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Reductive Coupling of Methyl α-Bromo-α-Chlorocarboxylates.

Monica Boni, Franco Ghelfi*, Ugo M. Pagnoni and Claudia Zucchi

Dipartimento di Chimica dell' Università, Via Campi 183, I-41100, Modena (Italy)

Abstract: CuBr-$LiOCH_3$ in methanol efficiently promotes the reductive coupling of methyl α-bromo-α-chlorocarboxylates to dimethyl α,α'-dichloro-succinates.

The reductive coupling of α,α-dihalo acid esters[1] is very little investigated; as far as we know, only few examples of preparation of fumaric and maleic ester derivatives, using Cu(*0*)-DMSO[2] or CH_3MgBr-CuI[3] are reported.

Recently, on studying the reactivity of α-chloro-α-bromo and α,α-dichloro acid esters, which can be prepared easily and with high yields,[4,5] we observed that CuBr-$LiOCH_3$ in methanol promotes unexpectedly a reductive coupling of methyl α-bromo-α-chlorocarboxylates to dimethyl α,α'-dichloro-succinate derivatives. Alkoxocopper(*I*) has been previously used for alkoxydehalogenation of aromatic,[6a] vinylic[6b] and alkyl[6c] halides, and copper(*I*) complexes for Wurtz-type condensation of halomethyl benzenes.[6a,b,c]

CuBr alone is not able to transform methyl α-bromo-α-chlorocarboxylates in methanol; in the presence of $LiOCH_3$, however, a clean and fast coupling occurs through the selective abstraction of bromine atoms (Table 1). On adding the pale green CuBr salt to the methylate solution a yellow-green precipitate is formed, which changes to blue after substrate addition, since cuprous ions are oxidized to cupric ones. Although Cu(*0*) can be produced from $CuOCH_3$,[6] hardly it works in this case since its formation needs longer reaction times and higher temperatures;[6a] furthemore no coupling is obtained on replacing CuBr by Cu(*0*). The relatively greater reducing power of Cu(I) ions in the presence of the methoxide ligand is rationalized in terms of the "filled/filled"destabilizing interaction between an oxygen lone pair and a copper occupied d_π orbital.[8]

The best results have been obtained with stoichiometric amounts of CuBr and 3 equivalents of lithium methylate at room temperature. Starting from a number of methyl α-bromo-α-chlorocarboxylates homocoupled products are prepared in excellent yields (Table 2). α,α-Dichloro acid esters are less reactive and give the corresponding α-chloroesters as the main products. The reductive coupling must be carried out in a flask open to air, since under N_2 methyl α-bromo-α-chlorohexanoate is mainly transformed into α-bromo-α-chlorohexanamide (60%).[9]

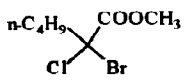
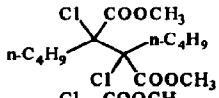
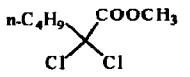
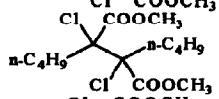
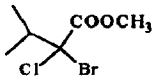
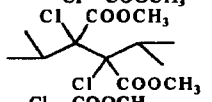
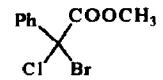
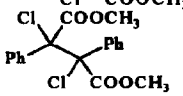
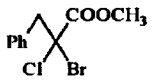
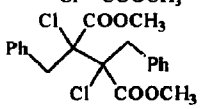
Nucleophilic substitution of an intermediate enolate on methyl α-bromo-α-chlorocarboxylates is rejected, since no coupling is obtained when methyl α-chlorohexanoate (0.5 mmol) and methyl α-bromo-α-chlorohexanoate (0.5 mmol) are treated at room temperature with $CuBr_2$ (1 mmol) and $LiOCH_3$ (3 mmol) in methanol (3 ml).[10] The addition of hydrogen donors (9 mmol / mmol of substrate), like cyclohexane or cumene, to the reaction does not

TABLE 1. Reaction of methyl α-bromo-α-chlorohexanoate with CuBr-$LiOCH_3$[a)]

Item	CuBr (mmol)	$LiOCH_3$ (mmol)	CH_3OH (ml)	time (h)	conversion (%)	coupling product (%)
1)	1	0	3	20	3	0
2)	1	2	2	20	87	74
3)	1	3	4	4	100	81
4)	1	3	6	18	100	73
5)	9	3	4	20	95	69
6)	1[b)]	3	3	4	63	22
7)	0.5[c)]	3	4	12	64	17

a) substrate = 1mmol; b) CuCl; c) Cu(*0*)

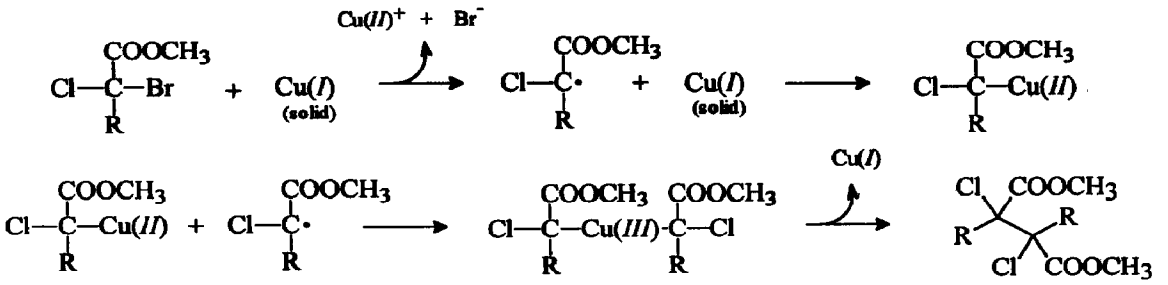
TABLE 2 : Homocoupling of α,α-dihalo acid esters with CuBr-$LiOCH_3$

Entry	Substrate	Product	Time (h)	Yield[a)] (%)	Diastereomers ratio *(dl / meso)*[b)]
1			4	81(83)	1:1
2			20	8[c)]	1:1
3			12	90(90)	1:1
4			4	86[d)]	1.6:1
5			4	82	1:1

a) In parenthesis the yields for the ten times scaled up reactions are reported; b) determined by ^1H NMR;
c) methyl α-chlorohexanoate 39 %, unreacted substrate 23%, α,α-dichlorohexanamide 22%;
d) dimethyl α,α'-dimethoxy-α,α'-diphenyl-succinate 5%.

increase the little amount of monodehalogenated ester, thus ruling out a free radical process.

These experimental evidences, together with the aborted coupling observed on solid removal from the reaction before substrate addition, strongly account for a process developing in heterogeneous phase at copper(*I*) centres.[11] A tentative rationalization of the results is outlined in Scheme 1. The radical formed by bromine abstraction from methyl α-bromo-α-chloro ester[7,12] rapidly reacts with a cuprous centre to form an organocupric adduct, which traps another radical to afford an unstable Cu(*III*) intermediate; a reductive elimination[13] of Cu*(I)* affords the coupling product.



Scheme 1

EXPERIMENTAL PART

^{1}H NMR[14] spectra were recorded on a Bruker WP80 spectrometer or a Bruker AMX 400WB. Mass spectra were obtained on a combined HP 5890 GC - HP 5989A MS Engine. Reagents and solvents were standard grade commercial products and used without further purification. Methyl α,α-dihalocarboxylates were prepared according to known procedures.[4,5]

General procedure for the reductive coupling. In a necked round bottom flask (10 ml), $LiOCH_3$ (3 mmol) is prepared by cautious addition of LiH (3 mmol) to CH_3OH (3-4 ml). When sparkling stops, the α,α-dihalocarboxylate ester (1 mmol) and then CuBr (1 mmol) are added at room temperature to the vigorously stirred mixture. The reaction is monitored by GC; when the substrate disappears, the mixture is diluted with 5% HCl (7 ml) and extracted with CH_2Cl_2 (2 x 2 ml). The organic phases are collected, dried over Na_2SO_4 and evaporated. Since by-products are more volatile than dimethyl α,α'-dichloro-α,α'-dialkyl-succinate, they are removed on distillation under vacuum (0.01 mmHg).

Special case.- With methyl 2-Br-2-Cl-3-methylbutanoate, 1.1 mmol of CuBr are required for a complete conversion.

dimethyl α,α'-dichloro-α,α'-dibutyl-succinate

^{1}H NMR (δ, $CDCl_3$): *d,l* and *meso-forms*, 0.90 (6H, t, 2 x CH_3-C); 1.00-2.60 (12H, m, 2 x C-$(CH_2)_3$-CCl); 3.78 (6H, s, 2 x -$COOCH_3$). IR (neat): 1740 and 1770 (C=O) cm^{-1}. MS (EI, 70 eV) *m/z*: 291 (9%) [M^+- Cl]; 259 (100%) [M^+- Cl - CH_3OH]; 163 (54%) [$M^+/2$].

Found: C, 51.5; H, 7.3%. $C_{14}H_{24}Cl_2O_4$ requires C, 51.38; H, 7.39%.

dimethyl α,α'-dichloro-α,α'-diisopropyl-succinate

^{1}H NMR ($CDCl_3$): *d,l-form*, 0.834 (6H, d, J= 6.5 Hz, 2 x -CH_3); 1.157 (6H, d, J= 6.5 Hz, 2 x -CH_3); 2.416 (2H, ept, 2 x -C<u>H</u>$(CH_3)_2$); 3.714 (6H, s, 2 x -$COOCH_3$). *Meso-form*, 0.827 (6H, d, J= 6.5 Hz, 2 x -CH_3); 1.186 (6H, d, J= 6.5 Hz, 2 x -CH_3); 2.946 (2H, ept, 2 x -C<u>H</u>$(CH_3)_2$); 3.694 (6H, s, 2 x -$COOCH_3$). IR (neat): 1730 and 1750 (C=O) cm^{-1}. MS (EI, 70 eV) *m/z*: 188 (100%) [M^+- Cl - CH_3OH - C_3H_7]; 149 (43%) [$M^+/2$].

Found: C, 48.1; H, 6.6%. $C_{12}H_{20}Cl_2O_4$ requires C, 48.17; H, 6.74%.

dimethyl α,α'-dichloro-α,α'-dibenzyl-succinate

^{1}H NMR ($CDCl_3$): *d,l-form*, 3.402 (2H, d, 2 x -C<u>H</u>-Ph); 3.636 (6H, s, 2 x -$COOCH_3$); 3.963 (2H, d, 2 x -C<u>H</u>-Ph); 7.101-7.422 (10H, m, 2 x -C_6H_5). *Meso-form*, 3.553 (6H, s, 2 x -$COOCH_3$); 3.784 (2H, d, 2 x -C<u>H</u>-Ph); 3.844 (2H, d, 2 x -C<u>H</u>-Ph); 7.101-7.422 (10H, m, 2 x -C_6H_5). IR (neat): 1730 and 1770 (C=O) cm^{-1}. MS (EI, 70 eV) *m/z*: 327 (8%) [M^+- Cl - CH_3OH]; 197 (7%) [$M^+/2$]; 91 (100%) [Ph-CH_2^+].

Found: C, 60.8; H, 5.2%. $C_{20}H_{20}Cl_2O_4$ requires C, 60.77; H, 5.10

dimethyl α,α'-dichloro-α,α'-diphenyl-succinate

^{1}H NMR ($CDCl_3$): *d,l-form*, 3.88 (6H, s, 2 x -$COOCH_3$); 6.95-7.55 (10H, m, 2 x C_6H_5). *Meso-form*, 3.84 (6H, s, 2 x -$COOCH_3$); 6.95-7.55 (10H, m, 2 x C_6H_5). IR (neat): 1740 (C=O) cm^{-1}. MS (EI, 70 eV) *m/z*: 331 (2%) [M^+- Cl]; 183 (100%) [M^+/2].

Found: C, 58.7; H, 4.3%. $C_{18}H_{16}Cl_2O_4$ requires C, 58.87; H, 4.39%.

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