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SELECTIVE AROMATIC NUCLEOPHILIC SUBSTITUTION OF 4-(DIMETHYLAMINO)-2-METHOXY-3-(TRIFLUOROACETYL)QUINOLINE WITH THIOLS – DFT CALCULATION STUDY

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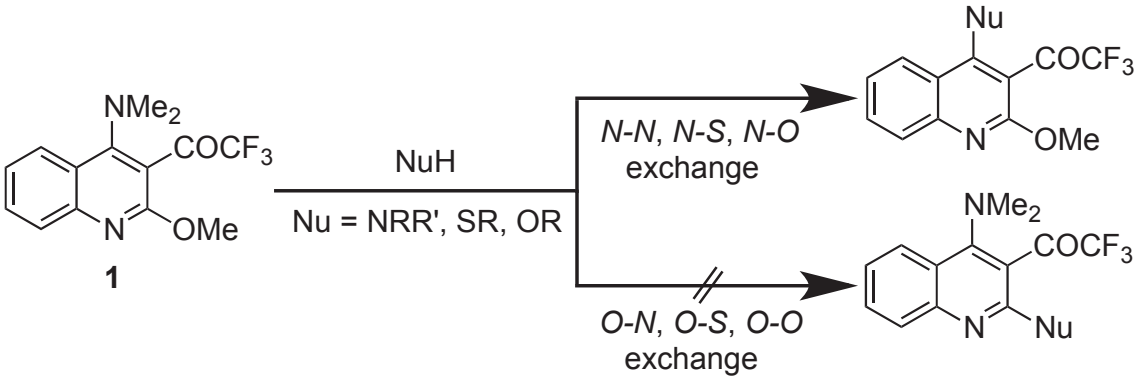
Abstract – The nucleophilic aromatic substitution proceeds exclusively at the 4-position of 4-(dimethylamino)-2-methoxy-3-(trifluoroacetyl)quinoline **1** by the reaction with various thiols to give the corresponding *N*-*S* exchanged products solely, and no *O*-*S* exchange reactions at the 2-position are performed. Our DFT calculation study provides a rational explanation regarding this complete selectivity based on energies of the adducts **6**, **7** which are corresponding to the *O*-protonated Meisenheimer complexes at carbonyl oxygen in 3-trifluoroacetyl group. It was also investigated about influences of the solvents on the present unique selective substitution with thiols referring the results for the analogous selective substitution on **1** using amines as a nucleophile.

It is well known that a variety of researches have been conducted to explore synthetic methodologies for novel kinds of fluorine-containing heterocycles. In the various sphere of life science, their capability as active ingredients have often drawn attention because of the unique biological activity.[1-4] In recent years, we have succeeded in building the convenient synthetic methods which avail to access novel fluorine-containing 4-methoxypyrazolo[4,3-*c*]quinolines,[5] 6-methoxy-1,4-diazepino[6,5-*c*]quinolines,[5] 5-methoxypyrimido[5,4-*c*]quinolines,[6] 5-methoxybenzo[*h*][1,6]naphthyridines,[6] 6-methoxydibenzo-[*b,h*][1,6]naphthyridines,[7] and 6-methoxythiochromeno[3,2-*c*]quinolines.[7] The Scheme 1 shows the key step reaction on the above studies, that is a unique highly selective aromatic nucleophilic substitution of 4-dimethylamino moiety of trifluoroacetylated quinoline **1** with appropriate nucleophiles (Nu).[7,8] It is interesting to note that the nucleophilic substitution of **1** with thiols easily occurs in the absence of any base or catalyst at the 4-position exclusively, and dimethylamino group, which is characterized as poor leaving group compared to methoxy group at the 2-position, is readily substituted with the corresponding

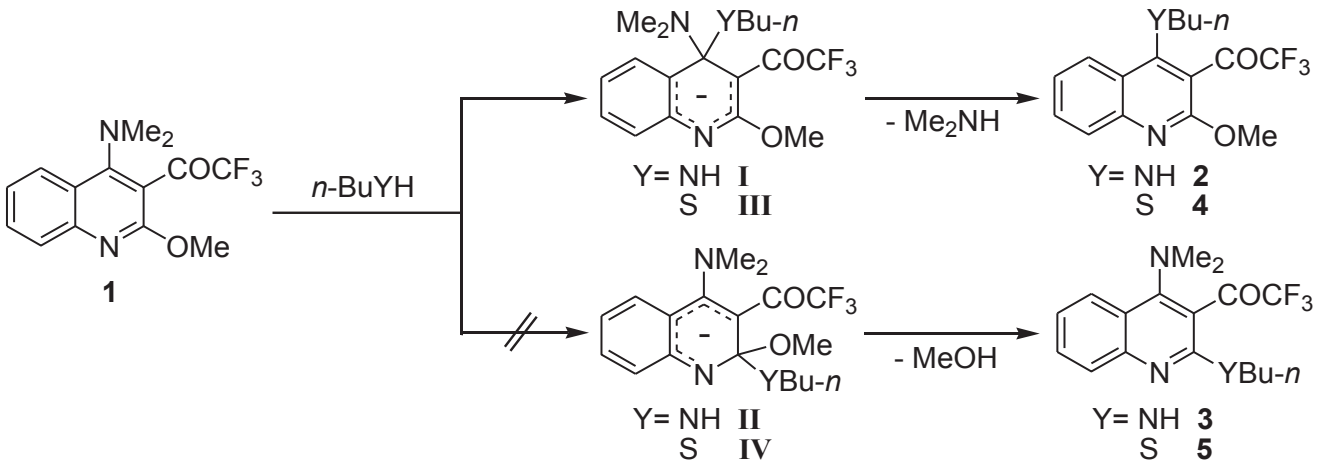


Scheme 1

sulfenyl groups to afford the *N*-*S* exchanged products solely.[7]

We here wish to present the DFT calculation (RB3LYP/6-31G*) study on the reaction of **1** with *n*-butanethiol as a representative model to get significant outcomes which show the rational explanation as to the complete selectivity on the thematic substitution of **1**. In addition, influences of the solvents on this unique selectivity will be also discussed by making use of C-PCM model calculations.

In our previous paper,[9] the DFT calculation has resulted in the selective aromatic nucleophilic substitution of **1** with *n*-butylamine to afford the *N*-*N* exchanged products exclusively.[7] It was clarified that the frontier electron density (LUMO) at the 4-position of **1** is much higher than that at the 2-position in that study.[9] This means that nucleophiles prefer to attack on the 4-position rather than the 2-position of **1**. However, the complete selectivity was explained more explicitly on the basis of the relative stabilities of the Meisenheimer complexes **I** and **II** which should determine the reaction rate on these alternative courses giving **2** and **3**, respectively (Scheme 2).[9] The nucleophilic substitution of **1** with *n*-butanethiol



Scheme 2

giving **4** and **5** can be assumed to proceed according to a similar manner via the corresponding Meisenheimer complexes **III** and **IV**, respectively. The processes affording **I** and **II** from **1** are interpreted as shown in the following equations (eq. 1 and eq. 2).

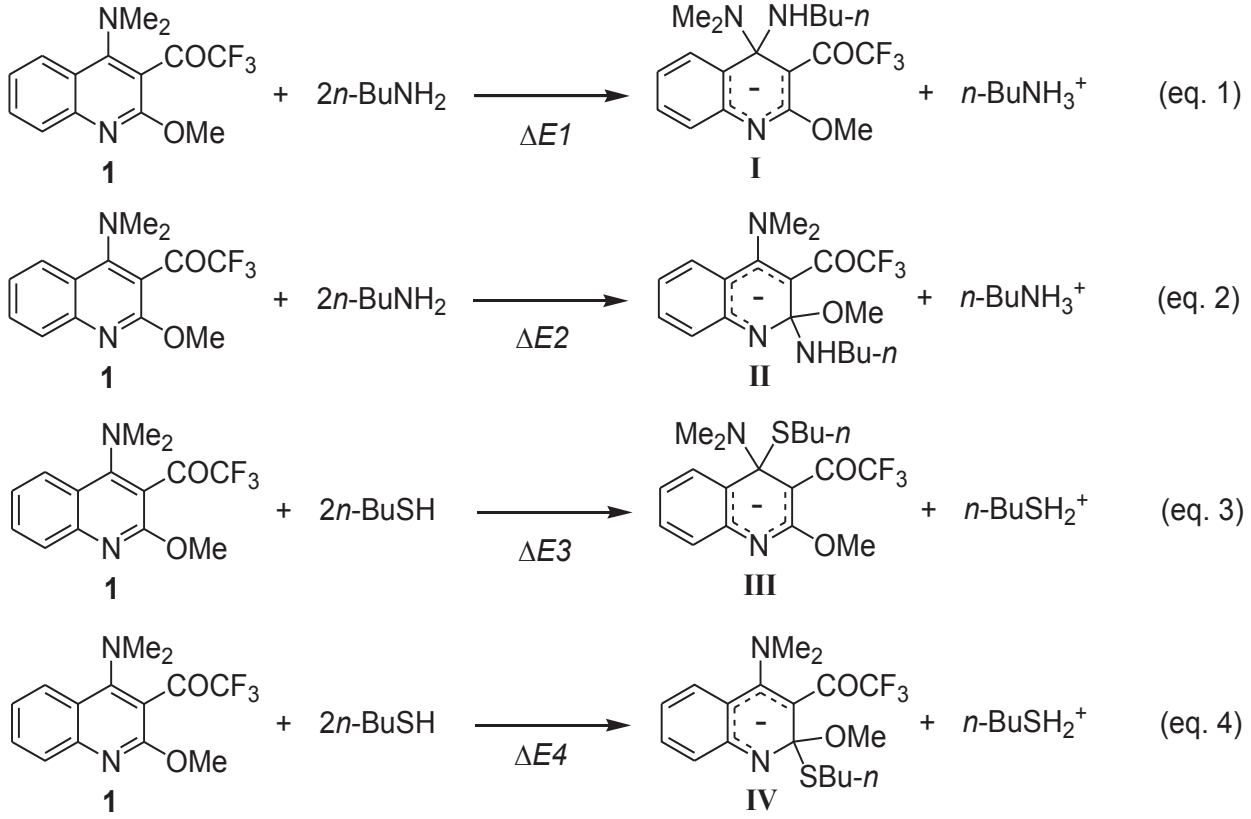
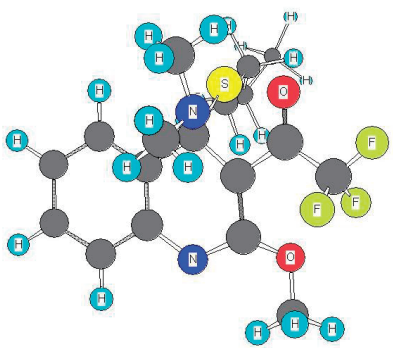


Table 1. Energy changes, Δ*E1-4* (kcal/mol) on eq. 1-4

Equations	Energy	Without solvent model	Solvent	
			Mesitylene	MeCN
eq. 1	Δ*E1*	116.0	58.1	14.9
eq. 2	Δ*E2*	134.2 (+18.2)[a]	75.8 (+17.7)[a]	31.7 (+16.8)[a]
eq. 3	Δ*E3*	159.6	106.7	64.0
eq. 4	Δ*E4*	170.7 (+11.1)[b]	117.4 (+10.7)[b]	82.2 (+18.2)[b]

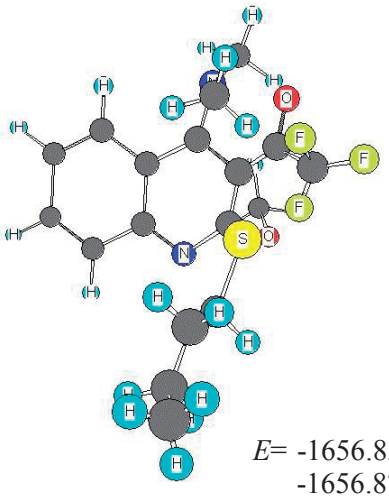
a) Δ*E2* - Δ*E1* (= energy difference between **I** and **II**).
b) Δ*E4* - Δ*E3* (= energy difference between **III** and **IV**).

Meanwhile, eq. 3 and eq. 4 indicate the respective processes from **1** to intermediates **III** and **IV** on the reactions with *n*-butanethiol. Computed structures of Meisenheimer complexes **III** and **IV** are depicted together with their energies in Figure 1 and the energy changes Δ*E1-4* on eq.1-4 are summarized in Table 1. The intermediate **III** is estimated to be 10.7 kcal/mol[10] more stable than **IV** on the basis of energy value in mesitylene (experimental conditions).



III

E= -1656.85052 a.u.
-1656.89246 a.u. (in mesitylene)
-1656.92616 a.u. (in MeCN)

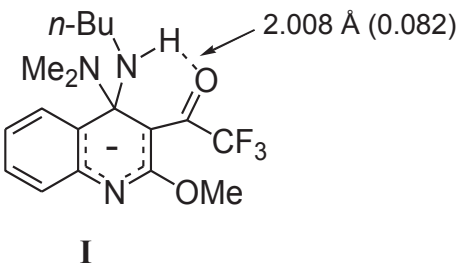


IV

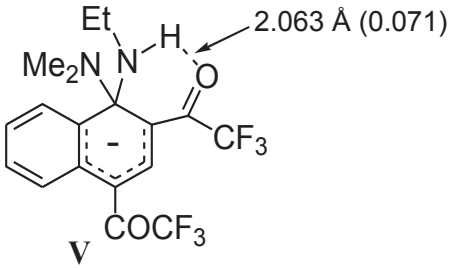
E= -1656.83290 a.u.
-1656.87551 a.u. (in mesitylene)
-1656.89716 a.u. (in MeCN)

Figure 1

This result seems to indicate the predominant formation of **III** and consequent *N*-*S* exchanged product **4** by the reaction of **1** with *n*-butanethiol. However, thiols do not have enough properties of the basicity strength to perform eq. 3 and eq. 4 compared to amines. In the case of the reaction of **1** with *n*-butylamine giving the *N*-*N* exchanged product **2**, $\Delta E1$ is calculated to be 14.9 kcal/mol in acetonitrile,[11] which suggests that the rate determining step, from **1** to **I** (eq. 1), readily proceeds under experimental mild conditions.[7,9] In contrast to this, $\Delta E3$ for the step from **1** to **III** (eq. 3) is estimated to be more than 100 kcal/mol in mesitylene (experimental conditions). This value is too large to perform this rate determining step for the *N*-*S* exchange reaction giving **4** from **1**. Consequently, the *N*-*S* exchanged product **4** is not formed through the reaction pathway in Scheme 2 due to not including its assumable intermediate **III**.



I

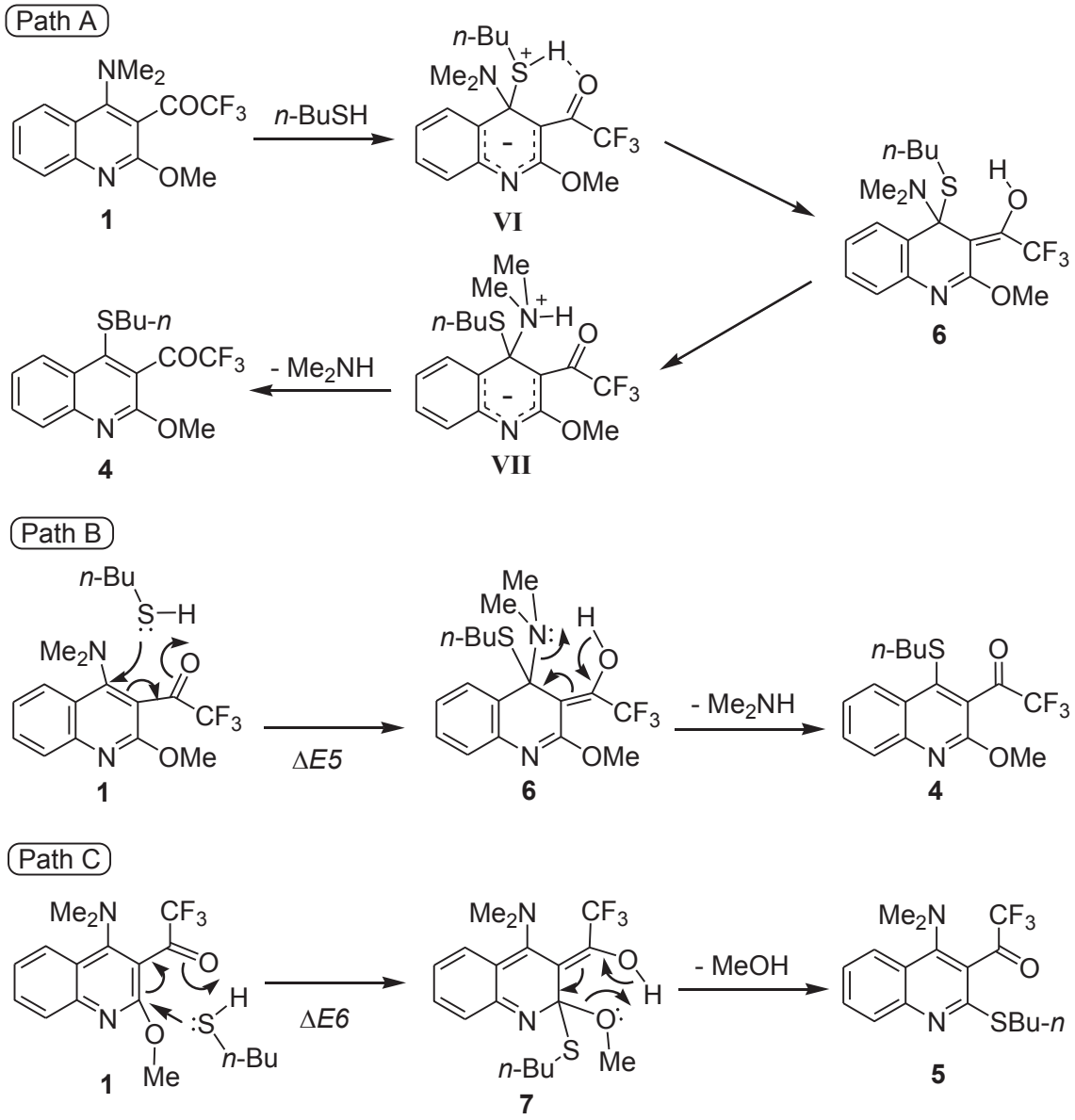


V

Figure 2

It has been found that the Meisenheimer complex **I** has intramolecular hydrogen bond between amino proton and carbonyl oxygen in 3-trifluoroacetyl group.[9] The similar intramolecular hydrogen bond is also observed in the Meisenheimer complex **V**. The intermediate **V** is given on the aromatic

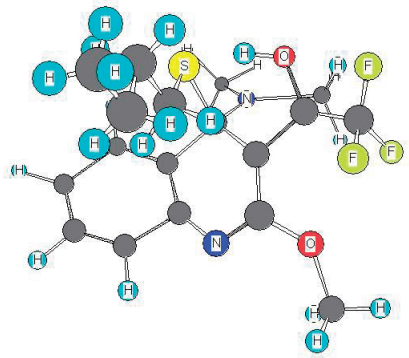
nucleophilic substitution course of 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene with ethylamine, and stabilized by the contribution of its hydrogen bond effectively.[12] In Figure 2 are indicated the computed values of distance and Mulliken bond orders (in parentheses) concerning these hydrogen bonds.



Scheme 3

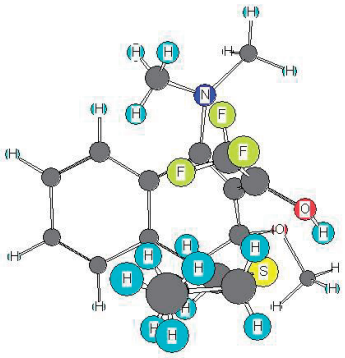
These knowledges prompted us to examine Path A in Scheme 3 as an alternative route. We have attempted the structural optimization of intermediate **VI** to come to the result in which either adduct **6** or pair of substrate **1** and *n*-butanethiol have suggested that the attack of *n*-butanethiol to the 4-position of **1** gives **6** directly. Quite similarly the structural optimization for intermediate **VII** has led to a computation in which the *N*-*S* exchanged product **4** and dimethylamine would be formed. These calculation results on Pass A can emphasize consideration concerning Pass B.[13]

Additionally, similar Path C is one of plausible mechanisms for the substitution of **1** at the 2-position. As depicted, the first step should control the determination of reaction rate on both Path B and C, which consists of aromatic pyridine ring system destruction. Figure 3 illustrates optimized structures of intermediates **6** and **7** together with their energies. Moreover, Table 2 exhibits the respective estimated energy changes on rate determining steps of Pass B ($\Delta E5$) and Path C ($\Delta E6$). On the reaction from **1** to **6** in mesitylene (experimental conditions), the energy change $\Delta E5$ does not exceed more than 25.4 kcal/mol. Furthermore, it shows the value more than 80 kcal/mol lower than $\Delta E3$ (eq. 3, Table 1) which is the route via Meisenheimer complex **III** (Scheme 2). These results accord well with the hypothesis which is explained by the formation of *N*-*S* exchanged product **4** derived from intermediate **6** along Path B. It is obviously different from that comprised of *N*-*N* exchange reaction of **1** with amines via Meisenheimer complexes. Meanwhile, $\Delta E6$ on Path C is ca. 70 kcal/mol less than $\Delta E4$ which is estimated for the process from **1** to the corresponding Meisenheimer complex **IV** (eq. 4). It is simply indicating that the *O*-*S* exchange is undergone along the Path C route even if the reaction of **1** with thiols is possible at the 2-position.



6

E= -1657.38204 a.u.
-1657.38848 a.u. (in mesitylene)
-1657.39386 a.u. (in MeCN)



7

E= -1657.34961 a.u.
-1657.35698 a.u. (in mesitylene)
-1657.36379 a.u. (in MeCN)

Figure 3

Table 2. Energy changes (kcal/mol) on rate determining steps of Pass B and Pass C

Path	Energy	Without solvent model	Solvent	
			Mesitylene	MeCN
B	$\Delta E5$	22.4	25.4	26.0
C	$\Delta E6$	42.8 (+20.4)[a]	45.2 (+19.8)[a]	44.8 (+18.8)[a]

a) $\Delta E6$ - $\Delta E5$ (= energy difference between **6** and **7**).

Different from the reaction with *n*-butylamine (Δ*E1* and Δ*E2*, Table 1),[11] the values of both Δ*E5* and Δ*E6* are not varied (< 1 kcal) even though acetonitrile is applied instead of mesitylene. Acetonitrile makes a reaction condition being more polar than mesitylene but above results mean that the reaction rates from **1** to **6** and **7** in acetonitrile will not be more accelerated than those in mesitylene. The intermediate **6** is ca. 20 kcal/mol more stable than **7** in mesitylene. Such large difference of the stability rationally explains the exclusive formation of the *N*-*S* exchange products like **4** by the reaction of **1** with thiols in refluxing mesitylene. The adduct **7** is more instable than **6** since aromatic system of benzene ring (quinoid form)[14] comes into destruction in addition to its pyridine ring of **7**. The energy difference (Δ*E6* - Δ*E5*), which is correspond to the energy difference between **6** and **7**, is estimated to be 18.8 kcal/mol in acetonitrile and does not vary so much from the value (19.8 kcal/mol) in mesitylene. Accordingly, the reaction of **1** with thiols occurs selectively at the 4-position and gives the corresponding *N*-*S* exchange products solely even though much more polar acetonitrile is used as a solvent instead of mesitylene. The difference of stability between **6** and 7 (Δ*E6* - Δ*E5*) resembles that between **I** and **II** (Δ*E2* - Δ*E1*, Table 1) from the viewpoint of solvent effect. It appears to decrease the stability difference slightly in more polar solvent (acetonitrile) than less polar that (mesitylene) according to the values in both cases. In either case, the difference between **6** and **7** (Δ*E6* - Δ*E5*) is ca. 2 kcal/mol larger than that between **I** and **II** (Δ*E2* - Δ*E1*) in both solvents. These results may contribute to show higher selectivity for the substitution at the 4-position on the reaction of **1** with thiols compared with the similar reaction with amines.

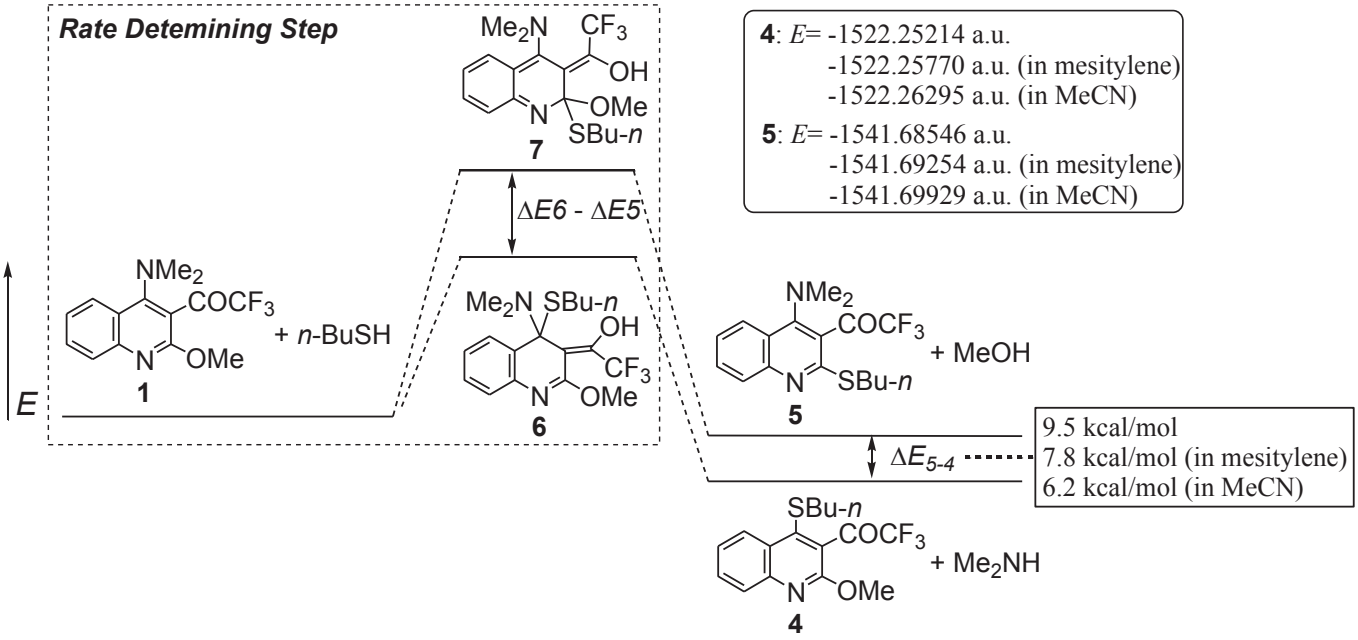


Figure 4

Finally, we have investigated calculation analyses concerning *N*-*S* and *O*-*S* exchanged products, **4** and **5** respectively. The diagrams in Figure 4 exhibit the computed energies of **4** and **5** for two substitution courses accessing **4** and **5** from **1**. It can be noted that the *N*-*S* exchange reaction accessing **4** via **6** has 7.8 kcal/mol (in mesitylene) advantage in total over the *O*-*S* exchange reaction which gives **5** via **7** even though the second elimination steps (**6**→**4**, **7**→**5**) is taken into account. Therefore, the *N*-*S* exchanged products **4** will be assumed to be produced selectively even if all substitution processes are thermodynamically controlled in refluxing mesitylene (experimental conditions).[7]

In conclusion, our DFT calculation study has achieved rational explanation about an exclusive formation of the *N*-*S* exchanged products prepared by selective nucleophilic substitution at the 4-position of 3-trifluoroacetylquinoline **1** with thiols. Different from the substitution of **1** with amines, the reaction with thiols does not proceed through the corresponding Meisenheimer complexes **III** but takes alternative reasonable reaction path (Path B) through intermediate **6**. The complete selectivity on this nucleophilic substitution at the 4-position is rationally explained by much more stability of the adduct **6** relative to **7** which is assumed to be formed by attack of thiols at the 2-position of **1** to give the *O*-*S* exchanged product **5**. Our calculations also predicts selective formation of the *N*-*S* exchanged products from **1** even if much more polar acetonitrile is used as a solvent instead of mesitylene.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 16.[15] For geometrical optimizations, it was performed with the 6-31G* basis set using B3LYP.[16] For a solvation calculation, C-PCM model[17] was used. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[18] force field and subsequent semi-empirical PM3[19] optimizations.

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10. 1 a.u. = 627.5 kcal/mol.
11. The value of Δ*E1* (58.1 kcal/mol) in mesitylene is ca. 43 kcal/mol larger than that (14.9 kcal/mol) in MeCN predicting that much more enhanced conditions are needed if mesitylene is used as a solvent instead of acetonitrile for the *N*-*N* exchange reaction of **1** with amines.
12. N. Ota, T. Nakada, T. Shintani, Y. Kamitori, and E. Okada, *Int*. *J. Org*. *Chem*., 2018, **8**, 273.
13. In Path B, each step from **1** to **6** and **6** to **4** would proceed concertedly.
14. Obvious bond alternation is observed on benzene ring in **7**. Bond lengths (Å) and Mulliken bond orders (in parentheses) about benzene rings in **6** and **7** are followings. **6**: C4a-C5= 1.401 (1.401); C5-C6= 1.396 (1.425); C6-C7= 1.396 (1.425); C7-C8= 1.391 (1.442); C8-C8a= 1.404 (1.383); C4a-C8a= 1.413 (1.361). **7**: C4a-C5= 1.439 (1.193); C5-C6= 1.267 (1.618); C6-C7= 1.432 (1.227); C7-C8= 1.364 (1.636); C8-C8a= 1.445 (1.191); C4a-C8a= 1.470 (1.103).
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