Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Synthesis of Thiazolidino [3,2-a] Pyrimidine Derivatives

Edwige Jeanneau-Nicolle [a], Martine Benoit-Guyod [a] & Gérard Leclerc [a]

[a] Groupe de Pharmacochimie Moléculaire, Laboratoire de Chimie Organique , UFR de Pharmacie - Université Joseph Fourier , (Grenoble I), BP 138, 38240, Meylan-Cedex, France

Published online: 24 Sep 2006.

To cite this article: Edwige Jeanneau-Nicolle , Martine Benoit-Guyod & Gérard Leclerc (1991) One-Pot Synthesis of Thiazolidino [3,2-a] Pyrimidine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:14, 1443-1454, DOI: 10.1080/00397919108016417

To link to this article: http://dx.doi.org/10.1080/00397919108016417

SYNTHETIC COMMUNICATIONS, 21(14), 1443-1454 (1991)

ONE-POT SYNTHESIS OF THIAZOLIDINO [3,2-a] PYRIMIDINE DERIVATIVES.

Edwige Jeanneau-Nicolle, Martine Benoit-Guyod *
and Gérard Leclerc.

* Groupe de Pharmacochimie Moléculaire, Laboratoire de Chimie Organique, UFR de Pharmacie - Université Joseph Fourier (Grenoble I), BP 138, 38240 Meylan-Cedex, France.

Dedicated to Prof. André Boucherle who inspired this work.

Abstract : Reaction of 2-aminothiazoline with an aromatic aldehyde and an activated methylene group (malonitrile, diethylmalonate or ethylcyanoacetate) gave the title compounds. The structures are unambiguously assigned using spectroscopic data and chemical proofs.

Since late 1970, our laboratory has been interested in heterocycles containing both sulfur and nitrogen atoms such as aminothiazoline and thiazolidine derivatives[1-5]. More specifically, 2-aminothiazoline derivatives are immunomodulators[6-8], psychotrops[7-9], and anticancer agents[9-10].

Report here is an easy and fast method for the synthesis of new 2-aminothiazoline derivatives namely thiazolidino [3,2-a] pyrimidines. The structures obtained are unambiguously identified. The reaction needs an activated methylene group derivative, an aromatic aldehyde

and 2-aminothiazoline. It is generally admitted that this type of reaction proceeds *via* a 1,4-nucleophilic addition of 2-aminothiazoline on the benzylidene intermediate[11]. Noteworthy when the methylene group compound contains only one electron attractive substituent (*e.g.* benzyl cyanide) the cyclisation failed as it was reported for pyrazolo [1,5-a] pyrimidine derivatives[12].

As expected 2-aminothiazoline, with its two nitrogen atoms which behave as main reactionnal sites, gives two kinds of regio-isomers[13-14] : 5- and 7-oxo, and 5- and 7-amino (Reaction Scheme 1) whose structures are assigned by spectroscopy (^{1}H-NMR, ^{13}C-NMR, IR, UV, MS).

The main products obtained by Method A (**7a-d** and **5a-d**, Table 1) are dihydropyrimidines. Those obtained by Method B (**7e-f** and **5g-h**, Table 2) and Method C (**5i-p**, **5s-t** and **7l-m**, Table 3) are non hydrogenated pyrimidines.

The preparation of oxothiazolidino [3,2-a] pyrimidines (**5a-f** and **7a-f**) requires a basic ethanol medium (piperidine or potassium carbonate) while the formation of aminothiazolidino [3,2-a] pyrimidines (**5i-p** and **7l-m**) requires neither acid nor basic medium.

For the first time in the oxothiazolidino [3,2-a] dihydropyrimidine series, the structure of regioisomers has been unambiguously confirmed by the synthesis of **5**, a reference compound, as described in a Rhône-Poulenc patent (Method E)[15].

The structure of this compound has been established by X-ray radiocrystallography (Debarre *et al.*, unpublished results). It is the same product that we obtained by decarboxylation of **5a** (Method D)[16-17] (Reaction Scheme 2). Physico-chemical and spectroscopic data of **5** and decarboxylated **5a** allows us to attribute a 5-oxo structure to **5a**. Accordingly, **5b**, **5c** and **5d**, having the same spectroscopic characteristics, can be considered as 5-oxo derivatives.

In the synthesis of aminothiazolidino [3,2-a] pyrimidines, it was possible to find together with **5i** and **5l**, the compounds **5s** and **5t**

Reaction Scheme 1

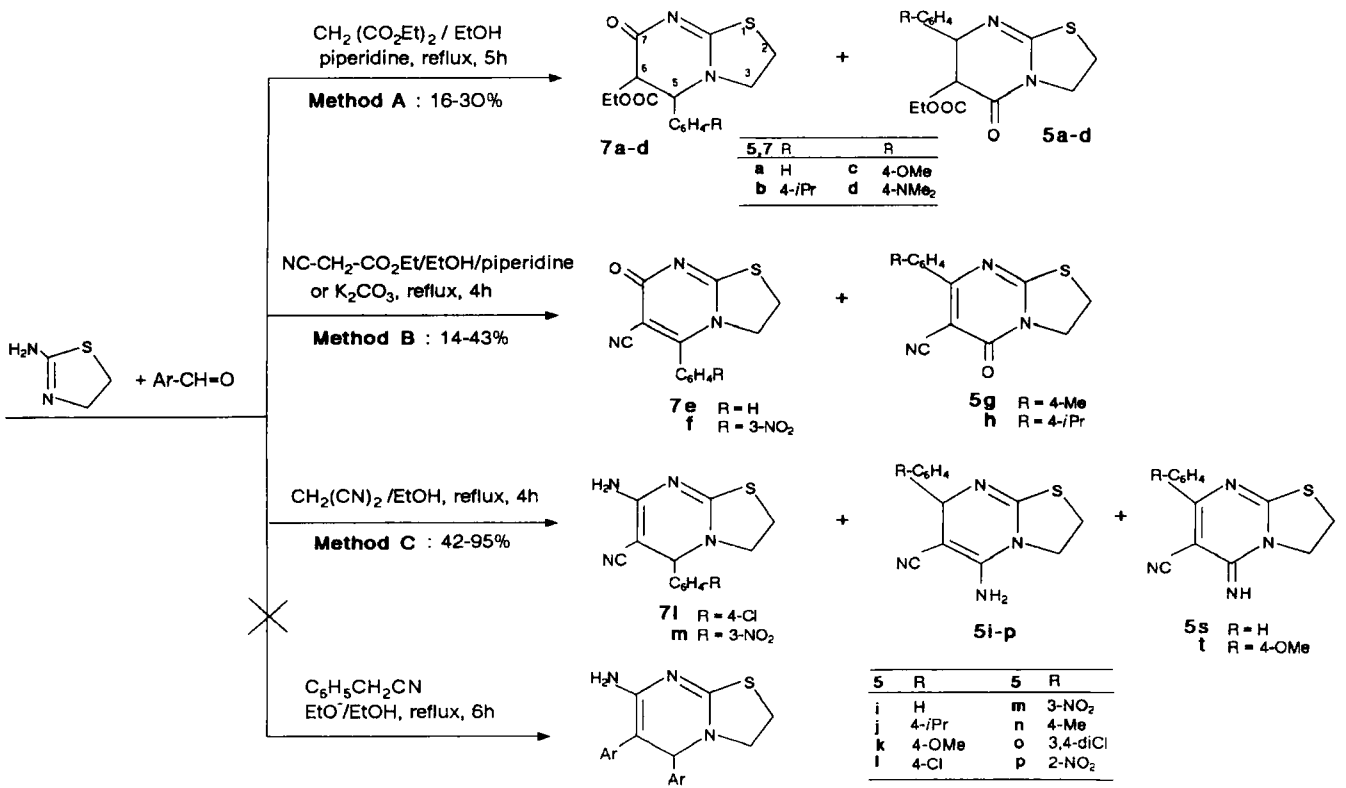


Table 1. 5- and 7-oxo-thiazolidino [3,2-a] dihydropyrimidine-6-ethylcarboxylates (Method A) and compound 5

Product [a]	mp. (°C)	Yield [b] %	Molecular Formula [c]	MS(70 e.v.) m/z (%)	IR [d] ν (cm^{-1})	UV [e] λ max (nm)	^{1}H NMR($CDCl_3$) [f] δ (ppm), J (Hz)
5	115-116 115 (Lit.[15])	50[g] 10[h]	$C_{12}H_{11}N_2S$	-	1685,1625		4.27-3.96(2m,2H),3.33(t,2H) 2.73-2.39(2q,2
5a	112-113	11	$C_{15}H_{16}N_2O_3S$ (304.4)	304(5) 231(100)	1725,1690 1630,1020	225.7	5.13(d,1H,J=10.6),4.13(q,2H) 4.30-4.06(2m,2H),3.53(d,1H,J=10.6), 3.26(t,2H),1.13(t,3H)
7a	142-143	5	$C_{15}H_{16}N_2O_3S$ (304.4)	304(15) 131(100)	1730,1660 1520,1020	254.5	4.98(d,1H,J=7.3),4.15(q,2H), 3.71(t,2H)3.65(d,1H,J=7.3) 3.36-3.23(2m,2H)1.17(t,3H)
5b	123-124	4	$C_{18}H_{22}N_2O_3S$ (346.5)	346(11) 273(100)	1730,1690 1620,1020	221.9	5.12(d,1H,J=9.7),4.12(q,2H) 4.26-4.08(2m,2H),3.55(d,1H,J=9.7) 3.25(t,2H),1.13(t,3H)
7b	152-153	12	$C_{18}H_{22}N_2O_3S$ (346.5)	346(10) 218(100)	1730,1670 1530,1020	254.5	4.93(d,1H,J=7.4),4.09(q,2H) 3.68(t,2H),3.62(d,1H,J=7.4) 3.29-3.21(2m,2H),1.11(t,3H)
5c	oil	4	$C_{16}H_{18}N_2O_4S$ (334.3)	334(20) 261(100)	1730,1690 1630,1020	226.5	5.14(d,1H,J=10.0),4.16(q,2H) 4.30-4.14(2m,2H),3.57(d,1H,J=10.1) 3.30(t,2H),1.18(t,3H)
7c	154-155	26	$C_{16}H_{18}N_2O_4S$ (334.3)	334(4) 206(100)	1730,1660 1520,1020	254.5	4.96(d,1H,J=7.8),4.16(q,2H) 3.71(t,2H)3.68(d,1H,J=7.8) 3.34-3.24(2m,2H)1.20(t,3H)
5d	118-119	7	$C_{17}H_{21}N_3O_3S$ (347.4)	347(15) 274(100)	1740,1700 1640,1040	259.7	5.02(d,1H,J=9.5),4.08(q,2H) 4.19-4.04(2m,2H),3.48(d,1H,J=9.5) 3.19(t,2H),1.12(t,3H)
7d	170-171	14	$C_{17}H_{21}N_3O_3S$ (347.4)	347(23) 219(100)	1745,1670 1530,1040	259.5	4.78(d,1H,J=8.6),4.05(q,2H) 3.50(t,2H),3.57(d,1H,J=8.5) 3.20-3.12(2m,2H),1.09(t,3H)

[a] Recrystallization from 95% EtOH. [b] Yield of analytical product. [c] Satisfactory microanalyses obtained: C±0.29; H±0.15; N±0.26. [d] IR in KBr 2%. [e] UV in absolute EtOH. [f] Except **5** (CD_3COCD_3). Only principal groups of protons. [g] Method D. [h] Method E.

Table 2. 5- and 7-oxothiazolidino [3,2-a] pyrimidine-6-carbonitriles (Method B)

Product [a]	mp. (°C)	Yield [b] %	Molecular Formula [c]	IR [d] ν (cm^{-1})	UV [e] λ max (nm)	^{1}H NMR (DMSO d6) [f] δ (ppm)
7e	179-180	14	$C_{13}H_9N_3OS$ (257.3)	2217,1665,1540, 1485,1030	245	4.56(t,2H),3.68(t,2H)
7f	191-192	43	$C_{13}H_8N_4O_3S$ (300.3)	2210,1660,1545, 1500,1030	247.9	4.59(t,2H),3.71(t,2H)
5g	230-231	38	$C_{14}H_{11}N_3OS$ (269.3)	2220,1655,1550, 1490,1035	296	4.54(t,2H),3.67(t,2H)
5h	160-161	24	$C_{16}H_{15}N_3OS$ (297.4)	2225,1660,1550, 1490,1032	297.7	4.58(t,2H),3.55(t,2H)

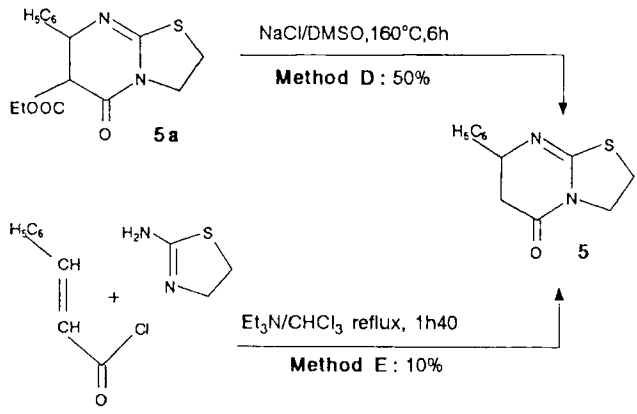
[a] Recrystallization from 95% EtOH except compound **7f** (95%EtOH/DMSO) and **5g** (DMSO)
[b] Yield of analytical product. [c] Satisfactory microanalyses obtained: C ± 0.16 ; H ± 0.21 ; N ± 0.13.
[d] IR in KBr 2%. [e] UV in absolute EtOH. [f] Only principal groups of protons.

Table 3. 5- and 7-aminothiazolidino [3,2-a] pyrimidine-6-carbonitriles.(Method C)

Product [a]	mp. (°C)	Yield [b] %	Molecular Formula [c]	MS(70 e.v.) m/z (%)	IR [d] ν (cm^{-1})	UV [e] λ max (nm)	^{1}H NMR(DMSO d_6) [f] δ (ppm),J (Hz)
5i	196-197	90	$C_{13}H_{12}N_4S$ (256.3)	256(100) 179(83)	3330-3180, 2180,1660	214(307)	6.46(s,2H),5.13(s,1H) 3.97(m,2H,),3.28(t,2H),
5j	190-191	42	$C_{16}H_{18}N_4S$ (298.4)	-	3360-3195, 2200,1655	215(312)	5.69(s,2H),5.17(s,1H)4 4.08(m,2H),3.69(t,2H)
5k	194-195	70	$C_{14}H_{14}N_4S$ (286.4)	286(100) 219(94)	3360-3120, 2190,1660	216(305)	6.46(s,2H),5.14(s,1H), 3.98(m,2H),3.28(t,2H)
5l	196-197	40	$C_{13}H_{11}ClN_4S$ (290.8)	179(100) 291(21)	3380-3170, 2190,11660	217(310)	6.55(s,2H),5.22(s,1H),, 4.04(t,2H),3.35(t,2H)
7l	214-215	5	$C_{13}H_9ClN_4S$ (290.8)	179(100) 291(5)	3370-3180, 2190,1650-1590	242(342)	6.18(s,1H),5.20(s,1H), 3.72-3.262m,2H),3.26(t,2H)m
5m	180-181	70	$C_{13}H_{11}N_4O_2S$ (301.3)	179(100) 301(25)	3350-3200, 2200,1650	216(309)	6.59(s,2H),5.38(s,1H), 4.02(m,2H),3.32(t,2H)
7m	250-251	5	$C_{13}H_{11}N_4O_2S$ (301.3)	179(100) 301(13)	3360-3220, 2200,1660-1590	245(342)	6.29(s,2H),5.43(s,1H), 3.70-3.24(2m,2H)3.28(t,2H)
5n	198-199	73	$C_{14}H_{14}N_4S$ (270.4)	-	3350-3140, 2190,1650	216(302)	6.47(s,2H),5.15(s,1H), 4.04(m,2H),3.34(t,2H)
5o	190-191	50	$C_{13}H_{10}Cl_2N_4S$ (325,2)	-	3350-3190, 2190,1660	214(309)	5.83(s,2H)5.26(s,1H) 4.19(m,2H),3.72(t,2H)
5p	182-183	90	$C_{13}H_{11}N_4O_2S$ (301.3)	-	3345-3180, 2200,1670	216(294)	6.73(s,2H),5.80(s,1H), 4.05(dt,2H),3.34(t,2H)

[a] Recrystallization from 95% EtOH (except **5i** : EtOH/DMSO (95:5) , **5j** : 60% EtOH , **5p** : absolute EtOH).
[b] Yield of pure product. [c] Satisfactory microanalyses obtained: C ± 0.30 ; H ± 0.29 ; N ± 0.37. [d] IR in KBr 2%
[e] UV in absolute EtOH. [f] Except **5j** and **5o** : in CD_3COCD_3

Reaction Scheme 2



(Table 4) which are iminothiazolidino [3,2-a] pyrimidines. ^{1}H NMR and MS data agree with these structures. Moreover oxidation of the amine **5i** by hydrogen peroxide in ethanol refluxing (48 h) gives the imine **5s** and allows us to unambiguously attribute a 5-imino structure to derivatives **5s** and **5t**.

Experimental Section:

Material and Methods: TLC analyses were performed on Kieselgel 60 F_{254} or neutral aluminium oxide 90 F_{254} plates, column chromatography was performed with Kieselgel 40 (0.063-0.200 mm) or neutral aluminium oxide 90 (0.063-0.200 mm) purchased from Merck. Most commercially available reagents were purchased form Aldrich, Fluka or Prolabo at a purety of 98% or better. Only aromatic aldehydes were distilled before use.

Table 4. Iminothiazolidino [3,2-a] pyrimidine-6-carbonitriles (Method D)

Product [a]	mp. (°C)	Yield [b] %	Molecular Formula [c]	MS(70 e.v.) m/z (%)	IR [d] ν (cm^{-1})	UV [e] λ_{max} (nm)	^{1}H NMR(DMSO d_6) [f] δ (ppm),J (Hz)
5s	202-203 (254.3)	5	$C_{13}H_{10}N_4S$	254(100) 1615,1540	3280,2200, 274,217)	258(358, 3.65(t,2H)	7.22(s,1H),4.45(t,2H)
5t	214-215 (284.3)	5	$C_{14}H_{12}N_4S$	284(100) 1620,1580	3280,2200,	215(312) 3.64(t,2H)	7.20(s,1H),4.43(t,2H)

[a] Recrystallization of **5s** : EtOH/DMSO (95:5), of **5t** : 95% EtOH.
[b] **5s** is formed with **5l** (yield 90%) and **5t** with **5k** (yield 70%).
[c] Satisfactory microanalyses obtained: C±0.21; H±0.01; N±0.40
[d] IR in KBr 2%
[e] UV in absolute EtOH
[f] Only principal groups of protons.

Melting points were determinated on a Kofler bench and are uncorrected. IR spectra (KBr 2%) were recorded on a Philips PU SP3-100 spectrophotometer. UV spectra (absolute ethanol) were recorded on a Philips PU SP7-100 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were obtained on Bruker WP 100, Bruker AC 200, Bruker AM 300 and Bruker AM 400 MHz spectrometers. Mass spectra were determined on NERMAG quadrupole R10-10C using an ionization voltage of 70 eV [electron impact (E.I.) spectra].

Method A : 5- and 7-oxothiazolidino [3,2-a] dihydro-pyrimidine-6-ethylcarboxylates (5a-d + 7a-d).

To a stirred solution of 2-aminothiazoline (10.2 g,100 mmol), diethyl malonate (16 g, 100 mmol), and aromatic aldehyde (100 mmol) in absolute ethanol (300 mL), are added five drops of piperidine. The reaction mixture is heated under reflux for 5 h, and monitored by TLC on silica plates [eluent : toluol/methanol (80:20) or EtOAc/hexane (50:50)].

7-oxo products generally crystallize from the solution concentrated to 20% of its initial volume. 5-oxo products crystallize from filtrates of

corresponding 7-oxo products. 7- and 5-oxo compounds can also be separated by column chromatography. **5c** and **7a** can only be purified, after complete evaporation of ethanol, by column chromatography on silica gel [**5c** : toluol/methanol (98:2) ; **7a** : EtOAc/hexane(50:50)]. Yields are based on pure products obtained after repeated recrystallization from 95% EtOH.

^{13}C NMR($CDCl_3$) δ (ppm) : **5a**:167.7(C_5),163.2(C_{10}),157.4(C_9),63.3(C_7)10.6), 61.7(C_{11}), 53.5(C_6),46.6(C_3),26.3(C_2),13.9(C_{12}).**7a**:177.4(C_9),167.5(C_{10})169.6(C_7),61.9(C_{11});53.3(C_6) 52.9; (C_3)26.3(C_2) 13.9(C_{12}). **5b**:167.7(C_5),163.2(C_{10}),148.8(C_9),62.9(C_7); 61.8(C_{11}) 53.9(C_6),46.7(C_3) ,26.5(C_2), 13.8(C_{12}). **7b**: 177.5(C_9)167.4(C_{10}) ,169.8(C_7), 60.6(C_5); 61.8(C_{11}),53.2(C_6), 52.9(C_3),26.3(C_2); 13.8(C_{12})

Method B : 5- and 7-oxothiazolidino [3,2-a] pyrimidine-6-carbonitriles (7e-f + 5g-h).

2-aminothiazoline (10.2 g, 100 mmol), ethylcyanoacetate (11.3 g, 100 mmol) and aromatic aldehyde (100 mmol) are dissolved in ethanol (200 mL) and refluxed for 4 h. Products **7e** and **5g** were obtained with K_2CO_3 (100 mmol) and **7f** and **5h** with five drops of piperidine. The reaction mixture is concentrated to 50%. The solid product is collected by filtration and recrystallized from 95% EtOH (**7e**, **5h**), DMSO (**5g**), or a mixture of EtOH/DMSO (95/5) (**7f**).

Method C : 5-aminothiazolidino [3,2-a] pyrimidine-6-carbonitriles (5i-p).

2-aminothiazoline (10.3 g, 100 mmol), malonitrile (6.6 g, 100 mmol) and aromatic aldehyde (100 mmol) in ethanol (300 ml) are stirred under reflux for 4 h. For **5p** instead, an iced-cooled bath is used. **5m** required a dropwise addition of malonitrile in ethanol. The solid isolated by filtration, is generally recrystallized from 95% EtOH ; except **5i** and **5s** [95% EtOH/DMSO (95:5)], **5j** (60% EtOH) and **5p** (absolute EtOH).

7-aminothiazolidino[3,2-a]pyrimidine-6-carbonitriles(7l-m)
The filtrates arising from the filtration of **5l** (for **7l**), and **5m** (for **7m**) (cf. Method C) are concentrated under pressure to 20% of its initial volume. The precipitate obtained is recrystallized from 95% EtOH, followed by a second recrystallization from DMSO (for **7m** only).

5-iminothiazolidino [3,2-a] pyrimidine-6-carbonitriles(5s-t)
The filtrate arising from the filtration of **5i**, evaporated *in vacuo* to 20%, gives a precipitate of **5s**, recrystallized from 95% EtOH/DMSO (95:5). In the same manner, filtrate of **5k** afford **5t** (recrystallized from 95% EtOH).

Method D : 5-oxo-7-phenyl-thiazolidino [3,2-a] dihydro-pyrimidine (5).
A solution of compound **5a** (0.9 g, 3 mmol) and anhydrous NaCl (1.9 g, 3.3 mmol) in anhydrous DMSO (3 mL) is refluxed under nitrogen for 6 h at 160°C (oil bath). After cooling, distilled water (20 mL) is added, and the mixture is extracted with $CHCl_3$ (2x30 mL). The organic phases are washed with distilled water (20 mL), dried (Na_2SO_4) and the solvent evaporated. The residue is purified by column chromatography on silica gel with EtOAc/hexane (50:50) as eluent.

Method E : 5-oxo-7-phenyl-thiazolidino [3,2-a] dihydro-pyrimidine (5).
To a mixture of 2-aminothiazoline (4.1 g, 40 mmol) and triethylamine (4.04 g, 40 mmol) in $CHCl_3$ (14.4 mL), is added dropwise a solution of cinnamoyl chloride (6.66 g, 40 mmol) in $CHCl_3$ (3.4 mL). The reaction mixture is refluxed for 1h40, and then cooled in an ice-bath. The precipitate obtained by filtration is washed by $CHCl_3$ (2x5mL). Organic phases are washed by distilled water (5 mL), dried (Na_2SO_4),

concentrated and purified by column chromatography on alumina with cyclohexane/$CHCl_3$ (60:40). The final product is recrystallized from 95% EtOH and then from isopropanol.

Acknowledgement : we gratefully acknowledge the financial support by the Institut Mérieux, Lyon, France.

References:

(1) Cohen-Addad, C.; Viallet, M.P. *Cryst. Struct. Comm.* **1978**, *7*, 341.

(2) Viallet, M.P. *Thesis,* Grenoble **1979**.

(3) Viallet, M.P.; Boucherle, A.; Cohen-Addad, C., *Eur. J.Med. Chem.* **1979**, *14*, 553.

(4) Hamri, A.; Pera, M.H.; Fillion, H. *J. Heterocyclic Chem.* **1987**, *24*, 1629.

(5) Jeanneau-Nicolle, E. *Thesis,* Grenoble **1990**.

(6) Doria, G.; Passarotti, C.; Sala, R.; Magrini, R.; Sberze, P.; Tibolla, M.; Cesarini, R.; Arcari, G.; Castello, R.; Toti, D. *Il Farmaco-Ed. Sci.* **1985**, *40(12)*, 885.

(7) Di Braccio, M.; Roma, G.; Mazzei, M.; Balbi, A.; Testa, R. *Il Farmaco-Ed. Sci.* **1986**, *41(3)*,183.

(8) Fabre, J.L.; Farge, D.; James, C. *French Patent* 2574408, (1986); C.A. **1986**, *107*, 39845.

(9) Bell, S.C.; Wei, P.H.L. *J. Med. Chem.* **1976**, *19*, 524.

(10) Japanese Patent 58 24,590, (1983); C.A. **1983**, *98*, 215611.

(11) Kambe, S.; Saito, K.; Sakurai, A.; Midorikawa, H. *Synthesis* **1980**, 366.

(12) Vaquero, J.; Fuentes, L.; Del Castillo, J.C.; Perez, M.I.; Garcia, J.L.; Soto, J.L. *Synthesis* **1987**, 33.

(13) Brown, G.R.; Dyson, W.R *J. Chem. Soc.* **1971**, 1527.

(14) Brown, G.R. *J. Chem. Soc.* **1973**, 2022.

(15) Debarre, F.; Fabre, J.L.; Farge D.; James, C. *European Patent* 0045251 A1, **1981**; C.A. **1982**, *96*, 181302.

(16) Krapcho, A.P.; Lovey, A.J. *Tetrahedron Lett.* **1973**, *12*, 957.

(17) Krapcho, A.P.; Jahngen, E.G.E.; Lovey, A.J. *Tetrahedron Lett.* **1974**, *13*, 1091.

(Received in UK 3 April, 1991)