Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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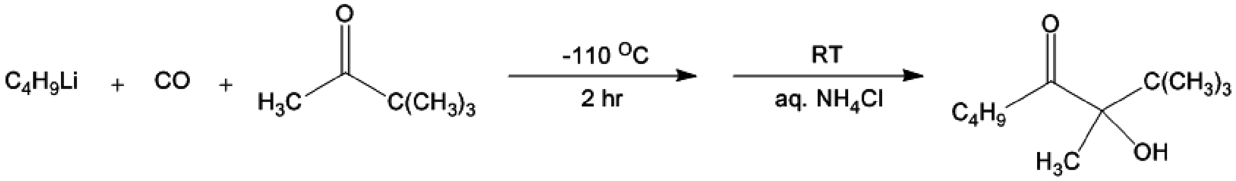
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.069.0114

Organic Syntheses, Coll. Vol. 8, p.343 (1993); Vol. 69, p.114 (1990).

DIRECT NUCLEOPHILIC ACYLATION BY THE LOW-TEMPERATURE, IN SITU GENERATION OF ACYLLITHIUM REAGENTS; α-HYDROXY KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE FROM PINACOLONE

[4-Octanone, 3-hydroxy-2,2,3-trimethyl-]



Submitted by Richard Hui and Dietmar Seyferth[1].
Checked by Hiroshi Koyano and Ryoji Noyori.

1. Procedure

A 2-L, three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter that contained a low-temperature thermometer, and a no-air stopper that held a gas dispersion tube for the introduction of carbon monoxide (Note 1). The flask was charged with 400 mL each of tetrahydrofuran (THF) and diethyl ether, 100 mL of pentane, and pinacolone (7.92 g, 79.1 mmol) (Note 2). The reaction solution was cooled to −110°C (Note 3) and (Note 4) under an argon atmosphere and carbon monoxide (Note 5) was bubbled in for 30 min. Then a solution of butyllithium (2.53 *N* solution in pentane, 31.0 mL, 78.43 mmol) (Note 6) was added at 0.6–1.0 mL/min by means of a syringe pump (Note 7). The reaction mixture was orange after the addition had been completed. The reaction mixture was stirred at −110°C for 2 hr while the carbon monoxide stream was continued. The liquid nitrogen Dewar was removed, and the reaction mixture was allowed to warm to room temperature over the course of 1.5 hr, during which time the color changed to yellow. The reaction mixture subsequently was quenched by the addition of 300 mL of saturated ammonium chloride solution, which resulted in a light-yellow organic layer and a clear, colorless aqueous phase. The aqueous layer was separated and washed twice with 100 mL of pentane. The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The solvents were removed by fractional distillation (9-in. Vigreux column). The residue was distilled through a 7-cm jacketed column to give 9.7–10.8 g (67–73%) of 3-hydroxy-2,2,3-trimethyloctan-4-one, 97% pure by GLC, bp 120–122°C (30 mm), and n_{D}^{20} 1.442 (Note 8).

2. Notes

1. All glassware was dried for 15 hr in an oven at ca. 110°C and assembled while still warm.
2. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Pentane was distilled from lithium aluminum hydride and stored in bottles under a positive pressure of nitrogen. Pinacolone was distilled from potassium carbonate prior to use, bp 106°C (760 mm).
3. Total-immersion-type low-temperature pentane thermometers (Kessler) were used to measure the temperature in the partial immersion mode. The readings are usually 7–8°C higher compared to the actual temperature under our reaction conditions. The temperatures reported here are all corrected by subtracting 7°C from the thermometer readings. The checkers used a Delta MC-20R digital thermometer (Sato Keiryoki Co., Japan). Temperature control is very important to obtain a satisfactory yield.
4. The temperature was controlled by moving a liquid-nitrogen-filled Dewar flask up and down with a lab jack.
5. Carbon monoxide, purchased from Matheson Gas Products or Nihon Sanso Co., was used without further purification.
6. Butyllithium in pentane was purchased from Alfa Products, Morton/Thiokol, Inc. and was titrated by

the method of Gilman and Cartledge.[2] The checkers used a 1.56 *N* hexane solution purchased from Mitsuwa Chemical Co. after titration by the Kofron–Baclawski procedure.[3]

7. Orion Research Inc., Model 341 was used. Alternatively, if a syringe pump is not available, the organolithium solution may be added manually by syringe, very slowly and at a reasonably constant rate.

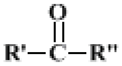
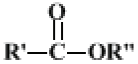
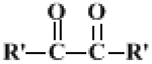
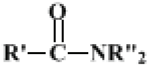
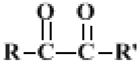
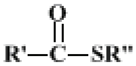
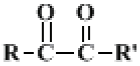
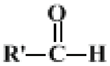
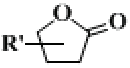
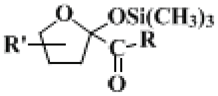
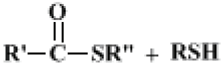
8. GLC conditions were as follows: 2-m × 5-mm glass column packed with 20% silicone SE-30 on Chromosorb W AW; gas flow: 0.8 kg/cm^2; temperature program 100–275°C at 6°C per minute; retention times: n-C_9H_{20}, 4.9 min; 3-hydroxy-2,2,3-trimethyloctan-4-one, 12.5 min. Spectral properties of the product are as follows: IR(thin film, NaCl) cm^{-1}: 3350–3580 (br, s, ν_{OH}), 2985 (s), 2872 (m), 1695 (s, $\nu_{C=O}$), 1480 (m), 1465 (s), 1462 (s), 1395 (s), 1220 (m), 1170 (m), 1125 (s), 1040 (s), 990 (m), 910 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 0.92 (t, 3 H, $J = 7.3$, CH_2-CH_3), 0.97 (s, 9 H, $C(CH_3)_3$), 1.33 (tq, 2 H, $J = 7.3, 7.3$, CH_2=CH_3), 1.34 (s, 3 H, CH_3), 1.60 (tt, 2 H, $J = 7.6, 7.6$, $CH_2CH_2C(O)$), 2.52 (dt, 1 H, $J = 15.2, 7.6$, a proton of $CH_2C(O)$), 2.60 (dt, 1 H, $J = 15.2, 7.6$, a proton of $CH_2C(O)$), 3.64 (s, 1 H, OH).

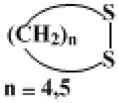
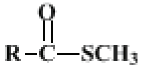
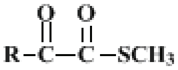
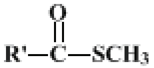
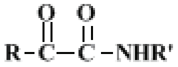
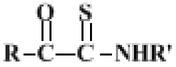
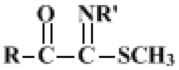
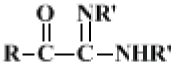
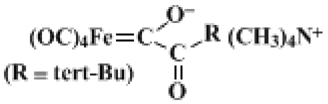
3. Discussion

In situ generated acyllithium reagents not only can acylate ketones, but also can acylate aldehydes,[11] esters,[12] lactones,[15] isocyanates and isothiocyanates,[17] carbodiimides,[18] carbon disulfide and carbonyl sulfide,[16] organic disulfides,[14] and trialkylchlorosilanes.[10] For reviews, see [4] and [13] This direct, nucleophilic acylation procedure, when applicable, makes unnecessary the usually applied method of "masked acyl anion equivalents" for nucleophilic acylation.[5] [6] [7] [8] The present procedure finds only very limited applicability in the case of aryllithium/CO systems,[9] but seems to be generally applicable to alkyllithium systems.

TABLE I

LOW-TEMPERATURE, IN SIRU, DIRECT NUCLEOPHILIC ACYLATION WITH THE RLi/CO REAGENT

Electrophile	Quench Reagent	Product	Reference
$(CH_3)_3SiCl$	H_2O	 $(CH_3)_3Si-\overset{O}{C}-R$	[10]
 $R'-\overset{O}{C}-R''$	H_2O	 $R-\overset{O}{C}-C(OH)R'R''$	[11,12]
 $R'-\overset{O}{C}-OR''$	H_2O	 $R'-\overset{O}{C}-\overset{O}{C}-R'$	[12]
 $R'-\overset{O}{C}-NR''_2$	H_2O	 $R-\overset{O}{C}-\overset{O}{C}-R'$	[13]
 $R'-\overset{O}{C}-SR''$	H_2O	 $R-\overset{O}{C}-\overset{O}{C}-R'$	[14]
 $R'-\overset{O}{C}-H$	H_2O	 $R'-\overset{O}{C}-CH(OH)R'$	[11]
	$(CH_3)_3SiCl$		[15]
R'SSR'	H_2O	 $R'-\overset{O}{C}-SR'' + RSH$	[14]

	CH_3I	 $R'-\overset{O}{\overset{\|}{C}}-S(CH_2)_nSCH_3$	14
S_8	CH_3I	 $R-\overset{O}{\overset{\|}{C}}-SCH_3$	14
COS	CH_3I	 $R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-SCH_3$	16
CS_2	CH_3I	 $R'-\overset{O}{\overset{\|}{C}}-SCH_3$	16
R'NCO	H_2O	 $R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-NHR'$	17
R'NCS	H_2O	 $R-\overset{O}{\overset{\|}{C}}-\overset{S}{\overset{\|}{C}}-NHR'$	17
	CH_3I	 $R-\overset{O}{\overset{\|}{C}}-\overset{NR'}{\overset{\|}{C}}-SCH_3$	17
R'N=C=NR'	H_2O	 $R-\overset{O}{\overset{\|}{C}}-\overset{NR'}{\overset{\|}{C}}-NHR'$	18
$Fe(CO)_5$		 $(OC)_4Fe{=}C(O^-)-C(=O)-R\;(CH_3)_4N^+$ (R = tert-Bu)	19

References and Notes

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

benzophenone ketyl

$(CH_3)_3SiCl$

CH_3I

S_8

COS

CS_2

$Fe(CO)_5$

potassium carbonate (584-08-7)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

carbon monoxide (630-08-0)

nitrogen (7727-37-9)

Pinacolone (75-97-8)

sodium (13966-32-0)

carbon disulfide (75-15-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

3-Hydroxy-2,2,3-trimethyloctan-4-one,
4-Octanone, 3-hydroxy-2,2,3-trimethyl- (85083-71-2)

carbonyl sulfide