COMMUNICATION

N-Alkylation and [2,3]-sigmatropic rearrangement of *N*-allyl α-amino esters

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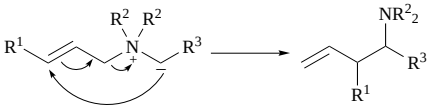
***N*-Alkylation of *N*-allyl α-amino esters and [2,3]-Stevens rearrangement occur in one pot on warming in the solvent DMF, with the bases K_2CO_3 and DBU; this *in situ* formation of the quaternary ammonium salts and rearrangement of the subsequent ylides gives *N*,*N*-dialkylated allyl glycine derivatives.**

As part of a project investigating the [2,3]-aza-Wittig rearrangement,[1,2] we have discovered a simple and convenient method for effecting the [2,3]-Stevens rearrangement. The [2,3]-Stevens rearrangement of ammonium ylides (Scheme 1) is a

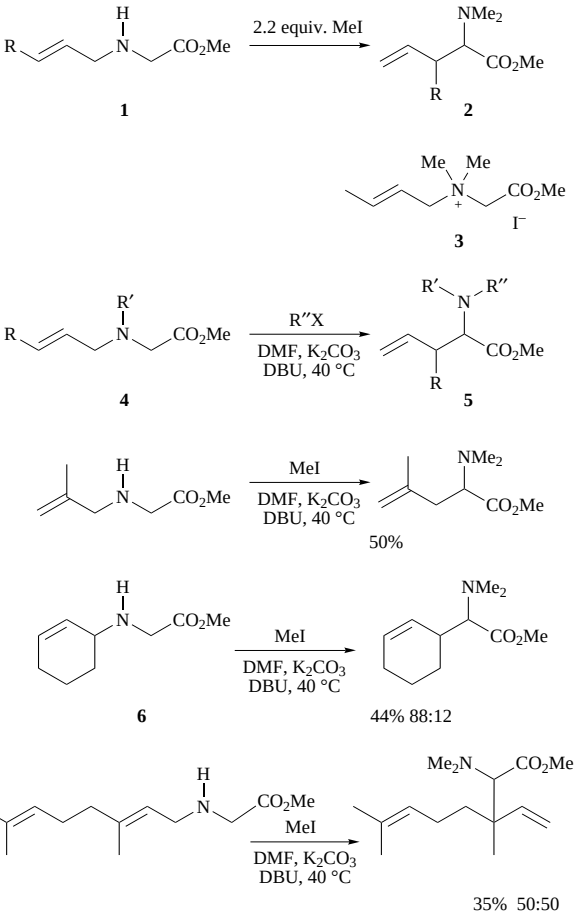


Scheme 1

useful carbon–carbon bond forming reaction in synthesis.[3] The rearrangement allows the formation of homoallylic amines including ring-expanded or ring-contracted amines. The ammonium ylides are commonly prepared by *N*-alkylation, followed by isolation of the salt and its treatment with a strong base (or fluoride ion desilylation).[4] An alternative approach to ylide formation using amine insertion into a carbene is currently proving popular.[5] Despite the simplicity of the former method, it suffers from the difficulties associated with the isolation of the quaternary ammonium salt and the use of a strong base (often KOBu^t or NaOH). We report in this communication that these drawbacks can be avoided using a one pot alkylation–rearrangement procedure.

In an attempt to mono-methylate the secondary amine **1**, R = Me with methyl iodide in MeCN, K_2CO_3, the [2,3]-Stevens rearrangement product **2**, R = Me and the ammonium salt **3** were isolated (Scheme 2). The ammonium salt **3** could be converted to the amine **2**, R = Me under standard conditions for the [2,3]-Stevens rearrangement (KOBu^t, THF, 40%). However, we were intrigued by the possibility that both the *N*-alkylation and the rearrangement could be carried out in one pot. On changing the solvent for *N*-alkylation from MeCN to DMF, the yield of the rearranged product **2**, R = Me increased significantly (Table 1, entry 2). Further improvement was obtained on addition of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and warming the mixture to 40 °C for 24 h. These conditions avoid isolation of the quaternary ammonium salt and allow the use of the simple *N*-allylated glycine methyl esters for the preparation of *C*-allyl glycine derivatives (Table 1, entries 4–6).

N-Alkylation and [2,3]-sigmatropic rearrangement can be carried out on secondary amines, such as **1**, and tertiary amines, such as **4**. Yields of the [2,3]-Stevens products are normally in the range 50–65% (Table 2). A mixture (inseparable by column chromatography) of diastereomers is formed using amines **4**, R ≠ H. Although it was possible to prepare the *N*-benzyl-*N*-methyl derivatives **5** (*e.g.* R′ = Me, R″ = Bn), attempted dibenzylation and rearrangement of amine **1**, R = Me (with excess



Scheme 2

Table 1 [2,3]-Stevens rearrangement of secondary amines **1**

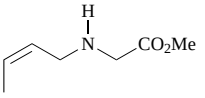
Entry	R	Conditions	Yield **2** (%)	Ratio
1	Me	MeCN, K_2CO_3, room temp.	10	60:40
2	Me	DMF, K_2CO_3, room temp.	45	60:40
3	Me	DMF, K_2CO_3, 40 °C	48	60:40
4	Me	DMF, K_2CO_3, DBU, 40 °C	58	60:40
5	H	DMF, K_2CO_3, DBU, 40 °C	50	—
6	Ph	DMF, K_2CO_3, DBU, 40 °C	62	50:50

$PhCH_2Br$) led only to the mono-benzylated amine **4**, R = Me, R′ = Bn.

The combined *N*-alkylation-[2,3]-Stevens rearrangement can be carried out successfully on a range of allylic amines, as illustrated in Scheme 2. Diastereoselectivities were improved (to 88:12) using the cyclohexenylamine **6**. We were disappointed, however, that attempts to rearrange the amine **7**, containing a (*Z*)-alkene, were unsuccessful. Treatment of the amine **8**, derived from alanine or phenylglycine methyl ester, with methyl

Table 2 [2,3]-Stevens rearrangement of tertiary amines **4**

Entry	R	R′	R″X	Yield **5**(%)	Ratio
1	H	Me	MeI	48	—
2	Me	Me	MeI	53	60:40
3	H	Me	$PhCH_2Br$	52	—
4	Me	Me	$PhCH_2Br$	65	60:40
5	H	CH_2Ph	MeI	51	—
6	Me	CH_2Ph	MeI	63	60:40



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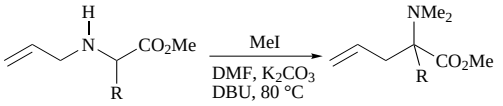
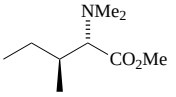


8 **9**

R = Me 42%
R = Ph 47%



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iodide, under the conditions described above, gave the quaternary ammonium salt, but none of the amino ester **9**. Increasing the temperature of the reaction to 80 °C, however, resulted in the formation of the desired α,α-disubstituted amino ester **9** (42–47%).

Hydrogenation of allyl glycine **2**, R = Me gives the diastereomeric *N*,*N*-dimethyl isoleucine methyl esters **10**, which were compared with an authentic sample of *anti*-**10**, prepared from L-isoleucine. This confirmed that the major isomer from rearrangement of the amine (*E*)-**1**, R = Me, has the *anti* stereochemistry, which is in line with expectations, based on related [2,3]-Stevens rearrangements.[3]

Experimental

N-Alkylation and rearrangement of the amine 1, R = Me

Methyl iodide (0.1 cm^3, 1.4 mmol) was added to the amine **1**, R = Me (100 mg, 0.7 mmol) and K_2CO_3 (0.19 g, 1.4 mmol) in dry DMF (0.5 cm^3) under argon. After 20 min, the mixture was warmed to 40 °C and DBU (0.23 cm^3, 1.4 mmol) was added. After 24 h, the mixture was poured into saturated $NaHCO_3$ (5 cm^3) and extracted with $CHCl_3$ (3 × 5 cm^3). The organic layer was washed with brine (2 × 5 cm^3), dried (Na_2SO_4) and purified by column chromatography on silica gel, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) to give the amine **2**, R = Me (69 mg, 58%), as a mixture of diastereomers a and b (60:40); ν_{max}(neat)/cm^{-1} 1730 (C=O) and 1645 (C=C); δ_H(400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 7, Me^a), 1.05 (3H, d, *J* 7, Me^b), 2.30 (12H, s, NMe_2^a and NMe_2^b), 2.50–2.69 (2H, m, CH^aCH_3 and CH^bCH_3), 2.89 (1H, d, *J* 10, $CHCO_2Me^a$), 2.97 (1H, d, *J* 10, $CHCO_2Me^b$), 3.64 (3H, s, CO_2Me^a), 3.70 (3H, s, CO_2Me^b), 4.90–5.12 (4H, m, $CH{=}CH_2^a$ and $CH{=}CH_2^b$), 5.66 (1H, ddd, *J* 17, 10 and 7, $CH{=}CH_2^a$), 5.78 (1H, ddd, *J* 17, 10 and 7, $CH{=}CH_2^b$); δ_C(100 MHz, $CDCl_3$) 16.92, 17.57, 37.42, 37.70, 41.12, 41.48, 50.41, 50.65, 72.52, 72.72, 114.36, 115.50, 140.21, 140.95, 171.40, 171.47 (Found M^+ 171.1260. $C_9H_{17}NO_2$ requires *M*, 171.1259); *m*/*z* 171 (M^+, 2.3%), 116 (M − C_4H_7, 25), 112 (M − CO_2Me, 20), 57 (100).

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