

## Deacyloxy-alkylation of 2-Acyloxy-tetrahydrofurans and -tetrahydropyrans by Reformatsky Reagents†

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A novel type of Reformatsky reaction between 2-acetoxytetrahydrofuran derivatives, ethyl bromoacetate, and zinc affords ethyl(2-tetrahydrofuranyl)acetates in the presence of a small amount of  $\text{TiCl}_4$ ; this reaction is also applicable to 2-acetoxytetrahydropyran derivatives.

The formation of carbon-carbon bonds at the 2-position of cyclic ethers has attracted much recent interest. Many reactions have been reported starting from lactol derivatives,<sup>1,2</sup> but the reaction of these compounds with Reformatsky reagents has not been reported so far.

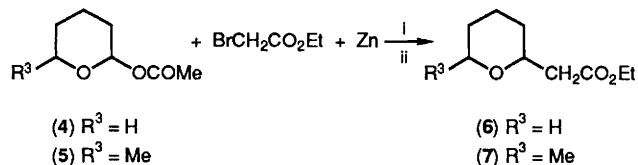
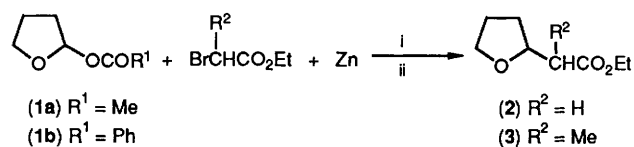
We report herein a novel procedure for direct introduction of an alkoxy-carbonylmethyl group ( $-\text{CH}_2\text{CO}_2\text{R}$ ) to the 2-position of cyclic ethers using Reformatsky reagents. We first examined the reaction of 2-acetoxytetrahydrofuran (**1a**) with ethyl zinc-bromoacetate prepared from ethyl bromoacetate and zinc powder under ultrasonic irradiation; several examples are listed in Table 1. It was found that the addition of Lewis acid catalyst and the use of dichloromethane as a

**Table 1.** Deacyloxy-alkylation of 2-acyloxy-tetrahydrofurans and -tetrahydropyrans by Reformatsky reagents.<sup>a</sup>

Substrate	R <sup>2</sup>	Conditions		% Yield <sup>b</sup>
		Solvent	t/min	
( <b>1a</b> )	H	$\text{CH}_2\text{Cl}_2$	5	83
( <b>1a</b> )	Me	$\text{CH}_2\text{Cl}_2$	5	97 ( <i>erythro</i> : <i>threo</i> 1 : 1)
( <b>1b</b> )	H	$\text{CH}_2\text{Cl}_2$	5	81
( <b>4</b> )	H	$\text{CH}_2\text{Cl}_2$	10	59
( <b>5</b> ) <sup>c</sup>	H	$\text{CH}_2\text{Cl}_2$	10	60 ( <i>cis</i> : <i>trans</i> 1 : 2.5) <sup>d</sup>
( <b>5</b> ) <sup>c</sup>	H	$\text{Et}_2\text{O}$	10	60 ( <i>cis</i> : <i>trans</i> 1 : 4.5) <sup>d</sup>

<sup>a</sup> All reactions were run at 40 °C, using 1 : 2.4 : 3.6 : 0.1 molar ratio of reactants:  $\text{BrCHR}^2\text{CO}_2\text{Et}$  : Zn :  $\text{TiCl}_4$ . <sup>b</sup> Isolated yield after silica-gel column chromatography. <sup>c</sup> *Cis* : *trans* = 2 : 1. <sup>d</sup> Determined from <sup>1</sup>H NMR spectra. See ref. 4(a).

† Deacyloxy-alkylation is a reaction in which deacyloxylation and alkylation occur instantaneously; previously known as a condensation reaction.



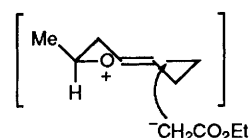
**Scheme 1.** Reagents and conditions: i, 10 mol%  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $40^\circ\text{C}$ , 5–10 min; ii, 10% aq.  $\text{HCl}$ .

solvent were very important for this reaction. The use of a catalytic amount (10 mol%) of  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  caused the reaction to proceed smoothly to afford ethyl(2-tetrahydrofuran-2-yl)acetate (**2**) in good yield<sup>3</sup> within 5 min (Scheme 1), although the reaction resulted in very low yield without  $\text{TiCl}_4$ . Benzene, toluene, and tetrahydrofuran (THF), which are commonly used as solvents for the Reformatsky reaction, did not give good results.‡ This deacyloxy-alkylation using Reformatsky reagents was also applicable to 2-acyloxytetrahydropyran substrates. When 2-acetoxy-6-methyltetrahydropyran (**5**) was used as a substrate, the reaction proceeded stereoselectively to afford *trans* isomers predominantly in dichloromethane or diethyl ether.

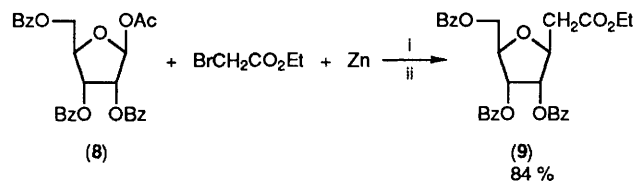
In contrast with the *cis* selectivity in reported intramolecular cyclization methods<sup>4</sup> to prepare 2,6-disubstituted pyrans, *trans* selectivity in this work would be explained by considering the mechanism *via* an oxocarbenium ion intermediate. Nucleophilic attack of the Reformatsky reagent on this cyclic oxocarbenium ion would be favoured from the opposite side of the methyl substituent (see Figure 1).

In addition, we have applied this reaction to carbohydrate synthesis. The reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose (**8**) with ethyl zinc-bromoacetate in the presence of  $\text{TiCl}_4$  (50 mol%) proceeded stereoselectively to give solely

‡ Reactions of (**1**) with ethyl zinc-bromoacetate, giving (**2**), in various solvents were examined at  $40^\circ\text{C}$ : in benzene, 60 min, 27% yield; in toluene, 90 min, 30% yield; in THF, 60 min, 27% yield.



**Figure 1**



**Scheme 2.** Reagents and conditions: i, 50 mol%  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $40^\circ\text{C}$ , 6 h; ii, 10% aq.  $\text{HCl}$ .

the alkylated product (**9**) (84% yield, Scheme 2), which is an important precursor for the synthesis of  $^3\text{C}$ -nucleosides.<sup>5</sup> The reaction path to give the  $\beta$ -anomer could be explained by considering neighbouring group participation (1,2-*trans* effect).<sup>6</sup>

Received, 7th March 1990; Com. 0/01044H

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