One-pot Synthesis of Pyrrolizidine and Amino Acid Derivatives from Diallyl Amines

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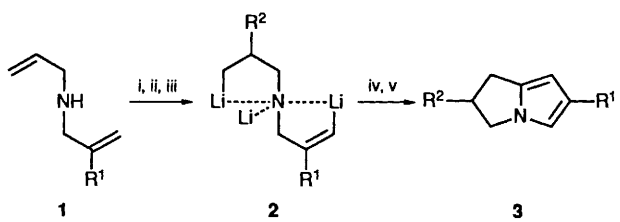
The successive reaction of diallyl amines **1** with several alkyllithium reagents and diethyl carbonate leads, after hydrolysis, to the corresponding pyrrolizidine derivatives **3** in a one-pot process; the reaction of intermediates **2** with carbon dioxide affords (*Z*)-amino acids **8**, (*E*)-amino esters **9** or *N*-substituted butyrolactams **10**.

Five-membered ring nitrogen heterocycles are present in many natural products, *e.g.* the pyrrolizidine alkaloids[1] or pyrrolic skeletons[2] such as pyrrole pigments.[3] The allylamines can be lithiated at the vinylic position,[4] and their further reaction with diethyl carbonate leads to α,β-butyrolactams.[5] We have recently reported[6] the regio- and stereo-selective lithiation of diallyl amines of the type **1**, which yields the corresponding lithiated intermediates **2**, and we herein describe the direct preparation of pyrrolizidine and amino acid derivatives by *in situ* reaction of intermediates **2** with diethyl carbonate or carbon dioxide.

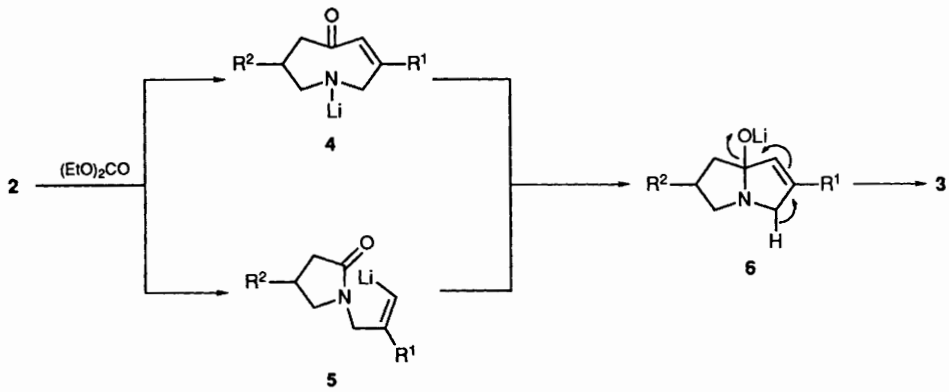
The successive treatment of diallyl amines **1** with n-butyllithium at −50 to −30 °C, t-butyllithium at temperatures ranging between −30 and 20 °C, and n-butylithium in the



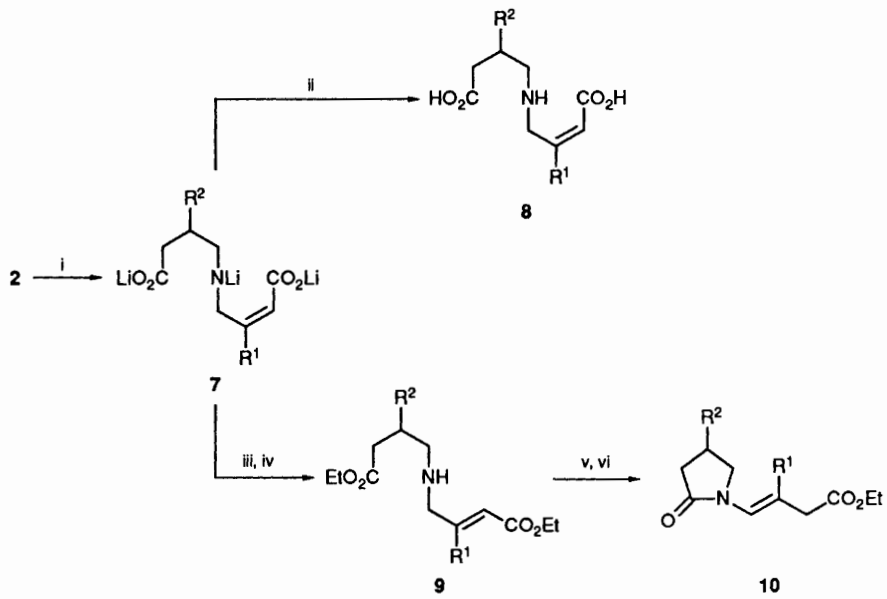
1 **2** **3**

a; R^1 = H
b; R^1 = Me

Scheme 1 *Reagents and conditions*: i, Bu^nLi, −50 to −30 °C; ii, Bu^tLi, −30 to 20 °C; iii, Bu^nLi/TMEDA, 20 °C or Bu^tLi, −20 to 20 °C; iv, $(EtO)_2CO$, −50 to 20 °C; v, H_2O



Scheme 2



Scheme 3 *Reagents and conditions*: i, CO_2, −78 to 20 °C; ii, H_2O, pH 6; iii, EtOH/HCl, reflux, 24 h; iv, Na_2CO_3/H_2O; v, MeLi, −20 to 20 °C; vi, H_2O

presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) or t-butyllithium at −20 to 20 °C led to intermediates **2**;[6] the *in situ* reaction of these trianionic species with diethyl carbonate at −50 to 20 °C afforded after hydrolysis the corresponding pyrrolizidine derivatives **3** (Scheme 1 and Table 1).

The reaction of the trianion **2** with diethyl carbonate presumably involves the formation of either an eight-membered ring **4** or a butyrolactam **5**, which spontaneously cyclize to yield the corresponding hemiaminal **6**; this intermediate undergoes aromatization under the reaction conditions to give the pyrrolizidine derivatives **3** (Scheme 2).

However, the reaction of these trianionic intermediates **2** with carbon dioxide did not occur with further cyclization to compounds **3**. Instead, the corresponding amino acid salts **7** were formed, which after hydrolysis gave the (*Z*)-amino acid **8**.† The subsequent esterification of **7** with anhydrous ethanol and hydrogen chloride takes place with isomerization of the carbon–carbon double bond giving the corresponding (*E*)-amino ester **9**‡ as the only reaction product. The treatment of compounds **9** with methyllithium afforded, also with isomerization, the *N*-substituted butyrolactams **10** (Scheme 3 and Table 1).

A typical reaction was performed as follows. A solution of n-butyllithium (5 mmol) in hexane was added to a solution of the amine **1** (5 mmol) in diethyl ether (25 ml) at −50 °C under argon and stirred for 20 min at temperatures ranging between −50 and −30 °C. A solution of t-butyllithium (5 mmol) in pentane was added to the resulting mixture at −30 °C with further stirring for 2 h while the temperature was allowed to rise to 20 °C. The mixture was cooled to −20 °C, a solution of t-butyllithium (5 mmol)§ in pentane was added and stirring

† ^{1}H NMR spectroscopy showed that the products **8** were exclusively the (*Z*)-stereoisomers (J = 11.5 Hz).

‡ ^{1}H NMR spectroscopy showed that the products **9** were exclusively the (*E*)-stereoisomers (J = 16 Hz).

§ When n-butyllithium was used, TMEDA (5 mmol) was added at 20 °C.

was continued for 2 h between −20 and 20 °C. After cooling to −50 °C, diethyl carbonate (5 mmol) was added, and stirring was continued while the temperature was allowed to rise to 20 °C. The resulting mixture was then hydrolysed with water and extracted with diethyl ether. The organic layer was dried (Na_2SO_4), the solvents were removed (15 mmHg), and the residue was purified by distillation (see Table 1).

Table 1 Preparation of pyrrolizidine derivatives **3**, (*Z*)-amino acids **8**, (*E*)-amino esters **9**, and *N*-substituted butyrolactams **10** from diallyl amines **1**

Starting amine	Electrophile	Product[a]	% Yield[b]	B.p./°C[c]
1a	$(EtO)_2CO$	**3a** (R^2 = Bu^n)	85	52–54
1a		**3a** (R^2 = Bu^t)	79	50–52
1b		**3b** (R^2 = Bu^n)	76	67–69
1b		**3b** (R^2 = Bu^t)	74	64–66
1a	CO_2	**8a** (R^2 = Bu^n)	42	Oil
1a		**9a** (R^2 = Bu^n)	82	123–125
1a		**9a** (R^2 = Bu^t)	78	117–119
1a		**10a** (R^2 = Bu^n)	68	95–96
1a		**10a** (R^2 = Bu^t)	63	92–94

[a] All products were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield based on the starting amine **1**. [c] 0.1 mmHg.

Received, 26th June 1990; Com. 0/02887H

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