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Stereoselective Organozinc Addition Reactions to 1,2-Dihydropyrans for the Assembly of Complex Pyran Structures

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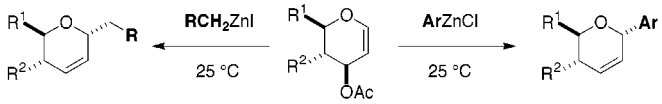
ABSTRACT



Nucleophilic addition of organozincs to 1,2-dihydropyranyl acetates represents a new, broadly defined method for the stereocontrolled synthesis of α-substituted pyrans. The products obtained from this process are versatile materials that can be used to construct *C*-glycosides and other functionalized pyran structures of import. The occurrence of pyranyl groups in both natural products and therapeutically active agents confers added value to the studies described herein.

Substituted pyrans are ubiquitous structural elements in natural products having important biological activities.[1] One strategy used frequently for the synthesis of these heterocycles conjoins carbon nucleophiles with monosaccharide-based starting materials.[2,3] Though highly valuable, this approach for pyran assembly is generally restricted to certain nucleophilic structural types.[1b,2c] We have devised, therefore, a new process that makes possible the facile coupling of differentially substituted organozinc reagents with 1,2-dihydropyranyl acetate derivatives (Figure 1). This method is particularly advantageous for pyran synthesis because of the availability of zinc species from organohalides and the compatibility of such carbon nucleophiles with diverse functional groups.[4] The range of accessible 1,2-dihydropyran starting materials from either monosaccharides or through highly effective hetero-Diels−Alder protocols further augments this chemistry.[5] The versatile 2,3-unsaturated products obtained from these organozinc addition reactions are converted readily into *C*-glycosides or other pyran structures of import. Current widespread interest in such compounds as biochemical probes or as potential therapeutics provides added justification for the studies described herein.

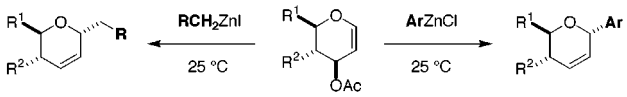


Figure 1. Organozinc additions for pyran synthesis.

Lewis acid mediated Ferrier reactions of glycals with carbon nucleophiles are performed most commonly with

(1) (a) Bycroft, B. W. *Dictionary of Antibiotics and Related Substances*; Chapman and Hall: London, 1988. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55.

(2) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Tarrytown, NY, 1995; Vol. 13. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995. (c) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153−175. (d) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron* **1996**, *52*, 6397−6408. (e) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20.

(3) For some leading references on 2,6-disubstituted pyran synthesis from acyclic precursors, see: (a) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955−959. (b) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837. (c) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, 3145−3163. (d) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093.

(4) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford University Press: Oxford, 1999.

(5) (a) Ooi, T.; Maruoka, K. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, pp 1237−1254. (b) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482−10483. (c) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. (d) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246−1255.

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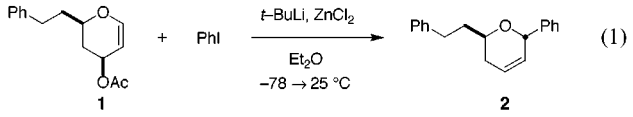
arenes, silyl enol ethers, and allylmetal reagents.[2] Monoalkylzinc species can be made to react with tri-*O*-acetyl-D-glucal, but only in combination with excess molar equivalents of promoters such as $BF_3{\cdot}OEt_2$ or TMSOTf (1−6 equiv).[6] These reactions afford moderate yields of *C*-glycoside products with α,β-anomeric ratios ranging from 2 to 9:1. To our knowledge, examples of arylzinc couplings with 1,2-dihydropyran derivatives have not been described.[7−9] We wished to formulate a method for organozinc additions that: 1) enables use of both aryl- and alkyl-derived zinc reagents in the absence of strongly reactive Lewis acids; 2) occurs with dihydropyran substrates other than, but still including, those prepared from sugars; and 3) gives products with high α/β anomeric stereocontrol.[10] In accord with these objectives, a lead discovery was made through preliminary experiments with acetate **1** (eq 1). Mixing of this compound with an Et_2O

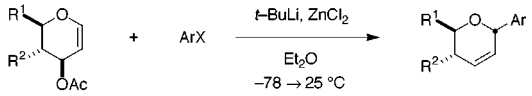


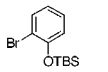
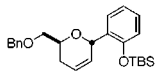
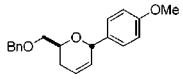
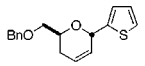
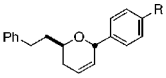
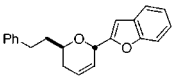
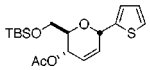
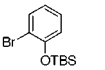
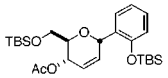
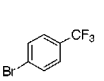
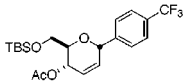
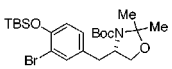
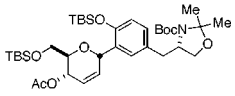
(1)

solution of PhZnCl (PhLi, $ZnCl_2$) led to rapid consumption (<1 h, 25 °C) of the starting materials and furnished the desired target **2** with >10:1 α/β selectivity in 88% yield.[11,12] Interestingly, the choice of Et_2O as solvent proved critical to the success of this coupling process. Reactions performed in THF and DME gave only small amounts of **2** after lengthy reaction times (>16 h).

A series of substituted phenyl- and heteroarylzinc reagents has been tested in reactions with three structurally disparate dihydropyrans (Table 1). In all cases, the organozinc was prepared at −78 °C by transmetalation of the lithiated aryl species with $ZnCl_2$. Subsequent coupling reactions performed at 25 °C smoothly afforded the α-anomeric product as the predominant stereoisomer (6 to 10:1 ds) in isolated yields of 66−88%. Aryl substitution with either electron-withdrawing or -donating groups appears to have little influence on coupling rates or efficiencies. Importantly, the presence of

Table 1. Arylzinc Additions to 1,2-Dihydropyran Substrates



entry	ArX	product	yield[a]
1			82
2			81
3			74
4			R = CF_3 78 = OMe 88 = F 85
5			66[b]
6			69[c]
7			75
8			77
9			75

[a] Reported product yields are on diastereomerically pure material; α,β-anomeric selectivities are estimated to be >10:1 for all entries except 5 and 6. [b] 6:1 α/β ratio based on ^{1}H NMR. [c] 7:1 α/β ratio based on ^{1}H NMR.

silyl ether, ester, and carbamate functional groups is tolerated under the reaction conditions (entries 1, 6−9). Following our protocol, certain heteroaromatic-derived zinc reagents (entries 3, 5, 6) also proved viable as coupling partners. Collectively, these findings highlight a new, facile, and generally applicable method for the synthesis of *C*-arylpyranosides.[2e,13]

We wished to extend further the organozinc−dihydropyran coupling method to include substrates derived from alkylhalides. Studies to this end focused specifically on protocols that would make possible the generation of alkylzinc species with Zn metal, thereby obviating use of lithium carbanion reagents and low-temperature reaction conditions. Methods for Zn insertion into alkylhalides that employ polar, coordinating solvent media (e.g., NMP, DMA), however, proved incompatible with dihydropyran coupling.[4] The reactivity of alkylzinc reagents prepared from Zn(Cu) couple in toluene (65 °C) using only 2 equiv of DMA as an essential additive was therefore examined.[14] Under these conditions with added

(6) (a) Thorn, S. N.; Gallagher, T. *Synlett* **1996**, 185−187. (b) Dorgan, B. J.; Jackson, R. F. W. *Synlett* **1996**, 859−861. (c) Orsini, F.; Pelizzoni, F. *Carbohydr. Res.* **1993**, *243*, 183−189. Also, see: Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711−6714.

(7) Dunkerton has described a unique, Pd-catalyzed coupling of phenyl-, tolyl-, and naphthylzinc chloride with C1-acetoxy 2,3-unsaturated pyrans; see: (a) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89−107. (b) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2814−2816.

(8) Aryl Grignards add to glycal derivatives under Pd- or Ni-catalysis; see: Moineau, C.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1998**, *63*, 582−591. Also, see: Frappa, I.; Sinou, D. *J. Carbohydr. Chem.* **1997**, *16*, 255−276.

(9) For *C*-arylglycoside synthesis with $ArB(OH)_2$, see: Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013−2015.

(10) Dihydropyran starting materials were prepared following published protocols; see: (a) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386. (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413−9436. (c) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082−2089.

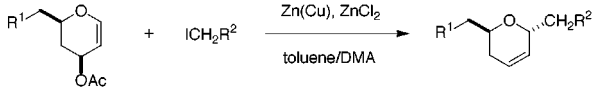
(11) Product stereochemistry was assigned on the basis of ^{1}H NMR coupling constants and ^{1}H NMR NOE measurements; see Supporting Information for details. Formation of the α-anomer as the predominant stereoisomer is consistent with either an S_N1- or S_N2'-type addition.

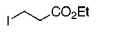
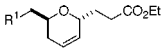
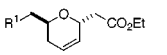
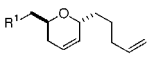
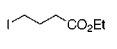
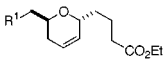
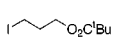
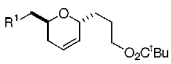
(12) In each entry indicated to have >10:1 diastereoselectivity, trace amounts of the β-pyranoside are identified in the ^{1}H NMR of the unpurified reaction mixture.

(13) *C*-Arylpyranosides have demonstrated therapeutic activity, see: (a) Kirshning, A.; Chen, G.-w.; Dräger, G.; Schuberth, I.; Tietze, L. *Biorg. Med. Chem.* **2000**, *8*, 2347−2354. (b) Kuribayashi, T.; Ohkawa, N.; Satoh, S. *Biorg. Med. Chem. Lett.* **1998**, *8*, 3307−3310.

$ZnCl_2$, the homoenolate, $EtO_2CCH_2CH_2ZnI$ **3**, reacted with **1** to give the C1-alkylated, α-anomeric product in 72% yield (Table 2, entry 1). In subsequent investigations we have

Table 2. Alkylzinc Additions to 1,2-Dihydropyran Substrates

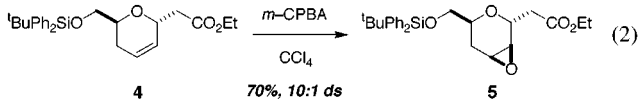


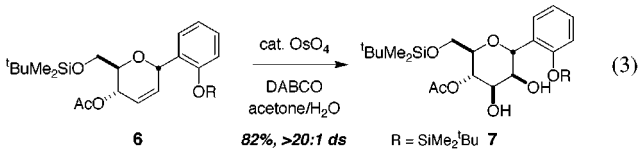
entry	ICH_2R^2	product	R^1	yield[a]
1			CH_2Ph $OSiPh_2{}^tBu$	72 72
2[b]			CH_2Ph $OSiPh_2{}^tBu$	60 60
3			CH_2Ph $OSiPh_2{}^tBu$	63 63
4			CH_2Ph	67
5			CH_2Ph	69

[a] Reported product yields are on diastereomerically pure material; α,β-anomeric selectivities are estimated to be >10:1. [b] Optimal reaction conditions use CH_2Cl_2 as solvent, see Supporting Information for full details.

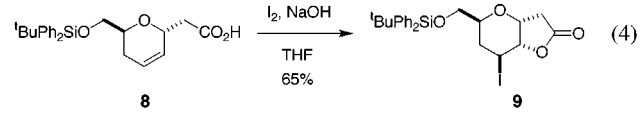
shown that 1,2-dihydropyrans participate in reactions with both ester-derived and unsaturated alkylzinc reagents (entries 2−5). The availability of the starting materials and the simplicity of the experimental protocol make this coupling process particularly well-suited for the preparation of *trans*-2,6-dialkyl-substituted pyrans. Structural units of this type are found in a number of important macrolide antibiotics but, in general, require more indirect methods for preparation.[15]

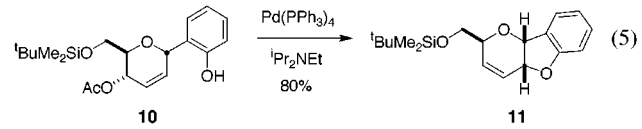
Products obtained from organozinc−dihydropyran coupling are converted into unique tetrahydropyran derivatives following any number of selective protocols. Oxidation reactions with 2,3-unsaturated pyrans afford epoxide **5** or diol **7** with excellent stereocontrol (eqs 2, 3).[16] The latter





compound is representative of aryl *C*-glycoside substructures found commonly in the angucycline family of natural products.[1a,17] In addition, bicyclic products, **9** and **11**, can be assembled efficiently through iodolactonization and palladium-catalyzed π-allyl ring closures (eqs 4, 5). These





heterocycles can function as useful scaffolds for creating added molecular complexity and thus may find multiple applications in synthesis.

Nucleophilic addition of organozincs to dihydropyranyl acetates represents a new, broadly defined method for stereocontrolled α-pyran synthesis. The advantages of this process for the preparation of substituted tetrahydropyrans derive from both the salient properties of zinc carbanions and the flexibility of the unsaturated hydropyran products for further functional group manipulation. Continued efforts to exploit organometallic-based reaction strategies for assembling complex cyclic ether and cyclic amine derivatives are ongoing.

Acknowledgment. Mr. Patrick Lindner is thanked for his help with the preparation of dihydropyran starting materials. D.P.S. is an NIH postdoctoral fellow. J.D.B. gratefully acknowledges Merck Research Laboratories, Pfizer, and Stanford University for generous support.

Supporting Information Available: General experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010273E

(14) A related protocol for alkylzinc formation has been described; see: Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5559−5562.

(15) Examples of such natural products include: (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027−11028. (b) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847−868. (c) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5351−5354.

(16) Stereochemical assignments based on ^1H NMR coupling constant and NOE data.

(17) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103−137.