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REDUCTIVE COUPLINGS OF ACID CHLORIDES MEDIATED BY SmI_2

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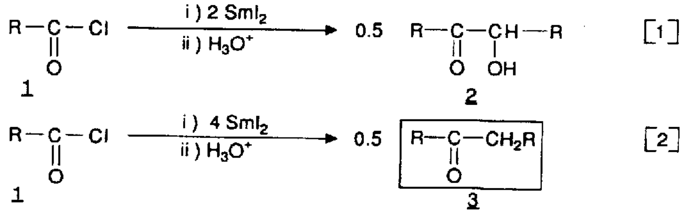
Summary : Reductive couplings of acid chlorides and of acid chlorides with aldehydes or ketones in presence of an excess of SmI_2 produce ketones in moderate to good yields.

We have previously investigated the reactivity of various acid chlorides in the presence of diiodosamarium. For example we discovered decarbonylation of α-alkoxyacid chlorides and double cyclisation reactions^{1,2}. We also reported that two equivalents of SmI_2 can achieve coupling of arylic acid chlorides into α-diketones, coupling of aliphatic acid chlorides into α-ketols (reaction [1])^3 and condensation of acid chlorides with aldehydes or ketones into α-ketols (reaction [3])^4. We wish to report here that in the presence of an excess of SmI_2 ketones are obtained in both cases instead of ketols.

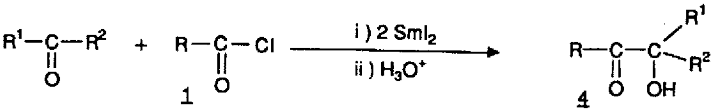
Aliphatic acid chlorides 1 are transformed at room temperature, with an excess of SmI_2 (four equivalents), directly into ketone 3 in good yields (60-80%) within a few hours (reaction [2], Table I). For example to a stirred solution of SmI_2 0.1 N in THF (80 mL, 8 mmol) was slowly added a solution of cyclohexylcarboxylic acid chloride (293 mg, 2 mmol) in THF (10 mL). After 0.5 hour at room temperature the reaction mixture was yet blue , due to excess of SmI_2 , and was quenched with HCl 0.1N and treated as previously described^4. Ketone 3c is isolated (166 mg) in 80 % yield.

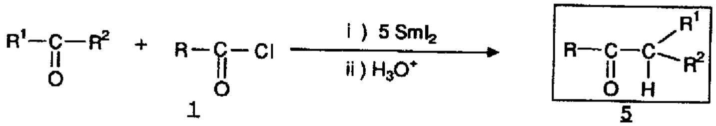


$$\underset{\mathbf{1}}{R-\overset{O}{\overset{\|}{C}}-Cl} \xrightarrow[\text{ii) } H_3O^+]{\text{i) } 2\ SmI_2} 0.5\ \underset{\mathbf{2}}{R-\underset{O}{\underset{\|}{C}}-\underset{OH}{\underset{|}{C}H}-R} \qquad [1]$$

$$\underset{\mathbf{1}}{R-\overset{O}{\overset{\|}{C}}-Cl} \xrightarrow[\text{ii) } H_3O^+]{\text{i) } 4\ SmI_2} 0.5\ \underset{\mathbf{3}}{\boxed{R-\underset{O}{\underset{\|}{C}}-CH_2R}} \qquad [2]$$

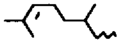
We found that acid chlorides react with aldehydes and ketones at room temperature with an excess of SmI_2 (usually five equivalents) allowing the direct formation of ketones 5 (reaction [4], see Table II). In the standard procedure a solution of acid chloride in THF is slowly added to the mixture of SmI_2 and ketone, for example citronellic acid chloride (375 mg, 2 mmol, in 10 mL THF) to decanone (234 mg, 3 mmol) and SmI_2 (100 mL, 0.1 N, 10 mmol). After 18 h at room temperature and usual workup, ketone 5d (172 mg, 56 %) is isolated.


[3]


[4]

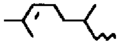
In the case of 5a a 80:20 mixture of isomeric ketones 4-dodecanone and 3-dodecanone is obtained. Amount of 4-dodecanone increases by using an excess of propanal. Diphenyl carbamoyl chloride is reactive towards cyclohexanone, leading to amide 5f. Inanaga reported that HMPA accelerates various transformations mediated by SmI_2[5]. For our reactions addition of HMPA increases the rate of formation of ketones but also the amount of by-products and seems useless.

TABLE I : FORMATION OF KETONES 3 $RC(O)CH_2R$

	R	t(h)^a	Isolated yield %
3a	1-Adamantyl	1^b	60
3b	$n-C_8H_{17}$	18	60
3c	Cyclohexyl	0.5	80
3d		18	73^c

a) Reactions in THF at room temperature except(b), 4 equiv. SmI_2.
b) Reaction at 60°C.
c) 90:10 mixture of diastereomers.

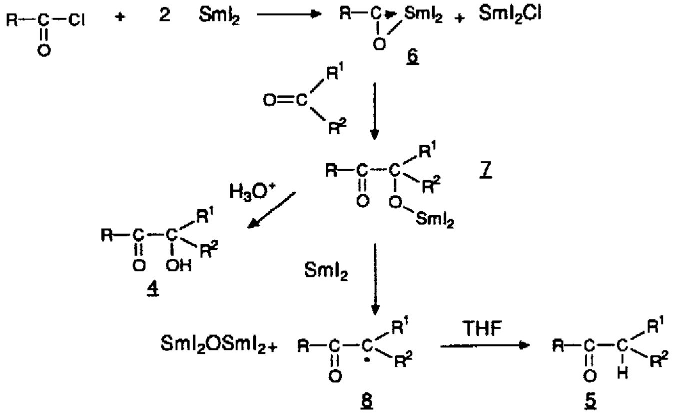
TABLE II : FORMATION OF KETONES 5 $RC(O)CH(R^1)(R^2)$

	R	R^1, R^2	t(h)^a	Isolated yield %
5a	$n-C_8H_{17}$	H, CH_2CH_3	0.75	70^b
5b	$n-C_8H_{17}$	$-(CH_2)_5-$	5	62
5c	CH_3	$-(CH_2)_5-$	0.3	30
5d		CH_3, $(CH_2)_7CH_3$	16	56^c
5e	Ph	CH_3, $CH=C(CH_3)_2$	18	30^d
5f	Ph_2N	$-(CH_2)_5-$	100	49

a) Reactions in THF at room temperature, 5 equiv. SmI_2.
b) 4-Dodecanone:3-dodecanone : 80:20.
c) 50:50 mixture of diastereomers.
d) Conjugated ketone is not observed.

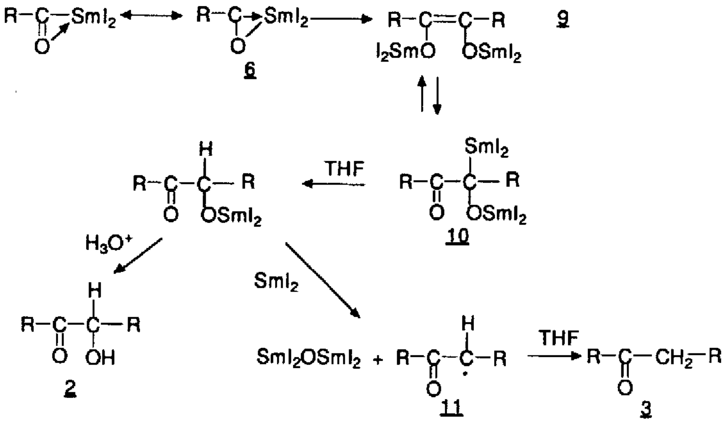
During the course of formation of ketones 3 and 5, G.C. analysis of aliquots of the reaction mixture show that ketols 2 and 4 respectively are first formed and then reduced by SmI_2. We checked that reduction of the ketol 4b (R = n-C_8H_{17}, R^1COR^2 = cyclohexanone) occurs when using three equivalents of SmI_2 and also leads to ketone 5b in 82% yield[6].

Several mechanisms can be postulated to explain formation of 5. Previous studies of reactions of acid chlorides with SmI_2[4] as well as with $SmCp_2$[10] have shown acyl samarium are transient species in the reaction of divalent samarium compounds with acid chlorides. Involvement of a samarium enolate seems to be ruled out as no incorporation of deuterium in ketone 5b after deuterolysis has been noticed. The reaction mixture was also unreactive towards tert-butyl dimethyl chlorosilane and product 5b was recovered after mild hydrolysis. We propose that the acyl samarium species 6 reacts with ketone leading to samarium ketolate 7 which after further reaction with SmI_2 eliminates SmI_2OSmI_2 with direct formation of α-keto radical 8 which abstracts H from THF (Scheme I).



SCHEME I

A tentative mechanism for the formation of ketones 3 is depicted in Scheme II. Acyl samarium species 6 under its carbenoid form duplicates giving an enediolate intermediate 9. Such coupling of formyl complexes have been found for some samarium compounds[11]. As no incorporation of deuterium on ketol 2a (R = 1-adamantyl) has been observed after deuterolysis of the reaction mixture, we suggest the enediolate is in equilibrium with a samarium ketolate 10. In the latter the samarium carbon bond is cleaved by THF. The last step should involve an α-keto radical which abstracts hydrogen from THF. This assumption is supported by the absence of deuterium incorporation in ketone 3a after deuterolysis.



SCHEME II

The present work allows a one pot synthesis of ketones in mild conditions. Scope and mechanism of the reactions [2] and [3] are under investigation.

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