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

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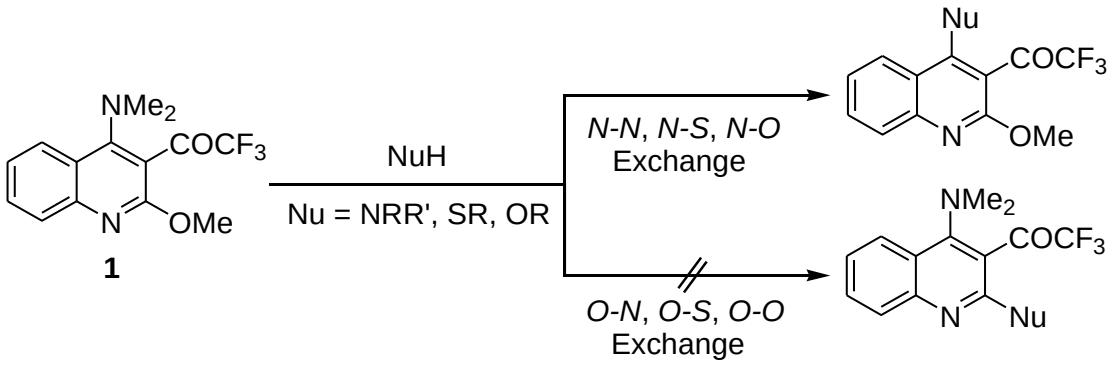
Abstract – The nucleophilic aromatic substitution proceeds exclusively at the 4-position of 4-dimethylamino-2-methoxy-3-(trifluoroacetyl)quinoline **1** by simple alcoholysis to give the corresponding *N*-*O* exchanged products solely, and no *O*-*O* exchange reactions at the 2-position are performed. Our DFT calculation study provides a rational explanation regarding this complete selectivity based on relative energies of the intermediates **VII**, **VIII** which are corresponding to the *O*-protonated Meisenheimer complexes at carbonyl oxygen in 3-trifluoroacetyl group. The reaction pathway for the present unique selective substitution with alcohols is elucidated by referring to the analogous selective substitutions on **1** with amines and thiols as nucleophiles.

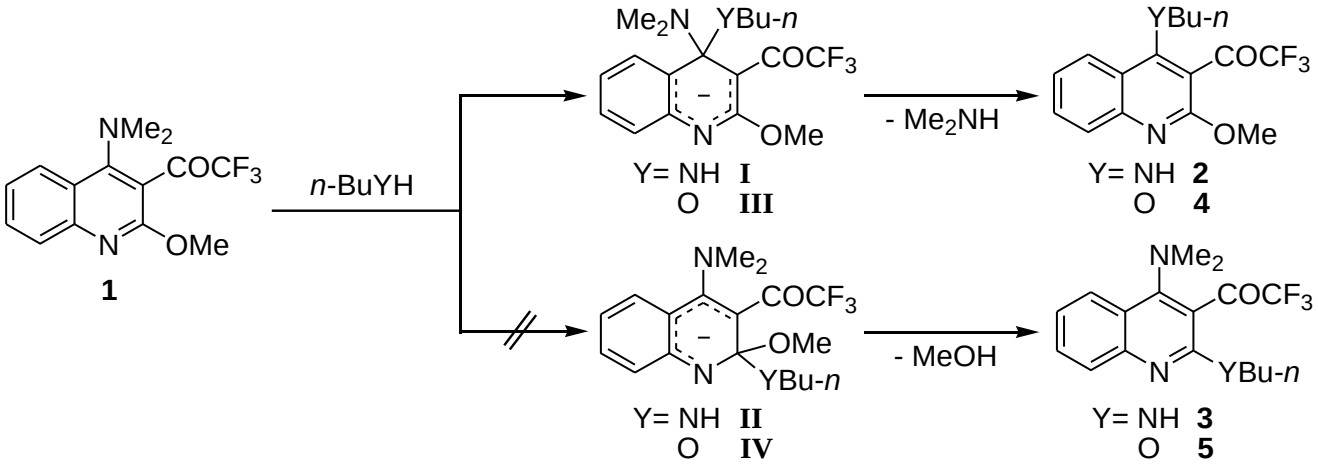
Fluorine-containing heterocycles have been very fascinating synthetic targets for a variety of studies because their potentially high and unique biological activities have often drawn much attention for the various scope in life science research.[1-4] In recent years, we have succeeded in establishing 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 key step reaction on the above studies is a unique highly selective aromatic nucleophilic substitution of 4-dimethylamino moiety of trifluoroacetylated quinoline **1** with appropriate nucleophiles (Scheme 1).[7,8] It is impressive that the nucleophilic substitution of **1** with alcohols are easily performed at its 4-position exclusively by simple alcoholysis to give the *N*-*O* exchanged products solely without base or acid catalytic condition.[7] It is commonly known that alkoxy groups are better leaving group than dialkylamino groups in nucleophilic substitution

reactions. Also, in the nucleophilic substitution at carbonyl center, transesterification occurs more easily than the transformation from amides to the corresponding esters. Comparatively speaking, it is interesting that dimethylamino group at the 4-position is selectively substituted by alkoxy groups and methoxy group at the 2-position remains unchanged in the present reaction.



Scheme 1

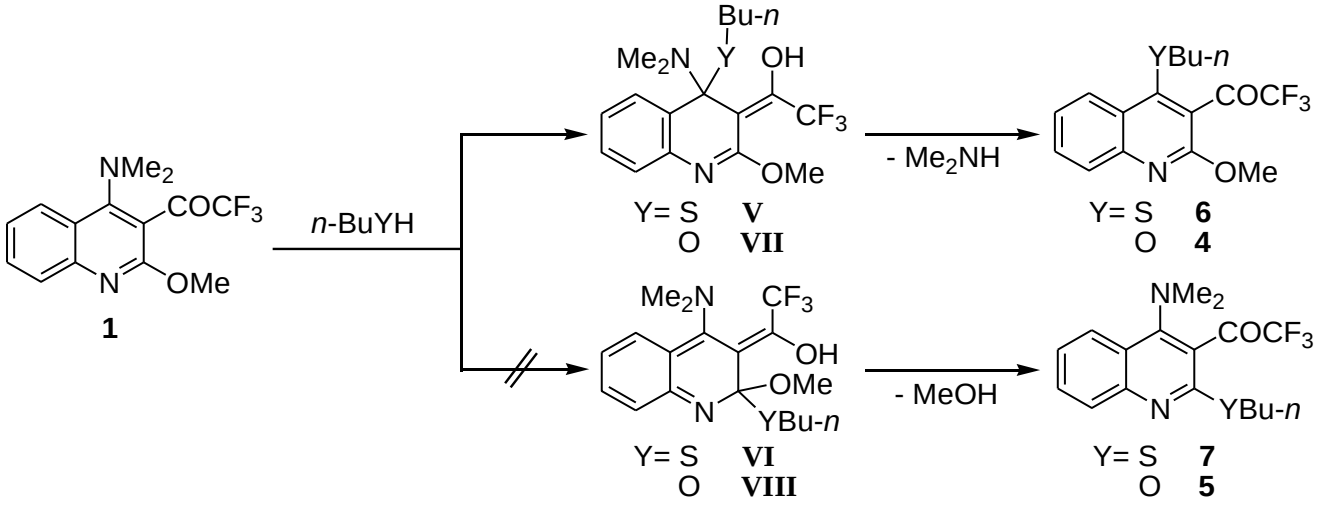
We here wish to present the DFT calculation (RB3LYP/6-31G*) study on the reaction of **1** with *n*-butanol as a representative model to provide the rational explanation as to the complete selectivity on the captioned substitution of **1**. In addition, influences of the solvents on this unique selectivity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



Scheme 2

As we reported in the previous paper,[9] the frontier electron density (LUMO) at the 4-position of **1** is much higher than the one at the 2-position. This means that nucleophiles prefer to attack on the 4-position rather than the 2-position of **1**. However, the complete selectivity appeared in the reaction of **1** with *n*-butylamine 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] In contrast to this, Scheme 3 exhibits the nucleophilic substitution path of **1** with *n*-butanethiol, on which the reaction course had a preference for passing through an intermediate **V**.[10] The exclusive selectivity at the 4-position is attributed to much more stability of **V** accessing the *N*-*S* exchanged product **6** than **VI** leading to the *O*-*S* exchanged product **7**.



Scheme 3

Firstly we investigated the appropriateness on the intermediates type and pathways depicted in Scheme 2 and Scheme 3, for the present *N*-*O* exchange reaction from **1** to **4**. The processes affording **III** and **IV** from **1** are interpreted as shown in eq. 1 and eq. 2, whilst those giving **VII** and **VIII** are corresponding to eq. 3 and eq. 4, respectively. Computed energy changes ΔE1-4 on these equations are summarized in Table 1. The energy change ΔE1 for the process giving Meisenheimer complex **III**[11] from **1** (eq. 1) was estimated to be ca. 150 kcal/mol[12] without solvent model. The corresponding ΔE1 is reduced in *n*-butanol due to a polar medium, but the value over 53 kcal/mol is too large to process the formation of **III** from **1**. The ΔE2 for the formation of **IV**[11] is additionally larger than ΔE1. In contrast, the energy change ΔE3 from **1** to the intermediate **VII**[11] is less than 15 kcal/mol in *n*-butanol. These results apparently indicate that the *N*-*O* exchanged product **4** is formed not via ionic Meisenheimer complex **III** (Scheme 2) but via neutral intermediate **VII** (Scheme 3) even in polar protic *n*-butanol which stabilize ionic intermediates. Table 1 also exhibits that the intermediate **VII** is ca. 20 kcal/mol (ΔE4−ΔE3) more stable than **VIII**.[11,13] Accordingly, such large difference of stability between **VII** and **VIII** causes exclusive formation of **VII** leading the *N*-*O* exchanged product **4** as a sole product.

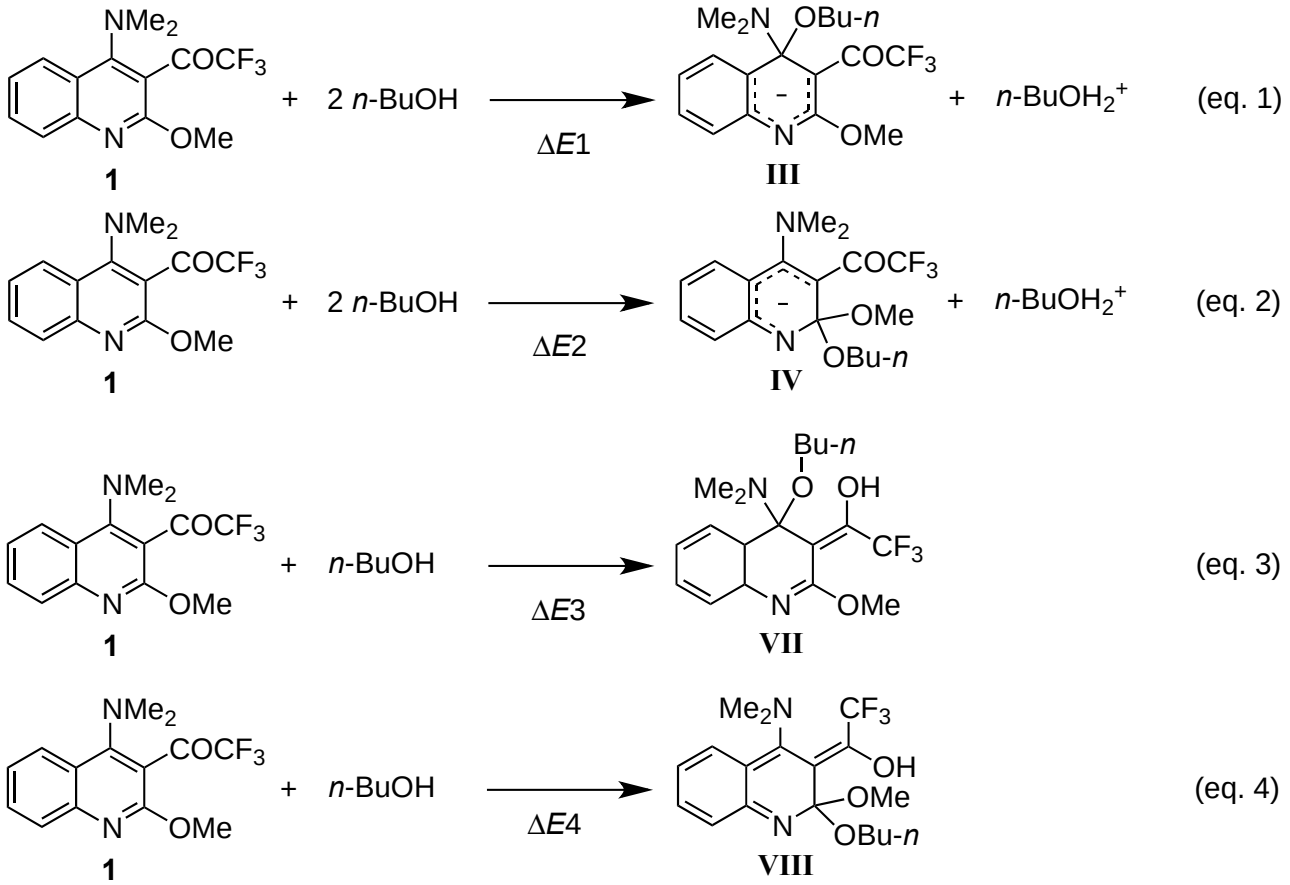


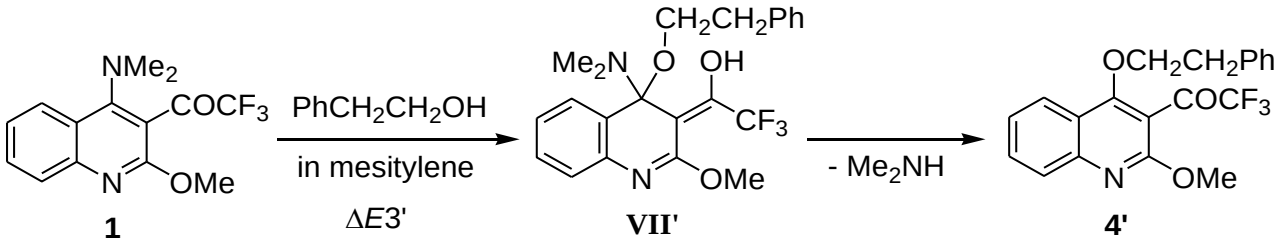
Table 1. Energy changes, Δ*E*1-4 (kcal/mol) on eq. 1-4

Equations	Energy	Without solvent model		Solvent					
				n-BuOH		MeCN		Mesitylene	
eq. 1	Δ*E*1	152.5		53.7		50.2		96.2	
eq. 2	Δ*E*2	163.4	(+10.9)[a]	67.2	(+13.5)[a]	63.8	(+13.6)[a]	108.5	(+12.3)[a]
eq. 3	Δ*E*3	9.8		14.3		14.5		13.5	
eq. 4	Δ*E*4	30.8	(+21.0)[b]	34.0	(+19.7)[b]	34.2	(+19.7)[b]	33.9	(+20.4)

[a] Δ*E*2−Δ*E*1 (= energy difference between **III** and **IV**).

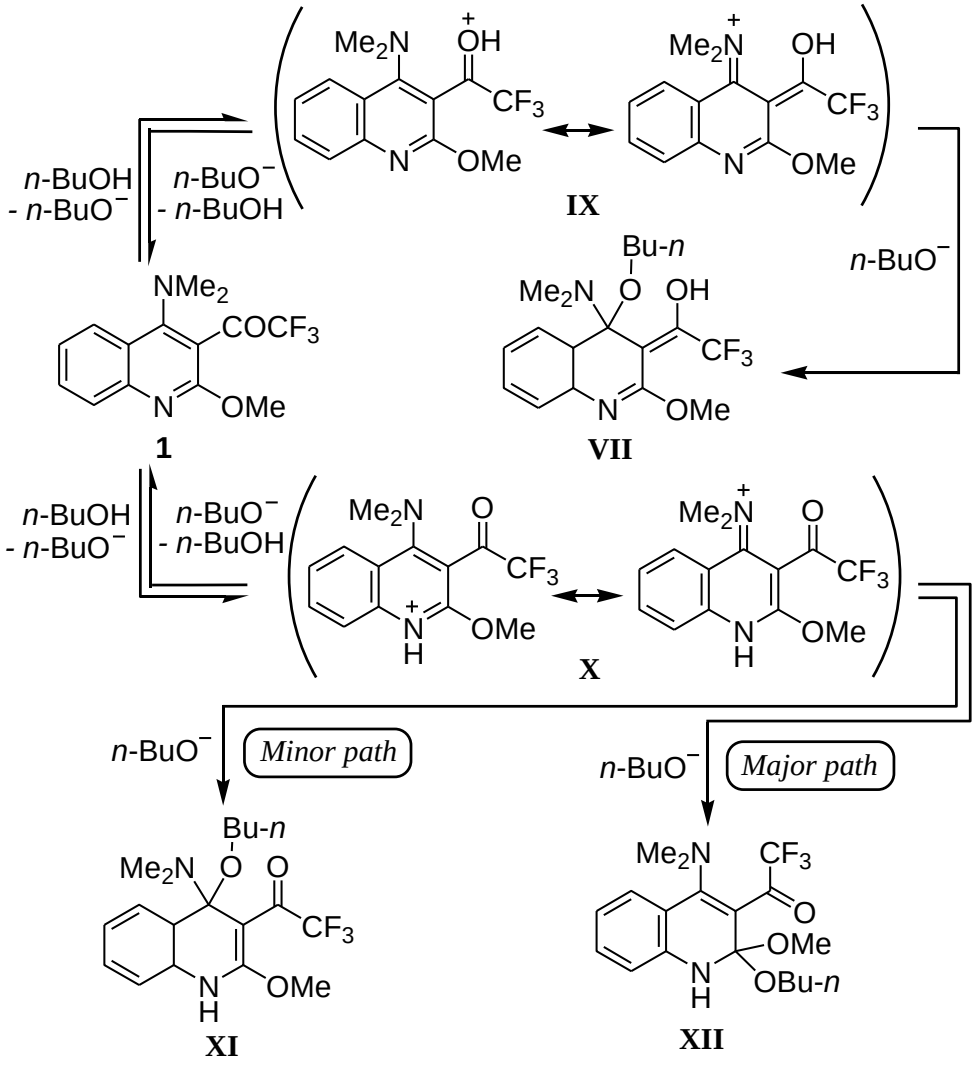
[b] Δ*E*4−Δ*E*3 (= energy difference between **VII** and **VIII**).

It is found that a small deviation of Δ*E*3 within 1 kcal/mol are observed by comparing the solvent effect between acetonitrile as a polar aprotic medium, mesitylene as a nonpolar medium, and *n*-butanol. This result suggests that the present *N*-*O* exchange reaction is scarcely influenced by kinds of the solvent used. Indeed, *N*-*O* exchange of **1** with excess phenethyl alcohol readily proceeds in refluxing mesitylene (Scheme 4).[7] The energy change Δ*E*3' to form **VII'**[11] from **1** is estimated as 14.3 kcal/mol, which is a result quite similar to Δ*E*3 for the reaction of **1** with *n*-butanol under alcoholysis conditions (Table 1). These calculation results are consistent with the above experimental results.



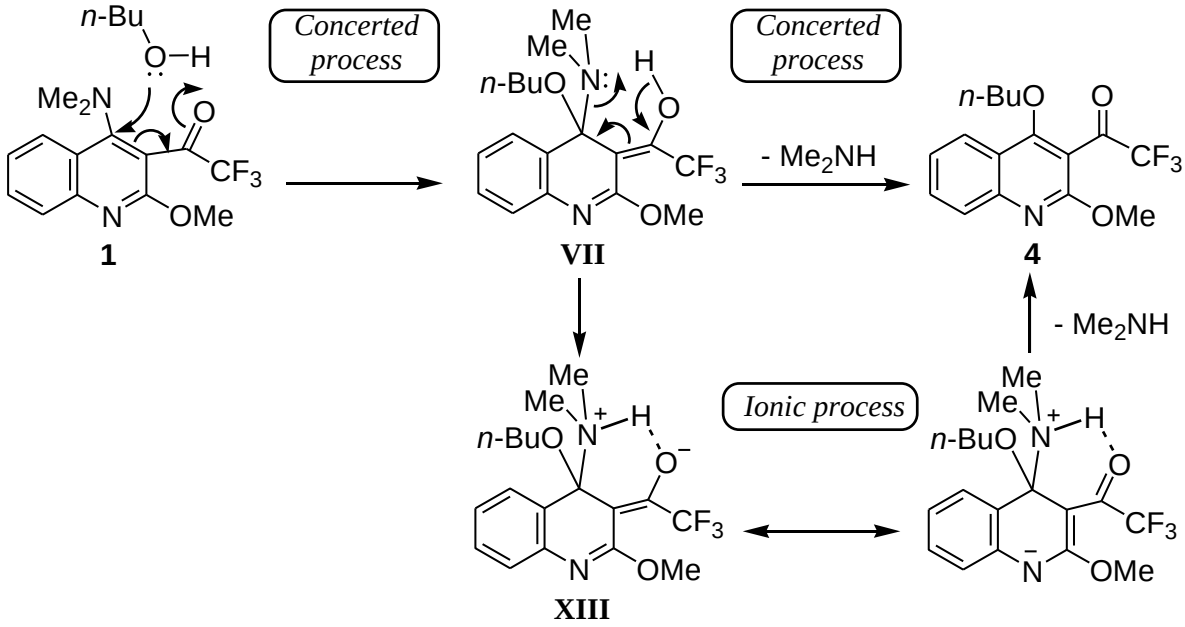
Scheme 4

As for the transformation from **1** to adduct **VII**, a cation **IX** can be generated for a hypothetical reaction-steps composing this alcoholysis as shown in Scheme 5. However, computed energy change for the process from **1** to **IX**[11] exceeds 63 kcal/mol in *n*-butanol and is larger than Δ*E*1 (53.7 kcal/mol) for the transformation from **1** to Meisenheimer complex **III**. In addition, our calculation results indicate that cation **X**[11] is 5.8 kcal/mol more stable than **IX** and, therefore, protonation on **1** predominantly occurs



Scheme 5

at ring-nitrogen to afford cation **X**. Nucleophilic attack of *n*-butoxide anion at the 4-position and the 2-position of **X** give the corresponding adducts **XI** and **XII**, respectively. Subsequent elimination of dimethylamine from **XI** and methanol from **XII** give **4** and **5**, respectively. Since our calculation reaches an outcome on which the adduct **XII**[11] is 1.1 kcal/mol more stable than **XI**,[11] the ionic pathways depicted in Scheme 5 result in major formation of adduct **XII**, consequently, to afford the *O*-*O* exchanged product **5** as a final product. These predictions are inconsistent with the experimental results and, therefore, indicate that intermediate **VII** is not given by such ionic processes via **X**. Like the case of the *N*-*S* exchange reaction of **1** with thiols,[10] concerted process takes part in the direct formation of **VII** from **1**, as illustrated in Scheme 6.



Scheme 6

Next, we would like to discuss in regard to the elimination step from **VII** to **4**. As shown in Scheme 6, the concerted elimination of dimethyamine from **VII** analogous to the case of the *N*-*S* exchange reaction is one of the reasonable processes. Furthermore, ionic process via betaine **XIII** may be plausible pathway on the reaction in polar *n*-butanol. Our calculation results indicate that **XIII**[11] is 9.7 kcal/mol more stable than **VII** to presume prototropy from **VII** to **XIII** proceeding easily in *n*-butanol. Hydrogen bonding between amino proton and carbonyl oxygen (bond length: 1.856 Å, Mulliken bond order: 0.14) would be one of the reason for the stabilization of betaine **XIII**. The elimination of dimethylamine from **XIII** stabilizes the system with the range of 6.3 kcal/mol to give **4** easily. Different from the case of the reaction with *n*-butanethiol,[10] the present *N*-*O* exchange reaction is predicted to take the ionic process in Scheme 6.

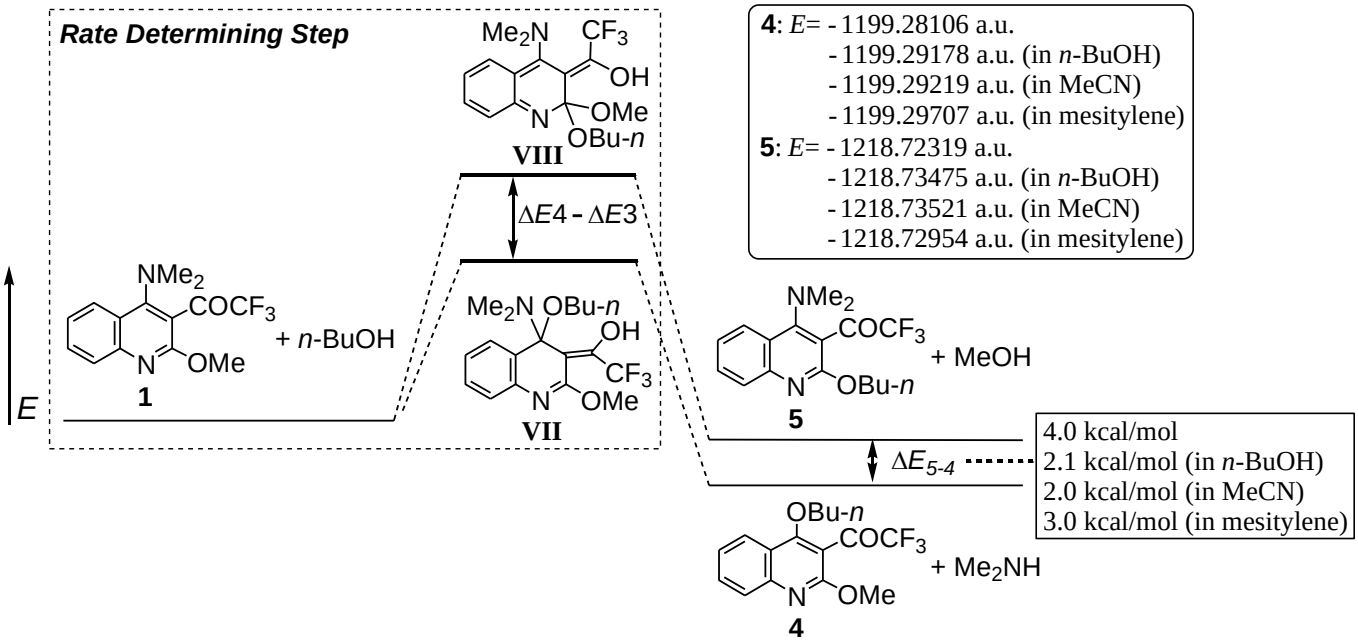
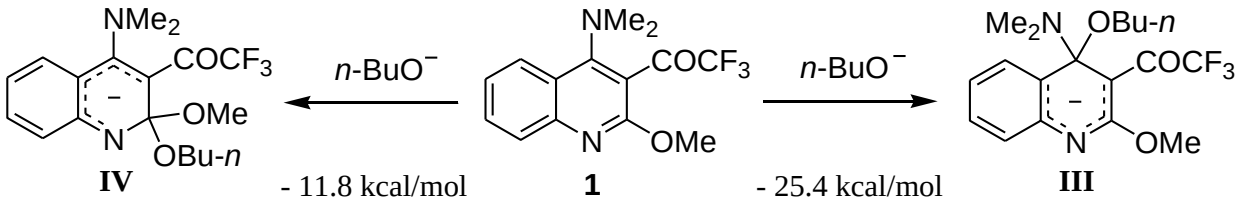


Figure 1

Finally, we have investigated calculation analyses concerning *N*-*O* and *O*-*O* exchanged products, **4** and **5**, respectively. The diagrams in Figure 1 exhibit the computed energies of **4** and **5** for two substitution courses accessing **4** and **5** from starting material **1**. The addition step from **1** to high-energy intermediate **VII** and **VIII** should be a rate determining step for the present substitution reaction. It can be noted that the *N*-*O* exchange reaction accessing **4** via **VII** has 2.1 kcal/mol (in *n*-butanol) advantage in total over the *O*-*O* exchange reaction which gives **5** via **VIII** even though the second elimination steps (**VII** to **4**, **VIII** to **5**) is considered. Therefore, the *N*-*O* exchanged products **4** will be assumed to be produced selectively even if all substitution processes are under thermodynamic control in refluxing *n*-butanol (experimental conditions[7]).



Scheme 7

Additionally, we tried to calculate energy profile for the reaction of **1** with *n*-butoxide in *n*-butanol even though the experimental data has not been given yet. Computed energy changes from **1** to Meisenheimer complexes **III** and **IV** are - 25.4 kcal/mol and - 11.8 kcal/mol, respectively (Scheme 7).

These results suggest that the reaction of **1** with *n*-butoxide readily occurs under mild conditions to afford the corresponding *N*-*O* exchanged product **4** selectively via more stable intermediate **III** than **IV**.

In conclusion, our DFT calculation study has succeeded in rationally explaining about an exclusive formation of the *N*-*O* exchanged products resulted by highly selective nucleophilic substitution at the 4-position of 3-trifluoroacetylquinoline **1** with alcohols. Similar to the substitution of **1** with thiols, the reaction with alcohols does not proceed via the corresponding Meisenheimer complexes **III** but takes the reaction path through intermediate **VII** even under alcoholysis conditions. It is also predicted that the present *N*-*O* exchange reaction is scarcely influenced by polarity of the solvent used. The calculation results for the reaction of **1** with *n*-butoxide suggest that much more mild conditions can be adoptable for the reaction of **1** with various alkoxides giving the corresponding *N*-*O* exchanged products than the present alcoholysis ones. It is also worth noting that the protonation on **1** is predicted to give quinolinium cation **X** and consequently the *O*-*O* exchanged product **5** selectively via adduct **XII**. These findings can propose a methodology for the selective *O*-*O* exchange reaction at the 2-position of **1** under the appropriate acid catalytic condition to access quinolines such as **5**. The reaction of **1** with metal alkoxide and that with alcohols in the presence of acid catalysts are now under investigation.

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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11. Computed energies (in *n*-butanol) for the intermediates appear in the nucleophilic substitution of **1** with *n*-butanol are followings. **III**: -1333.95872 a.u.; **IV**: -1333.93712 a.u.; **VII**: -1334.43375 a.u.; **VIII**: -1334.40230 a.u.; **VII'**: -1486.85253 a.u.; **IX**: -1101.22622 a.u.; **X**: -1101.23554 a.u.; **XI**: -1334.43989 a.u.; **XII**: -1334.44165 a.u.; **XIII**: -1334.44922 a.u.
12. 1 a.u. = 627.5 kcal/mol
13. The intermediate **VIII** is more instable than **VII** since aromatic system of benzene ring comes into destruction (quinoid form) in addition to its pyridine ring in **VIII**.
14. Computed $\Delta E3'$ under alcoholysis ($PhCH_2CH_2OH$) conditions is 14.7 kcal/mol.
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