

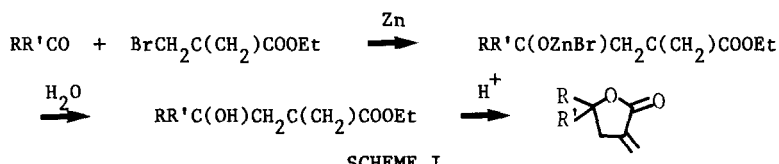
**REFORMATSKY-TYPE REACTIONS IN AQUEOUS MEDIA. USE OF BROMOMETHYL-
ACRYLIC ACID FOR THE SYNTHESIS OF α -METHYLENE- γ -BUTYROLACTONES.**

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Abstract: A new method for the preparation of α -methylene- γ -butyrolactones is described.

Reformatsky-type conditions usually require the reflux of ethyl α -bromomethylacrylate with a ketone or an aldehyde in an organic solvent, in the presence of zinc powder (1). The formed alcoolate makes the reaction conditions basic and good to excellent yields are only obtained when the carbonyl substrate is nonenolizable (2). The presence of acidic hydrogens favors aldol-type side-reactions, resulting in considerable drop of the yield. These reactions are especially useful for the one-pot preparation of α -methylene- γ -butyrolactones (Scheme I):



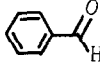
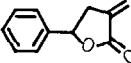
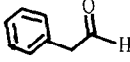
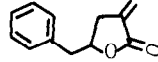

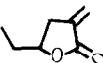
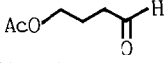
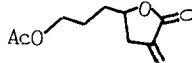

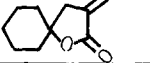
We have reasoned that if the reaction was conducted under slightly acidic conditions such inconveniences could be avoided and that even methacrylic acid could be used instead of esters. We are now reporting the results of this study.

RESULTS

When phenylacetaldehyde (1 equivalent) was treated for 4 hours with ethyl α -bromomethylacrylate (1 equivalent) in the presence of zinc powder (1.2 equivalent) in refluxing THF, followed by acidic treatment to ensure cyclization, only 15 % of γ -phenylmethyl- α -methylene- γ -butyrolactone was obtained. Use of a solvent mixture (THF and trimethyl borate) (3) did not improve the yield. Zinc activation (4) only resulted in the decomposition of the starting ester. We have repeated the reaction using slightly acidic aqueous medium: the aldehyde, the ester and commercial zinc powder were heated for 5 hours in a 5:2 THF: water mixture saturated in ammonium chloride. The yield of isolated γ -phenylmethyl- α -methylene- γ -butyrolactone was 75 % (Method A).

Furthermore, bromomethylacrylic acid could be used directly (once neutralized with triethylamine), under the same conditions, with an overall 52 % yield (Method B). These procedures have been used with a number of aldehydes and ketones. The results are reported in Table I.

TABLE I

CARBONYL COMPOUNDS	PRODUCTS ^b	YIELDS % ^a		LITT.
		METHOD A	METHOD B	
		98	90	100 (1)
		75	52	15 (7)
		68	55	^d 23 (5)
		70	--	^c 12
		77	47	31 (6)

a) Yields calculated for isolated products; b) The spectra (NMR and IR) were compared with authentic samples; c) Prepared by the usual method (ref.1); d) The reaction was run at 40°C.

TYPICAL EXPERIMENTAL PROCEDURES

METHOD A.

In a saturated aqueous solution of ammonium chloride containing 2 mL THF was added phenylacetaldehyde (0.23 mL, 2.0 mmoles), ethyl α -bromomethylacrylate, (0.39 g, 2.0 mmoles), and zinc powder (0.16 g, 2.4 mmoles, commercial 20 mesh (Prolabo) powder. The mixture was heated at 60°C and stirred for 12h at this temperature. After cooling to room temperature, the mixture was extracted with ether (3 x 20 mL). After removing ether from the combined extracts and redissolving in toluene (10 mL), p-toluenesulfonic acid (0.15 g) was added, the mixture was stirred at room temperature for 2h and extracted as usual with ether. Column chromatography (silica gel) of the residue (eluent ether-hexane 8:2) gave pure α -methylene- γ -phenylmethyl- γ -butyrolactone (0.28g, 1.5 mmoles, 75% yield). The compound was identified by IR and NMR spectra.

METHOD B

A similar procedure was used with α -bromomethylacrylic acid. This acid (0.50 g, 2.0 mmoles) was dissolved in THF (2 mL) and triethylamine (0.42 mL, 2.0 mmoles) was added. To this solution was added: water (5 mL) saturated with ammonium chloride, phenylacetaldehyde (0.23 mL, 2.0 mmoles), zinc powder (0.16 g, 2.4 mmoles) and treated as above.

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