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FAVORSKII-TYPE REARRANGEMENT OF α-CHLORO KETIMINES

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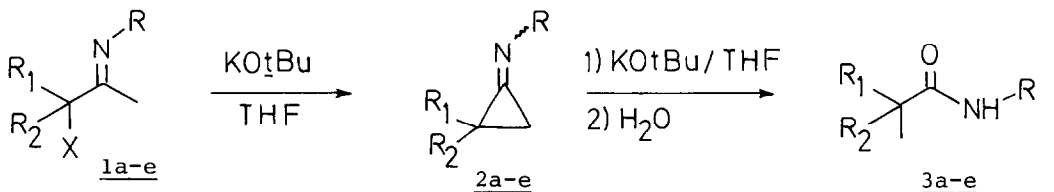
Abstract : The first examples of the Favorskii-type rearrangement of α-monochloro ketimines are reported. The regiospecific opening of the intermediate cyclopropylideneamines parallels the opening of cyclopropanones under Favorskii-conditions.

The base-induced skeletal rearrangement of α-halo ketones into carboxylic acid derivatives is well-known as the Favorskii rearrangement, to which much mechanistic research has been devoted.[2] The chemistry of the nitrogen analogues of α-halo ketones, i.e. α-halo imines, has not been fully exploited in synthetic and mechanistic organic chemistry.[3] Accordingly, only two reports on the Favorskii-type rearrangement of α-halo ketimines have been reported hitherto, namely, first, the alkoxide induced stereospecific conversion of α,α-dichloro-



a X=Br; R_1=t-Bu; R_2=H; R=alkyl, aryl

b X=Cl; R_1=Me; R_2=H; R=i-Pr

c X=Cl; R_1=Me; R_2=H; R=t-Bu

d X=Cl; R_1=R_2=Me; R=i-Pr

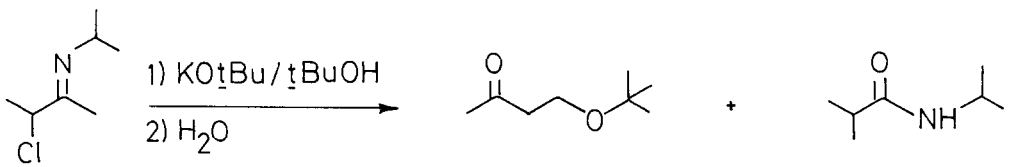
e X=Cl; R_1=Ph; R_2=H; R=i-Pr

methylketimines into cis-α,β-unsaturated imidates,[4] and, second, the t-butoxide induced rearrangement of sterically hindered α-bromoketimines (e.g. 1a) into

the corresponding carboxylic amides.[5] It is the latter paper which prompted us to uncover our own results in this field.

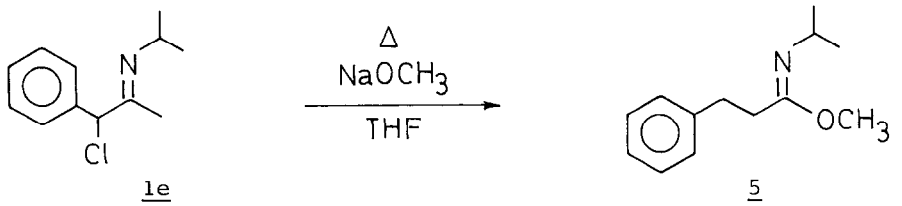
We have found that α-chloro ketimines 1b-d rearrange with potassium t-butoxide in tetrahydrofuran into the branched carboxylic amides 3a-e (yields 62-71 %). This is the first report of the Favorskii-type rearrangement of α-monochloro ketimines. Under the same circumstances, bulky substituted α-bromo ketimines 1a were recently found to afford 1,3-dehydrobromination with formation of the isolable cyclopropylideneamines 2a,[5,6] i.e. the nitrogen analogues of cyclopropanones. Secondary α-chloro ketimines 1b,c (R_1=CH_3; R_2=H; R=i-Pr, t-Bu) rearranged under mild conditions (RT, 2 hrs), but tertiary α-chloro ketimines 1d (R_1=R_2=CH_3; R=i-Pr) required prolonged heating to induce rearrangement (Δ 48 hrs).

N-(3-chloro-2-butylidene)isopropylamine 1b underwent a similar skeletal rearrangement into amide 3b by refluxing with potassium hydroxide in dioxane, while a competition between Favorskii-type rearrangement and elimination-Michael addition was observed with potassium t-butoxide in t-butanol. After aqueous work-up, the reaction led to a 3:1 mixture of 4-t-butoxy-2-butanone 4 and N-isopropyl 2-methylpropanamide 3b, respectively.



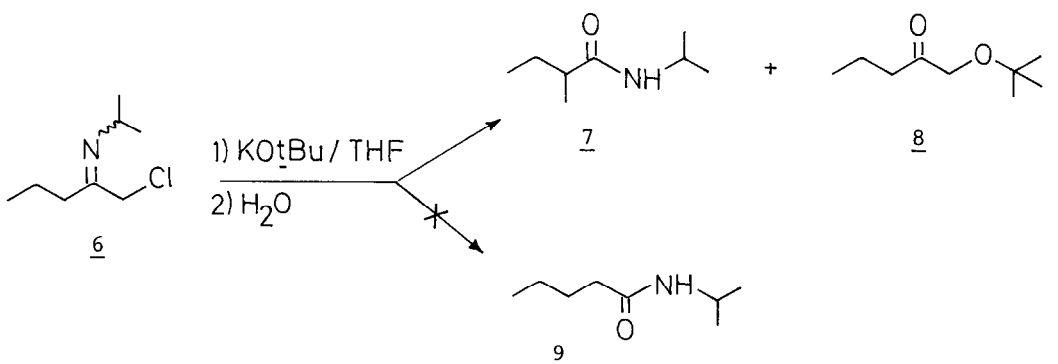
1b 4 3b

Several interactions of strong bases, e.g. DABCO or sodium methoxide, in non-protic solvents (benzene, THF, ether, diisopropyl ether) have been tested towards α-chloro ketimines, but only in the case of the activated α-phenyl-α-chloro ketimine 1e (R_1=Ph; R_2=H; R=i-Pr) consumption of starting material was observed. In the latter case, the reaction of sodium methoxide in tetrahydrofuran under reflux (24 hrs) furnished the rearranged methyl imidate 5 in nearly quantitative yield.



1e 5

Although evidence was gained that the rearrangement of α-halo ketimines into amides 3 occurs via cyclopropylideneamines 2 by the isolation of the latter bulky substituted derivatives (R_1=t-Bu),[5,6] we provide an alternative evidence for a Favorskii-type rearrangement. Indeed, an alternative reaction pathway would be the semi-benzilic rearrangement. While both mechanisms would give branched amides 3 with substrates 1, the semi-benzilic rearrangement would produce a linear amide (e.g. 9) when an α-chloromethyl ketimine, like 6, is used as starting material. No trace of the linear amide 9 could be detected when N-(1-chloro-2-pentylidene)isopropylamine 6 was brought into reaction with potassium t-butoxide in tetrahydrofuran (RT, 2 hrs). Instead, the Favorskii amide 7 was isolated in 21 % yield (GLC) next to the α-substitution product, i.e. 1-t-butoxy-2-pentanone 8 (71 %), the latter resulting from hydrolysis of the intermediate α-t-butoxyketimine.



6 7 8 9

From the results presented in this paper, it seems that the intermediate aliphatic cyclopropylideneamines 2 are opened in such a way as to produce the most stable carbanion, i.e. the one leading to the more branched carboxylic

amide. However, the directory influence of a phenyl substituent (R_1=Ph) caused the intermediate 2e to open at the more branched side, giving rise to the more stable benzylic anion. This reactive behaviour parallels the ring opening of the corresponding cyclopropanones.[2b,7,8]

We are currently investigating more facets of the rearrangements discussed in this paper.

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