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Regioselective pyridazine synthesis from tetrazines and alkynyl sulfides†

Chika Yamamoto,^a Koyo Numata,^a Minori Suzuki^{a,b} and Suguru Yoshida [✉]

A regioselective synthesis of trisubstituted pyridazines from tetrazines and alkynyl sulfides is described. Various pyridazines were selectively prepared by the inverse-electron-demand Diels–Alder reaction and subsequent denitrogenation. Good transformability of sulfur substituents allowed us to synthesize a range of pyridazines without regioisomers.

Introduction

Regioselective Diels–Alder reactions are fundamental ways to synthesize diverse molecules having 6-membered rings, serving in a broad range of disciplines including natural product synthesis, pharmaceutical sciences, and materials chemistry.¹ For example, electron-rich Danishefsky–Kitahara diene **1** reacts with electron-poor dienophiles, such as methacrolein (**2**), to afford cyclohexanones with high regioselectivity (Fig. 1A).² This is achieved through the significant interaction between the HOMO of dienes and the LUMO of dienophiles, aligning the carbon atoms with the highest coefficients. Herein, we describe a unique regioselective synthesis of pyridazines through the inverse-electron-demand Diels–Alder (IEDDA) reactions of tetrazines and alkynyl sulfides.

Tetrazines play pivotal roles as reactive dienes in IEDDA reactions due to their remarkable electron-deficient nature.^{3–6} Indeed, a few distinctive transformations were found in pioneering studies on pyridazine synthesis through the IEDDA reactions of tetrazines with alkynes followed by denitrogenative aromatization.⁶ In 1970, Sauer found that 3-phenyl-1,2,4,5-tetrazine reacts with ynamine **5** without activators to provide pyridazine **6** in excellent yield with interesting regioselectivity (Fig. 1B, upper).^{6a} Also, regioselective pyridazine synthesis was achieved from tetrazine **4a** and phenylacetylene (**7a**) by Meresz (Fig. 1B, lower).^{6b} However, it is not easy to synthesize multisubstituted pyridazines from tetrazines owing to the immature

IEDDA chemistry of tetrazines with alkynes from synthetic and theoretical aspects.

Recently, we revisited the tetrazine reactions with alkynes,⁷ in which efficient conditions using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)⁸ as a solvent and detailed scope of accessible disubstituted pyridazines were disclosed (Fig. 1C, upper). Indeed, regioselective pyridazine formation was achieved by treatment of tetrazine **4a** with aromatic alkyne **7a** in HFIP (Fig. 1C, upper). Unfortunately, we found that it is challenging to accomplish the regioselective reaction of tetrazine **4a** with aliphatic alkyne **7b** (Fig. 1C, lower). In addition, the DFT calculation of the reaction between tetrazines and alkynes served in the prediction of regioselectivities. It is worth noting that regioselective IEDDA reactions took place although substantial differences were not observed in the frontier molecular orbitals of 3-phenyl-1,2,4,5-tetrazine (**4a**) and phenylacetylene (**7a**), suggesting that significant secondary orbital interaction between two benzene rings led to the regioselectivity.

With the success of our previous study in mind, we directed our attention to the reactions of tetrazines with heteroatom-substituted alkynes (Fig. 1D). Inspired by the pioneering study of Sauer (Fig. 1B, upper),^{6a} we hypothesized that heteroatom substituents can control the regioselectivity and serve in the synthesis of a wide variety of multisubstituted pyridazines by further transformations. Pyridazines are of great importance as bioactive compounds.^{9,10} Therefore, facile synthesis of multisubstituted pyridazines from simple modules including heteroatom-substituted alkynes would contribute to various research fields such as pharmaceutical sciences and agrochemistry. Good accessibility of stable heteroatom-substituted alkynes,¹¹ compared to reactive and unstable ynamines,¹² should be a clear benefit for pyridazine synthesis. In this study, after screening a broad range of heteroatom-substituted alkynes in the tetrazine reaction, we have developed a facile method to prepare trisubstituted pyridazines regioselectively from tetrazines and alkynyl sulfides through uncommon interactions between tetrazine substituents and sulfanyl groups.

^aDepartment of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Nijjuku, Katsushika-ku, Tokyo 125-8585, Japan.
E-mail: s-yoshida@rs.tus.ac.jp

^bLaboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

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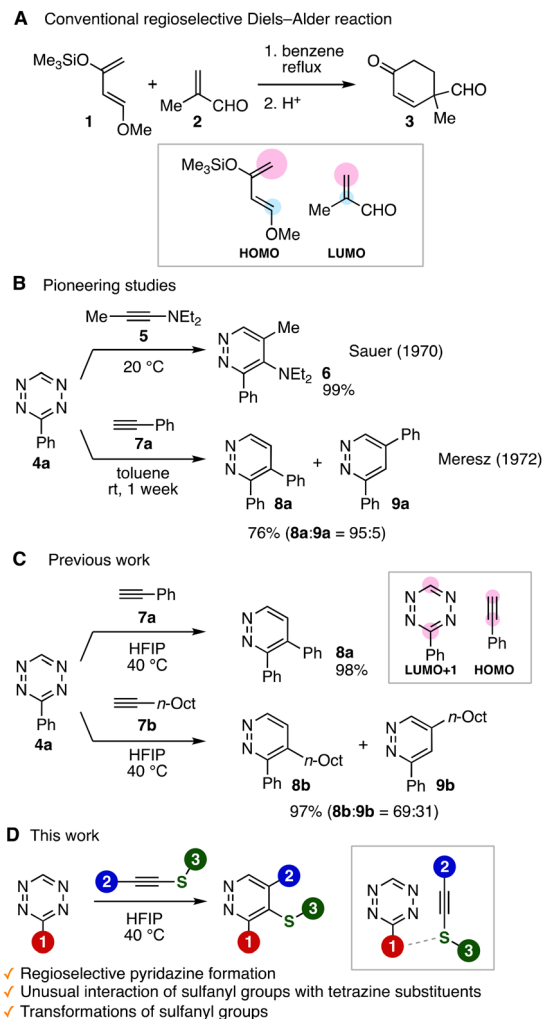


Fig. 1 (A) Conventional regioselective Diels–Alder reaction. (B) Pioneering studies. (C) Our previous study. (D) This work.

Results and discussion

Diels–Alder reaction and subsequent denitrogenation efficiently took place to afford trisubstituted pyridazines **11** and/or **12** bearing heteroatom substituents from tetrazine **4a** with various heteroatom-substituted alkynes **10** (Fig. 2). After examining the reactions in HFIP at 40 °C, we changed the reaction conditions in several cases. For example, aromatic alkynes having N, S, and P substituents showed good reactivities with tetrazine **4a** (Fig. 2A and B). When ynamide **10a** was treated with tetrazine **4a** in *p*-xylene at 150 °C, we achieved the synthesis of aminopyridazines **11a** and **12a** in moderate yields, where 4-amino-substituted pyridazine **12a** was obtained as a major product. Desired pyridazines **11a** and **12a** were not obtained when the reaction was performed in HFIP at 40 °C. Treatment of alkynyl sulfide **10b** with tetrazine **4a** in toluene at 110 °C or in HFIP at 40 °C provided pyridazines **11b** and **12b** in high yields, in which the formation of 5-sulfanylpyridazine **11b** was slightly favored. Pyridazine **11c** bearing a phosphinyl

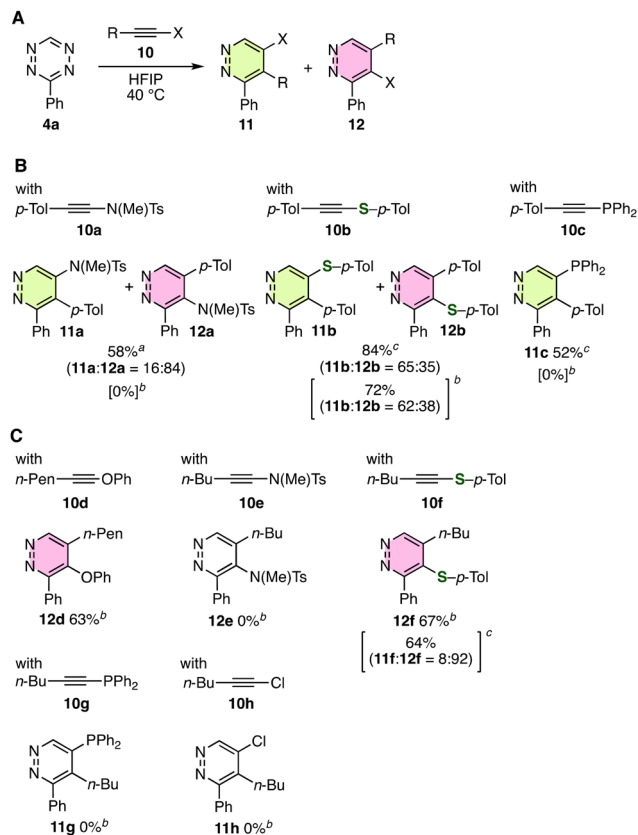


Fig. 2 Synthesis of pyridazines from tetrazine **4a** using various heteroatom-substituted alkynes. (A) General scheme. (B) Products when using aromatic alkynes. (C) Products when using aliphatic alkynes. ^a The reaction was conducted in *p*-xylene at 150 °C. ^b The reaction was conducted in HFIP at 40 °C. ^c The reaction was conducted in toluene at 110 °C. See the ESI† for details.

group was prepared selectively from alkynyl phosphine **10c** without forming 4-phosphinyl-substituted pyridazine **12c**, although desired pyridazine **11c** was not obtained when the reaction was conducted in HFIP at 40 °C. Notably, efficient pyridazine synthesis was accomplished by using a variety of heteroatom-substituted alkynes **10a–10c** which showed low reactivities and thus were easy to purify with silica-gel column chromatography, although the pioneering study was conducted using significantly reactive and easily hydrolyzable ynamine **5**. Considering that 3,4-diphenyl-1,2,4,5-pyridazine (**8a**) was obtained selectively by treatment of tetrazine **4a** with phenylacetylene (**7a**) by the significant interaction between two phenyl groups, competitive effects of the amino or sulfanyl group would lead to the formation of 4-heteroatom-substituted pyridazines **12a** and **12b**.

We then examined pyridazine synthesis from tetrazine **4a** and heteroatom-substituted aliphatic alkynes **10d–10h** (Fig. 2A and C). As a result, the selective preparation of pyridazines **12d** and **12f** was achieved when using alkynyl ether **10d** and sulfide **10f**, respectively. Particularly, it is noteworthy that 4-sulfanylpyridazine **12f** was selectively synthesized by treatment of tetrazine **4a** with alkynyl sulfide **10f** in HFIP at 40 °C due to the



good transformability of sulfanyl groups. The selectivity was slightly decreased when the reaction was performed in toluene at 110 °C. In contrast, pyridazines **11e/12e**, **11g/12g**, or **11h/12h** were not obtained by the reactions of **4a** with alkyne **10e**, **10g**, or **10h**, where the formation of complex mixtures of products was observed. These results clearly showed that alkynyl sulfides efficiently reacted with tetrazine **4a** and the unique selectivity was controlled by the sulfanyl group.

A wide range of pyridazyl sulfides **12** were successfully synthesized from 3-phenyl-1,2,4,5-tetrazine (**4a**) and various alkynyl sulfides (Fig. 3A and B). For example, 4-ethylthio-substituted pyridazine **12i** was selectively obtained in good yield by treatment of tetrazine **4a** with ethyl-4-tolyethynyl sulfide (**10i**) in HFIP at 40 °C, where 5-sulfanylpuridine **11i** was not observed. We accomplished the selective synthesis of pyridazines **12j** and **12k** in high yields from the corresponding alkynyl sulfides leaving sulfanyl, hydroxy, and ester moieties untouched. Of note, ethyl-3-hydroxy-3-methyl-1-butynyl sulfide also reacted with tetrazine **4a** to afford pyridazine **12l** having a bulky tertiary alcohol moiety. Pyridazines **12m** and **12n** with *n*-dodecyl and 4-chlorophenyl groups were efficiently prepared from tetrazine **4a** and the corresponding alkynyl sulfides. Also,

we synthesized a mixture of pyridazines **11o** and **12o** from tetrazine **4a** and ethyl 4-tolyethynyl sulfide (**10o**).

Various tetrazines participated in the selective pyridazine synthesis with alkynyl sulfide **10i** (Fig. 3A and C). Indeed, pyridazines **12p** and **12q** were successfully synthesized from tetrazines having electron-rich aromatic rings without forming 5-sulfanyl-substituted pyridazines. Reactions of tetrazines having electron-deficient aryl groups with alkynyl sulfide **10i** took place smoothly to furnish pyridazines **12r–12t** without affecting fluoro, chloro, and bromo groups. It is worth noting that the selective pyridazine formation was also realized when using 3-benzyl- or 3-(2-(methoxycarbonyl)ethyl)-1,2,4,5-tetrazine to provide **12u** or **12v**, respectively, in which 5-sulfanylpuridazines **11** were not obtained. Unfortunately, we failed in the preparation of tetrasubstituted pyridazine **12w** from 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine and sulfide **10i**.

To our surprise, the regioselectivity was completely switched only by changing the sulfur substituents from sulfanyl to sulfinyl or sulfonyl groups (Fig. 4A and B).¹³ For instance, 5-sulfinyl-substituted pyridazine **11x** was synthesized selectively from tetrazine **4a** with ethyl 1-hexyn-1-yl sulfoxide (**10p**). Reactions of alkynyl sulfoxides with tetrazine **4a** proceeded smoothly to afford 5-sulfinyl-substituted pyridazines **11y–11aa** without the formation of regioisomers **12**. We also accomplished the selective synthesis of 5-sulfonyl-substituted pyridazines **11ab** and **11ac** from the corresponding alkynyl sulfones, where 4-sulfonylpuridazines **12** were not observed.

Transformations of 4-sulfanylpuridine **12i** indicated that a wide variety of pyridazines can be synthesized through the selective pyridazine formations from tetrazines and alkynyl sulfides (Fig. 5A). Sulfoxide **12x** was prepared by the oxidation

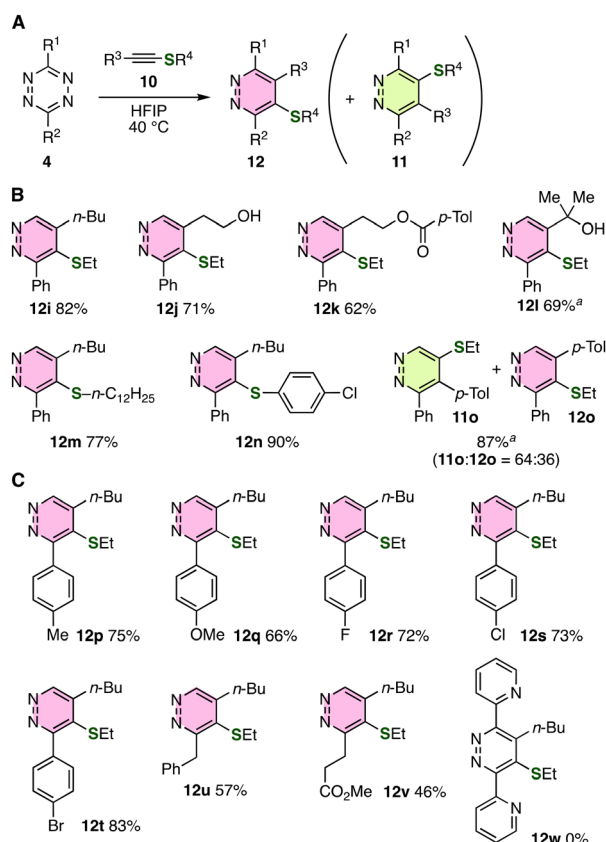


Fig. 3 Synthesis of pyridazines from tetrazines and alkynyl sulfides. (A) General scheme. (B) Products from **4a** with various alkynyl sulfides. (C) Products from ethyl 1-hexyn-1-yl sulfide (**10i**) with various tetrazines. See the ESI† for details. ^aThe reaction was conducted in toluene at 110 °C instead of HFIP at 40 °C.

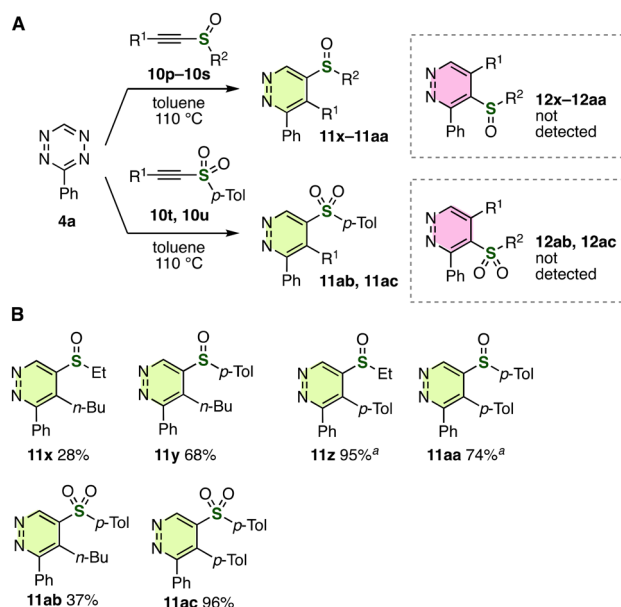


Fig. 4 Synthesis of pyridazines from tetrazine **4a** and alkynyl sulfoxides or sulfones. (A) General scheme. (B) Products. See the ESI† for details. ^aThe reaction was conducted in toluene at 110 °C instead of HFIP at 40 °C.



of sulfide **12i** in the presence of a molybdenum catalyst in moderate yield (Fig. 5A, upper).¹⁴ Since the synthesis of 4-sulfanyl-substituted pyridazine **12x** was difficult by the reaction of **4a** with alkynyl sulfoxide **10p**, this result demonstrates the advantage of this protocol *via* the reaction of tetrazines with alkynyl sulfides and subsequent *S*-oxidation. We then succeeded in the reduction of sulfide **12i** furnishing 5-butyl-3-phenylpyridazine (**13**) under palladium-catalyzed conditions (Fig. 5A, lower).¹⁵ Since it is not easy to prepare pyridazine **13** from tetrazine **4a** and 1-hexyne due to the poor selectivity in the case of aliphatic alkyne (Fig. 1C, lower), it is worth noting that the selective synthesis of disubstituted pyridazines having alkyl substituents was realized through pyridazine formation followed by reduction. The reduction of sulfoxide **11aa** was realized under conditions using titanium(IV) chloride and triphenylphosphine to afford sulfide **11b** (Fig. 5B).¹⁶ A regioisomeric mixture of **11b** and **12b** was obtained when tetrazine **4a** was treated with alkynyl sulfide **10b** (Fig. 2C). In contrast, the selective pyridazyl sulfoxide formation from **4a** and *p*-tolyl-*p*-tolylethynyl sulfoxide and subsequent *S*-reduction resulted in the preparation of pyridazine **11b** without 4-sulfanyl-substituted pyridazine **12b**. These results clearly show that selective pyridazine formation from tetrazines and sulfur-substituted alkynes followed by further transformations allowed us to synthesize diverse multisubstituted pyridazines without isomers.

To gain insight into the origin of the unique selectivity for the tetrazine reaction with alkynyl sulfides, we analyzed the reaction mechanism by theoretical calculations based on the DFT method (ω B97X-D/6-311+G(d,p))⁵ⁿ (Fig. 6). These results obviously support the reaction pathways forming pyridazines **11ad** and **12ad** *via* the IEDDA reaction between tetrazine **4a** and alkynyl sulfide **10i** and subsequent removal of nitrogen, in which activation energies for the denitrogenation were significantly smaller than those for the IEDDA reactions (Fig. 6A and B). The theoretical pathway in the gas phase for 4-sulfanylpyridazine **12i** requires 2.4 kcal mol⁻¹ lower activation energy than that for the isomer **11i**, showing good agreement between the DFT calculations and experimental results. The difference of activation energies was slightly increased when the calculation was conducted in polar solvents. These results are in good

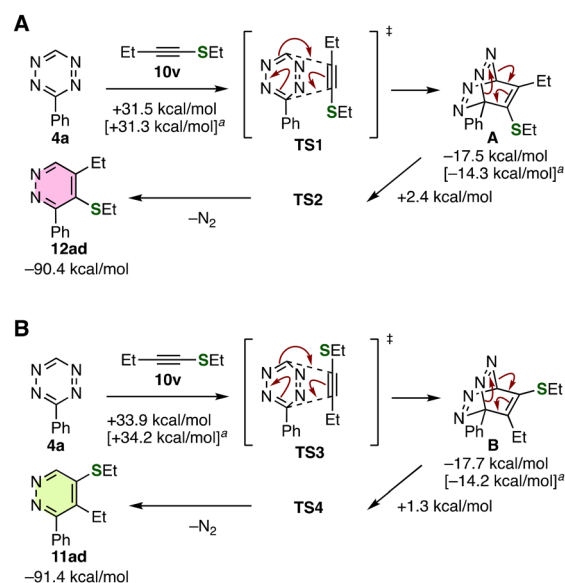


Fig. 6 Calculated plausible reaction pathways for the synthesis of pyridazines **12ad** (A) and **11ad** (B) by a DFT method (ω B97X-D/6-311+G(d,p)). Respective energy differences are shown. ^aCalculated energy differences in polar solvents. See the ESI† for details.

agreement with the experimental result that 4-sulfanylpyridazine **12f** was obtained as a major isomer not only in HFIP at 40 °C but also in toluene at 110 °C.

The detailed computational analysis provided a clue for the favored transition state structure **TS1** forming 4-sulfanylpyridazine **12ad** compared to **TS3** for isomer **11ad** (Fig. 7 and 8). The frontier molecular orbital (FMO) theory analysis of tetrazine **4a** and alkynyl sulfide **10v** indicates the energy gap between

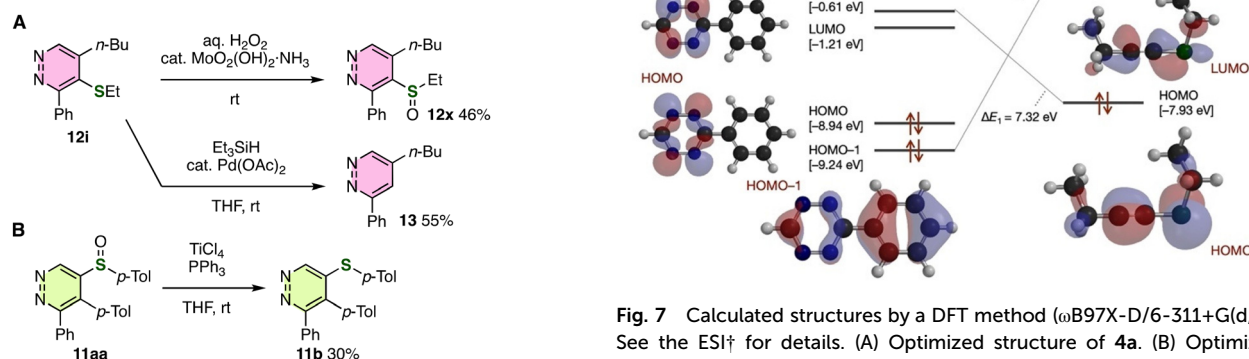


Fig. 7 Calculated structures by a DFT method (ω B97X-D/6-311+G(d,p)). See the ESI† for details. (A) Optimized structure of **4a**. (B) Optimized structure of **10v**. (C) FMO analysis between **4a** and **10v** with structures and orbital levels of LUMO+1, LUMO, HOMO, and HOMO-1 of **4a** and LUMO and HOMO of **10v**.

Fig. 5 (A) Transformations of pyridazine **12i**. (B) Reduction of sulfoxide **11aa**. See the ESI† for details.



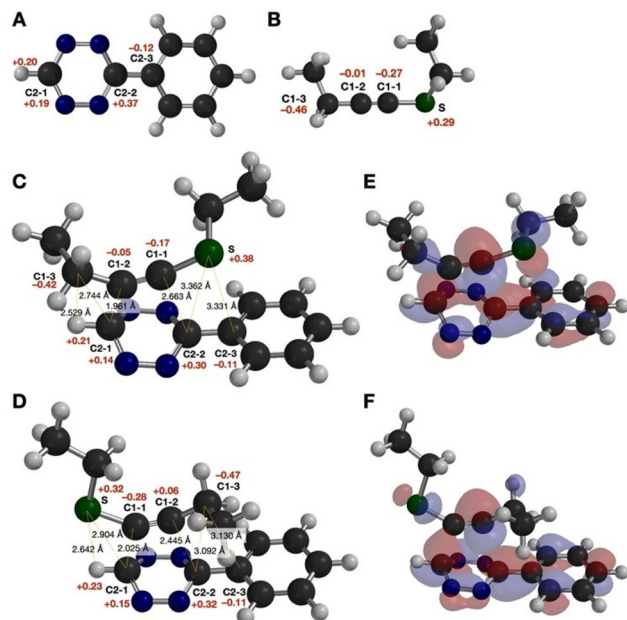


Fig. 8 Charge distribution analysis of **4a** (A), **10v** (B), **TS1** (C), and **TS3** (D). Natural atomic charges were calculated by a DFT method (ω B97X-D/6-311+G(d,p)). The calculated charges are shown as red numbers. Atomic distances are shown as black numbers. See the ESI† for details. LUMOs of **TS1** (E) and **TS3** (F).

LUMO+1 of tetrazine **4a** and HOMO of alkynyl sulfide **10v** is significantly lower than that between HOMO–1 of **4a** and LUMO of **10v** (Fig. 7A–C), supporting that the pyridazine formation proceeds *via* the IEDDA reaction, while the regioselective pyridazine formation is not explained by the orbital analysis. In the transition state structure **TS1** for major isomer **12ad**, the $n-\pi^*$ interaction between the sulfur atom of alkynyl sulfide **10v** and the phenyl group of tetrazine **4a** was suggested by the positive charge at the sulfur atom due to the electron donation to the electron-deficient benzene ring (Fig. 8A–C), LUMO of the transition state (Fig. 8E), and shorter distances of S–C2-2 and S–C2-3 than the sum of van der Waals radii (Fig. 8C) in comparison to **TS3** for isomer **11ad** (Fig. 8D and F). These results suggested that the significant $n-\pi^*$ interaction of the sulfur with the tetrazine substituent realized the selective synthesis of 4-sulfanyl-substituted pyridazines.

Conclusions

In summary, we found that a wide variety of pyridazines could be synthesized from 3-substituted 1,2,4,5-tetrazines and alkynyl sulfides. Unique regioselectivities were controlled by the interaction between sulfanyl groups and tetrazine substituents which was supported by theoretical calculations. Further studies such as applications to construct a vast pyridazine library for drug discovery, regiocontrolled IEDDA reactions using alkynyl sulfides with various electron-deficient dienes, and detailed theoretical studies of IEDDA reactions involving

energy decomposition analysis based on the distortion/interaction model^{17,18} are ongoing in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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