ACES Asian Chemical Editorial Society

doi.org/10.1002/asia.202100562

CHEMISTRY AN ASIAN JOURNAL
Full Paper

One-Pot and Two-Chamber Methodologies for Using Acetylene Surrogates in the Synthesis of Pyridazines and Their D-Labeled Derivatives

Maria S. Ledovskaya,[a] Mikhail V. Polynski,[a, b] and Valentine P. Ananikov*[a, b]

Abstract: Acetylene surrogates are efficient tools in modern organic chemistry with largely unexplored potential in the construction of heterocyclic cores. Two novel synthetic paths to 3,6-disubstituted pyridazines were proposed using readily available acetylene surrogates through flexible C_2 unit installation procedures in a common reaction space mode (*one-pot*) and distributed reaction space mode (two-chamber): (1) an interaction of 1,2,4,5-tetrazine and its acceptor-functionalized derivatives with a CaC_2–H_2O mixture performed in a two-chamber reactor led to the corresponding pyridazines in quantitative yields; (2) [4 + 2] cycloaddition of 1,2,4,5-tetrazines to benzyl vinyl ether can be considered a universal synthetic path to a wide range of pyridazines. Replacing water with D_2O and vinyl ether with its trideuterated analog in the developed procedures, a range of 4,5-dideuteropyridazines of 95–99% deuteration degree was synthesized for the first time. Quantum chemical modeling allowed to quantify the substituent effect in both synthetic pathways.

Introduction

Nitrogen heterocycles are one of the most important structural motives in drug design and development because of the wide range of diversities and biological activities they possess.[1] More than 75% of the FDA-approved drugs currently available on the market contain a nitrogen heterocycle as a core fragment.[2] The number of biologically active nitrogen heterocycles is constantly growing,[1,2] with a significant demand in the synthesis of new structures.

Pyridazines, six-membered heterocycles containing a unique and valuable N–N structural motif, are widely present in a variety of natural products and pharmaceutically active compounds (Figure 1).[3] Among them, Sulfachloropyridazine possesses antibiotic activity,[3c] Hydralazine has anti-hypertensive activity,[3d,g] Pyridazomycin is an antibiotic and antifungal agent,[3e,f] Minaprine and relatives are AchE inhibitors,[4] and a range of pyridazines demonstrate anti-inflammatory activity.[5] Recently, a number of 3,6-disubstituted pyridazines demonstrated antitumor activities,[6] what forces us to admit a high potency of the pyridazine cycle in the construction of new pharmaceuticals. The pyridazine ring was specifically ranked by pharmaceutical companies as one of the best potential heterocycles for the design of new drugs.[7]

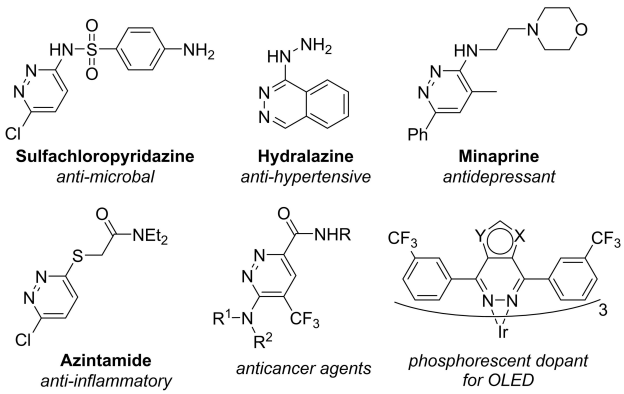


Figure 1. Selected examples of valuable pyridazines.

The potential of pyridazines in the construction of drugs is not the only way of their application. The pyridazine moiety was also efficiently applied as a main skeleton unit in fluorescent dyes.[8] Substituted pyridazines have demonstrated high potential in the creation of chemical multicolor fluorescent sensors due to their sensitivity to pH.[8b] Taking into account the abovementioned considerations, the development of simple and efficient methods for the synthesis of structurally diversified pyridazines is in high demand.

In this article, we thoroughly investigated the interaction between 1,2,4,5-tetrazines and acetylene surrogates, a calcium carbide-water mixture and benzyl vinyl ether. The [4 + 2] cycloaddition of 1,2,4,5-tetrazines to unsaturated carbon-carbon bonds and sequential nitrogen elimination (and benzyl alkohol, if benzyl vinyl ether was used as an acetylene surrogate) can lead to the formation of a pyridazine moiety (Figure 2A). We proposed and compared two different strategies for using acetylene surrogates (Figure 2A) depending on the compatibility of reaction components. We demonstrated that a

[a] Dr. M. S. Ledovskaya, Dr. M. V. Polynski, Prof. Dr. V. P. Ananikov
Institute of Chemistry
Saint Petersburg State University
Universitetsky prospect 26, Saint Petersburg 198504 (Russia)
E-mail: val@ioc.ac.ru

[b] Dr. M. V. Polynski, Prof. Dr. V. P. Ananikov
N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences
Leninsky prospect 47, Moscow, 119991 (Russia)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/asia.202100562

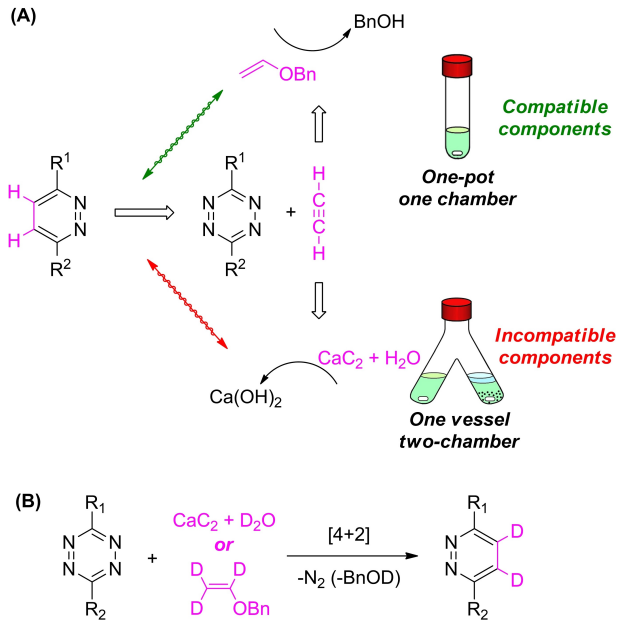


Figure 2. (A) Two strategies for using acetylene surrogates in the synthesis of pyridazines. **(B)** The proposed methodology for using surrogates of acetylene-d_2 in the synthesis of highly deuterated 4,5-dideuteropyridazines.

practically desirable and efficient "one vessel" approach can be designed for either type of reactive C_2 unit by implementation in a *one-pot* or two-chamber manner (see inserted graphics in Figure 2). The results of this study suggest two simple, economical and efficient synthetic paths to 3,6-disubstituted pyridazines and demonstrate a range of applicability of both methods.

The substitution of hydrogen atoms in a drug molecule to deuterium is a novel opportunity to alter its physical and chemical properties[9] and to improve the pharmaceutical activity of a specific molecule.[10] This property of deuterium underlies a great variety of mechanistic studies in chemistry and pharmacokinetic profile evaluation in medicine.[10–11] The substitution of hydrogen to deuterium allowed to alter reaction selectivities in total syntheses and to enhance the metabolic stability of a specific VMAT2 inhibitor (Tetrabenazine, which was modified by a replacement of six hydrogen atoms with deuterium atoms), allowing less frequent drug dosing.[12] In view of recent advances in this field,[12–13] the development of new synthetic paths to deuterium-labeled compounds, particularly heterocycles, is very demanding.

The application of deuterated acetylene surrogates in the developed procedures (CaC_2–D_2O mixture or benzyl D_3-vinyl ether, see Figure 2B) led to 4,5-dideuteropyridazines. For the first time, were proposed two simple and economical synthetic paths to D_2-labeled pyridazines, which allowed high levels of deuteration (95–99%) to be achieved in only one synthetic step and did not require any harsh reagents or complex equipment.

For the first time, a complete reaction space involving both acetylene and its surrogate (Figure 2) was explored here with quantum-chemical modeling and correlated with the experiment. High validity of computational modeling was demonstrated recently for obtaining mechanistic insight into cycloaddition reactions and exploring/optimizing synthetic procedures, including those catalyzed by transition metal complexes[14] and organocatalysts,[15] as well as classic concerted cycloadditions.[16,17]

Results and Discussion

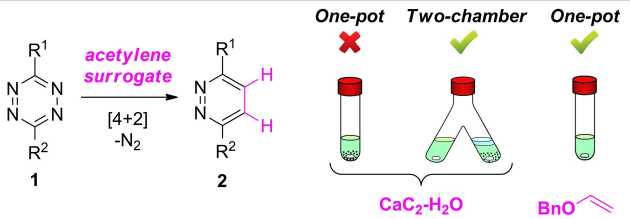
The use of calcium carbide in organic chemistry is very promising: CaC_2 is a nontoxic solid material that can be easily handled (unlike acetylene itself) and can be applied in a diversity of synthetic transformations.[18] However, there are some leaks in the application of calcium carbide as a source of acetylene. CaC_2 is a solid and almost inert material insoluble in organic solvents that can only react with water at room temperature, releasing acetylene and calcium hydroxide. This fact means that a number of possible chemical transformations of *one-pot* carbide-derived acetylene are limited by water- and base-insensitive reactions.

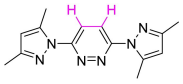
In previous studies, we proposed applying a two-chamber reactor to separate water- and base-sensitive substrates from calcium carbide and water.[19] Using this methodology, we successfully synthesized a range of pyrazoles and their labeled derivatives, 4,5-dideuteropyrazoles, from calcium carbide.[19a] Additionally, we started an investigation of CaC_2 reactivity in Diels-Alder reactions, obtaining 3,6-dichloropyridazine-4,5-$^{13}C_2$ in quantitative yield.[19b]

The second way to perform water- and base-sensitive reactions with acetylene is to replace it with vinyl ethers.[20] Vinyl ethers are readily available and relatively nontoxic compounds with well-known physical characteristics that can be used as safe and easily dosed acetylene surrogates.[20–21] From a certain point of view, vinyl ethers can be described as simple and safe reagents compared to acetylene itself. Using vinyl ethers entirely excludes intermediate gas formation and excessive pressure in the reaction vessel. Previously, we successfully demonstrated that primary vinyl ethers can be used as acetylene surrogates in the synthesis of pyrazoles.[20]

First, the possibility of direct *one-pot* synthesis of pyridazines from calcium carbide and 1,2,4,5-tetrazines **1a–j** was investigated. However, 1,2,4,5-tetrazines **1a–d** are base-sensitive compounds, so only trace amounts of the desired pyridazines **2a**, **b** were observed in the reaction mixtures, and **2c**, **d** were not detected in the reaction mixtures at all (Table 1, entries 1–4). Pyridine-substituted tetrazine **1e** reacted with CaC_2, giving **2e** in 19% yield (Table 1, entry 5). CaC_2 reactivity towards 1,2,4,5-tetrazines containing electron donating groups (EDG) was also poor: 3,6-dimethoxy-1,2,4,5-tetrazine **1f** did not react, 3-chloro-6-methoxy-substituted derivative **1g** gave **2g** in 5% yield (Table 1, entry 6,7). Better results were observed at continuous heating (21 days) of **1h** in the presence of the CaC_2–H_2O mixture – the yield of pyridazine **2h** was 35% (Table 1, entry 8). The reaction of **1i** with carbide-derived acetylene led to the formation of **2i** in 70% yield, and **2j** was obtained in only 5% yield (Table 1, entry 9,10). All processes

Table 1. The reactions of 1,2,4,5-tetrazines with acetylene surrogates.



Entry	Product [R^1, R^2]	The source of C_2H_2-fragment, product yield [%] [a]		
		CaC_2–H_2O		Benzyl vinyl ether [d]
		one-pot [b]	Y/H-tube [c]	
1	R^1=R^2=H (**2a**)	*traces*	99 (99)	90
2	R^1=R^2=Cl (**2b**)	*traces*	99 (99)	99
3	R^1=R^2=Br (**2c**)	0	99 (99)	80
4	R^1=R^2=CO_2Me (**2d**)	0	99 (99)	99
5	R^1=R^2=2-Py (**2e**) [e]	19	99 (99)	99 (95)
6	R^1=R^2=OMe (**2f**)	*NR*	*traces*	95 (83)
7	R^1=OMe, R^2=Cl (**2g**)	5	6	95 (90)
8	R^1=NEt_2, R^2=Cl (**2h**)	35 (30)	*traces*	30 [f]
9	R^1=R^2=Ph (**2i**)	70	4	96 (91)
10	 **2j**	5	1	97 (93)

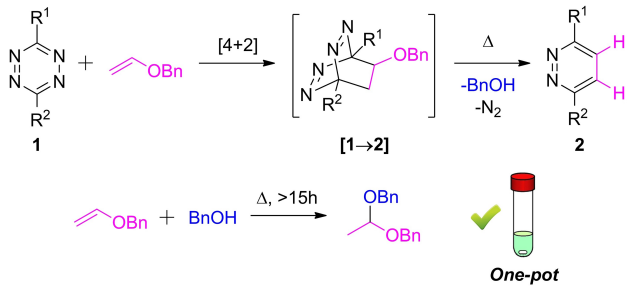
[a] Isolated yield shown in parentheses. [b] The reaction was performed in a sealed tube using 0.3 mmol of **1a–j**, 2 mmol of CaC_2, 4 mmol of water, and 1,4-dioxane (0.6 ml) at 100 °C for 5 d. [c] The substrate part was loaded with 0.3 mmol of **1a–j** and 1.0 ml of 1,4-dioxane, benzene or $CHCl_3$, in the 2nd part were placed 2 mmol of CaC_2, 4 mmol of water and a solvent – 1,4-dioxane, benzene or $CHCl_3$ (0.6 ml), rt, 5–7 d. [d] 0.3 mmol of **1a–j**, benzyl vinyl ether (0.6 mmol), 1,4-dioxane or benzene (0.6 mmol), 100 °C, 1 h–21 d (TLC/NMR-control). [e] 2-Py is 2-pyridyl. [f] 30 µl of Et_3N was added to the reaction mixture.

were accompanied by side reactions, so we decided to explore another method of acetylene generation.

Since some of the studied 1,2,4,5-tetrazines can decompose in direct contact with the CaC_2–H_2O mixture, we decided to use a two-chamber reactor for acetylene generation. In previous studies, we demonstrated that a two-chamber reactor is highly recommended[19] for base- and water-sensitive substrates, so we tested the scope of 1,2,4,5-tetrazines in reactions with calcium carbide in a two-chamber reactor. The reactions of tetrazines **1a–e** with carbide-derived acetylene in a two-chamber reactor proceeded smoothly, giving the corresponding pyridazines **2a–e** in quantitative yields (Table 1, entries 1–5). However, acetylene is an unactivated alkyne, so its reactivity towards EDG-substituted 1,2,4,5-tetrazines **1f–h**, 3,6-diphenyl-1,2,4,5-tetrazine **1i** and 3,6-*bis*(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine **1j** was low: the desired pyridazines **1f–j** were obtained in only up to 6% yields (Table 1, entries 6–10). Therefore, we could conclude that this method is suitable for the synthesis of pyridazine **2a** and its electron withdrawing group (EWG)-containing derivatives. The introduction of any electron-donating substituent retarded the cycloaddition reaction. A significant advantage of two-chamber reactor application is that the procedure of product isolation can be simplified to solvent removal, giving the opportunity to reach nearly 100% yields in the reactions of active 1,2,4,5-tetrazines **1a–e** with acetylene.

Despite the good results in the synthesis of pyridazines **2a–e**, their electron donating group-containing analog synthesis was still challenging. Summarizing the results of the experiments including calcium carbide usage as a surrogate of acetylene, one can propose that the CaC_2–H_2O mixture should be replaced with a neutral analog to avoid 1,2,4,5-tetrazine decomposition at elevated temperatures (most of the tetrazines decomposed in the presence of $Ca(OH)_2$). Recently, we demonstrated that benzyl vinyl ether can be used as an acetylene surrogate in 1,3-dipolar cycloaddition reactions.[20] In this way, pyrazoles were obtained in up to quantitative yields in a *one-pot* manner. This path seemed very promising, so we decided to investigate the chemical behavior of benzyl vinyl ether in the reactions with 1,2,4,5-tetrazines. The reactivity of benzyl vinyl ether towards tetrazines **1a–e** was good: at heating for 1–48 h, the corresponding pyridazines were obtained in good to quantitative yields (Table 1, entries 1–5). The results of less reactive tetrazine testing were exceptionally good: the yields of 3-chloro-6-methoxy-, diphenyl- and *bis*(3,5-dimethyl-1*H*-pyrazol-1-yl)-substitutioned pyridazines **2g**, **2i**, and **2j**, respectively, were almost quantitative (Table 1, entries 7, 9, and 10). In this case, it took 5–10 days to achieve full conversion of the corresponding 1,2,4,5-tetrazine. Even 3,6-dimethoxy-1,2,4,5-tetrazine **1f** reacted with benzyl vinyl ether, giving dimethoxy-substituted pyridazine **2f** in 95% yield within 14 days (Table 1, entry 6). The less reactive 3-chloro-6-diethylamino-1,2,4,5-tetrazine **1h** reacted with an excess of benzyl vinyl ether in the presence of Et_3N, producing pyridazine **2h** in 30% yield within 3 weeks (Table 1, entry 8). Triethylamine was used for benzyl vinyl ether protection from decomposition in the presence of **1h**.[18i] The resulting pyridazines can be easily isolated with standard protocols, so this synthetic path is totally suitable for the synthesis of electron donating group-substituted pyridazines, which cannot be obtained from calcium carbide using a two-chamber reactor.

By studying the NMR spectra of the reaction mixtures, we noted that with increasing reaction time, the content of benzyl vinyl ether decreased, but it could not be connected directly with product formation. At the same time, acetaldehyde dibenzyl acetal was detected in the NMR spectra of the reaction mixtures. And, the contents of acetal increased over time. A small admixture of it was detected after ~15 h in the reaction mixtures, and a more significant quantity was observed with an increase in reaction time. We proposed that the interaction of tetrazine **1** with benzyl vinyl ether leads to the formation of intermediate [**1**→**2**] (Scheme 1, top). According to the literature, this process is a synchronous concerted cycloaddition,[17d,22] which is followed by the elimination of a molecule of benzyl alcohol, nitrogen and a desired pyridazine **2**. The next possibility was that upon heating, benzyl alcohol can react with the vinyl moiety, leading to acetaldehyde dibenzyl acetal formation (Scheme 1, bottom). This is consistent with previously reported data on the conversion of vinyl ethers to acetales.[23] An additional experiment demonstrated that heating the mixture of benzyl vinyl ether and benzyl alcohol in dioxane to



Scheme 1. The proposed reaction mechanism and side product formation.

100 °C for 48 h lead to the formation of acetaldehyde dibenzyl acetal.

Due to the abovementioned considerations, an additional portion of benzyl vinyl ether was added to the reaction mixtures with electron donating group-substituted compounds **1 f–h** because the latter required more time to achieve full conversion of tetrazine than **1 a–e**, **1 i**, **j**.

Since an excess of acetylene surrogates was used in the developed procedures, it was necessary to investigate the problem of starting materials and waste recyclability. Regarding calcium carbide, a number of rational decisions have been proposed previously. Calcium carbide reacts with water, producing acetylene and calcium hydroxide. In previous works, it was proposed to reuse $Ca(OH)_2$ in the synthesis of a new portion of calcium carbide.[18b] Undoubtedly, it is not a single way of its utilization. Recently, it was proposed to use calcium hydroxide, which was produced from CaC_2, in the production of construction materials.[24]

During our study, it was noted that it is possible to separate the desired pyridazine product from the uncovered benzyl vinyl ether, benzyl alkohol and from the aforementioned side product, acetaldehyde dibenzyl acetal. Certainly, uncovered benzyl vinyl ether can be collected and reused. Acetaldehyde dibenzyl acetal easily transforms to benzyl alkohol, and the latter can be reused in the synthesis of benzyl vinyl ether.

Furthermore, we applied the developed procedures for the construction of D_2-labeled pyridazines. In this way, 1,2,4,5-tetrazine **1 a** and its electron withdrawing group-containing derivatives **1 b–e** reacted with calcium carbide and D_2O in a two-chamber reactor, giving desired 4,5-dideuteropyridazines **3 a–e** in quantitative yields and excellent deuterium incorporation values (98–99%, Table 2, entries 1–5). The reaction was performed in 1,4-dioxane to prevent undesirable deuterium-hydrogen exchange.[20,25]

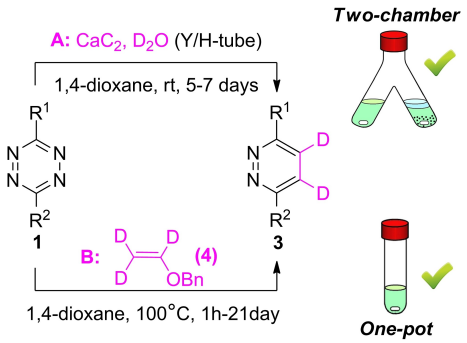
To obtain D_2-labeled pyridazines from the less active 1,2,4,5-tetrazines, benzyl trideuterovinyl ether **4** was synthesized by a previously reported procedure.[18j,20] The interaction of **4** with tetrazines **1 e–j** led to the corresponding 4,5-dideuteropyridazines in up to quantitative yields and 95–98% deuteration degree (Table 2, entries 5–10). Moving from the most reactive 3,6-*bis*(pyridin-2-yl)-1,2,4,5-tetrazine **1 e** to the less reactive 3-dimethoxy-1,2,4,5-tetrazine **1 f** and 3-chloro-6-diethylamino-1,2,4,5-tetrazine **1 h**, we observed a significant decrease in the reaction rates. The reaction of benzyl trideuterovinyl ether **4** with pyridine-containing substrate **1 e** required only 1 hour to achieve full conversion, **1 a–d** reacted with **4** in up to 2 days, and 100% conversion of **1 i** and **1 j** was achieved in five days. Tetrazines, which contained strong electron donating substituents, required noticeably more time and additional portions of benzyl trideuterovinyl ether **4** to achieve full conversion of tetrazine. Therefore, 3-chloro-6-methoxy-1,2,4,5-tetrazine **1 g** reacted with **4** in 10 days, and dimethoxy-substituted tetrazine **1 f** required 14 days to achieve high conversion of the substrate. Analysing the results, summarized in Table 1, we concluded that inasmuch as **1 h** required 21 days to achieve moderate conversion using any acetylene surrogate. The best choice was to apply a CaC_2–D_2O mixture in a *one-pot* manner to synthesize **3 h** due to an easier purification procedure: a single admixture of starting material presence, but not a mixture of **3 h** with **1 h**, **4** and its side products. Therefore, a direct interaction of the CaC_2–D_2O mixture and **1 h** at heating led to **3 h** in 35% yield and 96% deuterium incorporation value.

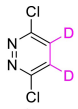
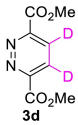
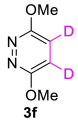
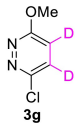
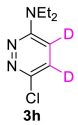
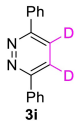
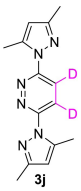
We performed quantum chemical modeling of the cycloaddition of acetylene and benzyl vinyl ether to 1,2,4,5-tetrazines (Figure 3). The same substituents R^1 and R^2 were selected in the model reaction as were used in the experiments. The proposed cage-like intermediates **A** and **B** can be formed via the cycloaddition preceded by the formation of prereaction complexes **1′** and **1″**. In both pathways, transition states, **TS1** and **TS2**, corresponding to the concerted addition were found. We selected the quantum chemical semiempirical method GFN2-xTB[26] for geometry optimizations and vibrational frequency calculations, as it reproduced the geometries obtained by DFT calculations.[20] Single-point energy evaluations at the ωB97X-V/def2-TZVP-gCP and RIJCOSX-PBE0-D4/def2-TZVP levels followed geometry optimizations. Below, we abbreviate ωB97X-V/def2-TZVP-gCP//GFN2-xTB and RIJCOSX-PBE0-D4/def2-TZVP//GFN2-xTB as ωB97X-V/TZ//XTB2 and PBE0-D4/TZ//XTB2, respectively.

The formation of weakly bound preaddition complexes **1′** and **1″** was an endergonic process due to the loss of translational entropy. In the case of the acetylene path, the formation of the model van der Waals complex **1′** is endergonic by at least 6.6 kcal/mol and up to 10.8 kcal/mol, according to the calculations at the ωB97X-V/TZ//XTB2 level (Table 3, PBE0-D4/TZ//XTB2: 7.0 and 10.8 kcal/mol). The formation of **1″** is in many cases even more endergonic, reaching 14.4 kcal/mol for R^1=R^2=H (Table 3, PBE0-D4/TZ//XTB2: 12.3 kcal/mol). Since the preaddition complex formation was markedly endergonic, we considered the sum of the Gibbs free energies in processes **1**→**TS1** and **1**→**TS2** as the proper and experimentally relevant free energy of activation in the cycloaddition stage, not **1′**→**TS1** and **1″**→**TS2**, see below.

The free energy change in step **1′**→**TS1** depends significantly on the electron-donating/withdrawing effect of the substituents (Table 3). Electron withdrawing substituents facilitate the addition of acetylene. The lowest free energy of 5.7 was observed with R^1=R^2=COOMe, according to the calculations at the ωB97X-V/TZ//XTB2 level. In contrast, the addition to 1,2,4,5-tetrazine with R^1=R^2=NEt_2 was hampered, and $\Delta G_{1'\rightarrow TS1}$ was equal to 34.7 kcal/mol.

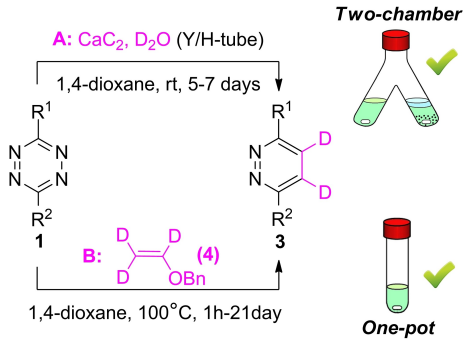
Table 2. The construction of 4,5-dideuteropyridazines using acetylene surrogates.



Entry	Product	Method[a]	Time	Yield[b]	*IP*[c]
1	 **3a**	**A**	7d	99 (99)	99
2	 **3b**	**A**	7d	99 (99)	99
3	 **3c**	**A**	7d	99 (99)	99
4	 **3d**	**A**	7d	99 (99)	98
5	 **3e**	**A/B**	5d/1 h	99 (99)/ 99 (98)	98/98[d]
6	 **3f**	**B**	14d	95 (87)	98
7	 **3g**	**B**	10d	96 (80)	97
8	 **3h**	**C**	21d	35 (30)	96
9	 **3i**	**B**	5d	99 (96)	95
10	 **3j**	**B**	5d	99 (95)	97

[a] Method **A**: The substrate part was loaded with 0.3 mmol of **1 a–j** and 1.0 ml of 1,4-dioxane; in the 2nd part 2 mmol of CaC_2, 4 mmol of water and 1,4-dioxane (0.6 ml) were placed; rt, 5–7 d. Method **B**: 0.3 mmol of **1 a–j**, **4** (0.6 mmol), 1,4-dioxane (0.6 mmol), 100 °C, 1 h–21 d (TLC/NMR-control). Method **C**: *One-pot* procedure using 0.3 mmol of **1 h**, 2 mmol of CaC_2, 4 mmol of D_2O, 1,4-dioxane (0.6 ml), 100 °C, 21 d. [b] Isolated yield shown in parentheses. [c] *IP* is a degree of deuterium incorporation. [d] Py is 2-pyridyl; the deuteration degree may be underestimated due to overlapping NMR signals.

Table 2. continued



Entry	Product	Method[a]	Time	Yield[b]	*IP*[c]

First and foremost, $\Delta G_{1\rightarrow TS1}$ correlates well with experimental observations. The reaction time was approximately seven days (see Table 3). Taken within the framework of the transition state theory, a reference value of ~26.5 kcal/mol corresponds to a reaction kinetic constant that, in turn, allows for a reaction to proceed in several days.[27] With $R^1{=}R^2$ equal to H, Cl, Br, COOMe, and Pyr, the reaction proceeds to full conversion. In line with this, $\Delta G_{1\rightarrow TS1}$ is equal to 24.2, 28.5, 28.2, 12.3, and 23.5 kcal/mol, according to the calculations at the ωB97X-V/TZ//XTB2 level. $\Delta G_{1\rightarrow TS1}$ with $R^1{=}R^2{=}$Br is slightly greater than the threshold value. However, acetylene's cycloaddition to **1** with $R^1{=}R^2$ equal to H, Cl, Br, COOMe, Pyr proceeds with free activation energies of 20.8, 24.7, 24.5, 12.3, and 21.0 kcal/mol, according to the modeling at the PBE0-D4/TZ//XTB2 level.

The cases of $R^1{=}$OMe and $R^2{=}$Cl, $R^1{=}R^2{=}$Ph, $R^1{=}NEt_2$ and $R^2{=}$Cl, and $R^1{=}R^2{=}C_5H_7N_2$ are borderline, as $\Delta G_{1\rightarrow TS1}$ is above the threshold of ~26.5 kcal/mol by several kcal/mol in these cases. Indeed, only minor reactivity was observed in the experiments described above in Table 1. Note that 1,2,4,5-tetrazine with $R^1{=}R^2{=}NEt_2$ is expected to be unreactive.

A similarly strong substituent effect was confirmed by quantum chemical modeling of the benzyl vinyl ether path (see Table 4). $\Delta G_{1''\rightarrow TS2}$ varied from 9.3 (6.0) kcal/mol with the withdrawing COOMe to 40.2 (36.8) kcal/mol with the highly donating NEt_2, as calculated at the ωB97X-V/TZ//XTB2 and PBE0-D4/TZ//XTB2 levels. Combining $\Delta G_{1''\rightarrow TS2}$ with the endergonic $\Delta G_{1\rightarrow 1''}$ can give us an estimation of the reaction's **1**→**2** kinetic feasibility.

Note that the addition of benzyl vinyl ether was performed at a significantly higher temperature of 100 °C and reaction times up to 21 days (Table 1). We avoided thermochemical calculations at 100 °C because the reaction was performed in solution. Consequentially, we needed to model solvent effects. The selected SMD approach (solvation model based on [electron] density) was parameterized to estimate the Gibbs free energy of solvation of organic substances under standard

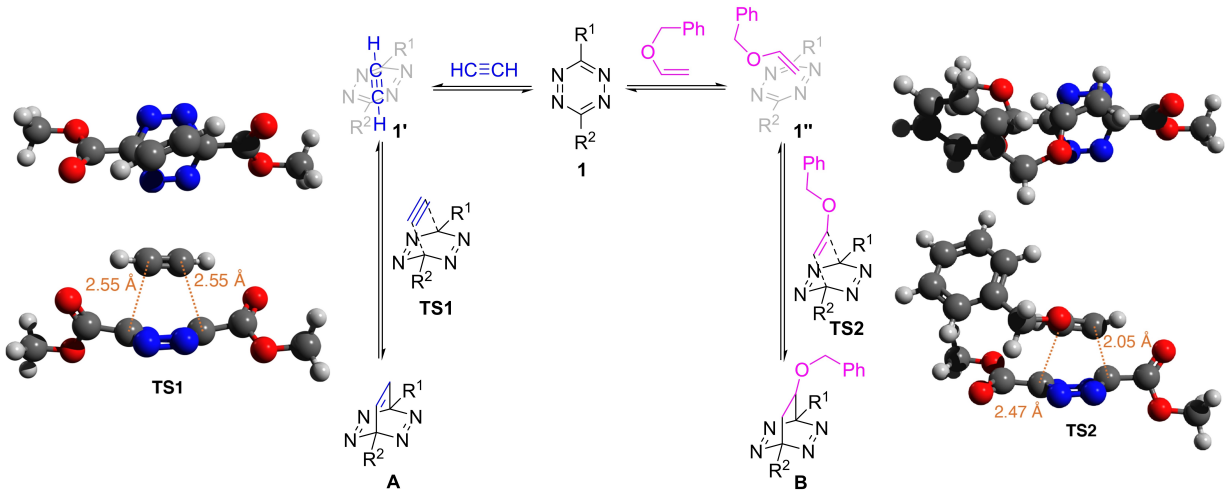


Figure 3. Model formations of cycloaddition intermediates in the acetylene (*left*) and benzyl vinyl ether (*right*) paths. Representative optimized structures of transition states are shown with the interatomic distances between bonding atoms.

Table 3. Free energies of the transformations along the acetylene path (Figure 3, left) in kcal/mol.

R^1, R^2 [a]	$\Delta G_{1\rightarrow1'}$	$\Delta G_{1'\rightarrow TS1}$	$\Delta G_{1\rightarrow TS1}$	$\Delta G_{1'\rightarrow A}$	$\Delta G_{1\rightarrow A}$	$\Delta G_{1\rightarrow2}$
Br	9.3[b] (9.0)[c]	18.8 (15.6)	28.2 (24.5)	−34.5 (−36.4)	−25.1 (−27.4)	−114.8 (−111.7)
Cl	8.9 (8.6)	19.6 (16.1)	28.5 (24.7)	−34.2 (−35.8)	−25.3 (−27.2)	−113.0 (−109.9)
COOMe	6.6 (7.0)	5.7 (5.4)	12.3 (12.3)	−45.1 (−46.2)	−38.5 (−39.2)	−125.6 (−120.7)
H	10.8 (10.1)	13.4 (10.6)	24.2 (20.8)	−36.8 (−40.6)	−26.0 (−30.5)	−107.0 (−104.2)
NEt_2	10.8 (10.9)	34.7 (30.0)	45.5 (40.9)	−7.5 (−6.9)	3.3 (4.0)	−91.1 (−88.1)
OMe	9.1 (8.9)	25.9 (21.5)	35.0 (30.5)	−24.9 (−26.0)	−15.8 (−17.1)	−105.3 (−102.1)
Ph	8.8 (8.7)	20.8 (17.5)	29.7 (26.1)	−27.4 (−28.3)	−18.6 (−19.6)	−103.2 (−99.7)
2-Pyridyl	7.1 (7.2)	16.4 (13.8)	23.5 (21.0)	−35.4 (−36.2)	−28.3 (−29.0)	−116.0 (−112.2)
NEt_2, Cl	9.2 (9.1)	29.1 (24.6)	38.3 (33.7)	−16.9 (−17.4)	−7.7 (−8.2)	−100.3 (−97.3)
OMe, Cl	8.9 (8.7)	23.2 (19.1)	32.0 (27.8)	−28.4 (−29.9)	−19.5 (−21.2)	−108.6 (−105.5)
$C_5H_7N_2$[d]	10.4 (10.2)	22.3 (18.9)	32.7 (29.1)	−34.2 (−33.8)	−23.9 (−23.6)	−110.9 (−107.2)

[a] The para-substituent, see Figure 3; [b] without parentheses: computed at the RIJCOSX-ωB97X-V/def2-TZVP-gCP//GFN2-xTB level; [c] in parentheses: RIJCOSX-PBE0-D4/def2-TZVP; SMD was used to account for bulk solvent effects (1,4-dioxane); [d] 3,5-dimethyl-1*H*-pyrazol-1-yl.

Table 4. Free energies of the transformations along the benzyl vinyl ether path (Figure 3, right), in kcal/mol.

R^1, R^2 [a]	$\Delta G_{1\rightarrow1''}$	$\Delta G_{1''\rightarrow TS2}$	$\Delta G_{1\rightarrow TS2}$	$\Delta G_{1''\rightarrow B}$	$\Delta G_{1\rightarrow B}$	$\Delta G_{B\rightarrow A}$	$\Delta G_{1\rightarrow2}$
Br	10.1[b] (9.9)[c]	10.5 (7.9)	20.5 (17.8)	−19.4 (−16.5)	−9.3 (−6.7)	7.7 (5.3)	−91.2 (−85.7)
Cl	8.7 (8.5)	13.4 (10.2)	22.1 (18.7)	−18.2 (−15.0)	−9.5 (−6.5)	7.7 (5.3)	−89.4 (−83.8)
COOMe	8.2 (8.5)	9.3 (6.0)	17.5 (14.5)	−26.7 (−22.3)	−18.5 (−13.8)	3.5 (0.6)	−102.1 (−94.7)
H	14.4 (12.3)	5.0 (3.8)	19.4 (16.1)	−24.4 (−21.4)	−10.0 (−9.1)	7.5 (4.7)	−83.5 (−78.2)
NEt_2	9.8 (10.2)	40.2 (36.8)	49.9 (47.0)	18.5 (23.1)	28.2 (33.4)	−1.4 (−3.4)	−67.6 (−62.0)
OMe	7.7 (8.3)	27.3 (22.7)	35.0 (31.0)	−7.2 (−3.8)	0.5 (4.5)	7.3 (4.4)	−81.8 (−76.0)
Ph	8.8 (8.8)	20.4 (16.6)	29.2 (25.4)	−9.9 (−5.6)	−1.1 (3.2)	6.0 (3.2)	−79.7 (−73.7)
2-Pyridyl	6.3 (6.2)	15.6 (12.3)	21.9 (18.5)	−12.4 (−8.0)	−6.1 (−1.8)	1.4 (−1.2)	−92.5 (−86.2)
$C_5H_7N_2$[d]	8.3 (9.0)	20.6 (16.8)	28.9 (25.7)	−14.9 (−10.0)	−6.6 (−1.0)	6.3 (3.5)	−76.7 (−71.3)

[a] The substituents, see Figure 3; [b] without parentheses: computed at the RIJCOSX-ωB97X-V/def2-TZVP-gCP//GFN2-xTB level; [c] in parentheses: RIJCOSX-PBE0-D4/def2-TZVP; SMD was used to account for bulk solvent effects (1,4-dioxane); [d] 3,5-dimethyl-1*H*-pyrazol-1-yl.

conditions of 25 °C and 1 atm. A temperature change of +75 °C can significantly alter the solubility of potentially volatile organic substances. Therefore, performing SMD calculations in our case can introduce errors that cannot be estimated yet. We thus used standard free energies of activation to roughly estimate the reactivity of benzyl vinyl ether in cycloaddition to 1,2,4,5-tetrazines *relative* to that of acetylene. However, one should note that the presented values are for a comparison only. Note that elevated temperatures in the heterocycle synthesis with benzyl vinyl ether are required to facilitate BzO^- and H^+ elimination. See a related discussion in our previous work.[20]

A value of 33 kcal/mol can be taken as a roughly estimated reference for $\Delta G^{\neq}$ that corresponds to a reaction proceeding in several days at 100 °C, according to the Eyring transition state theory.[27] Table 4 demonstrates that almost all 1,2,4,5-tetrazines can react with benzyl vinyl ether. The only exception is highly unreactive 3,6-*bis*(diethylamino)-1,2,4,5-tetrazine. Therefore,

subquantitative yields of approximately 90% with benzyl vinyl ether could be a result of possible side reactions. Additionally, elevated temperatures allow activation of almost all 1,2,4,5-tetrazines in the cycloaddition except for the most unreactive.

Considering the last columns in Tables 3 and 4, we see that the whole reaction **1**→**2** is highly exergonic with $\Delta G_{1\to 2}$ below ~90 kcal/mol along the acetylene path and ~62 kcal/mol along the benzyl vinyl ether path. The expected thermodynamic driver of the reaction is the elimination of N_2, which has a strong chemical bond. $\Delta G_{B\to A}$ in Table 4 also demonstrates that the transition from the right to left pathway via the elimination of BnOH immediately after cycloaddition is moderately unfavorable in most cases. However, at elevated temperatures, such a pathway cannot be excluded.

We conducted a virtual Hammett study to quantify the substituent effect in the cycloadditions of acetylene and benzyl vinyl ether and the whole reaction **1**→**2**. A standard linear dependence of reaction (activation) free energy on the substituent effect was assumed (correspondingly, ΔG_{rxn} and $\Delta G^{\neq}$). Additionally, we assumed that the total substituent effect of R^1 and R^2 could be approximated by the sum of individual Hammett constants for para-substituents, $\sigma_P^{R^1}$ and $\sigma_P^{R^2}$. Therefore, a linear approximation of ΔG_{rxn} and $\Delta G^{\neq}$ should be valid:

$$\Delta G_{rxn} \text{ or } \Delta G^{\neq} = c_P\left(\sigma_P^{R^1} + \sigma_P^{R^2}\right) + \Delta G_0,\ \sigma_P^{R^1} + \sigma_P^{R^2} = \sigma_P, \qquad (1)$$

where ΔG_0 is the intercept value corresponding to the reaction (activation) free energy when $\sigma_P^{R^1} = \sigma_P^{R^2} = 0$, i.e., $R^1{=}R^2{=}H$. The obtained approximations for $\Delta G_{1\to A}$, $\Delta G_{1\to B}$, $\Delta G_{1\to TS1}$, and $\Delta G_{1\to TS2}$, as well as the computed ωB97X-V/TZ//XTB2 level values, are depicted in Figure 4.

Table 5 summarizes the results of linear fits. Good correlations were obtained in all cases, with R^2 values exceeding 0.83. Root-mean-square deviations are significant, however. We suppose that many factors, e.g., substituent steric effects, cannot be captured by simple equation (1). Formulating a general multivariate linear model is beyond the scope of the present study and would require a separate mechanistic and QSAR study.

A significant electronic substituent effect on the formation of intermediates **A** and **B**, whole reaction **1**→**2**, and the free energy of activation is evident. The obtained absolute values of c_P exceed 10.9 and 18.2 kcal/mol for $\Delta G^{\neq}$ of acetylene and benzyl vinyl ether. The difference of 10–20 kcal/mol can significantly change the kinetic feasibility, as seen in the experiments described above.

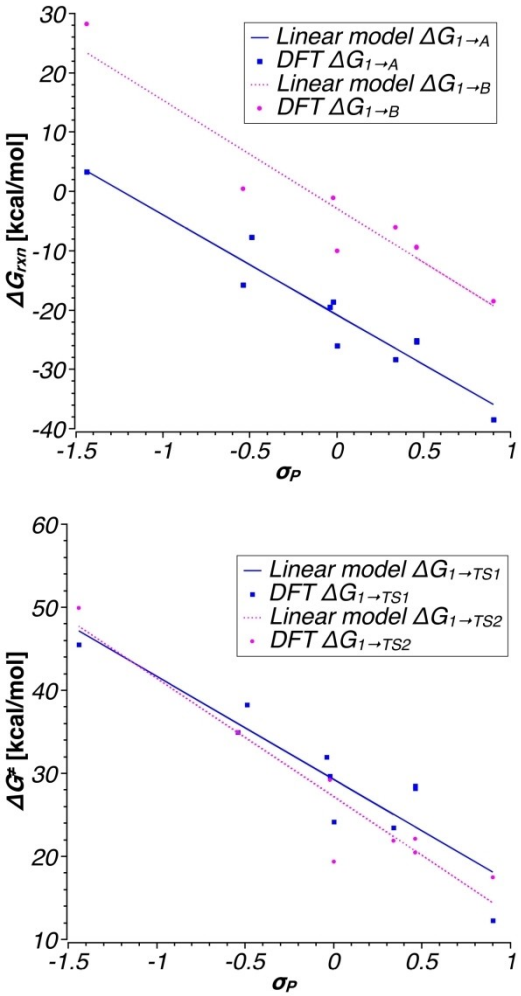


Figure 4. Correlation of the sum $\sigma_P^{R^1} + \sigma_P^{R^2}$ with ΔG_{rxn} and $\Delta G^{\neq}$. Scatter plots show the values calculated at the ωB97X-V/TZ//XTB2 level (solvent effects included). Linear approximations of ΔG_{rxn} and $\Delta G^{\neq}$ according to equation (**1**) are also shown.

Conclusions

To summarize, two convenient and cost-efficient paths to 3,6-disubstituted pyridazines and their 4,5-dideuterated analogs of high levels of deuterium incorporation were proposed. Most of the described 4,5-dideuteropyridazines were obtained for the first time. Calcium carbide and benzyl vinyl ether are both suitable for use as acetylene surrogates in [4+2] cycloaddition with 1,2,4,5-tetrazines.

Table 5. Summary of the linear fitting. c_P, ΔG_0, MD, and RMSD are in kcal/mol.

	1→TS1	1→A	1→2 [*via* A]	1→TS2	1→B	1→2 [*via* B]
R^2	0.83[a](0.85)[b]	0.92 (0.90)	0.90 (0.91)	0.90 (0.90)	0.90 (0.87)	0.89 (0.90)
c_P	−12.4 (−10.9)	−16.8 (−17.6)	−13.6 (−13.1)	−14.2 (−14.2)	−18.2 (−18.8)	−13.4 (−12.9)
ΔG_0	29.3 (25.8)	−20.8 (−22.2)	−109.0 (−105.6)	27.2 (23.9)	−2.9 (0.8)	−85.7 (−79.8)
RMSD[c]	3.5 (2.8)	3.2 (3.8)	2.9 (2.7)	3.2 (3.2)	4.1 (5.0)	3.2 (2.9)

[a] Without parentheses: the values computed at the RIJCOSX-ωB97X-V/def2-TZVP-gCP//GFN2-xTB level were used for the linear fits; [b] in parentheses: RIJCOSX-PBE0-D4/def2-TZVP values were used; [c] root-mean-square deviation.

The calcium carbide-water (D_2O) mixture demonstrated excellent reactivity towards 1,2,4,5-tetrazine and 1,2,4,5-tetrazines, which contain electron withdrawing substituents: the reaction proceeded well at room temperature, leading to 3,6-disubstituted pyridazines and 4,5-dideuteropyridazines, respectively, in quantitative yields. The reaction of calcium carbide and water with 1,2,4,5-tetrazine demonstrated the best results in distributed reaction space mode (two-chamber reactor). A two-chamber reactor allowed separation of a source of basic calcium hydroxide, a mixture CaC_2–H_2O, and base-sensitive tetrazines. The application of a two-chamber reactor simplified the isolation procedure to solvent evaporation, making the synthesis of EWG-containing pyridazines and 4,5-dideuteropyridazines of 98–99% deuteration degree from 1,2,4,5-tetrazines and calcium carbide exceptionally convenient and environmentally friendly.

Concerning benzyl vinyl ether and benzyl D_3-vinyl ether, we can consider this approach reliable for the efficient synthesis of a wide range of pyridazines and 4,5-dideuteropyridazines. The use of benzyl vinyl ether and its deuterated analog led us to propose a convenient *one-pot* methodology, since vinyl ethers are compatible with any 1,2,4,5-tetrazines. Benzyl vinyl ether and benzyl D_3-vinyl ether demonstrated excellent reactivity in [4 + 2] cycloaddition to less active 3,6-diphenyl-1,2,4,5-tetrazine, 3,6-*bis*(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine, which has bulky substituents, and even to electron donating group-containing 1,2,4,5-tetrazines. Using the developed procedures, a number of pyridazines and 4,5-dideuteropyridazines of 95–98% deuteration degree were obtained in up to 99% yields.

The strong substituent effect was confirmed and quantified by quantum chemical calculations. The cycloaddition of acetylene to disubstituted 1,2,4,5-tetrazines was performed under ambient conditions, which, with the strong substituent effect, led to a limited scope, i.e., 1,2,4,5-tetrazines bearing electron-donating substituents were unreactive. Using benzyl vinyl ether as an acetylene surrogate allowed us to perform the reaction at elevated temperatures, which alleviates the substituent effect in the cycloaddition, widening the synthetic methodology's scope. No significant mechanistic difference between the *one-pot* and *two-chamber* methods was found in quantum chemical calculations. The latter method is, however, significantly more versatile since it allows reactions at higher temperatures.

A linear model including only the electronic substituent effect is suboptimal and gives significant deviations. A comprehensive QSAR study of the reaction mechanism will be a future project.

Experimental Section

General

All chemicals were purchased from Sigma Aldrich, Alfa Aesar and Acros Organics in reagent grade or better quality and used without further purification. Tetrazines **1a–c**, **j** were synthesized by procedures reported previously.[19b,28] D_3-vinyl ether was synthesized by a previously reported procedure.[20] NMR spectra were recorded on Bruker Avance III (^{1}H 400 MHz; ^{13}C 101 MHz) and Bruker Avance 500 (^{1}H 500 MHz; ^{13}C 126 MHz) spectrometers. Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.16) as internal standards. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF 10223 spectrometer using electrospray ionization (ESI). Reactions were monitored by TLC analysis using Merck UV-254 plates. Preparative column chromatography was performed on Merck silica gel 60 (230–400 Mesh), which was previously treated with triethylamine.

Computational Details

We used ORCA 4.2.1.[29] GFN2-xTB[26] was selected to perform geometry optimizations and vibrational frequency calculations. Vibrational mode analysis was performed with a finite differences procedure ("NUMFREQ"). Thermochemical corrections were computed within the ideal gas and QR-RHO approximations.[30] A modified version (which allows for thermochemical calculations involving XTB-optimized structures) of the Otherm script[31] by the Duarte group was used to conduct all thermochemical calculations except those involving N_2 and HC≡CH molecules representing the $D_{\infty h}$ symmetry group. For thermochemical calculations involving the latter two molecules, the original ORCA 4.2.1 was used. Acetylene and nitrogen were treated as ideal gases in the standard state in thermochemical calculations. All other intermediates and transition states were considered as solutes (1 M).

All transition states had one imaginary mode corresponding to (un) binding of an acetylene or benzyl vinyl ether molecule. According to the vibrational mode analysis, all intermediates, reaction products, and reactants had no imaginary modes. Solvent effects were accounted for by using SMD.[32] SMD calculations were performed at the M06-2X/6-31 + G* level,[33] as in our previous related work.[20] Calculated data are included in the supporting information.

Single-point energy evaluations at optimized geometries were performed with two DFT functionals, PBE0[34] and ωB97X-V.[35] In PBE0 calculations, the D4 dispersion correction[36] was included. In ωB97X-V calculations, the nonlocal correlation term was calculated self-consistently ("SCNL"). Geometrical counterpoise corrections[37] were computed using the original code by the Grimme group. The RIJCOSX approximation was used to speed up calculations.[38] The def2-TZVP[39] and Def2/J[40] basis sets were selected. In all DFT calculations, Kohn-Sham matrices were recalculated in each KS-SCF iteration ("directresetfreq 1"). Dense integration grids were used, "GRID6", "GridX6", and "vdwgrid3"; also, the "NOFINALGRID" option was switched on. Tight convergence criteria, "TightSCF," were selected in KS-SCF procedures.

All electronic energies, enthalpies, and free energies are included in the supporting information. Linear regression was performed using the scikit-learn library.[41]

General procedure A: The synthesis of pyridazines and D_2-pyridazines using calcium carbide in a two-chamber reactor

The reaction was performed in a two-chamber reactor of reversed Y-tube type or H-tube type. The substrate part of the two-chamber reactor was loaded with 0.3 mmol of **1a–e** and 1.0 ml of 1,4-dioxane, benzene or $CHCl_3$ (1,4-dioxane in the case of deuterated pyridazine synthesis). In the 2nd part of the reactor, 2 mmol of CaC_2 and a solvent (0.6 ml) were placed. Then, 4 mmol of water (or D_2O) was added carefully to the carbide vessel. The reactor was thoroughly sealed with a cup, and the stirring was started carefully

at small speeds (100 rpm) to avoid vigorous acetylene formation and undesirable transfer of water to the substrate part. When the release of acetylene almost stopped, the stirring was gradually intensified (up to 1400 rpm), and the reaction mixture was stirred at room temperature for the next 5–7 days. Then, the contents of the substrate part were carefully collected using a syringe, and the solvent was evaporated to give pure pyridazine **2a–e** or **3a–e**.

General procedure B: The application of benzyl vinyl ether and benzyl D_3-vinyl ether as C_2H_2/C_2D_2 surrogates in the synthesis of pyridazines and D_2-pyridazines

The reaction tube was loaded with 0.3 mmol of **1a–j**, 0.6 mmol of benzyl vinyl ether or benzyl D_3-vinyl ether **4** and 0.6 ml of 1,4-dioxane. After sealing, it was heated to 100 °C until 100% conversion of tetrazine was achieved (TLC/NMR-control). If necessary, an additional portion of benzyl vinyl ether or **4** can be poured into the reaction mixture to achieve full conversion. Then, the solvent was evaporated, and the resulting pyridazines **2a–j** and **3a–j** were purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1).

General procedure C: The synthesis of 2h and 3h from calcium carbide in a one-pot manner

The reaction tube was loaded with 0.3 mmol of **1h**, 2 mmol of CaC_2 and 0.6 ml of 1,4-dioxane. Then, water or D_2O (4 mmol) was carefully added, the tube was sealed, and the reaction mixture was stirred at 100 °C for 21 days. After this, the product was isolated by column chromatography (SiO_2, hexane/ethyl acetate 10:1).

Pyridazine 2a was synthesized by procedure **A**, yield 24 mg (99%). Colorless oil (lit. m.p. −6.4 °C).[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (t, J=3.5 Hz, 2H, $H^{3,6}$), 7.46 (t, J=3.5 Hz, 2H, $H^{4,5}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (2CH=N), 126.4 (2CH). HRMS (ESI) Calcd. for $C_4H_4N_2Na^+$ $[M+Na]^+$ 103.0267, found 103.0263.

3,6-Dichloropyridazine 2b was synthesized by procedure **A**, yield 44 mg (99%). Colorless solid. M.p. 69 °C (lit. 69 °C).[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (2 C), 130.5 (2CH). HRMS (ESI) Calcd. for $C_4H_3Cl_2N_2^+$ $[M+H]^+$ 148.9668, found 148.9669.

3,6-Dibromopyridazine 2c was synthesized by procedure **A**, yield 71 mg (99%). Orange solid. M.p. 95–97 °C (lit. 115–116 °C).[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7(2 C), 133.5 (2CH). HRMS (ESI) Calcd. for $C_4H_3Br_2N_2^+$ $[M+H]^+$ 238.8637, found 238.8633.

Dimethyl pyridazine-3,6-dicarboxylate 2d was synthesized by procedure **A**, yield 58 mg (99%). Colorless solid. M.p. 191–193 °C (lit. 195–196 °C).[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 2H), 4.10 (s, 6H, 2OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 ($2CO_2Me$), 152.9 (2 C), 128.5 (2CH), 53.8 (2OMe). HRMS (ESI) Calcd. for $C_8H_9N_2O_4^+$ $[M+H]^+$ 197.0557, found 197.0557.

3,6-Di(pyridin-2-yl)pyridazine 2e was synthesized by procedure **A**, yield 69 mg (99%). Colorless solid. M.p. 177–178 °C (lit. 178–179 °C).[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77–8.72 (m, 4H), 8.69 (s, $2H_{pyridazine}$), 7.90 (td, J=7.8, 1.8 Hz, 2H), 7.40 (ddd, J=7.5, 4.8, 1.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (2 C), 153.5 (2 C), 149.5 (2CH), 137.4 (2CH), 125.3 (2CH), 124.9 (2CH), 121.9 (2CH). HRMS (ESI) Calcd. for $C_{14}H_{11}N_4^+$ $[M+H]^+$ 235.0978, found 235.0980.

3,6-Dimethoxypyridazine 2f was synthesized by procedure **B**, yield 35 mg (83%). Colorless solid. M.p. 98–100 °C (lit. m.p. 103.6–104.8 °C).[47] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H, 2CH), 4.05 (s, 6H, 2OMe). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (2 C), 121.5 (2CH), 54.7 (2OMe). HRMS (ESI) Calcd. for $C_6H_9N_2O_2^+$ $[M+H]^+$ 141.0659, found 141.0659.

3-Chloro-6-methoxypyridazine 2g was synthesized by procedure **B**, yield 43 mg (90%). Colorless solid. M.p. 86–87 °C (lit. 88–88.5 °C).[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J=9.2 Hz, 1H, H-4), 6.95 (d, J=9.2 Hz, 1H, H-5), 4.11 (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (C), 151.2 (C), 130.9 (CH^4), 120.2 (CH^5), 55.3 (OMe). HRMS (ESI) Calcd. for $C_5H_6ClN_2O^+$ $[M+H]^+$ 145.0163, found 145.0166.

3-Chloro-6-diethylaminopyridazine 2h was synthesized by procedure **C**, yield 55 mg (30%). Orange viscous oil (lit. m.p. 51–53 °C).[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J=9.6 Hz, 1H, H-4), 6.71 (d, J=9.6 Hz, 1H, H-5), 3.56 (q, J=7.1 Hz, 4H, $2CH_2$), 1.20 (t, J=7.1 Hz, 6H, $2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C), 145.2 (C), 128.7 (CH), 113.9 (CH), 43.2 ($2CH_2$), 12.8 ($2CH_3$). HRMS (ESI) Calcd. for $C_8H_{13}ClN_3^+$ $[M+H]^+$ 186.0793, found 186.0791.

3,6-Diphenylpyridazine 2i was synthesized by procedure **B**, yield 63 mg (91%). Colorless solid. M.p. 217–218 °C (lit. 219–220 °C).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.15 (m, 4H), 7.94 (s, $2H_{pyridazine}$), 7.58–7.49 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 ($2C_{pyridazine}$), 136.2 (2 C), 130.2 (2CH), 129.2 (4CH), 127.1 (4CH), 124.4 ($2CH_{pyridazine}$). HRMS (ESI) Calcd. for $C_{16}H_{13}N_2^+$ $[M+H]^+$ 233.1073, found 233.1077.

3,6-*Bis*(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine 2j was synthesized by procedure **B**, yield 75 mg (93%). Colorless solid. M.p. 170–172 °C (lit. 178–180 °C).[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, $2H_{pyridazine}$), 6.05 (s, $2H_{pyrazole}$), 2.74 (s, 6H, 2Me), 2.30 (s, 6H, 2Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (2 C), 151.3 (2 C), 142.4 (2 C), 122.9 ($2CH_{pyridazine}$), 110.1 ($2CH_{pyrazole}$), 14.9 (2Me), 13.7 (2Me). HRMS (ESI) Calcd. for $C_{14}H_{16}N_6Na^+$ $[M+Na]^+$ 291.1329, found 291.1329.

4,5-Dideuteropyridazine 3a was synthesized by procedure **A**, yield 24 mg (99%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (2CH), 126.0 (t, J=25.7 Hz, 2CD). HRMS (ESI) Calcd. for $C_4H_2D_2N_2Na^+$ $[M+Na]^+$ 105.0392, found 105.0391

3,6-Dichloro-4,5-dideuteropyridazine 3b was synthesized by procedure **A**, yield 45 mg (99%). Beige solid. M.p. 65–67 °C. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 130.1 (t, J=27.0 Hz, 2CD). HRMS (ESI) Calcd. for $C_4HD_2N_2Cl_2^+$ $[M+H]^+$ 150.9793, found 150.9791.

3,6-Dibromo-4,5-dideuteropyridazine 3c was synthesized by procedure **A**, yield 71 mg (99%). Yellow solid. M.p. 108–110 °C. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (2 C), 133.0 (t, J=27.1 Hz, 2CD). HRMS (ESI) Calcd. for $C_4HD_2N_2Br_2^+$ $[M+H]^+$ 240.8763, found 240.8767.

Dimethyl 4,5-dideuteropyridazine-3,6-dicarboxylate 3d was synthesized by procedure **A**, yield 59 mg (99%). Colorless solid. M.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 ($2CO_2Me$), 152.8 (2 C), 128.0 (t, J=26.8 Hz, 2CD), 53.8 (2OMe). HRMS (ESI) Calcd. for $C_8H_7D_2N_2O_4^+$ $[M+H]^+$ 199.0682, found 199.0682.

4,5-Dideutero-3,6-di(pyridin-2-yl)pyridazine 3e was synthesized by procedure **A**, yield 70 mg (99%). Colorless solid. M.p. 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J=8.0 Hz, 2H), 8.71 (d, J=4.6 Hz, 2H), 7.88 (td, J=7.8, 1.7 Hz, 2H), 7.38 (ddd, J=7.3, 4.9, 0.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (2 C), 153.5 (2 C), 149.5 (2CH), 137.3 (2CH), 124.85 (2CH), 124.83 (t, $J_{C\text{-}D}$=26.2 Hz, 2CD), 121.8 (2CH). LCMS (ESI-TOF) Calcd. for $C_{14}H_9D_2N_4^+$ $[M+H]^+$ 237.1104, found 237.1109.

4,5-Dideutero-3,6-dimethoxypyridazine 3f was synthesized by procedure **B**, yield 37 mg (87%). Colorless solid. Start sublimating at 40 °C. M.p. 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 6H, 2OMe). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1 (2 C), 121.1 (t, $J_{C\text{-}D}$=25.9 Hz, 2CD),

54.7 (2OMe). HRMS (ESI) Calcd. for $C_6H_7D_2N_2O_2^+$ $[M+H]^+$ 143.0784, found 143.0785.

3-Chloro-4,5-dideutero-6-methoxypyridazine 3 g was synthesized by procedure **B**, yield 35 mg (80%). Colorless solid. M.p. 89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (C), 151.2 (C), 130.5 (t, $J_{C\text{-}D}$ = 26.6 Hz, CD^4), 119.8 (t, $J_{C\text{-}D}$ = 26.3 Hz, CD^5), 55.4 (OMe). HRMS (ESI) Calcd. for $C_5H_4D_2ClN_2O^+$ $[M+H]^+$ 147.0289, found 147.0291.

3-Chloro-6-diethylamino-4,5-dideuteropyridazine 3 h was synthesized by procedure **C**, yield 17 mg (30%). Orange solid. M.p. 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (q, J = 7.1 Hz, 4H, $2CH_2$), 1.20 (t, J = 7.1 Hz, 6H, $2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (C), 145.1 (C), 128.5 (t, $J_{C\text{-}D}$ = 26.4 Hz, CD), 113.9 (t, $J_{C\text{-}D}$ = 26.0 Hz), 43.3 ($2CH_2$), 12.8 ($2CH_3$). HRMS (ESI) Calcd. for $C_8H_{11}D_2ClN_3^+$ $[M+H]^+$ 188.0918, found 188.0916.

4,5-Dideutero-3,6-diphenylpyridazine 3 i was synthesized by procedure **B**, yield 67 mg (96%). Colorless solid. M.p. 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.15 (m, 4H), 7.57–7.48 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 ($2C_{pyridazine}$), 136.2 (2 C), 130.2 (2CH), 129.2 (4CH), 127.1 (4CH), 124.0 (t, $J_{C\text{-}D}$ = 25.5 Hz, 2CD). HRMS (ESI) Calcd. for $C_{16}H_{11}D_2N_2^+$ $[M+H]^+$ 235.1199, found 235.1200.

4,5-Dideutero-3,6-*bis*(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine 3 j was synthesized by procedure **B**, yield 77 mg (95%). Colorless solid. M.p. 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, $2H_{pyrazole}$), 2.75 (s, 6H, 2Me), 2.31 (s, 6H, 2Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (2 C), 151.3 (2 C), 142.5 (2 C), 122.6 (t, $J_{C\text{-}D}$ = 27.8 Hz, 2CD), 110.1 ($2CH_{pyrazole}$), 14.9 ($2CH_3$), 13.7 ($2CH_3$). LCMS (ESI-TOF) Calcd. for $C_{14}H_{15}D_2N_6^+$ $[M+H]^+$ 271.1635, found 271.1639.

3,6-Dimethoxy-1,2,4,5-tetrazine 1 f: To the round bottom flask were placed 120 mg of 3,6-dichloro-1,2,4,5-tetrazine **1 b**, 150 mg of sodium methoxide and 2 ml of dry methanol. The reaction mixture was stirred at room temperature for 24 hours, then the solvent was evaporated, and the product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 10:1), giving pure **1 f** as a red crystals (100 mg, 89%). M.p. 65 °C (lit. 62 °C).[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (2 C), 56.8 (2OMe). HRMS (ESI) Calcd. for $C_4H_6N_4O_2Na^+$ $[M+Na]^+$ 165.0383, found 165.0390.

3-Chloro-6-methoxy-1,2,4,5-tetrazine 1 g: To the round bottom flask were placed 80 mg of 3,6-dichloro-1,2,4,5-tetrazine **1 b**, 30 mg of sodium methoxide and 2 ml of 1:1 mixture dry methanol/1,4-dioxane. The reaction mixture was stirred at room temperature for 2 hours, the solvent was evaporated, and the product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 10:1), giving pure **1 g** as orange crystals (72 mg, 93%). M.p. 60–62 °C (lit. 66–68 °C).[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (C), 164.6 (C), 57.5 (OMe). HRMS (ESI) Calcd. for $C_3H_3N_4OClNa^+$ $[M+Na]^+$ 168.9888, found 168.9893.

3-Chloro-6-diethylamino-1,2,4,5-tetrazine 1 h: To the round bottom flask 80 mg of 3,6-dichloro-1,2,4,5-tetrazine **1 b** and 1 ml of dry 1,4-dioxane were placed. To the resulting mixture, 50 µl of triethylamine and 120 µl of pure diethylamine were added. The reaction mixture was stirred at room temperature for 24 hours, and then 5 ml of water and 5 ml of chloroform were added to the reaction vessel. The organic layer was separated, and the aqueous layer was extracted three times with small portions of $CHCl_3$. The combined organic extracts were washed twice with water and then dried over Na_2SO_4. After solvent removal, pure **1 h** was obtained as an orange-red viscous oil (140 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (q, J = 7.1 Hz, 4H, $2CH_2$), 1.27 (t, J = 7.1 Hz, 6H, $2CH_3$).[53] ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 159.1 (C), 42.8 ($2CH_2$), 12.5 ($2CH_3$). HRMS (ESI) Calcd. for $C_6H_{10}N_5ClNa^+$ $[M+Na]^+$ 210.0517, found 210.0517.

Acknowledgements

We gratefully acknowledge financial support from the Russian Science Foundation (Project N° 19-73-10032). The authors express their gratitude to the Resource Centres of Saint Petersburg State University: Magnetic Resonance Research Centre and Chemical Analysis and Materials Research Centre.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: acetylene · cycloaddition · deuterium · labeling · pyridazine

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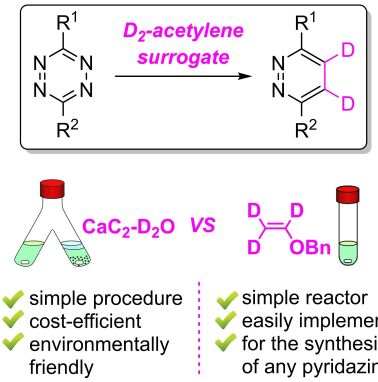
Manuscript received: May 25, 2021
Revised manuscript received: June 18, 2021
Accepted manuscript online: June 21, 2021
Version of record online: ■■, ■■■

FULL PAPER

Two novel synthetic paths to 3,6-disubstituted pyridazines and 4,5-dideuteropyridazines from 1,2,4,5-tetrazines and acetylene surrogates were proposed. CaC_2 demonstrated excellent results in reactions with 1,2,4,5-tetrazine and acceptor-substituted derivatives, and benzyl (D_3-) vinyl ether was found to be a better choice for reactions with donor-substituted tetrazines. Competitive experiments and quantum chemical calculations were performed for mechanistic study.



*Dr. M. S. Ledovskaya, Dr. M. V. Polynski, Prof. Dr. V. P. Ananikov**