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REACTION OF 3-HYDRAZONO-1,1,1-TRIFLUORO-2-ALKANONES WITH LAWESSON REAGENT ACCESSING 6-TRIFLUOROMETHYL- 3,6-DIHYDRO-2H-[1,3,4]THIADIAZINES

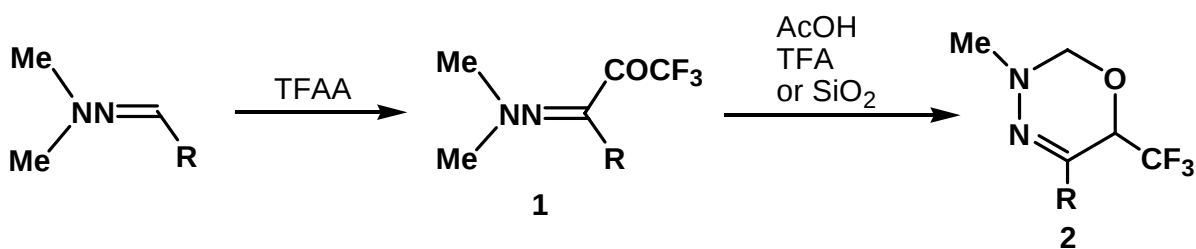
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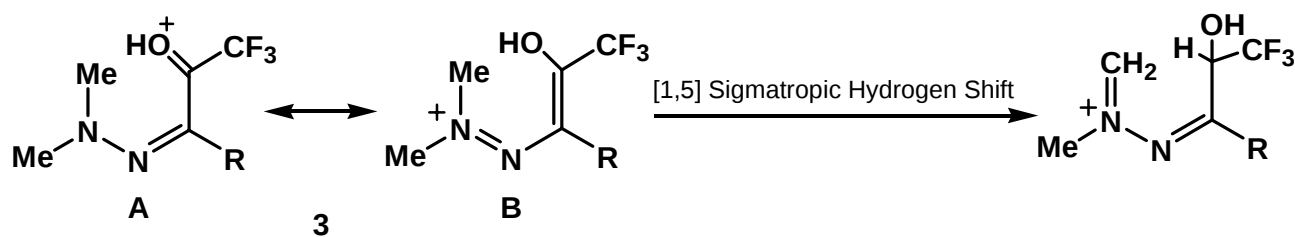
Abstract - The reaction of 3-dimethylhydrazono-1,1,1-trifluoro-2- alkanones (**1**) with Lawesson reagent affording 6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]thiadiazines (**4**) was elucidated in detail. The results indicate [1,5]sigmatropic hydrogen shift from *N*-methyl group to thiocarbonyl carbon on 3-dimethylhydrazono-1,1,1-trifluoro-2-alkanethiones (**5**) should readily proceed as a key step in this cyclization reaction. Similar [1,5]sigmatropic hydrogen shift on selenium analogues of **1** as well as that on imines derived from **1** are also studied on the basis of molecular orbital calculations.

INTRODUCTION

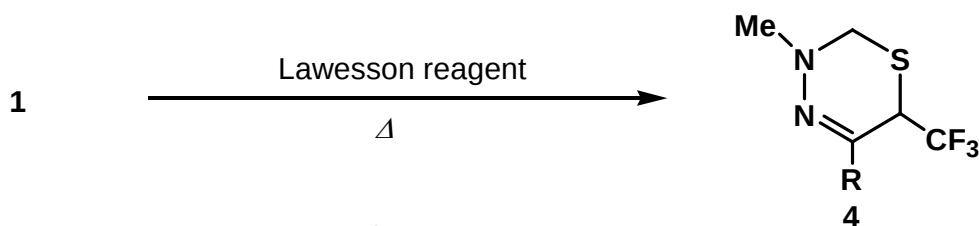
Fluorine-containing heterocycles are very fascinating target for synthetic organic chemists because of their potentially high physiological activities.¹⁻⁴ Previously we reported a novel cyclization reaction of 3-dimethylhydrazono-1,1,1-trifluoro-2-alkanones (**1**)⁵ in the presence of acid catalysts accessing 6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazines (**2**) (Scheme 1).^{6,7} Our recent study⁸ on the basis of molecular orbital calculations strongly suggested [1,5]sigmatropic hydrogen shift from *N*-methyl



Scheme 1

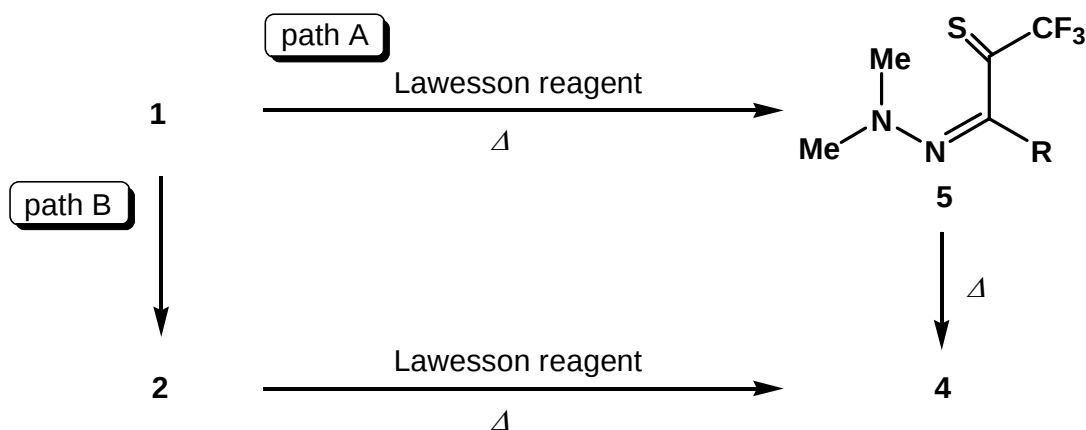


group to carbonyl carbon on cations (**3**, **A**) to be a key step for this cyclization reaction (Scheme 2). On the other hand, we found an analogous cyclization reaction proceeds to afford 6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]thiadiazines (**4**) when **1** is treated with Lawesson reagent (Scheme 3).⁹ This thiadiazine formation reaction occurs on more extended substrates than the former oxadiazine formation reaction in Scheme 1. In addition, no acid catalyst is necessary for the reaction from **1** to thiadiazines (**4**). These findings prompted us to study this interesting thiadiazine formation reaction more in detail.



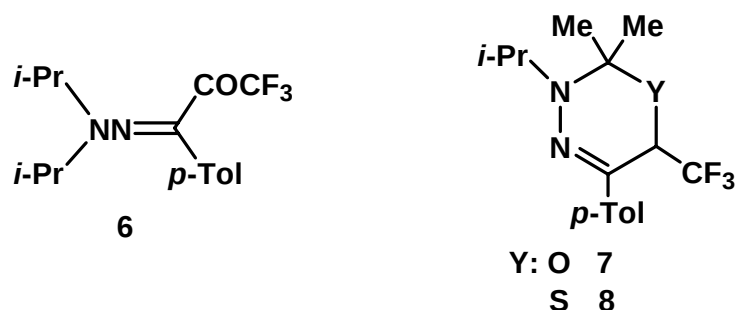
RESULTS AND DISCUSSION

As is shown in Scheme 4, two pathways are possible for the reaction from 3-dimethylhydrazono-1,1,1-trifluoro-2-alkanones (**1**) to thiadiazines (**4**). One is the pathway from **1** to **4** via 3-dimethylhydrazono-1,1,1-trifluoro-2-alkanethiones (**5**) as intermediates (path A). The other is that containing cyclization reaction from **1** to oxadiazines (**2**) and subsequent O-S exchange reaction accessing **4** (path B). Taking it into account that Lawesson reagent is one of convenient reagents to prepare thiocarbonyl compounds from

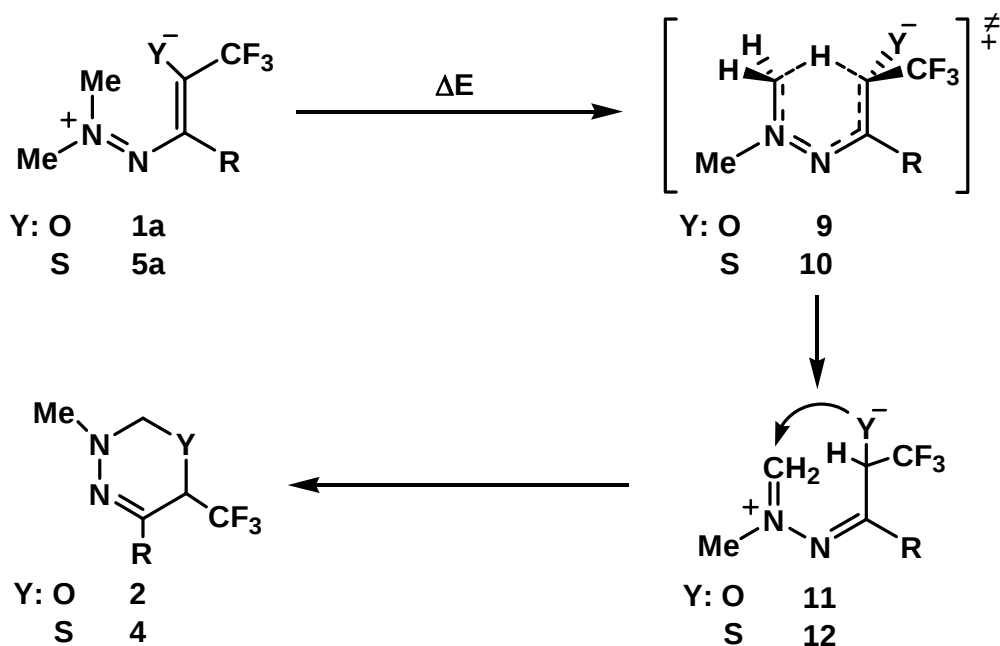


carbonyl compounds, path A seems to be more reasonable than path B. However oxadiazine (**2**, R= Ph) was yielded when hydrazoneketone (**1**, R= Ph) was heated for 16 h in refluxing CCl_4 ⁵ and, indeed, the transformation of **2** (R= *p*-Tol) to thiadiazine (**4**, R= *p*-Tol) with the use of Lawesson reagent readily occurred in refluxing benzene.⁹ These facts suggest a possibility of path B.

To clarify whether thiadiazines (**4**) form along path A or path B, we tried to detect intermediates by sampling experiment about the reaction of **1** (R= *p*-Tol) with Lawesson reagent. However, we could detect neither hydrazoneothione (**5**, R= *p*-Tol) nor oxadiazine (**2**, R= *p*-Tol) at any stages of the reaction in spite of careful inspection of ^1H NMR spectra of all samples of the reaction mixture.



Although our attempt to detect the reaction intermediates resulted in failure, the following results apparently reveal that path B is unlikely. The reaction of **1** (R= H) with Lawesson reagent in refluxing benzene afforded the corresponding thiadiazine (**4**, R=H) in 49% yield,⁹ whereas **1** (R= H) was remained intact and no oxadiazine (**2**, R= H) was obtained under the controlled conditions in the absence of Lawesson reagent. Similarly, thermal reaction of hydrazoneketone (**6**) which could be converted easily to thiadiazine (**8**) on treatment with Lawesson reagent, did not afford the corresponding oxadiazine (**7**).⁹



Scheme 5

From these facts, we concluded that the reaction of hydrazoneketones (**1**) affording thiadiazines (**4**) proceeds along path A.

Taking it into consideration that a key step of acid catalyzed cyclization reaction of hydrazoneketones (**1**) affording oxadiazines (**2**) is [1,5]sigmatropic hydrogen shift from *N*-methyl group to carbonyl carbon on cations (**3**),⁸ we studied about analogous [1,5]sigmatropic hydrogen shift on hydrazone thiones (**5**) together with that on hydrazoneketones (**1**). As is illustrated in Scheme 5, annulation of betaines (**11** and **12**) after the hydrogen shift leads to the corresponding oxadiazines (**2**) and thiadiazines (**4**), respectively. On the basis of the 6-31G* level density functional calculations (RB3LYP/6-31G*//RB3LYP/6-31G*), we estimated transition state structures **9**, **10** (Figure 1) as well as activation energies (Table 1) for [1,5]sigmatropic hydrogen shift on ketones (**1a**) and thiones (**5a**) in Scheme 5.

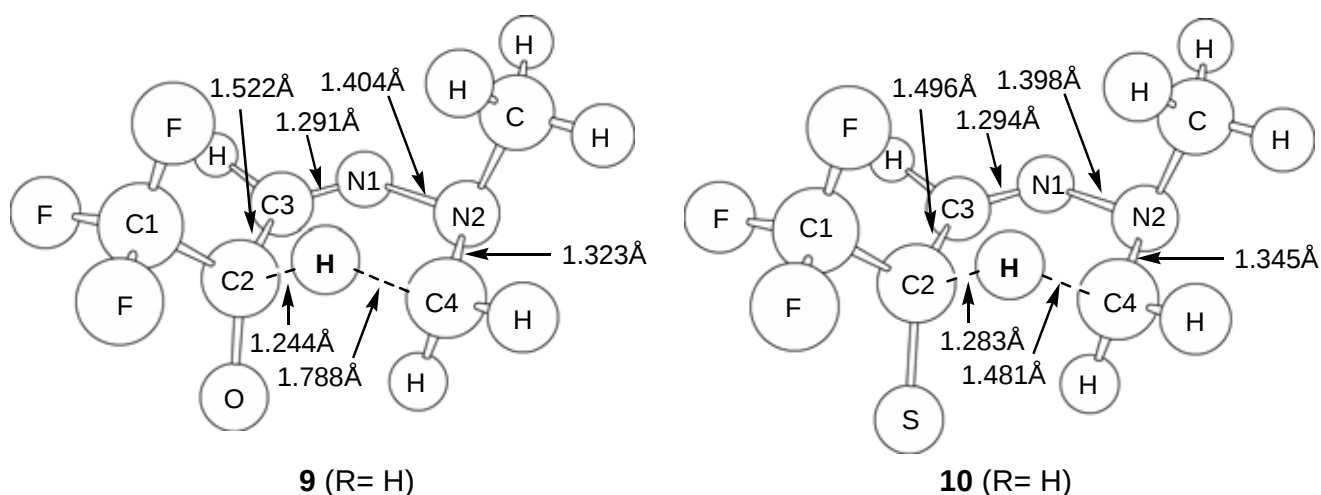


Figure 1

Activation energy (ΔE) of [1,5]sigmatropic hydrogen shift is estimated as 57.0 kcal/mol for **1a** (R= H) and 40.1 kcal/mol for **5a** (R= H). Relatively high activation energy for ketone (**1a**, R= H), which is ca. 17 kcal/mol higher than that for thione (**5a**, R= H), is compatible with the experimental results where **1** (R= H) could not be converted to oxadiazine **2** (R= H) whereas **1** (R= H) treated with Lawesson reagent gave

Table 1. Activation energy (ΔE) of [1,5]sigmatropic hydrogen shift on **1a** and **5a**.

Substrate	R	Y	ΔE (kcal/mol)
1a	H	O	57.0
5a	H	S	40.1
1a	Ph	O	49.2 (52.9) ^a
5a	Ph	S	32.5 (37.3) ^a

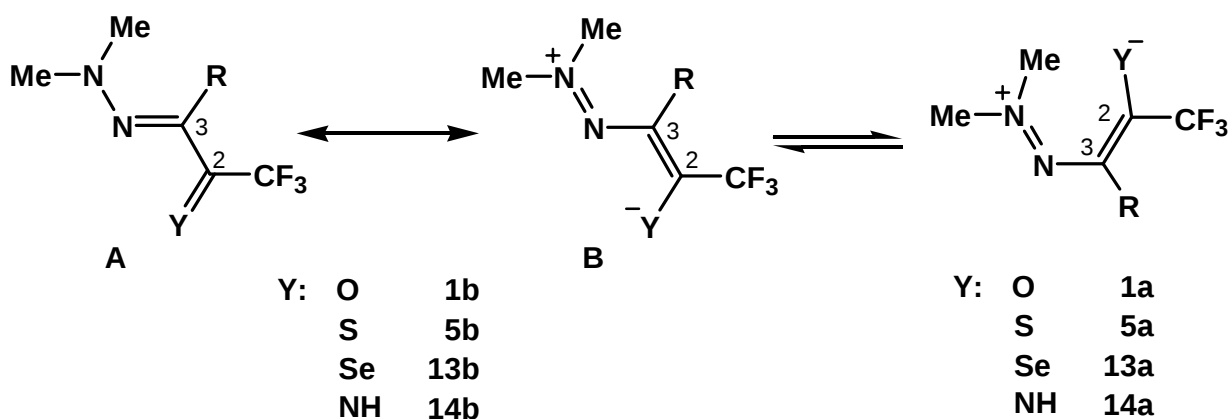
a) Values in parentheses are ΔE calculated using RMP2/6-31G*//RMP2/6-31G*.

thiadiazine (**4**, R= H) successfully.⁹ Phenyl substituent at C3 decreases ΔE on both ketones (**1a**) and thiones (**5a**). In these cases too, ΔE for **5a** (R= Ph) is ca. 17 kcal/mol lower than that for **1a** (R= Ph). The results of calculation clearly reveal that [1,5]sigmatropic hydrogen shift occurs more easily on thiones (**5a**) than ketones (**1a**). The activation energy values, 30 – 40 kcal/mol for thiones (**5a**) are consistent with the reaction conditions from **1** to **4** in Scheme 3.

Taking above all results into consideration, we can present one of the most reasonable mechanism for the reaction from hydrazoneketones (**1**) to thiadiazines (**4**) as follows. Lawesson reagent transforms **1** to thioketones (**5**; **5a**), and subsequent [1,5]sigmatropic hydrogen shift from *N*-methyl group to thiocarbonyl carbon on **5** (**5a**) affords betains (**12**) followed by intramolecular nucleophilic attack of S⁻ toward terminal CH₂ on **12** to give thiadiazines (**4**) (Scheme 5).¹⁰

In Table 2 are listed Mulliken bond populations¹¹ of N-N, N-C3, and C2-C3 bonds in ketone (**1b**, R= H) and thione (**5b**, R= H) (Scheme 6).¹² Multiple bonding character of N-N and C2-C3 bonds in **5b** increases compared to that in **1b**. In contrast, multiplicity of N-C3 bond in **5b** is less than that in **1b**. These indicate more enhanced contribution of canonical form **B** on thiones (**5b**) in comparison with ketones (**1b**). Apparently the more dienic character of **5** (**5b**) is correlated with the lower activation energy for [1,5]sigmatropic hydrogen shift on **5** (**5a**).

Mulliken bond populations were also calculated about selenones (**13b**; Y= Se) and imines (**14b**; Y= NH),

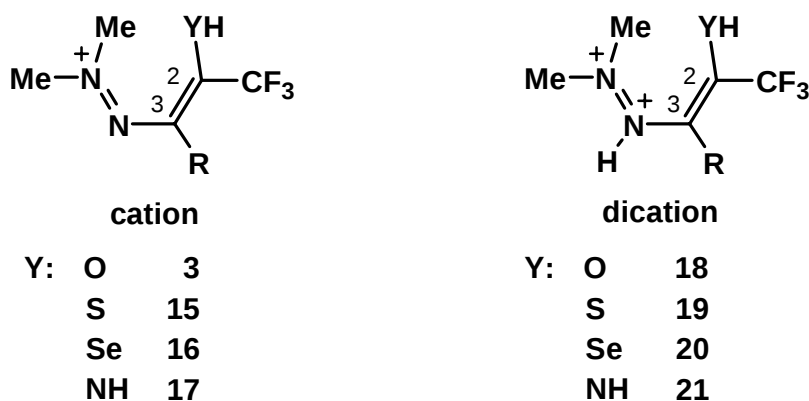


Scheme 6

Table 2. Mulliken bond populations of N-N, N-C3, and C2-C3 bonds in **1b**, **5b**, **13b**, and **14b**.

Molecule (R= H)	N - N	N - C3	C2 - C3
1b	1.254	1.518	1.024
5b	1.260	1.489	1.123
13b	1.263	1.462	1.160
14b	1.176	1.579	1.003

which are seen in Table 2. The values reveal more enhanced dienic character in **13b** in comparison with thiones (**5b**), and less contribution of canonical form **B** in **14b** compared to ketones (**1b**). These results suggest that the corresponding [1,5]sigmatropic hydrogen shift from *N*-methyl group to C2 proceeds more easily on selenones (**13a**) than on thiones (**5a**), but hardly occurs on imines (**14a**). On the other hand, our previous investigation⁸ indicates that activation energy of the corresponding [1,5]sigmatropic hydrogen shift decreases in the order of ketones (**1a**), cations (**3**), and dications (**18**).



Taking these findings into consideration, we computed activation energies (ΔE) of [1,5]sigmatropic hydrogen shift on the corresponding cations (**15** – **17**), dications (**19** – **20**), and neutral molecules (**5a**, **13a**, **14a**) of thiones, selenones, and imines. The results are summarized in Table 3.

In each series of neutral molecules, cations, and dications, the activation energies decrease in the order

Table 3. Activation energies (ΔE , kcal/mol) of [1,5]sigmatropic hydrogen shift.

Neutral molecules				Cations				Dications			
	Y	R	ΔE		Y	R	ΔE^a		Y	R	ΔE^a
1a	O	H	57.0	3	O	H	38.1 ^b (-18.9)	18	O	H	34.6 ^b (-22.4)
1a	O	Ph	49.2	3	O	Ph	28.8 ^b (-20.4)	18	O	Ph	18.1 ^b (-31.1)
5a	S	H	40.1	15	S	H	33.5 (-6.6)	19	S	H	29.5 (-10.6)
5a	S	Ph	32.5	15	S	Ph	23.1 (-9.4)	19	S	Ph	13.9 (-18.6)
13a	Se	H	36.1	16	Se	H	31.8 (-4.3)	20	Se	H	27.5 (-8.6)
13a	Se	Ph	28.4	16	Se	Ph	22.2 (-6.2)	20	Se	Ph	13.6 (-14.8)
14a	NH	H	64.8	17	NH	H	36.6 (-28.2)	21	NH	H	38.5 (-26.3)
14a	NH	Ph	59.0	17	NH	Ph	26.4 (-32.6)	21	NH	Ph	20.8 (-38.2)

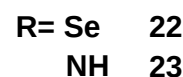
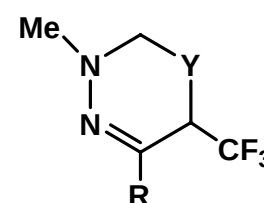
a) Values in parentheses are energy differences from ΔE for the corresponding neutral molecules.

b) Ref. 8

of ketones ($Y=O$), thioketones ($Y=S$), and selenoketones ($Y=Se$) when R is fixed as either H or Ph . These results are comparable with the suggestion on the basis of Mulliken bond populations as mentioned above. In all cases of ketones (**1a**), thioketones (**5a**), selenoketones (**13a**), and imines (**14a**), protonation reduces ΔE (series of cations) and diprotonation additionally diminishes ΔE (series of dications) except for the case of **21** ($R=H$). Protonation is found to be effective especially in the system of ketones (**1a**) and imines (**14a**). Acid catalysis is also predicted to be effective for [1,5]sigmatropic hydrogen shift on thioketones (**5a**) and selenoketones (**13a**). It is, moreover, exhibited that Ph substituent at $C3$ reduces activation energy in the range of ca. 6 – 18 kcal/mol. In particular, ΔE values for dications **18** ($R=Ph$), **19** ($R=Ph$), and **20** ($R=Ph$) are very small, less than 20 kcal/mol. This suggests that with the use of appropriate acid catalyst [1,5]sigmatropic hydrogen shift on thioketones (**5**; **5a**) and selenoketones (**13a**) would proceed successfully even at ambient temperature, since the corresponding [1,5]sigmatropic hydrogen shift on ketones (**1**; **1a**) readily occurs at room temperature in the presence of TFA.⁸

CONCLUSION

In conclusion, we can present the most reasonable mechanism for the cyclization reaction of 3-dimethyldrazono-1,1,1-trifluoro-2-alkanones (**1**) with Lawesson reagent affording 6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]thiadiazines (**4**). Molecular orbital calculations suggest a concerted [1,5]sigmatropic shift of *N*-methyl hydrogen to thiocarbonyl carbon on thioketones (**5**), of which activation energy is lower than that of the corresponding [1,5]sigmatropic hydrogen shift on ketones (**1**) yielding 6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]oxadiazines (**2**), to be a key step in the overall reaction processes. Moreover, the results predict a possibility of new synthetic pathways accessing 6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]selenadiazines (**22**) and 6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]triazines (**23**).



COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 02.¹³ All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP¹⁴ level. The starting geometries employed for all optimizations were resulted from semi-empirical PM3¹⁵ optimizations. The calculations for energy of intermediates (**1**; $R=Ph$, **5**; $R=Ph$) as well as transition states (**9**; $R=Ph$, **10**; $R=Ph$) were also taken with the 6-31G* basis set

at MP2¹⁶ level together with B3LYP level.

EXPERIMENTAL

Sampling Experiments for the Reaction of 3-Dimethylhydrazono-3-(*p*-tolyl)-1,1,1-trifluoro-2-propanone (**1**, R= *p*-Tol) with Lawesson Reagent

A solution of **1** (R= *p*-Tol, 258.2 mg, 1 mmol) and Lawesson reagent (208.4 mg, 0.5 mmol) in benzene (50 mL) was stirred at 80 °C under nitrogen. After 0.5, 1, 3, and 5 h, each 1.25 mL of the reaction mixture was pulled out by a syringe. After evaporation of the solvent, the residues (sample 1, 2, 3, and 4, respectively) were analyzed by ¹H NMR spectroscopy. The ratio (**1** : **4**) of each sample calculated from signal intensities of the corresponding NMe protons^{5,9} was 19 : 81 (after 0.5h), 36 : 64 (after 1 h), 65 : 35 (after 3 h), and 71 : 29 (after 5 h).

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