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ADDITION OF ORGANOMAGNESIUM REAGENTS TO CYANOHYDRIN-O-SILYL ETHERS: AN EFFICIENT AND FLEXIBLE SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED ACYLOINS

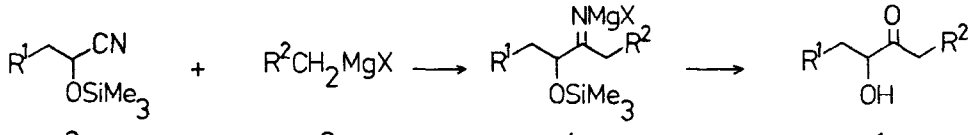
Melvyn Gill*, Milton J. Kiefel and Deborah A. Lally
Department of Organic Chemistry, University of Melbourne, Parkville, Victoria, 3052, Australia.

Abstract: Acyloins are prepared in high yields via reaction between Grignard reagents and O-trimethylsilyl ethers of aldehyde cyanohydrins: the method is particularly useful for the preparation of discrete acyloins in which the substituents are unsymmetrically disposed about the α-hydroxyketone moiety.

Acyloins (α-hydroxyketones) are valuable starting materials for the preparation of a wide variety of heterocycles[1] and carbocyclic compounds.[2] As part of a synthetic project we required several acyloins of the type 1 in which R^1 and R^2 were different aryl residues and in which the relative position of the substituents about the α-hydroxyketone moiety was unequivocally defined.

Among the most efficient general routes to α-hydroxyketones are the classical acyloin condensation of esters[3,4] and the biomimetic thiazolium salt catalysed coupling of aldehydes.[5] Unfortunately, both of these processes are severely limited in their application to the synthesis of unsymmetrically substituted acyloins by cross-coupling reactions and consequent lack of regiocontrol.[6]

We report here a chemically efficient and versatile route to acyloins which proves particularly useful for the synthesis of compounds of the type 1 ($R^1 \neq R^2$).



2 3 4 1

The success of the method relies on the fact that reaction of cyanohydrin-O-TMS ethers of the type 2 (1 eq) with Grignard reagents (3) (1.5 eq) in ether at reflux affords the intermediates (4) which do not suffer attack by the organometallic reagent.[7] Furthermore, subsequent hydrolysis of 4 (2M HCl, r.t., 16h) is not accompanied by any equilibration, e.g., 1a ⇌ 1b,[8] and after chromatography the acyloins are obtained in high yields. The method has proven effective for the synthesis of a range of unsymmetrical acyloins (Table).[8]

Our results extend the synthetic utility of cyanohydrin-O-silyl ethers,

which have been employed to date almost exclusively in a nucleophilic capacity.[9] Their effective role as electrophiles has been limited hitherto to reductive[10] and hydrolytic[11] transformations (see also ref. 7).

The acyloin synthesis described herein is superior in efficiency and flexibility to methods based on acyl carbanion chemistry,[12] particularly in those cases where the aldehyde component or the acyloin itself is unduly sensitive.[13]

Entry	Cyanohydrin Derivative[a] R^1 in 2	Grignard Reagent	Acyloin 1 R^1	Acyloin 1 R^2	Yield (%)[b]
a	Ph	4-MeO-$C_6H_4CH_2MgCl$	Ph	4-MeO-C_6H_4	79
b	4-MeO-C_6H_4	$PhCH_2MgCl$	4-MeO-C_6H_4	Ph	77
c	3,4-$(MeO)_2$-C_6H_3	$PhCH_2MgCl$	3,4-$(MeO)_2$-C_6H_3	Ph	79
d	3,4-$(MeO)_2$-C_6H_3	4-MeO-$C_6H_4CH_2MgCl$	3,4-$(MeO)_2$-C_6H_3	4-MeO-C_6H_4	78
e	Ph	CH_3CH_2MgBr	Ph	CH_3	85
f	CH_3CH_2	$PhCH_2MgCl$	CH_3CH_2	Ph	78
g	4-MeO-C_6H_4	n-C_4H_9MgBr	4-MeO-C_6H_4	n-C_3H_7	79
h	n-C_3H_7	4-MeO-$C_6H_4CH_2MgCl$	n-C_3H_7	4-MeO-C_6H_4	78
i	Ph	CH_3MgI	Ph	H	83
j	H	$PhCH_2MgCl$	H	Ph	79

a) Prepared in near quantitative yield from the corresponding aldehyde and cyanotrimethylsilane.
b) Refers to yield of isolated, chromatographically and spectroscopically homogeneous material.

Our application of the acyloins 1a - 1d to the synthesis of several fungal metabolites is proceeding and will be reported in the full paper.

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