

DIRECT ANOMERIC SUBSTITUTION OF PYRANYL ESTERS USING ORGANOCOPPER REAGENTS

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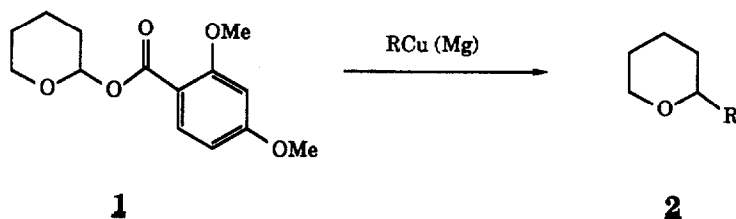
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Summary : *2-Substituted tetrahydropyrans were obtained by direct anomeric substitution of tetrahydropyranyl 2,4-dimethoxybenzoate, using Grignard-derived organocopper reagents.*

Tetrahydropyrans are common structural elements in terpenoids, pheromones, antibiotics, C-glycosides, and other biologically active natural products¹. Accordingly, numerous methods for their preparation have been explored². Nevertheless, procedures for direct conversion of readily available 2-tetrahydropyranyl ethers to the 2-substituted derivatives by nucleophilic displacement are limited, as a consequence of the low reactivity of the anomeric center. Notable exceptions are the room temperature displacement of 2,4-dichlorophenoxide³ or N-hydroxysuccinimide⁴, from the corresponding tetrahydropyranyl ethers, by alkyl and aryl Grignard reagents.

Prompted by recent reports of differential nucleofugicity in 1,3-dioxan-4-ones⁵, we examine 2-tetrahydropyranyl esters **1**, as alternative substrates, and describe herein their



reactivity towards various organocopper reagents at low temperature to give 2-substituted tetrahydropyrans **2**.

A survey of representative esters, including p-toluate, pivalate, and acetate, suggested 2,4-dimethoxybenzoate would possess a favorable combination of nucleofugicity, resistance to attack at the carbonyl group, and ease of preparation. However, ester **1** proved generally to be unreactive towards various organolithium-derived copper reagents, and under forcing conditions suffered ester cleavage. In contrast, smooth displacement affording **2** was achieved with Grignard-derived copper reagents. These results are summarized in the table.

Reagent	Copper salt	R			
		nC ₄ H ₉	nC ₈ H ₁₇	Ph	CH ₂ Ph
RCu	CuCN	65	31	28	b
RCu	CuBr.Me ₂ S	95	57	95	70
R ₂ CuMg _{1/2}	CuCN	37	30	23	b
R ₂ CuMg _{1/2}	CuBr.Me ₂ S	80	55	78	50
R ₃ Cu ₂ Mg	CuCN	b	13	b	b
R ₃ Cu ₂ Mg	CuBr.Me ₂ S	95	27	95	54

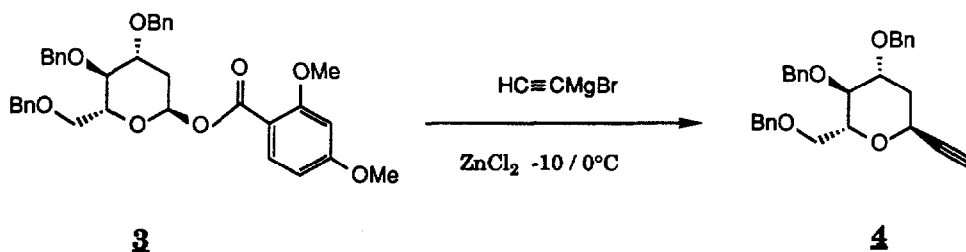
Table. Yield^a of **2** utilizing Grignard-derived copper reagents (^a per cent of isolated product; ^b not determined).

In all cases, reagents prepared from the cuprous bromide-dimethyl sulfide complex were superior to those made from cuprous bromide or cyanide. Likewise, organocopper(I) reagents were somewhat better than cuprates or higher order cuprates. The observation that displacements were more efficient in ether than in tetrahydropyran as the solvent is consistent with the Lewis acid character of magnesium salts and their propensity for coordination to soft bases.

Typical procedure: preparation of 2-butyltetrahydropyran:

To an ethereal solution (10 ml) of butylcopper(I) bromide-dimethyl sulfide complex (1.13 mmol, 3.0 equiv.), at -50°C , under an argon atmosphere, was added dropwise an ethereal solution (2 ml) of **1** (0.37 mmol). After 1-2h, the reaction was quenched with 20% aqueous ammonium hydroxide and the mixture was extracted several times with ether. The combined organic layers were washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and concentrated under reduced pressure, at ambient temperature. Chromatography of the residue over silica gel afforded essentially pure 2-butyltetrahydropyran in more than 95%.

The methodology presented above complements current procedures for substitution at anomeric centers and is compatible with most functional groups. However, extension of this approach to highly oxygenated C-glycosides will require additional study. For example, the O-glycoside **3** was stable to a variety of lithium/magnesium organocopper species, although, in the presence of ZnCl_2 , it added magnesium acetylide with retention of configuration to give **4** (70%) (scheme 2).



Scheme 2.

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