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REGIOSPECIFIC NUCLEOPHILE-INDUCED FRAGMENTATION OF α,α-DICHLORO-β-IMINOCARBONYL COMPOUNDS

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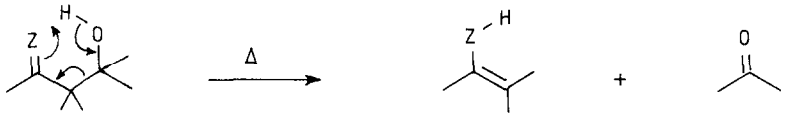
ABSTRACT : The reaction of α,α-dichloro-β-(N-alkyl or N-aryl)iminocarbonyl compounds with nucleophiles resulted in a regiospecific fragmentation to afford α,α-dichloroketimines.

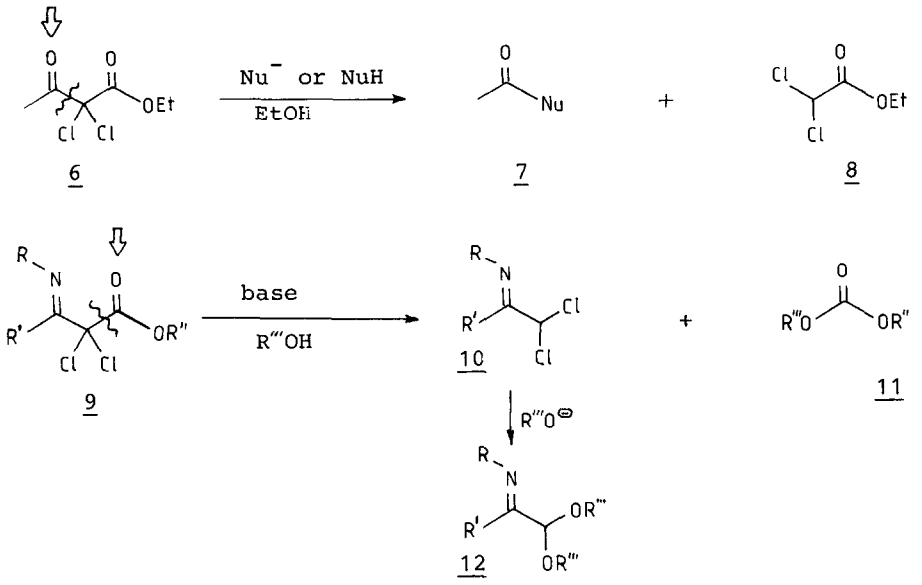
Retro-ene type reactions have been studied already extensively in the literature. Major attention has been given to substrates containing an olefinic double bond (1 : Z=CR_1R_2; homoallylic alcohols), while many examples of the fragmentation of β-hydroxycarbonyl compounds 2 (Z=O) are known[1-3] (the base-induced fragmentation of β-ketocarbonyl compounds also belongs to this category of reactions). Mechanistic studies have revealed that these thermal reactions



1 Z = CR_1R_2
2 Z = O
3 Z = NR

occur via a six-membered cyclic transition state[4]. Retro-ene reactions of β-hydroxyimines 3 (Z=NR) have been rarely reported. Examples of the latter reactions are the dealdolization of diacetone alcohol catalyzed by primary amines,[5] fragmentation of a β-ketoaldimine[6] and some reactions in which the imino function is a part of a heteroaromatic ring[7-9]. We would like to report now on more general retro-ene type reactions of α,α-dichloro-β-ketoimines.

On reaction with weak nucleophiles in ethanol, α,α-dichloro-β-ketoester 6 was reported to fragment at the C_2-C_3 bond yielding (ethyl) dichloroacetate 8 and carbonyl compounds 7[10]. We found that the regiospecificity of this fragmentation could be reversed by masking the β-keto group as a ketimine. As a result, α,α-dichloro-β-(N-alkyl of N-aryl)imino esters 9, easily accessible from chlorination of the corresponding enaminoesters with two equivalents of N-chlorosuccinimide in carbon tetrachloride[12] or from imination of the corresponding carbonyl compounds[13], reacted with a variety of bases (sodium methoxide, potassium t-butoxi-

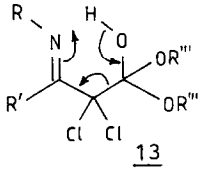


de, potassium cyanide, potassium carbonate) in alcoholic medium (methanol, ethanol) under reflux to afford α,α-dichloromethylketimines 10 (Table). Catalytic amounts of the basic substances are sufficient, but the reaction can also be run at a slower rate without these catalysts. In addition, the regiospecific splitting can also be performed with sodium methoxide or potassium t-butoxide in THF or ether (at room temperature for KOtBu). The fragmentation reaction of α,α-dichloro-β-(N-alkyl)iminoesters 9 (R=alkyl) with sodium methoxide in methanol (2 N, 2 equiv) during one hour under reflux leads to N-alkyl α,α-dichloromethylketimines 10 but, under nearly the same conditions (NaOMe/MeOH, 2 N, 2 equiv, Δ 6hr), α,α-dichloro-β-(N-phenyl)iminoesters 9 (R=C_6H_5) are converted into α,α-dimethoxymethylketimine 12 (R‴ = Me, R=C_6H_5) in good yield. It was already known that N-aryl α-haloketimines were much more reactive than their N-alkyl analogues toward nucleophilic substitution[13]. However, the substitution reaction (10 → 12) is also possible for N-alkyl derivatives under more stringent conditions (NaOMe/MeOH; 4 N; 20 equiv; Δ 24h).

Masking the carbonyl function of 6 at the 3-position as an imine resulted in a complete reversion of the site of fragmentation (i.e. C_1-C_2 fission). The more electrophilic carbonyl group in 9 is apparently selectively attacked and the final products 10 together with the corresponding dialkyl carbonate 11 are formed, possibly via cyclic transition state 13 in the case of reactions in alcohols.

TABLE : Regiospecific Fragmentation of α,α-Dichloro-β-iminocarbonyl Compounds

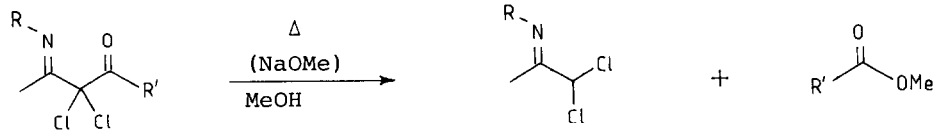
Starting Compound	R	R'	R"	Reaction Conditions	Reaction products
9a	i-Pr	Me	Me	NaOMe/MeOH 1N 1.2 equiv. Δ1.7h	83% 10a (bp 48-53°C/11 mmHg)
9a	i-Pr	Me	Me	NaOMe/MeOH 4N 20 equiv. Δ24h	86% 12 (R'''=Me; R=i-Pr)
9a	i-Pr	Me	Me	NaOMe/ether 5 equiv. Δ45 min.	95% 10a
9a	i-Pr	Me	Me	KOtBu/THF 2 equiv. RT 1h	90% 10a (+ 90% di-t-Butyl carbonate and 10% t-Butyl methyl carbonate)
9a	i-Pr	Me	Me	K_2CO_3/MeOH 1 equiv. Δ1,5h	95% 10a
9b	C_6H_5	Me	Me	NaOMe/MeOH 3 equiv. 2N, Δ20h	70% 12 (R'''=Me; R=C_6H_5) (bp 72-78°C/0.02 mmHg)
9b	C_6H_5	Me	Me	KCN/MeOH 2 equiv. Δ20h	75% 10b
9c	C_6H_5	Me	Et	KCN/MeOH 2 equiv. Δ8h	90% 10b
14a	i-Pr	Me	-	NaOMe/MeOH 0,1 equiv. 0.025N Δ1h	96% 10a
14b	C_6H_5	C_6H_5	-	MeOH Δ4h	92% 10b (+ 100% methyl benzoate)



13

This regiospecific fragmentation reaction is also applicable for α,α-dichloro-β-iminoketones 14 as exemplified with methanol (with or without a catalytic amount of sodium methoxide).

The new reactions described in this communication allow the synthesis of 1,1-dichloro-2-alkanones following a novel efficient strategy involving conversion of a methylketone into a β-ketoester ($MeOCOOMe/NaH/C_6H_6$), double chlorination (SO_2Cl_2/CH_2Cl_2), imination (RNH_2/ether/$TiCl_4$)[13] to afford 9, fragmentation



14a R = i-Pr, R'=Me
14b R = R'= C_6H_5

10a R = i-Pr
10b R = C_6H_5

15

(base/MeOH) and acidic hydrolysis (HCl 2N). When applied to the synthesis of 1,1-dichloro-2-propanone, this compound was obtained in 88% overall yield starting from methyl acetoacetate (via 9; R=i-Pr).

The reactions of imines 9 and 14 described in this communication are remarkable in that the corresponding α-halogenated carbonyl compound are known to react in a totally different way (reversed fragmentation[10,11] or Favorskii rearrangement and subsequent decarbonylation[14]). Research is in progress to determine the scope and limitations of this potential reaction.

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