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Electrophile-induced Cyclization of γ,δ-Alkenylimines as a Synthetic Route to Pyrrolidines and Piperidines

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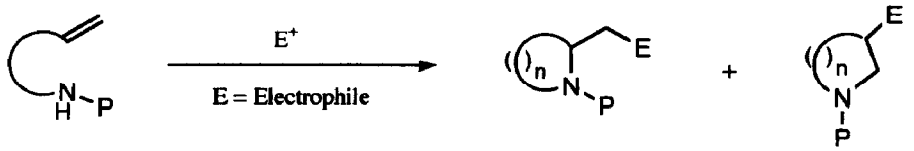
Abstract: Cyclization of γ,δ-alkenylimines with bromine in dichloromethane gave instantaneous formation of cyclic iminium bromides, which were converted into either pyrrolidines or piperidines, depending upon the substitution pattern. This reaction has been applied in the synthesis of 2-azaspiro compounds.

Electrophile-mediated cyclizations that lead to polysubstituted heterocycles have attracted considerable interest over recent years.[1] The principal advantages of this synthetic process are that the precursors are often readily assembled and the key cyclization step may be carried out using a variety of electrophilic triggers, offering access to a wide range of functionalized heterocycles.[2] The direct electrophile-induced cyclization of alkenylamines to nitrogen heterocycles has rarely been employed owing to difficulties connected with this kind of reaction.[1-3] However, intramolecular aminomercuration of alkenyl-



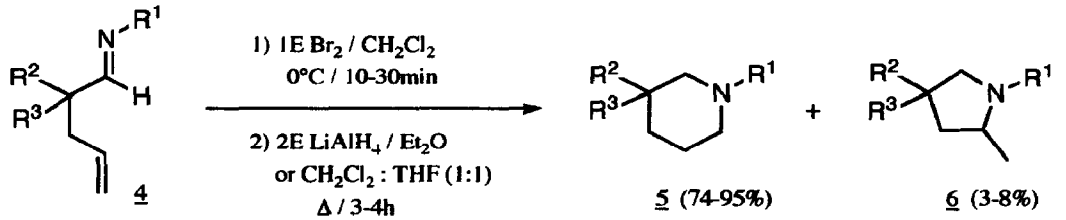
1 P = Protective group 2 3

amines met with success giving rise to organomercury substituted pyrrolidines or piperidines.[4] A drawback of the synthetic method of organomercurials is the toxicity of the end products and the limited synthetic value of the organomercurials for further elaboration. As a consequence, a variety of ω-alkenylamine derivatives, e.g. carbamates,[3,5,6] amides,[7] imidates,[8,9] thioimidates,[10,11] ureas,[12] isoureas,[13] etc. have been cyclocondensed under the influence of electrophiles, including iodine, bromine, phenylselenenyl halides, phenylselenophthalimide, etc...[1-3] All these N-substituted ω-alkenylamine derivatives have in common that the nitrogen atom has become dramatically reduced in nucleophilic power, resulting in less side reactions.

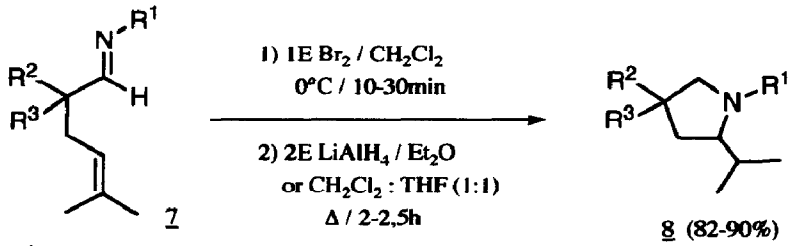
It is surprising to note that the corresponding imines have not been used in such electrophile-induced cyclisations, except in a phenylselenenyl bromide induced reaction.[14] In this preliminary note, results on the latter type of cyclisation process, with γ,δ-alkenylimines using bromine as cyclisation mediator,

are disclosed. The advantage of the use of bromine in this type of electrophile induced ring closures of γ,δ-unsaturated imines is the possibility to form functionalized 1-pyrrolinium derivatives, which can easily be elaborated further.

γ,δ-Alkenylimines 4 and 7 react instantaneously with equimolecular amounts of bromine in dichloromethane at 0°C to afford cyclic iminium salts, e.g. 9, which can be isolated by evaporation of the



R^1= i-Pr, t-Bu, $(CH_2)_2C_6H_5$
R^2,R^3= Me, $(CH_2)_5$



R^1= i-Pr, t-Bu
R^2,R^3= Me, $(CH_2)_5$

solvent or which can be characterized by in situ formation in an NMR-tube ($CDCl_3$). It follows that the nucleophilicity of the imino nitrogen is high enough to substitute the intermediate bromonium ion (π-complex) formed upon reaction of bromine with the olefinic double bond. The resulting cyclic iminium salts are suitable precursors for the synthesis of pyrrolidines 6, 8 or piperidines 5. Due to the bromomethyl substituent of the 1-pyrrolinium salts, bicyclic intermediates are formed upon reaction with nucleophiles. In the case of α-allylimines 4, these bicyclic aziridinium intermediates 10 suffer ring

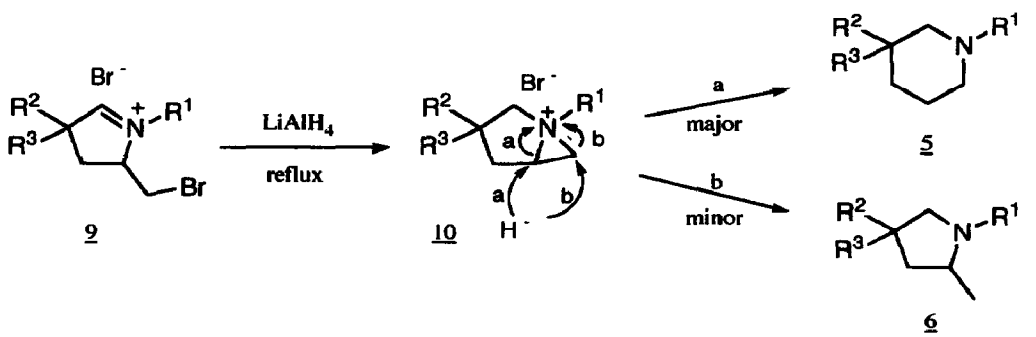
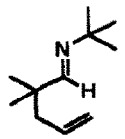
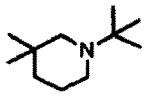
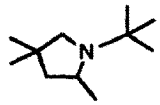
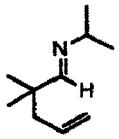
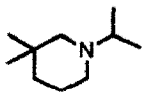
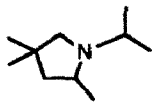
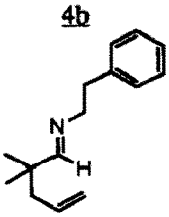
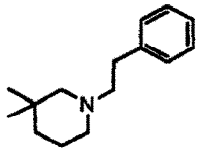
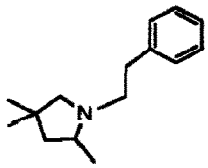
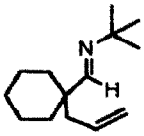
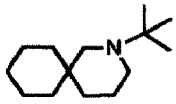
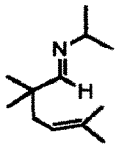
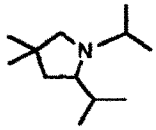
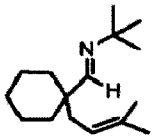
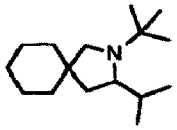


Table 1 : Conversion of γ,δ-Alkenylimines 4, 7 into Piperidines 5 and Pyrrolidines 6, 8.

Substrate	Reaction conditions[a] 4,7 → 5,6,8	Piperidine	Pyrrolidine
 4a	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, Et_2O, Δ, 4h	 5a (78%)[b]	 6a (8%)[c]
 4b	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, CH_2Cl_2:THF (1:1), Δ, 4h	 5b (87%)[d]	 6b (3%)[d]
 4c	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, Et_2O, Δ, 3h	 5c (85%)[d]	 6c (4%)[d]
 4d	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, CH_2Cl_2:THF (1:1), Δ, 3h	 5d (74%)[e]	-
 7a	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, Et_2O, Δ, 2h	-	 8a (90%)[b]
 7b	1) 1 Equiv. Br_2, CH_2Cl_2, 0°C, 15 min. 2) 2 Equiv. $LiAlH_4$, Et_2O or CH_2Cl_2:THF (1:1), Δ, 2,5h	-	 8b (82%)[e]

[a] After the cyclisation reaction, carried out with bromine in dichloromethane at 0°C, and after evaporation of the solvent, $LiAlH_4$ is added portionwise at 0°C to the suspended or dissolved intermediate iminium salt. [b] Purification by distillation. [c] Percentage in the reaction mixture; the minor cyclic amine was isolated by preparative gas chromatography. [d] Purification by preparative gas chromatography. [e] Purification by flash chromatography with ethyl acetate-hexane as eluent.

opening from two sides, thereby showing a selectivity for ring expansion. This pattern of transformations is verified by reactions with nucleophilic hydrides. The reaction of 1-pyrrolinium bromides 9 with portionwise added lithiumaluminium hydride in ether or in a tetrahydrofuran-dichloromethane mixture (1:1) under reflux gave rise to a mixture of piperidines 5 and pyrrolidines 6 in which the ring expanded piperidine 5 predominated by far. On the other hand, only pyrrolidines 8 were obtained from α-prenylimines 7 using the above two-step sequence. The results on the synthesis of pyrrolidines 6, 8 and piperidines 5 are compiled in Table 1. The mechanism for the conversion of 5-(bromomethyl)-1-pyrrolinium bromides 9 with lithiumaluminium hydride into piperidines 5 is interpreted as an initial reduction of the iminium bond followed by intramolecular nucleophilic substitution to form a bicyclic aziridinium intermediate 10. The aziridinium species undergoes ring opening by hydride attack at the more substituted side (path a) to form piperidines 5. Ring opening at the less substituted carbon of the aziridinium intermediate (path b) affords a little amount of the 1-substituted 3,3,5-trimethylpyrrolidines 6 (3-8%).

In conclusion, a facile cyclization process of γ,δ-alkenylimines 4 and 7 into piperidines 5 and pyrrolidines 6 and 8 has been developed via an electrophile-assisted ring closure reaction. It is noteworthy that the use of cyclohexane carboxaldimines 4 and 7 (R^2, $R^3=(CH_2)_5$) leads to the synthesis of spirocyclic amines 5d and 8b. The latter have attracted widespread synthetic interest as the 2-azospiro[5.5]decane and 2-azaspiro[5.4]undecane skeleton is incorporated in several alkaloids.

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