyllithium in hexane available from Alfa Products, Morton Thiokol, Inc.
4. The submitters used 98% pure β-ionone available from Aldrich Chemical Company, Inc. without further purification.
5. The submitters used diethyl chlorophosphate available from Aldrich Chemical Company, Inc.
6. Reduced yields of product were obtained by the checkers when reaction time at room temperature was reduced from 2–3 hr to 1½ hr.
7. After extraction with hydrochloric acid, the pentane layer, on addition of 100 mL of water, formed a poorly separating emulsion. Checkers found that, by addition of 100 mL of saturated aqueous sodium bicarbonate to this pentane–water emulsion, two easily separable layers can be formed.

8. The distilled product was found to be slightly yellow, and deepened to orange at room temperature. Storage at −5°C maintained the initial coloration for several weeks.
9. The product displays the following data: n_D^{24} 1.5130; IR (neat) cm^{-1}: 3300 (s), 2920 (s), 2080 (m), 1770 (w), 1630 (w), 1600 (w), 1455 (s), 1380 (m), 1355 (m), 1200 (m), 1030 (m), 960 (s); ^1H NMR ($CDCl_3$, TMS) δ: 1.01 (s, 6 H), 1.2–1.8 (m with a singlet at 1.71, 7 H), 1.85–2.15 (m, 2 H), 2.90 (d, 1 H, $J = 2$), 5.42 (dd, 1 H, $J = 17$ and 2), 6.67 (d, 1 H. $J = 17$); ^{13}C NMR ($CDCl_3$, TMS) δ: 19.17, 21.48, 28.75, 33.07, 33.98, 39.59, 77.29, 83.10, 111.36, 131.38, 136.90, 142.33.
10. The GLC trace (SE-30) of the reaction mixture shows essentially one peak (≥98) in the product region. In separate 5–20-mmol scale experiments, the GLC yields observed by using a paraffin internal standard were 90–95%.

3. Discussion

This procedure is based on a study of conversion of methyl ketones into terminal alkynes.[2] The scope of the procedure may be indicated by the results summarized in Table I.

TABLE I
CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES VIA ENOL PHOSPHATES

Ketone	Base[a]	Yield of Acetylene (%) GLC	Isolated
β-Ionone	LDA	95	85
Dihydro-β-ionone	LDA	90	85
Acetophenone	LDA	85	80
Pinacolone	LDA	90	78
Cyclohexyl methyl ketone	LDA	85	80
2-Octanone	LDA	23	—
2-Octanone	LTMP	75	—
6-Methyl-5-hepten-2-one	LDA	25	—
6-Methyl-5-hepten-2-one	LTMP	75	61

[a]LDA = lithium diisopropylamide; LTMP = lithium 2,2,6,6-tetramethylpiperidide.

As can be seen in Table I, lithium diisopropylamide (LDA) is a satisfactory base in cases where the carbon group (R) of a methyl ketone ($RCOCH_3$) either is bulky or does not contain an α-methylene or α-methine group. In the other cases, LDA is relatively ineffective. In such cases, however, the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in place of LDA gives satisfactory results. The LTMP procedure appears to be the only documented method that is satisfactory for the conversion of the above-mentioned type.

The submitters have attempted the conversion of β-ionone into the desired dienyne by various known methods. In general, those involving acidic reagents or reaction conditions yielded the desired product in low yields (<50%) along with by-products, such as isomeric allenes, that appear near the product on GLC traces (SE-30). Such procedures include (a) PCl_5 in benzene, then $NaNH_2$ in NH_3;[3] (b) PCl_5 and 2,6-lutidine, then $NaNH_2$ in NH_3;[4] (c) $POCl_3$ in DMF, then NaOH;[5] and (d) $(CF_3SO_2)_2O$, CCl_4, pyridine, then heat.[6] Also unsatisfactory in the hands of submitters was a method involving the use of hydrazine in triethylamine, then iodine and triethylamine in THF, then methanolic potassium hydroxide.[7] A procedure involving the use of sodium ethoxide, then diethyl chlorophosphate, and finally $NaNH_2$ in NH_3,[8] on the other hand, converted β-ionone into the desired dienyne in ≤73% GLC yield. The procedure reported here may be viewed as a modification of the method described above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 411

References and Notes

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

METHYL KETONES

Lithium 2,2,6,6-tetramethylpiperidide

PCl_5

NH_3

$POCl_3$

$(CF_3SO_2)_2O$

methanolic potassium hydroxide

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

NaOH (1310-73-2)

sodium bicarbonate (144-55-8)

CCl_4 (56-23-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

Acetophenone (98-86-2)

Pinacolone (75-97-8)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

2,6-Lutidine (108-48-5)

Pentane (109-66-0)

hydrazine (302-01-2)

2-Octanone (111-13-7)

magnesium sulfate (7487-88-9)

$NaNH_2$ (7782-92-5)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

DMF (68-12-2)

hexane (110-54-3)

triethylamine (121-44-8)

Cyclohexyl methyl ketone (823-76-7)

diethyl chlorophosphate (814-49-3)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

β-Ionone,
Dihydro-β-ionone

(E)-Buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene,
Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)- (73395-75-2)

6-Methyl-5-hepten-2-one (110-93-0)