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Microwave-Assisted Synthesis of 3,6-Di(pyridin-2-yl)pyridazines: Unexpected Ketone and Aldehyde Cycloadditions

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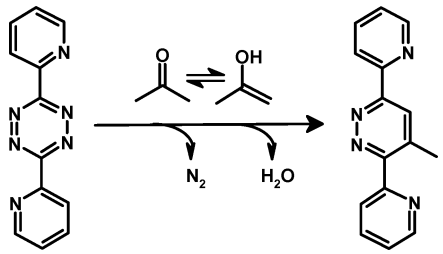

3,6-Di(pyridin-2-yl)pyridazines are an interesting class of compounds because of their metal-coordinating ability resulting in the self-assembly into [2×2] gridlike metal complexes with copper(I) or silver(I) ions. These and other substituted pyridazines can be prepared by the inverse-electron-demand Diels−Alder reactions between acetylenes and 1,2,4,5-tetrazines. In this contribution, the effect of (superheated) microwave conditions on these generally slow cycloadditions is described. The cycloaddition of acetylenes to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine could be accelerated from several days reflux in toluene or *N*,*N*-dimethylformamide to several hours in dichloromethane at 150 °C. In addition, the unexpected cycloaddition of the enol tautomers of various ketones and aldehydes to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine is described in detail providing an alternative route for the synthesis of (substituted) pyridazines.

Introduction

The inverse-electron-demand Diels−Alder reaction of 1,2,4,5-tetrazines with a variety of acetylenes and alkenes is an effective synthetic route toward substituted and/or functionalized pyridazines.[1−10] The resulting substituted pyridazines have attracted much attention in the fields of organic chemistry for mechanistic investigations[1,3,6−10] as well as in the field of natural-product syntheses.[4,5,7,10,11] Moreover, 3,6-di(pyridin-2-yl)pyridazines (DPPs) are well-known for their metal-coordinating properties. The addition of copper(I) ions to these ligands results in a self-assembly process to [2×2] gridlike metal complexes.[8,12,13] With silver(I) ions, the DPPs can also self-assemble into [2×2] gridlike metal complexes,[14,15] although various other types of silver(I) metal complexes have been observed as well.[16,17] Inverse-electron-demand Diels−Alder reactions between acetylenes and tetrazines directly yield aromatic pyridazines after

(1) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342−4346.
(2) Butte, W. A.; Case, F. H. *J. Org. Chem.* **1961**, *26*, 4690−4692.
(3) Heldmann, D. K.; Sauer, J. *Tetrahedron Lett.* **1997**, *38*, 5791−5794.
(4) Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329−6337.
(5) Sparey, T. J.; Harrison, T. *Tetrahedron Lett.* **1998**, *39*, 5873−5874.
(6) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885−2896.
(7) Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593−3598.
(8) Hoogenboom, R.; Kickelbick, G.; Schubert, U. S. *Eur. J. Org. Chem.* **2003**, 4887−4896.
(9) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889−3892.
(10) Sauer, J. *Comprehensive Heterocyclic Chemistry II*; Pergamon: London, 1996; Vol 6, pp 901−965.
(11) Che, D.; Wegge, T.; Stubbs, M. T.; Seitz, G.; Meier, H.; Methfessel, C. *J. Med. Chem.* **2001**, *44*, 47−51.
(12) Youinou, M.-T.; Rahmouni, N.; Fischer, J.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 775−778.
(13) Hoogenboom, R.; Wouters, D.; Schubert, U. S. *Macromolecules* **2003**, *36*, 4743−4749.
(14) Baxter, P. N. W.; Lehn, J.-M.; Kneisel, B. O.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1978-1981.
(15) Weissbuch, I.; Baxter, P. N. W.; Kuzmenko, I.; Cohen, H.; Cohen, S.; Kjaer, K.; Howes, P. B.; Als-Nielsen, J.; Lehn, J.-M.; Leiserowitz, L.; Lahav, M. *Chem. Eur. J.* **2000**, *6*, 725−734.
(16) Constable, E. C.; Housecroft, C. E.; Kariuki, B. M.; Neuburger, M.; Smith, C. B. *Aust. J. Chem.* **2003**, *56*, 653−655.
(17) Constable, E. C.; Housecroft, C. E.; Neuburger, M.; Reymann, S.; Schaffner, S. *Chem. Commun.* **2004**, 1056−1057.

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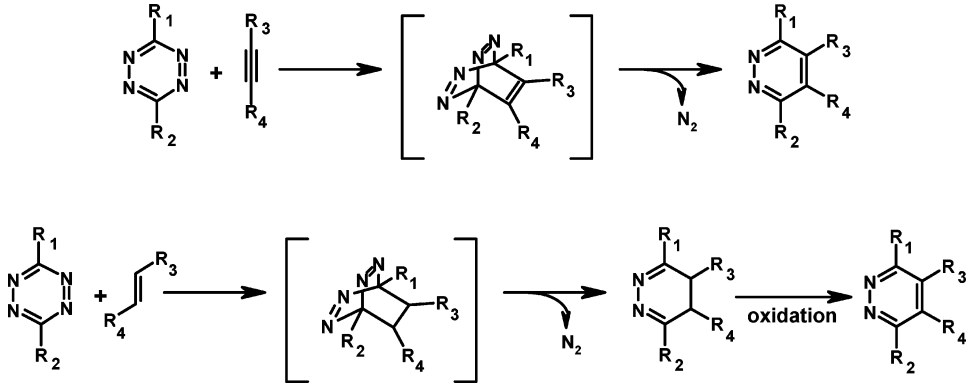
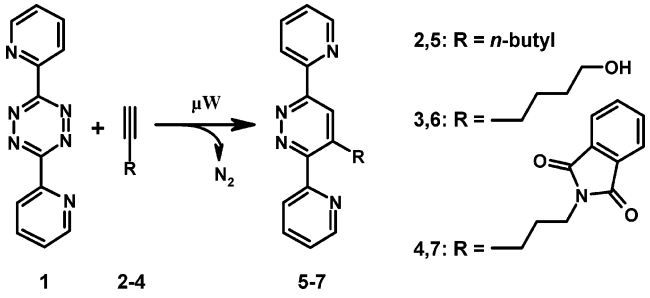
SCHEME 1. Schematic Representation of the Inverse-Electron-Demand Diels−Alder Reaction between 1,2,4,5-Tetrazines and Alkynes (Top) or Alkenes (Bottom)



elimination of nitrogen as depicted in Scheme 1 (top). Electron-rich alkynes readily undergo the Diels−Alder reaction, but electron-deficient acetylenes require more stringent reaction conditions.[8,18] When alkenes are applied as dienophiles, the Diels−Alder reactions result in dihydropyridazines after elimination of nitrogen. Therefore, the preparation of substituted pyridazines via alkene cycloadditions requires an additional oxidation step as depicted in Scheme 1 (bottom). To accelerate these Diels−Alder reactions with alkenes, electron-rich groups that easily undergo elimination, such as, e.g., methoxy or morpholino, are often attached to the double bond.[5,10]

Here, we report our investigations on the microwave-assisted inverse-electron-demand Diels−Alder reactions with 3,6-di-(pyridin-2-yl)-1,2,4,5-tetrazine (**1**) resulting in substituted DPPs. In recent years, microwave irradiation was demonstrated to be a valuable tool in organic synthesis resulting in faster and cleaner reactions that sometimes exhibit different reactivities due to specific microwave absorption.[19] Cycloadditions were also successfully achieved under microwave irradiation,[20] and more specifically, also intramolecular inverse-electron-demand Diels−Alder reactions between 1,2,4-triazines and indoles[21] or imidazoles[22] could be performed under (superheated) microwave conditions in high-boiling solvents such as *N*,*N*-dimethylformamide (DMF) or *o*-dichlorobenzene.

TABLE 1. Overview of the Investigated Microwave-Assisted Inverse-Electron-Demand Diels−Alder Reactions between 3,6-Di(pyridin-2-yl)tetrazine (1) and Different Alkynes 2−4



1 **2-4** **5-7**

entry	acetylene	solvent	reaction temp (°C)	reaction time (min)	product	isolated yield (%)
1	**2**	DMF	160	5		
2	**2**	DMF	200	5		
3	**2**	DMF	225	15	**5**	49
4	**2**	CH_2Cl_2	150	90	**5**	69
5 CH[a]	**2**	CH_2Cl_2	150	90	**5**	65
6	**3**	CH_2Cl_2	150	90	**6**	78
7	**4**	CH_2Cl_2	150	60	**7**	83
8	**2**	acetone	150	60	mixture	na

[a] CH stands for conventional heating.

Results and Discussion

In our initial experiments, the slow cycloaddition of 1-hexyne (**2**) to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1**) was attempted under microwave irradiation (Table 1).[23] After 5 min heating to 160 or 200 °C in DMF under microwave irradiation, no reaction was observed. However, after 15 min heating to 225 °C, the intense violet reaction mixture turned brown and the *n*-butyl DPP **5** could be isolated in 49% yield. This low yield is due to the high reaction temperature, which induces decomposition of the tetrazine resulting in, e.g., 2-cyanopyridine and 3,6-di(pyridin-2-yl)-dihydro-1,2,4,5-tetrazine.[24] To circumvent the use of high-boiling solvents, the cycloaddition of 1-hexyne (**2**) was also attempted in dichloromethane (CH_2Cl_2) under superheated microwave conditions. The Diels−Alder reaction in CH_2Cl_2 yielded the desired DPP **5** after only 90 min heating to 150 °C. Although the reaction mixture turned brown, the product could be isolated by column chromatography (69% isolated yield), which is comparable to the yield obtained with conventional heating in toluene (71%).[8] Besides the acceleration, the use of CH_2Cl_2 also simplifies the workup procedure that includes evaporation of the solvent. To probe whether the observed acceleration is due to microwave effects, the cycloaddition of 1-hexyne was attempted in dichloromethane at 150 °C with conventional heating. This reaction resulted in DPP **5** in 65% isolated yield, which is similar to the microwave-assisted cycloaddition. However, the reason for the observed acceleration in CH_2Cl_2 when compared to DMF is not yet understood.

(18) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54−62.
(19) For a recent review on microwave-assisted synthesis, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.
(20) Review on microwave-assisted cycloadditions: De la Hoz, A.; Diza-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659−3673.
(21) Lindsey, C. W.; Wisnoski, D. D.; Wang, Y.; Leicester, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495−4498.
(22) Lahue, B. R.; Lo, S.-M.; Wan, Z.-K.; Woo, G. H. C.; Snyder, J. K. *J. Org. Chem.* **2004**, *69*, 7171−7182.
(23) This reaction required 16 h of DMF reflux under conventional heating.
(24) Both these side products were identified by GC-MS.

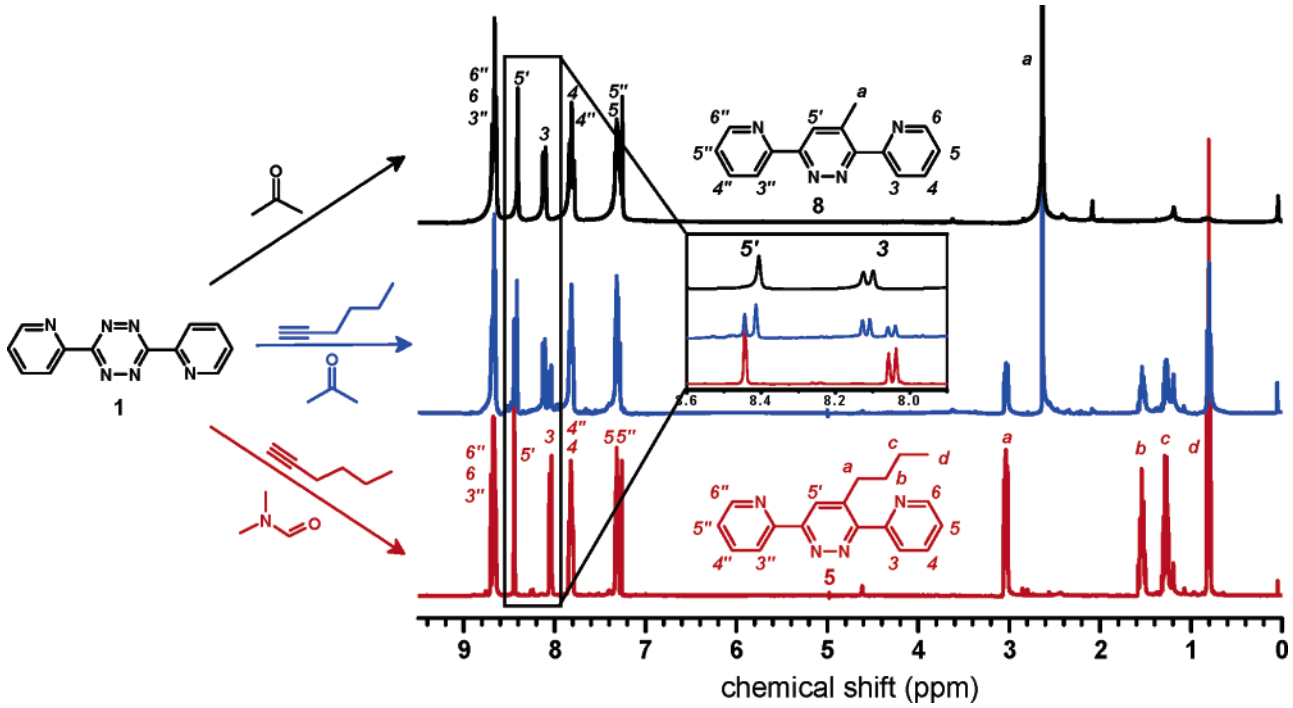
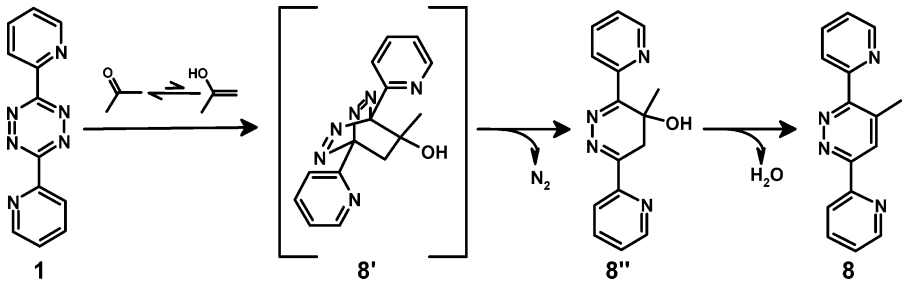


FIGURE 1. ^{1}H NMR spectra obtained after the reaction between tetrazine (**1**) and 1-hexyne (**2**) in DMF (bottom) and acetone (middle) together with the spectrum obtained after heating **1** in acetone (top). Assignments are based on ^{1}H-^{1}H COSY. The inset shows an enlargement of the H-3 and H-5′ resonances illustrating the appearance of different DPPs. All spectra were recorded in $CDCl_3$.

SCHEME 2. Proposed Reaction Mechanism for the Inverse-Electron-Demand Diels−Alder Reaction of Tetrazine 1 with the Enol Tautomer of Acetone (Propen-2-ol)



Inspired by these first results, the cycloadditions of 5-hexyn-1-ol (**3**) and 1-phthalimido-4-pentyne (**4**) to tetrazine **1** were also attempted under microwave irradiation in CH_2Cl_2 at 150 °C (90 and 60 min, respectively; entries 5 and 6, Table 1). Both DPPs **6** and **7** were obtained in good yields, whereby the yield of the hydroxybutyl-pyridazine **6** is higher than the yield obtained after 40 h reflux in toluene (70%).[8] The 3,6-di(pyridin-2-yl)-4-phthalimidopropylpyridazine (**7**) was prepared for the first time, and it could serve as a precursor for an amino-functionalized DPP. These results clearly demonstrate the advantage of superheated microwave conditions for the inverse-electron-demand Diels−Alder reactions.

In a next step, the cycloaddition of 1-hexyne to tetrazine **1** was attempted in acetone (150 °C) to avoid the use of chlorinated solvents. This cycloaddition was completed after only 30 min. However, gas chromatography (GC-MS) and ^{1}H NMR spectroscopy unexpectedly revealed the presence of two different DPPs: the expected *n*-butyl DPP **3** and 3,6-di(pyridin-2-yl)-4-methylpyridazine **8** were identified. Heating a solution of tetrazine **1** in neat acetone (150 °C; 30 min) under microwave irradiation also resulted in the formation of 3,6-di(pyridin-2-yl)-4-methylpyridazine (**8**; 75% isolated yield), which demonstrates that acetone participates in the inverse-electron-demand Diels−Alder reaction. ^{1}H NMR spectra of the microwave Diels−Alder reactions of tetrazine **1** and 1-hexyne **2** in DMF and acetone as well as the ^{1}H NMR spectrum after heating a solution of **1** in acetone are shown in Figure 1 demonstrating the formation of the different DPPs.

Heating tetrazine **1** in acetone with conventional heating to 150 °C in a pressure reactor also resulted in the formation of DPP **8** (67% isolated yield). Up to this moment, only cycloadditions of alkenes and alkynes to tetrazines were reported. Therefore, it can be concluded that the enol tautomer of acetone (propen-2-ol) participates in the cycloaddition instead of the keto tautomer. Even though the amount of the enol tautomer present in acetone is significantly less than the amount of the keto tautomer,[25] the electron-rich hydroxyl group of the propen-2-ol facilitates the inverse-electron-demand Diels−Alder reaction. The proposed reaction mechanism for the cycloaddition of acetone to tetrazine **1** is depicted in Scheme 2. Reaction of propen-2-ol with tetrazine **1** results in the formation of the

(25) Keefle, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862−4868.

TABLE 2. Overview of the Investigated Microwave-Assisted Inverse-Electron-Demand Diels−Alder Reactions between 3,6-Di(pyridin-2-yl)tetrazine 1 and Various Ketones and Aldehydes[a]

entry	solvent (reagent)	boiling point (°C)	reaction temp (°C)	reaction time (min)	product	R_1[a]	R_2[a]	isolated yield (%)
1	acetone	56	150	30	**8**	CH_3	H	75
2 CH[b]	acetone	56	150	30	**8**	CH_3	H	69
3	2-butanone	80	150	30	**9**	CH_2CH_3	H	15
					10	CH_3	CH_3	35
4	3-pentanone	101	180	60	**11**	CH_2CH_3	CH_3	13
5	3-methyl-2-butanone	94−95	180	30	**12**	*i*-propyl H		na[c]
					13	pyridazine		na[c]
6	water	100	150	20	**14**	ring-opened		96
7	acetaldehyde	21	120	30	**15**	H	H	84
8	butanal	75	150	30	**9**	CH_2CH_3	H	48
9	hexanal	131	170	30	**5**	*n*-butyl	H	16
10	octanal	171	200	30	**16**	*n*-hexyl	H	9

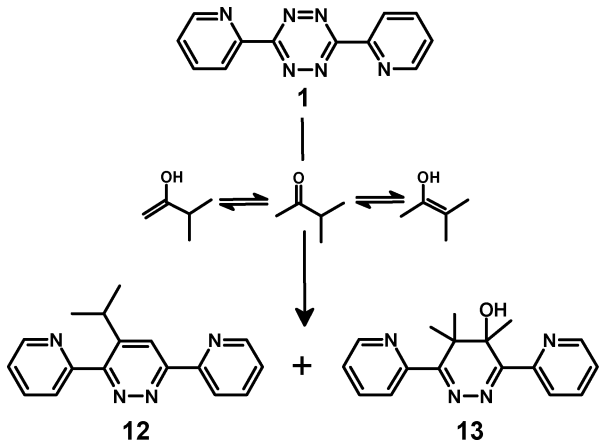
[a] R_1 and R_2 represent the substituents on the 4 and 5 position of the resulting 3,6-di(pyridin-2-yl)pyridazines. [b] CH stands for conventional heating. [c] This product mixture was only used for GC-MS analysis.

unstable intermediate **8′** that spontaneously converts into the second intermediate 3,6-di(pyridin-2-yl)-4-hydroxy-4-methyldihydropyridazine (**8″**) by elimination of nitrogen. Under the applied reaction conditions (150 °C, microwave heating), rapid elimination of water occurs resulting in 3,6-di(pyridin-2-yl)-4-methylpyridazine (**8**). This proposed reaction mechanism is further supported by previous investigations that revealed a shift of the keto−enol equilibrium to the enol tautomer under high-temperature and -pressure conditions.[26,27] The enol tautomer of acetone has, to the best of our knowledge, never been applied as the reagent in cycloadditions. However, the endiamine tautomers of amidines have been previously used in inverse-electron-demand Diels−Alder reactions.[28]

Encouraged by the successful cycloaddition of acetone, tetrazine **1** was heated in several other ketones as depicted in Table 2 (entries 1−4). The reaction with 2-butanone at 150 °C under microwave irradiation yielded cycloadducts of both enol tautomers 1-buten-2-ol and 2-buten-2-ol, namely, 3,6-di(pyridin-2-yl)-4-ethylpyridazine (**9**) and 3,6-di(pyridin-2-yl)-4,5-dimethylpyridazine (**10**). Even though the more stable 2-buten-2-ol tautomer is present in a larger extent in 2-butanone than the 1-buten-2-ol tautomer, both DPPs **9** and **10** were present in a 1:1 ratio in the crude ^{1}H NMR spectrum (not shown). This inconsistency can be explained by the higher electron density of the double bond of the 1-buten-2-ol that results in a higher reactivity of this tautomer which, apparently, compensates the lower abundance. In addition, the lower sterical hindrance of the cycloaddition of the 1-buten-2-ol tautomer could also play an important role in the higher observed reactivity.

The two different DPPs **9** and **10** could be separated by repetitive column chromatography (2 × aluminum oxide; 1 × silica) resulting in 15% (**9**) and 35% (**10**) isolated yields. The inverse-electron-demand Diels−Alder reactions with 3-pentanone and 3-methyl-2-butanone did not proceed at 150 °C under microwave irradiation. However, these cycloadditions also proceeded at 180 °C, whereby decomposition of tetrazine **1** was observed resulting in very low yields, namely, 13% isolated yield of 3,6-di(pyridin-2-yl)-4-ethyl-5-methylpyridazine (**11**). The reaction between **1** and 3-methyl-2-butanone was performed

SCHEME 3. Schematic Representation of the Inverse-Electron-Demand Diels−Alder Reaction between Tetrazine 1 and 3-Methyl-2-butanone



to provide a sufficient basis for the proposed reaction mechanism via the enol tautomers. Reaction of the enol tautomers, 3-methyl-1-buten-2-ol and 3-methyl-2-buten-2-ol, with tetrazine **1** would result in 3,6-di(pyridin-2-yl)-4-*iso*-propylpyridazine (**12**) and 3,6-di(pyridin-2-yl)-4-hydroxy-4,5,5-trimethyldihydropyridazine (**13**; Scheme 3).

The dihydropyridazine **13** cannot aromatize by elimination of water, and thus, the presence of this hydroxy-pyridazine **13** would confirm the proposed reaction mechanism. GC-MS of the crude reaction mixture indeed revealed the presence of DPP **12** and dihydropyridazine **13** together with many side products such as 3,6-di(pyridin-2-yl)-4-*iso*-propyl-5-hydroxy-dihydropyridazine, 3,6-di(pyridin-2-yl)-1,2,4,5-dihydropyridazine, 2,5-di-(pyridin-2-yl)-1,3,4-oxadiazole, and 2-pyridinecarboxylic acid (pyridin-2-ylmethylene)hydrazide (Figure 2). Similar complex reaction mixtures were obtained for all cycloadditions that were performed at temperatures above 170 °C because of the decomposition of tetrazine **1**.

The deliberate insertion of water to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1**) was also attempted by heating **1** in water for 20 min to 150 °C under microwave irradiation. Although the violet tetrazine did not dissolve in water at ambient temperature, microwave heating resulted in the quantitative formation of 2-pyridinecarboxylic acid (pyridin-2-ylmethylene)-hydrazide as white precipitate (**14**; 96% isolated yield; Scheme 4). Previously, the synthesis of **14** was only reported via Schiff

(26) Osugi, J.; Mizukami, T.; Tachibana, T. *Rev. Phys. Chem. Jpn.* **1966**, *36*, 8− 19.
(27) Kuhlmann, B.; Arnett, E. M.; Siskin, M. *J. Org. Chem.* **1994**, *59*, 3098−3101.
(28) Boger, D. L.; Kochanny, M. J. *J. Org. Chem.* **1994**, *59*, 4950−4955.

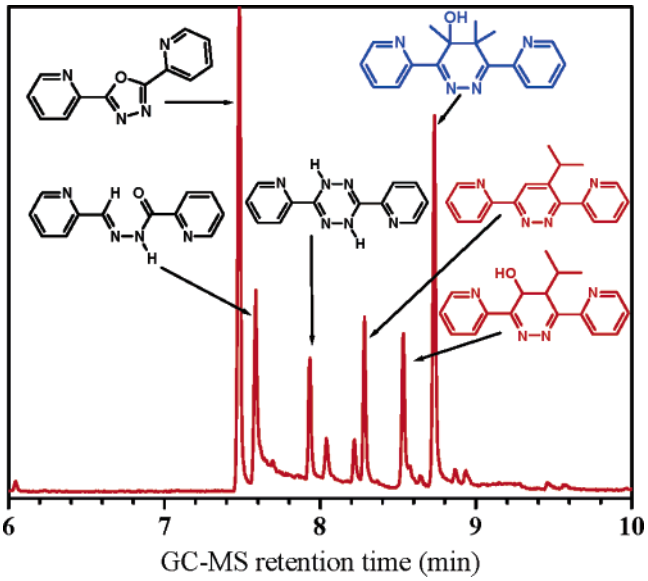
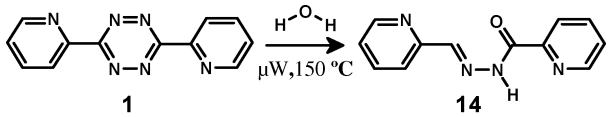


FIGURE 2. GC-MS spectrum obtained of the crude reaction mixture showing the presence of both DPP **12** and dihydroDPP **13**.

SCHEME 4. Reaction Observed upon Heating Tetrazine 1 in Water to 150 °C under Microwave Irradiation Resulting in 2-Pyridinecarboxylic Acid (Pyridin-2-ylmethylene)hydrazide (14)



base condensation of 2-pyridinecarboxaldehyde and 2-pyridinecarboxylic acid hydrazide.[29] The advantages of the application of water as the reagent under superheated microwave conditions were also recognized in other recent publications.[30,31]

From the literature, it is known that the enol tautomers of aldehydes are present in a larger extent when compared to ketones.[25] Therefore, a series of aldehydes were tested in the inverse-electron-demand Diels−Alder reaction with tetrazine **1** (Table 2, entries 6−9). When heating a mixture of **1** in acetaldehyde to 120 °C under microwave irradiation, the unsubstituted DPP **2** was formed in good yield demonstrating that superheated aldehydes are also suitable reagents in the inverse-electron-demand Diels−Alder reaction. The cycloadditions of butanal, hexanal, and octanal required 150, 170, and 200 °C, respectively. After 30 min heating, GC-MS of the crude reaction mixtures revealed full conversion of tetrazine **1** and the presence of the expected pyridazine, the corresponding dihydropyridazine, and dihydrotetrazine. The dihydropyridazine was not observed in such large quantities in the case of the ketone cycloadditions. From these results, it can be concluded that the dihydropyridazines resulting from aldehyde addition are more stable and the elimination of water is slower. Nevertheless, the ethyl DPP **9**, *n*-butyl DPP **5**, and *n*-hexyl DPP **16** could be obtained in reasonable yield and purity, whereby the yield (and ease of purification) decreased with longer chain lengths because of the required higher reaction temperatures that result in decomposition of tetrazine **1**.

Conclusions

In conclusion, the cycloadditions of alkynes to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1**) could be accelerated under superheated microwave conditions. Moreover, a novel mechanism for the synthesis of substituted DPPs was described in which ketones and aldehydes are applied as dienophiles in the inverse-electron-demand Diels−Alder reaction with tetrazine **1**. This strategy avoids the use of gaseous reagent-like acetylene, propyne, and butyne for the synthesis of DPPs with short side chains. Furthermore, the cycloadditions of 2-butanone to 3-pentanone yielded the formation of noncyclic dialkyl-substituted DPPs for the first time. Although, we have only demonstrated the cycloaddition of ketones and aldehydes to 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1**), this novel synthetic pathway might also be applied for the synthesis of substituted pyridazines in general. Moreover, the higher abundance of the enol tautomers of ketones and aldehydes under superheated microwave conditions could provide new opportunities in organic synthesis.

Experimental Section

Materials and Instrumentation. All compounds were used without further purification. 3,6-Di(pyridin-2-yl)-1,2,4,5-tetrazine was synthesized according to a literature procedure.[2]

^{1}H NMR and ^{13}C NMR were recorded on 300 or 400 MHz spectrometers. Chemical shifts are given in parts per million relative to TMS or solvent signals for proton and carbon spectra. ^{1}H-^{1}H COSY (compounds **5** and **8**) and ^{1}H-^{13}C HMQC (compound **5**) experiments were performed to assign the signals. UV−vis spectroscopy was performed utilizing 1 cm cuvettes. The GC-MS mass values are reported as mass/charge ratio (*m*/*z*). All GC spectra were measured with a column temperature program from 80 to 300 °C (25 °C/min) and a 3 min hold time at 300 °C. The injection temperature was 300 °C, and the detector temperature was 250 °C. Elemental analyses were performed for CHNS-O. Melting points were determined utilizing a differential scanning calorimeter (DSC) under a nitrogen atmosphere with a heating rate of 5 K min^{-1}. Microwave-assisted synthesis was performed utilizing an Emrys Liberator microwave synthesizer (Biotage) utilizing capped reaction vials. All microwave reactions were performed with temperature control (IR sensor).

Synthesis of 3,6-Di(pyridin-2-yl)-4-*n*-butylpyridazine (5). Microwave A: A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) and 1-hexyne (**2**, 67 mg, 0.84 mmol) in DMF (2.5 mL) was heated for 15 min to 225 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product **5** was purified by column chromatography (Al_2O_3, chloroform as eluent) yielding the product as a yellowish solid (60 mg, 49%).

Microwave B: A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) and 1-hexyne (**2**, 67 mg, 0.84 mmol) in CH_2Cl_2 (2.5 mL) was heated for 90 min to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product **5** was purified by column chromatography (Al_2O_3, chloroform as eluent) yielding the product as a yellowish solid (84 mg, 69%).

Microwave C: A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in hexanal (2.0 mL) was heated for 30 min to 150 °C under microwave irradiation. After evaporation of the solvent, the brown residue was purified by column chromatography (SiO_2, ethyl acetate/hexane (1:1)) yielding the product **5** as a yellowish solid (20 mg, 16%).

(29) Richardson, D. R.; Becker, E.; Bernhardt, P. V. *Acta Crystallogr. Sect. C* **1999**, *55*, 2102−2105.
(30) Vasudavan, A.; Verzal, M. K. *Synlett* **2004**, 631−634.
(31) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672−3679.

Mp 70−71 °C. ^{1}H NMR ($CDCl_3$, ^{1}H-^{1}H COSY): δ 8.75−8.70 (m, 3H, H-6,3″,6″), 8.49 (s, 1H, H-5′), 8.09 (d, J = 8.1 Hz, 1H, H-3), 7.89 (dt, J = 8.1, 2.2 Hz, 2H, H-4,4″), 7.40 (dt, J = 8.1, 1.5 Hz, 2H, H-5,5″), 3.08 (t, J = 8.1 Hz, 2H, CCH_2), 1.59 (quintet, J = 7.3 Hz, 2H, CCH_2CH_2), 1.32 (sixtet, J = 7.3 Hz, 2H, CH_2CH_3), 0.86 (t, J = 8.1 Hz, 2H, CH_3). ^{13}C NMR ($CDCl_3$, ^{1}H-^{13}C HMQC): δ 159.2 (C-3′), 157.3 (C-6′), 156.5 (C-2), 153.7 (C-2″), 149.4 (C-6″), 148.5 (C-6), 142.9 (C-4′), 137.2 (C-4″), 136.9 (C-4), 125.6 (C-5′), 124.8 (C-3), 124.6 (C-5″), 123.5 (C-5), 121.8 (C-3″), 32.0 (CCH_2), 31.9 (CCH_2CH_2), 22.6 (CH_2CH_3), 13.8 (CH_2CH_3). $C_{18}H_{18}N_4$: calcd C 74.46, H 6.25, N 19.29; found C 74.44, H 6.09, N 19.04. MALDI-TOF-MS: m/z [M$^+$] 291 (100%). UV−vis (chloroform): λ_{max} 288 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-(1-hydroxybutyl)pyridazine (6). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 500 mg, 2.1 mmol) and 5-hexyne-1-ol (**3**, 312 mg, 3.2 mmol) in dichloromethane (4.0 mL) was heated for 90 min to 150 °C under microwave irradiation. After evaporation of the solvent, the product (**6**, 504 mg, 78%) was obtained by column chromatography (SiO_2 with ethyl acetate).

Mp 79.5−80 °C. ^{1}H NMR ($CDCl_3$): δ 8.79−8.70 (m, 3H), 8.48 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.88 (dt, J = 7.7, 2.2 Hz, 2H), 7.40 (dt, J = 8.2, 2.2 Hz, 2H), 3.62 (q, J = 4.9 Hz, 2H), 3.08 (t, J = 8.2 Hz, 2H), 2.01 (t, J = 4.9 Hz, 1H), 1.78 (quintet, J = 8.2 Hz, 2H), 1.62 (quintet, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 158.7, 157.0, 155.9, 153.1, 149.1, 148.3, 142.4, 137.0, 136.8, 125.5, 124.7, 124.5, 123.5, 121.6, 61.5, 31.5, 31.4, 25.8. $C_{18}H_{18}N_4O$: calcd C 70.6, H 5.9, N 18.5; found C 71.0, H 5.7, N 18.5. MALDI-TOF-MS: m/z [M$^+$] 307 (100%). UV−vis (chloroform): λ_{max} 288 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-phthalimidopropylpyridazine (7). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) and phthalimidopentyne (**4**, 180 mg, 0.84 mmol) in CH_2Cl_2 (2.5 mL) was heated for 1 h to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al_2O_3, ethyl acetate/hexane (1:1) as eluent). Upon slow evaporation of a solution in chloroform/hexane (1:1), the product **7** was obtained as white crystals (147 mg, 83%).

Mp 168 °C. ^{1}H NMR ($CDCl_3$): δ 8.74−8.71 (m, 2H), 8.54 (d, J = 4.7 Hz, 1H), 8.51 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.92−7.78 (m, 4H), 7.75−7.65 (m, 2H), 7.39 (t, J = 6.2 Hz, 1H), 7.32 (t, J = 6.2 Hz, 1H), 3.78 (t, J = 6.8 Hz, 2H), 3.18 (t, J = 8.1 Hz, 2H), 2.11 (quintet, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 168.0, 158.5, 157.1, 155.7, 153.2, 149.2, 148.2, 141.2, 136.9, 136.7, 133.7, 131.9, 125.5, 124.5, 124.5, 123.4, 123.0, 121.5, 37.6, 30.2, 28.7. $C_{25}H_{19}N_5O_2$: calcd C 71.25, H 4.54, N 16.62; found C 71.14, H 4.57, N 16.35. GC-MS retention time (min): 16.12 [M$^+$] 422 (100%). UV−vis (chloroform): λ_{max} 290 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-methylpyridazine (8). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in acetone (2.5 mL) was heated for 30 min to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al_2O_3, CH_2Cl_2). Upon slow evaporation from chloroform/hexane (1:1), the product **8** was obtained as white crystals (78 mg, 75%).

Mp 119 °C. ^{1}H NMR ($CDCl_3$, ^{1}H-^{1}H COSY): δ 8.76−8.6 (m, 3H, H-6,3″,6″), 8.47 (s, 1H, H-5′), 8.18 (d, J = 7.9 Hz, 1H, H-3), 7.88 (tt, J = 7.8, 2.3 Hz, 2H, H-4,4″), 7.37 (dt, J = 5.9, 1.0 Hz, 2H, H-5,5″), 2.69 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$): δ 159.0, 156.9, 156.1, 153.3, 149.2, 148.3, 138.3, 137.0, 136.6, 126.6, 124.5, 124.5, 123.4, 121.6, 20.2. $C_{15}H_{12}N_4$: calcd C 72.56, H 4.87, N 22.57; found C 72.50, H 4.84, N 22.33. GC-MS retention time (min): 8.04 [M$^+$] 249 (100%). UV−vis (chloroform): λ_{max} 289 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-ethylpyridazine (9) and 3,6-Di(pyridin-2-yl)-4,5-dimethylpyridazine (10). Microwave A: A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in 2-butanone (2.5 mL) was heated for 30 min to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al_2O_3, CH_2Cl_2). Fraction 1 was further purified by column chromatography (Al_2O_3, ethyl acetate and SiO_2, ethyl acetate) resulting in 3,6-di(pyridin-2-yl)-4-ethylpyridazine (**9**) as a white solid (16 mg, 15%). Fraction 2 of the first column was crystallized upon slow evaporation from chloroform/hexane (1:1) yielding the product 3,6-di(pyridin-2-yl)-4,5-dimethylpyridazine (**10**) as yellowish crystals (38 mg, 35%).

3,6-Di(pyridin-2-yl)-4,5-dimethylpyridazine (**10**). Mp 97 °C. ^{1}H NMR ($CDCl_3$): δ 8.73 (d, J = 6.1 Hz, 4H), 7.98 (d, J = 7.6 Hz, 4H), 7.89 (dt, J = 7.6, 1.8 Hz, 4H), 7.39 (dt, J = 6.1, 1.3 Hz, 4H), 2.50 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 158.5, 156.7, 148.4, 136.9, 136.7, 124.9, 123.2, 15.5. $C_{15}H_{12}N_4$: calcd C 73.26, H 5.38, N 21.36; found C 73.16, H 5.40, N 21.52. GC-MS retention time (min): 8.55 [M$^+$] 263 (100%). UV−vis (chloroform): λ_{max} 275 nm.

Microwave B: A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in butanal (2 mL) was heated for 30 min to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, ethyl acetate/hexane (1:1)) resulting in 3,6-di(pyridin-2-yl)-4-ethylpyridazine (**9**) as a white solid (53 mg, 48%).

3,6-Di(pyridin-2-yl)-4-ethylpyridazine (**9**). Mp 100 °C. ^{1}H NMR ($CDCl_3$): δ 8.76−8.72 (m, 3H), 8.53 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.89 (tt, J = 7.7, 1.9 Hz, 2H), 7.40 (dt, J = 6.1, 1.5 Hz, 2H), 3.12 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.9, 157.2, 156.2, 153.4, 149.2, 148.2, 143.7, 136.9, 136.6, 124.6, 124.5, 124.4, 123.3, 121.8, 25.5, 13.7. $C_{15}H_{12}N_4$: calcd C 73.26, H 5.38, N 21.36; found C 72.98, H 5.42, N 21.56. GC-MS retention time (min): 8.21 [M$^+$] 263 (100%). UV−vis (chloroform): λ_{max} 287 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-ethyl-5-methylpyridazine (11). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in 3-pentanone (2.5 mL) was heated for 60 min to 180 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al_2O_3, ethyl acetate) resulting in 3,6-di(pyridin-2-yl)-4-ethyl-5-methylpyridazine (**11**) as a yellowish solid (15 mg, 13%).

Mp 52−54 °C. ^{1}H NMR ($CDCl_3$): δ 8.74 (t, J = 5.1 Hz, 2H), 7.95 (d, J = 7.8 Hz, 1H), 7.92−7.85 (m, 3H), 7.40 (dt, J = 5.1, 1.5 Hz, 2H), 2.99 (q, J = 7.5 Hz, 2H), 2.55 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.3, 158.7, 156.98, 156.97, 148.6, 148.5, 142.2, 136.9, 136.8, 136.2, 125.1, 124.9, 123.31, 123.29, 21.6, 14.9, 13.4. $C_{15}H_{12}N_4$: calcd C 73.89, H 5.84, N 20.27; found C 73.47, H 5.91, N 20.57. GC-MS retention time (min): 8.64 [M$^+$] 277 (100%). UV−vis (chloroform): λ_{max} 273 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-isopropylpyridazine (12) and 3,6-Di(pyridin-2-yl)-4-hydroxy-4,5,5-trimethyldihydropyridazine (13). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in 3-methyl-2-butanone (2.5 mL) was heated for 30 min to 180 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the residue was analyzed by GC-MS.

GC-MS retention time (min): 2.71 [pyridine-2-carboxaldehyde, 4%], 4.27 [3-(pyridin-2-yl)-1,2,4,5-tetrazine, 9%], 7.48 [2,5-di-(pyridin-2-yl)-1,3,4-oxadiazole, 30%], 7.59 [2,5-di(pyridin-2-yl)-2,3-dihydro-1,3,4-oxadiazole, 4%], 7.93 [3,6-di(pyridin-2-yl)-dihydro-1,2,4,5-tetrazine, 7%], 8.28 [3,6-di(pyridin-2-yl)-4-*i*-propylpyridazine **21**, 10%], 8.53 [3,6-di(pyridin-2-yl)-4-*i*-propyldihydropyridazine, 12%], 8.73 [3,6-di(pyridin-2-yl)-4-hydroxy-4,5,5-trimethyldihydropyridazine **22**, 24%].

Synthesis of 2-Pyridinecarboxylic Acid (Pyridin-2-ylmethylene)hydrazide (14). The synthesis of this compound has been previously reported by Schiff base condensation of 2-pyridinecarboxaldehyde and 2-pyridinecarboxylic acid hydrazide (no yield or characterization data reported).[29]

A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in water (2.0 mL) was heated for 20 min to 150 °C under

microwave irradiation. Cooling to 38 °C resulted in the formation of a white precipitate. After addition of methanol (5.0 mL), a clear solution was obtained and the solvent was evaporated under reduced pressure. The 2-pyridinecarboxylic acid (pyridin-2-ylmethylene)-hydrazide **14** was obtained pure (91 mg, 96%) by slow evaporation from an ethyl acetate/hexane (2:1) solution.

Mp 156 °C. ^{1}H NMR ($CDCl_3$): δ 11.21 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 4.7 Hz, 1H), 8.38 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.85 (dt, J = 7.8, 1.6 Hz, 1H), 7.70 (dt, J = 8.0, 1.3 Hz, 1H), 7.44 (dt, J = 4.9, 0.9 Hz, 1H), 7.25 (dt, J = 4.7, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 160.1, 152.6, 149.1, 148.6, 148.5, 147.8, 137.3, 136.1, 126.6, 124.1, 122.7, 121.0. $C_{12}H_{10}N_4O$: calcd C 63.71, H 4.46, N 24.76; found C 63.42, H 4.47, N 24.24. GC-MS retention time (min): 7.59 [M^+] 227 (100%). UV−vis (chloroform): λ_{max} 305 nm.

Synthesis of 3,6-Di(pyridin-2-yl)pyridazine (15). A solution of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1**, 100 mg, 0.42 mmol) in acetaldehyde (2 mL) was heated to 120 °C for 30 min under microwave irradiation. After evaporation of the acetaldehyde, the brown residue was filtered over aluminum oxide (chloroform as eluent) and recrystallized from ethanol yielding the product **15** as yellowish crystals (83 mg, 84%).

Mp 178−179 °C. ^{1}H NMR ($CDCl_3$): δ 8.80 (m, 4H), 8.75 (s, 2H), 7.97 (dt, J = 7.7, 2.2 Hz, 2H), 7.47 (dt, J = 7.7, 1.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 158.0, 153.2, 150.0, 137.2, 125.1, 124.7, 121.6. MALDI-TOF-MS: m/z [M^+] 235 (100%). UV−vis (chloroform): λ_{max} 299 nm.

Synthesis of 3,6-Di(pyridin-2-yl)-4-*n*-hexylpyridazine (16). A solution of 3,6-di(pyridin-2-yl)tetrazine (**1**, 100 mg, 0.42 mmol) in octanal (2.5 mL) was heated for 30 min to 200 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, chloroform/methanol (95:5)) resulting in 3,6-di(pyridin-2-yl)-4-*n*-hexylpyridazine (**16**) as an impure yellowish solid (15 mg, 9%). However, the obtained amount was too small for further purification.

^{1}H NMR ($CDCl_3$): δ 8.78−8.70 (m, 3H), 8.50 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.90 (dt, J = 7.5, 1.5 Hz, 2H), 7.40 (m, 2H), 3.09 (t, J = 7.9 Hz, 2H), 1.60 (quintet, J = 7.9 Hz, 2H), 1.30−1.22 (m, 6H), 0.87 (t, J = 7.2 Hz, 2H).

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