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SYNTHESIS AND REACTIVITY OF METHYL γ-AZIDO BUTYRATES AND ETHYL δ-AZIDO VALERATES AND OF THE CORRESPONDING ACID CHLORIDES AS USEFUL REAGENTS FOR THE AMINOALKYLATION

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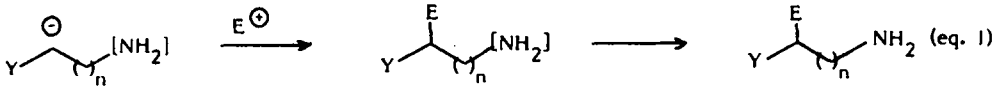
Abstract - The azidoesters **13** and **14** and the corresponding acid chlorides **22** and **23** are shown to be interesting reagents for the nucleophilic and electrophilic aminoalkylation. α-substituted methyl γ-azidobutyrates **13** and ethyl δ-azido valerates **14** are easily accessible by alkylation of the lithium enolates of the parent compounds **13a** and **14a** respectively. Their chemoselective reduction leads to 3-substituted lactams **18** and **19**. The acid chlorides **22** and **23** issued from **13** and **14** react with nucleophilic reagents, i.e. the carbanion of Meldrum acid, trimethylphosphite and n-butylmanganous iodide giving the ω-azido,β-ketoesters **25** and **26**, the ω-azido, α-acylphosphonates **29** and **30** and the ω-azido ketones **38** and **39** respectively in good yields. The treatment of **25** and **26** by Ph_3P in anhydrous ether leads to the cyclic β-enaminoesters **27** and **28** whereas the α-acylphosphonates give the cyclic iminophosphonates **33** and **34a** in good yields. These cyclizations occur via an intramolecular aza-Wittig reaction.

Introduction

The direct introduction in a molecule of a chain bearing a primary amino function either in an nucleophilic or electrophilic way is not an easy problem.

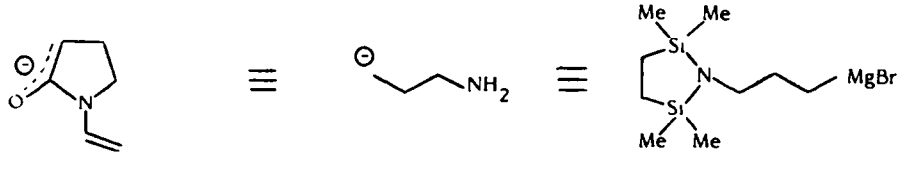
This stems from the facts that, in the case of nucleophilic aminoalkylation, the carbanion **1**, where Y may be an hydrogen, an alkyl group or an electron withdrawing group, must be chemoselectively gene-



(eq. 1)

1 **2** **3**

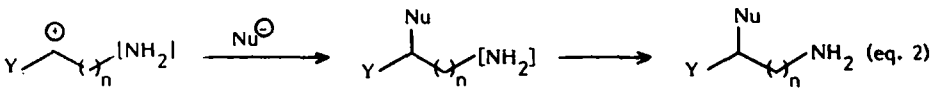
rated in the presence of the potential primary amino group [NH_2], the electrophile must react selectively at the carbanionic center and finally, the transformation **2** → **3** must be chemoselective. The solutions to such a problem are scarce in the literature [1]. The sodium enolate of N-vinylpyrrolidone [2] **4** and the Grignard reagent [3] **6** were used as synthetic equivalents of the synthon **5**. Another solution involving tin che-



4 **5** **6**

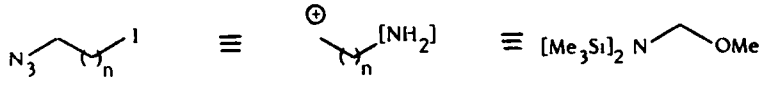
mistry has been recently reported by us [4].

The question of chemoselectivity is similarly encountered in the electrophilic aminoalkylation process (equation 2). In this case, the potential primary amino group should not react with the electrophilic



7 8 9

center α to Y or with the nucleophile $Nu^{\ominus}$. In addition, the transformation **8** → **9** must be chemoselective. Primary amino protected electrophilic reagents, i.e. the synthetic equivalents of the synthons **7** (n = 0) are numerous [5]. The most interesting reagent for this electrophilic aminomethylation may be the N,N-bis (trimethylsilyl) methoxymethylamine **10** [6]. We have recently proposed the use of the iodoazides **11** and **12** as reagents for the electrophilic aminoethylation and propylation [7].



11 : n = 1
12 : n = 2

7, Y = H

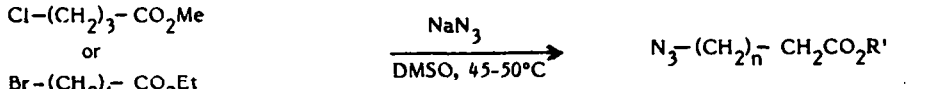
10

In this paper we report on the synthesis and reactivity of γ-azido methyl butyrates **13** and δ-azido ethylvalerates **14** and of the corresponding acid chlorides as useful reagents for the aminoalkylation. The remarkable stability of the azido group in a number of reaction conditions is also shown.

13 **14**

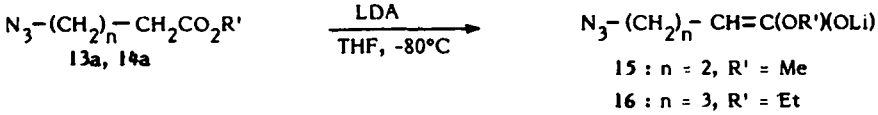
Results and discussion

The parent azides **13a** and **14a** were readily obtained from the γ-chloro methylbutyrate and δ-bromo ethylvalerate by a nucleophilic substitution with NaN_3 in DMSO at 45-50°C.

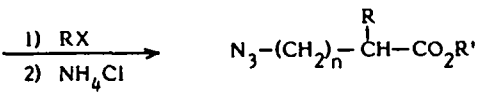


13a, n = 2, R' = Me ; yield 95 %
14a, n = 3, R' = Et ; yield 97 %

The metallation of **13a** and **14a** was performed in THF using LDA as a base at -80°C [8] generating the corresponding lithium enolates **15** and **16**. The alkylation of these enolates with methyliodide and allylbromide gave the alkylated azidoesters **13b,c** and **14b,c** in 79 to 89 % isolated yields. These reactions have been scaled up to 0.2 mole without yield decrease. It is worthy of note that, in the reaction



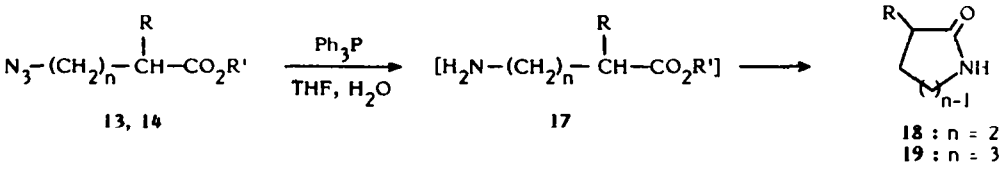
15 : n = 2, R' = Me
16 : n = 3, R' = Et



13b : n = 2, R = R' = Me
13c : n = 2, R = allyle, R' = Me
14b, n = 3, R = Me, R' = Et
14c : n = 3, R = allyle, R' = Et

conditions, the lithium enolates **15** and **16** are stable [9]. No intramolecular alkylation with an SN_2 displacement of the azide ion leading to the methoxycarbonyl cyclopropane or ethoxycarbonyl cyclobutane was observed. Furthermore, the addition of the enolates to the azido group which would have led to triazolinones [10] did not occur.

The azido function in the esters **13** and **14** was chemoselectively reduced at room temperature to the corresponding primary amines **17** (Ph_3P, THF, H_2O [11]) which spontaneously cyclized to give the lactams **18** and **19**.



13, 14 **17** **18** : n = 2; **19** : n = 3

The results are summarized in table I.

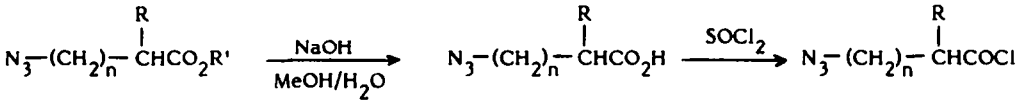
Table I - Synthesis of the lactams **18** and **19**

N°	n	R'	Yield % [a]
18a	2	H	75
18b	2	CH_3	72
18c	2	$-CH_2CH=CH_2$	70
19a	3	H	77
19b	3	CH_3	70
19c	3	$-CH_2CH=CH_2$	69

[a] Yields are of isolated pure products.

The spectroscopic data relevant to lactams **18** and **19** are in agreement with their structure and are reported in the experimental section. This method provides an easy access to 3-substituted lactams and should be of wide applicability.

The azidoesters **13** and **14** were easily saponified by treatment with dilute sodium hydroxyde in methanol-water at room temperature for 4 hours leading to the acids **20** and **21** after acidification. The treatment of the acids by freshly distilled thionyl chloride without solvent gave the acid chlorides **22** and **23** in good yields (table II). It is again interesting to note the inertness of the azido group under such reaction conditions.



13 **20** **22** : n = 2

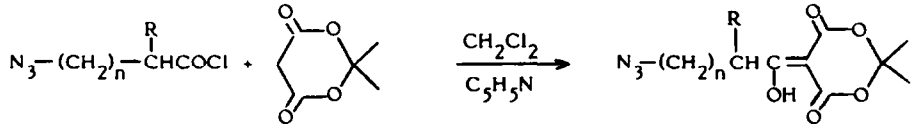
14 **21** **23** : n = 3

Table II - Synthesis of the acids **20** and **21** and the acid chlorides **22** and **23**.

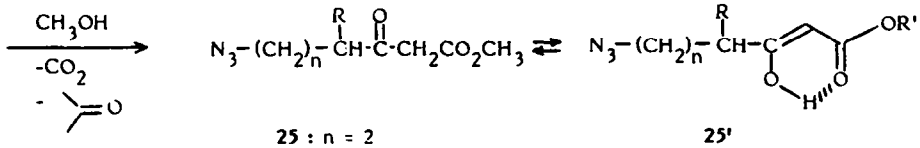
n	R'	N°	Yield % [a]	N°	Yield % [a]
2	H	**20a**	93	**22a**	90
2	CH_3	**20b**	92	**22b**	88
2	$CH_2CH=CH_2$	**20c**	89[b]	**22c**	86
3	H	**21a**	90	**23a**	92
3	CH_3	**21b**	93	**23b**	93
3	$CH_2CH=CH_2$	**21c**	90[b]	**23c**	87

[a] Yields are of isolated pure products. [b] These two acids are thermally unstable and could not be distilled.

We have studied the reaction of the acid chlorides **22** and **23** with some nucleophilic reagents. The Meldrum's acid reacts with **22** and **23** in dichloromethane in the presence of pyridine to give the derivatives **24** which were not purified but dissolved in methanol and maintained at reflux for 3 hours.



22, 23 **24**



25 : n = 2 **25'**
26 : n = 3 **26'**

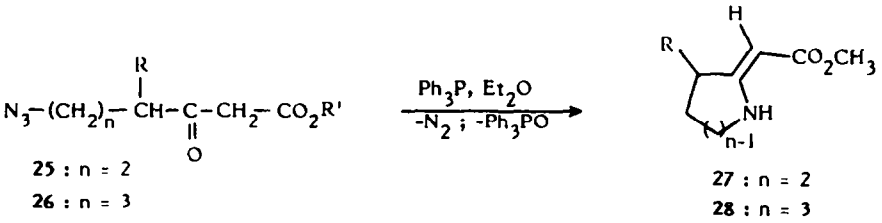
This Yonemitsu reaction [12] led to the ω-azido-β-ketoesters **25** ⇌ **25'** and **26** ⇌ **26'**. The obtained results are reported in the table III. It is interesting to note the influence of the R group on the yield

Table III - Synthesis of the ω-azido-β-keto esters **25** and **26** and of the β-enaminoesters **27** and **28**

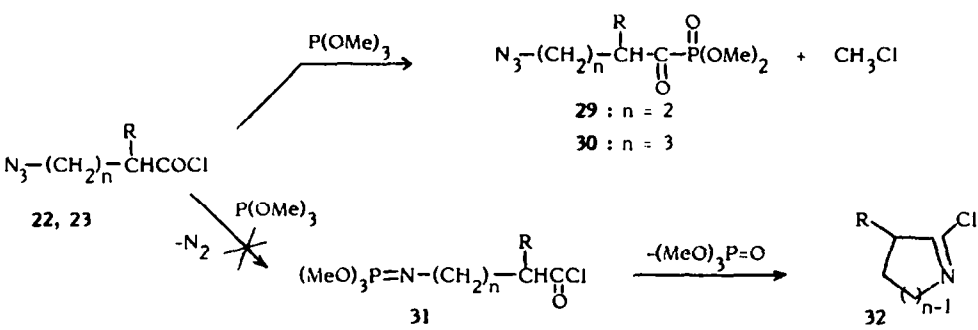
n	R	N°	Yield %[a]	**25/25'**[b] or **26/26'**	N°	Yield % [a]
2	H	**25a**	84	100/0	**27a**	90
2	CH_3	**25b**	56	79/21	**27b**	95
2	$-CH_2CH=CH_2$	**25c**	45	78/22	**27c**	76
3	H	**26a**	80	100/0	**28a**	92
3	CH_3	**26b**	52	78/22	**28b**	94
3	$-CH_2CH=CH_2$	**26c**	47	79/21	**28c**	87

[a] Yields refer to isolated pure products. [b] Equilibrium ratio in $CDCl_3$.

of this reaction. When R = H, the yields are almost quantitative whereas for R = CH_3 or $-CH_2CH=CH_2$, the yields fall in the range of 50 to 60 %. We were not able to obtain better results even by changing the reaction conditions (base, solvent, temperature). It seems reasonable to admit that the attack of the anion of the Meldrum's acid on the carbonyl of the acid chloride is sensitive to steric effects. The azides **25** and **26** were allowed to react with one equivalent of Ph_3P in anhydrous ether under nitrogen according to [13]. The β-enamino esters **27** and **28** were obtained in excellent yields thus showing the efficiency of the intramolecular Wittig-like reaction.



The β-enaminoesters **27** and **28** have the Z stereochemistry. This stems from I.R. and ^1H NMR arguments in agreement with earlier observations [13,14,15]. It was of interest for us to perform the reaction of the azidoacid chlorides **22** and **23** with trimethylphosphite in order to establish whether an Arbuzov reaction leading to the acylphosphonates **29** and **30** or a Staudinger reaction leading to the iminophosphoranes **31** which would then cyclize to the iminochlorides **32** or a competition between these two possibilities would occur. When trimethylphosphite is slowly added to a solution of **22** or **23** in dichloromethane at 0°C



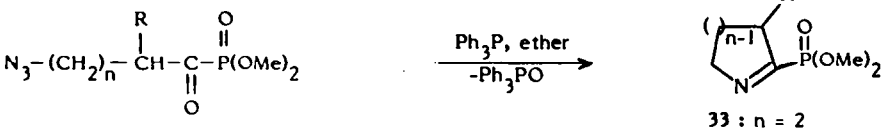
under nitrogen, the Arbuzov reaction is exclusively observed giving the acylphosphonates **29** or **30** in excellent yields (table IV). All the spectroscopic data corroborate the structures **29** and **30** and are reported in the experimental section. The ^{13}C chemical shift of the C=O group ($\simeq$ 210 ppm) is worthy of note.

Table IV - *Synthesis of the α-acylphosphonates* **29** *and* **30** *and of the iminophosphonates* **33** *and* **34**.

n	R	N°	Yield % [a]	N°	Yield % [a]
2	H	**29a**	80	**33a**	65
2	CH_3	**29b**	94	**33b**	72
2	$-CH_2CH=CH_2$	**29c**	95 [b]	**33c**	70
3	H	**30a**	82	**34a**	68
3	CH_3	**30b**	80	**34b**	(c)
3	$-CH_2CH=CH_2$	**30c**	95 [b]	**34c**	(c)

[a] Yields of isolated pure products. [b] These derivatives are thermally unstable and could not be distilled. Yields refer to crude products showing one set of signals by ^1H and ^{13}C NMR. [c] Reaction not performed.

The acylphosphonates **29** and **30** are moisture sensitive [15]. Their hydrolysis gives back the azido-acids **20** and **21**. The treatment of **29** and **30** with one equivalent of Ph_3P in anhydrous ether gave the 1-pyrrolines **33** and 1-piperideines **34** respectively bearing a $(MeO)_2P(O)$ group in the 2 position. When



29 : n 2

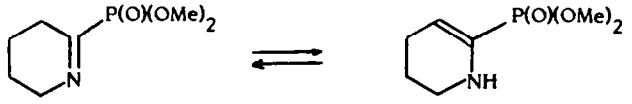
30a : n = 3, R = H

33 : n = 2

34a : n = 3, R = H

exposed to moisture, the cyclic imines **33** and **34** hydrolyze to give the lactames **18** and **19** and dimethyl-phosphite.

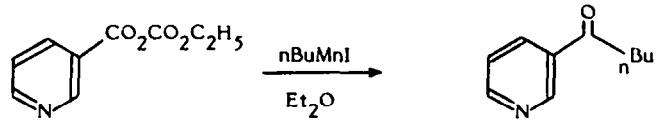
The 1-piperideine **34a** showed an interesting behaviour in solution. A solvent dependant tautomeric equilibrium imine-enamine could be seen by ^1H NMR. The vinylic hydrogen in **35a** appears as a doublet



34a **35a**

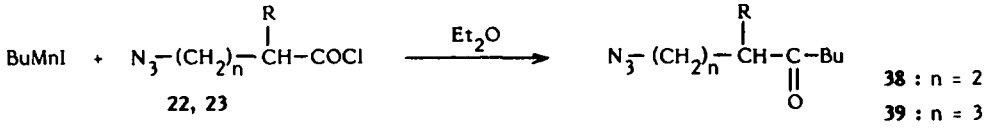
of triplets at 5.35 ppm ($^3J_{HH}$ = 4,0 Hz and $^3J_{PH}$ = 15,9 Hz). The equilibrium ratio **34a/35a** is shifted from 55/45 in $CDCl_3$ to 13/87 in CCl_4. In fact, these structures are reminiscent of α,β-insaturated α-aminoacids where the enamino form is the only one seen by NMR.

The acylation of organomanganous reagents by carboxylic acid chlorides, anhydrides or acylcarbonates proceeds under mild conditions and affords alkyl, alkenyl, alkynyl and aryl ketones in high yields [17]. Nevertheless, if the acylating agent bears a nitrogen containing functionnality, the results are not as good. For example, the reaction of the nicotinic derivative **36** with n-butylmanganous iodide gave the ketone **37** in a 38 % yield [18].



36 **37** : 38 %

So, it seemed of interest to us to test the behaviour of organomanganous derivatives towards the azido acid chlorides **22** and **23**. The n-butylmanganous iodide reacts with the acid chlorides **22** and **23** to give after hydrolysis the azidoketones **38** and **39** in 60 % isolated yields. The results are summarized



22, 23

38 : n = 2

39 : n = 3

in the table V. This is a simple access to these interesting azidoketones which can be easily transformed into cyclic imines by simply reacting them with triphenylphosphine [19]. One can also note that this methodology leads to ketones with the carbons α and α' to the carbonyl group dissymmetrically substituted. This avoids the eventual regioselectivity problem if one wants to prepare **38b** from **38a** for example via enolate alkylation.

Table V - Synthesis of the azido ketones **38** and **39**.

N°	n	R	Yield % [a]
38a	2	H	66
38b	2	CH_3	60
39a	3	H	58
39b	3	CH_3	60

[a] Yields of isolated pure products.

Conclusion

In this paper, we have described some new reagents which may be useful for either the nucleophilic or electrophilic aminoalkylation. The inertness of the azido function towards many reagents either electrophilic or nucleophilic makes it one of the most interesting potential primary amino group.

Experimental

Caution ! Because of their potentially explosive character, all the purification steps of the azido derivatives must be carried out with the appropriate protection under a well ventilated hood.

General methods

Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methyl 4-chlorobutyrate, ethyl 5-bromovalerate, methyliodide, allylbromide, thionyl chloride were distilled prior to use. Dimethylsulfoxyde (DMSO) was used as received from Aldrich. Melting points were taken with a Kofler apparatus. NMR spectra were recorded on the following spectrometers : Bruker WP 80 CW (80 MHz for ^1H) and Bruker WP 80 DS (20.115 MHz for ^{13}C). They were recorded in $CDCl_3$, chemical shifts are reported in δ downfield from tetramethylsilane (TMS) used as an internal standard, and coupling constants are given in Hertz (Hz). The following notations are used for multiplicity : s, singlet ; d : doublet ; t : triplet ; q : quartet. IR spectra were determined with a Perkin-Elmer 225 spectrometer on liquid films unless otherwise indicated. High resolution mass spectra (electron impact, 70 eV) were obtained with a Varian MAT 311 (Centre de Mesures Physiques de l'Université de Rennes). Analytical thin layer chromatography (TLC) was performed by using silica gel 60 F 254 aluminum plates. The following abbreviations are used for eluting solvent systems : E, diethyl ether ; PE, petroleum ether (b.p. ≤ 65°C) ; E/PE (a/b), diethyl ether/petroleum ether mixture in a relative ratio a/b (volume by volume). Column chromatography was performed over Merck 60 silica gel (230-400 mesh). Unless otherwise noted, reactions were carried out under a nitrogen atmosphere with magnetic stirring in flame dried glassware.

Synthesis of the methyl-γ-azidobutyrate **13a** and ethyl-δ-azido valerate **14a**

To a solution of 300 mmoles of the methyl-γ-chlorobutyrate (40.97 g) or the ethyl-δ-bromovalerate (62.72 g) in 150 ml of DMSO were added with stirring 450 mmoles of sodium azide (29.25 g). Then, the suspension was heated (45-50°C, oil bath) with stirring for 24 h. After cooling, water (300 ml) was added and the mixture extracted with ether (3 x 100 ml). The ether extracts were washed with brine (100 ml) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude oil thus obtained was purified by short path distillation.

13a : 40.82 g, $Eb_{0.01}$ = 30°C, yield : 95 %.
IR, ν : 2092 (N_3) ; 1723 (C=O). ^1H NMR δ : 1.72 - 2.14 (m, 2H) ; 2.32 - 2.59 (m, 2H) ; 3.37 (t, 2H, J = 6.5) ; 3.69 (s, 3H). Anal. % calc. for $C_5H_9N_3O_2$: C, 41.96 ; H, 6.29 ; N, 29.37. Found : C, 41.70 ; H, 6.25 ; N, 29.12.

14a : 49.80 g, $Eb_{0.01}$ = 40°C, yield : 97 %.
IR, ν : 2090 (N_3) ; 1720 (C=O). ^1H NMR δ : 1.30 (t, 3H, J = 7.1) ; 1.50 - 1.97 (m, 4H) ; 2.25-2.53 (m, 2H) ; 3.20 - 3.33 (m, 2H) ; 4.17 (q, 2H, J = 7.1). Anal. % calcd for $C_7H_{13}N_3O_2$: C, 49.12 H, 7.60 ; N, 24.56. Found : C, 49.27 ; H, 7.56 ; N, 24.13.

Metallation and alkylation of the azides **13a** and **14a**. General procedure.

In a 1 l three necked flask fitted with a nitrogen inlet, a septum, a pentane thermometer and a magnetic stirring bar were introduced 350 ml of anhydrous THF and 120 mmoles (12.14 g, 16.8 ml) of freshly distilled (over CaH_2) diisopropylamine. The mixture was cooled to -80°C and 110 mmoles of butyllithium (68.74 ml of a 1.6 M solution in hexane) were added via syringe. The resulting colorless

solution was stirred for 0.5 h at this temperature at which time a solution of 100 mmoles of the azido esters **13a** (14.3 g) or **14a** (17.12 g) in 100 ml of THF was slowly transfered via a double ended needle so that the temperature remains below -80°C. The reaction mixture was stirred at this temperature for 15 minutes after the end of the addition. Then, 110 mmoles (1.1 equivalents) of methyliodide (15,6 g, 6.8 ml) or allylbromide (13.30 g, 9.05 ml) were slowly added via syringe. The temperature was kept at -80°C for 30 minutes and then allowed to reach -20°C in 2 h. The reaction mixture was quenched by adding 50 ml of a saturated NH_4Cl solution and then extracted with ether (3 x 100 ml). The organic extracts were dried over Na_2SO_4. The solvents were removed in vacuo and the crude oil purified by bulb to bulb transfer (oven temperature given) or column chromatography.

13b : 13.95 g, Eb_{18} = 75-80°C.
IR, ν : 2096 (N_3) ; 1727 (C=O). ^1H NMR, δ : 1.22 (d, 3H, J = 7.0) ; 1.53 - 2.28 (m, 2H) ; 2.37 - 2.80 (m, 1H) ; 3.35 (t, 2H, J = 6.8) ; 3.69 (s, 3H). Anal. % calcd for $C_6H_{11}N_3O_2$: C, 45.85 ; H, 7.00 ; N, 26.75. Found : C, 45.44 ; H, 6.90 ; N, 26.66.

13c : 14.33 g after column chromatography (E/PE = 1/3).
TLC, Rf 0.6 (E/PE 1/3). IR, ν : 2090 (N_3) ; 1728 (C=O) ; 1634 (C=C). ^1H NMR, δ : 1.67 - 2.10 (m, 2H) ; 2.20 - 2.85 (m, 3H) ; 3.35 (t, 2H, J = 6.6) ; 3.69 (s, 3H) ; 4.90 - 5.25 (m, 2H) ; 5.48 - 6.05 (m, 1H). Anal. % calcd for $C_8H_{13}N_3O_2$: C, 52.46 ; H, 7.01 ; N, 22.95. Found : C, 52.45 ; H, 7.26 ; N, 22.95.

14b : 16.43 g, $Eb_{0.01}$ = 60°C.
IR, ν : 2090 (N_3) ; 1715 (C=O). ^1H NMR, δ : 1.20 (d, 3H, J = 7.0) ; 1.30 (t, 3H, J = 7.0) ; 1.45-1.92 (m, 4H) ; 2.25 - 2.70 (m, 1H) ; 3.20 - 3.45 (m, 2H) ; 4.15 (q, 2H, J = 7.00). Anal. % calcd for $C_8H_{15}N_3O_2$: C, 51.89 ; H, 8.10 ; N, 22.70. Found : C, 51.66 ; H, 7.84 ; N, 22.81.

14c : 17.20 g, $Eb_{0.01}$ = 80°C.
IR, ν : 2088 (N_3) ; 1723 (C=O) ; 1630 (C=C). ^1H NMR, δ : 1.28 (t, 3H, J = 7.0) ; 1.47 - 1.87 (m, 4H) ; 2.12 - 2.62 (m, 3H) ; 3.17 - 3.45 (m, 2H) ; 4.17 (q, 2H, J = 7.0) ; 4.92 - 5.25 (m, 2H) ; 5.48-6.05 (m, 1H). Anal. % calcd for $C_{10}H_{17}N_3O_2$: C, 56.87 ; H, 8.05 ; N, 19.90. Found : C, 57.10 ; H, 8.10 ; N, 19.80.

Synthesis of lactams **18** and **19**. General procedure.

To a solution of 10 mmoles of the azidoesters **13** or **14** in 10 ml of THF were added 10 mmoles of triphenylphosphine (2.62 g) and 10 mmoles of water (180 µl). The solution was kept at room temperature for 12 hours. Then, the solvent was removed in vacuo and the residue dissolved in 50 ml of a 1/1 mixture of ether and petroleum ether. The triphenylphosphine oxide was collected by filtration and the crystals were thoroughly washed with cold ether. After removal of the solvents, the products were purified by column chromatography.

18a : 0.638 g, m.p. = 23-24°C identical in all respects with a commercially available sample.

18b : 0.712 g, m.p. 56-57°C.
TLC, Rf = 0.4 (E/MeOH 95/5). IR (Nujol) ν : 3290, 3180 (NH, broad) ; 1674 (C=O). ^1H NMR, δ : 1.25 (d, 3H, J = 6.6) ; 1.47 - 2.10 (m, 1H) ; 2.12 - 2.75 (m, 2H) ; 3.22 - 3.50 (m, 2H) ; 7.37 (br s, 1H). ^{13}C NMR, δ : 15.9 ; 29.9 ; 36.1 ; 40.4 ; 182.0. Anal. % calcd for C_5H_9NO : C, 60.60 ; H, 9.09 N, 14.14. Found : C, 60.29 ; H, 9.08 ; N, 13.94.

18c : 0.875 g, m.p. = 58-59°C.
TLC, Rf 0.4 (E/MeOH 95/5). IR (Nujol) ν : 3280, 3190 (NH, broad) ; 1658 (C=O). ^1H NMR δ : 1.72 - 2.80 (m, 5H) ; 3.22 - 3.53 (m, 2H) ; 4.92 - 5.25 (m, 2H) ; 5.55 - 6.10 (m, 1H) ; 7.60 (br.s, 1H). ^{13}C NMR, δ : 26.7 ; 35.0 ; 40.6 ; 40.7 ; 116.8 ; 135.7 ; 180.5. Anal. % calcd for $C_7H_{11}NO$: C, 67.20 ; H, 8.80 ; N, 11.20. Found : C, 67.22 ; H, 8.47 ; N, 11.09.

19a : 0.763 g, m.p. = 37-39°C. Identical in all respects with a commercially available sample.

19b : 0.791 g, m.p. 48-49°C.
TLC, Rf = 0.44 (E/MeOH 95/5). IR (Nujol) ν : 3290, 3200 (NH broad) ; 1666 (C=O). ^1H NMR δ : 1.25 (d, 3H, J = 7.4) ; 1.47 - 2.72 (m, 5H) ; 3.10 - 3.50 (m, 2H) ; 7.78 (br s, 1H). ^{13}C NMR δ : 17.5 ; 21.4 ; 29.4 ; 36.0 ; 42.4 ; 176.3. Anal. % calcd for $C_6H_{11}NO$: C, 63.71 ; H, 9.73 ; N, 12.38. Found : C, 63.47 ; H, 9.59 ; N, 12.50.

19c : 0.959 g, m.p. = 38- 39°C.
TLC, Rf = 0.45 (E/MeOH 95/5). IR (Nujol) ν : 3280, 3190 (NH broad) ; 1658 (C=O). ^1H NMR δ : 1.42 - 2.29 (m, 7H) ; 3.17 - 3.47 (m, 2H) ; 4.92 - 5.25 (m, 2H) ; 5.55 - 6.20 (m, 1H) ; 6.75 (br s, 1H). ^{13}C NMR δ : 21.4 ; 25.8 ; 36.0 ; 40.7 ; 42.4 ; 116.9 ; 136.5 ; 174.8. Anal. % calcd for $C_8H_{13}NO$: C, 69.06 ; H, 9.35 ; N, 10.07. Found : C, 68.75 ; H, 9.51 ; N, 10.03.

Synthesis of the acids **20** and **21**. General procedure

To 100 mmoles of the azidoesters **13** and **14** were added 120 ml of a 1N aqueous solution of NaOH (120 mmoles, 1.2 equivalents) and the minimum of methanol to make the reaction mixture homogenous. After 4 hours at room temperature, the methanol was removed in vacuo. The aqueous solution was extracted with ether (2 x 50 ml) and acidified to pH = 0 with concentrated HCl. The acids were then extracted with ether (2 x 100 ml) and the organic phase dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the azido acids were purified by Kugelrohr distillation (oven temperature

given). The acids **20c** and **21c** could not be distilled. The crude was maintained under vacuum (0.1 mm Hg) for two hours at room temperature and used as such in the next step.

20a : 12.05 g, $Eb_{0.01}$ = 75-80°C.
IR, ν : 2930 (OH, broad) ; 2085 (N_3) ; 1698 (C=O). ^1H NMR δ : 1.75 - 2.17 (m, 2H) ; 2.51 (t, 2H, J = 7.0) ; 3.41 (t, 2H, J = 6.5) ; 11.27 (br s, 1H). Anal. % calcd for $C_4H_7N_3O_2$: C, 37.20 ; H, 5.42 ; N, 32.55. Found : C, 37.49 ; H, 5.49 ; N, 32.69.

20b : 13.15 g, $Eb_{0.01}$ = 85-90°C.
IR, ν : 2930 (OH, broad) ; 2080 (N_3) ; 1686 (C=O). ^1H NMR, δ : 1.30 (d, 3H, J = 7.0) ; 1.50 - 2.33 (m, 2H) ; 2.45 - 2.95 (m, 1H) ; 3.41 (t, 2H, J = 6.8) ; 14.83 (br s, 1H). Anal. % calcd for $C_5H_9N_3O_2$: C, 41.95 ; H, 6.29 ; N, 29.37. Found : C, 42.11 ; H, 6.37 ; N, 28.95.
20c : 15.04 g.
IR, ν : 2930 (OH, broad) ; 2090 (N_3) ; 1691 (C=O). ^1H NMR, δ : 1.70 - 2.15 (m, 2H) ; 2.20 - 2.83 (m, 3H) ; 3.37 (t, 2H, J = 6.8) ; 4.95 - 5.45 (m, 2H) ; 5.53 - 6.08 (m, 1H) ; 14.75 (br s, 1H). Mass spectrum, exact mass calcd for $C_7H_{11}NO_2$ $[M-N_2]^+$ m/z = 141.078, found m/z = 141.079.

21a : 12.87 g, $Eb_{0.01}$ = 80-85°C.
IR, ν : 2930 (OH, broad) ; 2090 (N_3) ; 1695 (C=O). ^1H NMR, δ : 1.55 - 1.97 (m, 4H) ; 2.33 2.60 (m, 2H) ; 3.22 - 3.53 (m, 2H) ; 14.72 (br s, 1H). Anal. % calcd for $C_5H_9N_3O_2$: C, 41.95 ; H, 6.29 ; N, 29.37. Found : C, 42.12 ; H, 6.47 ; N, 29.38.

21b : 14.60 g, $Eb_{0.01}$ = 85-90°C.
IR, ν : 2925 (OH, broad) ; 2085 (N_3) ; 1695 (C=O). ^1H NMR δ : 1.25 (d, 3H, J = 6.9) ; 1.47 - 2.00 (m, 4H) ; 2.45 - 2.75 (m, 1H) ; 3.22 - 3.50 (m, 2H) ; 14.50 (br s, 1H). Anal. % calcd for $C_6H_{11}N_3O_2$: C, 45.85 ; H, 7.00 ; N, 26.75. Found : C, 46.21 ; H, 6.99 ; N, 26.47.

21c : 16.47 g
IR, ν : 2925 (OH, broad) ; 2085 (N_3) ; 1691 (C=O). ^1H NMR δ : 1.45 - 1.95 (m, 4H) ; 2.12 - 2.67 (m, 3H) ; 3.10 - 3.50 (m, 2H) ; 4.92 - 5.28 (m, 2H) ; 5.50 - 6.05 (m, 1H) ; 14.49 (br s, 1H). Mass spectrum, exact mass calcd for $C_8H_{13}NO_2$ $[M-N_2]^+$ m/z = 155.086 ; found : m/z = 155.086.

Synthesis of the acid chlorides **22** and **23**. General procedure.

To 50 mmoles of the acids **20** or **21** were added at 0°C via syringe 60 mmoles of freshly distilled thionyl chloride (7.14 g, 4.37 ml). The solution was kept at room temperature for 15 h and then 1 h at 40°C (oil bath). The excess of $SOCl_2$, HCl and SO_2 were eliminated in vacuo and the oily residue distilled with a short path.

22a : 6.63 g, $Eb_{0.01}$ = 28°C.
IR, ν : 2088 (N_3) ; 1785 (C=O). ^1H NMR, δ : 1.97 (q, 2H, J = 7.0 and 6.5) ; 3.02 (t, 2H, J = 7.0) ; 3.41 (t, 2H, J = 6.5).

22b : 6.66 g, $Eb_{0.01}$ = 30-32°C.
IR, ν : 2090 (N_3) ; 1784 (C=O). ^1H NMR, δ : 1.41 (d, 3H, J = 6.9) ; 1.60 - 2.47 (m, 2H) ; 2.87 - 3.37 (m, 1H) ; 3.47 (t, 2H, J = 6.6). Mass spectrum, exact mass calcd for $C_5H_8N_3O$ $[M-Cl]^+$ m/z = 126.066, found 126.066.

22c : 8.06 g, $Eb_{0.01}$ = 40°C.
IR, ν : 2080 (N_3) ; 1782 (C=O). ^1H NMR δ : 1.72 - 2.45 (m, 2H) ; 2.47 - 2.67 (m, 2H) ; 2.87 - 3.28 (m, 1H) ; 3.42 (t, 2H, J = 6.6) ; 5.00 - 5.35 (m, 2H) ; 5.48 - 6.03 (m, 1H). Mass spectrum, exact mass calcd for $C_7H_{11}NO$ $[M-Cl-N_2 + H]^+$ m/z = 125.084, found m/z = 125.084.

23a : 7.43 g, $Eb_{0.01}$ = 40-42°C.
IR, ν : 2085 (N_3) ; 1780 (C=O). ^1H NMR δ : 1.45 - 2.08 (m, 4H) ; 2.99 (t, 2H, J = 6.6) ; 3.35 (t, 2H, J = 6.2). Mass spectrum, exact mass calcd for $C_5H_8N_3O$ $[M-Cl]^+$ m/z = 126.066, found : 126.066.

23b : 8.16 g, $Eb_{0.01}$ = 42°C.
IR, ν : 2090 (N_3) ; 1786 (C=O). ^1H NMR, δ : 1.35 (d, 3H, J = 6.9) ; 1.47 - 2.12 (m, 4H) ; 2.70 - 3.12 (m, 1H) ; 3.34 (t, 2H, J = 6.2).

23c : 8.76 g, $Eb_{0.01}$ = 60-62°C.
IR, ν : 2085 (N_3) ; 1780 (C=O). ^1H NMR, δ : 1.28 - 2.03 (m, 4H) ; 2.45 - 2.62 (m, 2H) ; 2.72 - 3.12 (m, 1H) ; 3.45 (t, 2H, J = 6.2) ; 5.00 - 5.30 (m, 2H) ; 5.48 - 6.03 (m, 1H). Mass spectrum, exact mass calcd for $C_8H_{13}NO$ $[M-Cl-N_2 + H]^+$ m/z = 139.099, found : 139.099.

Reactions of the acid chlorides **22** and **23** with nucleophiles.

Synthesis of the β-ketoesters **25** and **26**. General procedure

To a chilled solution (0°C) of 10 mmoles (1.44 g) of Meldrum acid in 10 ml of anhydrous CH_2Cl_2 were added 20 mmoles (1.58 g, 1.61 ml) of anhydrous pyridine. After 0.5 h at 0°C, 11 mmoles of the acid chlorides **22** and **23** in 2 ml of CH_2Cl_2 were added and the reaction mixture was stirred for 18 h at room temperature. Then 4 ml of a 1N HCl solution was added. After decantation, washing with

water (2 ml) and drying (Na_2SO_4), the solvent was removed in vacuo to give a red oily residue. This oil was dissolved in 10 ml of anhydrous methanol and the resulting solution refluxed for 3 h at which time the solvent was removed in vacuo and the oily residue purified by column chromatography.

25a : 1,55 g, TLC, Rf = 0.44 (E/PE 1/1).
IR, ν : 2081 (N_3) ; 1733 (C=O) ; 1706 (C=O). ^{1}H NMR, δ : 1.70 - 2.15 (m, 2H) ; 2.72 (t, 2H, J = 6.8) ; 3.37 (t, 2H, J = 6.5) ; 3.50 (s,2H) ; 3.75 (s, 3H). The enolic form could not be detected. ^{13}C NMR, δ : 22.9 ; 39.6 ; 49.1 ; 50.6 ; 52.4 ; 167.8 ; 201.9. Mass spectrum, exact mass calcd for $C_6H_8N_3O_2$ $[M-OCH_3]^+$ m/z = 154.062, found : 154.063.

25b : 1.11 g, TLC Rf = 0.50 (E/PE 1/1).
IR, ν : 2085 (N_3) ; 1735 (C=O) ; 1703 (C=O). ^{1}H NMR, δ : **25b** : 1.19 (d, 3H, J = 7.0) ; 1.37 - 2.37 (m, 2H) ; 2.58 - 3.03 (m, 1H) ; 3.35 (t, 2H, J = 6.8) ; 3.58 (s, 2H) ; 3.72 (s, 3H). **25'b** : 1.23 (d, 2H, J = 6.7) ; 5.08 (s, 1H) ; 15.09 (br s, 1H). The other signals could not be identified. ^{13}C NMR δ : **25b** : 16.3 ; 31.4 ; 43.7 ; 47.6 ; 52.3 ; 167.7 ; 205.4. **25'b** : 18.0 ; 33.0 ; 37.0 ; 51.2 ; 88.6 ; 173.3 ; 180.9. One of the signals could not be identified. Mass spectrum, exact mass calcd for $C_8H_{13}N_3O$ $[M-N_2]^+$ m/z = 171.099, found : m/z = 171.089.

25c : 1.02 g, TLC Rf = 0.59 (E/PE 1/1).
IR, ν : 2088 (N_3) ; 1731 (C=O) ; 1703 (C=O). ^{1}H NMR, δ : **25c** : 1.45 - 2.20 (m, 2H) ; 2.25 - 2.60 (m, 2H) ; 2.70 - 3.15 (m, 1H) ; 3.33 (t, 2H, J = 8.8) ; 3.53 (s, 2H) ; 3.75 (s, 3H) ; 5.00 - 5.35 (m, 2H) ; 5.55 - 6.03 (m, 1H). **25'c** : 5.03 (s, 1H) ; 15.05 (br s, 1H). The other signals could not be identified. Mass spectrum, exact mass calcd for $C_{10}H_{15}NO_3$ $[M-N_2]^+$ m/z = 197.105, found : m/z = 197.104.

26a : 1.61 g, TLC Rf = 0.45 (E/PE 1/1).
IR, ν : 2089 (N_3) ; 1722 (C=O) ; 1695 (C=O). ^{1}H NMR, δ : 1.55 - 1.95 (m, 4H) ; 2.53 - 2.78 (m, 2H) ; 3.22 - 3.47 (m, 2H) ; 3.49 (s, 2H) ; 3.75 (s, 3H). The enolic form was not detected. Mass spectrum, exact mass calcd for $C_8H_{13}NO_3$ $[M-N_2]^+$ m/z = 171.089, found : m/z = 171.089.

26b : 1.10 g, TLC Rf = 0.59 (E/PE 1/1).
IR, ν : 2085 (N_3) ; 1735 (C=O) ; 1703 (C=O). ^{1}H NMR, δ : **26b** : 1.13 (d, 3H, J = 7.0) ; 1.33 - 1.92 (m, 4H) ; 2.45 - 2.92 (m, 1H) ; 3.17 - 3.40 (m, 2H) ; 3.50 (s, 2H) ; 3.71 (s, 3H) ; **26'b** : 1.15 (d, 3H, J = 6.8) ; 5.00 (s, 1H) ; 15.06 (br s, 1H). The other signals were not identified. ^{13}C NMR δ : **26b** : 16.2 ; 26.5 ; 29.6 ; 46.1 ; 47.4 ; 51.4 ; 52.3 ; 167.8 ; 205.8. **26'b** : 18.1 ; 26.7 ; 31.2 ; 39.3 ; 51.2 ; 88.2. Anal. % calcd for $C_9H_{15}N_3O_3$: C, 50.70 ; H, 7.04 ; N, 19.71. Found : C, 50.61 ; H, 7.33 ; N, 19.63.

26c : 1.13 g, TLC Rf = 0.60 (E/PE 1/1).
IR, ν : 2088 (N_3) ; 1730 (C=O ; 1703 (C=O). ^{1}H NMR, δ : **26c** : 1.47 - 1.80 (m, 4H) ; 2.17 - 2.50 (m, 2H) ; 2.58 - 2.95 (m, 1H) ; 3.20 - 3.42 (m, 2H) ; 3.53 (s, 2H) ; 3.75 (s, 3H) ; 4.92 - 5.25 (m, 2H) ; 5.48 - 6.05 (m, 1H). **26'c** : 5.02 (s, 1H) ; 15.05 (br s, 1H). ^{13}C NMR δ : **26c** : 26.5 ; 27.5 ; 35.5 ; 48.5 ; 51.4 ; 52.3 ; 117.8 ; 134.7 ; 167.5 ; 205.0. **26'c** : 26.7 ; 29.1 ; 37.2 ; 45.3 ; 51.1 ; 89.9 ; 117.0 ; 135.5 ; 173.1 ; 179.8. Anal. % calcd for $C_{11}H_{17}N_3O_3$: C, 55.23 ; H, 7.11 ; N, 17.57. Found : C, 55.44 ; H, 6.99 ; N, 17.50.

Synthesis of the β-enaminoesters **27** and **28**

They were obtained according to [11] starting from 5 mmoles of the β-keto esters **25** and **26**.

27a : this reaction has been scaled up to 100 mmoles. Thus, 12.7 g of **27a** were obtained, m.p. 101-102°C [13].

27b : 0.736 g, $Eb_{0.01}$ = 70-75°C ; m.p. = 60- 62°C.
IR (Nujol), ν : 3345 (NH, broad) ; 1654 (C=O) ; 1593 (C=C). ^{1}H NMR, δ : 1.18 (d, 3H, J = 6.8); 1.37 - 1.83 (m, 1H) ; 1.95 - 2.42 (m, 1H) ; 2.55 - 3.08 (m, 1H) ; 3.30 - 3.65 (m, 2H) ; 3.64 (s, 3H) ; 4.50 (d, 1H, ^{4}J = 0.8) ; 7.92 (br s, 1H). ^{13}C NMR δ : 17.9 ; 31.1 ; 38.7 ; 45.5 ; 50.0 ; 75.6 ; 170.9 ; 171.5. Anal. % calcd for $C_8H_{13}NO_2$: C, 61.93 ; H, 8.38 ; N, 9.03. Found : C, 62.00 ; H, 8.52 ; N, 9.00.

27c : 0.688 g, $Eb_{0.01}$ = 75-80°C, m.p. = 44-45°C.
IR (Nujol), ν : 3350 (NH, broad) ; 1658 (C=O) ; 1597 (C=C). ^{1}H NMR, δ : 1.55 - 2.47 (m, 4H) ; 2.53 - 3.03 (m, 1H) ; 3.35 - 3.62 (m, 2H) ; 3.65 (s, 3H) ; 4.55 (d, 1H, ^{4}J = 0.8) ; 4.92 - 5.25 (m, 2H) ; 5.53 - 6.08 (m, 1H) ; 7.87 (br s, 1H). ^{13}C NMR δ : 28.0 ; 37.1 ; 43.3 ; 45.6 ; 50.1 ; 76.1 ; 117.2 ; 135.5 169.1 ; 171.4. Anal. % calcd for $C_{10}H_{15}NO_2$: C, 66.30 ; H, 8.28 ; N, 7.73. Found : C, 66.25 ; H, 8.10 ; N, 7.80.

28a : 0,713 g, $Eb_{0.01}$ = 75-80°C.
IR, ν : 3260 (NH, broad) ; 1630 (C=O) ; 1593 (C=C). ^{1}H NMR, δ : 1.50 - 2.00 (m, 4H) ; 2.25 - 2.50 (m, 2H) ; 3.17 - 3.42 (m, 2H) ; 3.62 (s, 3H) ; 4.35 (t, 1H, ^{4}J = 0.8) ; 8.70 (br s, 1H). ^{13}C NMR δ : 20.0 ; 22.9 ; 29.2 ; 41.4 ; 49.8 ; 80.1 ; 163.0 ; 171.1. Mass spectrum, exact mass calcd for $C_8H_{13}NO_2$, $M^{+\cdot}$ m/z = 155.094, found : m/z = 155.095.

28b : 0,794 g, $Eb_{0.01}$ = 75-80°C.
IR, ν : 3270 (NH, broad) ; 1650 (C=O) ; 1593 (C=C). ^{1}H NMR, δ : 1.20 (d, 3H, J = 7.0) ; 1.30 - 2.05 (m, 4H) ; 2.20 - 2.72 (m, 1H) ; 3.17 - 3.40 (m, 2H) ; 3.60 (s, 3H) ; 4.46 (d, 1H, ^{4}J = 0.8) ; 8.80

(br s, 1H). ^{13}C NMR δ : 20.4 ; 20.6 . 28.2 ; 32.5 ; 41.3 ; 49.8 ; 79.2 ; 168.1 ; 171.5. Anal. % calcd for $C_9H_{15}NO_2$: C, 63.90 ; H, 8.87 ; N, 8.28. Found : C, 63.93 ; H, 8.83 ; N, 8.31.

28c : 0,848 g, $Eb_{0.01}$ = 85°C. TLC Rf = 0.56 (E/PE 1/1).
IR, ν : 3260 (NH, broad) ; 1630 (C=O) ; 1575 (C=C). ^{1}H NMR, δ : 1.42 - 2.03 (m, 4H) ; 2.20 - 2.58 (m, 3H) ; 3.17 - 3.45 (m, 2H) ; 3.62 (s, 3H) ; 4.46 (d, 1H, ^{4}J = 0.8) ; 4.90 - 5.23 (m, 2H) ; 5.50 - 6.08 (m, 1H) ; 8.80 (br s, 1H). ^{13}C NMR δ : 19.8 ; 24.4 ; 37.4 ; 38.8 ; 41.3 ; 49.9 ; 80.1 ; 117.0 ; 136.1 ; 166.5 ; 171.4. Anal. % calcd for $C_{11}H_{17}NO_2$: C, 67.69 ; H, 8.71 ; N, 7.17. Found : C, 67.88 ; H, 8.46 ; N, 7.35.

Synthesis of the α-acylphosphonates **29** and **30**. General procedure.

To a chilled (≃ 0°C) solution of 10 mmoles of the acid chlorides **13** or **14** in 10 ml of anhydrous dichloromethane were slowly added with stirring 10 mmoles (1.20 ml) of freshly distilled trimethylphosphite. The resulting solution was maintained at 0°C for 1 h and then at room temperature for 15 h. Then, the solvent was removed in vacuo and the residual oil purified by bulb to bulb distillation (oven temperature given).

29a : 1.77 g , $Eb_{0.01}$ = 85-90°C
IR, ν : 2090 (N_3) ; 1683 (C=O). ^{1}H NMR, δ : 1.72 - 2.17 (quint., 2H, J = 6.5 and 7.0) ; 2.96 (t, 2H, J = 7.0) ; 3.37 (t, 2H, J = 6.5) ; 3.88 (d, 6H, $^3J_{PH}$ = 10.6). ^{13}C NMR δ : 21.9 (d, $^3J_{PC}$ = 5) ; 40.5 (d, $^2J_{PC}$ = 56) ; 50.5 ; 54.1 (d, $^2J_{PC}$ = 7) ; 209.8 (d, $^1J_{PC}$ = 166). Mass spectrum : exact mass calcd for $C_4H_6N_3O$ [M-PO$(OCH_3)_2$]$^+$ m/z = 112.051. Found : m/z = 112.049.

29b : 2.21 g, $Eb_{0.01}$ = 90-95°C.
IR, ν : 2090 (N_3) ; 1703 (C=O). ^{1}H NMR, δ : 1.25 (d, 3H, J = 7.0) ; 1.42 - 2.42 (m, 2H) ; 3.00 - 3.50 (m, 1H) ; 3.37 (t, 2H, J = 6.6) ; 3.88 (d, 6H, $^3J_{PH}$ = 10.6). ^{13}C NMR δ : 15.2 ; 30.8 (d, $^3J_{PC}$ = 2) ; 44.2 (d, $^2J_{PC}$ = 54) ; 49.1 ; 54.1 (d, $^2J_{PC}$ = 7) ; 213.1 (d, $^1J_{PC}$ = 161). Mass spectrum, exact mass calcd for $C_7H_{14}NO_4P$ [M-N_2]$^+$ m/z = 207.066. Found : m/z = 207.069.

29c : 2.46 g. This product could not be distilled. The crude oil was kept under vacuum (0.01 torr) for 2 h.
IR, ν: 2085 (N_3) ; 1701 (C=O) ; 1674 (C=C). ^{1}H NMR, δ : 1.65 - 2.92 (m, 4H) ; 3.20 - 3.65 (m, 3H) ; 3.99 (d, 6H, $^3J_{PH}$ = 10.6) ; 5.05 - 5.37 (m, 2H) ; 5.50 - 6.10 (m, 1H). Mass spectrum, exact mass calcd for $C_7H_{10}N_3O$ [M - PO$(OCH_3)_2$]$^+$ m/z = 152.082. Found : m/z = 152.080.

30a : 1.93 g, $Eb_{0.01}$ = 95-100°C.
IR, ν : 2080 (N_3) ; 1678 (C=O). ^{1}H NMR, δ : 1.50 - 2.00 (m, 4H) ; 2.83 - 3.08 (m, 2H) ; 3.25-3.50 (m, 2H) ; 3.89 (d, 6H, $^3J_{PH}$ = 10.6). ^{13}C NMR, δ : 19.7 (d, $^3J_{PC}$ = 4) ; 28.1 ; 43.0 (d, $^2J_{PC}$ = 55) ; 51.1 ; 54.1 (d, $^2J_{PC}$ = 8) ; 210.2 (d, $^1J_{PC}$ = 167). Mass spectrum, exact mass calcd for $C_5H_8N_3O$ [M - PO$(OCH_3)_2$]$^+$ m/z = 126.066. Found : m/z = 126.066.

30b : 1.99 g, $Eb_{0.01}$ = 100-105°C.
IR, ν : 2080 (N_3) ; 1678 (C=O). ^{1}H NMR, δ : 1.23 (d, 3H, J = 7.0) ; 1.42 - 2.12 (m, 4H) ; 3.03-3.47 (m, 3H) ; 3.89 (d, 6H, $^3J_{PH}$ = 10.6). ^{13}C NMR, δ : 15.1 ; 26.4 ; 28.6 ; 46.3 (d, $^2J_{PC}$ = 54) ; 51.3 ; 54.0 (d, $^2J_{PC}$ = 7) ; 213.6 (d, $^1J_{PC}$ = 158). Mass spectrum, exact mass calcd for $C_2H_6O_3P$ [M-$C_6H_{10}N_3O$]$^+$ m/z = 109.005. Found : m/z = 109.005.

30c : 2.61 g, non distillable. The crude oil is treated as for **29c**.
IR, ν : 2085 (N_3) ; 1719 (C=O) ; 1678 (C=C). ^{1}H NMR, δ : 1.37 - 2.05 (m, 4H) ; 2.08 - 2.80 (m, 2H) ; 3.05 - 3.47 (m, 3H) ; 3.89 (d, 6H, $^3J_{PC}$ = 10.6) ; 4.92 - 5.25 (m, 2H) ; 5.48 - 6.03 (m, 1H). Mass spectrum, exact mass calcd for $C_8H_{13}NO$ [M - $C_2H_5N_2O_3P$]$^+$ m/z = 139.099. Found m/z = 139.099.

Synthesis of the cyclic imines **33** and **34**

These compounds were obtained according to the procedure described in reference 19 starting from 10 mmoles of the acylphosphonates **29** or **30**. **33** or **34** were purified by bulb to bulb distillation (oven temperature given).

33a : 1.15 g, $Eb_{0.5}$ = 80-85°C.
IR, ν : 1680 (C=N). ^{1}H NMR, δ : 1.72-2.20 (m, 2H) ; 2.70 - 3.03 (m, 2H) ; 3.86 (d, 6H, $^3J_{PH}$ = 10.8) ; 3.93 - 4.30 (m, 2H). ^{13}C NMR, δ : 21.7 (d, $^3J_{PC}$ = 5) ; 38.6 (d, $^2J_{PC}$ = 31) ; 53.4 (d, $^2J_{PC}$ = 6) ; 64.2 (d, $^3J_{PC}$ = 35) ; 172.0 (d, $^1J_{PC}$ = 211). Mass spectrum, exact mass calcd for $C_6H_{12}NO_3P$, M$^+$: m/z = 177.050 ; found : m/z = 177.054.

33b : 1.37 g, $Eb_{0.01}$ = 60-65°C.
IR, ν : 1683 (C=N). ^{1}H NMR, δ : 1.33 (d, 3H, J = 7.1) ; 1.43 - 1.85 (m, 1H) ; 1.97 - 2.53 (m, 1H) ; 2.87 - 3.50 (m, 1H) ; 3.88 (2d, 6H, $^3J_{PH}$ = 10.8). The two methoxy groups are slightly diastereotopic ($\Delta\nu_2$ = 0.5 Hz), 3.95 - 4.28 (m, 2H). ^{13}C NMR, δ : 17.5 ; 31.2 (d, $^3J_{PC}$ = 5) ; 46.5 (d, $^2J_{PC}$ = 31) ; 53.3 (d, $^2J_{PC}$ = 6) ; 62.5 (d, $^3J_{PC}$ = 34) ; 181.0 (d, $^1J_{PC}$ = 203). Mass spectrum, exact mass calcd for $C_7H_{14}NO_3P$, M$^+$: m/z = 191.071 ; found : m/z = 191.072.

33c : 1.51 g, $Eb_{0.01}$ = 65-70°C.
IR, ν : 1674 (C=N). ^{1}H NMR, δ : 1.47 - 2.42 (m, 3H) ; 2.47 - 2.92 (m, 1H) ; 2.97 - 3.45 (m, 1H) ; 3.86 (dd, 6H, $^2J_{PH}$ = 10.9. The methoxy groups are slightly diastereotopic (Δν = 1 Hz) ; 3.85 - 4.22 (m, 2H) ; 4.95 - 5.25 (m, 2H) ; 5.48 - 6.03 (m, 1H). ^{13}C NMR, δ : 27.6 (d, $^3J_{PC}$ = 6) ; 35.8 ; 51.4

(d, $^2J_{PC}$ = 31) ; 53.4 (d, $^2J_{PC}$ = 6) ; 62.9 (d, $^3J_{PC}$ = 35) ; 117.3 ; 135.3 ; 174.3 (d, $^1J_{PC}$ = 204). Mass spectrum, exact mass calcd for $C_9H_{16}NO_3P$, M^+ : m/z = 217.086, found : m/z = 217.088.

34a : 1.30 g, $Eb_{0.01}$ = 70-75°C. This compound was isolated as a mixture of the two tautomers **34a** (A) and **35a** (B).

IR, ν : 3450 - 3330 (NH, broad) ; 1640 (C=N et C=C). ^1H NMR, δ : 1.62 - 2.00 (m, $4H_A$ + 2 H_B) ; 2.08 - 2.58 (m, $2H_A$ + $2H_B$) ; 3.10 - 3.45 (m, $2H_B$) ; 2.58 - 4.08 (m, $2H_A$) ; 3.77 (d, $6H_B$, $^3J_{PH}$ = 11.0) . 3.85 (d, $6H_A$, $^3J_{PH}$ 10.6) ; 5.35 (dt, $1H_B$, $^3J_{PH}$ = 15.9, $^3J_{HH}$ = 4.0) ; 6.95 (br s, $1H_B$). ^{13}C NMR, δ 21.0 — 22.7, 3 doublets with J_{PC}= 5, 2 C_A + 1 C_B ; 41.7 (d, $^3J_{PC_B}$ = 10) ; 42.2 (C_A) ; 50.9 (d, $^3J_{PC_A}$ = 30) ; 52.2 (d, $^3J_{PC_B}$ = 5) ; 52.4 (d, $^2J_{PC}$ = 5, $\underline{O}CH_3$ of form B) ; 53.3 (d, $^2J_{PC}$ = 7, $\underline{O}CH_3$ of form A) ; 111.7 (d, $^2J_{PC_B}$ = 14) ; 132.0 (d, $^1J_{PC_B}$ = 201) ; 167.6 (d, $^1J_{PC_A}$ = 195). Mass spectrum, exact mass calcd for $C_7H_{14}NO_3P$, M^+: m/z = 191.071, found : m/z = 191.070.

Synthesis of ω-azidoketones **38** and **39**

3 mmoles of n-butylmanganous iodide were prepared in anhydrous ether as described in ref. 18. The suspension was cooled to -40°C and 3 mmoles of the azidoacid chlorides **13** or **14** were added via syringe. The reaction mixture was stirred for 15 minutes at this temperature and then allowed to reach room temperature within two hours. The reaction was quenched at 0°C by adding 1 ml of a 0.5 N HCl solution. After extraction with ether (2 x 10 ml), the organic phases were washed with saturated sodium carbonate (3 ml), sodium thiosulfate (2 ml of 5 % aqueous solution) and dried over Na_2SO_4. The solvents were removed in vacuo and the azidoketones purified by column chromatography followed by bulb to bulb distillation (oven temperature given).

38a : 0.32 g, $Eb_{0.01}$ 45-50°C. TLC Rf = 0.50 (E/PE 25/75).

IR, ν : 2088 (N_3) ; 1703 (C=O). ^1H NMR, δ : 0.96 (non resolved triplet, 3H) ; 1.15 - 2.12 (m, 6H) ; 2.35 - 2.75 (m, 4H) ; 3.35 (t, 2H, J = 6.6). Anal. % calcd for $C_8H_{15}N_3O$: C, 56.80 ; H, 8.87 ; N, 24.85. Found : C, 56.62 ; H, 8.90 ; N, 24.68.

38b : 0.32 g, $Eb_{0.01}$ = 50-55°C. TLC Rf = 0.56 (E/PE 25/75).

IR, ν : 2088 (N_3) ; 1702 (C=O). ^1H NMR, δ : 0.94 (non resolved triplet, 3H) ; 1.12 (d, 3H, J = 7.0) ; 1.25 - 2.25 (m, 6H) ; 2.47 - 2.87 (m, 3H) ; 3.35 (t, 2H, J = 6.8). Anal. % calcd for $C_9H_{17}N_3O$: C, 59.01 H, 9.28 ; N, 22.95. Found : C, 58.70 ; H, 9.22 ; N, 22.92.

39a : 0.37 g, $Eb_{0.01}$ = 50-55°C. TLC Rf = 0.50 (E/PE 25/75).

IR, ν : 2090 (N_3) ; 1703 (C=O). ^1H NMR, δ : 0.95 (non resolved triplet, 3H) ; 1.12 - 1.95 (m, 8H) ; 2.33 - 2.62 (m, 4H) ; 3.20 - 3.45 (m, 2H). Anal. % calcd for $C_9H_{17}N_3O$: C, 59.01 ; H, 9.28 ; N, 22.95. Found : C, 58.75 ; H, 9.16 ; N, 23.16.

39b : 0.35 g, $Eb_{0.01}$ = 55-58°C. TLC Rf = 0.50 (E/PE 25/75).

IR, ν : 2090 (N_3) ; 1703 (C=O). ^1H NMR, δ : 0.91 (non resolved triplet, 3H) ; 1.08 (d, 3H, J = 6.8) ; 1.25 - 1.90 (m, 8H) ; 2.33 - 2.70 (m, 3H) ; 3.17 - 3.40 (m, 2H). Anal. % calcd for $C_{10}H_{19}N_3O$: C, 60.91 ; H, 9.64 ;N, 21.39. Found : C, 60.63 ; H, 9.71 ; N, 21.21.

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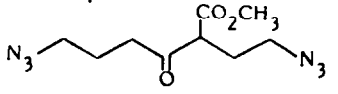
8 - The temperature inside the reaction flask must be below -80°C. If it is not the case, the alkylation reactions are not clean. For example : the bis azide **40** was isolated in one case resulting from an intermolecular acylation.



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