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Evaluation of dipole moment and electrophilicity on the nature of click-type coupling reaction between thioamide and sulfonyl azide

Muhammad Aswad, *Junya Chiba, Takenori Tomohiro, Yasumaru Hatanaka

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan

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ABSTRACT

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Keywords: Thioamide Dipole moment Sulfonyl azide Electrophilicity Coupling reaction A cooperated experimental and computational investigation on sulfonyl amidine formation from thioamides and sulfonyl azides is described. The data support a non-concerted two-step pathway for the coupling reaction and also indicate that dipole moment of thioamide and electrophilicity of sulfonyl azide would be significant factors for the reaction efficiency. A simple reactivity prediction of the coupling reaction was demonstrated by preliminary *in silico* evaluation for these factors, by which we successfully picked up a good pair of reactants with high reactivity among several thioamides and sulfonyl azides in stock.

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Click-type reaction has become increasingly important as the powerful approach of bio-orthogonal ligation method.¹ We recently reported a new class of click-type chemoselective reaction between thioamides and sulfonyl azides that furnishes sulfonyl amidines in the absence of any activation additives.² The reaction proceeds by mixing a thioamide and a sulfonyl azide at room temperature in various solvents. Increment of the solvent polarity enhances the reaction efficiency and water displayed the highest performance among solvents examined. These features of reaction well satisfy the prerequisite for the biological application. The solvent effect also suggests that the ionic resonance form of thioamides could be preferentially stabilized in polar protic solvents to accelerate the coupling reaction. In the previous report, we suggested an analogous mechanism to the coupling reaction of sulfonyl azides with thioacid derivatives (sulfo-click reaction),³ in which ionic states mainly contribute to the mechanism. In this report, we disclose a non-concerted twostep pathway for the coupling reaction based on both of the experimental and computational investigation of the reaction efficiency by varying the substituents on the respective phenyl rings in thioacetanilide and benzenesulfonyl azide, which enabled to design a combination of thioamide and sulfonyl azide resulting the desired amidine very efficiently in a high yield.

Scheme 1 shows possible two pathways for the coupling reaction in analogy to the proposed mechanism for the sulfo-click reaction^{3b,c} and 1,3-dipoler cycloadditions of organic azides and cyclic ketene derivatives.⁴ Thioamide derivatives favorably transform to the resonance structures⁵ T* that can react with electron-poor sulfonyl azides by an initial bond-formation



Scheme 1. Two plausible pathways of the coupling reaction.



Benzenesulfonyl azide

Figure 1. Energy levels of the frontier orbitals for benzenesulfonyl azide **1a** (left side) and thioacetanilide **2a** (right side) estimated by DFT (RB3LYP/6-311+G(d,p)) calculation. ΔE indicates energy difference of frontier orbitals. The sturctures are visualized with Jmol.⁹

^{*} Corresponding author. E-mail: chiba@pha.u-toyama.ac.jp

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Table 1. Reactivity of substituted benzenesulfonyl azides

R ¹ 1a-f	N ₃ +	S N H 2a	EtOH,	rt R ¹	O, O S N HN 3a−f				
entry	BA ^a	R^1	\mathbf{P}^{b}	Time ^c	Yield ^d	Charge of N ₃ ^e	Reactivity ^f	LUMO ^g	$\Delta E^{\rm h} \ge 10^4$
1	1a	Н	3a	20	63	-0.035	moderate	-0.0928	1236
2	1b	4-CH ₃	3b	20	46	-0.038	moderate	-0.0896	1268
3	1c	4-OCH ₃	3c	20	38	-0.042	low	-0.0868	1296
4	1d	3-NO ₂	3d	20	84	0.005	good	-0.1304	860
5	1e	3-CF ₃	3e	17	95	0.009	good	-0.1033	1131
6	1f	3,5-bis-CF ₃	3f	7	93	0.046	very good	-0.1144	1020

[1] = 1.0 M, [2] = 0.5 M. ^aSubstituted benzenesulfonyl azide. ^bProduct (sulfonyl amidine derivative). ^cReaction time (h). ^dIsolated yield (%). ^eCharge of the azide group based on the electron density (total Mulliken population) of the three nitrogen atoms constructing the azide estimated by DFT calculation (RB3LYP/6-311+G(d,p)). ^fBased on the isolated yield: low (0–45%), moderate (45–75%), good (75–100%), and very good (75–100% within 10 h). ^gLUMO energy (hartree). ^hEnergy difference (hartree) of the frontier orbitals between LUMO of **1a–f** and HOMO of **2a** (–0.2164 hartree).

between sulfur and nitrogen to give a linear adduct, followed by forming an intramolecular nitrogen-carbon bond to afford a thiatriazoline intermediate (path A). Succeeding retro-[3+2] cycloaddition furnishes sulfonyl amidine derivatives associated with N₂ gas generation and solid sulfur precipitation. Another pathway denoted as path B could be anticipated that T* can react with electron-deficient sulfonyl azides by simultaneous formation of sulfur-nitrogen and nitrogen-carbon bonds in a single [3+2] cycloaddition step to give the same thiatriazoline intermediate as path A.

To estimate the initial step of the reaction, we conducted density functional theory (DFT) calculation for benzenesulfonyl azide 1a and thioacetanilide 2a in the ground state (RB3LYP/6-311+G(d,p), see Supplementary data in detail).⁶ Figure 1 displays the frontier orbitals of the two compounds and their energy levels. This energy diagram clearly shows that the combination for the HOMO of thioacetanilide and the LUMO of benzenesulfonyl azide is energetically more reactive than the other HOMO-LUMO combination. In the former reactive combination, the HOMO-localization on sulfur of the thioamide was visualized as Figure 1 in contrast to almost no orbital phase on thiocarbonyl-carbon, suggesting that the sulfur would attack initially to the terminal nitrogen of the azide having the compatible LUMO phase with the sulfur. Subsequent intramolecular cyclization of the linear adduct gives a thiatriazoline by a nucleophilic attack to thiocarbonyl-carbon from azide-nitrogen adjacent to the sulfonyl-sulfur. The frontier orbitals in the less-reactive combination exhibit well-matched orbital phases between the nitrogen (HOMO) and the thiocarbonyl-carbon (LUMO). Although the HOMO-LUMO energy gap is relatively large, the desired nitrogen-carbon linkage would successively form because the two related atoms are intramolecularly settled at near position after the generation of the linear adduct. In addition, thioacetamide and 2-thiopiperidone have almost the same orbital phases as thioacetanilide in both HOMO and LUMO (Figure S1), therefore, the estimated reaction pathway would seem to be extensible to the coupling reaction in general. These computational examination revealed that the coupling reaction of thioamides and sulfonyl azides would prefer to go for the path A in Figure 1 rather than the path B, the simultaneous two-bonds formation via concerted [3+2] cycloaddition, which is similar to the reported mechanism for sulfo-click reaction with electron-deficient azides.3b,c

Based on the above computational estimation, we first anticipated that electrophilicity of the azide group may play an important role for the reactivity of the coupling reaction. Thus, we compared the electrophilicity, the computed charge of N_3 , with the experimental reactivity of the coupling reactions

performed by means of substituted benzenesulfonyl azides 1a-f and thioacetanilide 2a (Table 1). With the increasing of the negativity on azide, the isolated yields for 1b and 1c fell down in comparison to that for 1a (entries 1-3 in Table 1). The electrondonating groups reduced the charge of N₃ accompanied by raising LUMO energy level to be unstable, giving rise to the low isolated yields. On the other hand, electron-withdrawing groups on its phenyl ring seems to improve the reactivity (entries 4-6). Single functional group-substitution by -NO₂ or -CF₃ afforded good isolated yields with somewhat positive N₃-charge relative to the above 1a-c. NO₂-substituted 1d has the most stable LUMO level among the sulfonyl azide compounds in this report. Of course the narrow HOMO-LUMO gap ΔE is no doubt an important factor for the reactivity, however, electrophilicity of the azide group seems to be a dominant factor for the coupling reaction. Bis-CF₃ substitution on the phenyl ring supported this evaluation, that is, 1f exhibited good reactivity in shorter reaction time of 7 h with greater azide's positive-charge in spite of the ΔE for 1f is larger than that for 1d, indicating the importance of the electrophilicity so that stepwise, electrostatic-type mechanism of path A would be preferred rather than the concerted [3+2] cycloaddition-type path B. To check the reproducibility of the yields of the coupling reaction, 3a and 3f were synthesized in 3 runs, affording small deviations of the yields within $\pm 5\%$ in both cases.

Next, we anticipated for thioamides that both of the nucleophilicity on sulfur (δ) and the electrophilicity on thiocarbonyl-carbon (δ^{\dagger}) would be important for the reactivity based on the reaction mechanism of path A. In other word, dipole moment of thioamides would seemingly influence to the reactivity. Thus, we systematically varied the substituents on the phenyl ring of thioacetanilide (Table 2). Since each thioamide derivative shows its dipole moment with different direction, a decomposed-vector component of the dipole moment along with the C=S double-bond orientation, $D_{C=S}$, is brought into for fair comparison toward the reactivity. Methyl-substituted 2b showed moderate reactivity with almost the same isolated yield and D_{C=S} as those for 2a (entry 1,2). By means of the introduction of MeO- group, 2c exhibited small $D_{\text{C=S}}$ of 3.2 debye with low reactivity in an isolated yield of 37% (entry 3). In contrast, 2f displayed high $D_{C=S}$ of 5.0 debye with good reactivity in 81% yield (entry 6). As a consequence, $D_{C=S}$ would be a good indicator for the reactivity. On the other hand, NO₂-tethered 2d displayed slightly large D_{C=S} but low isolated yield, owing to the very large ΔE originated from the significant stabilization of HOMO energy level for 2d by the introduction of a powerful electron-withdrawing nitro-group (entry 4). The similar tendency was observed for 2g possessing two electron-withdrawing groups

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Table 2. Reactivity of substituted thioacetanilides



entry	TA ^a	\mathbb{R}^2	P ^b	Time ^c	Yield ^d	Dipole ^e	$D_{C=S}{}^{f}$	$\Delta D_{C=S}{}^{g}$	Reactivity ^h	HOMO ⁱ	$\Delta E^{\rm j} \times 10^4$
1	2a	Н	3a	20	63	4.2	4.1	0	moderate	-0.2164	1236
2	2b	4-CH ₃	3g	20	65	4.4	4.1	0	moderate	-0.2138	1212
3	2c	4-OCH ₃	3h	20	37	3.5	3.2	-0.9	low	-0.2119	1191
4	2 d	4-NO ₂	3i	20	31	6.6	4.4	0.3	low	-0.2361	1433
5	2e	4-F	3ј	20	73	4.3	4.3	0.2	moderate	-0.2211	1283
6	2f	4-CF ₃	3k	20	81	5.0	5.0	0.9	good	-0.2287	1359
7	2g	3,5-bisCF ₃	31	20	40	4.8	4.2	0.1	low	-0.2366	1438

[1] = 1.0 M, [2] = 0.5 M. ^aSubstituted thioacetanilide. ^bProduct (sulfonyl amidine derivative). ^cReaction time (h). ^dIsolated yield (%). ^eDipole moment (debye) of **2** estimated by DFT calculation (RB3LYP/6-311+G(d,p)). ^fDecomposed dipole moment (debye) along the C=S orientation. ^gDifference of D_{C=S} (debye) between **2** and **2a**. ^hBased on the isolated yield: low (0–45%), moderate (45–75%), and good (75–100%). ⁱHOMO energy (hartree). ^jEnergy difference (hartree) of the frontier orbitals between HOMO of **2a–i** and LUMO of **1a** (–0.0928 hartree).

Table 3. In silico evaluation of N₃-electrophilicity and dipole moment for a reactivity prediction of the coupling reaction.

entry	BA ^a	ΤA ^b	\mathbb{R}^1	\mathbb{R}^2	Charge of N ₃ ^c	Dipole ^d	D _{C=S} ^e	LUMO ^f	HOMO ^g	_
1	1g		3-OCH ₃		-0.035	6.8		-0.0893		O
2	1h		4-F		-0.028	3.5		-0.0965		S _{N3}
3	1i		4-CF ₃		-0.009	2.1		-0.1068		R ¹
4	1j		penta-F		0.080	2.5		-0.1108		ſg−j
5		2h		3-OCH ₃		3.0	3.0		-0.2184	
6		2i		3-F		5.5	5.4		-0.2227	S S
7		2ј		3-CF ₃		6.7	6.6		-0.2262	\mathbb{N}
8		2k		penta-F		4.4	4.2		-0.2319	2h–k

^aSubstituted benzenesulfonyl azide. ^bSubstituted thioacetanilide. ^cCharge of the azide group based on the electron density (total Mulliken population) of the three nitrogen atoms constructing the azide estimated by DFT calculation (RB3LYP/6-311+G(d,p)). ^dDipole moment (debye). ^eDecomposed dipole moment (debye) along the C=S orientation. ^fLUMO energy (hartree). ^eHOMO energy (hartree).



Scheme 2. The coupling reaction selected by the *in silico* estimation.

and a large ΔE with a moderate $D_{C=S}$, providing low reactivity (entry 7). These findings indicate that ΔE would be an important factor as well as $D_{C=S}$ for the reactivity. Fluorine-substituted **2f** afforded moderate reactivity with slightly favorable $D_{C=S}$ and somewhat unfavorable ΔE , suggesting the importance of balance between ΔE and $D_{C=S}$ for the reactivity (entry 5).

Finally, with the aim of predicting the efficiency of the coupling reaction, we simply estimated charge of N_3 and $D_{C=S}$ as well as the energy of frontier orbitals by preliminary DFT calculation for the additional four types of substituted benzenesulfonyl azides and thioacetanilides in stock (Table 3). Pentafluoro-substituted benzensulfonyl azides **1j** retained large positive N_3 -charge while **2j** showed great $D_{C=S}$ and not too-stable HOMO-energy level. Therefore, it was presumable that **1j** and **2j** would be the most reactive combination in Table 3. As expected, simple mixing of **1j** and **2j** in EtOH at room temperature afforded the product amidine **3m** in a good isolated yield within 2 h

(Scheme 2). Expansion the prediction to the coupling reaction in general as well as detailed transition-state analysis *in silico* is now underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at $\sim\sim$

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