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Polar [3+2] cycloaddition between N-methyl azomethine ylide and trans-3,3,3-trichloro-1-nitroprop-1-ene

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Abstract: Pyrrolidines are important heterocyclic organic compounds which show biological effects. Many of them are successfully used in medicine. These compounds can also be applied in industry, for example as dyes or agrochemical substances. Therefore, the study of pyrrolidines chemistry is important for modern science. In this paper the pyrrolidines synthesis in [3+2] cycloaddition between N-methyl azomethine ylide and *trans*-3,3,3-trichloro-1-nitroprop-1-ene was studied. The reaction was carried out experimentally and based on computational research. The obtained results show the reaction may be of a polar nature, and proceed under mild conditions leading to (3SR,4RS)-1-methyl-3-nitro-4-(trichloromethyl)pyrrolidine as a single reaction product. Probably, a similar protocol can be applied for analogous reactions involving other 2-substituted nitroethene analogues.

Keywords: [3+2] cycloaddition, nitroalkenes, ylides

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Introduction

Azomethine ylides are non-persistent, three-atom components (TACs) characterised by pseudoradical-type reactivity (Figure 1) [1]. Among other things, azomethine ylides are employed to form five-membered heterocyclic compounds via [3+2] cycloaddition (32CA) reaction. From the practical point of view, azomethine ylides are substrates for, in particular, the synthesis of compounds such as pyrrolidine analogues [2].

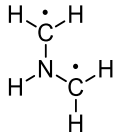
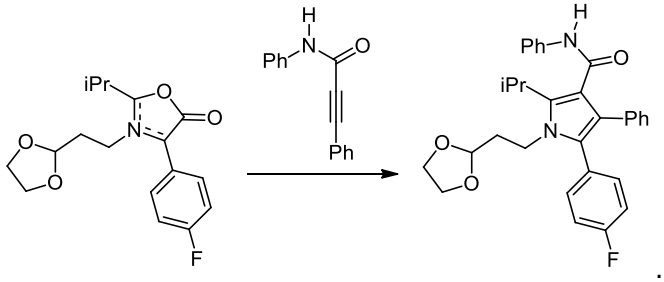


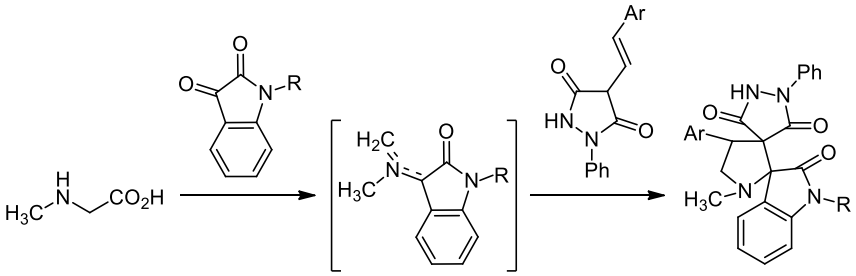
Figure 1. The structure of the simplest azomethine ylide presenting a pseudodiradical-type reactivity.

Obtained in a 32CA pyrrolidines are important heterocyclic organic compounds which show biological activity. Many of them are successfully used in medicine. The example is atorvastatin (Scheme 1) which has potential application in medicine not only as a drug used to lower LDL cholesterol in the blood, but also to prevent the progression of atherosclerosis. It is used for the treatment of diabetes and arterial hypertension [3].



Scheme 1. Synthesis of Atorvastatin, sold under the brand name *Lipitor*, in [3+2] cycloaddition reaction.

Another example is the 32CA reaction of isatin with sarcosine. In a course of the reaction, the azomethine ylide as a labile TAC occurs. The further TAC reaction with 1,2-bifunctionalysed ethene produces dispiropyrrolidine analogue (Scheme 2). The obtained product has an anti-inflammatory activity, which makes it an attractive component used as pharmacological agent that block the formation of edema [3].



Scheme 2. The reaction sequence between isatin and sarcosine to labile azomethine ylide and further [3+2] cycloaddition of TAC with ethene system.

In azomethine ylides the electronic effects play crucial role in 32CAs reaction course. Especially important aspect is alkene activation [4]. Higher activation of double bond with electron withdrawing group facilitates reaction, thus leading to higher reaction yields. For example, the 32CA involving 1,2-dicyanoethene described by *Mikio Hori et al.* proceeds rapidly giving the expected product with a high yield [5].

This work is a continuation of our study regarding the participation of azomethine ylides in 32CAs with conjugated nitroethenes. Previously, we analysed the course of the [3+2] cycloaddition process between N-methyl azomethine ylide (**1**) with extremely electrophilic *trans*-2-aryl-1-cyano-1-nitroethenes [6]. Currently, we have decided to shed some light on similar processes involving mono-β-substituted analogues of the nitroethene. As the model compound from this group we selected the *trans*-3,3,3-trichloro-1-nitroprop-1-ene (**2**), which reactivity was recently tested by us in several different-type cycloaddition reactions [7-10].

The molecular mechanism of the reaction cannot be defined a priori. At this moment several mechanisms should be considered regarding to 32CA reactions:

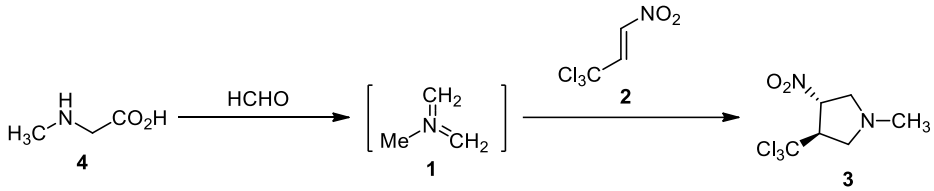
- Non-polar mechanisms including synchronical, non-synchronical or stepwise biradical mechanism;
- Polar mechanisms including synchronical, non-synchronical or stepwise zwitterionic mechanism;

Additionally, zwitterionic or biradical adducts with "extended conformation" may be exist in reaction environment independently of 3+2 cycloadducts. Last examples of possible stepwise [3+2] cycloadditions were very recently reviewed and discussed [11,12].

Results and discussion

The comparison of the global electrophilicities of reaction components (**1**: ω=0.38eV [8]; **2**: ω=3.27eV [9]) exhibits evidently the polar nature of the reaction tested. This suggests rather mild conditions for the [3+2] cycloaddition (**1**) + (**2**). The N-methylazomethine (**1**) ylide is not known as a stable compound. So, it should be generated in situ from sarcosine (**4**). On the other hand, the *trans*-3,3,3-trichloro-1-nitroprop-1-ene (**2**) is a moderately stable, but not commercially available. Thus, we prepared this component according to the procedures from the literature (see experimental part). In the course of our

research, we performed several tests, changing the reaction conditions, solvents as well as the reaction time. We established that the reaction proceeds effectively in the dry benzene, and under the molar excess of in situ generated ylide. During this, after only 3 h we detected the full conversion of the nitroalkene. The HPLC analysis of the postreaction mixture shows presence of only one reaction product, which was isolated using column chromatography with the excellent yield. Elemental analysis data gave the brutto formula $C_6H_9N_2O_2Cl_3$ for the isolated compounds. Next, we analysed a MS spectrum of obtain product. For the compound we detected a pseudomolecular ion 246.94 Da $(M+H)^+$, what corresponds with the formula proposed on the basis of elemental analysis. Further information on the structure of the isolated compound was obtained from the ^{1}H NMR spectrum. In particular, two multiplets as dd-type signals as well as two multiplets as ddd signals were detected within the range about 2.6-5.2 ppm, next to strong singlet (2.3 ppm) connected with the existence of protons of the methyl group. For the full characterisation of the isolated compound, its ^{13}C NMR spectrum was also registered and described (see experimental part). So, the structure of (3SR,4RS)-1-methyl-3-nitro-4-(trichloromethyl)pyrrolidine (**3**) can be assigned without any doubts for the isolated product. The course of the realised synthesis can be presented in the form described in Scheme 3.



Scheme 3. The reaction sequence of sarcosine (**4**) to labile azomethine ylide (**1**) and further [3+2] cycloaddition of TAC (**1**) with *trans*-3,3,3-trichloro-1-nitroprop-1-ene (**2**).

Lastly, we examined the title reaction from the thermodynamic point of view. Unfortunately, the thermodynamic state functions for the reagents as well as the reaction product are not known. Therefore, we decided to estimate respective H, S and G values using the quantum-chemical calculations at the M062X/6-311G(d) [13] level of theory. It was found that thermodynamic factors evidently stimulate the reaction equilibrium towards the adduct. In a similar way we examined also other alike processes involving other 2-substituted analogs of nitroethene, which are known as components of [3+2] cycloadditions [14-16]. Table 1 shows computational results. It was found that in all cases the reaction equilibrium is evidently shifted to the area of cycloadducts.

Table 1. Thermodynamic parameters for [3+2] cycloaddition reaction of N-methylazomethime ylide (**1**) and different 2-substituted analogs of nitroethene according to M062X/6-311G(d)(PCM) theory level.

Nitroalkene	ΔH [kcal/mol]	ΔS [cal/molK]	ΔG [kcal/mol]
trans-3,3,3-trichloro-1-nitroprop-1-ene (**2**)	-81,08	-50,64	-65,98
trans-3,3,3-fluoro-1-nitroprop-1-ene	-80,67	-47,84	-66,40
trans-1-nitroprop-1-ene	-73,01	-46,21	-59,23
trans-3-nitroacrylic acid	-81,96	-50,12	-67,02
trans methyl 3-nitroacrylate	-83,64	-47,98	-69,33
trans-3-nitroacrylonitrile	-76,52	-48,40	-62,09
trans-2-chloro-1-nitroethene	-76,87	-47,31	-62,76

Thus, the proposed protocol can be established as a rather universal for the preparation of new pyrrolidine analogues via 32CAs involving 2-substituted analogs of nitroethene.

Finally, it should be underlined, that in the light of the last discoveries [17,18], the mechanistic aspects of [3+2] cycloadditions of azomethine ylide molecular systems are very difficult and still require additional comprehensive studies. These issues regarding the title reaction will be subject of our further studies.

Conclusions

In this paper the [3+2] cycloaddition reaction between N-methyl azomethine ylide and *trans*-3,3,3-trichloro-1-nitroprop-1-ene was studied in experimental way and based on computational methods. In spite of obtained results it can be concluded the process proceeds very rapidly, under mild conditions. In a course of the reaction the expected (3SR,4RS)-1-methyl-3-nitro-4-(trichloromethyl)pyrrolidine is obtained as a single-type adduct with high yield. This was confirmed by comprehensive structural analysis such as CHN, MS, IR as well as ^{1}H and ^{13}C NMR. Based on computational study it can be observed the process may be of a polar nature. The conversion of addents is additionally stimulated by thermodynamic factors and the reaction equilibrium is evidently shifted to the area of cycloadduct. The similar protocol for analogous 32CA reactions involving other 2-substituted of the nitroethenes can be applied with high probability. For this purpose, further analysis may be helpful.

Experimental

General

Elemental analysis was carried out with a Perkin-Elmer PE-2400 CHN analyzer. IR spectra were registered on a FTS Nicolet IS 10 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-500 spectrometer (500 and 125 MHz, respectively) in $CDCl_3$. Tetramethylsilane (TMS) was used as an internal standard. HR-MS spectrum was performed on a Shimadzu LCMS-IT-TOF instrument with ES ionization (heat bock and CDL temperature 200 ºC), connected to Shimadzu Prominence chromatograph (two pumps LC-20AD equipped with Phenomenex Kinetex 2.6 µm C18 100A column (eluent: acetonitrile + water 65:35 vol). Monitoring of the reaction and control of the purity of compounds was carried out using a Knauer liquid chromatograph equipped with the UV detector and Lichrospher 5.0 µm 100-10 RP18 column, (eluent: methanol + water 75:25 vol).

Preparation of *trans*-3,3,3-trichloro-1-nitroprop-1-ene

To 35.00 g of 1,1,1-trichloro-2-acetoxy-3-nitropropane [19] dissolved in 240 mL of benzene 15.00 g of powdered sodium carbonate monohydrate was added. After refluxing vigorously for 4 h and allowing to cool, the mixture was filtered and the solvent distilled. Distillation of the residue under reduced pressure afforded 22.00 g (95,6 %) of yellow, oily, lachrymatory liquid (**2**) (b.p. 71-72/9mm) [20].

Preparation of (3SR, 4RS)-1-methyl-3-nitro-4-(trichloromethyl)pyrrolidine

A solution of *trans*-3,3,3-trichloro-1-nitroprop-1-ene (**2**) (0.76 g, 0.004 mol), sarcosine (**4**) (0.012 mol), and paraform (0.020 mol) in dry benzene (25 ml) was refluxed for 3 h. The obtained solution was filtered, and the solvent was evaporated under reduced pressure. The post-reaction mixture was separated using column chromatography on the SiO_2 as the stationary phase and using cyclohexane + ethyl acetate mixture (8:1 vol) as the mobile phase.

Yield 0,89 g (90,2 %). Pale yellow oil (**3**).

Elemental analysis: Calculated for $C_6H_9N_2O_2Cl_3$: 29.09 % of C, 11.31 % of N, 3.64 % of H.
Found: 29.14 % of C, 11.36 % of N, 3.60 % of H.

MS $(M+H)^+$ [m/z]: 246.94.

IR [cm^{-1}]: 1462 ($-CH_2-$), 1378, 1558 (NO_2), 1125, 1285 (-C-N-), 743 (C-Cl)

^{1}H NMR: (500 MHz, $CDCl_3$, 25 °C); δ = 2.34 (3H, s, CH_3), 2.61 (1H, dd, J = 9.59; J = 7.93, H-2), 3.02 (1H, dd, J = 11.34; J = 7.21, H-5), 3.45 (2H, brm, H-2' + H-5'), 4.45 (1H, ddd, J = 7.93; J = 4.11, H-3), 5.18 ppm (1H, ddd, J = 7.21; J = 4.11; J = 2.50, H-4)

^{13}C NMR: (125 MHz, $CDCl_3$, 25 °C); δ = 40.87 ($\underline{C}H_3$), 59.22 (C-2), 61.79 (C-5), 63.74 (C-3), 88.07 (C-4), 99.78 ppm ($\underline{C}Cl_3$)

Quantum-chemical calculations

All quantum-chemical calculations were performed using "Prometheus" cluster (CYFRONET regional computational center). The M06-2X functional [13] included in the GAUSSIAN 09 D.01 package [21] and the 6-311G(d) basis set were used. The similar computational level has already been successfully used for the exploration of mechanistic aspects of different cycloaddition processes [22-24]. The presence of the solvent in the reaction environment (benzene, ε = 2.2706) has been included in PCM algorithm [25].

Acknowledgements

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