N,N-(Dimethylamino)-2-pyrrolidinones from the Rearrangement of *N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichlorohydrazides Promoted by CuCl−*N,N,N*′,*N*′-Tetramethylethylendiamine

Franco Ghelfi*

Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41100, Modena, Italia

Andrew F. Parsons

Department of Chemistry, University of York, Heslington, York YO10 5DD, United Kingdom

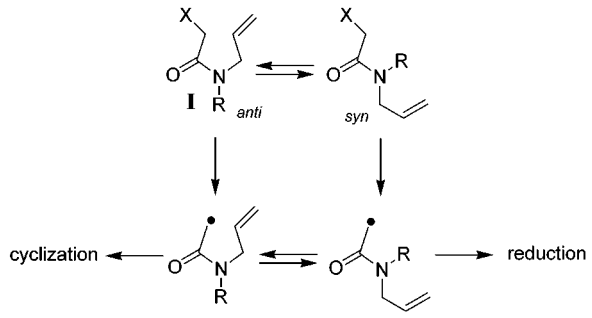
ghelfi.franco@unimo.it

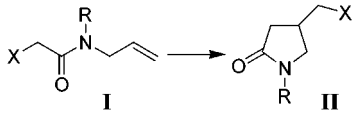
Received March 21, 2000

Owing to their important biological properties, 2-pyrrolidinones have received considerable attention by researchers and the interest continues to bloom.[1] The γ-lactam ring is frequently found in important drugs used in medicine.[2] Moreover, other bioactive molecules can be easily obtained by reduction of the 2-pyrrolidinone nucleus to give pyrrolidines,[3] or by cleavage of the amide bond.[4] The search for new procedures for the synthesis of 2-pyrrolidinones is therefore an important area.[5]

In recent years the cyclization of α-amide radicals, produced by radical additions to acrylamides or by atom abstraction reactions,[6−8] onto allylic or vinylic appendages has received considerable attention, and this represents a powerful and versatile method for the preparation of 2-pyrrolidinones.[9] This approach requires α-functionalized, usually halogenated, *N*-allyl amides as precursors for the α-amido radical.[9] Of the two main cyclization procedures, the Bu_3SnH[10] method or the atom transfer method,[11,12] the latter appears safer and more environmentally friendly, since toxic and difficult to remove tin compounds are avoided. In addition, the atom transfer method allows a versatile halogen atom to be introduced in the product (eq 1).[11]

Scheme 1





(1)

The most frequently used catalysts for the rearrangement are CuCl−bipyridine[11a] or $RuCl_2(PPh_3)_3$[11b] to which we have recently added CuCl−TMEDA.[11e,f] Compared to the first two catalysts, the use of CuCl−TMEDA shows some fundamental advantages. This includes a higher reactivity, so that reactions can be carried out at lower temperatures using a lower concentration of the catalyst. The catalyst is also inexpensive, and the reactions can be carried out in a range of (nonaromatic) solvents.

The cyclization of α-*N*-allyl-carbamoyl radicals is quite a difficult process and requires a high reaction temperature and/or the introduction of a large substituent on the nitrogen.[13] This is because of the high rotational barrier of C(O)−N bonds (12−15 kcal mol^{-1}), which restricts the interconversion of the syn and anti conformers. A large *N*-protecting group (R) changes the rotameric population and shifts the equilibrium toward the anti conformer which can cyclize (Scheme 1).[13−16] The change in conformer population is evident from the appearance of the peaks in the ^1H NMR spectra (recorded at room temperature in $CDCl_3$). Whereas, for example, broad signals are generally observed for *N*-allyl-*N*-benzyl-2,2-dichloroamides (which are a mixture of conformers), the corresponding *N*-allyl-2,2-dichloroamide signals[17] are much sharper because only the syn conformer is present.

* To whom correspondence should be addressed. Phone: 059/2055049. Fax: 059/373543.

(1) Galeazzi, R.; Mobbili, G.; Orena, M. *Targets Heterocycles* **1997**, *1*, 355.

(2) (a) Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180. (b) Hulme, C.; Moriarty, K.; Huang, F−C.; Mason, J.; McGarry, D.; Labaudiniere, R.; Souness, J.; Djiuric. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 399. (c) Silverman, R. B., II. *Farmaco* **1997**, *52*, 343.

(3) Okayama, T.; Araki, S.; Miyamae, T.; Morita, Y.; Morikawa, T.; Hagiwara, M. *Arzneim.-Forsch./Drug. Res.* **1997**, 47 (II), 1023.

(4) Herdei, C.; Hubmann, H. P. *Tetrahedron Asymmetry* **1992**, *3*, 1213.

(5) Giambastiani, G.; Pacini, B.; Porcelloni, M.; Poli. G. *J. Org. Chem.* **1998**, *63*, 804.

(6) Curran, D. P.; Porter, N.A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(7) Quirante, J.; Escolano, C.;, Costejà, L.; Bonjoch, J. *Tetrahedron Lett.* **1997**, *38*, 6901.

(8) Lipp, D.; Kozakiewicz, J. *Encyclopedia of Chemical Technology*, 4th ed.; Wiley: New York, 1991; p 266.

(9) (a) Ishibashi, H.; Sato, T.; Ikeda, M. J. *Synth. Org. Chem. Jpn.* **1995**, *53*, 85. (b) Nagashima, H.; Itoh, K. J. *Synth. Org. Chem. Jpn.* **1995**, *53*, 298.

(10) (a) Parsons, A.F.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1945. (b) Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308.

(11) (a) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464. (b) Rachita, M.A.; Slough, G.A. *Tetrahedron Lett.* **1993**, *34*, 6821−6824. (c) Ikeda, M.; Teranishi, H.; Nozaki, K.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1691. (d) Jasperse, C. P.; Curran, D.P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (e) Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *41*, 14031. (f) Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M.C.; Pagnoni, U. M.; Pinetti, A.; De Buyck, L.; Parsons, A. F. *Tetrahedron* **1999**, *55*, 5839.

(12) Clark, A. J.; Filik, R.P.; Thomas, G. H. *Tetrahedron Lett.* **1999**, *40*, 4885.

(13) Curran, D.P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(14) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.

(15) (a) Bryans, J. S.; Large, J. M.; Parsons, A.F. *Tetrahedron Lett.* **1999**, *4*, 3487. (b) Bryans, J.S.; Large, J. M.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2897.

(16) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625.

(17) Forti, L.; Ghelfi, F.; Munari, F.; Pagnoni, U. M. *Tetrahedron* **1995**, *45*, 12285.

10.1021/jo0004153 CCC: $19.00
Published on Web 08/26/2000

Table 1. Study of Cyclization of 4a[a]

entry	educt	catalyst	solvent	*T* (°C)	conv (%)	yield (%)	cis:trans[b]
1	**4a**	CuCl	CH_3CN	60	0	0	/
2	**4a**	$[Cu(TMEDA)_2]Cl$	CH_3CN	60	94	91	61:39
3	**4a**	$[Cu(TMEDA)_2]Cl$	EtOEt	60	54	51	60:40
4	**4a**	$[Cu(TMEDA)_2]Cl$	CH_2Cl_2	60	37	34	53:47
5	**4a**	$[Cu(TMEDA)_2]Cl$	EtOAc	60	99	97	77:23
6	**4a**	$[Cu(TMEDA)_2]Cl$	EOAc	80	100	88[c]	80:20
7	**4a**	$[Cu(TMEDA)_2]Cl$	EtOAc	40	75	71	64:36
8	**4a**	$[Cu(BiPy)_2]Cl$	EtOAc	60	13	5	60:40

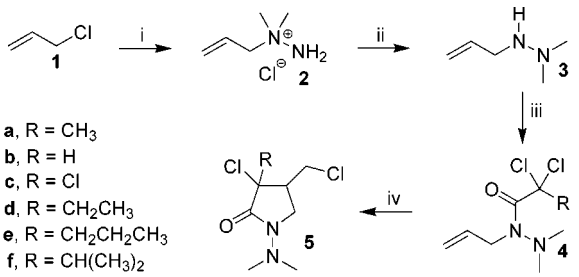
[a] 2×10^{-3} mol of **4a**, 2×10^{-4} mol of catalyst, and 4 mL of solvent were used; reaction time 20 h. [b]Ratio determined by GC. [c]10% of **6a** was detected.

Although benzyl protecting groups are usually preferred for the cyclization of amides, subsequent deprotection of the *N*-benzyl-lactam products by, for example, hydrogenolysis[18] is often problematic and the most general method involves the use of lithium or sodium in liquid ammonia.[19] There is, therefore, a need for a different protecting group which can both promote the efficient cyclization of amides and be easily removed from the lactam products.

The *N*-dialkylamino group is a potential candidate for replacing the *N*-benzyl protecting group. This could be more easily removed from cyclic products, as bonds between heteroatoms are weaker than those involving carbon atoms.[20] Thus, for example, the N−N bond of *N*,*N*-dimethylhydrazine is 10 kcal mol^{-1} weaker than the C−N bond of benzylamine.[21] In addition, the hydrazide functional group is found in biologically active lactams with antibiotic,[22] antidiarrheal,[23] anticonvulsant,[24] antiosteoporosis,[25] antitumor,[26] or antihypertensive[27] activities.

This work was undertaken so as to investigate the compatibility of the dialkylamino protecting group with the intramolecular halogen atom transfer reaction, and we now report that the cyclization of *N*-allyl-*N*′,*N*′-dimethyl-2,2-dichlorohydrazides can be effectively performed using CuCl/TMEDA in ethyl acetate (Scheme 2). As far as we are aware, the preparation of *N*-amino-2-pyrrolidinones has been neglected up till now, and only been achieved through either an intramolecular aza-ene reaction of γ,δ-unsaturated-azodicarbonyl educts,[28] or by cyclization of hydrazides with a good leaving group on the γ-carbon.[25]

Scheme 2[a]



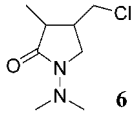
[a] (i) $(CH_3)_2NNH_2$, CH_3CN, reflux, 3 h (90%); (ii) NaOH, H_2O, 20−60 °C, 4 h (60%); (iii) $RCCl_2C(O)Cl$, CH_2Cl_2, reflux, 15 h (86−92%); (iv) $[Cu(TMEDA)_2]Cl$, EtOAc, 60 °C, 20 h (94−98%).

Initially, *N*-allyl-*N*′,*N*′-dimethyl hydrazine **3** was efficiently and easily prepared from allyl chloride by exploiting the two-step procedure reported by Konig (Scheme 2).[29] This could then be acylated to give hydrazides **4a**−**f**, and these reactions did not require the presence of a tertiary amine base, as the NMe_2 group (in **4a**−**f**) acted as a proton scavenger.

It was envisaged that the NMe_2 group in **4** (and **5**) could complex the CuCl and this could lead to cyclization in the absence of TMEDA or related amine ligands. However, preliminary reactions using only CuCl failed, and only starting material was isolated. This emphasizes the requirement for a bidentate, rather than a monodentate, amine ligand in these types of reaction. A number of reaction conditions were then investigated (Table 1) for the cyclization of **4a** using a ratio of TMEDA to CuCl, of 2:1,[11e] which presumably forms the tetrahedral $[Cu(TMEDA)_2]Cl$ complex.[12] Excellent results were achieved not only in acetonitrile but also in ethyl acetate, which is a safer and more ecofriendly solvent. In addition, since $[Cu(TMEDA)_2]Cl$ is partially soluble in ethyl acetate, the reaction workup was accomplished through a simple filtration (which allowed 50−65% of the copper to be recovered) followed by concentration of the reaction mixture and subsequent chromatography.

From the results obtained, two main conclusions can be drawn: first, that TMEDA is a more active ligand than bipyridine, and second, that the reaction temperature is critical. Indeed, the rearrangement cannot be carried out at temperatures above 60 °C, since hydro-de-halogenation of the cyclic dichloride can occur leading to *N*-(dimethylamino)-4-chloromethyl-3-methyl-pyrrolidin-2-one (**6**) (Figure 1), as evidenced by the isolation of **6** in 15% yield (mixture of cis:trans diastereoisomers, 47:53) from reaction of **5a** with 0.2 equiv of $[Cu(TMEDA)_2]Cl$ at 80 °C (20 h). The optimum reaction conditions (for **4a**) were then used for the cyclization of other hydrazides, **4b**−**f,**

(18) Gigg, R.; Conant, R. *Carbohydr. Res.* **1982**, *100*, C5.
(19) (a) Naito, T.; Honda, Y.; Bhavakul, V.; Yamaguchi, S.; Fujiwara, A.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1997**, *45*, 1932. (b) Webster, F. X.; Millar, J. G.; Silverstein, R. M. *Tetrahedron Lett.* **1986**, *27*, 4941. (c) Sugasawa, S.; Fujii, T. *Chem. Pharm. Bull.* **1958**, *6*, 587.
(20) Repič, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley: New York, 1998; p 8.
(21) (a) Golden, D. M.; Solly, R. K.; Gac, N. A.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 363. (b) Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas-Phase Unimolecular Reactions*; NSRDS-NBS, 1970; p 21. (c) See also: Marshalkin, M. F.; Yakhontov, L. N. *Russ. Chem. Rev.* **1986**, *55*, 1016.
(22) Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037.
(23) Butler, D. E.; Meyer, R. F.; Alexander, S. M.; Bass, P.; Kennedy, J. A. *J. Med. Chem.* **1973**, *16*, 49.
(24) Kornet, M. J. *J. Pharm. Sci.* **1984**, *73*, 405.
(25) Duffy, K. J.; Ridgers, L. H.; Desjarlais, R. L.; Tomaszek, T. A.; Bossard, M. J.; Thompson, S. K.; Keenan, R. M.; Veber, D. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1907.
(26) Yaegashi, T.; Sawada, S.; Furuta, T.; Yokokura, T.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1993**, *41*, 971.
(27) Matsumoto, Y.; Tsuzuki, R.; Matsuhisa, A.; Takayama, K.; Yoden, T.; Uchida, W.; Asano, M.; Fujita, S.; Yanagisawa, I.; Fujikura, T. *Chem. Pharm. Bull.* **1996**, *44*, 103.
(28) (a) Sarkar, T. K.; Gangopadhyay, P.; Satapathi, T. K. *Tetrahedron Lett.* **1999**, *40*, 395. (b) Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, *20*, 4185.
(29) Konig, K. H.; Zeeh, B. *Chem. Berichte* **1970**, *103*, 2052.



6

Figure 1.

Table 2. Rearrangement of 4 to 5[a]

entry	educts	products	yield[b](%)	cis:trans[c,d]
1	**4a**	**5a**	97 (99)	77:23 (82:18)
2[e]	**4b**	**5b**	17 (27)	34:66 (28:72)
3	**4c**	**5c**	94 (96)	/
4	**4d**	**5d**	98 (99)	84:16
5	**4e**	**5e**	96 (98)	85:15 (86:14)
6	**4f**	**5f**	96 (97)	96:4 (100:0)

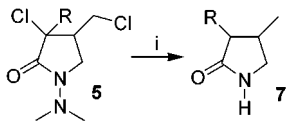
[a] Reaction temperature 60 °C. [b]Conversion in parentheses. [c]Ratio determined by GC. [d]Ratio of *N*-benzyl-2-pyrrolidinones in parentheses (ref 11). [e]Reaction temperature 80 °C.

to give **5c**−**f** in excellent yields (Table 2). Unfortunately, for **4b**, no reaction was observed at 60 °C, while at 80 °C, even on doubling the amount of catalyst, the rearrangement was slow (conversion 27% after 20 h) and unclean, giving **5b (**17%) mono-de-halogenated **4b** (4%) and other unidentified products. Clearly the *N*-allyl-*N*′,*N*′-dimethyl-2,2-dichlorohydrazides are less prone to attack by CuCl/TMEDA than the corresponding *N*-allyl-*N*-benzyl-2,2-dichloroamides.[11] This was confirmed by two comparative tests in which 1:1 mixtures of dichloride **4a**/*N*-allyl-*N*-benzyl-2,2-dichloropropanamide, and trichloride **4c**/*N*-allyl-*N*-benzyl-trichloroacetamide, were treated under the same (CuCl/TMEDA) reaction conditions. After 2 h, both mixtures showed complete disappearance of the *N*-benzyl precursors and only modest conversions for **4a** and **4c**, of 14% and 21%, respectively.

Products **5a** and **5d**−**f** were isolated as cis−trans mixtures (with a prevalence of one diastereoisomer), but these could not be separated by silica gel chromatography. As previously observed by us[11e,f] and later substantiated by Nagashima,[30] these type of cyclizations give predominantly the thermodynamically more stable isomer (i.e., those which have the bulkier C-3 and C-4 appendages on the opposite faces of the pyrrolidinone ring) because of isomerization at the C-3 center. As a consequence, the trans isomer for **5b** is formed predominantly.[31] For **5a** and **5d**−**f** the cis isomers[31] are preferentially formed (as confirmed by NOE experiments) as the C-3 alkyl groups are bulkier than the chloro substituent at C-3; steric interactions therefore force the C-3 chloro and C-4 chloromethyl groups to adopt a cis arrangement. It should be noted that similar cis−trans ratios have been observed for the corresponding *N*-benzyl-2-pyrrolidinones[11] (Table 2).

Our attention was then directed to the unexpected formation of mono-halogenated 2-pyrrolidinone **6**, which occurred during the rearrangement of **4a** at 80 °C. This is an interesting result since this is the first time that we have observed attack of the C(3)Cl bond by CuCl/TMEDA. Homolysis of the carbon−chlorine bond followed by reaction of the intermediate radical with a radicophile could provide a method for producing a variety of α-chloro-γ-lactams.[30] To investigate this possibility, mixtures of the catalyst, 1-hexene, and **5a** or **5c** were heated at 80−100 °C. Unfortunately, however, no trace of the addition adduct was detected, and hydro-de-halogenation at C(3) was the only reaction observed.

Scheme 3[a]



[a] (i) Raney-Ni, ethanol, 110 °C, 21−22 h: **7c** (R = H), 96%; **7e** (R = Pr), 95%, **7f**, (R = ^{i}Pr), 98%.

Finally, we investigated the removal of the dimethylamino group from **5e**. Cleavage of the N−N bond of hydrazides is known and can be accomplished with Li or Na in NH_3,[32] Raney-Ni,[33] or SmI_2.[34] Reaction with Raney-Ni is certainly the most practical approach, but unfortunately, hydro-de-chlorination was mainly observed on reaction of Raney-Ni with **5e** under the standard reaction conditions (i.e., ethanol at reflux for 22 h).[33] However hydrogenolysis of the N−N bond, together with hydro-de-chlorination, could be achieved when the mixture of Raney-Ni, **5e**, and ethanol was heated at 110 °C for 21 h in a closed Schlenk tube (Scheme 3). In a parallel experiment, reaction of *N*-benzyl-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one yielded only hydro-de-halogenated products, and this further emphasizes the difficulty of removing *N*-benzyl protecting groups from lactams. The hydrogenolysis procedure was then applied to the deprotection of the trichlorolactam **5c**, and the isopropyl-dichlorolactam **5f** (Scheme 3). The yields of the desired pyrrolidinones, **7c** and **7f**, were excellent, although for the efficient formation of **7f** we had to double the Raney-Ni/substrate ratio in order to drive the reaction to completion. This diminished reactivity is likely caused by the large isopropyl appendage, which shields the $(CO)N-N(CH_3)_2$ segment from the metal surface.[33]

In summary, treatment of *N*-allyl-*N*′,*N*′-dimethyl-2,2-dichlorohydrazides with CuCl/TMEDA in ethyl acetate[35] is a mild and easy method for preparing *N*-(dimethylamino)-2-pyrrolidinones. As the N−N bond in the lactam products can be easily and efficiently cleaved, this makes *N*-dimethylamino protection an attractive alternative to *N*-benzylic protection. We are currently developing methods for selective hydro-de-chlorination of the halo-lactams [with CuCl/TMEDA] and investigating the selective functionalization at C-5 of the pyrrolidinone ring using the *N*-dimethylamino group. The asymmetric synthesis of pyrrolidinones is also being investigated using enantiopure hydrazines as chiral auxiliaries.

Experimental Section

Reagents were standard grade commercial products and used without further purification. Solvents used in the cyclization were dried over three batches of 3 Å sieves (5% w/v, 12 h). CuCl, TMEDA and Raney-Ni were purchased from Fluka. *N*-Allyl-*N*′,*N*′-dimethyl hydrazine was prepared according to the procedure of Konig (Scheme 2).[29] 2,2-Dichloro-3-methyl-butanoic acid was synthesized starting from 2-(2-methyl-propyl)-4,5-dimethyl-

(30) Iwamatsu, S.; Kondo, H.; Matsubara, K.; Nagashima, H. *Tetrahedron* **1999**, *55*, 1687.

(31) The cis isomer carries the prior groups on the same face; instead the contrary is true for the trans one. See: Rachita, M. A.; Slough, G. A. *Tetrahedron Lett.* **1993**, *34*, 6821.

(32) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219.

(33) (a) Hinman, R. L. *J. Org. Chem.* **1957**, *22*, 148.

(34) Burk, M.J.; Feaster,. J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

(35) Ethyl acetate can also successfully replace acetonitrile in the rearrangement of *N*-allyl-*N*-benzyl-2,2-dichloroamides.

1,3-dioxolane,[36] whereas 2,2-dichlorobutanoic acid was obtained by chlorination (Cl_2) of the parent alcohol.[37] 2,2-Dichloroalkanoic acids were converted into the corresponding acyl chlorides using oxalyl chloride.[11f]

General Procedure for the Preparation of Chlorinated Hydrazides. In a double-necked round-bottom flask (100 mL), fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, were introduced CH_2Cl_2 (40 mL) and *N*-allyl-*N*′,*N*′-dimethyl-hydrazine (4.01 g, 40 mmol). A CH_2Cl_2 (20 mL) solution of 2,2-dichloropropanoyl chloride (6.46 g, 40 mmol) was then carefully added to the stirred solution, and the mixture obtained was heated to reflux. After 15 h, NaOH (5% w/v, 80 mL) was added at room temperature, and the stirring was continued for a further 2 h.[38] The organic phase was then separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over Na_2CO_3 and concentrated. Purification of the crude product by column chromatography on silica gel, using a petroleum ether (bp 40−60 °C)/diethyl ether gradient, afforded 8.28 g of **4a** (92%).

***N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichloropropionohydrazide (4a).** ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.64 (s, 6H), 3.96−4.13 (m, 2H), 5.17−5.42 (m, 2H), 5.83−6.08 (m, 1H). IR (film) 1666 (C═O) cm^{-1}. MS (EI, *m*/*z*) 224 (2, M^{35}), 99 (100). Anal. Calcd for $C_8H_{14}Cl_2N_2O$: C, 42.68; H, 6.27; N, 12,44. Found: C, 42.83; H, 6.37; N, 12.32. Oil.

***N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichloroacetohydrazide (4b).** According to the above protocol, 2,2-dichloroacetyl chloride (5.90 g, 40 mmol) was converted to **4b** (7.77 g, 92%). ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 6H), 4.05 (m, 2H), 5.17−5.38 (m, 2H), 5.82−6.07 (m, 1H), 6.94 (s, 1H). IR (film) 1690 (C═O) cm^{-1}. MS (EI, *m*/*z*) 210 (2, M^{35}), 99 (100). Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.83; H, 5.73; N, 13.27. Found: C, 39.74; H, 5.72; N, 13,13. Oil.

***N*-Allyl-*N*′,*N*′-dimethyl-trichloroacetohydrazide (4c).** According to the above protocol, trichloroacetyl chloride (7.27 g, 40 mmol) was converted to **4c** (9.04 g, 92%). ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 6H), 4.04 (m, 2H), 5.20−5.39 (m, 2H), 5.82−6.07 (m, 1H). IR (film) 1690 (C═O) cm^{-1}. MS (EI, *m*/*z*) 244 (1, M^{35}), 99 (100). Anal. Calcd for $C_7H_{11}Cl_3N_2O$: C, 34.24; H, 4.52; N, 11.41. Found: C, 34.34; H, 4.43; N, 11.52. Oil.

***N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichlorobutanohydrazide (4d).** According to the above protocol, 2,2-dichlorobutanoyl chloride (7.02 g, 40 mmol) was converted to **4d** (8.32 g, 87%). ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 2.54 (q, J = 7.2 Hz, 2H), 2.64 (s, 6H), 4.01 (m, 2H), 5.17−5.37 (m, 2H), 5.82−6.06 (m, 1H). IR (film) 1664 (C═O) cm^{-1}. MS (EI, *m*/*z*) 238 (3, M^{35}), 99 (100). Anal. Calcd for $C_9H_{16}Cl_2N_2O$: C, 45.20; H, 6.74; N, 11.71. Found: C, 45.31; H, 6.84; N, 11.56. Oil.

***N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichloropentanohydrazide (4e).** According to the above protocol, 2,2-dichloropentanoyl chloride (8.70 g, 40 mmol) was converted to **4e** (9.32 g, 92%). ^{1}H NMR ($CDCl_3$): δ 1.03 (t, J = 7.4 Hz, 3H), 1.61−1.84 (m, 2H), 2.41−2.54 (m, 2H), 2.63 (s, 6H), 4.36 (m, 2H), 5.17−5.35 (m, 2H), 5.82−6.04 (m, 1H). IR (film) 1666 (C═O) cm^{-1}. MS (EI, *m*/*z*) 252 (3, M^{35}), 99 (100). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: C, 47.44; H, 7.17; N, 11.07. Found: C, 47.32; H, 7.09; N, 11.15. Oil.

***N*-Allyl-*N*′,*N*′-dimethyl-2,2-dichloro-3-methyl-butanohydrazide (4f).** According to the above protocol, 2,2-dichloro-3-methyl-butanoyl chloride (8.71 g, 40 mmol) was converted to **4f** (8.71 g, 86%). ^{1}H NMR ($CDCl_3$): δ 1.20 (d, J = 6.6 Hz, 6H), 2.61 (s, 6H), 3.12 (ept, J = 6.6 Hz, 1H), 4.02 (m, 2H), 5.14−5.38 (m, 2H), 5.82−6.10 (m, 1H). IR (film) 1663 (C═O) cm^{-1}. MS (EI, *m*/*z*) 252 (3, M^{35}), 99 (100). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: C, 47.44; H, 7.17; N, 11.07. Found: C, 47.48; H, 7.08; N, 11.12. Oil.

General Procedure for Radical Cyclization. CuCl (0.02 g, 0.2 mmol) and **4a** (0.45 g, 2 mmol) were weighed in a Schlenk tube; then ethyl acetate (4 mL) and TMEDA (0.046 g, 0.4 mmol) were added, under argon. The mixture was stirred at 60 °C, and after 20 h filtered. The filtrate was concentrated and chromatographed, eluting with a petroleum ether (bp 40−60 °C)/diethyl ether/methanol gradient, to give **5a** (0.437 g, 97%), as a mixture of inseparable diastereomers (77:23).

***N*-(Dimethylamino)-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (5a).** ^{1}H NMR ($CDCl_3$): cis diastereomer, δ 1.80 (s, 3H), 2.55 (m, 1H), 2.71 (s, 6H), 3.15−3.93 (m, 4H); trans diastereomer, δ 1.68 (s, 3H), 2.73 (s, 6H), 2.95 (m, 1H), 3.30−3.82 (m, 4H). ^{13}C NMR ($CDCl_3$): cis diastereomer, δ 24.2 (q), 41.6 (t), 41.8 (t), 42.6 (q), 45.9 (d), 68.4 (s), 168.4 (s); trans diastereomer, δ 20.7 (q), 42.0 (t), 42.2 (t), 42.5 (s), 46.4 (d), 67.0 (s), 168.3 (s). IR (film) 1716 (C═O) cm^{-1}. MS (EI, *m*/*z*): 224 (16, M^{35}), 182 (100). Anal. Calcd for $C_8H_{14}Cl_2N_2O$: C, 42.68; H, 6.27; N, 12.44. Found: C, 42.54; H, 6.39; N 12.21. Oil.

***N*-(Dimethylamino)-4-chloromethyl-3-methyl-pyrrolidin-2-one (6).** On performing the rearrangement of **4a** at 80 °C, **6** (0.038 g, 10%) was also isolated. ^{1}H NMR ($CDCl_3$): trans diastereomer, δ 1.18 (d, J = 7.1, 3H), 2.13−2.29 (m, 2H), 2.60 (s, 6H), 3.16 (m, 1H), 3.44−3.55 (m, 3H); cis diastereomer, δ 1.09 (d, J = 7.5 Hz, 3H), 2.51−2.71 (m, 2H), 2.59 (s, 6H), 3.26 (m, 1H), 3.36−3.70 (m, 3H). ^{13}C NMR ($CDCl_3$): cis diastereomer, δ 14.6 (q), 41.5 (t), 37.9 (d), 39.1 (d), 42.9 (q), 45.6 (t), 173.2 (s); trans diastereomer, δ 9.7 (q), 36.6 (d), 41.4 (t), 42.9 (s), 43.4 (t), 41.0 (d), 173.3 (s). IR (film) 1712 (C═O) cm^{-1}. MS (EI, *m*/*z*) 190 (15, M^{35}), 148 (100). Anal. Calcd for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; N, 14.69. Found: C, 50.24; H, 8.01; N, 14.56. Oil.

***N*-(Dimethylamino)-3-chloro-4-chloromethyl-pyrrolidin-2-one (5b).** According to the general procedure, but heating at 80 °C, and using CuCl (0.04 g, 0.4 mmol) and TMEDA (0.093 g, 0.8 mmol), dichlorohydrazide **4b** (0.422 g, 2 mmol) was converted to **5b** (0.072 g, 17%). ^{1}H NMR ($CDCl_3$): cis diastereomer, δ 2.67 (s, 6H), 2.81 (m, 1H), 2.71 (s, 6H), 3.24−3.81 (m, 4H), 4.39 (d, J = 6.7 Hz, 1H); trans diastereomer, δ 2.69 (s, 6H), 2.83 (m, 1H), 2.95 (m, 1H), 3.30−3.81 (m, 4H), 4.27 (d, J = 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): cis diastereomer, δ 39.7 (d), 42.3 (t), 42.5 (t), 43.4 (q), 57.4 (d), 167.8 (s); trans diastereomer, δ 42.1 (t), 43.4 (q), 43.8 (t), 43.9 (d), 56.0 (d), 166.7 (s). IR (film) 1721 (C═O) cm^{-1}. MS (EI, *m*/*z*): 210 (11, M^{35}), 168 (100). Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.83; H, 5.73; N, 13.27. Found: C, 39.69; H, 5.53; N, 13.09. Oil.

***N*-(Dimethylamino)-3,3-dichloro-4-chloromethyl-pyrrolidin-2-one (5c).** According to the general procedure, trichlorohydrazide **4c** (0.491 g, 2 mmol) was converted to **5c** (0.462 g, 94%). ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 6H), 3.00−3.18 (m, 1H), 3.25−4.08 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 40.8 (t), 43.3 (t), 42.7 (q), 50.3 (d), 83.1 (s), 163.5 (s). IR (film) 1737 (C═O) cm^{-1}. MS (EI, *m*/*z*): 244 (12, M^{35}), 202 (68). Anal. Calcd for $C_7H_{11}Cl_3N_2O$: C, 34.24; H, 4.52; N,11.41. Found: C, 34.40; H, 4.48; N, 11.66. Light brownish solid; mp 43−44 °C.

***N*-(Dimethylamino)-3-chloro-4-chloromethyl-3-ethyl-pyrrolidin-2-one (5d).** According to the general procedure, dichlorohydrazide **4d** (0,478 g, 2 mmol) was converted to **5d** (0.469 g, 98%), as a mixture of inseparable diastereomers (84:16). ^{1}H NMR ($CDCl_3$): cis diastereomer, δ 1.06 (t, J = 7.5 Hz, 3H), 2.18 (m, 2H), 2.73 (s, 6H), 2.63−2.81 (m, 1H), 3.17−3.91 (m, 4H); trans diastereomer, δ 1.18 (t, J = 7.3 Hz, 3H), 1.64−1.88 (m, 2H), 2.74 (s, 6H), 2.83−2.97 (m, 1H), 3.58−3.81 (m, 4H). ^{13}C NMR ($CDCl_3$): cis diastereomer, δ 9.0 (q), 29.9 (t), 41.3 (d), 41.7 (t), 42.1 (t), 42.5 (q), 72.2 (s), 167.7 (s); trans diastereomer, δ 8.1 (q), 26.0 (t), 41.7 (t), 42.4 (t), 42.5 (q), 45.7 (d), 71.7 (s), 167.6 (s). IR (film) 1715 (C═O) cm^{-1}. MS (EI, *m*/*z*) 238 (22, M^{35}), 196 (100). Anal. Calcd for $C_9H_{16}Cl_2N_2O$: C, 45.20; H, 6.74; N, 11.71. Found: C, 45.06; H, 6.89; N, 11.84. Oil.

***N*-(Dimethylamino)-3-chloro-4-chloromethyl-3-propyl-pyrrolidin-2-one (5e).** According to the general procedure, dichlorohydrazide **4e** (0.506 g, 2 mmol) was converted to **5e** (0.486 g, 96%), as a mixture of inseparable diastereomers (85:15). ^{1}H NMR ($CDCl_3$): cis diastereomer δ 0.98 (t, J = 7.2 Hz, 3H), 1.15−2.20 (m, 4H), 2.70 (s, 6H), 2.58−2.80 (m, 1H), 3.10−3.90 (m, 4H). ^{1}H NMR ($CDCl_3$); trans diastereomer δ 0.98 (t, J = 7.0 Hz, 3H), 1.15−2.20 (m, 4H), 2.70 (s, 6H), 2.80−2.95 (m, 1H), 3.30−3.75 (m, 4H). ^{13}C NMR ($CDCl_3$): *cis* diastereomer δ 13.7 (q), 18.1 (t), 38.9 (t), 42.1 (d), 42.3 (t), 42.4 (t), 42.6 (q), 71.7 (s), 168.0 (s); trans diastereomer δ 13.7 (q), 17.1 (t), 35.1 (t), 38.7 (t), 41.9 (t), 42.6 (q), 46.1 (d), 71.1 (s), 167.8 (s). IR (film) 1712 (C═O) cm^{-1}. MS (EI, *m*/*z*) 252 (19, M^{35}), 210 (100). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: C, 47.44; H, 7.17; N, 11.07. Found: C, 47.61; H, 6.98; N, 11.24. Pale yellow solid; mp 33−38 °C.

***N*-(Dimethylamino)-3-chloro-4-chloromethyl-3-isopropyl-pyrrolidin-2-one (5f).** According to the general procedure, dichlorohydrazide **4f** (0.506 g, 2 mmol) was converted to **5f** (0.486

(36) Bellesia, F.; Boni, M.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.* **1994**, *35*, 2961.

(37) Bellesia, F.; De Buyck, L.; Ghelfi, F. *Synlett* **2000**, 146.

(38) It is imperative that the hydrazide is completely deprotonated otherwise the cyclization yields are considerably reduced.

g, 96%), as a mixture of inseparable diastereomers (96:4). ^{1}H NMR ($CDCl_3$): cis diastereomer, δ 1.06 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 2.53 (m, 1H), 2.74 (s, 6H), 2.65−2.88 (m, 1H), 3.18−3.93 (m, 4H); trans diastereomer, δ 1.13 (d, J = 6.4 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 2.18 (m, 1H), 2.74 (s, 6H), 2.85−2.97 (m, 1H), 3.36−3.85 (m, 4H). ^{13}C NMR ($CDCl_3$): cis diastereomer, δ 16.8 (q), 17.7 (q), 34.7 (d), 38.5 (d), 42.3 (q), 43.0 (t), 43.8 (t), 75.4 (s), 167.7 (s); trans diastereomer, δ 18.1 (q), 18.2 (q), 31.6 (d), 41.6 (t), 42.0 (t), 42.3 (q), 46.9 (d), 74.9 (s), 167.3 (s). IR (film) 1716 (C═O) cm^{-1}. MS (EI, *m*/*z*) 252 (13, M^{35}), 210 (79). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: C, 47.44; H, 7.17; N, 11.07. Found: C, 47.6; H, 7.15; N, 11.04. Oil.

General Procedure for Hydrogenolysis of 5 with Raney-Ni. Wet Raney-Ni (3.96 g) and **5e** (0.126 g, 0.5 mmol) were weighed in a Schlenk tube; then ethanol (2 mL) was added. The mixture was stirred at 110 °C, and after 21 h filtered. The filtrate was concentrated and chromatographed, eluting with a diethyl ether/methanol gradient, to give **7b** (0.067 g, 95%), as a mixture of inseparable diastereomers (66:34).

4-Methyl-3-propyl-pyrrolidin-2-one (7e). ^{1}H NMR ($CDCl_3$): δ 0.80−1.18 (m, 6H), 1.20−1.78 (m, 4H), 1.80−3.50 (m, 4H), 7.35 (bs, 1H). ^{13}C NMR ($CDCl_3$): minor diastereomer δ 14.4 (q), 19.2 (q), 21.2 (t), 27.3 (t), 32.6 (d), 45.3 (d), 48.4 (t), 181.3 (s); maior diastereomer δ 14.5 (q), 19.2 (q), 20.4 (t), 32.2 (t), 35.7 (d), 48.3 (t), 48.9 (d), 181.3 (s). IR (film) 1687 (C═O) cm^{-1}. MS (EI, *m*/*z*) 141 (2, M), 99 (67), 84 (100). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.24; H, 10.85; N, 9.79. Oil.

4-Methyl-pyrrolidin-2-one (7c). According to the general procedure, **5c** (0.123 g, 0.5 mmol) was converted to **7c** (0.048 g, 96%). ^{1}H NMR ($CDCl_3$): δ 1.16 (d, J = 6.6, 1H), 1.96 (dd, J = 6.7, 16.0 Hz, 1H), 2.50 (dd, J = 8.4, 16.0, 1H), 2.48−2.65 (m, 1H), 2.98 (dd, J = 5.9, 9.5, 1H), 3.52 (dd, J = 7.6, 9.4, 1H), 6.32 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 19.8 (q), 29.6 (d), 39.0 (t), 50.0 (t), 179.3 (s). IR (film) 1690 (C═O) cm^{-1}. MS (EI, *m*/*z*) 99 (100, M). Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.42; H, 9.04; N, 13.91. White solid; mp 48−51 °C.

4-Methyl-3-isopropyl-pyrrolidin-2-one (7f). According to the general procedure, but using 7.92 g of wet Raney-Ni and 4 mL of ethanol, **5f** (0.126 g, 0.5 mmol) was converted to **7f** (0.069 g, 98%), as a mixture of inseparable diastereomers (59:41). ^{1}H NMR ($CDCl_3$): δ 9.94−1.21 (m, 9H), 1.88−2.76 (m, 3H), 2.82−3.52 (m, 2H), 6.08 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 13.7 (q), 18.3 (q), 19.8 (q), 20.1 (q), 20.8 (q), 22.1 (q), 25.7 (d), 28.0 (d), 30.3 (d), 33.2 (d), 48.2 (t), 48.3 (t), 50.8 (d), 54.9 (d), 181.3 (s). IR (film) 1685 (C═O) cm^{-1}. MS (EI, *m*/*z*) 141 (3, M), 99 (70), 84 (100). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.20; H, 10.52; N, 10.11. White solid; mp 46−55 °C.

Acknowledgment. We thank the Ministero della Università e della Ricerca scientifica e Tecnologica (MURST) for financial assistance, Dr. Massimo Ferrari for the preparation of hydrazines, Prof. Emanuela Libertini for ^{1}H NMR spectra, and Jonathan Large/David Whittaker for ^{13}C NMR spectra.

JO0004153