Use of 3-halo-1-azaallylic anions in heterocyclic chemistry*

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Abstract: The synthetic potential of lithio 3-halo-1-azaallylic anions as building blocks in organic chemistry and especially in heterocyclic chemistry will be highlighted by the synthesis of functionalized imines, obtained after reaction of 3-halo-1-azaallylic anions with heteroatom-substituted electrophiles. Thus, the latter generated functionalized imines are suitable building blocks for the synthesis of a whole range of heterocycles and physiologically active compounds, including agrochemicals and pharmaceuticals. 3-Halo-1-azaallylic anions were used in the synthesis of *N*-alkyl-3,3-dichloroazetidines, 2,3-disubstituted pyrroles, piperidines, 2-substituted pyridines, 2-alkoxytetrahydrofurans, etc., from which a large range of useful and interesting chemicals can be produced, e.g., 2-azetines and 9-alkyl-2-phenyl-3aβ,4,6,7,8,9,9aβ,9bβ-octahydro-1*H*-pyrrolo[3,4,*h*]quinoline-1,3-diones. The utility of the present methodology is demonstrated by the synthesis of the pheromone (*S*)-manicone, the sulfur-containing flavor compound 2-[(methylthio)methyl]-2-butenal, and some agrochemical and pharmaceutical compounds.

INTRODUCTION

α-Heteroatom-substituted carbanions **1** (Scheme 1), stabilized by electron-withdrawing groups, are important synthons in organic chemistry [1]. Almost all combinations of heteroatoms (e.g., halogen, silicon, selenium, sulfur, etc.) and carbanion-stabilizing groups (e.g., alkoxycarbonyl, cyano, acyl, sulfonyl, sulfinyl, etc.) are useful, except the combination of halogens and acyl groups. In the latter case, β-haloenolates are difficult to handle or are not formed at all due to competition with other reactions of α-haloketones (cf. Favorskii reaction, epoxide formation, nucleophilic substitution, dehydrohalogenation, etc.). The selective conversion of α-haloketones into α-haloimines and subsequent regioselective deprotonation with sterically hindered strong bases offers an attractive synthetic potential by the use of more stable 3-halo-1-azaallylic anions **5** (Scheme 1). α-Haloimines **4** are easily accessible from α-haloaldehydes and α-haloketones by reaction with primary amines in the presence of drying agents such as magnesium sulfate (convenient for most aldehydes) and titanium(IV) chloride, the latter operating as activator of the carbonyl function and chemical remover of water produced during the reaction [2]. Deprotonation of α-haloimines with strong non-nucleophilic bases like lithium diisopropylamide in tetrahydrofuran results in the formation of 3-halo-1-azaallylic anions **5**, which react with electrophiles to produce substituted imines **6**. If functionalized electrophiles like alkyl halides carrying heteroatoms (oxygen, nitrogen, halogen) are used, it results in the formation of highly functionalized imines **6**, which are suitable building blocks for further elaboration. Alternatively, these imines **6** can be hydrolyzed to the corresponding functionalized α-haloaldehydes or α-haloketones **3**. These α-haloaldehydes (**3**; R² = H), α-haloketones (**3**; R² ≠ H), or α-haloimines (**6**) are all suitable building blocks for the synthesis of heterocycles of various kinds.

EWG = COOR', CN, R'C=O, SO$_2$R', S(=O)R', CONR'R", ..
X = halogen, SiR$_3$, SeR', SR', ..
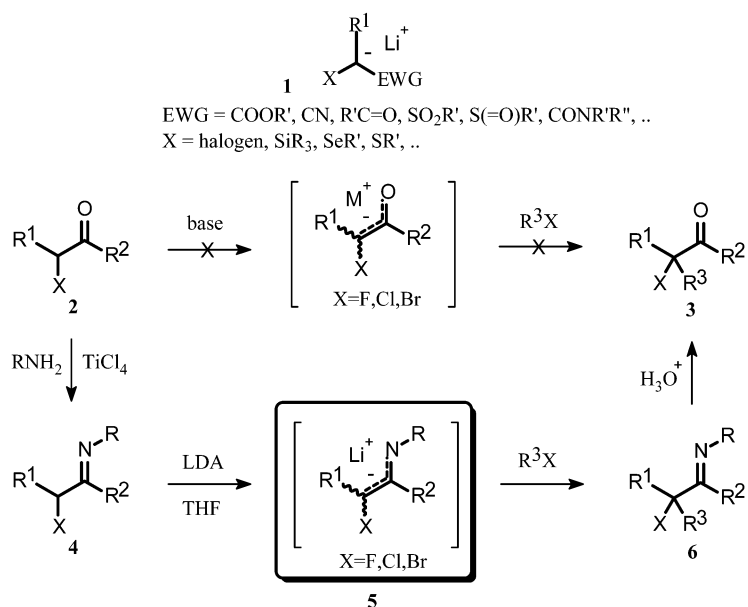
Scheme 1

As such, the detour from α-haloaldehydes or α-haloketones (**2**) to the corresponding functionalized α-haloaldehydes or α-haloketones **3** (R^3 carries the heteroatom functionality) via α-haloimines offers a great potential for the synthesis of a variety of interesting compounds.

Reports so far on the use of 3-halo-1-azaallylic anions have been rather scarce. The reports include alkylations [3], reactions with aldehydes, and ketones [4]. In one case of fluorinated species, temperature-dependent regioselective alkylations to α-fluoroimines could be achieved [5].

Because of the fact that α-haloimines are now available by a whole range of procedures, for example, the imination process of α-haloaldehydes or α-haloketones (vide supra), halogenation of imines with *N*-halosuccinimides [6], retro-aldol cleavage of β-iminoesters [7], hydrodehalogenation of α-bromo-α-chloroimines [8], the title deprotonated species (i.e., 3-halo-1-azaallylic anions) are now easily accessible. The deprotonation with lithium diisopropylamide in THF occurs completely and under mild conditions. It concerns a completely regiospecific reaction. Contrary to the generation of enolates, the formation of 3-halo-1-azaallylic anions proceeds smoothly at 0 °C. Thus, in terms of practical applications, it is important that cooling down to –78 °C is not always necessary, although some reactions with 3-halo-1-azaallylic anions require these low temperatures (vide infra). 3-Halo-1-azaallylic anions are relatively stable at 0 °C and can be kept under these conditions in THF for several hours. In general, 3-bromo-1-azaallylic anions are much less convenient to handle than the corresponding chloro analogs due to their instability. In general, it is recommended to use 3-chloro-1-azaallylic anions in the syntheses described here. These delocalized anions react with alkyl halides exclusively at the β-carbon (*C*-alkylation) while no *N*-alkylation has been observed so far. There is no proton transfer from the diisopropylamine, formed after deprotonation, to the anions generated. Finally, there is no condensation of 3-halo-1-azaallylic anions with the starting imine, with itself or with the end product. In other words, 3-halo-1-azaallylic anions are suitable reagents to be evaluated in organic synthesis.

In the present paper, three distinct topics of the reactivity of 3-halo-1-azaallylic anions will be highlighted. The first part concerns the alkylation with alkyl halides followed by treatment with base and hydrolysis as a three-step synthesis of α,β-unsaturated carbonyl compounds. This method will be applied to the synthesis of the alarm pheromone (*S*)-manicone (*Manica* sp.) and the flavor compound 2-[(methylthio)methyl]-2-butenal. The second part involves the reaction of 3-halo-1-azaallylic anions with alkyl halides that are functionalized with heteroatoms. This extra functionalization in the elec-

trophile allows further reactions to heterocycles, including piperidines, tetrahydropyridines, tetrahydro-furans, pyrrolidines, pyrroles, pyridines, azetidines, aziridines, and tetrahydroindoles. The third topic concerns the reaction of 3-halo-1-azaallylic anions with "HO⁺"-reagents in order to generate α-imino-ketones, which are known as flavor compounds.

RESULTS AND DISCUSSION

The synthesis of (*S*)-manicone **10** (Scheme 2) starts with the deprotonation of α-chloroketimine **4a** with LDA in THF at 0 °C, followed by reaction with (*S*)-1-bromo-2-methylbutane giving (*S*)-α-chloro-ketimine **7** in 97 % yield. Dehydrochlorination of the latter with potassium *t*-butoxide in DMSO at room temperature, and subsequent acid hydrolysis with oxalic acid gave a 83:17 mixture of α,β-unsaturated ketones **8** and **9**. This mixture of products was treated with rhodium(III) chloride in ethanol [9] to form the desired (*S*)-manicone **10** in 97 % yield with an enantiomeric excess of at least 99 % [10].
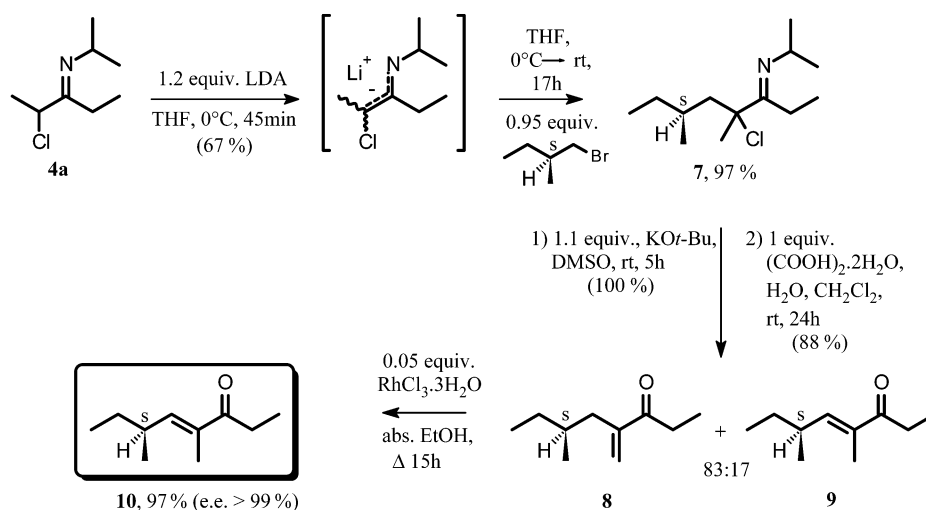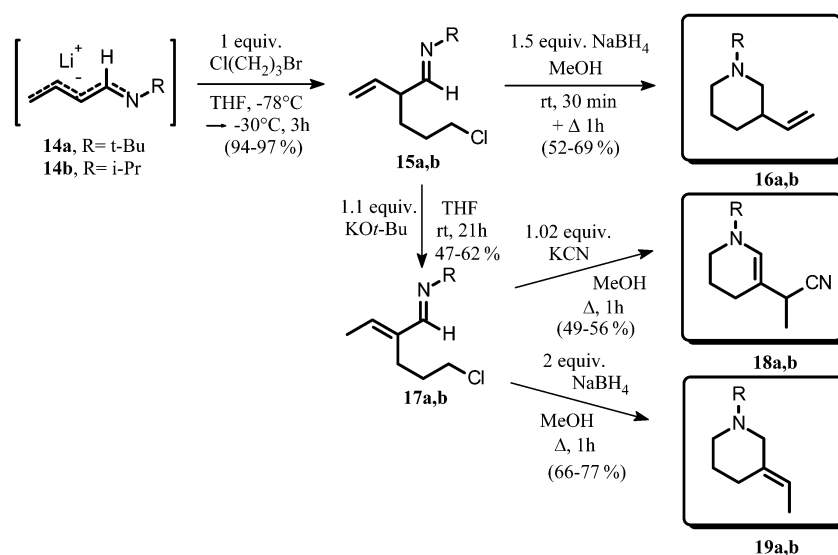

Scheme 2

2-[(Methylthio)methyl]-2-butenal **12** (Scheme 3) is a characteristic flavor compound of potato chips [11], yeast extracts [12], and cocoa [13], while it is a flavoring agent imparting a tomato and meat-
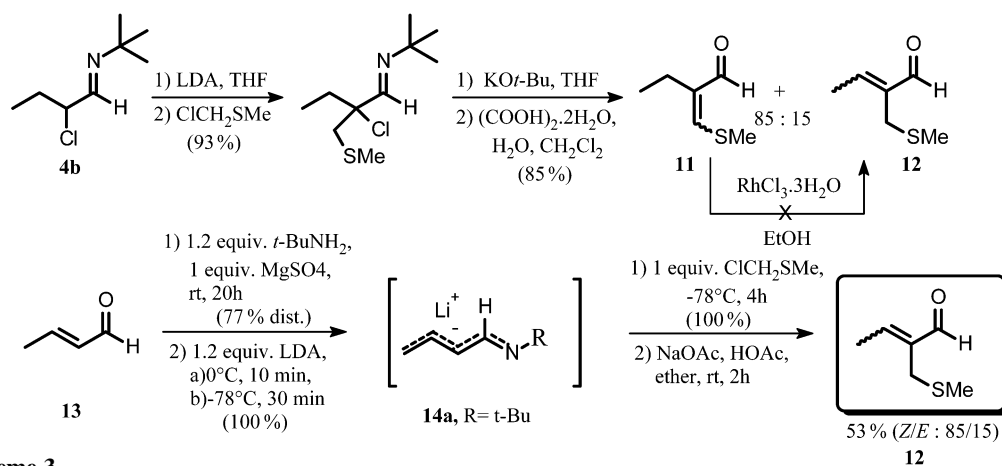
Scheme 3

like flavor [14]. The classic aldol condensation of methional with acetaldehyde results in low yields of impure material [11]. Application of the same protocol as above with α-chloroaldimine **4b** via α-(methylthio)methylation and subsequent dehydrochlorination and hydrolysis, afforded an 85:15 mixture of α,β-unsaturated aldehydes **11** and **12**, the ratio of which could not be changed in favor of the desired flavor compound by rhodium(III) chloride. Therefore, crotonaldehyde **13** was iminated with *t*-butylamine to give the corresponding enimine **20a**, which was deprotonated by LDA at –78 °C to 0 °C in THF to generate the delocalized anion **14a**, which reacted at the expected α-carbon with (chloromethyl)methylsulfide to afford the β-(methylthio)aldimine in quantitative yield. This compound was converted into the flavor compound **12** (*E/Z* 15:85) by sodium acetate in acetic acid in a biphase system with ether [15].

These delocalized anions **14a,b**, being equivalent to 3-halo-1-azaallylic anions, were suitable for the synthesis of piperidines by condensation with 1-bromo-3-chloropropane in THF (Scheme 4). The resulting δ-chloro-α-vinylaldimines **15a,b**, underwent reductive cyclization with sodium borohydride in methanol to 3-vinylpiperidines **16a,b**.
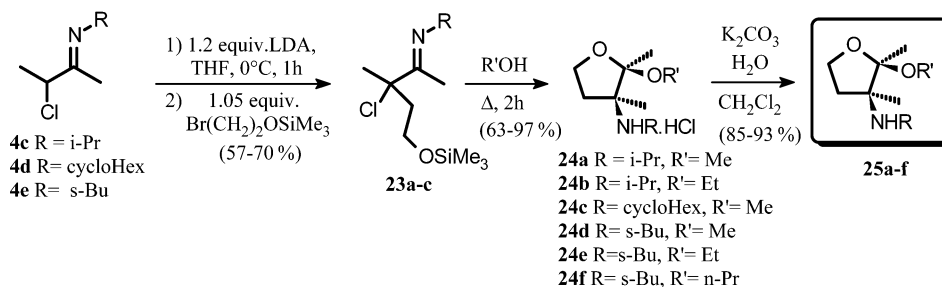

Scheme 4

Base-induced isomerization of **15a,b** to the conjugated imines **17a,b** gave access to tetrahydropyridines **18a,b** and 3-(ethylidene)piperidines **19a,b** (Scheme 4) by reaction with potassium cyanide or sodium borohydride, respectively.

An additional treatment with LDA gave rise to 1,2,3,4-tetrahydro-5-vinylpyridines **21a,b** in virtually quantitative yield. Such electron-rich aminodienes **21a,b** smoothly undergo Diels–Alder cycloaddition with *N*-phenylmaleimide in THF under reflux to provide tricyclic diazaheterocycles **22a,b** (Scheme 5).
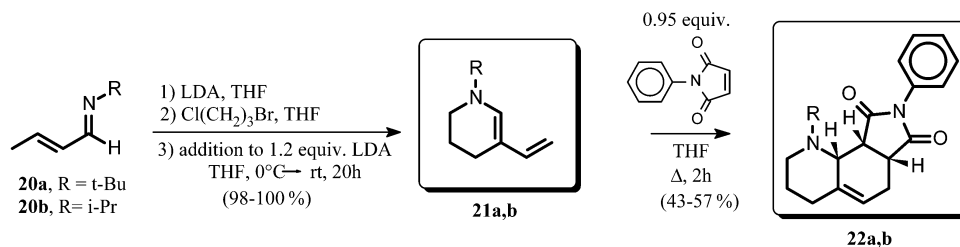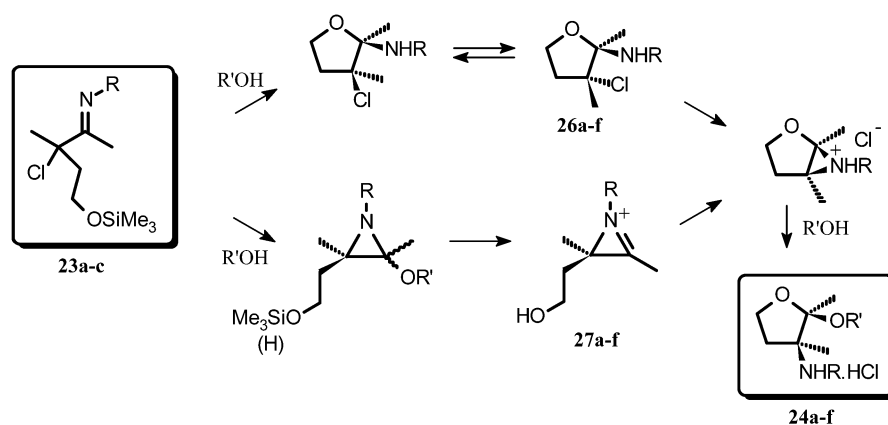

Scheme 5

Regiospecific deprotonation of α-chloroketimines **4c–e** with LDA (Scheme 6), followed by alkylation with 2-bromoethyl trimethylsilyl ether, produced γ-trimethylsilyloxy-α-chloroketimines **23a–c**, which cyclized with alcohols to afford *cis*-2-alkoxy-3-aminotetrahydrofurans **25a–f** in a stereospecific way after treatment with base. The mechanism was explained in terms of two possible routes involving either a *trans*-2-amino-3-chlorotetrahydrofuran **26a–f** (Scheme 7) or intermediate 2-alkoxyaziridines or azirinium ions (**27a–f**). Both routes lead to a bicyclic aziridinium ion, which opens up to the final tetrahydrofurans via a hydrogen bond-guided stereospecific attack of the alcohol to the transient oxonium ion [16].
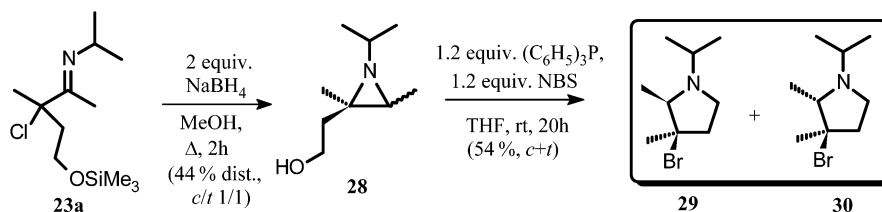

4c R = i-Pr
4d R= cycloHex
4e R= s-Bu

1) 1.2 equiv. LDA, THF, 0 °C, 1h
2) 1.05 equiv. Br(CH₂)₂OSiMe₃ (57–70 %)

23a-c

R'OH Δ, 2h (63–97 %)

24a R = i-Pr, R'= Me
24b R= i-Pr, R'= Et
24c R= cycloHex, R'= Me
24d R= s-Bu, R'= Me
24e R=s-Bu, R'= Et
24f R= s-Bu, R'= n-Pr

K₂CO₃ H₂O CH₂Cl₂ (85–93 %)

25a-f

Scheme 6

23a-c
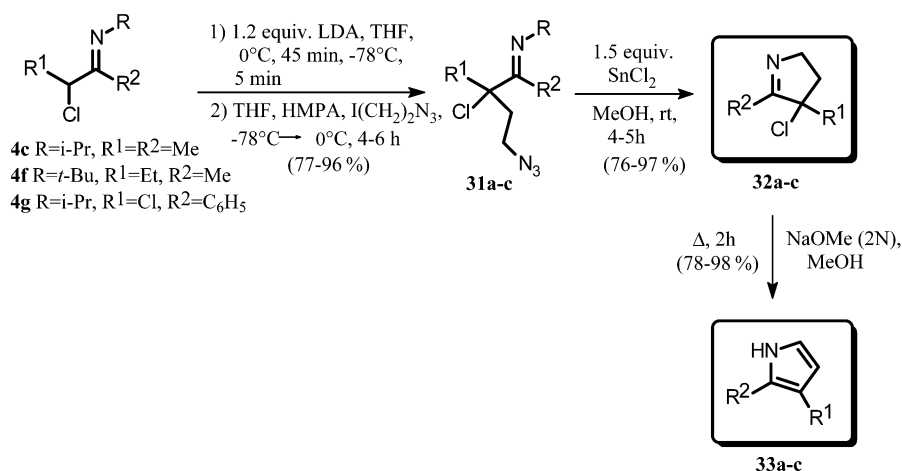
R'OH

26a-f

R'OH

27a-f

R'OH

24a-f

Scheme 7

These γ-trimethylsilyloxy-α-chloroketimines **23** (Scheme 8) are building blocks for the synthesis of aziridines and pyrrolidines. Reaction of imine **23a** with sodium borohydride in methanol affords a 1:1 mixture of *cis*- and *trans*-aziridine **28** by reduction of the imino bond followed by intramolecular nucleophilic substitution. Ring expansion of this aziridine was performed with triphenylphosphine and *N*-bromosuccinimide in THF to give a mixture of *cis*- and *trans*-3-bromopyrrolidines (54 % yield) via the intermediacy of a bicyclic aziridinium ion.
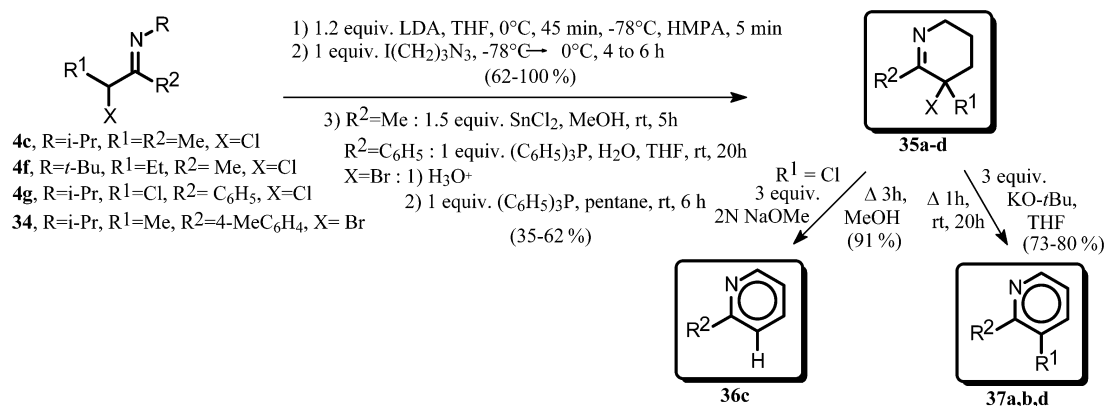

23a

2 equiv. NaBH₄ MeOH, Δ, 2h (44 % dist., c/t 1/1)

28

1.2 equiv. (C₆H₅)₃P, 1.2 equiv. NBS THF, rt, 20h (54 %, c+t)

29   +   **30**

Scheme 8

The introduction of a β-azidoethyl substituent at the α-position of α-chloroketimines **4c,f,g**, requires the addition of HMPA during the alkylation process (Scheme 9). The resulting γ-azido-α-chloroketimines **31a–c** undergo conversion into pyrrolines **32a–c** after reduction of the azido group by tin(II) chloride in methanol. Dehydrochlorination of the chloropyrrolines with sodium methoxide in methanol under reflux afforded pyrroles **33a–c** in excellent yields. This method tolerates the presence of an extra chlorine in the starting imine so as to give rise to 3-chloro-2-arylpyrroles. The latter heterocycles have a great interest in agrochemistry as fungicides, bactericides, and acaricides [17].


4c R=i-Pr, R¹=R²=Me
4f R=t-Bu, R¹=Et, R²=Me
4g R=i-Pr, R¹=Cl, R²=C₆H₅

1) 1.2 equiv. LDA, THF, 0°C, 45 min, -78°C, 5 min
2) THF, HMPA, I(CH₂)₂N₃, -78°C → 0°C, 4-6 h (77-96 %)

31a-c

1.5 equiv. SnCl₂ MeOH, rt, 4-5h (76-97 %)

32a-c

Δ, 2h (78-98 %)　NaOMe (2N), MeOH

33a-c

Scheme 9

Pyridines **36c** and **37a,b,d** were synthesized from α-chloroketimines **4c,f,g** and α-bromoketimine **34** (Scheme 10) in the similar way by the utilization of 3-azido-1-iodopropane [18].


4c, R=i-Pr, R¹=R²=Me, X=Cl
4f, R=t-Bu, R¹=Et, R²= Me, X=Cl
4g, R=i-Pr, R¹=Cl, R²= C₆H₅, X=Cl
34, R=i-Pr, R¹=Me, R²=4-MeC₆H₄, X= Br

1) 1.2 equiv. LDA, THF, 0°C, 45 min, -78°C, HMPA, 5 min
2) 1 equiv. I(CH₂)₃N₃, -78°C → 0°C, 4 to 6 h (62-100 %)
3) R²=Me : 1.5 equiv. SnCl₂, MeOH, rt, 5h
R²=C₆H₅ : 1 equiv. (C₆H₅)₃P, H₂O, THF, rt, 20h
X=Br : 1) H₃O⁺
2) 1 equiv. (C₆H₅)₃P, pentane, rt, 6 h (35-62 %)

35a-d

R¹ = Cl
3 equiv.
2N NaOMe

Δ 3h, MeOH (91 %)

Δ 1h, rt, 20h

3 equiv. KO-tBu, THF (73-80 %)

36c

37a,b,d

Scheme 10

3,3-Dichloro-1-azaallylic anions, derived from α,α-dichloroketimines **4g,h** by deprotonation with LDA, undergo an aldol reaction with aromatic aldehydes to give adducts, which, upon activation as mesylates, are conveniently converted into *cis*-3,3-dichloroazetidines **39a–c** and **40a–c** [19] by reaction with sodium borohydride or potassium cyanide (Scheme 11). The stereospecific formation of *cis*-azetidines **39a–c** and **40a–c** is explained by an Evans-type model of transition state, favoring the attack of the imino bond to occur from the site most remote from the larger substituent (Scheme 12).
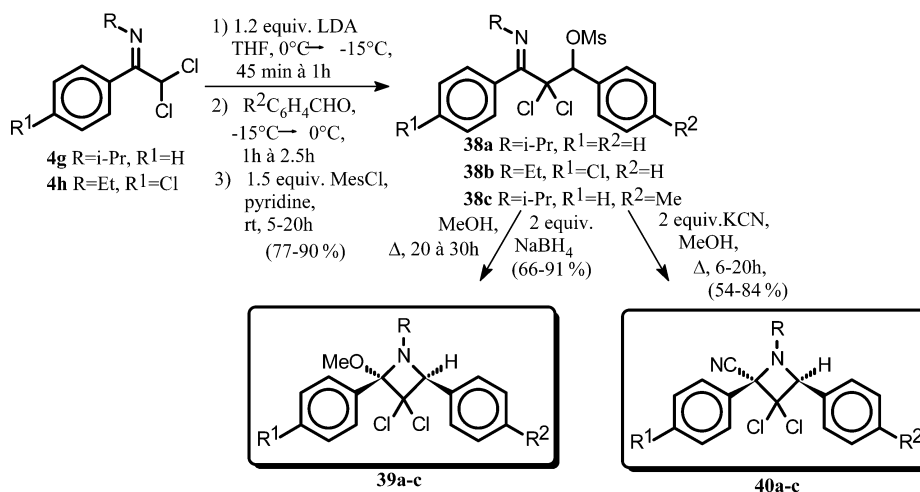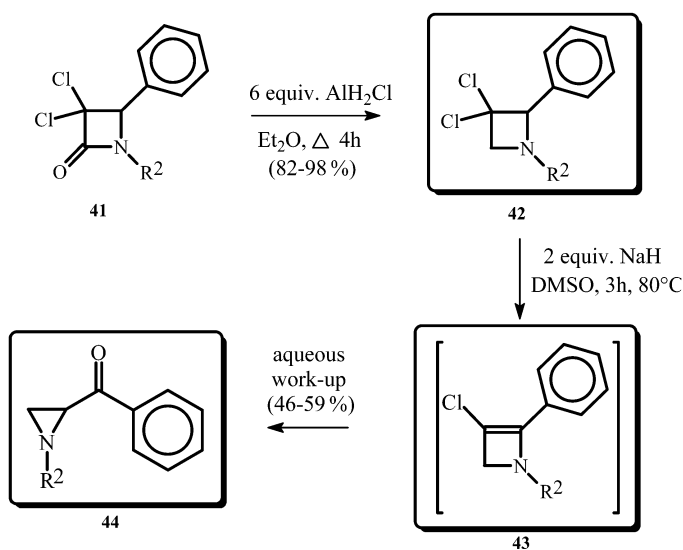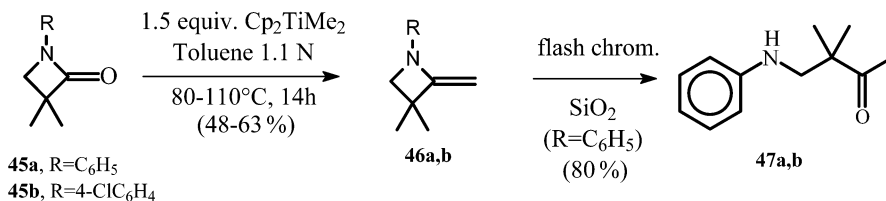
Scheme 11
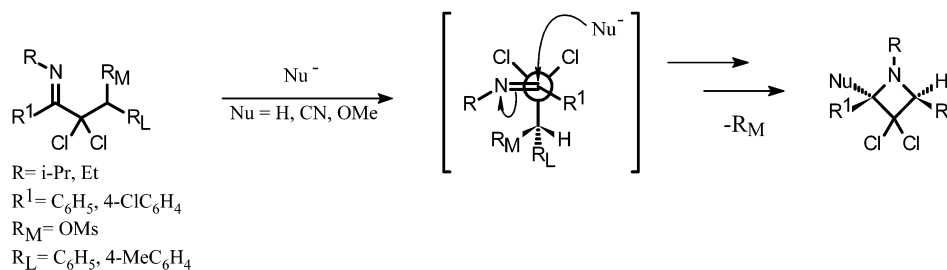
Scheme 12

An alternative synthesis of 3,3-dichloroazetidines consists of the reduction of 3,3-dichloroaze-tidin-2-ones (**41**, Scheme 13) with chloroalane in ether under reflux [20]. These 3,3-dichloroazetidines **42** are convertible into 2-azetines **43**, which suffer a rearrangement during aqueous work-up to 2-benzo-ylaziridines [20].
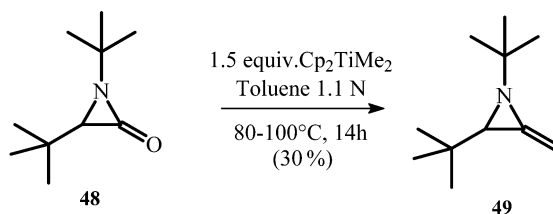

Scheme 13

2-Azetines **43** are very strained endocyclic enamines in a four-membered ring system. Another type of strained enamine in a four-membered ring is the exocyclic enamine **46a,b** (Scheme 14). A previous synthesis of such α-methylene azetidine **46a,b** proceeded by base-induced cyclization of β-chloroimines [21]. Another approach involves the reaction of β-lactams **45a,b** with dimethyl-titanocene in toluene [22]. Such methylenation of strained lactams is also possible with α-lactams **48**, but the yield of 2-methyleneaziridine **49** is only 30 % (Scheme 15) [23].
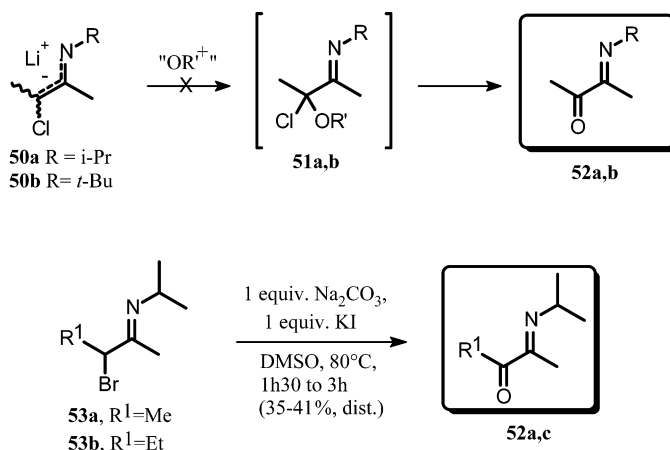

45a, R=C$_6$H$_5$
45b, R=4-ClC$_6$H$_4$

46a,b

47a,b

Scheme 14

48

49

Scheme 15

In theory, it should be possible to react 3-halo-1-azaallylic anions **50a,b** with a "OR'$^+$"-species in order to give rise to α-chloro-α-alkoxyketimines **51a,b**, which should convert to α-iminoketones **52a,b**. The latter compounds hold the very important α-iminoketo-functionality, which is essential for cracker flavor characteristics [24]. As such, these α-iminoketones **52a–c** are potential flavorants (Scheme 16). All attempts to put this idea in a useful reaction failed completely due to the fact that 3-halo-1-azaallylic anions **50a,b** are not compatible with the oxidizing behavior of the reagents used. Oxidizing reagents such as dimethyldioxirane, bistrimethylsilylperoxide, benzoylperoxide/K$_2$CO$_3$, MoO$_5$.Pyridine.HMPA (MoOPH) and 2-benzenesulfonyl-3-phenyloxaziridine did not give any suitable reaction as only tars were obtained under a variety of conditions. However, α-bromoketimines **53a,b** could be converted in

50a R = i-Pr
50b R= t-Bu

51a,b

52a,b

53a, R^1=Me
53b. R^1=Et

1 equiv. Na$_2$CO$_3$,
1 equiv. KI

DMSO, 80°C,
1h30 to 3h
(35-41%, dist.)

52a,c

Scheme 16

the desired α-iminoketones **52a**,**c** by a Kornblum-type reaction with sodium carbonate in DMSO in the presence of potassium iodide at 80 °C.

In summary, lithio 3-halo-1-azaallylic anions **5** have been proven to be suitable building blocks for organic synthesis. The protocol of regiospecific deprotonation of α-haloketimines, subsequent reaction of 3-halo-1-azaallylic anions **5** with functionalized electrophiles, and cyclization of the resulting functionalized α-haloketimines **6** proved to be a suitable method for the construction of a whole variety of heterocyclic compounds, including aziridines, azetidines, pyrrolidines, piperidines, pyrroles, pyridines, indoles, etc.

ACKNOWLEDGMENTS

REFERENCES

1. A. Krief. *Tetrahedron* **36**, 2531 (1980).
2. (a) H. Weingarten, J. P. Chupp, W. A. White. *J. Org. Chem.* **32**, 3246 (1967); (b) N. De Kimpe, R. Verhé, L. De Buyck, L. Moens, N. Schamp. *Synthesis* **22**, 43 (1982).
3. (a) L. Duhamel and J. Y. Valnot. *Tetrahedron Lett.* **35**, 3319 (1979); (b) N. De Kimpe, P. Sulmon, N. Schamp. *Angew. Chem.* **97**, 878 (1985).
4. P. Sulmon, N. De Kimpe, N. Schamp. *J. Org. Chem.* **53**, 4457 (1988).
5. J. T. Welch and K. V. Seper. *J. Org. Chem.* **53**, 2991 (1988).
6. (a) N. De Kimpe and N. Schamp. *Org. Prep. Proced. Int.* **11**, 115 (1979); (b) J. F. W. Keana and K. R. Schumaker. *Tetrahedron* **26**, 5191 (1970); (c) N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp. *Bull. Soc. Chim. Belg.* **84**, 417 (1975); (d) N. De Kimpe, R. Verhé, L. De Buyck, Sunari Tukiman, N. Schamp. *Tetrahedron* **35**, 789 (1979).
7. N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp. *Tetrahedron* **26**, 2709 (1985).
8. W. Aelterman, A. Eeckhaut, N. De Kimpe. *Synlett* **9**, 1283 (2000).
9. (a) P. A. Grieco, M. Nishizawa, N. Marinovic, W. J. Ehmann. *J. Am. Chem. Soc.* **98**, 7102 (1976); (b) D. F. Taber and B. P. Gunn. *J. Org. Chem.* **44**, 450 (1979); (c) H. J. Bestmann, A. B. Attygalle, J. Glasbrenner, R. Riemer, O. Vostrowsky. *Angew. Chem., Int. Ed. Engl.* **26**, 784 (1987); (d) H. J. Bestmann, A. B. Attygalle, J. Glasbrenner, R. Riemer, O. Vostrowsky, M. E. Costantino, G. Melikyan, E. D. Morgan. *Liebigs Ann. Chem.* 55 (1988).
10. N. De Kimpe and W. Aelterman. *Tetrahedron* **52**, 12815 (1996).
11. R. G. Buttery. *J. Agric. Food Chem.* **21**, 31 (1973).
12. (a) P. Werkhoff, W. Bretschneider, R. Emberger, M. Guentert, R. Hopp, M. Koepsel. *Chem. Mikrobiol. Technol. Lebensm.* **13**, 30 (1991); (b) *Chem. Abstr.* **115**, 7192r (1991).
13. W. Baltes. In *Lebensmittelchemie*, 3rd ed., p. 277, Springer Verlag, Berlin (1992).
14. (a) T. Yanai, A. Furuhata, H. Sakakibara, K. Kojo. *Jpn. Kokai Tokkyo Koho.* JP 60, 136, 55, 3, (C1.C07C149/14), 20 July 1985; (b) *Chem. Abstr.* **104**, 50077s (1986).
15. N. De Kimpe and W. Aelterman. *J. Agric. Food Chem.* **44**, 3598 (1996).
16. N. De Kimpe, W. Aelterman, K. De Geyter, J. P. Declercq. *J. Org. Chem.* **62**, 5138 (1997).
17. N. De Kimpe, K. Abbaspour Tehrani, C. Stevens, P. De Cooman. *Tetrahedron* **53**, 3693 (1997).
18. W. Aelterman, N. De Kimpe, V. Tyvorskii, O. Kulinkovich. *J. Org. Chem.* **66**, 53 (2001).
19. W. Aelterman and N. De Kimpe. *J. Org. Chem.* **63**, 6 (1998).
20. Y. Dejaegher, S. Mangelinckx, N. De Kimpe. *J. Org. Chem.* **67**, 2075 (2002).
21. P. Sulmon, N. De Kimpe, N. Schamp. *J. Org. Chem.* **63**, 4462 (1998).
22. (a) K. Abbaspour Tehrani and N. De Kimpe. *Tetrahedron Lett.* **41**, 1975 (2000); (b) N. De Kimpe and M. Boeykens. *J. Org. Chem.* **59**, 5189 (1994).

23. W. Aelterman. Ph.D. thesis, Ghent University, Ghent, Belgium, p. 84 (1998).
24. (a) W. Aelterman, N. De Kimpe, O. Kulinkovich. *Bull. Soc. Chim. Belg.* **106**, 703 (1997); (b) J. Demyttenaere, K. Abbaspour Tehrani, N. De Kimpe. *ACS Symposium Series* **826**, 150 (2002).