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Experimental and theoretical FMO interaction studies of the Diels–Alder reaction of 5-acetyl-3-methythio-1,2,4-triazine with cyclic enamines☆

Teodozja Lipińska*

Institute of Chemistry, University of Podlasie, 3 Maja 54, 08-110 Siedlce, Poland

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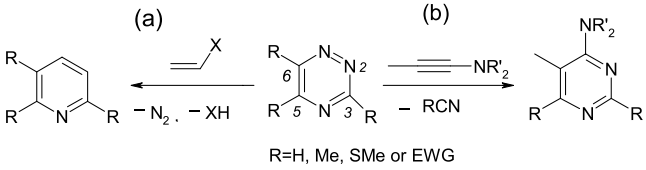
Abstract—Diels–Alder reaction of 5-acetyl-3-methylthio-1,2,4-triazine with five cyclic enamines has been reinvestigated in its preparative and theoretical aspects. Its regioselectivity has been developed practically, which is in agreement with theoretical consideration of the FMO interactions, including secondary orbital interactions in the transition state. Since the energetic demands are similar for all five pairs, it has been indicated that their reactivity differences can be explained by an influence of steric hindrance in the considered transition state. In result, the synthesis of the 3-acetyl-1-methylthiocycloalka[*c*]pyridines, as synthons for preparation of sempervirine and its analogues has been optimized. The subsequent side reaction has been detected as a serious problem, especially in the case of the six-membered enamine, which reacts with the acetyl group of the final product formed in the reaction mixture.

1. Introduction

In recent years aza-Diels–Alder reactions have been important methods for the synthesis and transformation of heterocyclic compounds.[2] Many chemists have developed applications of 1,2,4-triazines as azadienes in inverse electron demand cycloadditions [4+2],[3] both inter-[4] and intramolecular,[5] for the synthesis of many functionalized polyheterocyclic systems. The 1,2,4-triazine ring is known to undergo two different sequences consisting in Diels–Alder–*retro*-Diels–Alder reactions (DA–*r*DA).[6] The sequence that begins with cycloaddition of an electron-rich dienophile across C3–C6 of a 1,2,4-triazine moiety is more common. Then follows the loss of N_2 (*r*DA) and elimination of a small molecule HX (HNR_2 or HOR), which gives the pyridine ring as shown in Scheme 1a. Reactions of the 1,2,4-triazine ring itself[7] and its derivatives[2a,7b,8] with cyclic enamines lead to the synthesis of 3,4-annulated pyridines, important ring systems in pharmacologically interesting molecules.[8c,9] The ynamine dienophiles usually interact in the second sequence: cycloaddition across N2–C5 with subsequent loss of nitrile (*r*DA) and formation of the pyrimidine ring,[3b,4a,8a,10] (see Scheme 1b). In many cases, the two modes of the reaction can run with the formation of a mixture of products.[3b,4a]



Scheme 1. Scheme showing the two main ways in which the 1,2,4-triazine ring can undergo Diels–Alder reaction.

Many reactions with different combinations of substituted 1,2,4-triazine-azadiene with an electron-rich dienophile have been described recently.[11] However, their frontier molecular orbital (FMO) interactions, which can indicate the route of reaction, its regioselectivity and relationship between structure of reactants and the rate of reaction have not been investigated.

In our earlier investigation of the Diels–Alder reaction between 3-substituted 5-acyl-1,2,4-triazine and enamines, we demonstrated the synthetic usefulness of the replacement of –N=N– fragment of 1,2,4-triazine by –C=C– of enamines for the preparation of alkyl-heteroaryl ketones.[12] Then we applied reactions between pairs **1** and **2a–d** for obtaining 3-acetyl-1-(methylthio)cycloalka[*c*]pyridines **3a–d**, the key intermediates in the total synthesis of

☆ See Ref. 1.

Keywords: Aza Diels–Alder reaction; 1,2,4-Triazines; Frontier molecular orbitals interactions; Secondary FMOs interplay in transition state; 3-(Acetyl)-cycloalka[*c*]pyridines.
* Tel.: +48 25 6431013; fax: +48 25 6442045; e-mail: tlip@ap.siedlce.pl

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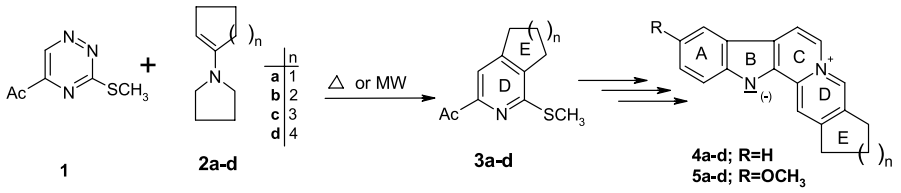


Scheme 2. Synthesis of the 3-acetyl-1-methylthiocycloalkene[*c*]pyridines **3a–d**, as synthons of the sempervirine type alkaloids, via cascade transformation of 5-acetyl-3-methylthio-1,2,4-triazine **1** with cyclic enamines.

pentacyclic indolo[2,3-*a*]quinolizine alkaloids; sempervirine **4b** (R=H, $n=2$),[13] its analogues with different E rings **4a**, **4c**,**d** (R=H, $n=1$, 3, 4)[14] and next, their methoxy derivatives **5a–d** (R=OCH_3, $n=1$–4)[15] (see Scheme 2). This paper presents the correlation of the experimental data and theoretical study of frontier molecular orbital interactions of **1** and **2a–d** in the Diels–Alder reaction in the aspect of optimization of the synthesis of the final products **3a–d**.

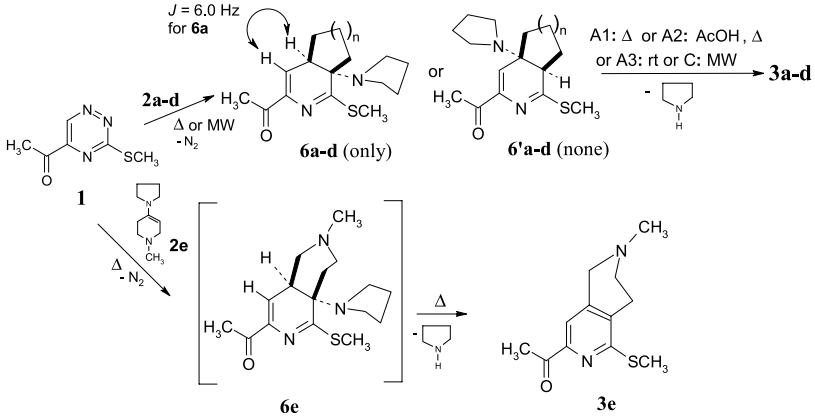
2. Results and discussion

Differences in the course of the Diels–Alder reaction between azadiene **1** and five–eight-membered cyclic enamines **2a–d** as dienophiles were observed during optimization of these processes and, in result, the yields of products **3a–d** varied. The present paper contains the proof of the correlation of the experimental data and the study of the frontier molecular orbital (FMO) interactions in this reaction. Because of the fact that the products **3a–d** are formed only in the first type of reaction (Scheme 1a), the yields should depend on regioselectivity and the rate of three-process cascade: cycloaddition of the enamines **2a–d** across C3–C6 positions of **1** (as the termini of azadiene), *retro*-Diels–Alder reaction (involves the loss of N_2) and cis-elimination (XH=pyrrolidine) towards rearomatization of the heterocyclic ring. These processes can be considered as depending on the frontier molecular orbital (FMO) interactions of reactants with the assumption that a concerted transition state exists in the first stage of a cascade reaction, and that emergence and disappearance of steric hindrance in the course of the first and further rearrangements play the most important role.

Recently, density functional theory (DFT) has been applied for full, quantitative consideration and optimization of the transition states of reactions.[16] We believe, however, that in the case of our investigated process, the basic study of the FMO interactions is fundamental[17] together with considering the possibility of emergence of the secondary (non-bonding) interaction in the course of transition state formation[18] and it gives very interesting and satisfying results.

2.1. Preparative results

2.1.1. Experimental regioselectivity of the Diels–Alder reaction of 1 with cyclic enamines 2a–e and structure elucidation of products 3a–e. In our experiments directed to the synthesis of condensed pyridines **3a–d** in the Diels–Alder reaction between 5-acetyl-3-methylthio-1,2,4-triazine **1** and enamines **2a–d** it was visible (TLC plates) that the consumption of the starting material was in all cases accompanied by the extrusion of nitrogen. This indicated that the first cycloaddition stage ran simultaneously with the *retro*-Diels–Alder reaction, causing emergence and disappearance of steric hindrance. In result, the two regioisomeric dihydropyridine systems **6a–d** or **6′a–d** (Scheme 3) can be formed as intermediates in this step, due to the two possible interaction of cyclic enamines. The second step consists of elimination of pyrrolidine and formation of the final products **3a–d**, in which the structures are independent of the regiochemistry of the dihydro-intermediates. We observed, however, that the two visible steps had different rates for enamines **2a–d**. With the increase of the enamine ring size, the rate of the first stage decreased and the rate of the second one increased. Since the reaction between **1** and the enamine with a small ring (**2a**) proceeded quickly towards a dihydropyridine-intermediate, which transformed slowly into **3a**, this intermediate compound could be isolated from the cooled reaction mixture by preparative



Scheme 3. Cascade reaction between **1** and **2a–e**.

thin-layer chromatography and its structure determined. In the ^{1}H NMR spectrum of this compound the signal of the dihydropyridine proton appears at 6.68 ppm as a doublet (J=6.0 Hz), which indicates structure **6a** (one enantiomer is shown on the Scheme 3), but not **6′a**. We observed (by TLC and ^{1}H NMR spectra) the slow rearrangement of **6a** into **3a** in solvents during isolation and measurement at room temperature. During GC/MS analysis, two substances were also observed on the chromatogram with t_R=11.9 and t_R=13.8 in ratio 12:88, which gave mass spectra with molecular peaks for **3a** (m/z=207) and **6a** (m/z=278).

We performed the reaction of **1** with 1,2,5,6-tetrahydro-*N*-methyl-4-(1-pyrrolidino)pyridine **2e** as dienophile (see Scheme 3) for the purpose of an additional regioselectivity investigation, because the structure of final product of cascade reaction in this case is influenced by regioselectivity of the first stage. From the X-ray structure of the product **3e** (Fig. 1) as 3-acetyl-6-methyl-1-methylthio-5,6,7,8-tetrahydro-2,6-naphthyridine (not 2,7-naphthyridine derivative, the second possible regioisomer), we deduced regioselectivity of the dihydrointermediate **6e**. This is in agreement with our earlier investigations of 5,6,7,8-tetrahydro-2,6-naphthyridine, which is substituted in the same way as **3e**, where in the ^{1}H NMR spectrum the NOE-effect in the resonance of *H*C4 (δ 7.44) and H_2C5 (δ 3.54) was observed.

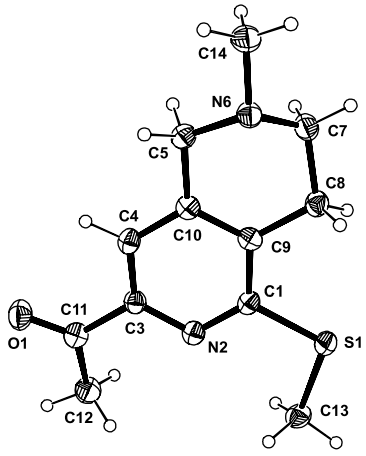
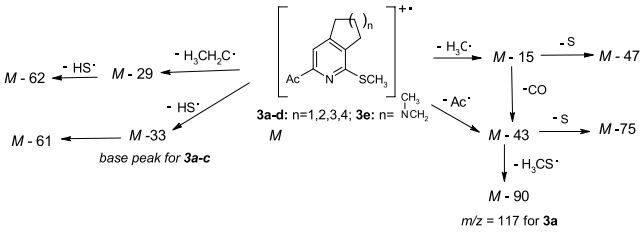


Figure 1. Molecular structure **3e** with thermal ellipsoids drawn at 50% probability level.

The two experiments discussed above show that in the reaction of 5-acetyl-3-methylthio-1,2,4-triazine **1** with all cyclic enamines **2a–e**, interactions occur between the C1′ of dienophiles **2a–e** and the C3 of the 1,2,4-triazine ring-diene **1**, and the C2′ of enamines with C6 of the azadiene, leading to formation of **6a–e** as intermediates in DA–*r*DA reaction sequences only (Scheme 3). These results are in agreement with the theoretical FMO interaction study, which is also described in this paper.

The structure of all products **3a–e** was determined by spectroscopic methods. A sharp absorption at a region 1686–1701 cm^{-1} in the IR spectra was assigned to the C=O bond. The ^{1}H NMR spectra of the **3a–e** showed only a single peak at a low field: 7.44–7.65 ppm, which indicated one aromatic proton *H*C3. In the aliphatic region of the spectra of **3a–d**, two three-proton singlets were presented for H_3CO and H_3CS and two two-proton triplets or multiplets for methylene groups bonded with pyridine ring. Other methylene groups gave multiplets in the high-field region. In this range the ^{1}H NMR spectrum of **3e** was different and corresponded to its structure. The resonance for *C*=O and H*C*3 of **3a–e** was observed in the ^{13}C NMR spectra at regions 200.0–201.0 and 113.0–118.0 ppm, accordingly. The peak for H_3*C*CO appeared at 25.8–26.2 ppm and for H_3*C*S at 12.4–13.8 ppm. The molecular ion peaks were noticeable in the electron-impact mass spectra of all products **3a–e**. The base peaks (100%) were assigned to the extrusion of ˙SH (M-33) from the molecules **3a–c**, ˙CH_3 (M-15) from the **3d** and of ˙NC_2H_6 (M-44) from the molecule **3e**. The main fragmentation paths of the molecules **3a–e** could be defined thanks to investigation of the MS spectra of these five molecules (see Scheme 4). In the mass spectrum of **3a** a three-peak sequence existed at m/z=118, 117 (M-90), 116, which indicated the existence of the naked ring skeleton of this molecule. Interestingly enough, in the spectra of **3b–e**, these peaks were also present (partial fragmentation of the aliphatic rings). In effect, the mass spectra for all products **3a–e** were identical in the region below m/z=116.



Scheme 4.

With the above mentioned results in hand, we started investigating the conditions and limitations of our method for the transformation of **1** into **3a–e**.

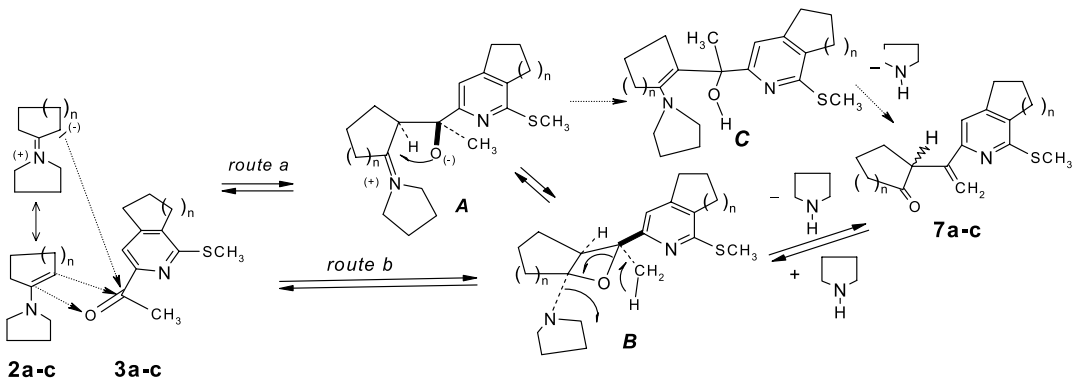
2.1.2. Optimization of the reaction conditions. We tested many solvents for the reactions of 5-acetyl-3-methylthio-1,2,4-triazine **1** with enamines **2a–e**. Some conditions and yields are shown in Table 1. It was clear that for the reactions of **1** with enamines **2a–d** the best conditions were in boiling ethanol. Reactivity of these dienophiles towards products **2a–d** was decreased when the large ring in the dienophile molecules was increased. For the reaction with enamine **2e**, that has different properties, the best conditions were in boiling dioxane. The courses of reactions were observed on TLC plates. Thus, it seemed that in the reaction of **1** with an equimolar amount of enamine **2a** in boiling solvents, complete consumption of substrate occurred within 15–20 min. When heating was stopped, the dihydro-intermediate could be isolated and its structure was established as **6a**. For complete rearrangement to compounds **3a** prolonged heating was necessary over 4–5 h (method **A1**) or the reaction mixture had to be left at room temperature for a longer period (method **A3**). The process of the pyrrolidine elimination was faster (only 15–30 min) when heating was continued in the presence of catalytic amount (10%) of acetic acid (method **A2**). There were smaller difficulties in elimination of pyrrolidine in the case

Table 1. Optimization of the synthesis of **3a–e** in the experimental scale 1 mmol of **1** in conventional heating in method **A**[a,b,c] (substrate **1** concentration 0.2 mol/dm^3), and under microwave irradiation in method **B**[d]

Entry	Enamine	Solvent	Molar ratio of **2a–e** to **1**	Reaction time		Product	Yield (%)
				For consumption of **1** in refluxing solvent	For complete transformation of the dihydrointermediate **6a–e** into final product		
1	**2a**	Benzene	1	20 min	method **A1**[a]:5 h	**3a**	50
2	**2a**	Benzene	1	20 min	method **A2**[b]:20 min	**3a**	65
3	**2a**	Benzene	1	20 min	method **A3**[c]:15 h	**3a**	52
4	**2a**	Ethanol	1	15 min	method **A1**:4 h	**3a**	65
5	**2a**	Ethanol	1	15 min	method **A2**:20 min	**3a**	75
6	**2a**	Ethanol	1	15 min	method **A3**:25 h	**3a**	57
7	**2b**	Benzene	0.95	4 h	method **A1**:5 h	**3b**	65
8	**2b**	Benzene	0.95	4 h	method **A2**:10 min	**3b**	55
9	**2b**	Toluene	0.95	2 h	—	**3b**	60
10	**2b**	Ethanol	0.95	1.5 h	method **A1**:1.5 h	**3n**	75
11	**2b**	Ethanol	0.95	1.5 h	method **A2**:10 min	**3b**	70
12	**2b**	Ethanol	0.95	1.5 h	method **A3**:15 h	**3b**	55
13	**2c**	Toluene	1.1	3 h	—	**3c**	28
14	**2c**	Ethanol	1.1	2.5 h	—	**3c**	54
15	**2c**	Chlorobenzene	1.1	method **B**[d]; 2.5 min	—	**3c**	40
16	**2d**	Toluene	2	5 h	—	**3d**	25
17	**2d**	Ethanol	2	15 h	—	**3d**	30
18	**2d**	Ethanol	2+1+1	25 h[e]	—	**3d**	23
19	**2d**	Chlorobenzene	3	method **B**[d]; 2.5 min	—	**3d**	45
20	**2e**	Ethanol	1.5	2 h	—	**3e**	25
21	**2e**	Toluene	1.5	7 h	—	**3e**	35
22	**2e**	Dioxane	1.5	5 h	—	**3e**	55

[a] Method **A1**: continuation of reflux in the same solvent.
[b] Method **A2**: refluxing in the presence of acetic acid.
[c] Method **A3**: left at room temperature.
[d] Method **B**: fast microwave heating of the high concentration reaction mixture in chlorobenzene at temperature 110 °C.
[e] Reaction without heating (room temperature 22 °C).

of **1** and **2b**, and these problems were absent in cases of **1** and **2c–e**, where new rings were larger. Products **3c–e** were formed simultaneously with disappearance of substrate **1** in reaction with the appropriate enamine. Reaction between **1** and 1-pyrrolidine-1-cyclooctene **2d** was very slow and gave a low yield using conventional heating. It turned out that the cascade process in this case was efficient when a high-concentration reaction mixture in chlorobenzene (with excess of enamine **2d**) was heated by microwave irradiation (1.5 min at 110 °C; method **B**). It means that in this case, the first step of reaction, cycloadduct [2+4] formation, had to run via the densely packed and hindered stage. In general, the speed of the first step diminished together with increasing the ring size of the enamines **2a–e** ring, which caused larger steric hindrances. However, the *retro*-Diels–Alder reactions, with N_2 extrusion, and then pyrrolidine elimination, were faster for larger rings. All reactions did not proceed cleanly. Different side products were noticed in the reaction mixture (on TLC plates), especially when the regime of process; the molar ratio of reactants and their concentration, was not respected. For enamines **2a–c**, the concentration **1** in solvent had to be no higher than 0.2 mol/dm^3. It is noteworthy than the high reactivity of enamines **2a**,**b** (and to a small degree **2c**) towards products **3a–b** was observed also as a tendency towards the formation of side products in the cases when excess of the enamines was used, and/or concentration of both reactants in solvent increased. One kind of the side-product possessing the lowest polarity (the highest R_f) was isolated from the reaction mixtures. After determination of the structure of the representative compound **7b** (see Scheme 5), it became clear that they were formed in reaction between products **3a–c** and excess



Scheme 5. Proposed mechanism of the consecutive reaction between products **3a–c** and appropriate enamine.

appropriate enamine **2a–c**, which existed in the reaction mixture. In Table 1 the optimal ratios of **2a–e** to **1** for minimization of this subsequent reaction are shown.

The best reaction conditions were established in entry 5 for **3a**, in entry 10 for **3a**, in entry 14 for **3c**, in entry 19 (under microwaves) for **3d** and in entry 22 for **3e**.

It is interesting that the strongest tendency to consecutive reaction was observed for **1** and **2b**, while it was not observed for **1** and **2d**. The side product **7b** was formed during synthesis of **3b** in all investigated methods and solvents. The best yield of **3b** (only a trace of **7b**) was obtained when **1** reacted with a deficiency of enamine **2b** and the concentration of reactants in solvents was no larger than 0.2 mol/dm^3. We noticed that in extreme conditions (*B* in experimental), when **1** reacted with double the amount of **2b** without solvent in room temperature, an exothermic reaction was observed and compound **7b** was isolated as a major product (30%), together with only 20% of **3b** and many other side products more polar than these two.

The mechanism of formation of **7a–c** in reaction of **3a–b** with the appropriate enamine is under investigation (Scheme 5). In the first stage, oxetane formation is a rational way for oxygen migration from the acetyl group to cycloalkane ring, in anhydrous reaction medium, and it can be formed in two ways. The first (route a) is preferred in polar solvents and starts with the enamine carbanion addition to acetyl group, as in the aldol type condensation. The subsequent step is the intramolecular nucleophilic attack of the oxygen on the imine carbon in the intermediate **A**, which leads to oxetane **B**. Its formation in the second possible way (route b) involves [2+2] photocyclization, like in the Paterno-Büchi reaction, and is preferred in non-polar solvents in presence of light. However, both mechanisms can take place as concurrently. The stereochemistry of oxetane **B** (one enantiomer is shown on the Scheme 5) can be determined in route a (intramolecular nucleophilic addition), as well as in route b (concerted cycloaddition). The second stage, oxetane rearrangement, is, in summary, the cis-1,4-elimination of pyrrolidine. This process can run as synchronous in six-membered transition state, where three changes are simultaneous: formation of methylene group, establishment of carbonyl group in cycloalkane from the oxetane oxygen and elimination of pyrrolidine via the intramolecular (or intermolecular) accepting proton by nitrogen from the methyl group. It seems that in the proposed mechanism, in the case of the six-membered enamine **2b**, steric hindrance does not exist, and this reaction can run more easily than for **3a**,**c** with appropriate enamine **2a**,**c**. An alternative mechanism via cycloadduct **C**, which gives product **7b** after dehydration and enamine hydrolysis, is less probable because the presence of an acidic reagent is necessary in this case. However, intermediate oxetane **B** and hydroxyenamine **C** have not been isolated so far.

We deduced the mechanism discussed above from the fact of isolation of **7b** and its structure. In order to further research the method of formation of the products **7a–c**, consisting in addition of enamine **2a–c** to acetyl group in the final products **3a–c** (Scheme 5), we have recently carried out experiments, where pure **3a–c** was reacted with appropriate enamine **2a–c** in refluxing ethanol (*C* in the experimental) or toluene. We have noticed that the equilibrium was established, when only trace concentration of compounds **7a–c** existed. This balance remained in the presence of light, but it moved towards the compounds **7a–c** after pyrrolidine was added. We have also detected in the reaction mixture other isomeric products in trace quantities. They will be investigated further. We aim at confirmation of existence of the oxetanes **B** and at the general application of the reaction of the heteroaromatic acetyl derivatives with cyclic enamines.

2.2. Study of the frontier molecular orbitals (FMOs) interactions

We studied the frontier molecular orbitals (FMOs) of the 5-acetyl-3-methylsulfanyl-1,2,4-triazine **1** as azadiene and cyclic enamines **2a–e** as dienophiles and considered their interactions in a concerted Diels–Alder reaction as a first step of a cascade rearrangement to the condensed pyridines **3a–e**. The FMOs model seemed capable of explaining the observed regioselectivity and reactivity differences.[17] Therefore, attempts were made to correlate the energies and coefficients of the FMOs for these reactants using the semi empirical MOPAC-AM1 methodology.[19] The graphs of calculated energy of the HOMOs and LUMOs of **1** (exactly) and **2a–e** (approximately) are shown in Figure 2. Their p_z coefficient pictures and values also are shown. The calculation suggests that the most efficient interaction, leading to product formation, occurs between the LUMO of the azadiene **1** ($LUMO_1$) and the HOMOs of dienophiles **2a–e** ($HOMO_{2a-e}$), not $HOMO_1$ and $LUMO_{2a-e}$. This means, it must be an inverse electron demand cycloaddition. From the picture of the p_z coefficients of $LUMO_1$ it is visible that either C3–C6 or N2–C5 positions can be the termini of diene in molecule **1**, which is in agreement with the two known reactivity sequences of 1,2,4-triazines in Diels–Alder reaction.

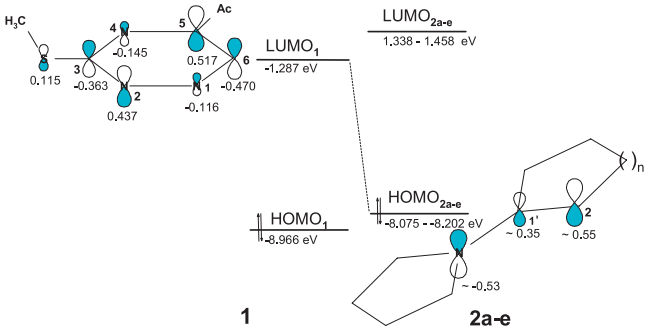


Figure 2. Calculated energy and the pictures (LCAO) of the FMOs (with p_z coefficients and their values) of **1** and **2a–e**, which interact in inverse electron demand [4+2] cycloaddition.

If one takes into consideration the fact that the larger coefficients of the FMOs of both reactants and the smaller coefficients of both reactants combine, an asynchronous transition state should be formed to predict the regioselectivity of cycloadduct. It turns out that there must be two possibilities interactions in these two directions. They are shown on the Figure 3, together with the calculated values

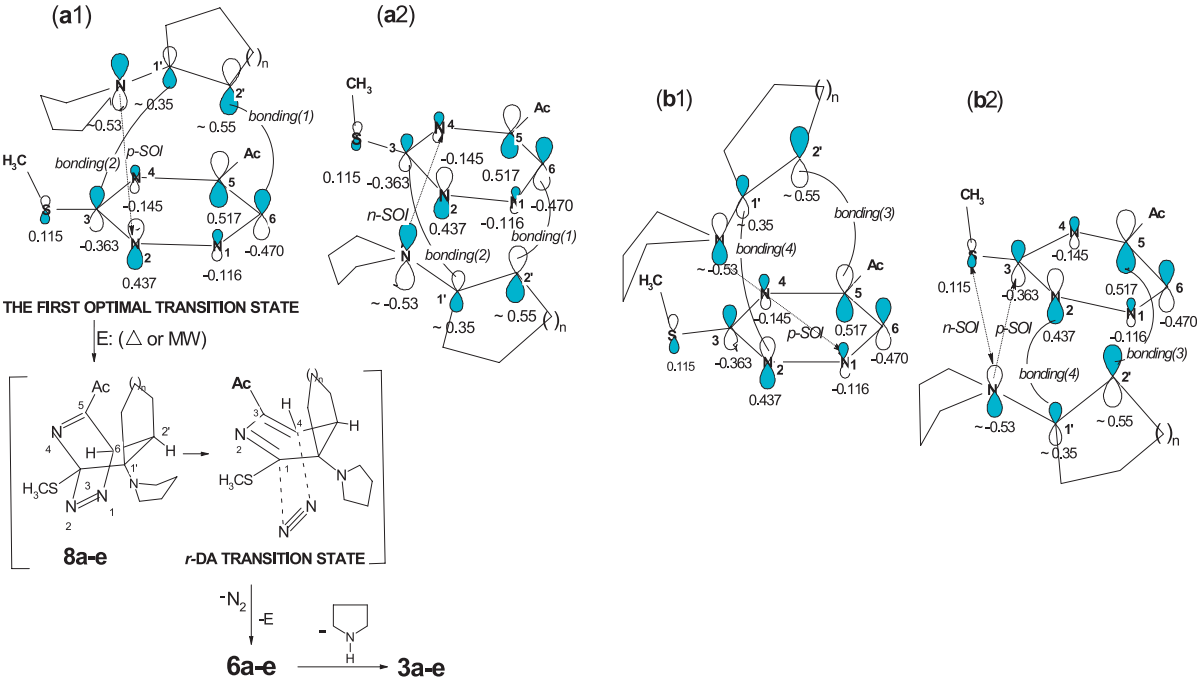


Figure 3. The study of the four possibilities of interaction of the FMOs in Diels–Alder reaction between **1** and **2a–e**: (a) two interaction ways of the enamines with the positions C3–C6 of azadiene **1**; (b) two interaction ways of the enamines with the positions N2–C5 of azadiene; (p-SOI, positive secondary orbitals interaction; n-SOI, negative secondary orbitals interaction) shows the tendency to form mainly by the (**a**1) way of the sensitive **8a–e** cycloadducts, which can limit the cascade rearrangement.

of p_z coefficients of the $LUMO_1$ and with the approximately values of p_z coefficients of the $HOMOs_{2a-e}$. The full values of the latter are given in Table 2. The energy gaps between the reactive frontier molecular orbitals are similar for all pairs **1** and **2a–e** (see Table 2, $\Delta E = E(LUMO_1) - E(HOMO_{2a-e})$) and they give no reason for different course of these reactions. Therefore, in search of a solution, we considered precisely all four possible ways of formation of the hypothetical transition state (see Fig. 3).

On Figure 3 it is visible that, when planar cyclic molecule **1** interacts with cyclic enamines **2a–e** to form (**a**1), (**a**2), (**b**1), (**b**2) possible transition states towards cycloaddition [4+2], we must take into consideration the possibility of bonding interactions between p_z coefficients (1,2,3,4), which appear at the ends of the azadiene and the dienophile molecules. In addition, other than bonding, molecular interplay can exist. Thus, it can be either beneficial and disadvantageous for transition state secondary orbital interactions (SOI). In the (**a**) cases the main interactions appear between C6 of azadiene **1** and C2′ of enamine **2a–e** (bonding (1), with larger p_z coefficients) and between C3 of **1** and C1′ of enamine (bonding (2), with smaller p_z coefficients). The first bonds are formed faster and are shorter than the second in the (**a**1) and (**a**2) transition states. Thus, there are concerted but asynchronous transition states. However, when these two ways of interaction are considered, it is visible that in the case of (**a**1), *exo*-regiochemistry of the Diels–Alder reactants, additional strong p_z-bonding interaction between N2 of azadiene and pyrrolidine nitrogen of enamine may occur. This secondary orbital interaction (SOI) is beneficial for the (**a**1) transition state stabilization (p-SOI: positive SOI). In the (**a**2) case (*endo*-regiochemistry), a small SOI between the pyrrolidine nitrogen and N4 of **1** has an adverse effect on the course of reaction (n-SOI: negative SOI). In the (**b**) situations the bonding interaction are as follows: the first between C5 of azadiene **1** and C2′ of dienophiles **2a–e** (bonding (3)), with larger p_z coefficients and the second between N2 of **1** and C1′ of **2a–e** (bonding (4), with smaller p_z coefficients). These bonding interactions are stronger than in case of the (**a**) combination because p_z(N2) and p_z(C5) coefficients are larger and their overlap with p_z coefficients of dienophiles **2a–e** are bigger, than with p_z(C3) and p_z(C6) coefficients in the (**a**) case. Aside from these, in case of the (**b**1) *exo*-regiochemistry, there is only a weak bonding interaction (p-SOI) between N1 of azadiene **1** and pyrrolidine nitrogen. In the case of (**b**2) *endo*-combination the reactants in the [4+2] cycloaddition, the p_z coefficients of pyrrolidine nitrogen must interact in transition state with two p_z coefficients: C3 and sulfur atom. The first of them has a bonding nature (p-SOI), but the second one is anti-bonding (n-SOI). In result, the reactants are, in both (**b**) cases, at a disadvantage in the transition states. In Table 2 it is shown that the differences between p_z coefficients for bonding interactions in the (**a**) and (**b**) directions (Δp_z) are similar and do not play a decisive role in the course of transition state formation and regioselectivity determination of the cascade reaction.

To sum up the above considerations, we have come to conclusion that the best situation for transition state formation is in the case (**a1**). This *exo*-combination of the azadiene moiety: C3–N4–C5–C6 and pyrrolidine nitrogen as dienophile substituent results from the secondary orbitals interaction, which can exist on the outside of the [4+2] electronic system. This is the optimal starting point for cascade transformation of compounds **1** in reaction with cyclic enamines **2a–e**. We can consider an increase in the

Table 2. The FMO energy of enamines **2a–e** with the values of p_z of their HOMOs, energy gaps between $LUMO_1$ and $HOMO_{2a-e}$ (ΔE), and differences between p_z coefficients (Δp_z) for bonding interactions in (**a**) and (**b**) directions (see Fig. 3)

No	Enamine				$\Delta E = E(LUMO_1) - E(HOMO_{2a-e}) = (-1.287) - E(HOMO_{2a-e})$ (eV)	Δp_z For bonding interaction			
	LUMO energy (eV)	HOMO				(a)		(b)	
		Energy (eV)	p_z (C1′)	p_z (C2′)	p_z (N)	(1) p_z(C6)–p_z(C2′)	(2) p_z(C3)–p_z(C1′)	(3) p_z (C5)–p_z(C2′)	(4) p_z(N2)–p_z(C1′)
2a	1.451	−8.075	0.352	0.552	0.510	6.788	−0.082	0.011	−0.035	0.085
2b	1.452	−8.144	0.377	0.575	0.549	6.857	−0.105	0.014	−0.058	0.060
2c	1.458	−8.112	0.348	0.530	0.533	6.825	−0.060	−0.015	−0.013	0.089
2d	1.434	−8.148	0.348	0.572	0.560	6.861	−0.098	−0.015	−0.055	0.089
2e	1.338	−8.202	0.348	0.557	0.550	6.915	−0.087	−0.015	−0.040	0.089

overlap of the orbitals forming the bonds as progress along the reaction path. It means that the Diels–Alder cycloadducts can have the **8a–e** structure. They can be considered as derivatives with the highest energy, which is necessary to overcome the activation barrier. The strained transition structures **8a–e** must react quickly (exothermic process) to give intermediates **6a–e** after nitrogen extrusion (*r*DA). Our considerations can be expanded in the situation when the starting formation of the first transition state and the second one run simultaneously. Then, after pyrrolidine elimination, products **2a–e** are formed. Steric hindrance increases in course of the formation of the first transition state and in the structure of cycloadducts **8a–e** for enamines with larger rings. This is the reason why the reactivity of hepta- and octa-membered enamines is smaller than penta- and hexa-membered, whereas the energetic demands are similar in all these cases. The structure of the sensitive Diels–Alder cycloadduct theoretically considered as **8a–e** is compatible with the experimentally established structure of the intermediate **6a** (^{1}H NMR) and the final product **3e** (X-ray).

3. Conclusion

In conclusion, this work contains correlations of the experimental data towards optimization and the theoretical calculations of the Diels–Alder reactions between 5-acetyl-3-methylthio-1,2,4-triazine **1** and cyclic enamines **2a–e**. We have demonstrated that the observed regioselectivity is in agreement with the theoretical considerations of the frontier molecular orbital interaction study, including secondary interplay in the course of transition state formation. Different reactivity of pairs of reactants, which have similar energetic demands, can also be explained as the influence of steric crowding of the considered transition state. In result, we have developed the synthetic strategy for the preparation of varied cycloalka[*c*]pyridines **3a–e**. The synthesized compounds contain the acetyl group in the C3 position, which opens access to further transformations, such as the Fischer indole synthesis or aldol type condensation.

4. Experimental

4.1. General

5-Acetyl-3-methylthio-1,2,4-triazine **1**[13,20] was prepared from 3-methylthio1,2,4-triazine,[21] via a two-step procedure described previously.[13] All reactions were performed under calcium chloride tube, in anhydrous solvents, which were dried in standard procedures[22] prior to use. Enamines **2a–e** were synthesized from commercial ketones and pyrrolidine (Aldrich) by Kuehne method.[23] Microwave reactor Synthewave 402 (Prolabo, 300 W, focused microwaves, open, rotating system of reaction vessel) with software (feedback temperature monitoring) was used. The course of reactions was monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm Merck silica gel plates ($60F_{254}$). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Melting points were determined on Boëtius microscopic plate and are uncorrected. All new

compounds were determined to be >95% pure by ^{1}H NMR. IR spectra (KBr pellets) were recorded on FT-IR Magna 760 (Nicolet) apparatus. Mass spectra and high-resolution measurements were obtained with an AMD 604 (Intectra, GmbH, Germany) spectrometer. GC/MS experiments were recorded on GC gas chromatograph-MS-QP550 mass detector (Shimadzu) with Zebron ZB-5, 30 M×0.25 mm ID×0.10 μM column. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz) and Mercury 400BB (400 MHz) spectrometers. Elemental analyses were obtained with Perkin-Elmer 2400-CHN analyzer. The AM1 method[19a] from the MOPAC,[19b] CAChe 5.0 Fujitsu software[19c] was employed for semi empirical calculations.

4.2. General procedures for Diels–Alder reaction between 1 and 2a–e

Method **A**. To a solution of **1** (1 mmol) in ethanol or other solvent listed in the Table 1 (5 mL) was added an enamine **2a** (1 mmol) or **2b** (0.95 mmol) or **2c** (1.1 mmol) or **2d** (2 mmol) or **2e** (1.5 mmol). The reaction mixture was refluxed under calcium chloride tube for the moment substrate **1** disappearing (monitored by TLC).

In the case of reaction between **1** and **2a**, and **1** and **2b**, an intermediate existed in the reaction mixture. Their complete transformation into products **3a** or **3b** was carried out with three ways: **A1**: continuation of reflux in the same solvent; **A2**: acetic acid (0.10 mmol) was added to the reaction mixture, which was refluxed for 20 min in the case of **3a** and 10 min in the case of **3b**; **A3**: the reaction mixture was stirred at room temperature.

Products **3c–e** were formed simultaneously with slow disappearance of substrate **1** in reaction with an excess of appropriate enamine **2c–e** in refluxing solvent.

In all reactions the solvent was removed under reduced pressure and product was isolated by silica gel column chromatography (eluent: 1:1 hexane/dichloromethane for **3a–d** and dichloromethane to 10:1 dichloromethane/acetone for **3e**).

Method **B**. To a solution of **1** (1 mmol) in chlorobenzene (0.5 mL) placed in a Pyrex cylindrical vessel was added enamine **2c** (1.1 mmol) or **2d** (2 mmol). The reaction mixture was irradiated in the Synthewave 402 microwave reactor. The temperature setpoint was programmed at 110 °C. Irradiation was stopped after 3.0 min from the moment the temperature began to rapidly increase. The reaction mixture was left to chill to 90 °C then was cooled to room temperature. Product **3c** or **3d** was isolated by silica gel column chromatography (1:1 dichloromethane/hexane).

4.2.1. 1-(1-Methylthio-6,7-dihydro-5*H*-[2]pyrindin-3-yl)-ethanone (3a). Colorless crystals with mp 68.5–69.5 °C (from dichloromethane/hexane); R_f=0.43 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (2H, quintet, J=7.6 Hz), 2.64 (3H, s), 2.70 (3H, s), 2.82 (2H, t, J=7.6 Hz), 2.94 (2H, t, J=7.6 Hz), 7.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.41 (S*C*H$_3$), 24.00 (*C*H$_2$), 26.02 (H$_3$*C*CO), 30.23 (*C*H$_2$), 32.64 (*C*H$_2$), 113.74 (*C*H), 141.01 (*C*), 151.73 (*C*), 153.38 (*C*), 154.16 (*C*), 200.09 (*C*O); IR (KBr): 3072, 2956, 2928, 2835, 1686, 1574, 1556, 1426, 1281, 1251, 1170, 923, 905, 581 cm^{-1}; EI-MS *m*/*z* (%): 207 (M$^+$, 50), 192 (10), 174 (100), 164 (8), 156 (9), 149 (12), 132 (8), 118 (5), 117 (4), 116 (5), 105 (4) 91 (3), 77 (7), 65 (7), 51 (8), 43 (10); HRMS (EI, M$^+$) calcd for $C_{11}H_{13}NOS$ 207.0718, found 207.0717. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.76; H, 6.28; N, 6.76; Found: C, 64.04; H, 6.40; N, 6.75.

4.2.2. 1-(1-Methylthio-5,6,7,8-tetrahydro-isoquinolin-3-yl)-ethanone (3b). Colorless crystals with mp 68–69 °C (from dichloromethane/hexane), described in our previous paper.[24] mp 62–63 °C (after sublimation). The new data; R_f=0.45 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.82 (2H, m), 1.84–1.92 (2H, m), 2.60 (2H, t, J=6.6 Hz), 2.61 (3H, s),2.70 (3H, s), 2.76 (2H, t, J=6.1 Hz), 7.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.99 (S*C*H$_3$), 21.87(*C*H$_2$), 22.87 (*C*H$_2$), 25.32 (*C*H$_2$), 25.83 (H$_3$*C*CO), 29.27 (*C*H$_2$), 117.96 (*C*H), 134.40 (*C*), 145.81 (*C*), 149.75 (*C*), 158.28 (*C*), 200.56 (*C*O); IR (KBr): 3064, 2933, 2920, 2866, 1691, 1579, 1549, 1415, 1394, 1357, 1287, 1240, 1174, 967, 951, 843, 819, 589 cm^{-1}; EI-MS *m*/*z* (%): 221 (M$^+$, 51), 206 (20), 188 (100), 170 (13), 160 (5), 146 (7), 130 (10), 117 (6), 103 (6), 91 (7), 77 (13), 65 (5), 51 (13), 43 (25).

4.2.3. 1-(1-Methylthio-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*c*]pyridin-3-yl)-ethanone (3c). Colorless crystals with mp 56–57 °C, (from dichloromethane/hexane); R_f=049 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59–1.67 (4H, m), 1.83–1.92 (2H, m), 2.58 (3H, s), 2.69 (3H, s), 2.77–2.83 (2H, m), 2.87–2.92 (2H, m), 7.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.85 (S*C*H$_3$), 25.80 (H$_3$*C*CO), 26.06 (*C*H$_2$), 26.88 (*C*H$_2$), 30.00 (*C*H$_2$), 32.28 (*C*H$_2$), 35.72 (*C*H$_2$), 118.17 (*C*H), 140.08 (*C*), 150.62 (*C*), 152.26 (*C*), 156.76 (*C*), 200.34 (*C*O); IR (KBr): 3066, 2945, 2921, 2849, 1701, 1574, 1545, 1445, 1417, 1393, 1350, 1350, 1291, 1261, 1194, 1149, 956, 920, 881, 843, 591 cm^{-1}; EI-MS *m*/*z* (%): 235 (70, M$^+$), 220 (65), 206 (25), 202 (100), 192 (20), 174 (65), 160 (18), 144 (9), 130 (7), 118 (9), 117 (8), 116 (8), 105 (5), 91 (10), 77 (10), 65 (6), 51 (11), 43 (12). Anal. Calcd for $C_{13}H_{17}NOS$*:* C, 66.34; H, 7.28; N,5.95; Found: C, 66.20; H, 7.35; N,5.85.

4.2.4. 1-(1-Methylthio-5,6,7,8,9,10-hexahydro-cycloocta-[*c*]pyridin-3-yl)-ethanone (3d). Colorless crystals with mp 101–102 °C, (from dichloromethane/hexane); R_f=0.52 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.42 (4H, m), 1.62–1.84 (4H, m), 2.62 (3H, s), 2.71 (3H, s), 2.75–2.81 (2H, m), 2.88–2.94 (2H, m), 7.54 (1H, s); ^{13}C NMR 100 MHz, $CDCl_3$: δ 13.51 (S*C*H$_3$), 25.82 (H$_3$*C*CO), 25.86 (*C*H$_2$), 26.01 (*C*H$_2$), 27.03 (*C*H$_2$), 28.10 (*C*H$_2$), 31.46 (*C*H$_2$), 32.37 (*C*H$_2$), 118.25 (*C*H), 137.72 (*C*), 150.36 (*C*), 150.75 (*C*), 157.40 (C), 200.52 (*C*O); IR (KBr): 3064, 2955, 2918, 2845, 1694, 1573, 1547, 1386, 1350, 1295, 1264, 1195, 1159, 1082, 1014, 899, 839, 598 cm^{-1}; EI-MS *m*/*z* (%): 249 (60, M+), 234 (100), 220 (25), 216 (32), 206 (31), 202 (28), 188 (25), 174 (12), 162 (5), 144 (4), 130 (9), 118 (9), 117 (8), 116 (9), 105 (6), 91 (10), 77 (12), 65 (9), 51 (12), 43 (20); HRMS (EI, M+) calcd for $C_{14}H_{19}NOS$ 249.1184, found 249.1192.

4.2.5. 1-(1-(Methylthio)-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl)-ethanone (3e). Yellow crystals with mp

102.5–103 °C, (from dichloromethane/diethyl ether, anhydrous); R_f=0.31 (3:1 dichloromethane/acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (3H, s), 2.62 (3H, s), 2.70 (3H, s), 2.74 (4H, s), 3.54 (2H, s), 7.44 (1H, s); NMR (100 MHz, $CDCl_3$): δ 12.85 (S*C*H$_3$), 25.79 (H$_3$*C*CO), 25.88 (N*C*H$_3$), 45.71 (*C*H$_2$), 51.89 (*C*H$_2$), 57.07 (*C*H$_2$), 115.21 (*C*H), 131.56 (*C*), 143.52 (*C*), 150.22 (*C*), 158.24 (*C*), 200.20 (*C*O); IR (KBr): 3066, 2966, 2920, 2837, 2774, 1690, 1580, 1555, 1415, 1367, 1348, 1291, 1247, 1177, 1126, 1061, 951, 902, 858, 809, 590 cm^{-1}; EI-MS *m*/*z* (%): 236 (70, M$^+$), 221 (54), 203 (33), 193 (37), 192 (100), 189 (8), 178 (4), 174 (15), 160 (4), 150 (11), 136 (4), 118 (4), 117 (3), 104 (3), 91 (3), 77 (4), 65 (4), 51 (6), 43 (7); HRMS (EI, M$^+$) calcd for $C_{12}H_{16}N_2OS$ 236.0983, found 236.0980. The X-ray structure is shown (Fig. 1) and its data are listed below.

4.3. Isolation and structure determination of intermediate of 6a

The mixture of 5-acetyl-3-methylthio-1,2,4-triazine **1** (42 mg, 0.25 mmol) and 1-(1-cyclopenen-1-yl)-pyrrolidine **2a** (0.25 mmol) in ethanol (2 mL) was refluxed for 15 min and cooled to 0 °C. TLC monitoring (50:1 dichloromethane/acetone) showed that the substrate **1** (R_f=0.65) disappeared but only a trace of product **3a** (R_f=0.75) existed in the reaction mixture besides predominantly the most polar compounds (R_f=0.28). The latter was isolated by preparative thin-layer chromatography using 50/1 dichloromethane/acetone as mobile phase. A white substance (53 mg, ~75%) was obtained, which was stored below 0 °C. In GC/MS measurements of this substance were observed two compounds: **3a** and **6a** on the chromatogram in ratio 12:88 with retention times t_R=11.9 and t_R=13.8, respectively, which gave MS spectra: for **3a** *m*/*z* (%): 207 (M$^+$, 40), 192 (6), 174 (100), 164 (5), 156 (8), 149 (5), 132 (8), 118 (5), 117 (4), 116 (5), 105 (4), 91 (8), 77 (8), 65 (7), 51 (9), 43 (80); for **6a** *m*/*z* (%): 278 (M$^+$, 9), 263 (57), 231 (97), 209 (6), 203 (13), 188 (15), 174 (10), 162 (10), 148 (7), 136 (100), 118 (11), 96 (9), 91 (16), 70 (47), 55 (39), 43 (85). The ^{1}H NMR spectrum also showed the presence of two compounds in the ratio 9:1, which was calculated from the integration ratio of peaks: 6.68 ppm (1H, d, J=6 Hz, for **6a** *H*C4) and 7.64 ppm (1H, s, *H*C4 for **3a**). This spectrum also showed two singlets at 2.43 and 2.48 ppm for resonance of two methyl groups of **6a**. Other aliphatic protons (15H) of this substance gave wide-ranging multiplets in 2.9–1.5 ppm region.

4.4. Isolation and structure determination of side product 7b

A. Reaction between **1** and **2b** *in molar ratio 1:2 in ethanol*. To a solution of 5-acetyl-3-methylthio-1,2,4-triazine **1** (169 mg, 1 mmol) in ethanol (5 mL) was added 1-(1-cyclohexen-1-yl)-pyrrolidine **2b** (2 mmol). The reaction mixture was refluxed for 5 h and cooled to room temperature. TLC monitoring (50:1 dichloromethane/acetone) showed that substrate **1** (R_f=0.65) disappeared but besides the product **3b** (R_f=0.77) the less polar compound **7b** (R_f=0.90) existed in the reaction mixture. After removing solvent under reduced pressure, careful isolation of products was achieved by column chromatography using dichloromethane/hexane 1:2 to 1:1 as eluent. Pure compound **7b** was obtained (60 mg, 20%) and then pure **3b** (44 mg, 20%). The purity of products were analyzed by TLC (dichloromethane; R_f for **1**, **3b**, **7b** was measured as 0.11, 0.45 and 0.70), GC/MS and ^{1}H NMR.

B. Reaction between **1** and **2b** *in molar ratio 1:2 without solvent*. To pure **1** (169 mg, 1 mmol) under argon was added dropwise **2b** (2 mmol) at room temperature during 5 min. Vigorous nitrogen extrusion and temperature increase to 40 °C occurred. Complete consumption of substrate **1** was observed (TLC monitoring using dichloromethane) after stirring for 30 min. The reaction mixture was resolved by column chromatography using dichloromethane/hexane 1:2 to 1:1 as eluent. Compound **7b** (90 mg, 30%) with R_f=0.70 (dichloromethane) and t_R=15.8 min (base peak *m*/*z*=301) was first isolated and then an intermediate fraction (35 mg, 12%), which contained **7b** and a trace of compound isomeric to **7b** with R_f=0.62 (dichloromethane) and t_R=16.2 min (base peak *m*/*z*=301) and next pure **3b** (44 mg, 20%).

C. Reaction between **3b** and **2b** *in ethanol*. To the solution of **3b** (110 mg, 0.5 mmol) in ethanol (2.5 mL) was added 1-(1-cyclohexen-1-yl)-pyrrolidine **2b** (0.5 mmol). The reaction mixture was refluxed under nitrogen for 3 h. It was observed (TLC monitoring, dichloromethane) that only trace concentration of **7b** was present in the reaction mixture besides starting material **3b**. Next, pyrrolidine (0.5 mmol) was added to the reaction mixture and reflux was continued for 3 h. After cooling, the solvent was evaporated under reduced pressure. The residue was resolved by column chromatography to afford: **7b** (39 mg, 26%), then an intermediate fraction (28 mg, 10%), which contained **7b** and its isomer in the molar ratio 1:2.5 (by GC/MS) and **3b** (17 mg, 15%). The purity of products were analysed by TLC (dichloromethane), GC/MS and ^{1}H NMR.

4.4.1. 2-[1-(1-Methylthio-5,6,7,8-tetrahydro-isoquinolin-3-yl)-vinyl]-cyclohexanone (7b). Colorless crystals with mp 52–53 °C, (from dichloromethane/hexane); R_f=0.70 (dichloromethane); GC/MS: 97/3 mixture of **7b**/its isomer was observed on the chromatogram with retention times t_R=15.8 (95%) and t_R=16.2 (3% *m*/*z*=301). MS spectrum for **7b** *m*/*z* (%): 301 (M$^+$, 67), 286 (95), 284 (45), 272 (78), 258 (60), 244 (45), 240 (61), 231 (77), 226 (40), 212 (10), 206 (13), 198 (11), 193 (28), 178 (100), 163 (12), 150 (12), 144 (16), 130 (30), 117 (18), 103 (22), 91 (26), 77 (33), 53 (31), 41 (91); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.68 (4H, m), 1.72–1.82 (2H, m), 1.83–1.91 (2H, m), 1.98–2.05 (4H, m), 2.61 (2H, t, J=6.5 Hz), 2.62 (3H, s), 2.76 (2H, t, J=5.6 Hz), 3.85 (2H, s), 5.56 (1H, br s), 7.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.12 (S*C*H$_3$), 21.88 (*C*H$_2$), 22.11 (*C*H$_2$), 22.41 (*C*H$_2$), 22.86 (*C*H$_2$), 25.41 (*C*H$_2$), 28.54 (*C*H$_2$), 29.29 (*C*H$_2$), 29.68 (*C*H$_2$), 46.06 (*C*H), 118.47 (*C*H), 125.50 (=*C*H$_2$), 132.40 (*C*), 134.38 (*C*), 145.89 (*C*), 149.62 (*C*), 158.14 (*C*), 200.44 (*C*O); IR (KBr): 3068, 2929, 2853, 2830, 1692, 1576, 1548, 1426, 1402, 1390, 1328, 1283, 1224, 1141, 1033, 997, 843, 762, 613; EI-MS *m*/*z* (%): (301 M$^+$, 100), 286 (72), 284 (45), 273 (32), 272 (57), 258 (48), 244 (30), 240 (46), 231 (60), 226 (28), 212 (72), 206 (12), 198 (7), 193 (24), 178 (70), 163 (9), 150 (7), 135 (7), 117 (10), 116 (7), 103 (11), 91 (8), 79 (6), 77 (35), 67 (29), 53

(6), 41 (15); HRMS (EI, M^+) calcd for $C_{18}H_{23}NOS$ 301.15004, found 301.14846.

4.5. Crystal data for 3e

$C_{12}H_{26}N_2O_2S$: $M=262.41$, crystal dimensions $0.60\times0.40\times0.30$ mm^3, monoclinic, space group P 21/c (no. 14), $a=7.9070(3)$ Å, $b=14.7600(7)$ Å, $c=21.5930(8)$ Å, $\beta=110.477(3)°$, $U=2360.82(17)$ Å^3, $Z=4$, $F(000)=295$, $D_c=0.738$ g m^3, $T=100(2)$ K, μ(Mo Kα)$=4.19$ mm^{-1}, Nonius Kappa-CCD diffractometer, $\theta_{max}=24.71°$, 3065 unique reflections, which were used in all calculations. The structure was solved by direct methods using the SHELXS-97 program[24] was refined by full matrix least-squares on F^2 using the program SHELXL-97.[25] H-atoms were included in idealized positions and refined isotropically. Refinement converged at $R1=0.0553$, $wR2=0.0908$ for all data and 295 parameters ($R1=0.0418$, $wR2=0.0849$ for 2569 reflections with $I_o>2\sigma(I_o)$). The goodness-of-fit on F^2 was equal 1.068. A weighting scheme $w=[\sigma^2(F_o^2+(0.0418P)^2+3.1964P)]^{-1}$ where $P=(F_o^2+2F_c^2)/3$ was used in the final stage of refinement. The residual electron density$=0.20/-0.21$ e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-264189. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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