From Azido Acids to Macrolactams and Macrolactones

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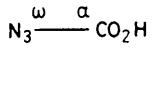
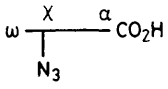
A new method is reported for the conversion of azido acids into lactams, *via* thioester formation and *in situ* azide reduction and cyclisation under high-dilution conditions; since the quantitative conversion of macrolactams to macrolactones has been shown to be feasible, this results in an indirect, alternative macrolactonisation procedure.

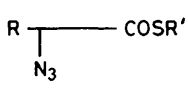
Natural products containing carboxamide functions in medium and large rings are abundant, the most important types being cyclic peptides and depsipeptides, macrolactamic alkaloids, and ansamycins.[1] Syntheses of these compounds often involve a macrolactamisation step which usually poses some specific problems.[2] In fact, the recent report of Steliou *et al.*[3] has shown that methods used to obtain medium-to-large size macrolides (heating of ω-hydroxyacids with dibutyltin oxide) cannot be applied to the preparation of analogous macrolactams. We report here a synthetic route to macrolactams, starting from azido acids rather than protonated or deprotonated amino acids.



(1a)



(1b)



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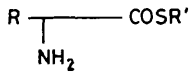
(2b) R = alkyl



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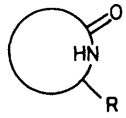
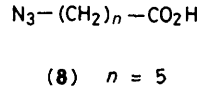
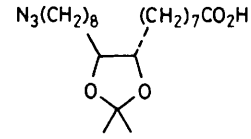


(4a) R = H
(4b) R = alkyl



(8) n = 5
(9) n = 10
(10) n = 11
(11) n = 14



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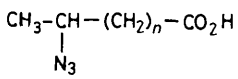
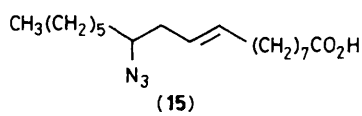


(13) n = 7
(14) n = 8



(15)

If ω-azido acids (**1a**) and χ-azido acids (**1b**), presumably soluble in most organic solvents, could be converted under smooth conditions into ω/χ-azido thioesters (**2**),[4] and these compounds reduced *in situ* to ω/χ-amino thioesters (**3**) under high-dilution conditions, cyclisation to lactams (**4**) would be effected in two synthetic steps [(**1**) → (**2**) → (**4**)]. Mukaiyama's thioesterification reaction (*i.e.*, using R'SSR' plus R''_3P)[5] seemed a good choice to perform step (**1**) → (**2**), but it posed the problem of how to avoid the well known reaction of phosphines with the azide group.† Moreover, reduction of azides to amines can be brought about by many reagents, in theory,[6] but here an extremely active and chemoselective reduction agent is required, one able to reduce the azide group quickly even under high-dilution conditions (otherwise only polymeric material would be obtained) and without affecting the thioester group.

Compounds (**8**)—(**15**) were chosen as appropriate substrates for our cyclisation studies. The carboxy groups of (**8**)—(**15**) were activated towards nucleophilic attack by converting them into the *S*-phenyl and *S*-2-pyridyl thioesters, using the known reaction of carboxylic acids with R'SSR' plus R''_3P,[5] as mentioned above. To prevent reaction of the phosphine with the azide group of compounds (**8**)—(**15**),† the reaction procedure was as follows: the azido acid (**1**) (1 mmol) was added to a mixture of triethylphosphine (2 mmol) and di-2-pyridyl disulphide (2.5 mmol) in cold benzene (3—5 ml) under nitrogen; after 30 min, benzenethiol (3 mmol) was added and the mixture was maintained at room temperature for 2—3 h until completion (t.l.c.). Filtration through a short column of silica gel with CH_2Cl_2–hexane (1 : 1) afforded pure ω/χ-azido *S*-phenylthioesters [(**2**), R'=Ph] in 88—95% yields. Similarly, but without adding benzenethiol, the ω/χ-azido *S*-2-pyridylthioesters [(**2**), R'=2-pyridyl] were obtained in 95—100% yields.

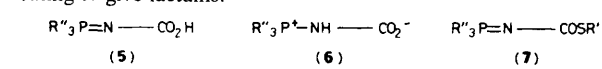
Cyclisation (macrolactamisation) was performed by adding a benzene solution of the precursor (1 mmol in 50 ml) during 6 h to a mixture of refluxing benzene or acetonitrile (150 ml) and the reagent(s), by three different methods: in method (**A**), a mixture of $SnCl_2$ (10 mmol), PhSH (30 mmol), and Et_3N (30 mmol) in a few ml of acetonitrile was added to the cyclisation flask; in method (**B**), the flask was charged similarly with $SnCl_2$ (15 mmol), pyridine-2-thione (60 mmol), and Et_3N, (60 mmol); and in method (**C**), the azides (**2b**) (1 mmol) were pre-reduced at 0—5 °C with a mixture of $SnCl_2$ (1.5 mmol), PhSH (4.5 mmol), and Et_3N (4.5 mmol) in benzene or toluene (*ca.* 10 ml) to afford solutions of complexed (**3b**) which, after removal of excess of reagent and byproducts by washing with cold aqueous Na_2CO_3, were dried and slowly added as before to a cyclisation flask containing HgO, 4 Å molecular sieves, and refluxing toluene (150 ml). The results are summarised in Table 1. The yields (the sum of the monomer and dimer yields) are generally excellent;‡ however, for method (**A**) with secondary azides (**2b**), reaction did not occur even in refluxing toluene. Practically the same yields were achieved without prior isolation of thioesters (*i.e.*, by straightforward addition of thioesterification mixtures into the cyclisation flask). It is believed that the reactive species in methods (**A**) and (**B**) are the $[Sn(SPh)_3]^-$ and $[Sn(SPy)_3]^-$ anionic species, respectively; in fact, the chemical ionization (CI) mass spectrum (negative ion) of the residue obtained from the benzene solution of Sn^{II}/PhSH/Et_3N shows the base peak at *m/z* 447, corresponding to the $[^{120}Sn(SPh)_3]^-$ species, together with other peaks (*m/z* 443—451) in the expected isotopic ratio. It must also be noted that the reducing power of the Sn^{II}/PhSH/Et_3N mixture is stronger than that of the Sn^{II}/PySH/Et_3N mixture.§

Table 1. Overall yields of lactams, monomer *vs.* dimer (w/w), from azido acids (**8**)—(**15**).

Azido acid	Thioester	Method (A)	Method (B)	Method (C)
(**8**)	R' = Ph	81 : 0		
(**8**)	R' = Py[a]		85 : 0	
(**9**)	R' = Ph	38 : 38		
(**9**)	R' = Py		38 : 40	
(**10**)	R' = Ph	34 : 42		
(**10**)	R' = Py		32 : 45	
(**11**)	R' = Ph	68 : 15		
(**11**)	R' = Py		65 : 12	
(**12**)	R' = Ph	80 : 5		
(**13**)	R' = Ph	[b]		35 : 38
(**13**)	R' = Py		30 : 48	
(**14**)	R' = Ph	[b]		45 : 35
(**14**)	R' = Py		32 : 42	
(**15**)	R' = Ph	[b]		63 : 20
(**15**)	R' = Py		48 : 30[c]	

[a] Py = 2-pyridyl. [b] Trace amounts of lactams (t.l.c.). [c] In xylene at 120 °C; 55 : 25 in refluxing xylene.

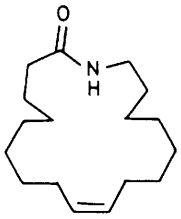
† This reaction gives ω-phosphazenido acids, (**5**) ⇆ (**6**), and some phosphazenido ester (**7**), which would not undergo cyclisation on heating to give lactams.



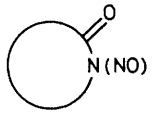
(5) (6) (7)

‡ It is likely that yields of monomers could be generally improved at the expense of those of dimeric lactams if addition was performed more slowly and if a large volume of a high-boiling solvent was used, but no systematic work has been done in this connection.

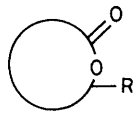
§ It would seem logical to reduce the azide with the stronger reagent, $[Sn(SPh)_3]^-$, and to work with the more reactive pyridyl thioester [*i.e.*, to apply method (**A**) on derivatives with R' = 2-Py], but the rapid SPh/SPy replacement that took place in the cyclisation flask ruled out such a combination.



(16)



(17a)



(18a) R = H
(18b) R = alkyl

We have quantitatively converted all lactams (**4a**) reported here, as well as lactam (**16**), into the corresponding *N*-nitroso derivatives, (**17a**), by means of reagents used to perform the 'pernitrosation' of peptides in cold acetonitrile:[7] $NO^+BF_4^-$/pyridine and $NO_2^+BF_4^-$/Me_2S/pyridine. Nitrosolactams (**17a**) were isolated and heated in anhydrous CCl_4 to give lactones (**18a**) in 94—100% yields.[8] On the other hand, lactams (**4b**), when nitrosated overnight at 0 °C with any of the above reagents, afforded directly and quantitatively lactones (**18b**). It is worth noting that double bonds and isopropylidene acetals remain untouched under these reaction conditions. Also, the application of the present method to (**13**), which we have prepared in six simple steps from commercial undec-10-enoic acid, constitutes a new synthesis of racemic phoracantolide I.[9]

In conclusion, an alternative strategy to perform macrolactamisations and macrolactonisations, starting from azido acids, is reported that seems readily amenable to further improvements. Application of such a cyclisation methodology to the synthesis of more complicated natural products is envisaged.

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