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Reactions of Protected Amino Acid Chlorides Mediated by SmI_2.

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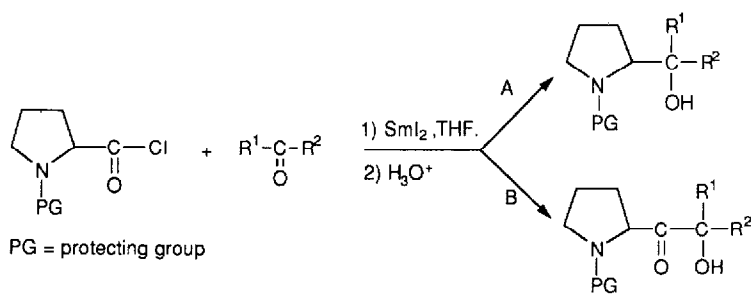
Key Words : Samarium diiodide ; aminoacid chlorides ; aminoalcohols ; ketones ; aldehydes ; decarbonylation.

Abstract : Reactions of N-protected amino acid chlorides with carbonyl compounds in the presence of SmI_2 were investigated. Decarbonylation followed by a cross coupling between amino moiety and aldehyde or ketone is observed. By the use of FMOC derivatives, N-protected amino alcohols were isolated in moderate yields.

We have investigated the reactivity of SmI_2 towards acid chlorides : coupling reactions and condensation reactions of acid chlorides with aldehydes or ketones led to α-ketols[1,2]. We have recently extended this reaction to $SmCp_2$, which displays the same reactivity. Interestingly the cyclopentadienyl ligand stabilizes the intermediate species and it has been established that acyl samarium compounds are involved in these reactions[3]. The reactivity of functionalized acid chlorides has also been examined. For ortho allyloxybenzoic acid chlorides, a double cyclization reaction takes place[4]. A different pathway is observed when α-alkoxyacid chlorides are reacted with aldehydes or ketones and SmI_2 to give 1,2-glycol monoethers[5]. In this reaction, decarbonylation of the acid chloride by SmI_2 occurs first, probably via an acyl radical intermediate. The α-oxygen atom is thought to play an important role in the decarbonylation probably through radical stabilization.

It was of interest to extend the above series of reactions of acid chlorides mediated by samarium diiodide to other α-heteroatom substituted acid chlorides, especially in the case of α-aminoacid chlorides. If these compounds follow the pattern of the chemistry described above, the product expected would be formed from the coupling of the reagents with or without decarbonylation. Path A would give a method for the synthesis of N-protected β-aminoalcohols and path B would lead to α-amino α'-ketols. We wish to report our first results obtained with proline derivatives.

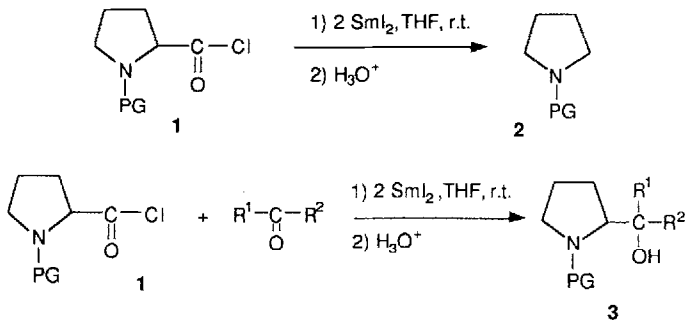


PG = protecting group

Various functional groups are able to protect the nitrogen of amino acids, preventing partial racemization (occuring from oxazolinone formation[6]) during formation of acid chlorides. For this purpose, the trifluoroacetyl group has been used[7]. N-Protection with oxycarbonyl derivatives has been studied and N-ethoxycarbonyl alanine chloride has been prepared[8]. More recently, stable aminoacid chlorides, N-protected with the FMOC group (9-fluorenylmethyloxycarbonyl) have been isolated and conveniently used for peptide synthesis[9,10].

The amino acid chosen here was L-proline because the N-protected atom has no hydrogen attached. In a preliminary study we compared the reactivity of SmI_2 towards proline chloride N-protected with trifluoroacetyl

1α and FMOC **1β** as protecting groups (PG). In the two cases, gas evolution occurs when **1α** or **1β** are reacted with SmI_2 and the decarbonylated product **2** is obtained in respectively 60% and 30% isolated yield. When a mixture of **1α** or **1β** with butanone or propanal was added to SmI_2 a condensation reaction was observed which led to N-protected aminoalcohols **3**. N-FMOC proline **1β** gave better yields (entries 1 and 3) and was selected for the subsequent experiments.



1α PG = $COCF_3$

1β PG = FMOC (9-Fluorenylmethyloxycarbonyl)

SmI_2 mediated reactions of various aldehydes and ketones with **1β** have been studied. Reactions are conducted differently according to the rate of pinacolization by SmI_2 of the carbonyl compounds[11] (a competiting reaction). When substrates, (aldehydes and unsaturated ketones) form pinacols rapidly, a mixture of 1 mmol of protected amino acid chloride and 1 mmol of carbonyl compound in 5 mL THF is added to SmI_2 (25 mL, 0.1 N) within 10 min at room temperature. If the carbonyl compound involved is a saturated ketone then it is added by a syringe to the SmI_2/THF solution just prior to the addition of the acid chloride solution. Gas evolution usually begins before the addition has been completed. The reaction is finished when gas evolution ends and when the mixture becomes yellow, usually within 0.5-2 hours. The workup involves hydrolysis with 0.1N hydrochloric acid, extraction with diethylether, then washing with sodium thiosulfate and brine and drying over $MgSO_4$. Products resulting from reactions of **1α** were analyzed by GC and GC/MS Compounds deriving from **1β** were purified by flash chromatography on silica and the NMR of the isolated compounds in agreement with the proposed structures[12]. Results are gathered in the Table.

In all the cases studied here, the formation of products proceeds *via* decarbonylation. The influence of experimental conditions was examined. For derivatives with N-trifluoroacetyl group, lowering the reaction temperature leads to an increase in the reaction yield which is nevertheless poor (entries 1, 2). Yields in **3b** and **3d** decreased when excess of aldehyde or ketone is used (entries 4, 7 compared to 3, 6). The moderate yields in compounds **3** are due mainly to two competitive reactions : the first is the decarbonylation of **1** followed by hydrogen (or proton) abstraction from THF which leads to formation of compounds **2** and the second is pinacolization. In the reactions involving acid chloride **1β** and ketones or aldehydes, N-FMOC pyrrolidine is obtained in *ca* 15 % yield.

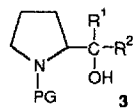
For non hindered carbonyl substrates such as propanal, cyclohexanone, cyclobutanone and 4-methyl pent-3-ene-2-one (entries 3, 6, 9, 12), the yield is improved in comparison with more bulky substrates such as cyclohexane carboxaldehyde or acetophenone (entries 5 and 11).

The experiment using the mesityl oxide (entry 12) showed only formation of alcohol **3i** to the exclusion of the ketone resulting from 1,4 addition to the carbonyl. The reaction favors 1,2 addition as has been already observed in the lanthanide chemistry[13].

Two diastereoisomers were formed for alcohols **3** (if $R^1 = R^2$) without diastereoselection (1/1 ratio). Only **3b** and **3g** formed separable diastereoisomers, which were isolated by preparative thin layer chromatography.

Complete loss of optical activity, probably occuring during the decarbonylation step, was observed for alcohols **3**.

The reactivity of N-FMOC phenylalanine chloride and N-FMOC alanine chloride in coupling reactions with propanal and butanone mediated by SmI_2 has been investigated. No coupling products were formed, only the N-FMOC-2-phenyl-ethylamine and N-FMOC-ethylamine have been isolated respectively in 80 and 65 % yields.

Table : Synthesis of 

3

	1	R^1COR^2	**3**	Yield (%)
1	**1α**	Propanal	**3a**	6[a]
2	**1α**	Propanal	**3a**	27[a,b]
3	**1β**	Propanal	**3b**	61[c]
4	**1β**	Propanal[d]	**3b**	28[c]
5	**1β**	Cyclohexanecarboxaldehyde	**3c**	38[c]
6	**1α**	Cyclohexanone	**3d**	53[a]
7	**1α**	Cyclohexanone[e]	**3d**	20[a]
8	**1β**	Cyclohexanone	**3e**	53[c]
9	**1β**	Cyclobutanone	**3f**	61[c]
10	**1β**	Butanone	**3g**	51[c]
11	**1β**	Acetophenone	**3h**	41[c]
12	**1β**	4-Methyl-3-pentene-2-one	**3i**	66[c]

[a] G.C.yield. [b] Reaction performed at -20°C instead of r.t. for others entries. [c] Isolated yield.
[d] Ratio **1β**/propanal : 1/1.5. [e] Ratio **1α**/cyclohexanone : 1/2.

Conclusions

This study shows that N-FMOC proline derivatives are useful in SmI_2 mediated reactions. Condensation on various aldehydes and ketones (cyclic, acyclic, unsaturated) leads to N-FMOC protected aminoalcohols in moderate yields. This later method complements reactions involving the formation of α-lithio pyrrolidine derivatives[14,15]. Further studies to extend this new method of preparation of amino alcohols[16,17] and investigate its mechanism are currently in progress.

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(11) Souppe J., Namy J.L., Kagan H.B. *Tetrahedron Lett.* **1984**, *25*, 2869.

(12) *^1H NMR* : δ N-FMOC proline **2**α : 7.77 (d, 2 H), 7.62 (d, 2 H), 7.37 (m, 4 H), 4.38 (d, 2 H), 4.25 (m, 1 H), 3.42 (t, 4 H), 1.89 (m, 4 H). **3b** More polar isomer : 7.78 (d, 2 H), 7.68 (d, 2 H), 7.33 (m, 4 H), 4.45 (m, 2 H), 4.22 (m, 1 H), 3.92 (m, 1 H), 3.70 (m, 1 H), 3.55 (m, 1 H), 3.30 (m, 1 H), 2.35 (m, 2 H), 1.88 (m, 4 H), 0.98 (t, 3 H). **3b** Less polar isomer : 7.78 (d, 2 H), 7.60 (d, 2 H), 7.35 (m, 4 H), 4.52 (m, 2 H), 4.23 (m, 1 H), 3.92 (m, 1 H), 3.73 (m, 1 H), 3.56 (m, 1 H), 3.28 (m, 1 H), 2.08 (m, 2 H), 1.83 (m, 4 H), 0.98 (t, 3 H). **3c** : 7.77 (d, 2 H), 7.60 (d, 2 H), 7.35 (m, 4 H), 4.72 (m, 1 H), 4.42 (m, 1 H), 4.20 (m, 1 H), 4.00 (m, 1 H), 3.55 (m, 2 H), 3.32 (m, 1 H), 2.05-1.55 (m, 15 H). **3e** : 7.78 (d, 2 H), 7.60 (d, 2 H), 7.36 (m, 4 H), 4.70 (bs, 1 H), 4.60 (m, 2 H), 4.25 (m, 2 H), 3.68 (m, 1 H), 3.20 (m, 1 H), 2.05-1.35 (m, 14 H). **3f** : 7.75 (d, 2 H), 7.58 (d, 2 H), 7.32 (m, 4 H), 4.68 (bs, 1 H), 4.42 (m, 2 H), 4.22 (m, 1 H), 3.99 (m, 1 H), 3.62 (m, 1 H), 3.37 (m, 1 H), 2.20-1.75.(m, 10 H). **3g** More polar isomer : 7.78 (d, 2 H), 7.60 (t, 2 H), 7.38 (m, 4 H), 5.45 (bs, 1 H), 4.38 (m, 2 H), 4.23 (m, 1 H), 3.98 (m, 1 H), 3.72, (m, 1 H), 3.28 (m, 1 H), 1.88 (m, 2 H), 1.69 (m, 2 H), 1.47 (m, 2 H), 1.00 (s, 3 H), 0.97 (t, 3 H). **3g** Less polar isomer : 7.78 (d, 2 H), 7.60 (d, 2 H), 7.35 (m, 4 H), 5.22 (bs, 1 H), 4.50 (m, 1 H), 4.40 (m, 1 H), 4.24 (m, 1 H), 3.97 (m, 1 H), 3.71 (m, 1 H), 3.22 (m, 1 H), 1.88 (m, 2 H), 1.70 (m, 2 H), 1.32 (m, 2 H), 1.10 (s, 3 H), 0.96 (t, 3 H). **3h** : 7.77 (d, 2 H), 7.57 (m,2 H), 7.30 (m, 9 H), 5.65 (bs, 1 H), 4.62 (m, 1 H), 4.27 (m, 3 H), 3.40 (m, 2 H), 1.90 (m, 2 H), 1.43 (m, 2 H), 1.62 (s, 3 H). **3i** : 7.75 (d, 2 H), 7.57 (d, 2 H), 7.32 (m, 4 H), 5.42 (bs, 1 H), 5.10 (s, 1 H), 4.60 (m, 1 H), 4.28 (m, 2 H), 3.95 (m, 1 H), 3.68 (m, 1 H), 3.24 (m, 1 H), 1.91 (m, 2 H), 1.82 (s, 3 H), 1.68 (m+s, 5 H), 1.30 (s, 3 H).

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(16) One may expect retention of optical activity by a control of the temperature if decarbonylation occurs on an acyl samarium species, by analogy with the stereochemical stability of α-lithio pyrrolidine derivatives[15].

(17) A very recent work published by Itoh, at the time of the submission of this paper shows formation of α-amino organosamarium species generated by a different route[18].

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