Tetrahedron Vol. 47, No. 46, pp. 9621-9628, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

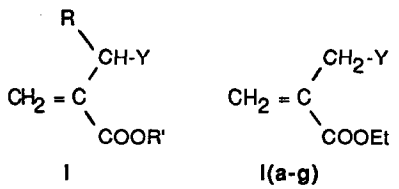
ADDITION OF BROMINE TO β'-(FUNCTIONAL ALKYL) α,β-UNSATURATED ESTERS STEREOSELECTIVE SYNTHESIS OF β-HALODERIVATIVES

Taïcir BEN AYED, Hassen AMRI and Mohamed Moncef EL GAIED*
Laboratoire de Chimie Organique, Faculté des Sciences , Campus Universitaire 1060 TUNIS (TUNISIE)

(*Received in Belgium* 8 *October* 1991)

ABSTRACT: A new convenient stereoselective synthesis of β-brominated β'-(functional alkyl) α,β-unsaturated esters has been developed by the reaction of tetraalkylammonium fluoride in HMPA with ethyl 2,3-dibromo 2-(functional alkyl) propionates which can be easily prepared by addition of bromine to β'-(functional alkyl) acrylates . An interpretation of the observed stereoselectivity is proposed.

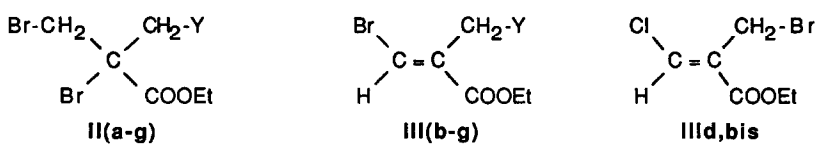
Many methods are available for the synthesis of β'- (functional alkyl) α,β-unsaturated esters **I**. They can be obtained efficiently from a Wittig-Horner reaction between phosphonic ester and aqueous formaldehyde in the presence of K_2CO_3 **(1)** or by coupling aldehyde and acrylic esters in the presence of DABCO as catalyst **(2,3)** (Scheme 1) . These Michael acceptors were used for the synthesis of biologically active products **(4,5,6)** and their electrophilic behaviour towards some organometallics was studied **(7,8)** .



I	a	b	c	d	e	f	g
Y	OH	OAc	F	Cl	Br	I	CH_2COOEt

Scheme 1

In this article we present our results on the nucleophilic behaviour of deactivated olefins **I(a-g)** towards bromine **(9)** providing polyhalogenated compounds **II(a-g)** which can then be transformed into previously unreported species **III(b-g)** and **IIId, bis** (Scheme 2) .



Scheme 2

A- BROMINATION OF β'-(FUNCTIONAL ALKYL) α,β-UNSATURATED ESTERS I(a-g)

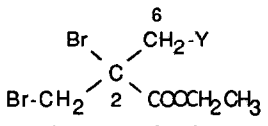
The addition of bromine to gem-difunctionalized alkenes **I(a-g)** at room temperature is very slow but

yields compounds **II(a-g)** . When the reaction temperature is raised to 76°C in CCl_4 the reaction rate is noticably increased as shown by the rapid disappearance of the bromine color. The boiling points and yields of polyhalogenated products **II(a-g)** are listed in Table1. Their structures are supported by IR, ^1H and ^{13}C NMR data (Table 2).

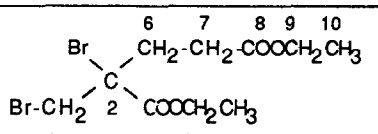
Table 1

	I	a	b	c	d	e	f	g
Yield (%)		69	73	75	80	80	83	73
Bp°C/mmHg		97/0,1	114/0,7	76/1,2	75/0,6	83/0,6	88/0,6	120/0,5

Table 2



II(a-f)



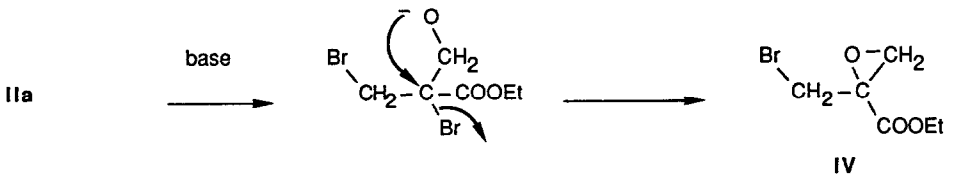
IIg

Ester II (a-g)	IR (cm^{-1})	NMR ^1H, δ(ppm), J(Hz) ($CDCl_3$/TMS)	NMR ^{13}C, δ(ppm), J(Hz) ($CDCl_3$/TMS)		
	1740(C=O)	1,33(3H,t,J=7);4,03(2H,AB,J=11)	35,73(C_1)	57,78(C_2)	165,70(C_3)
a	3600(O-H)	4,13(2H,s);4,33(2H,q,J=7)	62, 81(C_4)	13,80 (C_5)	62,43(C_6)
	1745(C=O)	1,33(3H,t,J=7);2,16(3H,s)	33, 31	56,92	169,15
b	1750(C=O)	4(2H,AB,J=11);4,31(2H,q,J=7) 4,58(2H,d,J=2)	62, 84 20,42($OC\underset{\underset{O}{\|}}{C}H_3$)	13,79 $O\overset{\overset{O}{\|}}{C}CH_3$)	64,06
		1,33(3H,t,J=7);4(2H,m)	33,21	56,53	166,29
c	1740(C=O)	4,33(2H,q,J=7);4,9(2H,d.d,J=5 and 46)	62,97	13,85	82,62 (d,J=-178,8)
		1,30(3H,t,J=7);4(2H,AB,J=11)	34,08	58,29	166,76
d	1740(C=O)	4,15(2H,AB,J=11);4,30(2H,q,J=7)	62,97	13,79	47,23
		1,31(3H,t,J=7);4,03(4H,AB,J=11)	35,78	57,77	165,70
e	1740(C=O)	4,30(2H,q,J=7)	62,79	13,79	35,78
		1,32(3H,t,J=7);4(2H,AB,J=11)	34,13	57,77	165,93
f	1740(C=O)	4,03(2H,AB,J=11);4,28(2H,q,J=7)	62,78	13,81	32,18
		1,30(6H,t,J=7);2,51(4H,s)	35,07(C_1)	60,73(C_2)	172,08(C_3)
g	1735(C=O)	3,93(2H,AB,J=11)	62,75(C_4)	14,80(C_5)	31,34(C_6)
	1740(C=O)	4,23(4H,q,J=7)	30,45(C_7) 13,86(C_{10})	167,95(C_8)	60,73(C_9)

B - STEREOSELECTIVE SYNTHESIS OF β-HALODERIVATIVES III(b-g)

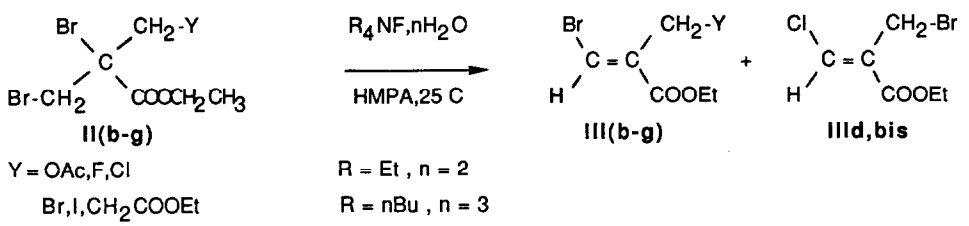
These results led us to undertake the synthesis of the unknown systems **III** bearing a bromine in the β position.

Treatment of **IIa** , under a various set of conditions (KOH /EtOH at 0°C , KF / 18-crown-6 in CH_2Cl_2 at reflux , NaOH/Et_2O at 0°C and $Bu_4NF,3H_2O$ /HMPA at 0°C) yielded epoxide **IV(10)** (Scheme 3).



Scheme 3

When **II(b-g)** are treated with bases such as hydroxides with or without the addition of phase transfer agent **(11)** or with alkoxides (EtONa , tBuOk ..) in the corresponding alcohols or DMSO **(12)**, uninteresting mixtures were obtained . However treatment of these polyhalogenated esters **II(b,c,e,f,g)** with a slight excess (1,5 equivalent) of tetraalkylammonium fluoride (R_4NF, nH_2O) **(13,14)** in HMPA at room temperature yielded the β-halo β'-(functional alkyl)α,β-unsaturated esters **III(b,c,e,f,g)**. These reactions are regio and stereoselective , the vinylic proton and ester group being in a cis configuration.

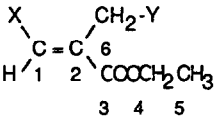


Under the same conditions, **IId** gave a mixture of **IIId** and **IIId, bis.** The isomers ratios are (10 : 90) and (45 : 55) respectively for the two reagents nBu_4NF, $3H_2O$ and Et_4NF, $2H_2O$. It should be noted that with the same reagents in DMF,the reaction is incomplete, even after three days . This is probably due to the lower efficiency of the base in DMF **(15,16)**. The best yields are obtained when esters **II(b-g)** are treated with nBu_4NF, $3H_2O$ (Table 3). Spectroscopic data (IR, ^1H and ^{13}C NMR) are consistent with the proposed structures of compounds **III(b-g)** and **IIId,bis** (Table 4). It is worth noting that there is good agreement between the experimental chemical shifts of vinylic protons and those calculated by Pascual's formula **(17)** (Table 3).

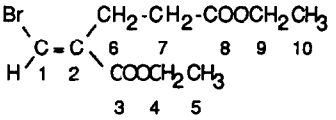
Table 3

Ester II(b-g)	β-Haloesters IIId	IIId,bis	Vinylic δH (ppm) found	calcd	Bp°C/mmHg	Yield(%)
b	100(E)	0	7,75	7,25	80/0,35	79
c	100(Z)	0	7,67	7,29	63/30	55
d	45(Z)	-	7,71	7,29	96 -100/30	70
d,bis	-	55(Z)	7,43	7,30		
e	100(Z)	0	7,69	7,29	130/30	79
f	100(Z)	0	7,66	7,29	60/0,2	73
g	100(E)	0	7,42	7,27	78/0,2	76

Table 4



III(b-f) X=Br , Y: (Scheme 1)
IIId,bis X=Cl , Y=Br

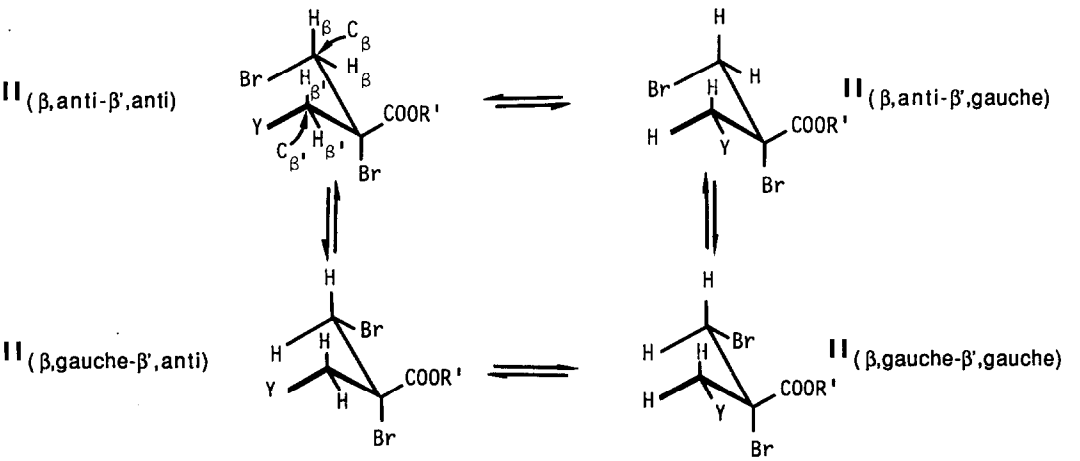


IIIg

Ester III(b-g)	IR (cm^{-1})	NMR ^{1}H, δ(ppm), J(Hz) (CDCl$_3$/TMS)	NMR ^{13}C, δ(ppm), J(Hz) (CDCl$_3$/TMS)		
b	1620 (C=C) and 1720 and 1740 (C=O)	1,33(3H,t,J=7);2,06(3H,s) 4,26(2H,q,J=7);4,96(2H,s) 7,8(1H,s)	128,36(C_1) 61,61(C_4) 20,55(O-C(=O)-CH_3)	133,37(C_2) 14,11(C_5)	170,32(C_3) 60,17(C_6) 163,4(O-C(=O)-CH_3)
c	1615(C=C) 1720(C=O)	1,33(3H,t,J=7);4,27(2H,q,J=7) 5,26(2H,d,J=10,5);7,67(1H,s)	121,85 (C_1) 61,93(C_4)	129,20(C_2) 14,18(C_5)	163,42(C_3) 76,70(C_6)
d	1610(C=C) 1720(C=O)	1,33(3H,t,J=7);4,18(2H,AB,J=11) 4,26(2H,q,J=7);7,71(1H,s)	132,78 61,80	136,75 14,18	163,10 23,16
d, bis	1610(C=C) 1720(C=O)	1,33(3H,t,J=7);4,36(2H,AB,J=11) 4,26(2H,q,J=7);7,43(1H,s)	132,52 61,80	136,75 14,18	163,10 36,82
e	1610(C=C) 1720(C=O)	1,33(3H,t,J=7);4,20(4H,AB,J=7) 4,23(2H,q,J=7);7,69(1H,s)	127,38 61,80	135,57 14,18	162,58 25,70
f	1610(C=C) 1720(C=O)	1,32(3H,t,J=7);4,26(2H,q,J=7) 4,3(2H,s);7,7(1H,s)	127,51 61,87	135,25 14,11	162,77 25,69
g	1610(C=C) 1715 and 1725(C=O)	1,26(6H,t,J=7);2,56 and 2,73(4H,2m);4,16(4H,q,J=7) 7,42(1H,s)	123,70(C_1) 61,28(C_4) 32,00(C_7) 14,18(C_{10})	136,80(C_2) 14,18(C_5) 162,63(C_8)	172,27(C_3) 25,37(C_6) 60,50(C_9)

DISCUSSION

Theoretically, four conformations $II_{(\beta,anti\text{-}\beta',anti)}$; $II_{(\beta,anti\text{-}\beta',gauche)}$; $II_{(\beta,gauche\ -\ \beta',anti)}$ and $II_{(\beta,gauche\ -\ \beta',gauche)}$ are compatible with the required transition states leading to β-elimination (Scheme 4).



Scheme 4

Removal of either H_β or $H_{\beta'}$ would provide two different regioisomers, however, in all cases but **IId**, the proton which is eliminated is H_β. The observed regioselectivity is quite ambiguous . It may be interpreted on the basis of the acidity of H_β when Y= CH_2COOEt,I,Br, Cl but not when Y=F, OAc . In contrast stereoselectivity can be easily rationalized by comparison of the stability of the two conformers $II_{\beta,anti}$ and $II_{\beta,gauche}$. In the corresponding Newman projections it appears that the former conformer is more favored than the latter with regard to steric and electronic effects (Scheme5).

$II_{\beta,anti}$ $II_{\beta,gauche}$

Scheme 5

In the case of **IId** , both H_β and $H_{\beta'}$ are involved in the elimination process .There is only partial regioselectivity , whereas stereoselectivity is conserved. The two most stable conformers $II_{\beta,anti}$(Scheme 5)

and $II_{\beta', anti}$ (Scheme 6) provide **IIId** and **IIId, bis** respectively having both the H and COOEt group in a cis arrangement .

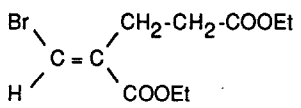
$II_{\beta',anti}$ $II_{\beta',gauche}$

Scheme 6

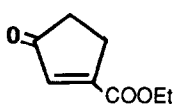
CONCLUSION

The present study has shown that bromine can be added easily to β'-(functional alkyl) acrylates **I(a-g)** providing polyhalogenated esters **II(a-g)** which can be transformed stereoselectively , in the presence of a suitable base , into β-bromo-β' (functional alkyl) acrylic acid esters **III(b-g)** and **IIId,bis.**

Such multifunctional molecules might be considered as useful substrates for various inter and intramolecular stereochemically controlled reactions . For example it would be reasonable to assume that a potential precursor of prostaglandins such as cyclopentenone **V** could be generated from **IIIg (18).**



IIIg



V

EXPERIMENTAL

The bromination reactions of different functionalized vinylic esters were achieved in 250 ml flasks equipped with magnetic stirrers, reflux condensers and dropping funnels. Carbon tetrachloride was distilled from $CaCl_2$ and stored over 4Å sieves. HMPA was purified by distillation. Reaction progress was monitored on a Intersmat 20 M gas chromatograph using a 3 m X 3mm column packed with 10 % SE 30.

^1H and ^{13}C NMR spectra were recorded on a JEOL C-HL 60 MHz and JEOL FX90MHz spectrophotometers with tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer.

The α – hydroxyalkylated acrylic esters **Ia** and the related compounds **I(b-g)** were prepared according to procedures given in references **(1,2).** Diethyl α-methyleneglutaric acid ester **Ig** was prepared according to the procedure given in reference **(8).**

BROMINATION OF β' - (FUNCTIONAL ALKYL) α,β-UNSATURATED ESTERS I(a-g)

General procedure

A solution of bromine (52 mmol) in CCl_4 (2O ml) was added dropwise to a refluxing solution of α,β-unsaturated ester(50mmol) in CCl_4 (100 ml) at such a rate that the bromine color gradually disappeared. The end of the reaction is indicated by the persistence of a brownish color . Excess bromine was removed by washing with aqueous solution of sodium thiosulfate . The organic layer was then washed and dried over magnesium sulfate. Filtration and removal of the solvant gave an oil which was purified by distillation under reduced pressure (Table1) .

SYNTHESIS OF β-HALODERIVATIVES III(b-g)

General procedure

To a solution of tetralkylammonium fluoride (R_4NF, nH_2O, R=Et, nBu) in (45mmol) HMPA (2Oml) was added dropwise with stirring at O°C, 3O mmol of di or trihalogenated ester **II(b-g)**. The reaction mixture was allowed to warm at room temperature and monitored by **G.C** until the starting halogenated ester had disappeared . The brown mixture was cooled to O°C and then neutralized with an aqueous solution of sulfuric acid (2N) (40 ml).The solution was extracted with hexane (40mlx5). The organic layers were combined and washed with water, dried over $MgSO_4$ and evaporated to give a crude oil. Distillation of the crude oil gave pure β-halogenated vinylic esters **III** (Table 3).

References

1. Villieras , J.; Rambaud,M. *Synthesis ,1982 , 924 and references cited therein .*
2. a)Hoffmann, H.M.R.; Rabe,J. *J. Org. Chem. 1985, 50,3849 . b) Angew. Chem. ,Int. Ed. Engl., 1983,22,795 . c) Angew. Chem., Int. Ed. Engl. 1985, 24,94.*
3. a)Brand,M; Drewes,S.E.; Pross,G.H.P . *Synth. Comm. 1986 , 883* . b) Papageorgiou,C; Benezra,C . *Tetrahedron Lett. 1984 , 25, 1303.*
4. Ohler,E.; Reininger,K ; Schmidt,U . *Angew. Chem., Int. Ed. Engl. 1970, 91, 57.*
5. Amri,H.; Rambaud,M.; Villieras,J . *Tetrahedron Lett. 1989, 30, 7381*
6. a) Grieco,P.A. *Synthesis, 1975 , 67 and references cited therein* . b) Loffler,A.; Pratt, R.D.; Pucknat,J.; Gelbard,G.; Dreiding,A.S. *Chimia, 1969 , 23 , 413* . c) Belaud,C.; Roussakis,C.; Letourneux,Y.; El Alami,N. ; Villieras,J . *Synth . Comm . 1985 ,11 , 1233* .
7. Amri,H .; Rambaud , M.; Villieras ,J . *J. Organomet. Chem. 1986 , C27, 308* .
8. Amri ,H.; Rambaud , M.; Villieras , J . *J. Organomet. Chem. 1990, 384, 1 and Tetrahedron, 1990, 46,3535.*
9. Mc Cleland, C. W. *synthetic Reagents, Pizey, J.S. Ellis Horwood Ltd., Vol. 5 , p. 107.*
10. IV: NMR ^1H ($CDCl_3$ / TMS) : 1,33(3H,t, J=7Hz); 3,16(2H,AB, J=6Hz) ; 3,73(2H,AB, J=11Hz) 4,3(2H,q, J=7Hz).
11. Charlton , J.L., Sayeed , V.A. , Lypka, G.N. .*Synth. Comm. 1981, 11,931.*

12. a) Norman, R.O.C.; Thomas, C.B. *J. Chem.Soc.* **1967** , *C 1115.* b) Traynham ,J.G.; Stone,D.B.; Couvillion,J.L., *J. Org. Chem.* **1967** ,*32, 510 and references cited therein .*
13. Bartsch,R.A.; *J.Org. chem.,* **1970**, *35, 1334 .*
14. Chollet,A.,J.P. Hagenbuch,J.P.; Vogel,P. *Helv. chim. acta* **1979** , *62, 511.*
15. Normant,J.F.; Deshayes,H. *Bull. Soc. Chim. Fr.* **1967** , *2455.*
16. Parker, A.J. *Quart. Rev.* **1962** , *163 .*
17. Pascual .C.; Meier,J.; Simon,W. Helv. *Chim. Acta* **1966**, *49,164.*
18. Bindra, J.S.;*The total Synthesis of Natural Products, Ap Simon , J. Wiley - Interscience Publication , New York (***1981***) , vol.4 , p . 353 .*