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An Improved Reduction Procedure in the Synthesis of Substituted Pyrrolidines via An Aminomercuration/ Reduction Sequence of Primary Alkenylamines

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AN IMPROVED REDUCTION PROCEDURE IN THE SYNTHESIS OF SUBSTITUTED PYRROLIDINES VIA AN AMINOMERCURATION/REDUCTION SEQUENCE OF PRIMARY ALKENYLAMINES.

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Abstract: Aminomercuration/reduction sequence of δ-alkenylamines is a typical route to substituted pyrrolidines. Backward reaction to the starting material is a major drawback which occurs during sodium borohydride reduction of the intermediate organomercurial. We describe here a new reduction procedure which prevents almost completely this backward reaction and leads to significant increases in the yields of pyrrolidines.

α-Phosphorylated pyrrolidines may constitute interesting precursors for a variety of potentially useful compounds such as stable β-phosphorylated pyrrolidinoxyl radicals[1] used in spin-labelling or MRI applications,[2] α-phosphorylated pyrrolin-1-oxides[3] used as spin-traps, or phosphorous analogs of proline.[4]

Our interest in the field of stable β-phosphorylated pyrrolidinoxyl radicals and α-phosphorylated pyrrolin-1-oxides led us to develop the synthesis of α-phosphorylated pyrrolidines via cyclisation of primary α-aminoalkenyl phosphonates.[1,5-6]

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The cyclisations of unsaturated primary amines previously reported in the literature involved either an electrophilic activation of the double bond or an intramolecular addition of an aminyl radical.[7-10] In the former approach, many electrophilic reagents were used, e.g. platinium,[11] palladium,[12] mercury salts,[13] organolanthanides[14] or, in a few cases, haloniums.

However, to our knowledge, a complete cyclisation without recovery of the starting material has never been reported.

We recently described the synthesis of pyrrolidinyl α-aminophosphonates via an aminomercuration/sodium borohydride reduction sequence of α-aminoalkenyl phosphonates.[5] Although the method gave rather satisfying results (conversion ratios generally superior to 60%), in some cases, significant amounts of starting material (20-100%) were recovered. However, ^{1}H and ^{31}P- NMR studies showed that in our experimental conditions[5] all the starting material was rapidly converted into a cyclic mercuric intermediate. The recovery of different amounts of the starting α-aminoalkenylphosphonates after the borohydride reduction step was then attributed to the formation of intermediate alkyl radicals which undergo a β-scission leading to an aminyl radical (Scheme 1, step ii). The formation of carbon-centered radicals **e** (Scheme 1) during the borohydride reduction was supported by the results of spin-trapping experiments using the pentamethoxynitrosobenzene as spin trap. The expected nitroxides **h** were observed even in the case of the organomercurial derived from compound **3** for which a complete recovery of the starting material was observed after reduction.

We also noticed that the amount of recovered starting α-aminoalkenylphosphonate increases with the stability and/or the steric hindrance of the intermediate alkyl radical **e** (Table 1).[5]

In the case of aminyl radical cyclisation (generated from *N*-chloro-*N*-alkylalk-4-enylamines), Tokuda et al.[9] reported a decrease of the cyclisation ratios when the stability of the intermediate cyclic radical decreased.

In order to prevent the unwanted backward reaction, we studied a modified sodium borohydride reduction procedure and also an alternative method using

Scheme 1

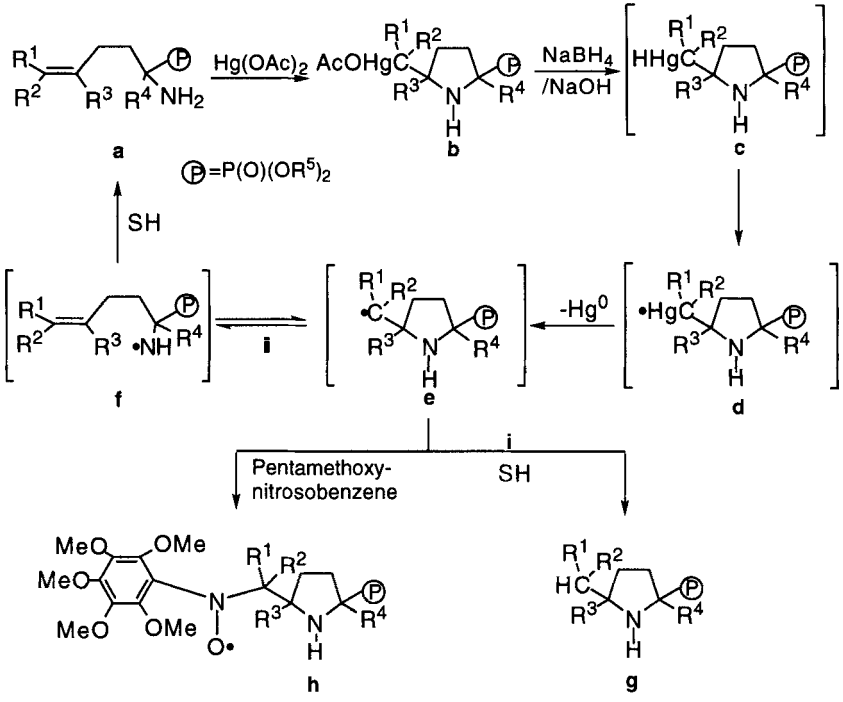
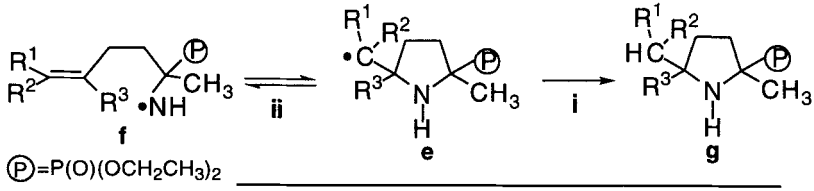
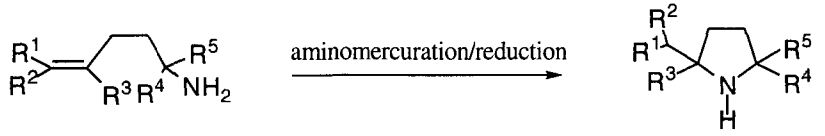


Table 1



R^1	R^2	R^3	Conversion ratios (%)
H	H	H	86
H	CH_3	H	55
CH_3	CH_3	H	37
H	H	CH_3	72
H	CH_3	CH_3	0

Scheme 2



1-8 **11-18**

Compounds	Products	R^1	R^2	R^3	R^4	R^5
1	11	H	$n\text{-}C_5H_{11}$	H	H	$P(O)(OC_2H_5)_2$
2	12	H	H	H	CH_3	$P(O)(OC_2H_5)_2$
3	13	H	CH_3	CH_3	CH_3	$P(O)(OC_2H_5)_2$
4	14	CH_3	CH_3	H	CH_3	$P(O)(OC_2H_5)_2$
5	15	H	H	CH_3	CH_3	$P(O)(OC_2H_5)_2$
6	16	H	H	H	CH_3	$P(O)(OCH(CH_3)_2)_2$
7	17	H	H	H	H	CH_3
8	18	H	H	CH_3	H	H

tributyltin hydride. The results obtained with compounds **1-8** (Scheme 2) are shown in table 2 and are compared to those given by the procedure we had previously used (procedure A).[5]

Tributyltin hydride is widely used as hydrogen donor in radical-chain reactions[7,8,15-16] and also in the reduction of organomercuric compounds.[8,16] Bowman[8] showed that during the reduction of compound **9**, using a high concentration of tributyltin hydride, the intermediate radicals **10** are quenched before any ring-opening could occur (Scheme 3).

With the aminoalkenylphosphonates which were investigated, the use of an excess of tributyltin hydride to reduce the intermediate organomercurial (Table 2, procedure B) led to various results but using this reduction procedure the cyclic compound **13** was never obtained. Moreover, the use of this procedure afforded considerable amounts of side-products which were not identified.

Table 2

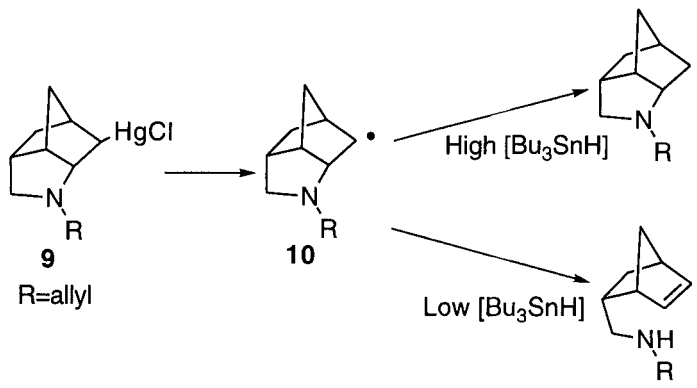
Compounds	Products	Conversion(%)[j]			Diastereoisomeric[k] ratios a/b (%)[j]		
		A	B	C	A	B	C
1	**11**	73	64	92	86/14	84/16	90/10
2	**12**	81	75	78	83/17	90/10	81/19
3	**13**	0	0	90	-	-	87/13
4	**14**	37	75	80	72/28	83/17	88/12
5	**15**	75	80	100	-	-	-
6	**16**	63	100	100	75/25	83/17	88/12
7	**17**	80	85	100	63/17		68/32
8	**18**	50	37	95	-	-	-

i: Experimental procedures: A: $Hg(OAc)_2$ 1eq, $NaBH_4$ 1eq, CH_2Cl_2; B: $Hg(OAc)_2$ 1eq, Bu_3SnH 1,8eq, THF, under N_2; C: $Hg(OAc)_2$ 1eq, $NaBH_4$ 2eq (reverse addition), CH_2Cl_2.

j: Based on ^1H and ^{31}P NMR of the crude mixture.

k: In the case of α-phosphorylated pyrrolidines **11-16**, the major diasteromers have the dialkoxyphosphoryl group and the alkyl group CHR^1R^2 in a *trans* configuration;[5] the configuration of the major diasteromer of compound **17** is the *trans* configuration.[17]

Scheme 3



However, the modified sodium borohydride procedure C led to significantly improved conversion ratios with a particulary significant change for compound **13**, which was obtained in 90% conversion ratio. In this procedure one mole of the intermediate organomercurial was added to two moles of sodium borohydride in order to favour hydrogen transfer to the carbon-centered radical **e** (Scheme1, step i) with respect to ring-opening (Scheme1, step ii). Procedure C is also convenient for the cyclisation of primary alkenylamines as shown by the high conversion ratios obtained with 1-methylpent-4-enylamine **7** and 1,4-dimethylpent-4-enylamine **8** (Table 2). In the case of quantitative conversion ratios (**5**-**7**) procedure C afforded pyrrolidinyl compounds in 80-90% yields while when residual starting material was present, 50 to 60% yields of chromatographied cyclic products were obtained. We also noticed that the diastereomeric ratios obtained for the cyclisation of compounds **1**-**8** were not significantly affected by changing the reduction procedures.

To conclude, we have found an improved reduction procedure of pyrrolidinyl organomercurials which constitutes a simple and very efficient way to improve the yields of substituted pyrrolidines obtained via an aminomercuration/reduction sequence of primary alkenylamines.

Experimental

^{1}H and ^{31}P NMR spectra were performed on a Bruker AC 100 (^{1}H, 100MHz; ^{31}P, 40.53MHz) spectrometer and ^{13}C NMR spectra on a Bruker AM 400 (^{13}C, 100.61MHz) spectrometer. Preparative TLC were performed on Merk Kieselgel 60 F254 plates. Elemental analyses were determined in the University of Aix-Marseille III. Mass spectra were realized in the University of Paris-Sud (Orsay) by G.C.M.S. with Chemical Ionization (NH_3). The synthesis of products **1**-**6**, **11**-**12** and **14**-**16** following procedure A has been previously described.[5] Alkenylamines were prepared and characterized according to the following references: **7**,[11] **8**.[18] The ^{1}H and ^{13}C NMR characteristics of pyrrolidines **17** and **18** were in good agreement with data given in the literature: **17**,[11,17] **18**.[19] The progress of the cyclisation of α-aminoalkenylphosphonates or alkenylamines following procedures A, B or C was

monitored by ^{1}H and/ or ^{31}P NMR. In the case of amines, reactions were driven in deuterated solvents.

General Procedures:

A: At room temperature, a suspension of mercuric acetate (4.2 mmol) in methylene chloride (20mL) was added to the unsaturated amine (4.2 mmol). After the end of addition, the reaction mixture was stirred for 10 min; sodium borohydride (4.2mmol) in 10% aqueous sodium hydroxide solution (2mL) was then added. After 1 hour, the mixture was saturated with sodium chloride, extracted with methylene chloride and dried over sodium sulfate. Filtration and removal of the solvent afforded the crude pyrrolidinyl compound.

B: The reaction was performed under inert atmosphere. At room temperature, a suspension of mercuric acetate (4.2 mmol) in THF (20 mL) was slowly added to a solution of the unsaturated amine (4.2 mmol). After 10 min, a solution of tributyltin hydride (7.6 mmol) in deoxygenated dry THF (2 mL) was added to the reaction mixture. After 1 h, the mixture was acidified with diluted (5%) hydrochloric acid and washed several times with ether. The aqueous layer was poured over sodium hydroxide, extracted with ether; the organic layer was dried over magnesium sulfate. Filtration and removal of the solvent gave the crude pyrrolidinyl compound.

C: The reaction was carried out as described for A, but the solution of the intermediate organomercurial was added to the sodium borohydride (8.4 mmol) in 20% aqueous sodium hydroxyde solution (2 mL).

Diethyl (2,5,5-trimethylpyrrolidin-2-yl) phosphonate (13a,b)

(Procedure C):

The crude product was purified by preparative TLC over silica gel eluting with 6:4 v/v pentane/acetone to give **13a,b** (54%).

^{1}H NMR (100MHz, $CDCl_3$) δ 0.77 (t, J = 7.1Hz, 3H, $CH_3CH_2C^*$), 0.97 (s, 3H, $CH_3C^*CH_2$), 1.19 (t, J =7.1Hz, 6H, 2 CH_3CH_2O), 1.22 (d, J=16.0Hz, 3H, CH_3C^*P), 1.4-2.5 (m, 5H, N*H*, 2 CH_2), 4.03 (m, 4H, 2 OCH_2). ^{31}P NMR (40.53MHz, $CDCl_3$) δ **13a**: 29.50, **13b**: 29.02. ^{13}C NMR (100.61MHz, C_6D_6)

13a: δ 9.39 (s, *C* H_3CH_2) 16.72 (d, *J* = 4.6Hz, 2 *C* H_3CH_2O), 25.45 (d, *J* = 7.7Hz, *C* H_3CP), 26.79 (s,*C* H_3CCH_2), 33.94 (C**C* H_2CH_3), 36.11 (*C* H_2), 36.24 (d, J= 5.9Hz, *C* H_2), 58,6 (d, *J* = 169.0Hz, *C* *P), 61.99 (CH_3C*CH_2), 61.65 (d, *J* = 7.4Hz, O*C* H_2), 62.85 (d, *J* = 7.4Hz, O*C* H_2). **13b**: 9.15 (s, *C* H_3CH_2) 16.72 (d, *J* = 4.6Hz, 2 *C* H_3CH_2O), 25.80 (d, *J* = 7.5Hz, *C* H_3CP), 27.85 (s,*C* H_3CCH_2), 34.22 (C**C* H_2CH_3), 35.16 (*C* H_2), 37.04 (d, J= 4.94Hz, *C* H_2), 52.20 (CH_3C*CH_2), 58.60 (d, *J* = 169.0Hz, *C* *P), 60.19 (d, J=170.5 Hz, *C**P), 61.99 (CH_3C*CH_2), 61.65 (d, *J* = 7.4Hz, O*C* H_2), 62.85 (d, *J* = 7.4Hz, O*C* H_2).

IR (neat): 3350, 1670, 1230, 1170, 1060 and 1040 cm^{-1}. MS: m/e 264 ($M\text{-}H^+$, 4.88), 139 (21.79), 126 (100).

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