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α,α-Cyclo*bis*alkylation of Aldehydes via ω-Haloaldimines

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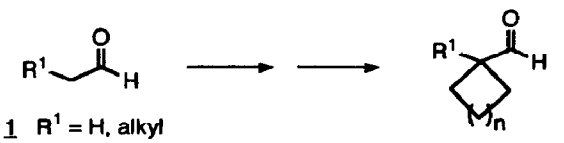
Abstract : The construction of a cycloalkyl ring at the α-position of aldehydes by cyclization of ω-haloaldimines is described. Alkylation of the corresponding aldimines with α,ω-dihaloalkanes followed by treatment with LDA results in a convenient access to α,α-cyclo*bis*alkylated aldimines which are hydrolyzed to the α,α-cycloalkylaldehydes.

Total synthesis of complex molecules often struggles with the introduction of ring systems in functionalized precursors. Therefore, attention was paid to the construction of a cyclobutane, a cyclopentane or a cyclohexane ring at the α-position of aldehydes and ketones, in which the α-carbon is part of the cycloalkane ring.



1 R^1 = H, alkyl

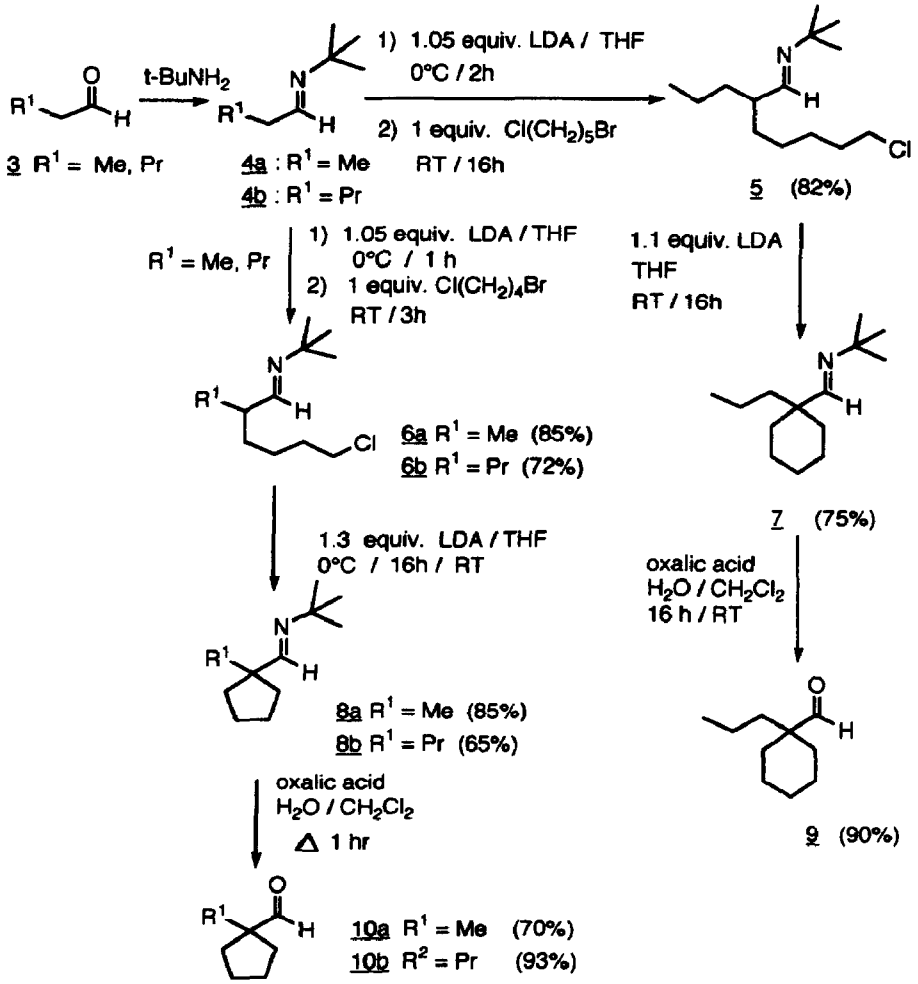
2 n = 1,2,3

Although this cyclo*bis*alkylation is well known for cyclic ketones,[1,2,3] the transformation is not straightforward for acyclic ketones[4,5,6] and certainly not for aldehydes. The alkylation of enolates derived from aldehydes with α,ω-dihaloalkanes at -78°C in tetrahydrofuran results in a complex mixture of compounds without formation of the desired ω-halogenated aldehydes or cycloalkane carboxaldehydes. In order to complete this transformation, a masked form of the aldehyde is used, e.g. the corresponding aldimine, followed by a facile conversion to the aldehyde after ringclosure. For

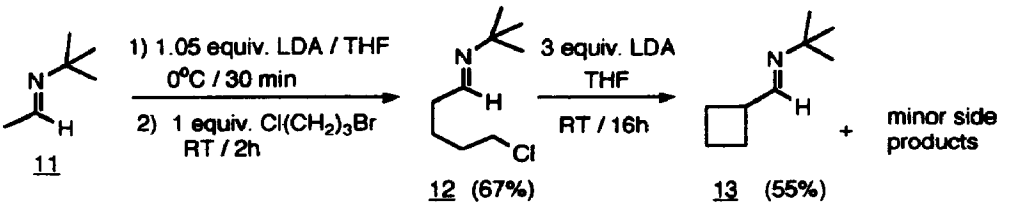
the α,α-cyclo*bis*alkylation of aldehydes, only one useful method has been described using activated oxazine derivatives which are cyclo*bis*alkylated, reduced and hydrolyzed to the desired aldehydes.[7,8] A similar procedure was used for the synthesis of 2-methylcyclopentanecarboxylic acid utilizing oxazolines as auxilliaries.[9]

In the present communication, an alternative method for the synthesis of cycloalkane carboxaldimines from aldimines is described. As the starting aldimines are easily accessible from the aldehydes and as aldimines are readily hydrolyzed into the corresponding aldehydes, this method represents a short route for the conversion of aldehydes 1 (R=H) into cycloalkane carboxaldehydes 2 (R=H).

Starting from aldehydes, such as ethanal, propanal or pentanal, the aldimines were formed by condensation of the aldehydes with t-butylamine using magnesium sulfate as a dehydrating agent.

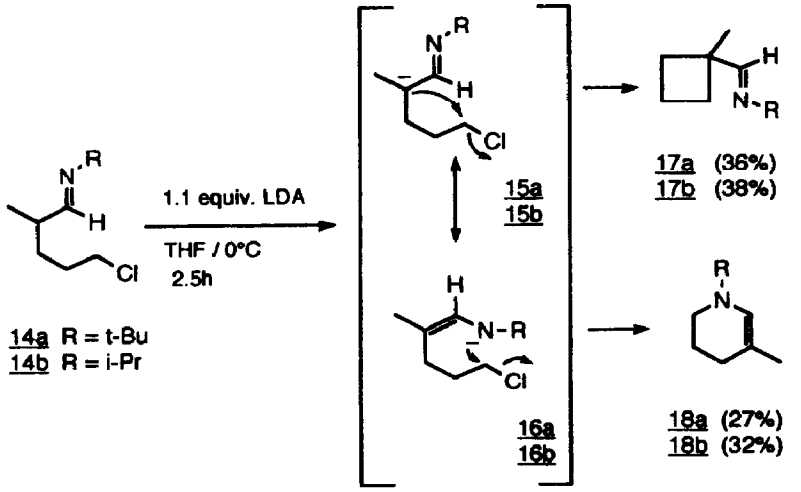


Aldimines 4 were deprotonated by lithium diisopropylamide (LDA) at 0°C and subsequently alkylated with α-bromo-ω-chloroalkanes forming the ω-chloroaldimines 5 and 6 in 72 - 85 % yield. Attention should be paid to the reaction temperature during alkylation (in order to avoid undesired side reactions) and to a fast aqueous work-up of the reaction mixture (in order to prevent hydrolysis of the ω-chloroaldimine). The electrophile should be added quickly to prevent dialkylation of the imine due to proton transfer. The ω-chloroaldimines 5 and 6 were then treated with lithium diisopropylamide in tetrahydrofuran, forming the 1-azaenolate anion which leads to intramolecular nucleophilic substitution. The α,ε-interactions of aldimines 6a and 6b led to N-[(1-alkyl-1-cyclopentyl)methylidene]t-butylamine 8a and 8b in 85% and 65% yield, respectively, after distillation. The aldimines 8 were then hydrolyzed upon treatment with 1 equivalent of oxalic acid in a two phase system (water/dichloromethane : 1/1) generating the cyclopentane carbaldehydes 10 in 70 - 93% yield. In the same way, the methodology was extended for the construction of the cyclohexane analogue 7 by an α,ζ-interaction initiated by LDA to give 7 in 75% yield. Hydrolysis with oxalic acid completed the synthesis of the cyclohexane carboxaldehyde 9 in 90% yield.



11 → 12 (67%) + 13 (55%)

The α,δ-interaction of aldimine 12, prepared in an analogous way from aldimine 11, resulted in a synthesis of N-[(cyclobutyl)methylidene]t-butylamine 13 (2.3 g, Yield 55%) together with some side products (probably due to the formation of the labile cyclic enamine by intramolecular N-alkylation). Distillation and hydrolysis with hydrochloric acid (2N) resulted in small amounts (20 %) of cyclobutane carboxaldehyde which is quite a labile compound.



Extension of the present method for the construction of a cyclobutane ring with an α-substituent with respect to the formimidoyl moiety led to a mixture of cyclobutanecarbaldimines 17 and the cyclic enamines 18. The introduction of the extra α-methyl substituent resulted in an enhanced stability of the 1-azaenolate anion 16, which may explain partially the formation of tetrahydropyridines 18. This molecular N-alkylation as a side reaction is known for the ring closure of δ-chloroaldimines by alkoxides[10] or the ring closure of γ- and δ-haloketimines.[11] In the latter two cases, no carbon alkylation was observed.[10,11]

In an attempt to perform one-pot syntheses of cyclobutane carbaldimines (e.g. 13, 17) from aldimines 4, the latter substrates were deprotonated by LDA in THF, reacted with 1-bromo-3-chloropropane, and deprotonated again by LDA. This procedure resulted in less pure cyclobutane carboxaldimines and in lower yields of the desired compounds. Alternatively, the treatment of aldimines 4 with 2.2 molar equivalents of LDA in THF and treatment with 1-bromo-3-chloropropane did not lead to better results compared to the procedure with isolation of the intermediate ω-haloaldimines.

In summary, the construction of a cyclopentyl or a cyclohexyl ring (and to a lesser extent of a cyclobutyl ring) at the α-position of aldehydes is described and classifies as a convenient and alternative synthetic method. The α,α-cycloalkylation consists of a 4-step procedure with an overall yield of 41 - 52 % without the use of hazardous or special reagents which makes the transformation attractive to use in organic methodology.

REFERENCES AND NOTES

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