Trifluoromethylalkenes in [2+3] cycloaddition reactions with nitrones

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Introduction
Fluorinated analogues of known biologically active compounds have been gaining increasingly more interest both from academic research institutions and large pharmaceutical companies [1÷5]. A fluorine atom or a fluorine-containing functional group incorporated into an organic compound molecule leads to major changes in physicochemical properties. It is assumed that when one hydrogen atom is substituted with a fluorine atom (or a methyl group is substituted by a trifluoromethyl group), no steric changes occur compared to the non-fluorinated molecule [6]. Therefore, considering spatial interactions the fluorinated molecule may bind the same receptors as the non-fluorinated compound. Furthermore, the high energy of the C-F bond [7, 8] prevents adverse metabolic reactions, thus increasing the stability of the compound, for example. Fluorinated analogues also exhibit increased lipophilicity and, as a result, faster diffusion through biological membranes [6, 9]. Those properties of fluorine-containing organic compounds make them important in drug synthesis. The known formulations which contain fluorinated compounds include the following local anaesthetics: enflurane, isoflurane, desflurane and sevoflurane and certain anti-cancer drugs, such as 5-fluouracil and capecitabine. The unique properties of organofluorine compounds are particularly evident when the molecule contains a xenobiotic trifluoromethyl group [10, 11]. Fluoxetine, found in the drug with a trade name Prozac, is an example of a widely used compound containing the trifluoromethyl group. The unique properties of fluorine are seen also in ciproflaxcin, an antibacterial, in which the cell penetration rate increases 70-fold compared to its non-fluorinated analogue [12]. Fluorine substitution at a specific position in the drug molecule may affect not only pharmacokinetic properties, such as absorption, drug distribution in tissues, excretion and course and rate of biotransformation, but also its pharmacokinetics, toxicity and improved efficacy.

As organofluorine compounds are rarely found in nature, organic synthesis is their primary source for pharmaceutical industry [11]. Most widely used [13] preparative approaches focus on the halogenation of aromatic moieties, while methods involving non-aromatic heterocyclic compounds are much more scarce. Halogenation reagents are usually extremely reactive which makes their safe use very difficult. Therefore, the concept of using structurally simple and commercially available starting compounds containing the CF₃ group is increasingly more popular in the synthesis of more complex cyclic compounds [9]. [2+3] cycloaddition (1,3-dipolar cycloaddition) is particularly important in the methodology of organofluorine compound synthesis [14]. In the present study, data for the [2+3] cycloaddition of dipolarophiles containing CF₃ groups with nitrones whose application in organic synthesis has been systematically investigated for many years [15÷19] are compared.

[2+3] cycloaddition reactions involving monosubstituted nitrones
N-alkylnitrones are unstable compounds [20], and they are added to [2+3] cycloaddition reactions in situ, by reacting suitable hydroxylamines with formaldehyde. They are strongly nucleophilic (ω<1eV[21]) and relatively readily react with π-deficient dipolarophiles activated by an electron-accepting CF₃ group.

For example, the [2+3] cycloaddition of (E)-3,3,3-trifluoro-1-phenylsulfonylprop-1-ene (1) to N-methylnitrone (2) [22] occurs in boiling toluene. The reaction is regio- and stereospecific and yields 4,5-trans-2-methyl-4-phenylsulfonyl 5-trifluoromethylisoxazolidine (3).

A similar reaction involving more strongly π-deficient (E)-1-phenyl-perfluoroprop-1-ene (4) is regiospecific as well, but in relatively milder conditions [23]. It yields 4,5-trans-2-methyl-4,5-difluoro-4-trifluoromethyl-5-phenylisoxazolidine (5).

N-benzyl nitrone (7) similarly reacts with (E)-1-aryl-perfluoroprop-1-enes [23].

C-monosubstituted nitrones are also added to the cycloaddition reaction in situ. The compounds are, however, formed in a different way, using isomerisation processes of suitable oximes. The [2+3] cycloaddition of perfluoro-2-methyl-2-pentene (9) to C-phenylnitrene is an example of such a reaction (10) [24]. It yields a mixture of stereoisomeric 3,5-cis (11) and 3,5-trans (12) 3-phenyl-4,4-di-(trifluoromethyl)-5-(perfluoroethyl)-5-fluoroisoxazolidines in a 6:4 ratio. Isomeric etheroximes are the side products of the reaction (13).
[2+3] cycloaddition reactions involving di- and trisubstituted acyclic nitrones

Disubstituted nitrones are more stable than monosubstituted nitrones and in many cases occur as stable geometric isomers [20]. C,N-dimethylnitrene (14), the simplest member of the group, was tested in a reaction with (E)-3,3,3-trifluoro-1-phenylsulfonylprop-1-ene (1) [22]. The cycloaddition proceeds in boiling toluene and yields one adduct only, identified as 3,4-trans-4,5-trans-2,3-dimethyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine (15).

The [2+3] cycloaddition of perfluoro-2-methyl-2-pentene (9) to (Z)-C-propyl-N-butylnitrene (15), in turn, yields a mixture of regioisomeric isoxazolidines (16) and (17) in a 2:1 ratio [25]. It is noted that we obtained compounds (16) and (17) as mixtures of stereoisomers, without their subsequent resolution.

However, the cycloaddition of hexafluoropropene (18) to (Z)-C-benzyl-N-methylnitrene (19) is regiospecific. The reaction yields 2-methyl-3-benzyl-4,5,5-trifluoro-4-(trifluoromethyl)-isoxazolidine (20) whose stereoconfiguration is unknown [26].

A different research group [27] investigated the course of the [2+3] cycloaddition of 3,3,3-trifluoropropene (21) to (Z)-C-phenyl-N-methylnitrene (22). The reaction yielded a mixture of 3,5-trans-(23) and 3,5-cis- (24) 3-phenyl-5-trifluoromethylisoxazolidines and 3,4-trans-3-phenyl-4-trifluoromethylisoxazolidine (25). The products form in a 50:23:27 ratio.

However, when hexafluoropropene 18 is used instead in the [2+3] cycloaddition to nitrene 22 a mixture of stereoisomeric 3,4-cis- (26) and 3,4-trans- (27) 2-methyl-3-phenyl-4,5,5-trifluoro-4-trifluoromethylisoxazolidines in a 3:1:1 ratio forms. [28]. However, the authors of the report could not resolve respective isomers. Their ratio was determined by 1H and 19F NMR spectra.

In the [2+3] cycloaddition of 3,3,3-trifluoro-2-phenylprop-1-ene (28) to (Z)-C-phenyl-N-methylnitrene (22) in boiling toluene, in turn, stereoisomeric 2-methyl-3,5-diphenyl-5-trifluoromethylisoxazolidines (29 and 30) in a 1:1 ratio form [29]. The same products with similar stereoselectivity may be synthesised in solvent-free conditions [30].

The reaction of nitrene 22 with (E)-3,3,3-trifluoro-1-carbomethoxyprop-1-ene (31) in toluene at 80°C yields a mixture of 3,4-cis-3-phenyl-4-carbomethoxy-5-trifluoromethylisoxazolidine (32), 3,4-trans-3-phenyl-4-carbomethoxy-5-trifluoromethylisoxazolidine (33) and 3,4-trans-3-phenyl-5-carbomethoxy-4-trifluoromethylisoxazolidine (34) [27]. When the mixture after the reaction is heated at 140°C isoxazolidine 32 slowly isomerises to thermodynamically more stable compounds 33 and 34.

When more electrophilic (E)-3,3,3-trifluoro-1-nitroprop-1-ene (35) is used in the cycloaddition to C-phenyl-N-methylnitrene (22), the process occurs in milder conditions and regiospecifically and stereoselectively yielding a mixture of 3,4-cis and 3,4-trans-2-methyl-3-phenyl-4-nitro-5-trifluoromethylisoxazolidines (36 and 37) in a 2.2:1 ratio [27, 31].

The [2+3] cycloaddition of 3,3,3-trifluoro-1-phenylsulfonylpropene 1 to C-phenyl-N-methylnitrene 22 is regio- and stereospecific [22]. The reaction yields 3,4-trans-3,5-cis-2,3-dimethyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine (38).

Similarly, one adduct only forms in the cycloaddition of 1,2-disubstituted trifluoromethylethenes with nitrene 22 [29, 30, 32]. The reaction involving (E)-3,3,3-trifluoro-2-hydroxy-1-carboethoxyprop-1-ene (39) is an example:

Furthermore, diarylnitrones have also been tested as components of the [2+3] cycloaddition with trifluoromethylated olefins. For example, the reaction of (E)-3,3,3-trifluoro-1-phenylsulfonylprop-1-ene (1) with (Z)-C,N-diphenylnitrene (41) is regio- and stereospecific yielding 3,4-trans-3,5-cis-2,3-diphenyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine (42) [22].
The \([2+3]\) cycloaddition of (E)-3,3,3-trifluoro-1-nitroprene (35) to (Z)-C,C,N-diphenylnitrone (41) at room temperature and in toluene, in turn, gives a mixture of stereoisomeric 3,4-cis (43) and 3,4-trans (44) 2,3-diphenyl-4-nitro-5-trifluoromethylisoxazolidines in a 3:1 ratio [31].

When heated, a mixture of hexafluoropropene (18) and nitrone (41) yields 3-fluoro-3-trifluoromethyl-1,4-diphenylnitroisoxazolidine (45) [32]. Detailed studies of the mechanism of this process led to a conclusion that isoxazolidine (45) is an initial, unstable product which is converted in the reaction conditions to \(\beta\)-lactam (46) [33].

However, the \([2+3]\) cycloaddition of a mixture of isomeric (E)-octafluorobut-2-enes (47) to nitrone (41) yields a mixture of two stereoisomeric cycloadducts (48, 49) [33].

Trisubstituted nitrone have been used as components of \([2+3]\) cycloaddition with trifluorinated olefins much more rarely. An example of such a process is a reaction between hexafluoropropene (18) and C,C-diphenyl-N-methyl nitrone (50). It gives 2-methyl-3,3-diphenyl-4,5,5-trifluoro-4-trifluoromethylisoxazolidine (51) [28].

The \([2+3]\) cycloaddition reactions involving cyclic nitrone

The reactive components of \([2+3]\) cycloadditions are also heterocyclic N-oxides, formally considered nitrone as well [20]. An example of such a cycloaddition is a reaction between hexafluoropropene (18) and 3-(tert-butoxy)-pyrrole N-oxide (53). It yields a mixture of stereoisomeric adducts (54 + 55) in a 3.8:1 ratio [28].

![Chemical structure diagram](image-url)

The \([2+3]\) cycloaddition of 3,3,3-trifluoro-1-carbomethoxypro-

pene (31) with 3,4-dihydroisoquinoline N-oxide (56) is less stereoselective [34]. It yields stereoisomeric 3,4-cis and 3,4-trans cyclo-
ducts (57 and 58) in a 1:3 ratio.

However, in a similar reaction involving 3,3,3-trifluoro-1-
nitroprene (35) stereoisomeric isoxazolidines (59 and 60) form in a 1:2 ratio [31].

Conclusions

\([2+3]\) cycloaddition reactions involving nitrone are a universal strategy for the synthesis of trifluoromethylated isoxazolidines. Both unstable monosubstituted nitrone, stable di- and trisubstituted nitrone and cyclic nitrone can be used in the reaction. It is noted that most of the reactions proceed regiospecifically and highly stereoselectively. They are stereospecific in certain cases. It is also quite important that the cycloadditions in question occur in relatively mild conditions, that is, at temperatures not higher than 110°C and frequently at room temperatures.

Literature

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