

ADDITION OF GRIGNARD REAGENTS TO O-TRIMETHYLSILYLATED CYANOHYDRINS:
SYNTHESIS OF ACYLOINS

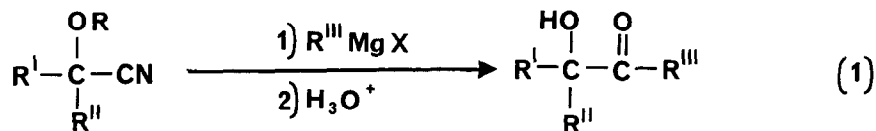
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Abstract: Grignard reagents have been found to react readily with O-trimethylsilylated cyanohydrins to afford, after acid hydrolysis of intermediates, good yields of acyloins.

The utility of α -hydroxyketones (acyloins) in organic chemistry is attested to by the great variety of methods which have been developed for their preparation.¹ Although the sodium/chlorotrimethylsilane induced "acyloin condensation"² of esters and the cyanide catalyzed "benzoin condensation"³ of aromatic aldehydes are useful for the respective syntheses of symmetrical acyloins and benzoin, the preparation of unsymmetrical α -hydroxyketones is usually more difficult. Of the many pertinent synthetic methods, few have the dual advantages of simplicity and generality.

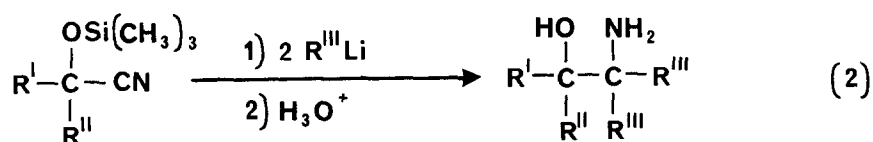
One established^{3,4} method for the preparation of acyloins involves the addition of a Grignard reagent to a cyanohydrin (eq. 1, R = H). Although in theory only two equivalents of



the Grignard reagent are required, in practice it is often necessary to employ a much larger excess; even so, acyloin yields are often low^{3,4}. Some improvement may be realized by protecting the hydroxyl group of the cyanohydrin as the tetrahydropyranyl or ethoxyethyl ether⁵. However, both the blocking and deblocking reactions occur with variable yields and involve extra steps.

We have now found that the addition of Grignard reagents to O-trimethylsilylated cyanohydrins⁶ provides a simple and general preparation of acyloins (eq. 1, R = (CH₃)₃Si). This procedure has several advantages: 1) O-trimethylsilylated cyanohydrins can be prepared⁷ in high yield and purity from a variety of aldehydes and ketones; 2) only a small (10-15%) excess of the Grignard reagent is used; and 3) in many cases most of the acyloin product separates from the aqueous layer from the reaction work-up in a very pure form, so product isolation involves simple filtration.⁸

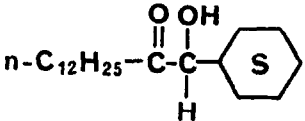
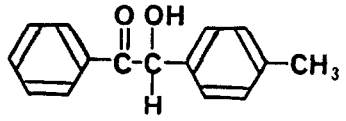
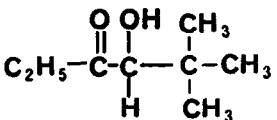
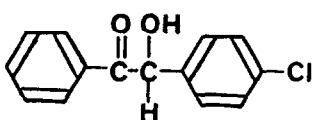
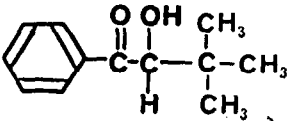
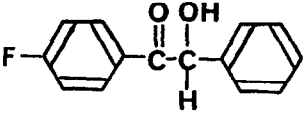
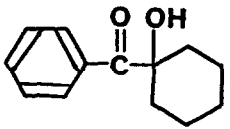
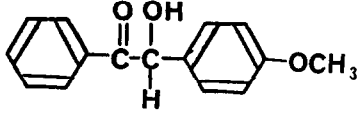
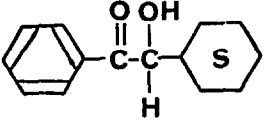
The reaction of organolithium reagents with O-trimethylsilylated cyanohydrins takes a different course. Attempts to react only one equivalent of n-butyl or phenyllithium with O-silylated cyanohydrins led to complex reaction mixtures containing little or no acyloin.⁹ However, the reaction of two equivalents of an organolithium reagent with O-silylated cyanohydrins has been reported¹⁰ as a method for the preparation of β -aminoalcohols (eq. 2).



The following procedure for the preparation of 4'-fluorobenzoin¹¹ is representative. A solution of 4-fluorophenylmagnesium bromide was prepared under argon from 4-bromofluorobenzene (5.5 ml, 50 mmol) and magnesium turnings (1.34 g, 55 mmol) in 75 ml of ether. To this stirred solution was added dropwise a solution of the O-trimethylsilylated cyanohydrin of benzaldehyde (9.0 g, 44 mmol) in 75 ml of ether. Stirring at room temperature was continued for 2 hours after the addition was complete, then the reaction mixture was cooled for 15 minutes in an ice bath. The reaction mixture was then poured onto 500 g of ice containing 20 ml of concentrated H₂SO₄. The layers were separated, the ether layer extracted twice with 100 ml portions of a 10% aqueous HCl solution, and the aqueous layers combined. After standing overnight at room temperature, a solid had crystallized from the water. Filtration and drying afforded 6.3 g of 4'-fluorobenzoin. The ether layer from the work-up was washed with brine, dried over MgSO₄, filtered and solvent evaporated to leave 6.51 g of an oily solid. ¹H-NMR analysis of this material indicated it to be a mixture of the desired benzoin and the O-trimethylsilylated benzoin (molar ratio 30:70). This mixture was dissolved in 75 ml of MeOH, one ml of a 10% aqueous HCl solution was added, and the solution allowed to stand at room temperature overnight. Solvent was then evaporated to leave a tan solid which was combined with the material from the filtration. Recrystallization from aqueous MeOH gave 7.99 g (79%) of 4'-fluorobenzoin, m.p. 108-109^o C; IR (Nujol) ν_{max} 3500, 1660, 1580, 1500, 1450, 1360, 1330, 970 cm⁻¹; ¹H-NMR (CDCl₃) δ 7.98 (2H, m), 7.4 (5H, s), 7.1 (2H, t, J=8Hz), 5.93 (1H, d, J=8Hz), and 4.56 (1H, d, J=8Hz). Anal. Calcd. for C₁₄H₁₁FO₂: C, 73.0; H, 4.8. Found: C, 72.8; H, 4.7.

Some representative results are presented in Table 1. It is apparent that the reaction of Grignard reagents with O-trimethylsilylated cyanohydrins constitutes a simple and versatile procedure for the preparation of aliphatic acyloins, "mixed" aromatic-aliphatic acyloins, and benzoins. Furthermore, these results extend the usefulness of O-silylated cyanohydrins in organic chemistry.

TABLE 1

ACYLOIN	YIELD, % ^a	BENZOIN	YIELD, % ^a
	66 ^{b,c}		69 ^h
	55 ^d		60 ⁱ
	42 ^e		79
	61 ^f		77 ^j
	73 ^g		

a) Yield of purified product. All compounds have been fully characterized including IR, NMR, combustion analysis and/or high resolution mass spectroscopy. b) This acyloin was the only example in this table which was obtained exclusively from the organic phase of the reaction work-up (see experimental example). c) bp 170-175°C (0.15 mm) (kugelrohr distillation); IR (film) ν_{max} 3450, 2900, 1700, 1450, 1440 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 4.08 (1H, m), 3.8 (1H, m), 2.48 (2H, t, J=7Hz) 2.0 - 1.0 (31H, 2m), and 0.9 (3H, m). d) bp 83-85°C (17 mm) [lit.¹², bp 100°C (17 mm)]. e) Pure product was obtained directly from the aqueous layer from the reaction work-up (see experimental example). NMR spectrum was in accord with literature¹³ data. f) mp 46-48°C. [lit.¹⁴, mp 48-49°C]. g) mp 89.5 - 90°C; IR (KBr) ν_{max} 3495, 1690, 1465, 1290, 1235, 1165, 1125, 840, 725, 695 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 8.04 - 7.85 (2H, m), 7.77 - 7.40 (3H, m), 4.97 (1H, s), 3.1 (1H, br s), and 1.96 - 0.8 (11 H, 2 m). Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$: C, 77.0; H, 8.3. Found: C, 76.7; H, 8.1. h) mp 117-117.5°C [lit.¹⁵, mp 116°C]. i) mp 111-112°C [lit.¹⁵, mp 116-117°C. j) mp 87-89°C [lit.³, mp 89°C].

References and Notes

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- (11) Nomenclature for substituted benzoin is somewhat in disarray in the literature. We have adopted the nomenclature system in the "CRC Handbook of Chemistry and Physics, 63rd Edition"; CRC Press, Inc.: Boca Raton, 1982; p. C-584, in which the primed numbered substituents are located on the benzoyl ring.
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