Journal de la Société Chimique de Tunisie
Volume III - n° 4 - Décembre 1992

DIRECT SUBSTITUTION OF VINYLIC BROMINE BY AN AMINO GROUP: SYNTHESIS OF DIMETHYL-α-(AMINOMETHYLENE) GLUTARIC ACID ESTERS

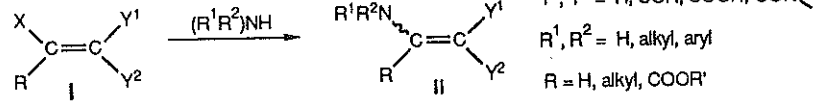
T. BEN AYED*, H. AMRI*, M.M. EL GAIED*, J. VILLIÉRAS**
* *Laboratoire de chimie organique, Département de chimie, Faculté des sciences, Campus universitaire, 1060 Tunis, Tunisie.*
** *Laboratoire de synthèse organique associé au CNRS, Faculté des sciences et des techniques, F-44072 Nantes Cedex 03, France.*

(Soumis en mars 1992, accepté en juin 1992)

Résumé: La substitution nucléophile de l' (E)-α-(bromométhylène)glutarate de diméthyle par des amines conduit, avec de bons rendements, à la formation des énamines correspondantes dont la stéréochimie a été déterminée par RMN.

Abstract: *Nucleophilic subtitution of bromine by amines on (E)-α-(Bromomethylene)glutaric acid ester leads to the corresponding enamines in high yields. Stereochemistry of the corresponding products is determined .*

Diversely substituted β-amino-α,β-unsaturated acid derivatives of type **II** are useful intermediates in organic synthesis (1-13). They are mostly prepared by the substitution of a vinylic halogen by an amine on type **I** molecules (scheme 1).

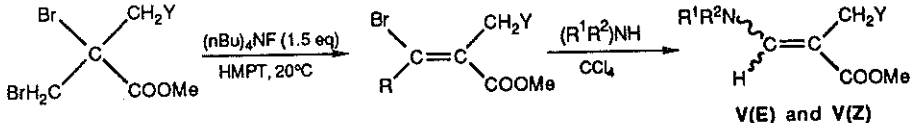


Scheme 1

Other methods involve the preparation of enamines from β-ketoesters (14,15), the reaction of β-bromoesters on nitriles (16) or their synthesis from thioamides (17).

It has been shown that the mechanism and the stereochemistry of the substitution reaction depend on the nature of the withdrawing groups and the configuration of the β-halogenovinylic compounds **I**, on the nucleophilicity of the amine and the conditions of the reactions (18-23).

Among the preparation of polyfonctionalized enamines, we wish to report here the synthesis of a new class of dimethyl α-(aminomethylene)glutaric acid esters **V** which can be efficiently carried out by reaction of primary and secondary amines on the **(E)**-brominated derivative **IV** (recently obtained by regio and stereoselective dehydrobromination of **III**) (24) in HMPT (scheme 2).



Scheme 2

Treatment of the halovinylic diester **(E)-IV** by secondary amines (pyrrolidine, morpholine and diethylamine) gives exclusively the corresponding enamines **V(f-h)** with retention of configuration, while in the presence of primary amine (n-propyl, n-butyl, isobutyl, cyclohexyl and benzylamine), the substitution leads to the formation of a mixture of **(E+Z)** enamines **V(a-e)**, the proportions of which depend on the bulk of amines (table 1).

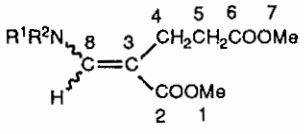
Table 1

Amine R_1	Amine R_2	Reaction time(h)	Bp°C mmHg	Yield %	Enamine V%	(E)	(Z)
$n\text{-}C_3H_7$	H	36	122/0.35	91	a	35	65
$n\text{-}C_4H_9$	H	24	-	89	b	40	60
$i\text{-}C_4H_9$	H	36	120/0.3	87	c	50	50
$c\text{-}C_6H_{11}$	H	12	-	82	d	60	40
$C_6H_5\text{-}CH_2$	H	12	-	87	e	75	25
C_2H_5	C_2H_5	7	130/0.3	77	f	100	0
$-(CH_2)_4-$		3	-	73	g	100	0
$-(CH_2)_2\text{-}O\text{-}(CH_2)_2-$		5	F:42-43°C	91	h	100	0

Structures of enamines **(E)-V(a-h)** and **(Z)-V(a-e)** are determined according to their characteristic spectral data (26, 27) (tables 2 and 3).

Table 2

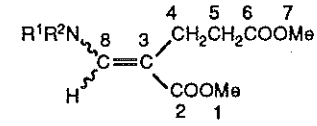
Enamines **V(a-h)**:
IR ν (cm^{-1}) and NMR ^1H($CDCl_3$/TMS), δ(ppm), J(Hz)



V	ν(C=C)/(C=O)	δH¹ and δH⁷	δH⁴ and δH⁵	δH⁸ (Z)	δH⁸ (E)	R¹, R²
a	1635/1685 1730	3.66, 3.72 (2s, 6H)	2.30, 2.40 (2s, 4H)	6.63 (d, 13Hz)	7.26 (d, 14Hz)	0.93 (t, 7Hz, 3H) ; 1.5 (sx, 7Hz, 2H) ; 3.1 (m, 2H) ; 7.8 (br,NH)
b	1645/1675 1730	3.56, 3.63 (2s, 6H)	2.33, 2.40 (2s, 4H)	6.56 (d, 13Hz)	7.20 (d, 14Hz)	0.93 (t, 7Hz, 3H) ; 1.1-1.7 (m, 4H) ; 3.1(m, 2H) ; 7.8 (br, NH)
c	1630/1670 1730	3.56, 3.64 (2s, 6H)	2.34, 2.43 (2s, 4H)	6.57 (d, 12Hz)	7.26 (d, 14Hz)	0.92 (d, 7Hz, 6H) ; 1.67 (m, 1H) ; 2.9 (t, 7Hz, 2H) ; 7.9 (br, NH)
d	1635/1670 1730	3.56, 3.63 (2s, 6H)	2.36, 2.43 (2s, 4H)	6.70 (d, 13Hz)	7.40 (d, 13Hz)	1.2(m, 11H) ; 7.8(br,NH)
e	1645/1675 1730	3.57, 3.63 (2s, 6H)	2.24, 2.30 (2s, 4H)	6.66 (d, 14Hz)	7.29 (d, 14Hz)	4.26 (d, 7Hz, 2H) ; 7.23 (m, 5H) ; 8.1 (br, NH)
f	1625/1675 1730	3.60, (1s, 6H)	2.43 (m, 4H)	-	7.16(s)	1.2 (t, 7Hz, 6H) ; 3.3 (q, 7Hz, 4H)
g	1665/1680 1730	3.61, (1s, 6H)	2.50 (m, 4H)	-	7.43(s)	1.93 (m, 4H) ; 3.5 (t, 7Hz, 4H)
h	1625/1680 1730	3.66, (1s, 6H)	2.56 (m, 4H)	-	7.23(s)	3.40(m, 4H) ; 3.7(m, 4H)

Table 3

Enamines **V(a-h)**:
NMR^{13}C($CDCl_3$/TMS), δ(ppm)



V	C-1	C-7	C-2	C-3	C-4	C-5	C-6	C-8	R_1, R_2
a (E)	51.6	50.7	174.1	95.8	35.8	20.1	170.4	148.4	50.7, 24.9, 11.5
a (Z)	51.3	50.3	175.6	91.7	33.6	26.1	169.7	152.5	
b (E)	51.5	50.6	174.9	95.8	35.4	20.0	170.6	148.6	48.7, 48.3 19.7, 13.7
b (Z)	51.2	50.3	175.5	91.5	33.5	26.0	169.8	152.6	
c (E)	51.5	50.6	174.0	95.6	35.4	20.0	170.5	148.9	56.6, 30.1, 19.7
c (Z)	51.1	50.2	175.5	91.2	33.4	26.0	169.7	152.9	
d (E)	51.5	50.5	174.0	95.9	35.0	20.0	170.4	146.6	56.5, 34.4, 24.7 24.5, 24.5 ,24,5
d (Z)	51.2	50.2	175.4	91.5	32.9	26.1	169.5	150.6	
e (E)	51.4	50.6	173.9	97.1	35.3	20.0	170.3	148.2	52.0, 128.7, 128.2 127.9, 127.4
e (Z)	51.2	50.4	175.3	92.9	33.3	25.9	169.4	152.0	127.1, 127.0
f (E)	51.3	50.9	173.8	94.3	35.3	21.3	170.9	147.2	47.5, 14.6
g (E)	51.3	50.8	173.4	95.5	35.9	21.3	170.4	146.0	51.3, 25.4
h (E)	51.4	51.1	173.4	97.2	34.6	21.5	170.5	147.9	50.8, 66.7

Experimental

Dimethyl α-(bromomethylene)glutaric acid ester **(E)-IV** used in the enamines synthesis **V(a-h)** was prepared according to references (24, 25).

The amines and the carbon tetrachloride were distilled before use. The progress and the end of the substitution reaction were controlled by GLC (Intersmat 20 M chromatograph using 3mx3mm column packed with 10% SE30). The yields of enamines were calculated on the basis of pure distilled **V(a,c,f)** or purified on silica gel **V(b,d,e,g,h)** products.

Infrared spectra were recorded on a Perkin-Elmer 257 infrared spectrophotometer as liquid films in $CHCl_3$ solution. ^1H and ^{13}C NMR spectra were recorded respectively on a JEOL C-HL-60 MHz and a JEOL FX - 90MHz spectrophotometers in $CDCl_3$ solution, with TMS as the internal standard .

General procedure

To a refluxed solution of **(E)**-dimethyl-α-(bromomethylene)glutaric acid ester **IV** (10 mmol) in 30 ml of carbon tetrachloride, the amine (40 mmol) was added dropwise over 30 minutes. The precipitate was filtered and the filtrate was poured into brine. The aqueous layer was extracted with methylene chloride (3x10ml) and the combined organic extracts were dried over $MgSO_4$. The oily residue obtained after evaporation of solvents in vacuo was taken up in dry ether and filtered again. Removal of ether led to a crude material which was purified by distillation under reduced pressure or by chromatography on silica gel (CH_2Cl_2-ether 60:40).

Aknowlegement : we thank the FNRST and the CNRS for financial support.

References

1 - Schmidt, R. R.; Talbiersky, J., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 204 - 205
2 - Sukari, M. A; Vernon, J. M , *Tetrahedron* **1983**. *39*, 793-796
3 - Adams, D.R; Dominguez, J. N; Pérez,J. A , *Tetrahedron Lett.* **1983**, *24*, 517 - 518
4 - Wasserman, H. H; Han, W. T , *Tetrahedron Lett.* **1984**, *25*, 3743 - 3746
5 - Tomioka, K.; Seo, W., Andò; K., Koga, K., *Tetrahedron Lett.* **1987**, *28*, 6637 - 6640
6 - Celerier, J. P.; Haddad, M.; Jacoby, D.; Lhommet, G. L., *Tetrahedron Lett.* **1987**, *28*, 6597 - 6600
7 - Schlessinger, R.; Tata, J. R.; Springer, J. P., *J. Org. Chem.* **1987**, *52*, 708 - 710
8 - Makabe, O.; Murai, Y.; Fukatsu, S., *Heterocycles* **1979**, *13*, 239 -246
9 - Mac Laren, J. A.; *Aust. J. Chem.* **1972**, *25*, 1293 -1299
10 - Kotodziejczyk, A. M.; Slebioda, M., *Synthesis* **1984**, 865 - 866
11 - Pohland,A. E.; Benson, W. R., *Chem. Rev.* **1966**, *66*, 161 - 197.
12 - Schmidt,R. R.; Talbiersky, J., *synthesis* **1977**, 869-871
13 - Grosdemange-Pale, C.; Chuche, J., *Tetrahedron Lett.* **1985**, *26*, 6183 - 6184
- Coqueret, X.; Bourelle-Wargnier, F.; Chuche, J., *Tetrahedron* **1986**, *42*_2263-2273
14 - Reynolds, G. A.; Hauser, C. R., *Org. Synth. Coll. vol. 3* **1955**, 374 - 375
15 - Mc Murry, J. E., *Org. Synth. Coll. vol 6* **1974**, 592 - 593
16 - Hannick, S. M.; Kishi, Y., *J. Org. Chem.* **1983**, *48*, 3833 - 3835.
17 - Sauvé, G; Le Berre, N.; Zacharie, B., *Tetrahedron Lett.* **1988**, *29*, 2299-2302
18 - Truce, W. E.; Gorbaty, M. L., *J. Org. Chem.* **1970**, *35*, 2113 - 2117.
19 - Chalchat, J. C.; Théron, F.; Vessière, R. , *Bull. Soc. Chim. Fr.* **1970**, 4486 - 4490
20 - De Ancos, B; Carmen. Maestro, M.; Martin, M. R. ; Farina, F. , *Synthesis* **1988**, 136 - 138
21 - Farina, F; Martin, M. V.; Sànchez, F., *Synthesis* **1983**, 397 - 98 *and references cited therein.*
22 - Rappoport, Z., *Acc. Chem. Res.* **1981**, *14*, 7.
23 - Chalchat, J. C.; Théron, F. , *Bull. Soc. Chim. Fr.* **1973**, 3361 - 3366.
24 - Ben Ayed, T; Amri, H.; El Gaïed, M. M., *Tetrahedron* **1991**, *47*, 9621 - 9628.
25 - Amri, H.; Rambaud, M.; Villieras, J., *J. Organomet. Chem.* **1990**, *381*, 1 - 11
- Amri, H.; Rambaud, M.; Villieras, J., *Tetrahedron* **1990**, *46*, 3535 - 3546.
26 - Pascual, C.; Meier, J.; Simon, W., *Helv. Chim. Acta.* **1966**, *42*, 164 - 168
27 - Barillier, D.; Strobel, M. P.; Paquer, D.; Morin, L., *Tetrahedron* **1983**, *39*, 767 - 775.