Review

Synthesis of Substituted α-Trifluoromethyl Piperidinic Derivatives

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Abstract: A comprehensive survey of pathways leading to the generation of α-trifluoromethyl monocyclic piperidinic derivatives is provided (65 references). These compounds have been synthesized either from 6-membered rings e.g., pipecolic acid or lactam derivatives by introduction a trifluoromethyl group, from pyridine or pyridinone derivatives by reduction, and from 5-membered rings e.g., prolinol derivatives by ring expansion, from linear amines by cyclization or from dienes/dienophiles by [4 + 2]-cycloaddition.

Keywords: nitrogen heterocycles; fluorine; piperidine; trifluoromethyl group; ring expansion; cyclization; cycloaddition

1. Introduction

Functionalized piperidinic derivatives are among the most ubiquitous heterocyclic cores in natural products and bioactive compounds, therefore a huge number of methods has been developed to prepare piperidinic derivatives [1–7]. With respect to the biologically active targets, there is great interest in introducing substituents that can increase their biological activity which can be related to an increase of the lipophilicity, the bioavailability and the metabolic stability. In this context, the trifluoromethyl group is often used as a bioisostere of a chloride or a methyl group to modulate the steric and electronic properties of a lead compound or to protect a reactive methyl group from metabolic oxidation. This substituent can also increase the lipophilicity of molecules [8].

Scheme 1. Precursors of α-trifluoromethyl piperidinic derivatives.
Herein, we report the synthesis of α-trifluoromethylpiperidinic derivatives of type A. These compounds have been synthesized either from 6-membered rings B and C by introduction of a CF$_3$ group, from pyridines D or pyridinones E by reduction, from 5-membered rings F by ring expansion, from linear amines G by cyclization, from dienes/dienophiles H/I by cycloaddition (Scheme 1). We will only report the formation of monocyclic piperidinic derivatives, and of bicyclic derivatives only when they were transformed into the monocyclic derivatives.

2. From Cyclic Substrates

2.1. From 6-Membered Rings

The synthesis of α-trifluoromethylpiperidines A has been achieved from pipecolic acid, from δ-lactams, from pyridines and from pyridinones.

2.1.1. From Pipecolic Acid

The first synthesis of 2-(trifluoromethyl)piperidine (2) was realized in 1962 by Raash [9], from the sodium salt of pipecolic acid (1) that was treated with sulfur tetrafluoride (SF$_4$) in the presence of HF at 120 °C. However, 2 was isolated in a very low yield of 9.6% (Scheme 2).

$$\text{O} \quad \text{N} \quad \text{CF}_3$$

Scheme 2. Synthesis of 2-trifluoromethyl piperidine from pipecolic acid.

2.1.2. From 2-Trifluoromethylpyridine

One easy access to 2-trifluoromethylpiperidine (2) was realized by hydrogenation of the commercially available 2-trifluoromethylpyridine (3) in the presence of Pd, Pt or Rh catalysts (Scheme 3) [10–12].

Scheme 3. Hydrogenation of α-trifluoromethylpyridine.

2.1.3. From Trifluoromethyl Pyridinones

Access to trifluoromethylpiperidinones 5 from trifluoromethylpyridinones 4 has been developed by hydrogenation in the presence of Pd/C. Lactams 5 were isolated in 45%–88% yield and subsequent reduction should lead to the 5-amino 2-trifluoromethylpiperidines 6 (Scheme 4) [13].

Scheme 4. Hydrogenation of trifluoromethylpyridinones.
2.1.4. From δ-Lactams

Since the first access to 2-trifluoromethylpiperidine (2) different methods have been developed to produce α-trifluoromethylpiperidines of type A from δ-lactams C via either enamines C1, or imines C2 or C3 (Scheme 5).

![Scheme 5. Synthesis of α-trifluoromethylpiperidines from δ-lactams.](image)

From Enamines C1

α-Trifluoromethyl cyclic enamines C1 can be good precursors of A as they are easily obtained from δ-lactams. When lactam 7 was treated with trichloroborane in the presence of an excess of CF3Br and HEPT, enamine 8 was formed in 30% yield via the formation of iminium species I which can be attacked by the CF3⁻ anion, generated from CF3Br. Intermediate II was thus produced and after a β-elimination, enamine 8 was formed (Scheme 6) [14]. A reduction of this enamine should lead to 2-trifluoromethylpiperidine 9. It is worth noting that CF3Br is not easy to handle as it is a gas and alternatives to synthesize 2-trifluoromethylpiperidines from δ-lactams from imines C2 and C3 have been devised.

![Scheme 6. Synthesis of α-trifluoromethylpiperidine from δ-lactam via enamine.](image)

From Imines C2

Imines of type C2 were synthesized in four steps from N-(diethoxymethyl)piperidin-2-one (10). First, 10 was subjected to a Claisen condensation with ethyl trifluoroacetate (NaH, CF3CO2Et) and,
after deprotection under acidic conditions (HCl), the corresponding fluorinated acyl lactam 11 was isolated as the hydrate, due to the ability of the electron-withdrawing CF$_3$ group to stabilize the tetrahedral adducts of such type of compounds [15].

The hydrolysis and the decarboxylation of perfluoro acyl lactam 11 under acidic conditions (6 M HCl) and heating at reflux led to III. When the decarboxylation was complete, the reaction was carefully made alkaline with KOH and hemiaminal 12 was obtained. After azeotropic removal of water or distillation, 12 was transformed into imine 13 (Scheme 7) [15].

![Scheme 7. Synthesis of α-trifluoromethylpiperidine from δ-lactam via imine.](image)

Imine 13 can be involved in a variety of reactions such as reduction, phosphorylation, alkylation under Friedel-Craft conditions, and Ugi-type reactions, producing a diversity of α-trifluoromethyl piperidinic derivatives. Imine 13 was transformed to 2-trifluoromethylpiperidine (2) in a yield of 71% by reduction with NaBH(OAc)$_3$ in MeOH (Scheme 8) [15].

![Scheme 8. Synthesis of α-trifluoromethylpiperidine from an imine by reduction.](image)

When 13 was treated with diethyl phosphite in the presence of boron trifluoride etherate (BF$_3$OEt$_2$) as the catalyst, 2-(trifluoromethyl)-2-ethylphosphonate piperidine (14) was obtained (92%) and easily transformed to the corresponding α-trifluoromethyl substituted cyclic α-aminophosphonic acid 15 by treatment with trimethylbromosilane in CHCl$_3$ followed by the addition of aqueous MeOH. It is worth pointing out that to avoid the formation of the ammonium salt, due to the liberation of HBr during the hydrolysis of the ester, the addition of propylene oxide was necessary and the free amino acid 15 was isolated (Scheme 9) [16].

![Scheme 9. Synthesis of 2-(trifluoromethyl)-2-ethylphosphonate piperidine from imine.](image)
Imine 13 was transformed to the piperidinic derivatives 16 when subjected to an Ugi-type reaction using isocyanides. Thus, when 13 was treated with an isocyanide (RNC) in the presence of CF$_3$CO$_2$H, piperidine 16 was formed via intermediate V (Scheme 10, eq. 1) [17]. It is worth mentioning that an azido-Ugi reaction was performed using isocyanate (RNC) in the presence of TMSN$_3$ in MeOH. Under these conditions, tetrazole 17 was obtained via intermediate VI. In addition, when benzylisocyanate (BnNC) was used, the corresponding piperidyltetrazole (17, R = Bn) was isolated and debenzylated by hydrogenolysis (H$_2$, Pd/C, MeOH) to produce 18 in good yield (96%) (Scheme 10, eq. 2) [18].

If tetrazole can be introduced at the α-position of α-trifluoromethylpiperidyl derivatives, using an Ugi-type reaction, other heterocycles such as pyrroles, indoles can also be introduced in the α-position by using a Friedel-Craft reaction. When imine 13 was treated with the non-protected pyrrole 19 in the presence of BF$_3$·OEt$_2$, the unexpected piperidine 20, possessing a C2-substituted pyrrole was obtained (67%) (Scheme 11, eq. 1). On the contrary, when the N-methylpyrrole 21 was involved in the Friedel-Craft reaction, piperidine 22, substituted in the α-position by the C3-substituted pyrrole, was isolated (Scheme 11, eq. 2). The same regioselectivity at C3 was observed with pyrrole 23. It is worth mentioning that no diastereoselectivity was observed with pyrrole 23 as a ratio of 1 to 1 was observed for 24 (Scheme 11, eq. 3). As noticed, the reaction with non-protected and protected pyrroles is very regioselective. This regioselectivity can be the result of steric interactions between the N-substituent of the pyrrole and the cyclic imine which can be quite significant due to the bulkiness of the trifluoromethyl group and its specific nature and, the C3 isomers were formed. When less steric interactions were present, e.g., with unprotected pyrroles, the C2-isomers were formed (Scheme 11, eq. 1) [19,20].
Indoles such 25 can also be involved in a Friedel-Craft reaction with imine 13 leading to the piperidines 26 in good yield (Scheme 12) [21].

From Imines C3

In imines 13, the CF$_3$ group is initially located in the α-position and then different R substituents can also be introduced in the α-position. From an imine intermediate, the reverse strategy can be used to access compound A, e.g., imines are synthesized from a δ-lactam and then the trifluoromethyl group is introduced. Thus, when imines 27, prepared from the corresponding δ-lactams, were treated with the Ruppert-Prakash reagent (TMSCF$_3$) in the presence of TFA and KHF$_2$, in MeCN, the α,α-disubstituted piperidines 28 were isolated in good yields. The activation of imines 27 under acidic conditions was necessary to obtained piperidines 28 (Scheme 13) [22].

It is worth mentioning that all the 2-trifluoromethylpiperidines were obtained in a racemic form, however, recently, we have reported a method that allows the synthesis of optically active substituted 2-trifluoromethylpiperidines by using a stereospecific ring expansion applied to 2′-trifluoromethylprolinols of type F.
2.2. From 5-Membered Rings

The ring expansion of pyrrolidines to piperidines via an aziridinium intermediate under kinetic and thermodynamic conditions is well-established [23–28]. This method was used to access piperidines 30, 30′ from prolinols 29, 29′.

Prolinols 29 and 29′ were prepared from L-proline in a seven-step sequence [29]. When prolinols 29 and 29′ were treated with DAST, I2/PPh3 or by Tf2O, followed by the addition of different nucleophiles (alcohols, amines, thiols, cuprates, cyanides), a diversity of 2-(trifluoromethyl)-3-substituted piperidines 30 and 30′ were obtained with good diastereo- and enantioselectivities (de > 94% and ee > 99%). The regioselective attack of the nucleophiles on the aziridinium intermediates VII/VII′ is due to the presence of the CF3 group (Scheme 14) [29,30].

Scheme 14. Synthesis of C3-substituted α-trifluoromethylpiperidines from L-proline.

3. From Non-cyclic Substrates

To synthesize 2-trifluoromethyl-substituted piperidines from non-cyclic substrates, a cyclisation step or a cycloaddition is necessary to access the piperidine skeleton.
3.1. Cyclization

3.1.1. By Metathesis

Metathesis reactions have changed the way molecules are constructed due to the commercialization of robust catalysts such as the Grubbs first and second generation catalysts, G-I and G-II, and the Grubbs-Hoveyda catalysts GH-II (Figure 1). Metathesis is a powerful method to access both carbo- and heterocyclic ring systems [31–35] and the reaction is useful to synthesize piperidines and particularly to synthesize 2-trifluoromethylpiperidinic derivatives.

![Catalysts for olefin metathesis.](image)

From Dienes

The ammonium salt of the 2-trifluoromethylpiperidine 2·HCl was formed from 36, which was obtained from the α-trifluoroaminodiene 35 when treated with G-I. This diene has been synthesized in six steps from the hemiacetal 31 which was transformed into imine 32 by treatment with the imine of benzophenone followed by a silylation step (ImSiMe₃). After an allylation under acidic conditions (allylTMS, BF₃·OEt₂), followed by a deprotection/protection sequence, the allyltrimfluoroamine 34 was isolated and allylated to produce the piperidinic core precursor 35. Thus, after treatment of 35 with G-I catalyst (1 mol %) in dichloromethane at rt, the unsaturated piperidine 36 was isolated in 91% yield. After hydrogenation (Pd/C, EtOH, rt, 24 h) and treatment with HCl, 2·HCl was isolated quantitatively (Scheme 15) [36,37]. Compared to the synthesis of 2 from piperolic acid the synthesis of 2 from 31 is more efficient in terms of yield (47.9% versus 9.6%).

![Synthesis of α-trifluoromethylpiperidine from trifluoromethylhemiacetal.](image)
A shorter synthesis of unsaturated piperidines from imines 37 using a Barbier-type reaction (allylBr, Zn, DMF, rt) followed by a N-allylation has been reported. The resulting dienic amino compound 38 was isolated in good yield. After treatment with G-I (5–10 mol %) the unsaturated piperidines 39 were isolated (Scheme 16) [38].

**Scheme 16.** Synthesis of α-trifluoromethylpiperidines from trifluoromethyliminines.

Starting from imines, the strategy is very versatile to access a variety of unsaturated piperidines and, particularly, 2-(trifluoromethyl)-2-substituted tetrahydropyridines. Thus, when imines 40 were treated with allylmagnesium bromide (THF, –78 °C) then allylated (NaH, allylbromide) dienes 42 were isolated in good yields and then involved in a ring-closing metathesis (RCM) using different catalysts such as G-I or the ruthenium catalyst J [39]. It is worth noting that the yields obtained with G-I are better than with catalyst J (Scheme 17) [40–43].

**Scheme 17.** Synthesis of α,α-disubstituted unsaturated piperidines from trifluoromethyliminines.

It is worth noting that the dienes, precursors of 2-(trifluoromethyl)-unsaturated piperidines, could be synthesized from trifluorodiacyl derivatives 44. Treatment of N,N-diallyl-N-methyamine by the diazo compound 44 in the presence of the copper catalyst [Cu(F3-acac)2], produced ylide VIII which, after a [2,3]-sigmatropic rearrangement, led to the dienic derivatives 45, precursor of the unsaturated piperidines 46 (Scheme 18) [43].

When the ring-opening metathesis (ROM)/ring-closing metathesis (RCM) was applied to 47, using the G-I catalyst (10 mol %), the unsaturated piperidines 48, substituted at C4, were isolated in good yields (74–86%) (Scheme 19) [44].
piperidines substituted at C5 can be produced by applying a RCM to enyne treated with G-I (10 mol %) the resulting unsaturated piperidine was obtained with an excellent yield (95%) (Scheme 20, eq 1). On the contrary, 2-(trifluoromethyl) unsaturated piperidines substituted at C5 can be produced by applying a RCM to enyne 49 (Scheme 20, eq 1). When this latter was treated with G-I (5 mol %) the resulting unsaturated piperidine 50 was obtained with an excellent yield (95%) (Scheme 20, eq 2).

It is worth noting that a substituent at C4 could not be introduced on the piperidinic core by using a RCM applied to enyne 49 (Scheme 20, eq 1). On the contrary, 2-(trifluoromethyl) unsaturated piperidines substituted at C5 can be produced by applying a RCM to enyne 51. When this latter was treated with G-I (5 mol %) the resulting unsaturated piperidine 52 was obtained with an excellent yield (95%) (Scheme 20, eq 2).

From Enynes

Scheme 18. Synthesis of α,α-disubstituted piperidines from trifluorodiazo derivatives.

Scheme 19. Synthesis of α-trifluoromethylpiperidines using a ROM/RCM sequence.

Scheme 20. Cont.
The alkyne can be substituted by different alkyl groups (compound 53), aryl groups (compound 55) and ketone (compound 57). In all cases, the corresponding unsaturated piperidinic compounds substituted at C5, were isolated in good yields (Scheme 20, eqs. 3, 4 and 5) [37,38,45]. It is worth mentioning that in the case of 55, when the aryl group is substituted in the para position the yields in 56 are good (60%–74%). On the contrary, when the aryl group is substituted in the ortho position, 55 is not transformed into 56 whatever the catalyst used, either the G-II or the GH-II catalysts [45].

3.1.2. By Cycloaddition

Only the cycloadditions leading to the monocyclic piperidinic core will be reported thus, the [2 + 2]-cycloaddition of allenynes [46] and the Paulson-Khan reaction [38,43,47] will be excluded.

[4 + 2]-Cycloaddition: Aza Diels-Alder

If imines are used as dienophiles, activation of the imine moiety either by electron-withdrawing substituents or by a Lewis acid is required for a successful [4 + 2]-cycloaddition. Imines 59, possessing three electron-withdrawing groups, are very reactive and the aza Diels-Alder reaction was achieved at low temperature in the presence of different dienes 60, to produce the corresponding unsaturated piperidines 61 in good yields. It is worth mentioning that phosphonylimines were less reactive than sulfonylimines as the reaction has to be performed at higher temperature and longer reaction times were required (120 h for phosphonylimines versus 14 h for sulfonylimines) (Table 1) [48].

When the silyloxydiene 62 was involved in the aza Diels-Alder reaction, piperidinone 63 was isolated after acidic treatment (Scheme 21) [48].
Aza Diels-Alder Reaction with 1-Azadiene

The unsaturated piperidine 67 was obtained from an aza Diels-Alder reaction between the iso-butyl vinyl ether 66 and the sulfinimine intermediates IX generated in situ from the trifluoromethyl α,β-unsaturated ketone 64 and the sulfinamide 65. In this aza Diels-Alder reaction, the HOMO orbital of 66 reacts with the LUMO orbital of the azadienes IX. The trifluoromethyl-piperidines 67 were obtained with a good diastereoselectivity in favor of the endo product. In addition, when the reaction was performed with an optically active sulfinamide, the cycloadduct was obtained with a good enantioselectivity (ee > 99%) (Scheme 22) [49].

Scheme 22. Aza Diels-Alder reaction with 1-azadienes.
3.1.3. 1,4-Addition: Aza-Michael

A Michael acceptor, tethered to a nucleophilic amine, can undergo an intramolecular 1,4-addition with concomitant formation of a piperidinic core. After the preparation of the optically active ω-amino α,β-unsaturated ketone 70 in three steps from the trifluoromethylhemiacetal 68, the aminoketone 70 was treated under basic conditions to produce the 2-trifluoromethyl-substituted piperidine 71 in 80% yield and with an excellent diastereoselectivity of 94:6 in favor of the cis-isomer. This piperidine was transformed to an analog of pinidinol (Scheme 23) [50].

![Scheme 23. Synthesis of α-trifluoromethylpiperidine by aza-Michael addition.](image)

2-Trifluoromethylpiperidines with a quaternary center at C2 were synthesized from hemiaminal 72 and an α,β-unsaturated ketone 73 in the presence of a chiral amine ((25,3S)-2-amino-N-((S)-1-hydroxy-3-phenyl-propan-2-yl)-3-methyl-pentanamide) under acidic conditions [para-nitrobenzoic acid (PNBA)]. Hemiaminal 72 reacts with the chiral amine to form intermediate 74 which then reacts with the enolized form of 73 to produce intermediate 75. An intramolecular aza-Michael reaction then occurs and the tricyclic compounds 76 were isolated in good yields and with excellent dr(s) and ee(s). After reduction of the ketone (NaBH₄) and cleavage of the C–S and N–S bonds (sodium naphthalide), piperidine 77 (R¹ = Ph) was isolated with a good enantiomeric excess (ee = 92%) (Scheme 24) [51].

![Scheme 24. Synthesis of chiral α-trifluoromethylpiperidines.](image)
3.1.4. Electrophilic-Induced Cyclization

Amino-iodo cyclization has been used to prepare 2-trifluoromethylpipericolic acid derivatives starting from the ω-unsaturated imine 78. The transformation of 79 to 80 was realized in a one-pot process with an excellent yield of 80%. After treatment of imine 78 with iodine in the presence of NaH, the bicyclic product 79 was formed and, when reacted with I₂, a migration of the CF₃ group took place leading to the diiodo derivative 80 via an iminium alcololate intermediate XI. The bicyclic compound 80 was then transformed into a variety of 2-trifluoromethylpipericolic acid derivatives 81 in a few steps (Scheme 25) [52,53].

![Scheme 25. Synthesis of α-trifluoromethylpipericolic acid derivatives.](image)

If in the electrophilic-induced cyclization of ω-aminoalkenes the CF₃ group was present in the starting material, on the contrary, in the electrophilic-induced cyclization of ω-amino alkynes the CF₃ was introduced after the cyclization.

When the ω-amino alkynes 82 were treated with AgF in the presence of H₂O, a hydroamination takes place to produce the enamino intermediate XII, which was reacted with TMSCF₃ to produce 2-trifluoromethylpipericidines 83 with excellent yields (88%–92%) (Scheme 26) [54].

![Scheme 26. Synthesis of α-trifluoromethylpipericidines by electrophilic-induced cyclization.](image)

3.1.5. Nucleophilic Attack of Iminium Ions

In reaction where iminium ions are involved, the iminium ion is attacked by a nucleophile such as in a Mannich type reaction and a Prins cyclization. A diastereoselective synthesis of 2-trifluoromethylpipericidines was realized by using an intramolecular Mannich reaction starting from the trifluoromethyl amine 84. After condensation of the latter with aldehydes, the formed imines
85 were transformed to the iminium intermediates XIII under acidic conditions (p-TsOH, refluxing toluene). A cyclization is taking place to produce the 2-trifluoromethylpiperidinic derivatives 86. The diastereoselectivity can be explained by the six-membered ring chair transition states XIV, in which the steric interactions are minimized (Scheme 27) [55-57].

Scheme 27. Synthesis of α-trifluoromethylpiperidines by an intramolecular Mannich reaction.

A silyl-aza-Prins reaction was also used to prepare highly functionalized 2-trifluoromethylpiperidines. Treatment of the vinyl silyl trifluoromethyl amine 87 with ethyl glyoxylate in the presence of InCl3 led to 88 via the iminium intermediate XV. After an intramolecular attack of the iminium XV by the vinyl silane, intermediate XVI was formed, a desilylation took place and piperidine 88 was isolated in 65% yield. This piperidine can then be transformed to the highly functionalized 2-trifluoromethylpiperidine 89 (Scheme 28) [58].

Scheme 28. Synthesis of an α-trifluoromethylpiperidine by a silyl-aza-Prins reaction.

3.1.6. Intramolecular Condensation of Aminoketones and Aminoesters

Intramolecular lactamization and hemiaminalization were used to build up the C–N bond of the 2-trifluoromethylpiperidinonic derivatives. 2-Trifluoromethyl lactam 93, which can lead to the corresponding piperidine by reduction, was synthesized in three steps from ketoester 90. After treatment of 90 with aniline (p-TsOH, toluene, reflux), imine 91 was reduced to the δ-aminoester 92 which was cyclized to the corresponding lactam 93 under basic conditions (NaH, THF) (Scheme 29) [59].
The α-substituted trifluoromethyl-δ-lactam 96 was prepared from the α-trifluoromethyl nitrosulfinamine 94, prepared in two steps from trifluoromethylhemiacetal 68. After a 1,4-addition of 94 to ethyl acrylate under basic conditions, the resulting aminoester 95 was treated with TFA to produce, after deprotection (NH₃, MeOH), the trifluoromethyl-δ-lactam 96 (Scheme 30) [60].

A lactamization was also utilized to access 2-trifluoromethyl-3-hydroxypiperidine 102. The latter was synthesized from aldimine 97 and the 2-trimethylsilyloxyfuran 98, and transformed into the unsaturated lactone 99 after treatment with TBSOTf. After hydrogenation, the obtained lactone 100 was transformed to the δ-lactam 101 under acidic conditions (H₂SO₄, 80%), and then to the 2,3-disubstituted piperidine 102 by reduction (LiAlH₄, AlCl₃) (Scheme 31) [61].
Due to the high reactivity of trifluoromethyl ketones they can be attacked by weak nucleophiles such as amines to form a hemiaminal. When the carboxylic trifluoromethyl ketones were treated with ammonium carbonate in refluxing toluene, the six-membered ring hemiaminal intermediates were formed and dehydrated under acidic conditions (p-TsOH, reflux) to furnish the unsaturated lactams (Scheme 32) [62].

Highly substituted 2-trifluoromethylpiperidines 112 were obtained from isoxazoles 106, trifluoromethylketoster 107, aldehydes 108 and ammonium acetate in ethanol. In this multicomponent reaction, isoxazoles 106 react with the enolized β-ketoester 107, to form intermediates 109 which can react with imines 110 (obtained by condensation of aldehydes 108 with NH₄OAc) to produce the aminotrifluoromethylketones 111. The intramolecular attack of the amino group to the highly reactive trifluoromethylketones led to the trifluoromethylpiperidines 112 (Scheme 33) [63].
3.1.7. Intramolecular Nucleophilic Substitution

The intramolecular nucleophilic displacement of a good leaving group by an amine is one of the most common methods to prepare six-membered nitrogen heterocycles. This method was used to synthesize 2-trifluoromethylpiperidines 114 from the highly reactive aziridines 113. The high reactivity of 113 is due to the presence of the trifluoromethyl group and the N-tosyl group. The attack of aziridine 113 by a variety of nucleophiles was very regioselective and produced intermediates XVII that cyclized according to an intramolecular nucleophilic substitution of the chloride to produce 114 (Scheme 34) [64].

\[
\text{Cl} \quad \text{Ts} \quad \text{N} \quad \text{CF}_3
\]

\[
\text{Nu} = \text{Cl}, \text{i-PrNH}, \text{i-BuNH}, \text{CN}, \text{SCN}, \text{OMe}, \text{OEt}
\]

Scheme 34. Synthesis of \(\alpha\)-trifluoromethylpiperidines from trifluoromethylaziridines.

3.1.8. Intramolecular Nucleophilic Attack of Aldehydes

The annulation of aminoaldehyde 115 was realized by an intramolecular attack of a diphenyl sulfonium species on an aldehyde. When aminoaldehyde 115 was reacted with the trifluoromethyl-vinyl diphenylsulfonium 116, the ylide intermediate XVIII was formed and a cyclization took place to produce XIX which led to the piperidino-epoxide 117. It is worth noting that 117 was isolated with a good yield (72%) and a good diastereoselectivity (dr > 20:1) (Scheme 35) [65].

\[
\text{Nu} = \text{Cl}, \text{i-PrNH}, \text{i-BuNH}, \text{CN}, \text{SCN}, \text{OMe}, \text{OEt}
\]
4. Conclusions

Despite the considerable synthetic efforts spent to synthesize 2-trifluoromethylpiperidinic derivatives, most of these compounds have been obtained in a racemic form. When they are optically active, the methods involve a chiral auxiliary or the starting material comes from the chiral pool. Thus, there is still a strong demand for catalytic enantioselective methods to efficiently access 2-trifluoromethylpiperidinic derivatives in high diastereo- and enantioselectivity.

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