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Regioselective pyridazine synthesis from tetrazines and alkynyl sulfides†

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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. 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). 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

Recently, we revisited the tetrazine reactions with alkynes,⁷ in which efficient conditions using 1,1,1,3,3,3-hexafluoro-2propanol (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 heteroatomsubstituted 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.

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

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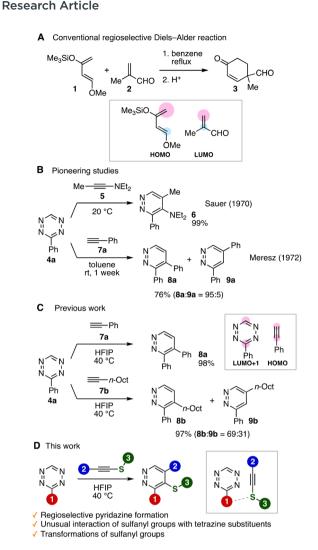


Fig. 1 (A) Conventional regioselective Diels-Alder Pioneering studies. (C) Our previous study. (D) This work.

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. ^aThe reaction was conducted in p-xylene at 150 °C. b The reaction was conducted in HFIP at 40 °C. ^cThe 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-tolylethynyl sulfide (10i) in HFIP at 40 °C, where 5-sulfanylpyridazine 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,

10 HFIP В HO' 12I 69% 12i 82% **12j** 71% 12k 62% p-Tol Ėн 110 Ėн 120 12m 77% 12n 90% 87%^a (110:120 = 64:36)С n-Bu n-Bu n-Bu SEt SEt Me 12p 75% ÓМе **12q** 66% 12s 73% n-Bu n-Bu SEt 12u 57% CO₂Me 12v 46% 12t 83%

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.

we synthesized a mixture of pyridazines 110 and 120 from tetrazine 4a and ethyl 4-tolylethynyl 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-sulfanylpyridazines 11 were not obtained. Unfortunately, we failed in the preparation of tetrasubstituted pyridazine 12w from 3,6-bis(2pyridyl)-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-sulfonylpyridazines 12 were not observed.

Transformations of 4-sulfanylpyridazine 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

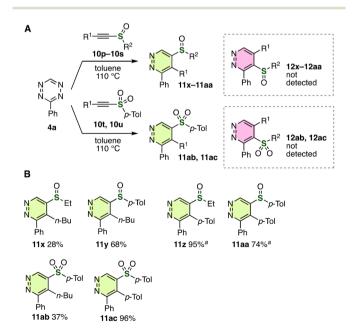


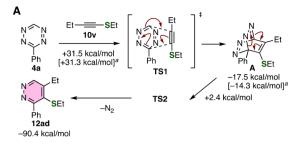
Fig. 4 Synthesis of pyridazines from tetrazine 4a and alkynyl sulfoxides or sulfones. (A) General scheme. (B) Products. See the ESI† for details. ^aThe reaction was conducted in toluene at 110 °C instead of HFIP at 40 °C.

Research Article

of sulfide 12i in the presence of a molybdenum catalyst in moderate yield (Fig. 5A, upper). 14 Since the synthesis of 4-sulfinyl-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-ptolylethynyl 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 $(\omega B97X-D/6-311+G(d,p))^{5n}$ (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. 5 (A) Transformations of pyridazine 12i. (B) Reduction of sulfoxide 11aa. See the ESI† for details.



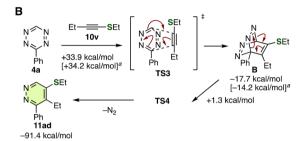
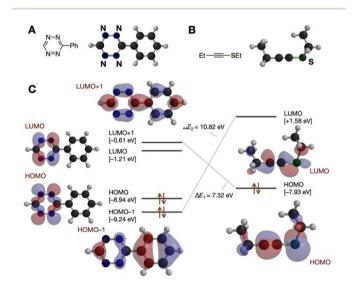


Fig. 6 Calculated plausible reaction pathways for the synthesis of pyridazines 12ad (A) and 11ad (B) by a DFT method (ωB97X-D/6-311+G(d,p)). Respective energy differences are shown. a Calculated energy differences in polar solvents. See the ESI† for details.

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



Calculated structures by a DFT method (ωB97X-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.

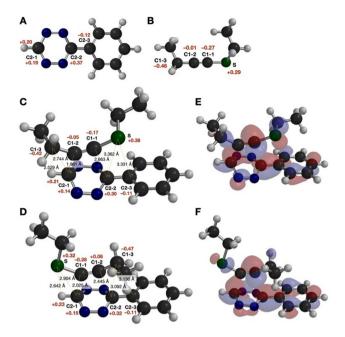


Fig. 8 Charge distribution analysis of 4a (A), 10v (B), TS1 (C), and TS3 (D). Natural atomic charges were calculated by a DFT method $(\omega B97X-D/6-311+G(d,p))$. The calculated charges are shown as red numbers. Atomic distances are shown as black numbers. See the ESI† for details. LUMOs of TS1 (E)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

Conflicts of interest

There are no conflicts to declare.

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