Karolina Kula

Agnieszka Łapczuk-Krygier (lapczuk@chemia.pk.edu.pl)
Institute of Organic Chemistry and Technology, Cracow University of Technology

DIAZAFLUORENE IN 1,3-DIPOLAR CYCLOADDICTION REACTIONS: SHORT REVIEW

DIAZAFLUOREN W REAKCJACH 1,3-DIPOLARNEJ CYKLOADDYCJI: KRÓTKI PRZEGLĄD

Abstract

This review is an attempt to systemise knowledge within the field of 1,3DC reactions of diazafluorene with different dipolarophiles. This paper is arranged according to the dipolarophile structure. We are hoping that this review can help organic chemists who deal with the preparation of five-membraned heterocycles.

Keywords: diazafluorene, 1,3-dipolar cycloaddition, 1,3-dipol

Streszczenie

Niniejszy przegląd stanowi próbę usystematyzowania stanu wiedzy w obszarze reakcji 1,3DC diazafluorenu z różnymi dipolarofilami. Materiał został uporządkowany na podstawie budowy dipolarofila. Mamy nadzieję, iż przegląd będzie pomocny chemikom organikom zajmującym się preparatyką związków heterocyklicznych.

Słowa kluczowe: diazafluoren, 1,3-dipolarna cykloaddycja, 1,3-dipol

1. Introduction

This publication is a review of literature concerning diazafluorene as a 1,3-dipole in 1,3-dipolar cycloaddition reactions, which enable creating heterocyclic compounds.

Pyrazolines are a diverse group of compounds, which demonstrate biological activity. These connections are often researched from a pharmacological perspective. They are characterised by an exceptional antibacterial [1, 2], antiviral [2, 3] as well as antifungal effect [2]. Apart from microbiological activity, pyrazolines stimulate the central nervous system (CNS), which in turn allows them to be used as means of treating illnesses, such as depression [4, 5] or epilepsy [5].

Moreover, the literature points towards using pyrazolines as painkillers [6, 7] or anti-inflammatory [2, 4, 6–9], antipyretics [5], antiulcer [6], antirheumatic [8] , antitubercular [5], anticancer [10] or hypotensive [5] drugs.

Pyrazolines are characterised by antioxidant activity [5]. These properties led scientists to research possibilities of using heterocyclic as antineoplastic drugs [3, 5].

Pyrazolines are also used in industry. They mostly serve as dyes [11–13]. They are used as insecticides and herbicides as well, however, to a lesser extent [11, 14].

The process of 1,3-dipolar cycloaddition (in brief 1,3DC) is the most universal method of creating five membered carbo- and heterocyclic compounds [13]. When using diazafluorene (as 1,3-dipole) as an addent, one can produce connections of a pyrazoline [11–26] skeleton within its structure. Those connections are valuable from a practical perspective [1–10]. In addition, cycloaddition with diazafluorene allows synthesis of spatially crowded groups of spiro-pyrazolines, an adduct otherwise hard to produce [27].

1,3DC reactions between diazafluorene and electrophilic dipolarophiles, which lead to heterocycles, were discovered at the beginning of the XX century. The eldest, and as such historically first record in literature of these reactions comes from 1916. German chemists *Staudinger* and *Galue* carried out a reaction between diazafluorene (1) and diphenylketene (2). As a result, they received 3-fluoren-4,40-diphenylpirazolin-5-on (3). The process is realised relatively mild conditions and has a yield of 15% [15].
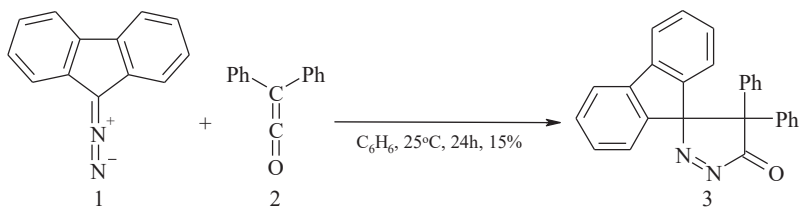

Fig. 1. Synthesis of 3-fluoren-4,4-diphenyl-Δ^1-pyrazoline-5-one (3)

2. Reactions of diazafluorene with dipolarophiles which has >C=C< an ethenyl core

Cycloaddition between diazafluorene (1) and dimethyl chlorofumarate (4) is an example of a reaction with dipolarophile with an ethenyl core. The process is realised a temperature of 25°C and benzene as a solvent, and has a 75% yield. Theoretically, it is possible for the >C=O bond from the dipolarophilic part of the compound to participate in this reaction. However, it remains intact as the reactivity of >C=C< part is relatively high. This is a typical phenomenon, which also occurs in other >C=C< and >C=O configurations [16, 18, 28].
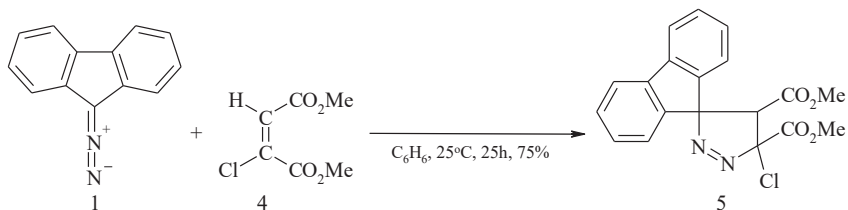

Fig. 2. Synthesis of 3-fluoren-4,5-dicarbonylmethoxy-5-chloro-Δ^1-pyrazoline (5)

Another example of a similar reaction is synthesis in which (3,3-dimethyl-2-phenyl-cyclopropenyl)-diphenylphosphin oxide (6) is present. In order for the process to occur, a temperature of 50°C and benzene as a solvent are required. The reaction is selective, similarly to the previous example, resulting in one of two possible regioisomeric adducts [16].
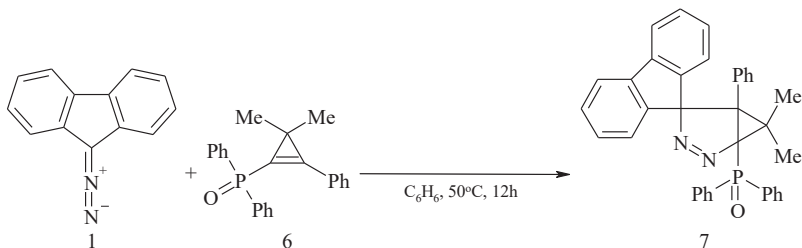

Fig. 3. Reaction between diazafluorene (1) and (3,3-dimethyl-2-phenylcyclopropenyl)-diphenylphosphin oxide (6)

Yet another similar cycloaddition with N-phenyl-maleimide (8) as dipolarophile can be observed in milder conditions, with a required temperature of 0°C [28].
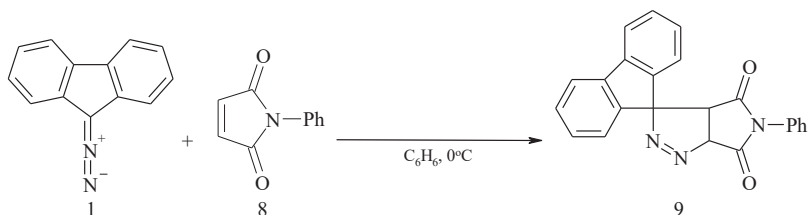

Fig. 4. Synthesis of 3-fluoren-4,5-dicarbonylmethoxy-5-chloro-Δ^1-pyrazoline (9)

Functionalised bicyclo[2.2.0]hex-5-enes, which are characterised by a sp^2-sp^2 strained system, also have been tested as dipolarophiles with >C=C<, for example, a reaction of diazafluorene (1) with 2,3-diazobicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic acid dimethyl ester (10) The process is realised at a temperature of 25°C and diethyl ether as a solvent, and leads to a single product [18].
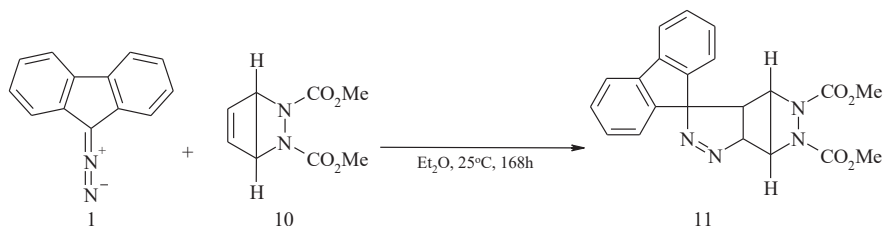

Fig. 5. Reaction between diazafluorene (1) and 2,3-diazobicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic acid dimethyl ester (10)

According to the authors, processes with 5-oxabicyclo[2.2.0]hex-2-en-6-one (12), 2-isopropyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (15), as well as 2,3-diazobicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic acid methyl ester (18), are carried out in a similar manner. They require a temperature between 0-40°C and diethyl ether as a solvent, forming two isometric end products. It is worth noting that by applying higher temperatures, the reaction's time can be shortened. However, temperatures which are too high can cause nitrogen to disappear from Δ^1-pyrazoline rings [18].

With regards to the reaction depicted below, the author states that a division of end product isomers is not possible [18].
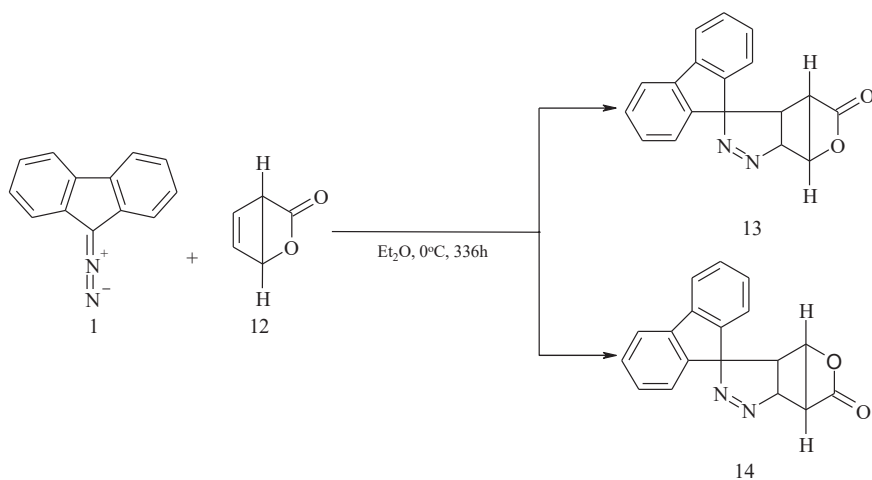

Fig. 6. Reaction between diazafluorene (1) and 5-oxabicyclo[2.2.0]hex-2-en-6-one (12)
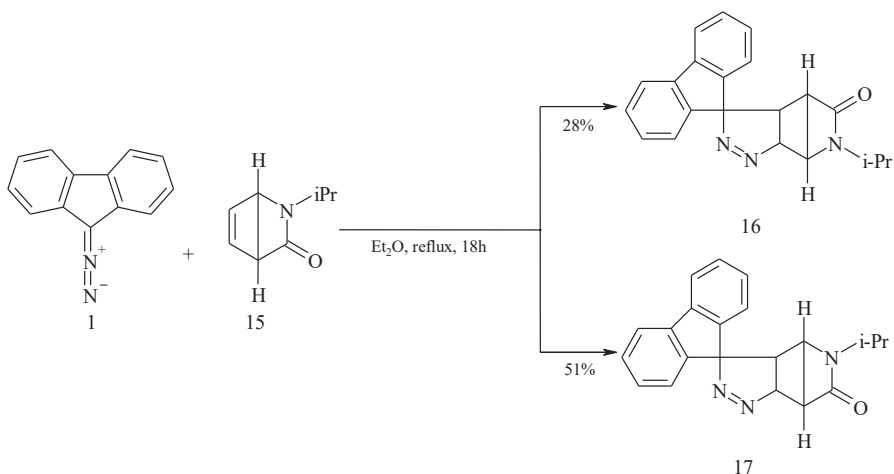
Fig. 7. Reaction between diazafluorene (1) and 2-isopropyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (15)
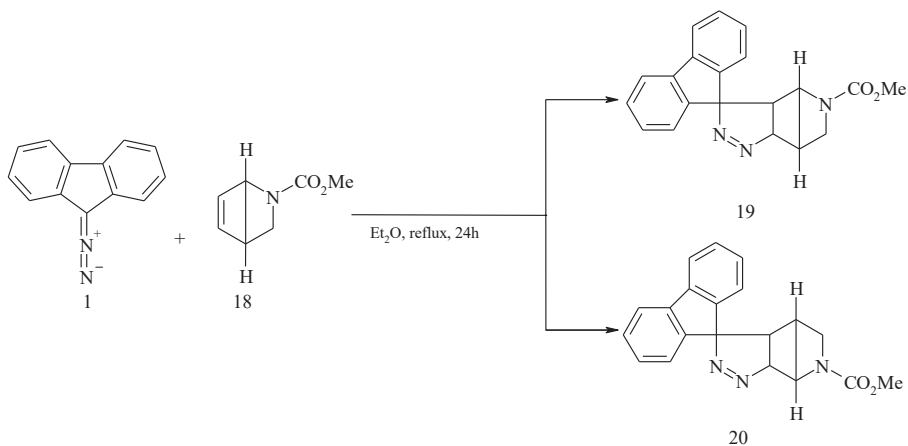

Fig. 8. Reaction between diazafluorene (1) and 2,3-diazobicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic
acid methyl ester (18)

Not all reactions between diazafluorene (1) and dipolarophile with an ethylene part result in a cyclic product. An example of an unexpected mechanism is a series of reactions with (E)-2-aryl-1-cyano-1-nitroethenes (21). They are realised at a temperature of 25°C and benzene as a solvent, and lead to derivatives of hydrazines. During the reaction, a particle of cyanonitrocarbene is eliminated, which in turn leads to an acyclic product [29].
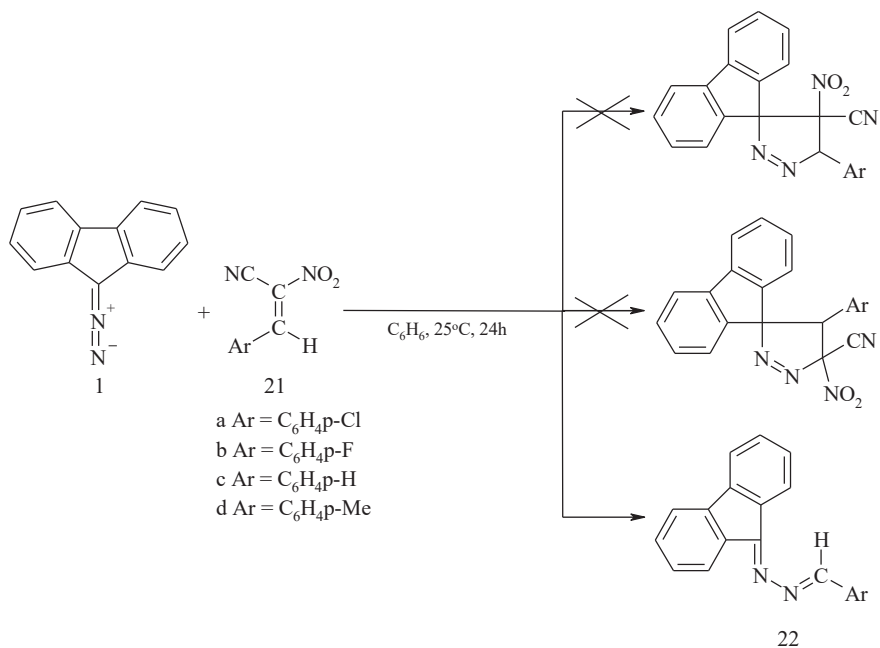
Fig. 9. Synthesis of 1-arylidene-2-(9H-fluoren-9-ylidene)-hydrazones (22a-d)

3. Reactions of diazafluorene with dipolarophiles which has $-C{\equiv}C-$ an acetylene core

According to literature, the first synthesis of dipolarophiles with an acetylene core was carried out in 1943. It is a reaction between diazafluorene (1) and propynoic acid methyl ester (23), described by *Aphen*, with an end result of one of two possible regioisomeric products – analogue of pyrazole. The processes is realised at a temperature of 25°C and diethyl ether as a solvent [14].
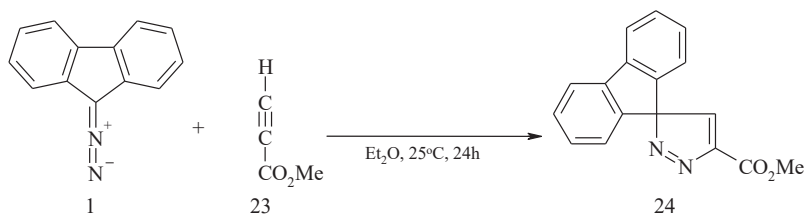

Fig. 10. Synthesis of 3,3-diphenylenepyrazolenine carbonic acid-(5)-methyl ester (24)

A reaction with dimethyl acetylenedicarboxylate (25) leads to synthesis of 3,3-diphenylene-pyrazolenine dicarbonic acid-(4,5)-dimethyl ester (26) under the same conditions [14].
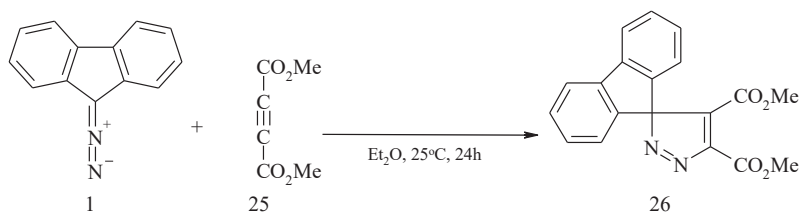
Fig. 11. Synthesis of 3,3-diphenylenepyrazolenine dicarbonic acid-(4,5)-dimethyl ester (26)

A synthesis with ditert-buthyl acetylenedicarboxylate (27) as dipolarophile is carried out in a similar manner. The processes is realised at a temperature of 25°C and benzene as a solvent [19].
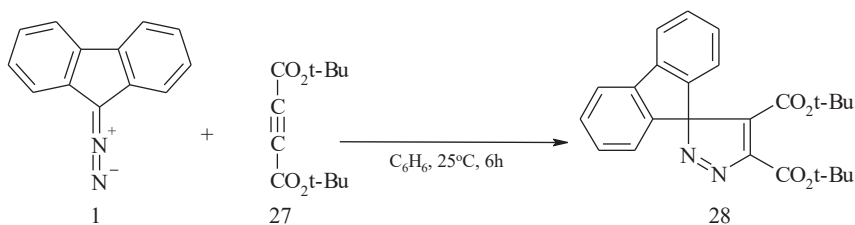

Fig. 12. Synthesis of 3,3-diphenylenepyrazolenine dicarbonic acid-(4,5)-ditert-buthyl ester (28)

Similarly, as a result of a reaction with phenylpropynoic acid methyl ester (29), one of two possible regioisomeric products can be created. The processes is realised at a temperature of 25°C and diethyl ether as a solvent [14].
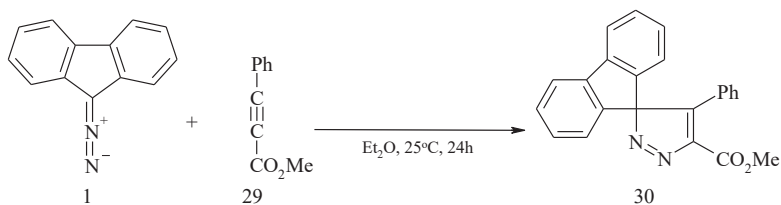

Fig. 13. Synthesis of 3,3-diphenylene-4-phenylpyrazolenine carbonic acid-(5)-methyl ester (30)

There is only one product of a reaction with FI-DIBO (31). Theoretically, cycloaddition at two parts of particles >C=C< and -C≡C- is possible. Moreover, the ethylene group is much more reactive than the acetylene core one. Nevertheless, the -C≡C- part is more exposed than >C=C<, and that determines the path of the reaction. The process is realised at a temperature of 20°C and dichlorometane as a solvent, and has a yield of 95% [12].
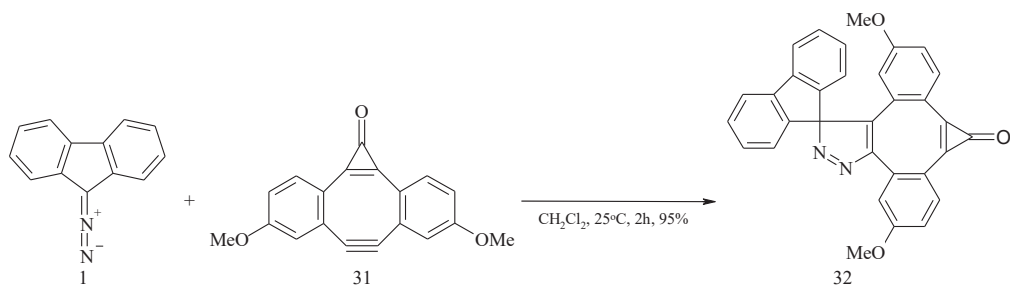
Fig. 14. Reaction between diazafluorene (1) and FI-DIBO (31)

During the process of cycloaddition with diazafluorene (1), syn-dibenzo-1,5-cyclooctadiene-3,7-diyne (33) two parts -C≡C-. As a result, a polycyclic adduct is created. The process is realised at a temperature of 25°C and benzene as a solvent, and has a yield of 46% [11].
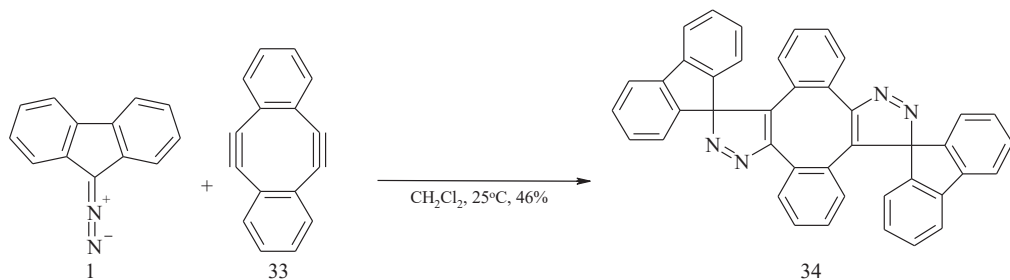

Fig. 15. Reaction between diazafluorene (1) and syn-dibenzo-1,5-cyclooctadiene-3,7-diyne (33)

1,3DC between diazafluorene (1) and 3-methyl-1,2-dehydrobenzene (35) leads to two isomers. The process is realised 1,4-dioxane as a solvent [12].
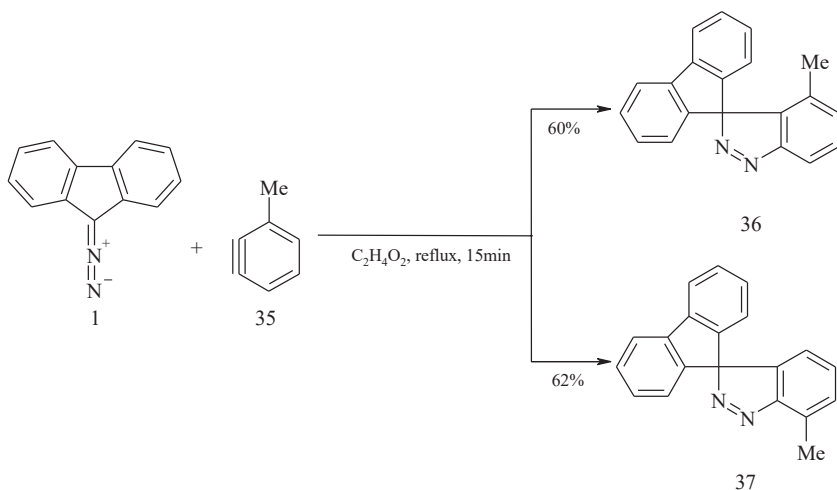

Fig. 16. Reaction between diazafluorene (1) and 3-methyl-1,2-dehydrobenzene (35)

A reaction between diazafluorene (1) and 1,2-dehydrobenzene (38), with a yield of 80%, is also known [13].
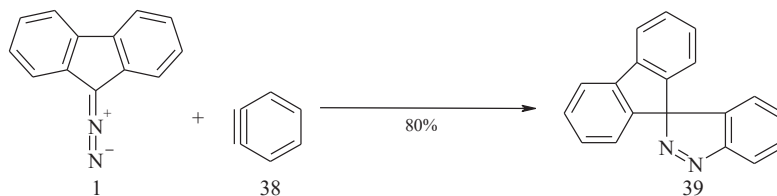

Fig. 17.   Reaction between diazafluorene (1) and 1,2-dehydrobenzene (38)

The most recent literature describes diazafluorene reactions with a series of derivatives of phenylethynyl sulfones The processes are realised at a temperature of 20°C under protection from light, and has a yield of 71–77% [30].
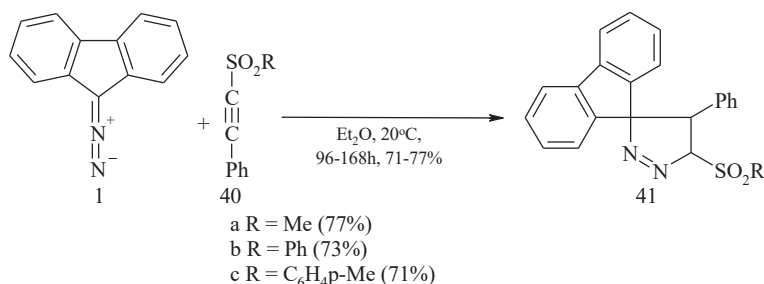

a R = Me (77%)
b R = Ph (73%)
c R = C₆H₄p-Me (71%)

Fig. 18.   Reaction between diazafluorene (1) and derivatives of phenylethynyl sulfones (40a-c)

4. Reactions of diazafluorene with dipolarophiles which has a heteroatomic core

According to literature, reactions of diazafluorene with dipolarophiles, which have a heteroatomic core, occur mostly on O=C< [20, 22] parts, creating oxadiazoline, -P=C< (phosphadiazoline) [23], and S=C< (thiadiazoline) [21, 25].

A reaction with 1,1,1,3,3-pentafluoro-2-propanone (42) is an example of 1,3DC diazafluorene (1) with dipolarophile with a carbonyl group. The process is realised at a temperature of 25°C and diethyl ether as a solvent [20].
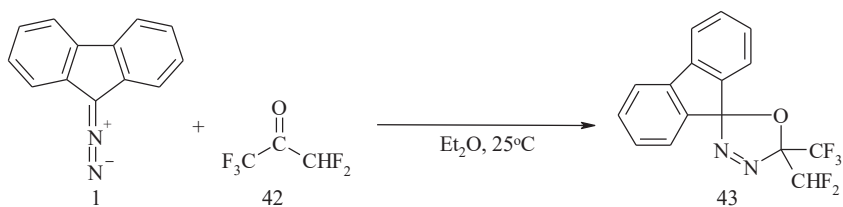
Fig. 19. Reaction between diazafluorene (1) and 1,1,1,3,3-pentafluoro-2-propanone (42)

Yet another example of a similar reaction is cycloaddition with acenaphthene quinine (44). The process is realised with benzene as a solvent as well as at a boiling temperature, and has a yield of 35% [22].
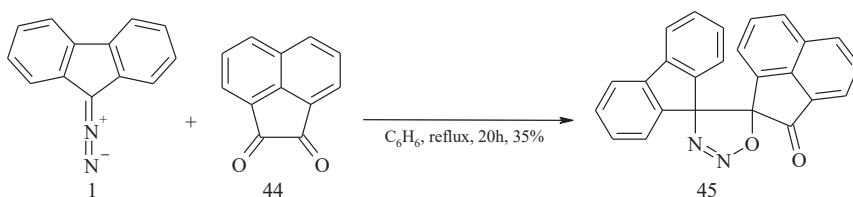
Fig. 20. Reaction between diazafluorene (1) and acenaphthene quinine (44)

A reaction with 2-acetyl-5-tert-butyl-1,2,3-diazaphosphole (46) is an example of 1,3DC diazafluorene (1) with dipolarophile which has a phosphadiazoline group -P=C<. The process is realised at a temperature of 20°C and cyclohexane as a solvent, and has a yield of 65% [23].
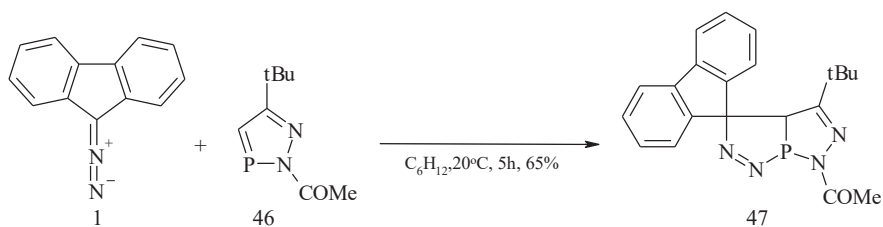

Fig. 21. Reaction between diazafluorene (1) and 2-acetyl-5-tert-butyl-1,2,3-diazaphosphole (46)

Similarly, reaction with 2-acetyl-5-methyl-1,2,3-diazaphosphole (48) leads to a cyclical product with a yield of 89%. The process is realised at a temperature of 20°C and hexane as a solvent (time 3h) [21].
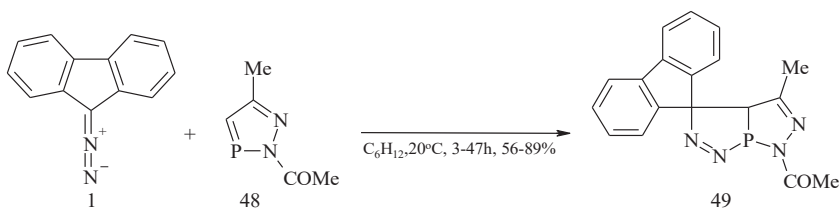
Fig. 22. Reaction between diazafluorene (1) and 2-acetyl-5-methyl-1,2,3-diazaphosphole (48)

Diazafluorene (1) also reacts with dipolarophile with thiadiazoline group S=C<. A reaction with methyl diethoxyphosphinecarbodithioate 1-oxide ester (50) creates 1,3,4-thiadiazoline. The process is realised at a temperature of -65°C and tetrahydrofuran as a solvent [21].
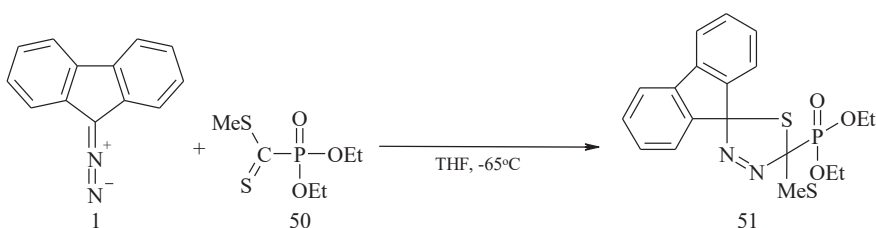
Fig. 23. Reaction between diazafluorene (1) and methyl diethoxyphosphinecarbodithioate 1-oxide ester (50)

A cycloaddition with adamantane-2-thione (52) is yet another example. The process is realised at a higher temperature and tetrahydrofuran as a solvent, and has a yield of 15% [25].
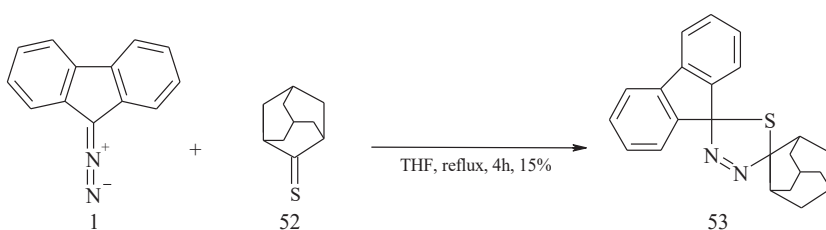
Fig. 24. Reaction between diazafluorene (1) and adamantane-2-thione (52)

5. Conclusions

The process of 1,3DC is the most universal method of creating five membered carbo- and heterocyclic compounds. When using diazafluorene (as 1,3-dipole) as an one of addent can produce connections of a Δ^1-pyrazoline skeleton within its structure. Those connections are valuable from a practical perspective. This review is an attempt to systemise the state of

knowledge in the field of 1,3DC reactions of diazafluorene with different dipolarophiles. This paper is arranged according to the dipolarophile structure, reviewed reactions with dipolarophiles, which has an ethenyl, an acetylene or heteroatomic core.

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