Pergamon

Tetrahedron Letters, Vol. 36, No. 7, pp. 1103-1106, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02405-7

Reductive Homo-Coupling of Methyl 2-Br-2-Cl-Carboxylates Promoted by CuBr-Fe^0

Marta Benincasa, Luca Forti, Franco Ghelfi*and Ugo M. Pagnoni

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

Abstract: Dimethyl 2,3-dialkyl-2,3-dichloro-butanedioates are efficiently prepared in dimethylformamide or dimethylsulphoxide, through reductive homo-coupling of methyl 2-bromo-2-chlorocarboxylates promoted by CuBr-Fe^0.

Recently we reported an efficient procedure for the preparation of dimethyl 2,3-dichloro-butanedioates by reductive coupling of methyl 2-bromo-2-chlorocarboxylates with CuBr-LiOCH$_3$ in methanol.[1] The lack of derivatives of fumaric and maleic esters among the reaction products differentiates this procedure from those reported in literature using Cu^0-DMSO[2] or CH$_3$MgBr-CuI[3] as reagents, which afford unsaturated dicarboxylates, selectively.

Though yields are good, our reported procedure is not quite satisfactory; the relatively high concentration of methoxide anions, indeed, gives rise to a nucleophilic substitution on substrate with an easy displaceable α-chloro atom (as in the case of dimethyl 2,3-diphenyl-2,3-dichloro-butanedioate) and also to a competing transesterification, actually restricting the procedure to methyl esters.

Since the redox potential of Cu^{II}/Cu^{I} couple can be remarkably modified by a change of solvent,[4] we tested CuBr in a series of solvents and found some reactivity in dimethylsulphoxide (DMSO) and in dimethylformamide (DMF). The amounts of cuprous salt required to achieve a complete conversion would have been lowered in the presence of an electropositive metal, reducing the CuBr$_2$ generated in the bromine abstraction from 2-bromo-2-chloroesters. On adding iron powder, in fact, a high yield reductive homo-coupling has been obtained with just a stoichiometric amount of CuBr. Remarkably, iron powder alone is not able to promote any conversion. Best results have been obtained under N$_2$ in commercial DMSO or anhydrous DMF at room temperature, and with an 1:1:1 ratio of substrate, CuBr and Fe^0 (Table 1, item 7-8). Less satisfactory results have been obtained on replacing CuBr by CuCl or CuBr$_2$.

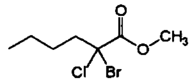
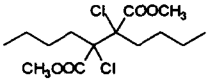
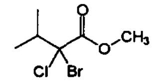
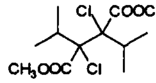
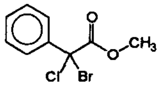
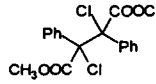
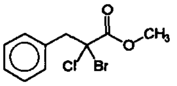
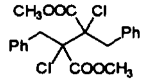
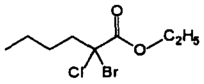
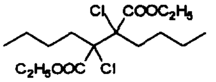
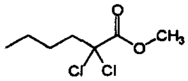
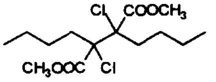
Since a FeCl$_2$-NaBr-Fe^0 combination (Table 1, item 9) promotes the reductive homo-coupling successfully and $E^0_{Fe(II)/Fe}$ is lower than $E^0_{Cu(I)/Cu}$, we suggest that the actual coupling reagent is FeBr$_2$ (see Scheme).

TABLE 1. The reaction [a] of methyl 2-bromo-2-chlorohexanoate with CuBr-Fe^0

item	DMF[b] (ml)	DMSO (ml)	CuBr (mmol)	Fe^0 (mmol)	conversion (%)	yields (%)
1	1	0	1	0	28	18
2	0	1	1	0	34	19
3	0	1	0	1	0	0
4	1	0	1	1	100	83
5	1	0	.5	1	92	61
6	0	1	1	1	100	78
7[c]	1	0	1	1	100	90
8[c]	0	1	1	1	100	87
9[c]	1	0	0[d]	1	100	73
10[c]	1	0	0[e]	1	94	77
11[g]	1	0	0[f]	1	100	79
12[h]	1	0	1	1	98	79
13[c,i]	1	0	1	1	96	36(36)[l]

a) substrate = 1mmol, room temperature, reaction time = 24 h; b) anhydrous solvent; c) under N_2; d) $FeCl_2$ (1 mmol)- NaBr (4mmol); e) $CuBr_2$ (.5 mmol); f) CuCl (1 mmol); g) reaction time 48 h; h) + H_2O (1 mmol); i) + 1-octene (10 mmol); l) in parenthesis are the yield of methyl 2-Cl-4-Br-2-butyl-decanoate.

TABLE 2. The reductive homo-coupling of methyl 2-Br-2-Cl-carboxylates with CuBr-Fe^0

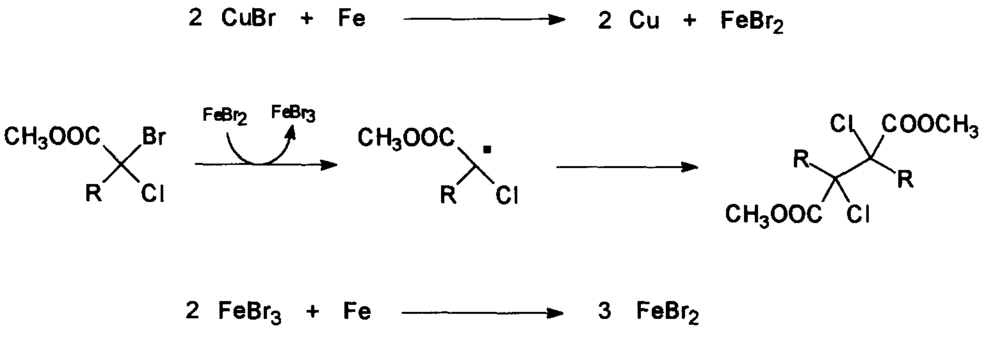
Substrate	Product	yield[a] (%) in DMSO	yield[a] (%) in DMF	Time (h)
		87	90	24
		93	90(91)[b]	24
		89(7)[c]	91(4)[c]	2[d]
		83	89	6[d]
		80	79	24
		/	8[e]	24

a) All products are 1:1 mixtures of *meso* and *dl* forms (determined by ^{1}H-NMR analysis); b) in parenthesis the larger scale preparation yield; c) in parenthesis the amount of fumaric and maleic derivatives; d) higher reactions times dramatically reduced the yields; e) 12% conversion.

Iron(II) salts (most frequently $FeCl_2$) have been largely used for the reductive coupling of haloalkanes;[5] only on a recent paper, however, a polyhalogenated ester, methyl trichloroacetate, has been treated with $FeCl_2$.[6] As far as we know, $FeBr_2$ has been only used for adiponitrile preparation by reductive coupling of 3-bromopropanonitrile.[7]

By this new CuBr-Fe^0 procedure, homocoupled products have been prepared easily from a number of methyl 2-bromo-2-chlorocarboxylates (Table 2), under milder conditions and with higher yields with respect to those obtained by CuBr-$LiOCH_3$ reagent; but, methyl 2,2-dichloro acid esters have still[1] provided poor conversions. The new method is suitable also for larger scale preparations, giving satisfactory yields with cheap reagents and low solvent volumes.

Since water has little influence (Table 1, item 12) on the reductive coupling, an ionic pathway through enolate intermediates appears unlikely. On the contrary, a radical type process agrees with the absence of diastereoselectivity in the products,[10] and with the formation of methyl 2-chloro-4-bromo-2-butyl-decanoate, the Kharasch addition adduct, on adding 1-octene to the reaction mixture (Table 1, item 13).[11] The intermediate radical can originate through an inner-sphere dissociative electron transfer process of the bromo atom from 2-bromo-2-chloroesters to $FeBr_2$ (Scheme).[5c-d,6]



Scheme

EXPERIMENTAL PART

Mass spectra were obtained on a HP 5989A MS Engine. Reagents and solvents were standard grade commercial products and used without further purification. DMF was dried over three batches of 3Å sieves (5% w/v, 12h). Methyl 2,2-dihalocarboxylates were prepared according to known procedures.[8,9]

General procedure for reductive coupling. To iron powder (1 mmol), in a Schlenk tube, CuBr (1 mmol), DMF or DMSO (1 ml) and the methyl 2-Br-2-Cl-carboxylate (1 mmol) were added under N_2 atmosphere. The mixture was stirred at room temperature, and, after the time reported in Table 2, diluted with 5% HCl (5 ml) and then extracted with CH_2Cl_2 (2 x 2 ml). Residual Cu^0 and Fe^0 were decanted. The organic phases were collected, dried over Na_2CO_3 and evaporated. The products were purified by distillation under vacuum (0.01 mmHg) and compared by GC-MS with samples prepared according to literature.[1]

Larger scale procedure. Methyl 2-Br-2-Cl-3-methyl-butanoate (40 mmol, 9.14 g) was treated with Fe^0 (40 mmoles, 2.23 g), CuBr (40 mmol, 5.74 g) in DMF (40 ml), following the above described conditions; the pure homo-coupled adduct was obtained in 91% yield.

Acknowledgements.- We thank the C.N.R. (Rome) and the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST) for financial assistance.

REFERENCES AND NOTES

1. Boni, M.; Ghelfi, F.; Pagnoni, U. M.; Zucchi, C. *Tetrahedron Lett.*, **1994**, 7263-7266.
2. Tezuka, Y.; Hashimoto, A.; Ushizaka, K.; Imai, K. *J. Org. Chem.*, **1990**, 55, 329-333.
3. Villieras, J.; Disnar, J.-R.; Normant, J.-F. *J. Organometal. Chem.*, **1974**, 81, 281-293.
4. Benari, M. D.; Hefter, G. T. *Aust. J. Chem.*, **1990**, 43, 1791-1801.
5. a) Khurana, J. M.; Maikap, G. C.; Metha, S. *Synthesis*, **1990**, 731-732. b) Onuma, K.; Yamashita, J.; Hashimoto, H. *Bull. Chem. Soc. Jpn.*, **1973**, 46, 333-334. c) Shirafuji, T.; Yamamoto, Y.; Nozaki, H. *Bull. Chem. Soc. Jpn.*, **1971**, 44, 1994-1995. d) Onuma, K.; Yamashita, J.; Hashimoto, H. *Bull. Chem. Soc. Jpn.*, **1970**, 43, 836-841.
6. Cornia, A.; Folli, U.; Sbardellati, S.; Taddei, F. *J.Chem. Soc. Perkin Trans. 2*, **1993**, 1847-1853.
7. Onsager, O. T. US Patent 3,671,567, *C. A.*, **1972**, 77, 75765b. Onsager, O. T. Ger. Offen. 2,121,177, *C. A.*, **1972**, 76, 33829z.
8. Boni, M.; Ghelfi, F.; Pagnoni, U. M.; Zucchi, C. *Bull. Chem. Soc. Jpn.*, **1994**, 67, 1622-1626.
9. Bellesia, F.; Boni, M.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.*, **1994**, 2961-2964.
10. Porter, N. A.; Krebs, P. J. *Topics Stereochemistry*, **1988**, 18, 103-111. Porter, N. A., Rosenstein, I. J. *Tetrahedron Lett.*, **1993**, 7865-7868.
11. Radical additions of polyhalogenated compounds to alkene, promoted by transition metal, are widespreadly used in organic synthesis and reviewed in: a) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.*, **1994**, 94, 519-564. b) Bellus, D. *Pure & Appl. Chem.*, 1985, 57, 1827-1838.

(*Received in UK* 27 *October* 1994; *revised* 5 *December* 1994; *accepted* 9 *December* 1994)