Preparation of Alkyl-Substituted Succinic Esters by Coupling of α-Halogenated Esters

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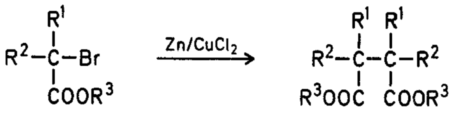
Several general methods are known for the preparation of substituted succinic esters. One of them involves the condensation of an α-halo ester with a malonic[1] or cyanoacetic ester[2] followed by decarboxylation. Tetrasubstituted succinic acids cannot be prepared by this method.

Other methods involve coupling: Kolbe electrolysis of malonic monoesters[3] or monoamides[4]; action of iodine on phenylacetic ester-enolates[5]; Wurtz condensation of α-bromoesters by means of silver[6], copper powder[7], or sodium[8].

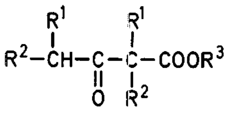
A similar Wurtz condensation of α-bromo-esters brought about by zinc, might be expected to occur in the preparation of Reformatzki reagents. However, only one example of this reaction appears to have been described: treatment of methyl α-bromophenylacetate with zinc in dimethyl sulfoxide yields appreciable amounts of dimethyl *meso*-diphenylsuccinate[9].

We wish to report that the Wurtz condensation of α-bromoesters (**1**) can be accomplished by reaction with zinc (or magnesium) and copper(II)-chloride in tetrahydrofuran. The results are listed in Table 1.



$R^2-C(R^1)(Br)-COOR^3 \xrightarrow{Zn/CuCl_2} R^3OOC-C(R^1)(R^2)-C(R^1)(R^2)-COOR^3$

1 **2**



$R^2-CH(R^1)-C(=O)-C(R^1)(R^2)-COOR^3$

3

The diastereoisomers of the esters **2** ($R^2 = H$) were formed in equal amounts. The β-keto-esters **3** which are the major products in the absence of copper chloride, were not detected. In the case of ethyl 2-bromopropanoate, ethyl propanoate and ethyl acrylate were identified as by-products. Under the same conditions, the Wurtz condensation of α-bromonitriles or amides does not occur.

Other attempts were made to couple methyl 2-bromopropanoate using various metals, metal salts, and solvents. The results (Table 2) show that the most suitable combination of reagents consists of zinc, copper(II)-chloride, and tetrahydrofuran.

The yields reported in the Tables correspond to distilled succinic esters (**2**), which were shown (G.L.C.) to be >95% pure and which were characterized by their N.M.R. spectra.

Table 1. Yields of Succinic Acid Esters (**2**) prepared from α-Bromocarboxylic Acid Esters (**1**) in Tetrahydrofuran using Zinc/Copper(II)-chloride as the Condensing Agent

R^1	R^2	R^3	Yield %
CH_3	H	C_2H_5	35
C_2H_5	H	C_2H_5	32
C_3H_7	H	C_2H_5	33
i-C_3H_7	H	CH_3	40[a]
CH_3	CH_3	CH_3	38
CH_3	CH_3	i-C_3H_7	25
C_2H_5	C_2H_5	C_2H_5	30

[a] Crystalline dimethyl *meso*-diisopropylsuccinate (F: 102°) was isolated.

Table 2. Yields of Dimethyl Dimethylsuccinate (**2**, $R^1 = R^3 = CH_3$, $R^2 = H$) obtained from Methyl 2-Bromopropanoate under Various Conditions

Metal	Salt	Solvent	Yield %
Mg	$CoCl_2$	THF	21
Mg	$NiCl_2$	THF	14
Mg	$CuCl_2$	THF	30
Zn	none	THF	0[a]
Zn	$CoCl_2$	THF	5
Zn	$CuCl_2$	THF	32
Zn	$CuCl_2$	benzene	~5
Zn	$CuCl_2$	DMSO	0
Zn	$CuCl_2$	DMF	15
Zn	CuBr	THF	1

[a] Methyl 2-methyl-3-oxopentanoate (**3**, $R^1 = R^3 = CH_3$, $R^2 = H$) was isolated (80%).

Methyl Tetramethylsuccinate (**2**, $R^1 = R^2 = R^3 = CH_3$): Copper(II)-chloride hydrate (9.5 g) was dessicated under reduced pressure. To the resultant anhydrous copper(II)-chloride (7.5 g, 0.055 mol) was added dry tetrahydrofuran (65 ml). The volume of the brown crystals increased and their color changed to bright orange, with evolution of heat. Zinc ribbon (3.6 g, 0.055 g-atom), methyl 2-bromo-2-methylpropanoate (4.9 g, 0.027 mol), and a trace of mercury(II)-bromide were added, and the mixture was heated to initiate the reaction. After 1 hr of refluxing, the mixture was cooled, decanted, acidified, and extracted with ether. The ether extract was washed with aqueous sodium hydrogencarbonate (a precipitate formed which dissolved upon addition of a saturated solution of ammonium chloride), then with water, dried, evaporated, and the residue distilled under reduced pressure; yield: 1.0 g (38%); $b.p._{20}$: 104–107°.

N.M.R. (CCl_4, HMDS as internal reference): 2 singlets at 1.12 and 3.52 ppm, ratio 2:1.

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