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TOWARDS DIDEOXYNUCLEOSIDES: THE SILICON APPROACH

Derek H. R. Barton, Doo Ok Jang and Joseph Cs. Jaszberenyi*

Department of Chemistry, Texas A&M University, College Station, Texas, 77843

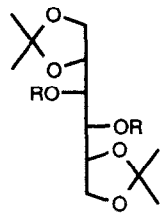
Abstract: Dixanthates, formed from *vic*-diols, can easily be transformed to the corresponding olefins with diphenylsilane in a new, high-yielding radical reaction.

The modification of biologically important Natural Products by deoxygenation and deamination is an important process in partial or total synthesis. The role of modified nucleosides in the fight against AIDS increases the importance of these synthetic procedures.

Most of the methods available for deoxygenation of sensitive biomolecules are based on radical chemistry[1]. There are, however, other, non-radical methods for transforming *vic*-diols to olefins[2]. The radical chemistry of the Barton-McCombie reaction[3] has been developed into a method of synthesis of olefins (dideoxy-didehydro-*vic*-diols). This was demonstrated[4] soon after the original publication on deoxygenation of secondary alcohols. A thiocarbonyl compound reacts easily with suitable radicals. In the first steps a monodeoxy carbon radical is formed; this then undergoes rapid radical beta-elimination resulting in the formation of the olefin. In order to overcome the problems associated with the use of tin compounds, there have been recent attempts to employ silicon hydrides in various radical reactions[5]. We have shown[6] that diphenylsilane is a good, commercially available substitute for tributyltin hydride in radical deoxygenations. Combined with the use of new thionocarbonates[7] high yields were achieved without the use of toxic tin derivatives[6]. We have assumed that the application of this diphenylsilane-based radical chemistry to the relatively cheaply and easily formed vic-dixanthates would furnish a simple radical method for the formation of olefins (and thus, 2',3'-didehydro-2',3'-dideoxynucleosides)[8].

Indeed, most of the dixanthates studied (Table 1, Scheme 1) gave the corresponding olefins in high yields. Thus, this method is of promise in obtaining bioactive olefins (carbohydrates, nucleosides) and (after hydrogenation) dideoxy compounds more easily than before. Another advantage of this method is that it is easier to purify and isolate the products after the radical reaction.

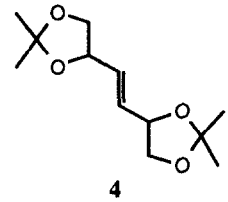
As a model, *meso*-hydrobenzoin (PhCH(OH)CH(OH)Ph, **1a**) was transformed to the corresponding dixanthate (PhCH(OC=SSMe)CH(OC=SSMe)Ph, **1b**) and deoxygenated to stilbene (PhCH=CHPh, **2**) in boiling dioxane with diphenylsilane (2.0 eq.) and azobisisobutyronitrile (AIBN) (0.5 eq.) (62-63%). The carbohydrate and nucleoside derivatives, however, gave much higher yields (Table 1).



3

a: R = H

b: R = CSSMe



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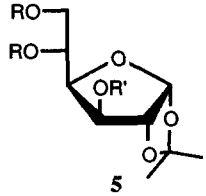
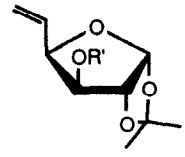


5

a : R = R' = H

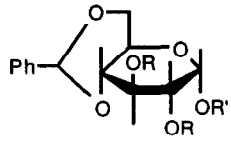
b : R = H, R' = Me

c : R = CSSMe, R' = Me



6

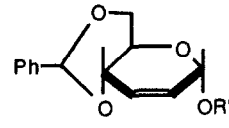
R' = Me



7

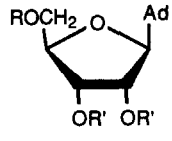
a : R = H, R' = Me

b : R = CSSMe, R' = Me



8

R' = Me

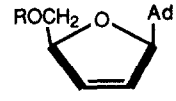


9

a : R = R' = H (adenosine)

b : R = Bu^tMe_2Si-, R' = H

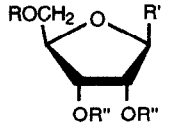
c : R = Bu^tMe_2Si-, R' = CSSMe



10

R = Bu^tMe_2Si-

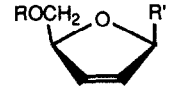
Ad = adenine



11

a : R = R" = H, R' = Uracil (uridine)

b : R = Bu^tMe_2Si-, R" = CSSMe, R' = MeU (N-methyl-uracil)



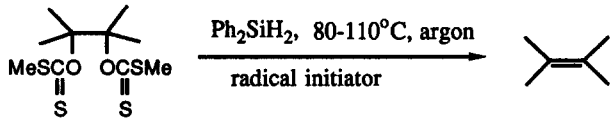
12

R' = MeU

R = Bu^tMe_2Si-

Scheme 1

Table 1 Synthesis of Olefins from *vic*-Dixanthates with Diphenylsilane.



Starting dixanthate	Product	Reagent (eq.) / Initiator (eq.)	Time (hr)	Solvent (boiling)	Yield (%)	Notes
1b	**2**	2.0 / 0.5 AIBN	1.0	dioxane	63[d] / 62[a]	a: inverse addition
3b	**4**	1.1 / 1.1 Et_3B[b]	0.5	benzene	66[d]	b: initiated with 1.1 eq O_2 (as dry air)
		2.2 / 1.2 AIBN	6.0	toluene	92[c]	c: by NMR
		2.2 / 1.8 AIBN	4.5	toluene	100[c]	
5c	**6**	2.2 / 1.0 AIBN	2.5	toluene	88[d]	d: isolated yield
7b	**8**	2.0 / 1.0 $(PhCOO)_2$	2.5	toluene	95[c]	
		2.0 / 2.0 AIBN	5.0	toluene	94[d] (97[c])	
		2.0 / 2.0 AIBN	3.3	dioxane	97[c]	
9c	**10**	2.0 / 0.8 AIBN	1.33	toluene	95[c] (90[d])	
		2.0 / 0.4 $(PhCOO)_2$	40 min.	toluene	93[c]	
11b	**12**	2.0 / 0.8 AIBN	1.33	toluene	97[c] (91[d])	

Typical procedure:

To a solution of the starting dixanthate **7b** (0.1850 g, 0.4 mmol) in dry toluene (3 ml), diphenylsilane (147 µl, 0.8 mmol) was added under argon.Then the solution was brought to boil and treated with 300 µl portions of a solution of AIBN in toluene at 30 minutes intervals (262.4 mg AIBN was dissolved in 6.0 ml dry toluene). The reaction was monitored by tlc. When the reaction was complete (Table 1) the solvent was evaporated in vacuum and the olefin isolated by column chromatography on silica gel (eluent: CH_2Cl_2) giving 93.5 mg (94%) of **8**[9].

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9. All the starting materials and products were characterized by comparison of their physical and spectral data to those of the authentic samples.

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