

**Preliminary communication**

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**$\alpha$ -Bromo-,  $\alpha$ -chloro-, and  $\alpha$ -trimethylsilyl-zinc ester enolates.  
New and universal Reformatsky-type Darzens and Peterson  
reactions \***

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**Abstract**

Low temperature reactions of ethyl dihaloacetates with carbonyl compounds in the presence of zinc/silver-graphite give  $\alpha$ -halo- $\beta$ -hydroxyalkanoates, which are readily converted into glycidates by base. Under the same conditions ethyl (bromo)(trimethylsilyl) acetate with aldehydes and ketones forms  $\alpha,\beta$ -unsaturated esters by a Reformatsky–Peterson reaction combination.

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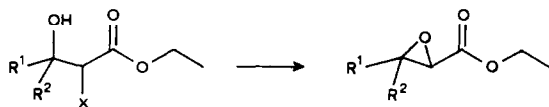
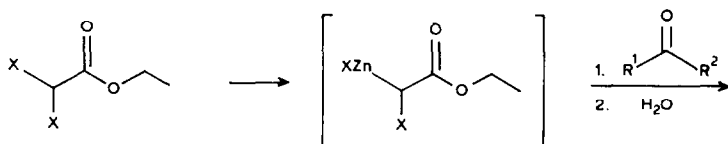
$\alpha,\beta$ -Epoxy alkanoates, i.e. glycidic esters [1,2], are valuable reagents for organic synthesis since they contain three electrophilic sites that can be transformed regioselectively and up to two chiral centers. They provide convenient routes to  $\alpha$ -keto esters as well as homologous carbonyl compounds owing to the ready decarboxylation of glycidic acids [1–3].

The Darzens condensation, a simple one-step glycidate synthesis via  $\alpha$ -halo ester enolates [1,2] has nevertheless not attained widespread use in preparative organic chemistry. Aldolization of enolizable carbonyl species [1,2], necessitating a continuing search for more appropriate bases [3,4], and a lack of stereoselectivity [5–7] limit its application. To avoid the spontaneous cyclisation of the intermediate  $\alpha$ -halo- $\beta$ -hydroxy alkanoates, which are valuable in  $\alpha$ -haloacrylate synthesis, chloro- or even the toxic fluoro-alkanoates have to be used [2,3].

Like these base-induced Darzens procedures, metal-induced glycidate formation is also rather restricted in scope. Conventional Reformatsky conditions are, with rare exceptions [8], inappropriate for the formation of  $\alpha$ -halo zinc ester enolates from the corresponding  $\alpha$ -dihaloalkanoates [9]. For success unusually weak amalgams containing dissolved zinc, magnesium or calcium in monoatomic form are essential [10], conditions at presently considered to be obsolete.

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\* This paper is dedicated to Prof. Dr. H. Weidmann on the occasion of his 60th birthday.



In the light of the substantial progress made in metal-induced reductions [12–16], the work described in this communication was directed towards new and widely applicable Reformatsky-type syntheses of  $\alpha$ -halo- $\beta$ -hydroxy-, glycidic- as well as  $\alpha,\beta$ -unsaturated esters from ethyl (dihalo)- or (bromo)-(trimethylsilyl)acetates [11] and carbonyl compounds.

The highly dispersed [17] zinc/silver on graphite [16] employed has a very high reactivity, far superior to that of amalgams. The advantages of this method can be seen from the Table 1. All reactions can be performed at low temperature, and with (dibromo)acetate even at  $-78^\circ\text{C}$ . In all the cases investigated,  $\alpha$ -halo- $\beta$ -hydroxyalkanoates, hitherto not readily accessible, are obtained in excellent yields, and form glycidates exclusively on treatment with base. As observed for methyl 4,6-*O*-benzylidene-3-deoxy- $\alpha$ -D-*erythro*-hex-2-ulopyranoside [18], diastereotopic ketones under these conditions form a single diastereoisomer of the halohydrin and also of the

Table 1

Zinc/silver-graphite induced syntheses of halohydrins, glycidates and  $\alpha,\beta$ -unsaturated esters <sup>a</sup>

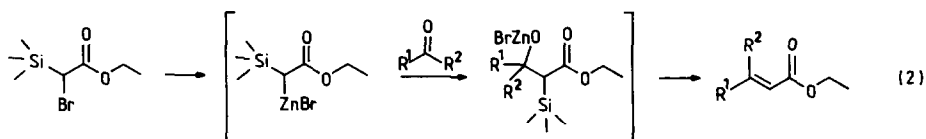
Reagent	Carbonyl compound		Temperature ( $^\circ\text{C}$ )	Reaction time (min)	Yield (%) halo- hydrin	Yield (%) glyci- date <sup>b</sup>	Yield (%) $\alpha,\beta$ -unsatu- rated ester
	R <sup>1</sup>	R <sup>2</sup>					
Br <sub>2</sub> CHCO <sub>2</sub> Et	Ph	Ph	-78	20	89	84	-
Br <sub>2</sub> CHCO <sub>2</sub> Et	Ph	Me	-78	20	86	80	-
Cl <sub>2</sub> CHCO <sub>2</sub> Et	Ph	Me	-20	40	90	78	-
Br <sub>2</sub> CHCO <sub>2</sub> Et	Ph	H	-78	10	94	91	-
Br <sub>2</sub> CHCO <sub>2</sub> Et		(CH <sub>2</sub> ) <sub>5</sub>	-78	35	90	81	-
Cl <sub>2</sub> CHCO <sub>2</sub> Et		(CH <sub>2</sub> ) <sub>5</sub>	0	60	88	78	-
Br <sub>2</sub> CHCO <sub>2</sub> Et	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	H	-78	10	82	76	-
Br <sub>2</sub> CHCO <sub>2</sub> Et		<sup>c</sup>	-78	20	95 <sup>d</sup>	93 <sup>d,e</sup>	-
(Br)(Me <sub>3</sub> Si)CHCO <sub>2</sub> Et	Ph	H	-78	15	-	-	89
(Br)(Me <sub>3</sub> Si)CHCO <sub>2</sub> Et	Ph	Ph	-78	20	-	-	84
(Br)(Me <sub>3</sub> Si)CHCO <sub>2</sub> Et		(CH <sub>2</sub> ) <sub>5</sub>	-78	35	-	-	88
(Br)(Me <sub>3</sub> Si)CHCO <sub>2</sub> Et	Me	H	-78	10	-	-	79

<sup>a</sup> All products gave satisfactory analytical and spectroscopic data. <sup>b</sup> *cis:trans*  $\geq 1:10$ . <sup>c</sup> Educt: Methyl 4,6-*O*-benzylidene-3-deoxy- $\alpha$ -D-*erythro*-hex-2-ulopyranoside. <sup>d</sup> Stereochemistry at branching point according ref. 16. <sup>e</sup> Halohydrin cyclisation with NaH in THF.

glycidate. This is in accordance with previous reports on zinc/silver-graphite induced Reformatsky reactions [16a,c].

In the light of these results, incorporation into the enolates of reactive functions other than halogen appeared to be of interest. Because of the great utility of  $\alpha$ -heteroatom substituted carbanions [19], zinc trimethylsilylacetate enolate, a potential Peterson reagent [20], was most interesting.

Since reaction of ethyl dibromoacetate with chlorotrimethylsilane in the presence of zinc/silver-graphite failed [21] to produce the desired ethyl (bromo)(trimethylsilyl)acetate [11], the procedure of Emde et al. [22] was employed. Reaction of this acetate with aldehydes and ketones under the conditions described above rapidly produced  $\alpha,\beta$ -unsaturated esters by a Reformatsky–Peterson reaction sequence.



### Experimental

**Zinc/Silver-graphite induced reactions of ethyl dihaloacetates with carbonyl compounds.** Potassium (1.2 g, 31 mmol) is added in portions with good stirring at 150 °C under argon to graphite (3.0 g, 250 mmol), previously degassed at that temperature for 15 minutes. The bronze-coloured  $C_8K$  formed in 10–15 minutes is suspended in anhydrous THF (30 ml) at ambient temperature and treated with a mixture of zinc chloride (2.0 g, 14.7 mmol) and silver acetate (0.2 g, 1.2 mmol) and the mixture is refluxed for 30 minutes then cooled to the temperature shown in Table 1. After addition of 10 mmol each of the carbonyl compound and ethyl dihaloacetate in THF (10 ml), the mixture is stirred until the reaction is complete (TLC), then filtered, and the solvent is evaporated and the residue subjected to column chromatography to give the corresponding halohydrin exclusively.

When the filtrate is diluted with diethyl ether (60 ml) and twice extracted with a saturated aqueous solution of  $K_2CO_3$ , the corresponding glycidate is obtained directly after usual work-up.

**Reformatsky–Peterson sequence.** A solution of ethyl (bromo)(trimethylsilyl)acetate (2.39 g, 10 mmol) and 10 mmol of the carbonyl compound in THF (10 ml) is added to a suspension of zinc/silver-graphite at  $-78^\circ C$ . The mixture is stirred at  $-78^\circ C$  for the time shown in Table 1, and work-up as described for halohydrins then gives the corresponding  $\alpha,\beta$ -unsaturated ester.

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