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COMPUTATIONAL STUDY FOR THE SELECTIVE AROMATIC NUCLEOPHILIC SUBSTITUTION ON 4-DIMETHYLAMINO-2-METHOXY-3-TRIFLUOROACETYLQUINOLINE

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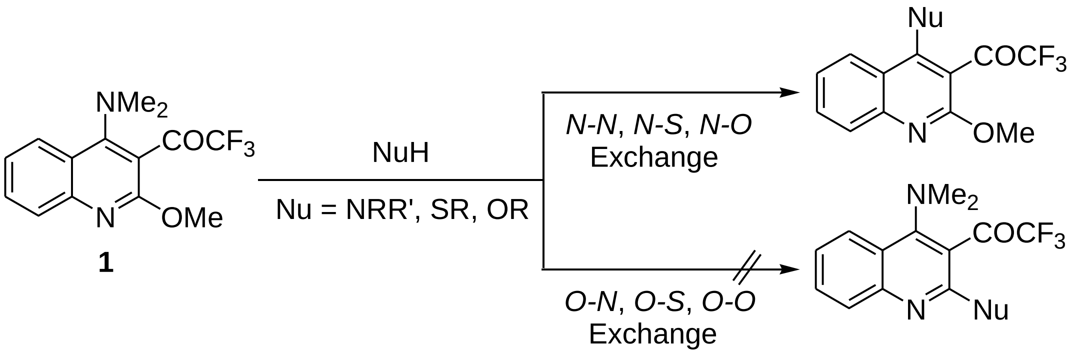
Abstract – The selective nucleophilic substitution on aromatic ring occurs at the 4-position of 4-dimethylamino-2-methoxy-3-trifluoroacetylquinoline **1** by the reaction with various amines to afford the *N-N* exchanged products solely, and any *O-N* exchange reactions at the 2-position are not performed. Our DFT calculation study led to a rational explanation of this unique selectivity based on the frontier electron densities (LUMO) of **1** and energies of the Meisenheimer complexes which were assumed to be formed as the intermediates on such substitution course. It was also investigated about the reaction of related 4-dimethylamino-2-methoxyquinolines bearing various electron-withdrawing groups at the 3-position.

INTRODUCTION

In the last few decades, a lot of approaches have been taken on the exploration of synthetic methodologies for novel kinds of fluorine-containing heterocycles since their potential biological activity might be often focused as unique active ingredients in the various areas of life science research.[1-4] In recent years, we have proposed the convenient synthetic methods successfully accessing 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 key reaction in common for these synthetic process is a highly selective aromatic nucleophilic substitution of 4-dimethylamino moiety of trifluoroacetylated quinoline **1** with appropriate nucleophiles (Nu) (Scheme 1).[7,8] At the 4-position occurs the aromatic nucleophilic substitution of **1** with various *N*-nucleophiles to afford the *N-N* exchanged products solely, while any *O-N* exchange reaction at the 2-position was not performed.[8] In this work, DFT calculation

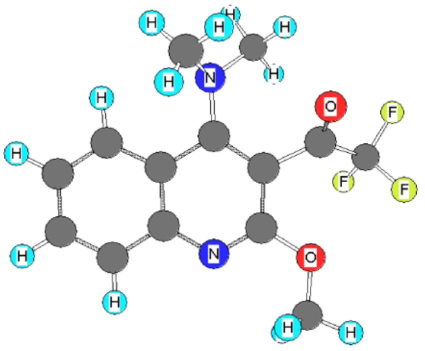


Scheme 1

(RB3LYP/6-31G*) study was examined for the reaction of **1** with *n*-butylamine as a representative model to find out an interesting outcome rationalizing the excellent selectivity on the present substitution of **1**. And, the influence by the 3-substituent on each ring was also discussed on analogous 4-dimethylamino-2-methoxyquinolines having 3-acetyl, 3-benzoyl, 3-cyano, and 3-nitro group instead of 3-trifluoroacetyl group.

RESULTS AND DISCUSSION

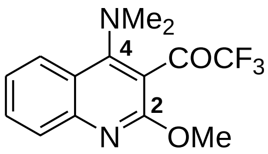
We started to clarify the relative reactivity of 2- and 4-position of trifluoroacetylated quinoline **1** with nucleophiles, which was the key substrate of the present aromatic nucleophilic substitution. At first, it was examined by evaluating the frontier electron densities (f_r) on LUMO of **1**. Figure 1 shows the computational optimized structure of **1** and its energy. Frontier and near frontier orbitals of **1**, LUMO, 2nd LUMO, and 3rd LUMO are depicted in Figure 2. Frontier electron densities on LUMO (f_r^{LUMO}) for 2- and 4-position of **1** are also indicated in Figure 1 together with the corresponding values on



1

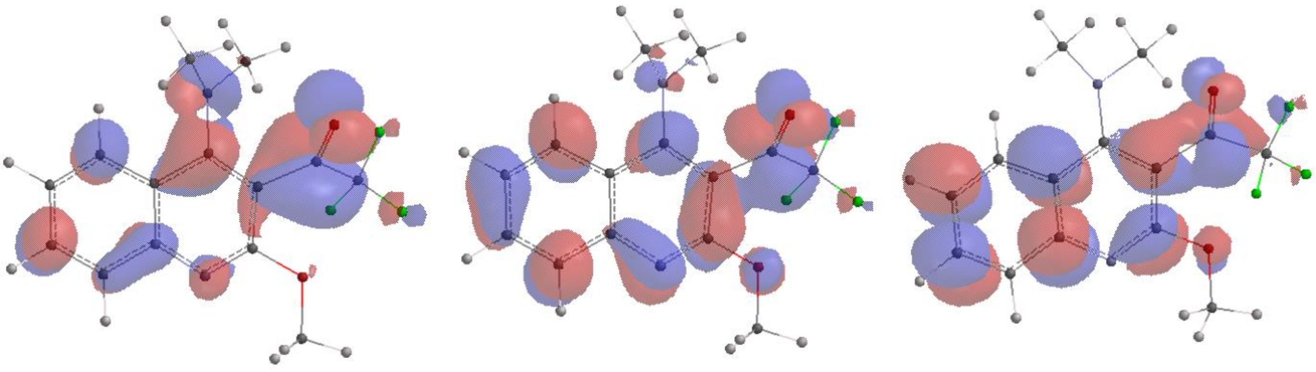
E= -1100.77654 a.u.

Frontier Electron Density



	E (eV)	ΔE (eV)	f_r	
			2-position	4-position
LUMO	-1.99	—	0.089	0.333
2nd LUMO	-0.99	1.00	0.328	0.236
3rd LUMO	-0.26	1.73	0.228	0.020

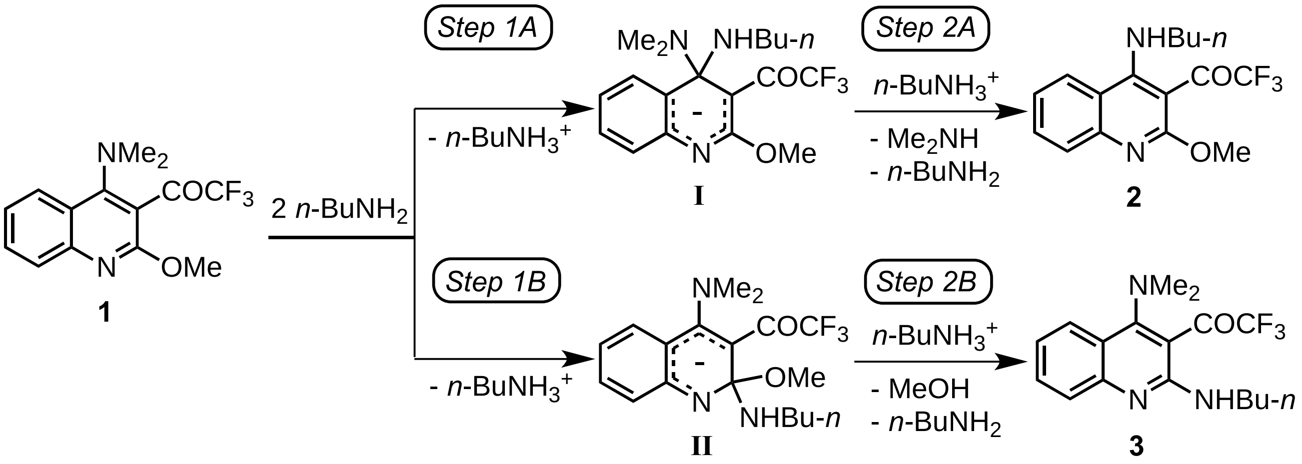
Figure 1



LUMO 2nd LUMO 3rd LUMO

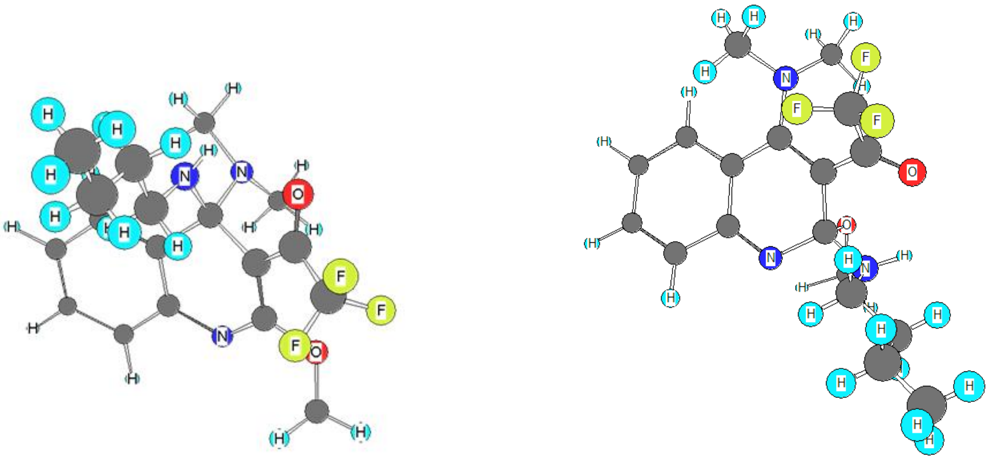
Figure 2

2nd ($f_r^{\text{2nd LUMO}}$) and 3rd LUMO ($f_r^{\text{3rd LUMO}}$). The value of f_r^{LUMO} at the 4-position is larger than the one of f_r^{LUMO}, $f_r^{\text{2nd LUMO}}$, and $f_r^{\text{3rd LUMO}}$ at the 2-position. Furthermore, the 2-position of **1** has minimal f_r^{LUMO} showing almost 0. In contrast, $f_r^{\text{2nd LUMO}}$ and $f_r^{\text{3rd LUMO}}$ of the 2-position are larger than the corresponding ones of the 4-position. However, the contributions of $f_r^{\text{2nd LUMO}}$ and $f_r^{\text{3rd LUMO}}$ are deemed to be not so large since the energy levels of 2nd and 3rd LUMO are calculated to be 1.00 eV and 1.73 eV, respectively, higher than the one of LUMO (see ΔE in Figure 1). These results suggest that nucleophilic attack on the 4-position is preferable rather than the reaction on the 2-position of **1**.



Scheme 2

Next, we examined the energies of Meisenheimer complexes **I** and **II**, the corresponding intermediates to the 4- and 2-substituted products, respectively (Scheme 2). The *n*-butylamine was adopted as a representative amine model for these calculations. The optimized structures of **I** and **II** are illustrated in Figure 3. The computationally simulated Meisenheimer complex **I** was 18.2 kcal more stable than **II**.[9] This result obviously indicates that the nucleophilic attack at the 4-position of **1** (*Step 1A*) giving the



I

E= -1314.01998 a.u.

II

E= -1313.99098 a.u.

Figure 3

intermediate **I** gets preference over the route having the attack at the 2-position of **1** (*Step 1B*) affording **II**. On the other hand, 9.4 kcal/mol more energy was needed for the elimination step from **I** to the 4-substituted product **2** (*Step 2A*) compared with the course to 2-substituted product **3** via **II** (*Step 2B*). Energy diagrams of the present two substitution courses are depicted in Figure 4.

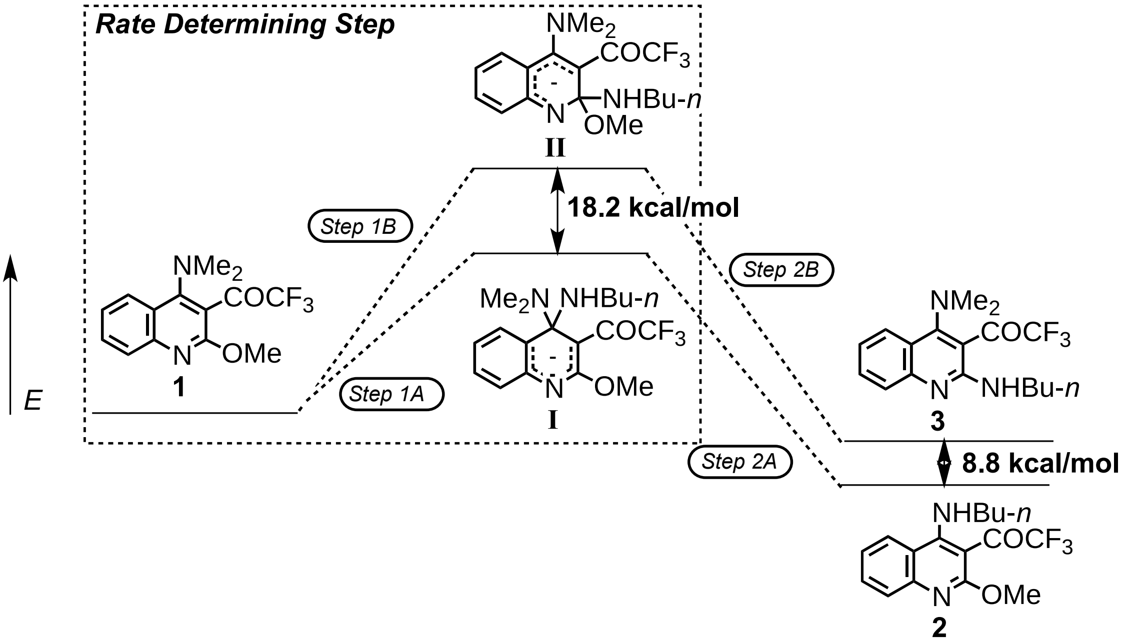
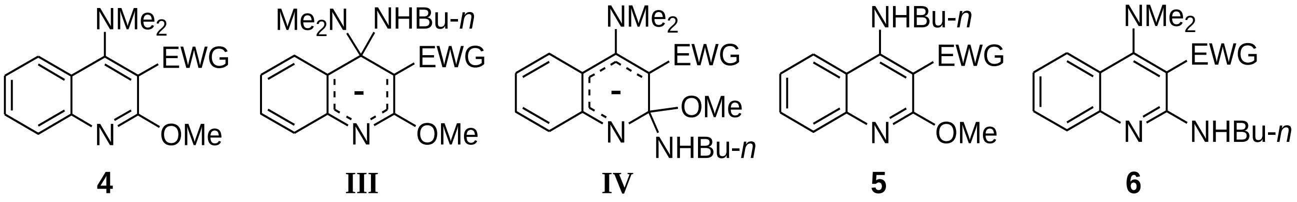


Figure 4

The rate determining steps of these substitution should be the former addition steps (*Steps 1A* and *1B*) giving the adducts **I** and **II** in which the aromatic pyridine-ring systems are destroyed. Even though taking the subsequent elimination steps (*Steps 2A* and *2B*) into account, *N-N* exchange reaction at the 4-position accessing **2** via **I** is totally 8.8 kcal/mol more advantageous than *N-O* exchange reaction at the 2-position giving **3** via **II**.[10]

Consequently, the highly selective nucleophilic substitution of **1** at the 4-position is rationally explained by both frontier electron densities of the substrate **1** and the energy profiles on the whole substitution processes in Scheme 2.

We successively investigated the electron-withdrawing effect of the 3-substituent on this nucleophilic substitution (Scheme 3). It was performed on the reactions of 3-acetyl- and 3-benzoylquinolines, **4a**,**b**, with *n*-butylamine, which have more poor electron-withdrawing carbonyl substituents than trifluoroacetyl group. Additionally, we carried out calculations for the analogous reaction of 3-cyano- and 3-nitroquinolines, **4c**,**d**, which have other kinds of strong electron-withdrawing groups instead of trifluoroacetyl group. No experimental report about such type of nucleophilic substitution on **4a-d** has ever been known.



4-6, III, IV	**a**	**b**	**c**	**d**
EWG	COMe	COPh	CN	NO_2

Scheme 3

The Table 1 shows frontier electron densities of LUMO (f_r^{LUMO}) and 2nd LUMO ($f_r^{\text{2nd LUMO}}$) at 2- and 4-position of quinolines **4a-d**, together with 3-trifluoroacetylquinoline **1** as a comparison. In all cases of **4a-d**, the values of f_r^{LUMO} at the 4-position is larger than the one at the 2-position respectively. It becomes to the prediction of predominant reactions at the 4-position as for these nucleophilic substitutions of **4a-d** according to these computed values.

The both 4-positions of acetylquinoline **4a** and cyanoquinoline **4c** have larger f_r^{LUMO} than the one of trifluoroacetylquinoline **1**. In contrast, **4a** and **4c** have much larger values than **1** as to the $f_r^{\text{2nd LUMO}}$ at the 2-positions. In addition, the 4-positions of **4a** and **4c** have very small $f_r^{\text{2nd LUMO}}$ less than 0.1 whereas the corresponding value at the 4-position of **1** is considerably large and comparable to the value of its 2-position. At the same time, benzoylquinoline **4b** and nitroquinoline **4d** have smaller f_r^{LUMO} of the 4-position compared with **1**, while $f_r^{\text{2nd LUMO}}$ at the same position of **4b** and **4d** are larger than the one of **1**.

As to the selectivity at the 4-position of **1**, it could not be accomplished by a simple comparison of these frontier electron densities between **1** and **4a**-**d**.

Table 1. Frontier electron densities $f_\mathrm{r}^{\mathrm{LUMO}}$ and $f_\mathrm{r}^{\mathrm{2nd\ LUMO}}$ on quinolines **1** and **4a**-**d**

Compound	EWG	Orbital	E (eV)	ΔE [a] (eV)	f_r 2-position	f_r 4-position
1	$COCF_3$	LUMO	-1.99		0.089	0.333
		2nd LUMO	-0.99	1.00	0.328	0.236
4a	COMe	LUMO	-1.52		0.025	0.420
		2nd LUMO	-0.54	0.98	0.467	0.083
4b	COPh	LUMO	-1.59		0.101	0.132
		2nd LUMO	-1.10	0.49	0.091	0.424
4c	CN	LUMO	-1.96		0.006	0.519
		2nd LUMO	-0.72	1.24	0.523	0.030
4d	NO_2	LUMO	-2.12		0.093	0.283
		2nd LUMO	-1.26	0.86	0.208	0.311

a) ΔE = (E of 2nd LUMO) – (E of LUMO)

Then, we computed energies of Meisenheimer complexes **IIIa**-**d** and **IVa**-**d**, which are summarized in Table 2 together with the corresponding trifluoroacetyl derivatives **I** and **II**. In all cases, Meisenheimer complexes **III** (the 4-position adducts giving the *N-N* exchange products **5**) are more stable than the other form **IV** (the 2-position adducts affording the *N-O* exchange products **6**). As a consequent, it gives preference to the nucleophilic substitutions at the 4-position over the same kind reactions at the 2-position on the route of **4a**-**d** to give the corresponding Me_2N - *n-BuNH* exchanged products **5a**-**d** selectively.

Table 2. Energies of Meisenheimer complexes **I**, **II**, **IIIa**-**d**, and **IVa**-**d**

Substrate	EWG	Energy of Meisenheimer Complex				Energy Difference
			E^4 (au)		E^2 (au)	$\Delta E^{2\text{-}4}$ (kcal/ mol) [a]
1	$COCF_3$	**I**	-1314.01998	**II**	-1313.99098	18.2
4a	COMe	**IIIa**	-1016.29815	**IVa**	-1016.27264	16.0
4b	COPh	**IIIb**	-1208.03622	**IVb**	-1208.01026	16.3
4c	CN	**IIIc**	-955.89362	**IVc**	-955.88274	6.8
4d	NO_2	**IIId**	-1068.15768	**IVd**	-1068.13644	13.3

a) $\Delta E^{2\text{-}4} = E^2 - E^4$

The energy differences ($\Delta E^{2\text{-}4}$) between **IIIa-d** and **IVa-d** are smaller than the one between **I** and **II**. Therefore, it is considered to provide poor selectivity for the reaction of quinolines **4a**-**d** to afford the corresponding *N-N* exchanged products **5a-d** compared with the reaction of trifluoroacetylquinoline **1** giving **2**. In addition, $\Delta E^{2\text{-}4d}$ between **IIIc** and **IVc** derived from cyanoquinoline **4c** suggested the poorest selectivity on the substitution of **4c** due to the least $\Delta E^{2\text{-}4z}$ value. The value of $\Delta E^{2\text{-}4}$ is increased in the order of trifluoroacetylquinoline **1** > acylquinolines **4a**,**b** > nitroquinoline **4d** > cyanoquinoline **4c**. The results suggest a selectivity for the substitution at the 4-position of these quinolines which is enhanced corresponding to this order.

In conclusion, an exclusive formation of the *N-N* exchanged products by selective nucleophilic substitution at the 4-position of 3-trifluoroacetylquinoline **1** with amines was rationally explained by our DFT calculation results. The high selectivity on this nucleophilic substitution at the 4-position of **1** was figured out by two factors. The first reason is much higher frontier electron density (LUMO) at the 4-position than the one at the 2-position on **1**. The comparison of energy difference gave the second reason that the Meisenheimer complexes **I** resulted by the attack of amines at the 4-position of **1**, which is assumed to be formed on the reaction course, is relatively more stable than the intermediates such as **II**. Our calculation results also suggested that the nucleophilic substitution with amines occurred selectively at the 4-position of acetyl-, benzoyl-, cyano-, and nitroquinolines **4a-d**. However, the selectivity on these quinolines was estimated to be inferior to the similar reactions of trifluoroacetylquinoline **1**.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 02 and PC SPARTAN 04.[11] For geometrical optimizations, it was performed with the 6-31G* basis set at B3LYP[12] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[13] force field and subsequent semi-empirical PM3[14] optimizations. The calculations for geometries of intermediates and their energies were also taken with the 6-31G* basis set at B3LYP level.

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9. 1 a.u. = 627.5 kcal/mol
10. Energy changes for *Steps 2A* and *2B* were calculated on the basis of the following equations.

$$\mathbf{1} + 2\ n\text{-BuNH}_2 \longrightarrow \mathbf{I} + n\text{-BuNH}_3^+ \quad (\textit{Step 1A})$$

$$\mathbf{I} + n\text{-BuNH}_3^+ \longrightarrow \mathbf{2} + \text{Me}_2\text{NH} + n\text{-BuNH}_2 \quad (\textit{Step 2A})$$

$$\mathbf{1} + 2\ n\text{-BuNH}_2 \longrightarrow \mathbf{II} + n\text{-BuNH}_3^+ \quad (\textit{Step 1B})$$

$$\mathbf{II} + n\text{-BuNH}_3^+ \longrightarrow \mathbf{3} + \text{MeOH} + n\text{-BuNH}_2 \quad (\textit{Step 2B})$$

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