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An Efficient Method for the Synthesis of Aromatic C-Nucleosides

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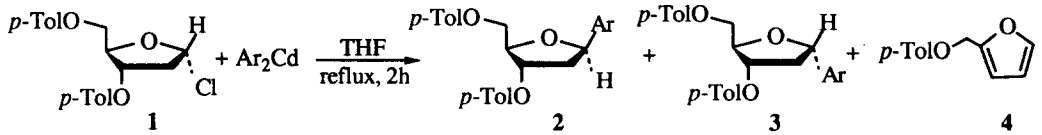
Abstract: Reaction of diarylcadmium or diarylzinc reagents with 1,2-dideoxy-3,5-di-*O*-*p*-toluoyl-1-chloro-α-D-ribofuranose affords 3,5-di-*O*-protected aromatic C-nucleosides in good yields.

As part of our ongoing program in the study of macromolecular recognition of RNA and DNA, we recently embarked on a project involving the use of nonpolar aromatic C-nucleosides as specific biophysical probes of noncovalent interactions.[1] Synthetic strategies have been developed for certain C-nucleosides[2] having typical heteroaromatics as the base moiety, such as pyrroles,[3] furans and thiophenes,[4] pyridines[5] and imidazoles,[6] as well as for the synthesis of several naturally occurring ribofuranosyl C-nucleosides, such as pseudouridine,[7] thiazofurin,[8] formycin and pyrazofurin.[9] However, good methods for attaching fully carbocyclic aromatic moieties to a deoxyribosyl or ribosyl sugar are lacking.[10] Millican and coworkers[11] reported a two-step procedure to prepare 1,2-dideoxy-3,5-di-*O*-benzoyl-1-phenyl-β-D-ribofuranose in 20% yield. In a study of ribosyl analogs of chloramphenicol, a protein synthesis inhibitor, Klein and coworkers[12] prepared β-D-ribofuranosylbenzene in poor yield. Recently we described the coupling of aryl Grignard reagents to an α-chloro substituted deoxyribose derivative to obtain the desired C-nucleosides in modest 20-25% yields.[1]

In an attempt to develop an improved method for the synthesis of such aromatic C-nucleosides we considered various alternative organometallic reagents for the carbon-carbon bond formation. We found that diarylcadmium and diarylzinc reagents undergo facile reactions with 1,2-dideoxy-3,5-di-*O*-*p*-toluoyl-1-chloro-α-D-ribofuranose (**1**)[13] to afford the C-nucleosides **2** and **3** (SCHEME I) in high yields.

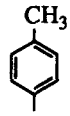
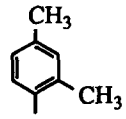
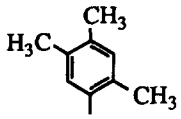
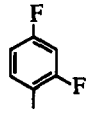
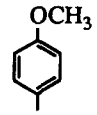
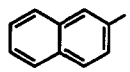
SCHEME I



1 **2** **3** **4**

In a typical experimental procedure, finely ground and oven-dried $CdCl_2$ (CAUTION)[14] or $ZnCl_2$ (0.6 mmol) was added to a freshly prepared solution of aryl Grignard reagent (1.2 mmol) in 2 mL of anhydrous THF under dry nitrogen atmosphere. After heating the mixture under gentle reflux for 2-3 h, a solution of **1** (0.5 mmol) in 3 mL of anhydrous THF was introduced at room temperature and the reaction was completed by refluxing the mixture for a further 2 h. Products were isolated by standard work-up and chromatographic procedures.[15] Yields of the desired β-anomers **2a-d**, **2f** and **2g** were consistently high (54-69%) (Entries 1-4 and 6, 7, Table 1), accompanied by 9-20% of the corresponding α-anomers **3a-d**, **3f** and **3g**. The diastereoselectivities (β /α) fall in the range 2.9-7.6 : 1, and the isomers are easily separated by column chromatography.

Table 1 : Reaction of chlorosugar **1** with various diarylcadmium species

Entry	Ar	Yield[a] : β-anomer **2**	α-anomer **3**	furfuryl *p*-toluate (**4**)	β/α
1		**2a**, 55%	**3a**, 14%	_[b]	3.9
2		**2b**, 58%	**3b**, 20%	_[b]	2.9
3		**2c**,65%	**3c**, 15%	_[b]	4.3
4		**2d**, 68%	**3d**, 9%	_[b]	7.6
5		**2e**,[c] 9% **2e**,[d] 48%	**3e**, _[b] **3e**,13%	42% 25%	 3.7
6		**2f**, 69%	**3f**, 14%	_[b]	4.9
7		**2g**, 54%	**3g**, 18%	_[b]	3.0

a) Isolated yields. b) No product isolated. c) THF, reflux. d) 40 °C. Spectrometric data of all compounds were in full accord with the structures proposed.

However, the diarylcadmium derived from 1-bromo-2,4-difluorobenzene under the above conditions provided the β-anomer **2e** in only 9% yield (Entry 5[c]), the major product of this reaction being furfuryl *p*-toluate (**4**) (42% yield). When the reaction was instead performed at 40 °C, there was an increased yield (48%) of **2e** and formation of **4** was significantly lowered (Entry 5[d]). In a separate experiment, the reactivity of **1** alone was studied and it was found that when heated under reflux in THF for 6 h, **1** underwent dehydrochlorination followed by aromatization furnishing furfuryl *p*-toluate (**4**) in 70% isolated yield. It would thus seem that the metallo-difluorobenzene species is either less reactive or is undergoing a competing reaction, resulting in its loss at higher temperature.

Electron-donating or neutral aromatic species underwent reaction with similar efficiencies (Table 1). The electron-deficient para-nitrobromobenzene did not form a Grignard in our hands. The high yields of the β-anomers observed for the reactions in Table 1 are consistent with preponderant direct S_N2 reaction occurring at the anomeric carbon center. Formation of the α-anomers in minor amounts is possibly the result of partial formation of an oxonium S_N1 intermediate which then reacts with the organometallic reagents with low diastereoselectivity.

Among various solvents we examined (Table 2), ethereal solvents appeared to be well suited; THF was preferred from the point of view of solubilities of the reactants. Examination of several metallophenyl species (Table 3) indicate that while cadmium and zinc reagents worked equally well, phenylmagnesium bromide provided only a moderate yield of **2a**. Similarly, reactions of some of the other arylmagnesium derivatives with **1** afforded products in only 10-20% yields (data not shown). With aryllithium and arylmercury reagents, the desired C-nucleosides could not be prepared; in those cases, isolated product was solely furfuryl *p*-toluate (**4**).

Table 2 : Reaction of Ph_2Cd with **1**

Solvent	Yield[a] : **2a**	**3a**
THF	55%	14%
Benzene	47%	18%
Et_2O	56%	16%

a) Isolated yields.

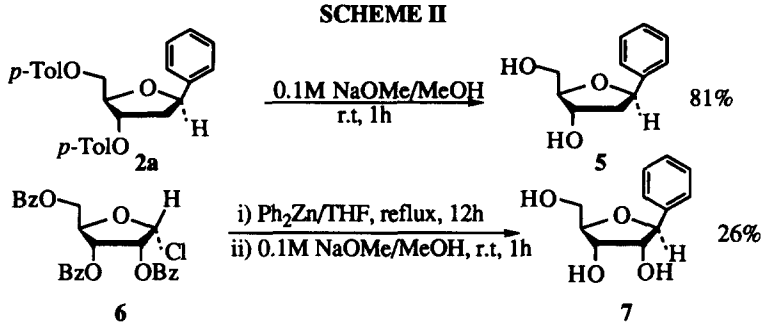
Table 3 : Reaction of aryl organometallics with **1**

Reagents	Yield[a] : **2a**	**3a**	**4**
PhLi	_[b]	_[b]	20%
PhMgBr	30%	15%	25%
Ph_2Cd	56%	14%	_[b]
Ph_2Zn	61%	11%	_[b]
Ph_2Hg	_[b]	_[b]	49%

a) Isolated yields. b) No product isolated.

The various 3,5-di-*O*-*p*-toluoyl nucleosides **2a-g** and **3a-g** can be conveniently deprotected, as is exemplified in the facile conversion of **2a** to **5** in 81% isolated yield, by treatment with 0.1M NaOMe/MeOH at room temperature for 1 h (SCHEME II). When applied to the α-chloro ribose derivative **6**, reaction with diphenylzinc in THF-reflux for 12 h was quite clean, but proceeded with poor conversion, and the deprotected nucleoside product **7** was obtained in a modest 26% overall yield after silica gel chromatography. Reaction of diphenylcadmium with **6** did not produce the desired product. Thus, this method may be useful in preparation of C-riboside derivatives, but it appears to be better suited for the preparation of deoxyribo-C-nucleosides.

SCHEME II



In conclusion, the use of diarylcadmium or diarylzinc reagents allows an efficient synthesis of aromatic C-nucleosides in the 2-deoxyribo- series with good diastereoselectivity. The method is mild, being compatible with base-labile ester functionality. The chlorosugar precursor is readily prepared on large scales without chromatography, and many bromoaryl precursors are commercially available or easily prepared. This method may therefore be of considerable practical utility in the preparation of modified nucleosides.

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14. Cadmium chloride is a toxic cancer suspect agent; care must be exercised in handling.
15. THF was removed under reduced pressure and the residue treated with cold dil. aq. AcOH (10 mL) to dissolve all precipitated solids followed by extraction of product into EtOAc (30 mL). Chromatography was performed using 'Baker' Silica Gel (40 μm), with 10-20% EtOAc / hexanes as eluent.

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