HETEROCYCLES, Vol. 53, No. 5, 2000, pp. 1065 – 1074, Received, 27th January, 2000

[4+2] CYCLOADDITION REACTION OF 3-HYDRAZONO-1,1,1-TRIFLUORO-2-ALKANONES TO 4,5-BIS(TRIFLUOROMETHYL)PYRIDAZINES

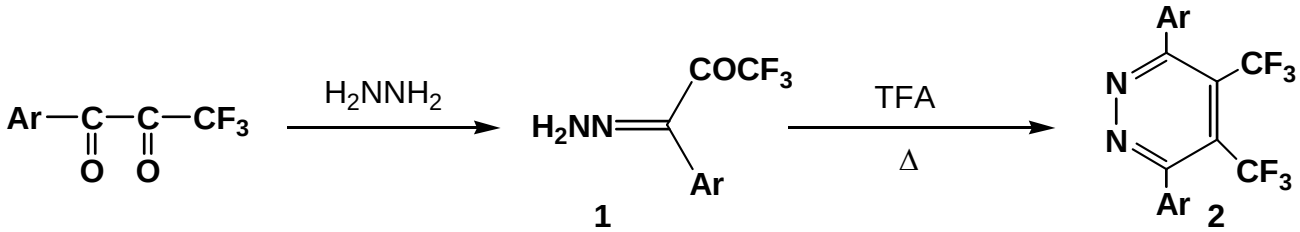
Yasuhiro Kamitori*

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Kobe 657-8501, Japan, e-mail: kamitori@cx.kobe-u.ac.jp

Abstract - Mechanisms for the reaction of 3-hydrazono-1,1,1-trifluoro-2-alkanons (**1**) to 4,5-bis(trifluoromethyl)pyridazines (**2**) in the presence of TFA are discussed on the basis of the 6-31G* level *ab initio* calculations. The results indicate a concerted [4+2] cycloaddition reaction of protonated **1** to be a key step for this reaction.

INTRODUCTION

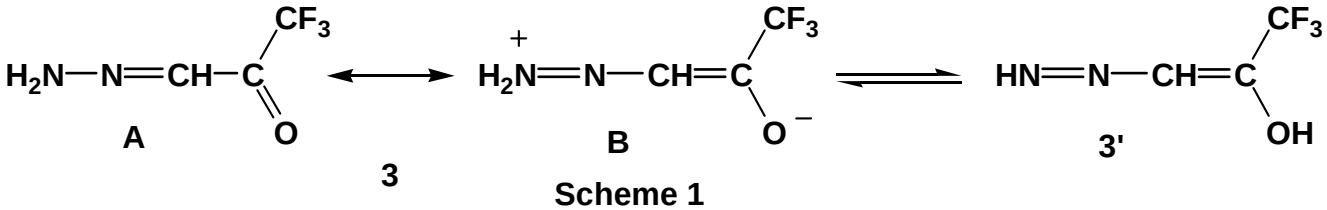
In the previous paper,[1] we reported a convenient synthetic method to prepare 4,5-bis(trifluoromethyl)pyridazines (**2**) starting from 1,1,1-trifluoro-2,3-alkanediones. The last step of this synthetic method contains a pyridazine-ring formation reaction from two molecules of 3-hydrazono-1,1,1-trifluoro-2-alkanone (**1**). This reaction is very interesting because a symmetrical structure of the products (**2**) suggests that the reaction process includes electrostatically unfavorable C-C bond formation between two electron deficient carbon centers neighboring trifluoromethyl groups. This prompted us to study about the reaction mechanisms for the process from hydrazones (**1**) to pyridazines (**2**).



RESULTS AND DISCUSSION

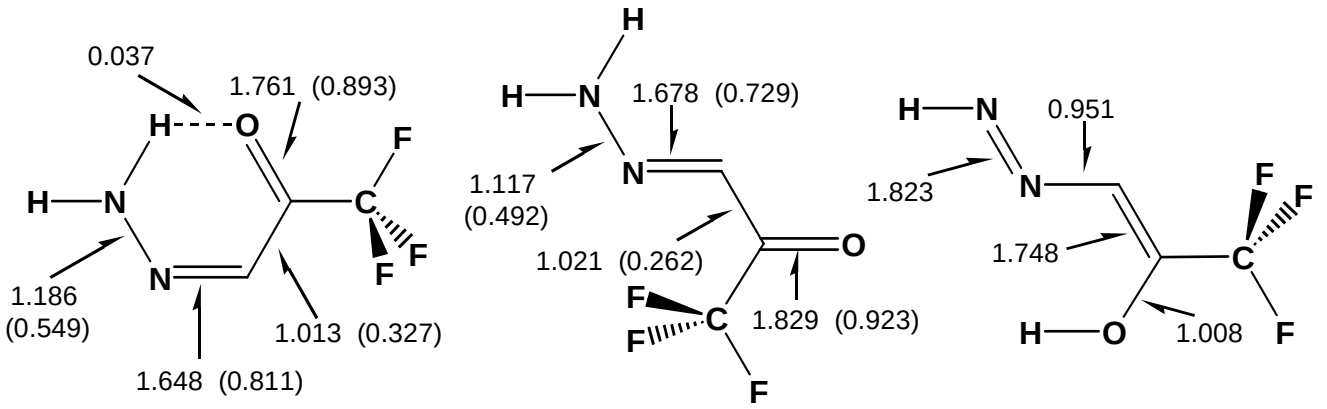
Structure of Starting Materials

To clarify a structure of starting materials (**1**), the 6-31G* level *ab initio* calculations were carried out for 3-hydrazono-1,1,1-trifluoro-2-propanone (**3**) as a model compound for hydrazones (**1**). An azaenamine structure together with a strongly electron withdrawing trifluoroacetyl group in hydrazone (**3**) makes a push-pull type highly polarized structure of **3** as shown in Scheme 1.



Scheme 1

Also, equilibrium between hydrazones (**3**) and isomeric azo olefin (**3'**) may be possible. The results of calculations are shown in Scheme 2 where geometrically optimized *syn* (**3a**) and *anti* (**3b**) isomers of hydrazone (**3**), and azoolefine (**3'**) are illustrated together with total energies and Mulliken bond populations[2] of them. The data in parentheses are π-bond orders[3] calculated for the



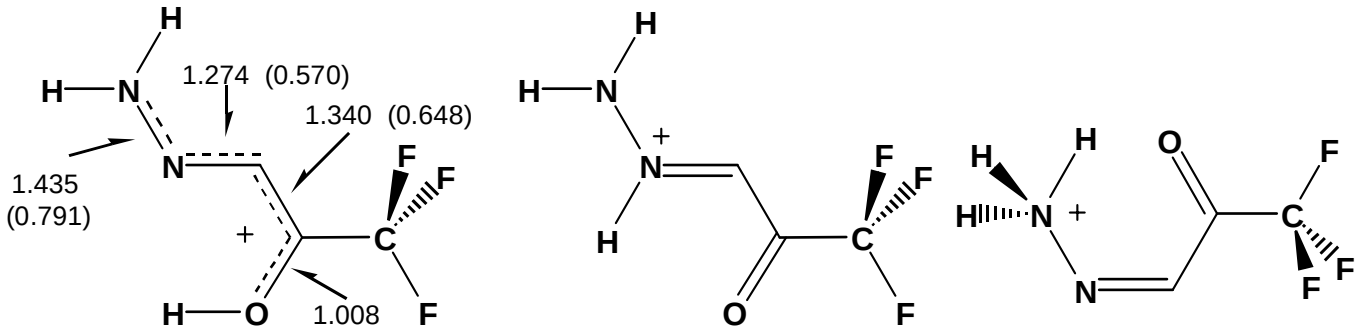
3a E = -597.374903 a.u. **3b** E = -597.373514 a.u. **3'** E = -597.353659 a.u.

Scheme 2

Illustrated structures on the basis of RHF/PM3.[4] Isomer (**3a**) was found to be 0.87 Kcal/mol more stable than **3b**. A little more stability of *syn* isomer (**3a**) could be attributed in a part to the week hydrogen bonding between amino hydrogen and carbonyl oxygen atom. On the other hand, azo olefin (**3'**) is 13.3 Kcal/mol less stable than hydrazone (**3a**). This means that **3** should be predominantly in the hydrazone form (**3a** or **3b**). In fact, we could not find any spectroscopic evidence about the formation of azo type isomers such as **3'** in the ^{1}H and ^{13}C NMR and IR spectra of hydrazones (**1**).[5] As was expected, π-bond orders calculated for C-N and C-C bonds of *syn* (**3a**)

and *anti* (**3b**) isomers reveal apparent contribution of the polarized canonical form **B** (Scheme 1) on these compounds.

We also tried estimation for the most stable protonated structure of **3** because of the fact that the reaction from hydrazones (**1**) to pyridazines (**2**) is mediated by strong acid catalysis. In the presence of acid such as TFA, reversible protonation should be possible at carbonyl oxygen, shifs base nitrogen, and terminal nitrogen atoms of hydrazone (**3**). In each case, the most stable



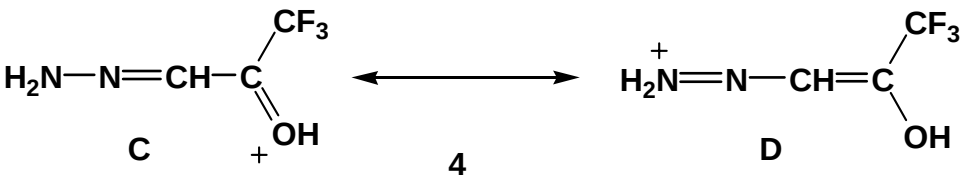
4b E = -597.700082 a.u.

4c E = -597.691914 a.u.

4d E = -597.696701 a.u.

Scheme 3

structure of resulted cation was estimated using the 6-31G* level *ab initio* calculations and the results are illustrated in Scheme 3. In all possible isomers and conformers in the each case, the most stable structures are **4b**, **4c**, and **4d**, respectively. The energy values of these three cations indicate that **4b** derived from hydrazone (**3**) by protonation at carbonyl oxygen atom is most stable, and the differences of energy larger than 2 Kcal/mol between cation (**4b**) and the other two cations suggest predominant formation of **4b** from hydrazone (**3**) in the presence of TFA. Mulliken bond populations and π-bond orders in Scheme 3 indicate exceeding multiple bonding characters on N-N and C-C bonds of cation (**4b**) in comparison with those of **3a** and **3b** (Scheme 2), and, namely, considerable contribution of the canonical form **D** in Scheme 4. Similar situation should be true for hydrazones (**1**), and this suggests more enhanced azoolefinic character of **1** by protonation at



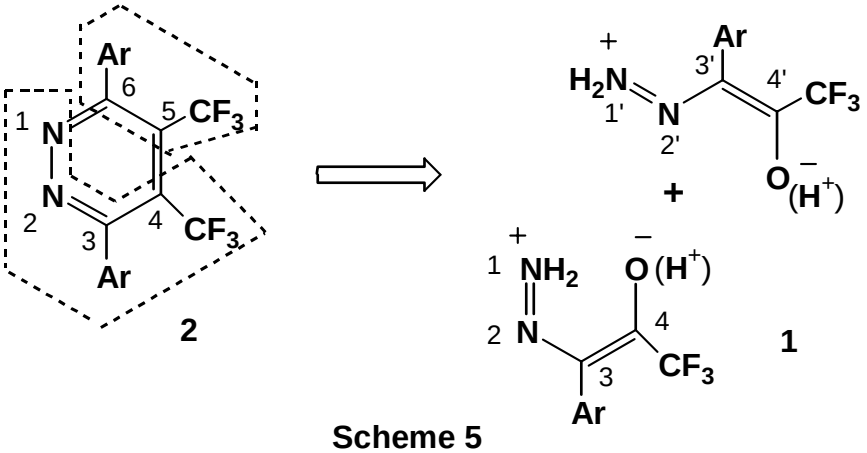
C **4** **D**

Scheme 4

carbonyl oxygen atom in the presence of TFA.

[4+2] Cycloaddition Reaction of 3-Hydrazono-1,1,1-trifluoro-2-alkanones

As is shown in Scheme 5, it is possible to fractionate the pyridazine ring unit of **2** into two parts. N1, N2, C3, and C4 atoms of one part can be attributed to N1, N2, C3, and C4 atoms of hydrazones (**1**), and C5 and C6 atoms of the other part is corresponding to C4′ and C3′ of **1**, respectively. Thus



Scheme 5

[4+2] type cycloaddition process between two molecules of hydrazones (**1**) is reasonable as a key step of the present pyridazine ring formation reaction from **1** to pyridazines (**2**). More enhanced azo olefinic, namely heterodienic character expected for hydrazones (**1**) in TFA as described above should be also favorable for such a cycloaddition process.

Concerted as well as stepwise processes are possible for such a type of cycloaddition reaction. To elucidate about this reaction process we tried analysis of frontier orbitals about hydrazone (**3**) and cation (**4**). Frontier orbitals of *syn* and *anti* isomers (**3a** and **3b**, respectively) as well as their energy levels are illustrated in Figure 1 together with those of cations (**4a** and **4b**). Also the frontier electron densities at N1, N2, C3, and C4, and phase distribution on the frontier orbitals calculated for these molecules (**3a** – **4b**) are listed in Table 1. As for the reaction from hydrazone (**3**) to **2** (Ar= H) in TFA, two cases are possible. One is [4+2] type cycloaddition reaction of hydrazone (**3**) with cation (**4**), and the other is that between two molecules of cation (**4**). In the former case, interaction between HOMO of hydrazone (**3**) and LUMO of cation (**4**) should be particularly important taking into account the energy levels of their frontier orbitals in Figure 1. In the latter case HOMO-LUMO interaction between a pair of cations (**4**) should become dominant in the reaction. We studied about the former case at first.

As for [4+2] type cycloaddition reaction between hydrazone (**3**) and cation (**4**), two patterns of

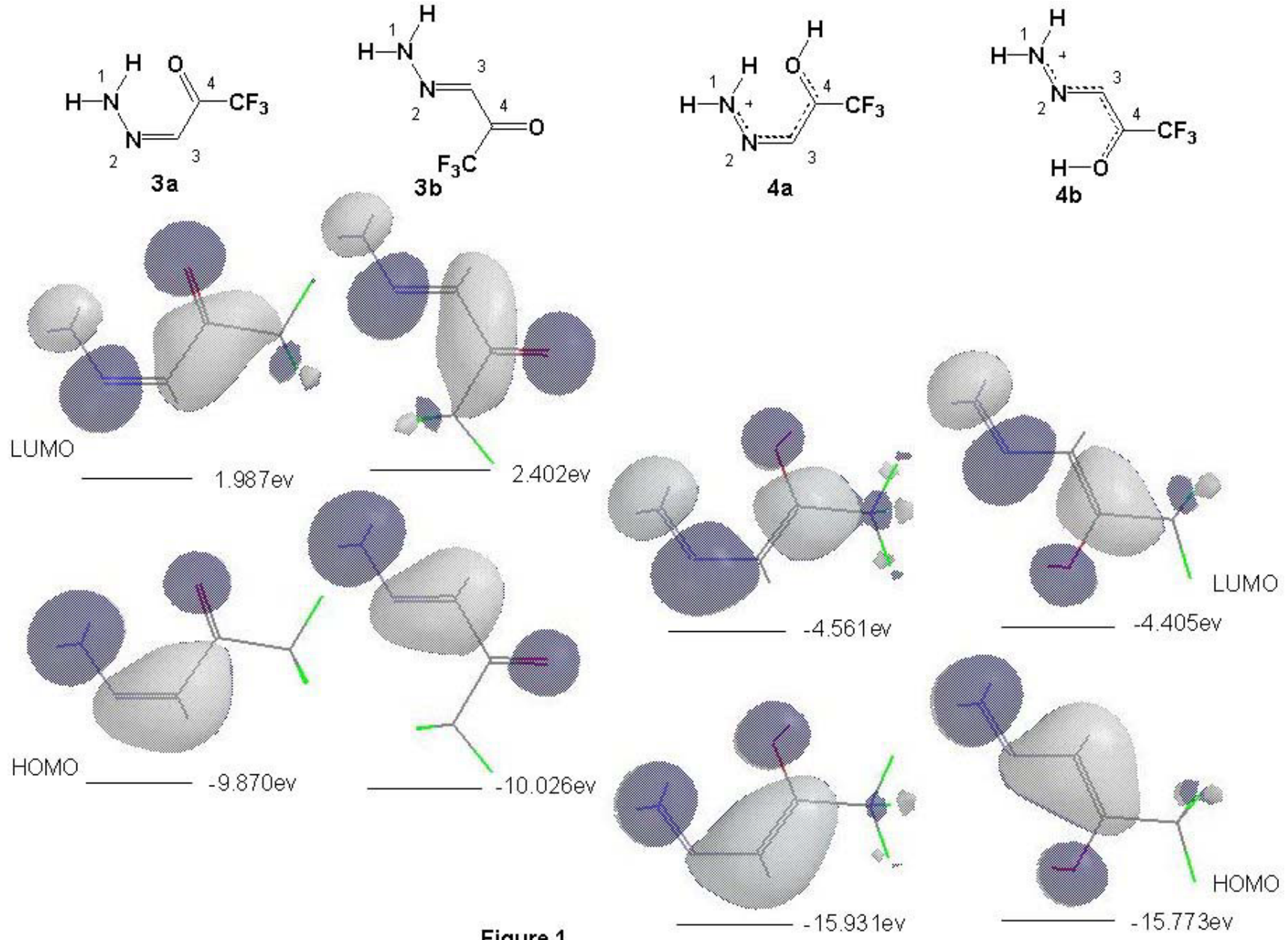

3a
3b
4a
4b
LUMO
1.987ev
2.402ev
HOMO
-9.870ev
-10.026ev
-4.561ev
LUMO
-4.405ev
-15.931ev
HOMO
-15.773ev

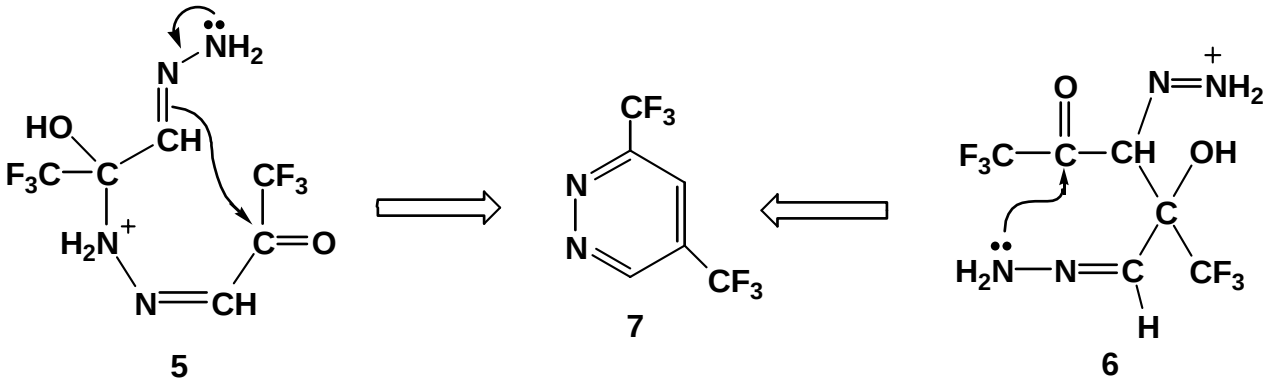
Figure 1

Table 1. Frontier Electron Densities at N1, N2, C3, and C4 Calculated for **3a**, **3b**, **4a**, and **4b**.*

	3a		**3b**		**4a**		**4b**	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
N1	0.6244 (-)	0.2318 (+)	0.6814 (-)	0.2051 (+)	0.2848 (-)	0.4894 (+)	0.4477 (-)	0.4174 (+)
N2	0.1143 (+)	0.6477 (-)	0.1508 (+)	0.7188 (-)	0.0148 (+)	0.6981 (-)	0.0360 (+)	0.7235 (-)
C3	0.5023 (+)	0.1083 (+)	0.4387 (+)	0.1961 (+)	0.5467 (+)	0.0168 (-)	0.5372 (+)	0.0082 (+)
C4	0.0053 (+)	0.5160 (+)	0.0018 (-)	0.4782 (+)	0.1814 (+)	0.5639 (+)	0.0904 (+)	0.6069 (+)

* Symbols in parentheses indicate phase distribution on the corresponding orbitals.

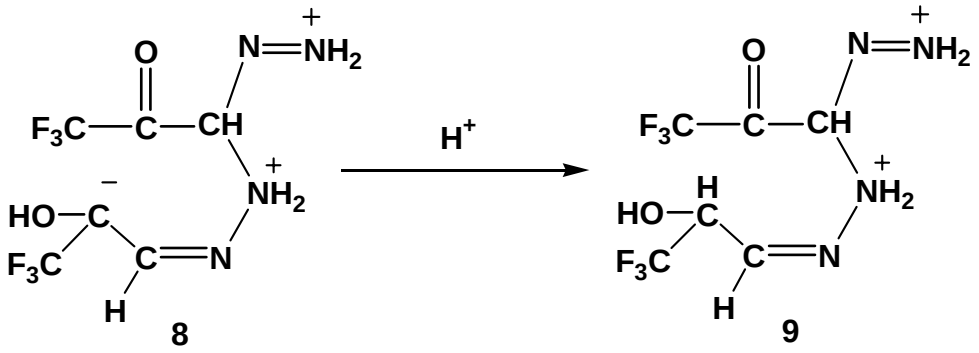
HOMO-LUMO interactions are possible. One is that leads to normal electron demand type reaction in which **3** acts as a diene and **4** as a dienophile. The other is that mediates inverse electron demand type reaction in which hydrazone (**3**) and cation (**4**) act as a dienophile and a diene, respectively. However, in both cases, frontier orbitals are not suitable for concerted [4+2]



Scheme 6

cycloaddition process, because very small frontier electron densities and, in some cases, misfitting of orbital phase between HOMO (**3a** and **3b**) and LUMO (**4a** and **4b**) are thought to be unfavorable for concerted processes. Therefore only stepwise processes which include nucleophilic attack of hydrazone (**3**) toward cation (**4**) followed by cyclization of resulted adducts should be possible in these cases. In addition, the data in Figure 1 and Table 1 reveal the highest frontier electron densities (HOMO) at N1 of **3a** and **3b**, and that (LUMO) at C4 of **4a** and **4b**, suggesting a preferential nucleophilic attack of N1 in hydrazone (**3**) toward C4 in cation (**4**). As is shown in Scheme 6, however, this leads to formation of adduct (**5**) and, consequently, 3,5-bis(trifluoromethyl)pyridazine

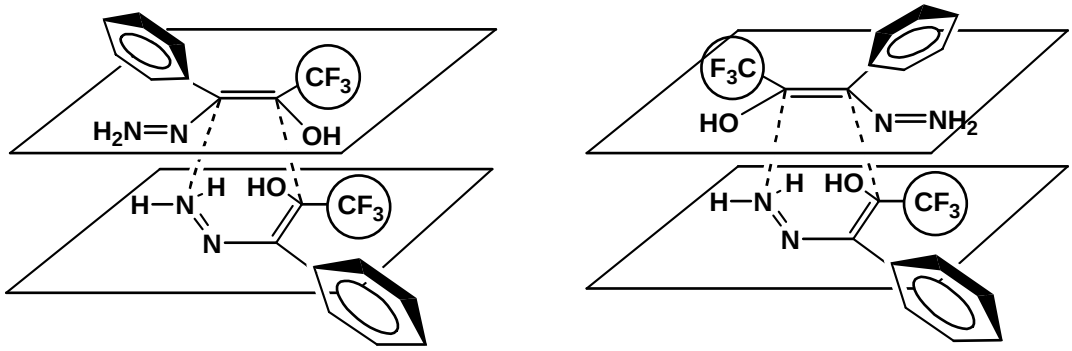
(**7**), the regioisomer of pyridazine (**2**; Ar= H). Similarly a nucleophilic attack of C3 which has next high frontier electron densities (HOMO) in hydrazone (**3**) toward C4 of cation (**4**) also affords regioisomer (**7**) *via* intermediate (**6**). As a minor product, **2** (Ar= H) may be obtainable when C3 of



hydrazones (**3a** and **3b**) attacks N1 of cations (**4a** and **4b**). However possible intermediate (**8**) in this process must be immediately quenched by TFA before desired cyclization to pyridazine (**2**; Ar= H) occurs, though we cannot deny a little possibility for formation of **2** from adduct (**9**). In any case, these are not compatible with the experimental results[1] in which neither regioisomers such as pyridazine (**7**) nor any products derived from them was obtained under the reaction conditions previously reported. Thus the mechanisms including interactions between HOMO of hydrazone (**3**) and LUMO of cation (**4**) can be excluded.

As for HOMO-LUMO interaction between two molecules of cation (**4**), following two cases are possible. One is that where HOMO of **4** as diene interacts with LUMO of **4** as dienophile (normal electron demand type) and the other is that where LUMO of **4** as diene interacts with HOMO of **4** as dienophile (inverse electron demand type). In the former case, concerted process should be unfavorable because of quite similar reasons mentioned previously for the reaction of hydrazone (**3**) with cation (**4**). Nucleophilic attack of N1 in **4a** (or **4b**) toward C3 in another molecule of **4a** (or **4b**) as well as that of C4 of **4a** (or **4b**) toward C4 of another molecules of **4a** (or **4b**) is obviously less preferred because of the highest frontier electron density (HOMO) at C3 in **4a** and **4b**. In any case, main product of these stepwise cyclization processes must be regioisomer (**7**). In contrast, HOMO-LUMO interaction in the latter case (inverse electron demand type) is suitable for concerted [4+2] cycloaddition process, because N1 and C4 in LUMO of cation (**4a**) and C3 and C4 in HOMO of **4b** (or **4a**) have sufficient frontier electron densities as well as fitting orbital phase in order to promote this process. However the frontier electron densities (LUMO) of cation (**4a**) is slightly

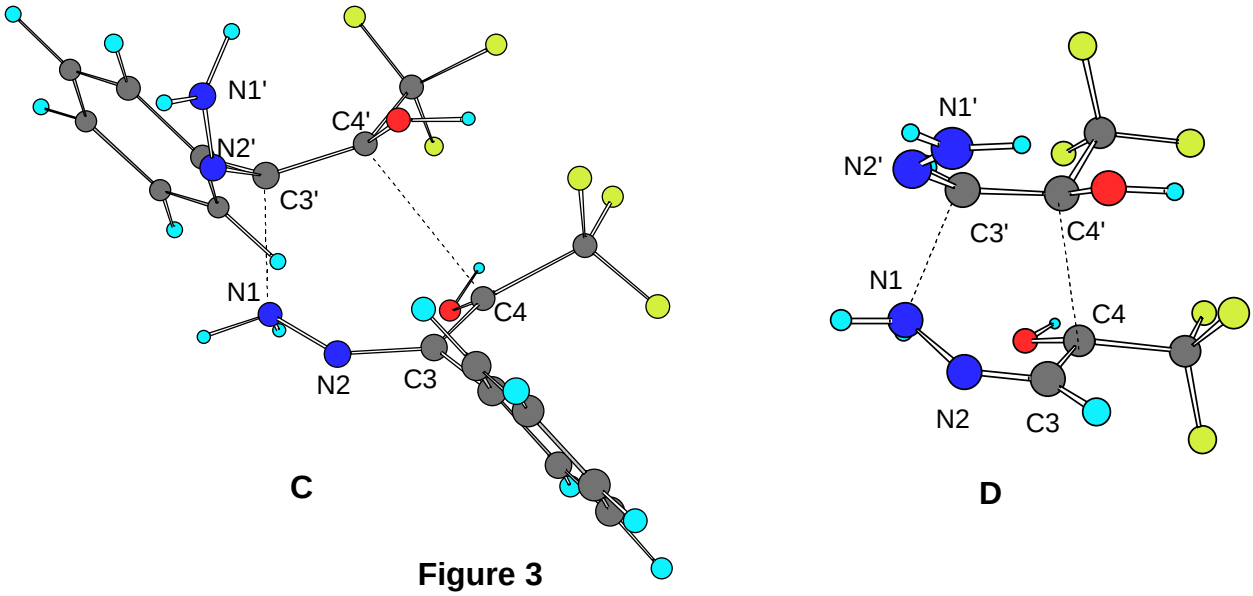
higher at C4 than at N1, and, at the same time, cations (**4a** and **4b**) has the highest frontier electron densities (HOMO) at C3, suggesting the strongest interaction between C4 and C3 in the transition state. The situation favors the formation of regioisomer (**7**) more than expected isomer (**2**; Ar= H),



A **B**

Figure 2

In order to explain the selective formation of pyridazines (**2**) from hydrazones (**1**), it is necessary to take steric factors into consideration. Starting material (**1**) has an aryl group which is omitted in the model compound (**3**). Possible transition state models for concerted process are illustrated about the representative cases in Figure 2. More steric hindrance should occur in model **B** where two bulky aryl groups are in a same side. On the other hand, less steric hindrance in model **A** should be advantageous to the formation of expected pyridazines (**2**). On the basis of PM3[4, 6] calculations, the optimized transition structure for model **A** can be roughly estimated as **C** in Figure 3. The estimated distance (2.70 Å) between C4 and C4′ is longer than that (1.90 Å) between N1 and C3′. In contrast, we could obtain no transition structure suitable for model **B** because of steric



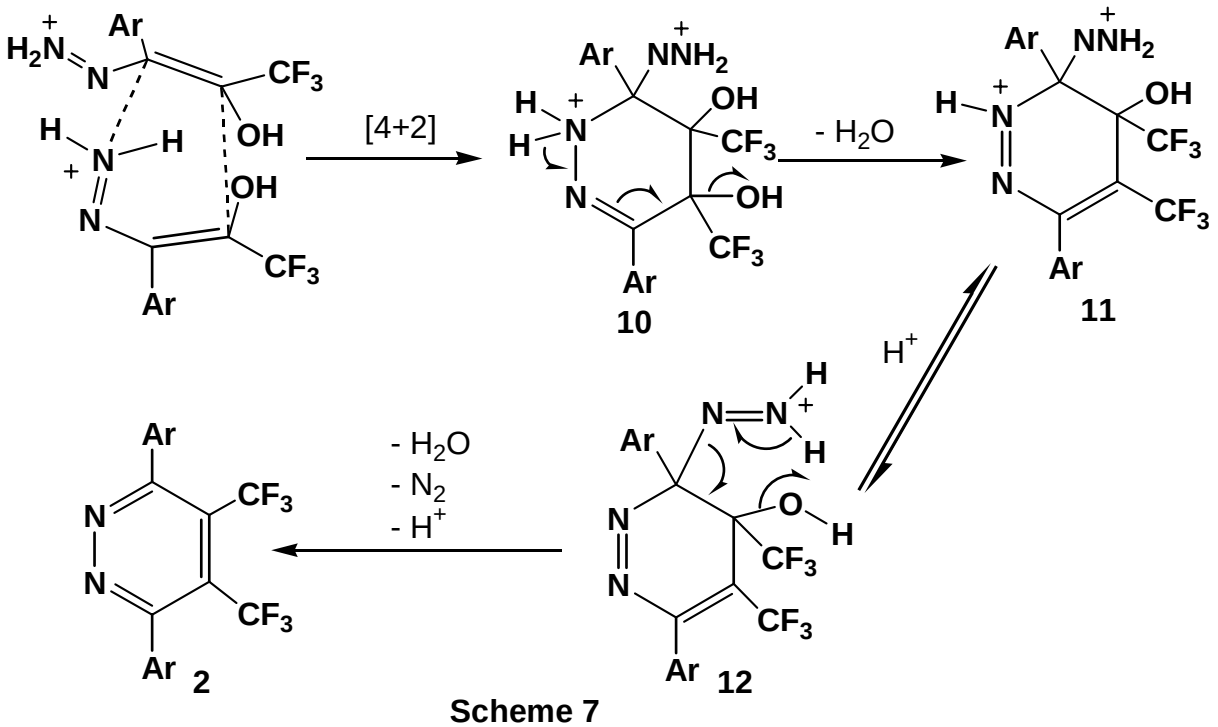
C **D**

Figure 3

repulsion strongly refusing the concerted process *via* model **B**. Quite similarly, steric hindrance should be significant in the case of stepwise process that includes nucleophilic attack of C3 in **1** (or cation of **1** corresponding to **4a** or **4b**) toward C4 in cation of **1** leading to **7** type pyridazine. These are probably the main reason why the present reaction gave only pyridazine (**2**) by concerted [4+2] cycloaddition process. We also carried out the 6-31G* level *ab initio* calculations to estimate the transition structure corresponding to model **A** about the model compounds (**4a** and **4b**). In Figure 3 is illustrated the computed transition structure **D** where the distances between C4 and C4′, and N1 and C3′ are calculated as 2.246 Å and 2.073 Å, respectively.

Possible Reaction Mechanism from Hydrazones (1) to Pyridazines (2)

Concerted [4+2] cycloaddition reaction *via* transition state model **A** gives intermediate (**10**) (Scheme 7). Acid catalyzed dehydration on **10** and subsequent elimination of N_2 and H_2O from resulted **11** or **12** accompanied with aromatization should afford pyridazine (**2**). This thought to be



Scheme 7

the most reasonable mechanism for the reaction from 3-hydrazono-1,1,1-trifluoro-2-alkanones (**1**) to 4,5-bis(trifluoromethyl)pyridazines (**2**) in TFA.

Conclusions

In conclusion, we can present the most reasonable mechanism for the reaction of 3-hydrazono-1,1,1-trifluoro-2-alkanones (**1**) to 4,5-bistrifluoromethylpyridazines (**2**) mediated by TFA.

Ab initio calculations for a model compound (**3**) suggest a concerted [4+2] cycloaddition reaction, namely inverse electron demand type hetero Diels-Alder reaction of protonated cations of **1** is a key step in the over all reaction processes. An extension of this reaction to general α-diketone monohydrazones is now under investigation and will be reported elsewhere.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN plus.[7] All *ab initio* calculations including geometry optimizations were performed with the 6-31G* basis set at the Hartree-Fock levels. The starting geometries employed for all optimizations were resulted from molecular mechanics calculations using SYBYL[8] force field and subsequent semi-empirical AM1[9] optimizations.

REFERENCES AND NOTES

1. Y. Kamitori, M. Hojo, and T. Yoshioka, *Heterocycles*, 1998, **48**, 2221.
2. R. S. Mulliken, *J. Chem. Phys*., 1955, **23**, 1833, 1841, 2338, 2343.
3. π-Bond orders were calculated on the basis of RHF/PM3 (single point energy) about the geometrically optimized structures on the basis of the 6-31G* level *ab initio* calculations.
4. J. J. P. Stewart, *J. Computer Aided Molecular Design*, 1992, **6**, 69.
5. For instance, **1** (R= *p*-Tol): mp 131-132**℃** (benzene); ^{1}H NMR ($CDCl_3$/ TMS) δ 2.34 (s, 3H, Me), 6.47 - 7.14 (br, 2H, NH_2), 6.85 - 7.38 (AA'BB'q, 4H, *J*= 8 Hz, ArH); ^{13}C NMR ($CDCl_3$/ TMS) δ 21.4 (Me), 117.3 ($^{1}J_{CF}$= 291.4 Hz, CF_3), 123.7, 128.8, 130.3, 140.3 (Ar), 139.6 (C=N), 177.7 ($^{2}J_{CF}$= 32.9 Hz, C=O); IR (KBr) 3430 (s), 3290 (s), 3200 (m), 1693 (s), 1545 (s), 1507 (m), 1375 (m), 1266 (s), 1228 (s), 1174 (s), 1142 (s), 1094 (s), 876 (s), 814 (m), 731 (m) cm^{-1}. There is no signal attributable to azo form such as **3**′ in ^{1}H and ^{13}C NMR spectra even at -50**℃**.
6. RHF/PM3 with CI (3 occupied + 3 unoccupied orbitals).
7. Wavefunction, Inc.
8. M. Clark, R. D. Cramer**III**, and N. van Opdensch, *J. Computational Chem*., 1989, **10**, 982.
9. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc*., 1985, **107**, 3908.