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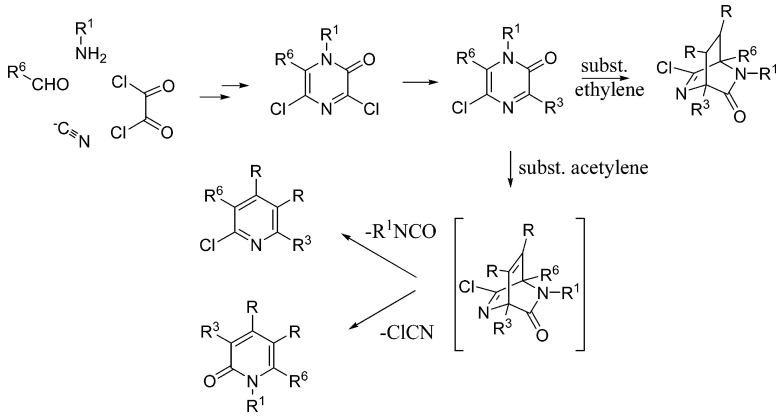

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The Application of "Click Chemistry" for the Decoration of 2(1*H*)-Pyrazinone Scaffold: Generation of Templates

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The "click chemistry" approach has been explored on the 2-(1*H*)-pyrazinone scaffold for the generation of pharmacologically interesting heterocyclic moieties. Huisgen 1,3-dipolar cycloaddition has been evaluated as the key step for the construction of the 1,2,3-triazole ring at the C-3 position of 2-(1*H*)-pyrazinones. Two different pathways have been successfully evaluated: (1) via C−C or C−O linkage of the acetylenic part to the C-3 position of the 2-(1*H*)-pyrazinone scaffold or (2) via azide introduction in the C-3 position. The subsequent application of "click chemistry" resulted in the formation of hitherto unknown skeletons. Microwave irradiation has successfully been applied in different steps of the sequence.

Introduction

1,2,3-Triazoles are important target molecules due to their widespread use and importance as potent pharmacophores.[1] It has been shown that several pyridyl- and pyrimidyl-substituted triazoles exhibit submicromolar activity against LPS-induced tumor necrosis factor-α (TNF-α),[1c] and some N-substituted phenyl-1,2,3-triazole-4-acylhydrazones show significant antiplatelet activity on arachidonic acid- and collagen-induced platelet aggregation.[1b] Furthermore, 1,2,3-triazoles have found extensive industrial use as corrosion inhibitors, dyes, photostabilizers, photographic materials, and agrochemicals.[2] Triazoles could become important pharmacophores in future drug discovery because they are stable and nonharmful. Additionally, they are more likely to be water-soluble, unlike their aryl counterparts, owing to their high dipole moments. Disubstituted 1,2,3-triazoles were traditionally prepared via a nonregioselective thermal 1,3-dipolar cycloaddition of an azide with a terminal alkyne to afford a mixture of 1,4- and 1,5-disubstituted isomers.[3] This could be advantageous if a library of compounds is targeted, but the lack of regioselectivity is a severe drawback in preparative chemistry. Recently, it was demonstrated that in the presence of a Cu(I) catalysist, this cycloaddition could be performed regioselectively, affording exclusively the 1,4-disubstituted 1,2,3-triazoles,[4] making the Huisgen 1,3-dipolar cycloaddition one of the fittest reactions for "click chemistry".[5]

In the course of the last two decades, our laboratory explored the 3,5-dichloro-2(1*H*)-pyrazinone system as an interesting gateway to the elaboration of different types of biologically active compounds.[6] A versatile synthesis of these templates has been developed starting from suitable aldehyde and amine building blocks, which upon consecutive treatment with cyanide and oxalyl chloride furnished the desired 2(1*H*)-pyrazinones in moderate to good yields (Scheme 1).[7] This approach allows the introduction of a wide variety of substituents at the N1- and the C6-positions of the pyrazinones. Furthermore, various substituents can easily be introduced at the C3-position upon addition−elimination reactions involving the sensitive imidoyl chloride moiety.[8] The multifunctionalized 2-azadiene system of these heterocycles was used in cycloaddition reactions with electron-rich and -poor dienophiles. Thus, they easily undergo inter- and intramolecular cycloaddition−elimination reaction with acetylenes (Scheme 1) generating, for example, pyridines and pyridinones,[9] α-carbolines and *β*-carbolinones,[10] (benzo)furo/pyranopyridines and -pyridinones,[11] pyrrolopyridin(on)es, and naphthyridin(on)es.[12] Many of these heterocycles represent interesting core structures for the synthesis of biologically active compounds as, for example, substance P antagonists. Upon inter- or intramolecular cycloaddition reaction with alkenes, bicyclic compounds are obtained (Scheme 1), which have been shown to be valuable building blocks for the synthesis of, for example, *β*-turn mimics[13] and the tricyclic core skeleton of the brevianamide family of natural products.[14] We have also described the transfer of this 2(1*H*)-pyrazinone chemistry from solution phase to solid phase, opening the way for the generation of combinatorial libraries.[9]

We, therefore, envisaged that the combination of our 2(1*H*)-pyrazinone chemistry with "click chemistry" could be extremely interesting for the generation of new scaffolds for drug discovery. Herein, we report our investigations on "click chemistry" for the decoration of the 2(1*H*)-pyrazinone scaffold, in view of generating biologically and pharmacologically interesting target molecules. The application of microwave irradiation in the different approaches has been investigated.

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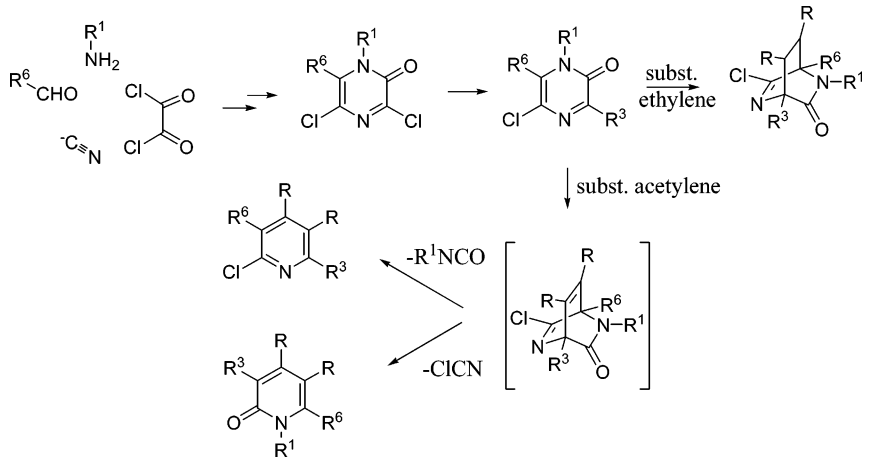
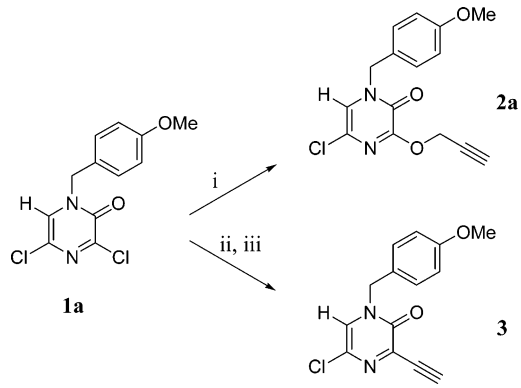
Scheme 1. General Synthesis and Cycloaddition Chemistry of 2(1*H*)-Pyrazinones



Scheme 2. Introduction of an Acetylene Unit at the C3-Position



(i) Propargyl alcohol, NaH, THF, r.t., 5 h; (ii) (trimethylsilyl)acetylene (1.9 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (5 mol %), Et_3N-DMF (1:1), MW, 50 W, 82 °C, 10 min; (iii) TBAF·$3H_2O$ (1.5 equiv), CH_2Cl_2/MeOH/THF (1:1:1), r.t., 15 min.

Results and Discussion

1,3-Dipolar Cycloadditions with "Acetylene-Functionalized" 2(1*H*)-Pyrazinones 2a and 3. As the starting point of our explorations, we decided to introduce an acetylene moiety at the C3-position of the 2(1*H*)-pyrazinone scaffold. Therefore, the 2(1*H*)-pyrazinone **1a** was reacted with propargyl alcohol to afford **2a** (Scheme 2). Alternatively, the pyrazinone **1a** was subjected to a microwave-enhanced Sonogashira reaction with (trimethylsilyl)acetylene, according to our previously reported procedure,[8] followed by desilylation upon treatment with tetrabutylammonium fluoride (TBAF), affording **3**. The pyrazinone **1a** was chosen as the starting material because the 4-methoxybenzyl group at the N1 position represents a mimic of the Wang resin, allowing the transfer of our strategy to the solid phase, as has been demonstrated.[9]

The conditions for the 1,3-dipolar cycloaddition were investigated and optimized for the reaction of the substrate **2a**, applying the electron-rich 4-methoxyphenyl azide (**4a**), which, according to the proposed mechanism,[4a] is expected to react easily (Scheme 3). The Cu(I) catalyst was generated in situ using copper wire and $CuSO_4$·$5H_2O$ (2 mol %). Because the application of the solvent mixture of *t*-BuOH and water (1:1) was causing solubility problems,[4a] THF was

Scheme 3. Microwave-Enhanced 1,3-Dipolar Cycloaddition of the 2(1*H*)-Pyrazinone-Derived Acetylene **2a** with Various Azides **4a**−**g**

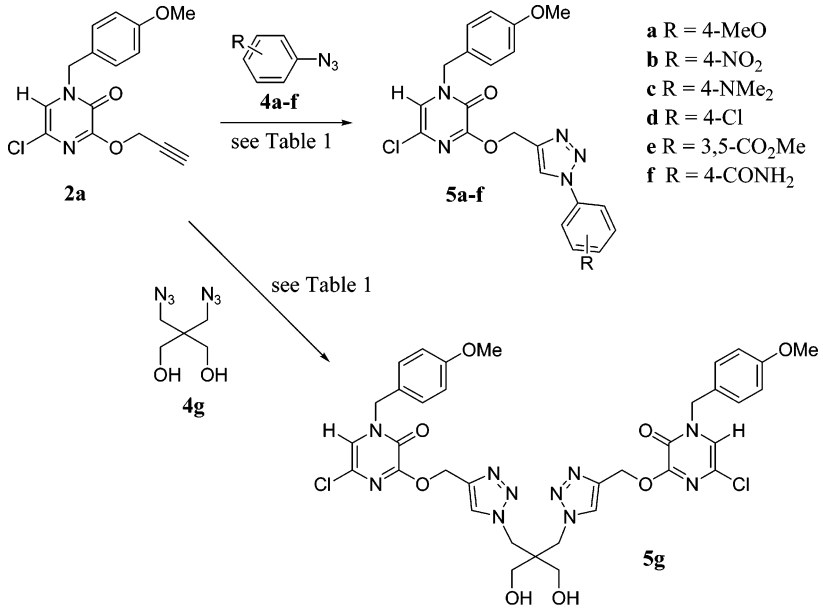


Table 1. Microwave-Enhanced 1,3-Dipolar Cycloaddition of 2(1*H*)-Pyrazinone-Derived Acetylene **2a** with Various Azides **4a**−**g**[a]

			t (min)		yield (%)	
entry	azide	ligand[b]	H_2O	*t*-BuOH/H_2O	H_2O	*t*-BuOH/H_2O
1	**4a**		20	15	82	84
2		6	10	05	82	84
3	**4b**		40	20	83	80
4		6	25	10	83	80
5	**4c**		20	5	82	72
6		6	10	2.5	82	76
7	**4d**		60	25	60[d]	81
8		7	30	15	80	81
9	**4e**		60	15	30[e]	45[d]
10		7	35	05	36	53[d]
11	**4f**		25	05	40	72
12		7	15	2.5	40	78
13	**4g**		60	03	21[e]	40
14		7	60	03	27	40

[a] All reactions were performed at a 0.1-mmol scale; 1.1 equiv of the azide was used in 2 mL of water or 1 mL each of water and *t*-BuOH, 20 mg of Cu wire, and 2 μL of a 1 M $CuSO_4$ solution; irradiations were performed at a ceiling temperature of 100 °C and 100 W maximum power. [b] 0.8 mol % of ligand **6** or 1 mol % of ligand **7** was used. [c] Yields are isolated yields. [d] The low yield is due to the partial hydrolysis of the ester groups. [e] Incomplete reaction.

added until a clear solution was obtained; however, upon stirring at room temperature, the reaction proceeded rather slowly, requiring 1.5 days, affording the triazole as the sole product.

In an effort to speed up the reaction, we decided to investigate the influence of microwave irradiation[15] using a dedicated monomode microwave apparatus of the companies Biotage or CEM.[16] Upon irradiation at a preselected maximum temperature of 100 °C, the reaction time could drastically be reduced to 15 min. Moreover, it was no longer necessary to use THF as a cosolvent (Table 1, entry 1). We found that the reaction could even be carried out in water as the sole solvent without influencing the yield noticeably but resulting in a slightly longer reaction time (20 min, Table 1, entry 1). All experiments were performed in capped vials without special precautions to exclude oxygen from the reaction mixture. The catalyses by Cu(II) seemed to be critical, because running this microwave-assisted reaction with copper wire as the sole Cu(I) source resulted in almost no conversion. To stabilize the air-sensitive Cu(I), the influence of two different types of triazole based ligands **6** and **7** was investigated (Figure 1). These ligands were easily synthesized applying standard techniques using "click chemistry".[17] Addition of one of the ligands **6** (0.8 mol %) or **7** (1−2 mol %) resulted in a substantial increase of the rate without any noticeable influence on the yield. For a conversion in a *t*-BuOH/H_2O mixture, the reaction time was reduced to only 5 min (as compared to 15 min) (Table 1, entry 2), whereas upon performing the reaction in water as the sole solvent, only 10 min (as compared to 20 min) was needed to reach completion. To verify that no thermal 1,3-dipolar cycloaddition occurred at 100 °C, an experiment was performed without the addition of copper wire or $CuSO_4$.

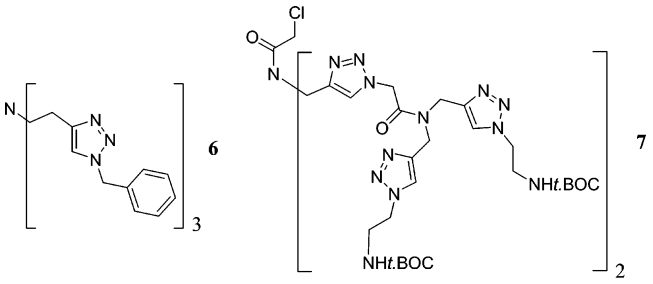


Figure 1. Triazole-based Cu (I) ligands used for the microwave-enhanced 1,3-dipolar cycloaddition.[17]

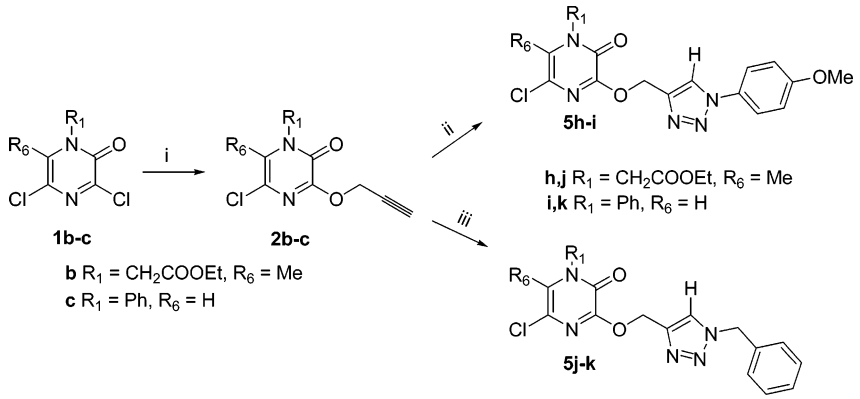
No reaction was observed after 20 min of microwave irradiation. This means that only Cu(I) is catalyzing the reaction. According to the proposed mechanism, this should result in a completely regioselective reaction. This was in agreement with the observation that only one regioisomer was formed upon microwave irradiation, as was indicated by ^{1}H NMR spectroscopy.

The optimized procedure was explored for different kinds of aromatic azides **4b**−**f** possessing electron-donating and -withdrawing substituents (Table 1, entries 3−12). As expected, the azides bearing an electron-donating group (**4a** and **4c**) reacted faster. The low yields obtained for the conversions of the diester **5e** are due to partial hydrolysis of the ester groups. Reaction of the pentaerythritol-derived bisazide **4g** resulted in the formation of a dimer, **5g**, in low to moderate yield. For all aromatic azides, the reaction time was substantially reduced upon the addition of one of the ligands **6** or **7**, without having a noticeable influence on the yield. The nature of the two investigated ligands does not seem to be important, because the rate and the yield of the reactions remained more or less the same. All the conversions performed in a *t*-BuOH/H_2O mixture can be carried out in water as the sole solvent, although the reaction time was considerably longer. For the compounds **5e**−**g**, this also resulted in a substantial decrease in yields.

To demonstrate the versatility of this approach, we decided to vary the pyrazinone core of the acetylene moiety and to use benzylic azides, instead, next to aromatic azides. Thus, 2-(1*H*)-pyrazinones **1b**−**c** were converted to the corresponding propargyl derivatives **2b**−**c** by reaction with propargyl alcohol in the presence of NaH in dry THF (Scheme 4). The reactions were found to be complete in 1h, and products **2b**−**c** were isolated in excellent yields of 89 and 91%, respectively (Scheme 4).

Then the 1,3-dipolar cycloadditions were investigated, generating the corresponding triazoles **5h**−**k**. To synthesize the triazoles **5h**,**i** we chose 4-methoxyphenyl azide **4a** as the coupling partner. The reactions were found to proceed smoothly in 10 min at 100 °C using a maximum irradiation power of 100 W, and the products **5h**,**i** were isolated in good yields of 76 and 72%, respectively (Scheme 4). For the generation of the triazoles **5j**,**k** we applied our recently communicated microwave-enhanced three-compomnent coupling protocol,[18] in which the azides are generated in situ from the corresponding halides and sodium azide. Thus, a mixture of one of the pyrazinones **2b**,**c**, BnBr (1.1 equiv), NaN_3 (1.1 equiv), Cu-wire, and aq $CuSO_4 \cdot 5H_2O$ was suspended in a 1:1 mixture of *t*-BuOH and H_2O and

Scheme 4. Synthesis and 1,3-Dipolar Cycloaddition of **2b**−**c**



(i) C_3H_3OH (1.2 equiv), NaH (80% on mineral oil, 1.2 equiv), THF, r.t., 1 h, 89% (**2b**), 91% (**2c**); (ii) 4-methoxyphenyl azide (1.2 equiv), Cu wire, aq $CuSO_4 \cdot 5H_2O$, 100 W, 100 °C, 10 min, 76% (**5h**), 72% (**5i**); (iii) Bn-Br (1.1 equiv), NaN_3 (1.1 equiv), Cu wire, aq $CuSO_4 \cdot 5H_2O$, 100 W, 125 °C, 10 min, 86% (**5j**), 89% (**5k**). All 1,3-dipolar cycloadditions were carried out on a 0.2-mmol scale with 40 mg of Cu wire and 4 μL of 1.0 M $CuSO_4$ solution.

Scheme 5. Microwave-Enhanced 1,3-Dipolar Cycloaddition of 2(1*H*)-Pyrazinone-Derived Acetylene **3** with Various Azides **4a**−**d**,**h**

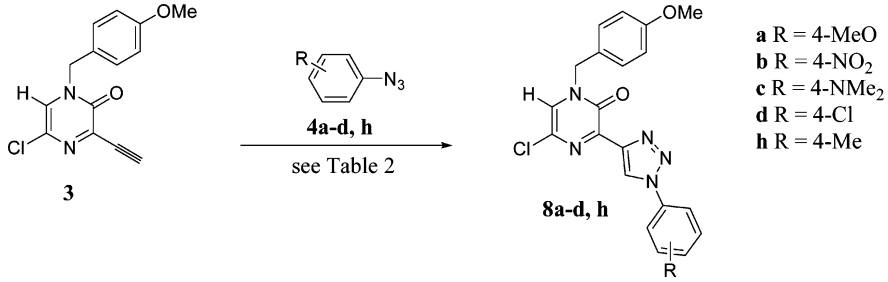


Table 2. Microwave-Enhanced 1,3-Dipolar Cycloaddition of the Acetylene-Derivatized 2(1*H*)-pyrazinone **3** with Various Azides **4a**−**d**,**h**[a]

entry	azide	*t* (min)	yield (%)[b]
1	**4a**	8	68
2	**4b**	14	27
3	**4c**	10	59
4	**4d**	10	64
5	**4h**	10	71

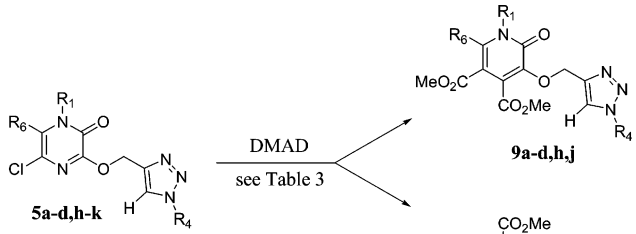
[a] All reactions were run at a 0.2-mmol scale; 1.5−2.0 equiv of the azide was used in 1 mL each of water, *t*-BuOH, and THF; 32 mg of Cu wire and 30 μL of a 2 N $CuSO_4$ solution; irradiations were performed at a ceiling temperature of 100 °C and 100 W maximum power. [b] Yields are isolated yields.

irradiated at 125 °C for 10 min using a maximum irradiation power of 100 W. The reactions were found to proceed smoothly, and the products **5j**,**k** were isolated in excellent yields of 86 and 89%, respectively (Scheme 4).

Then we turned our attention to the 1,3-dipolar cycloaddition of the acetylene **3** with the 4-methoxyphenyl azide **4a**, applying the optimized reaction conditions (Scheme 5). Due to solubility problems, a solvent mixture of *t*-BuOH/H_2O/THF (1:1:1) was used. Under microwave irradiation, very fast regioselective reactions took place, rendering the azides **8a**−**d**, **h** in 27−71% yield (Table 2).

Diels−**Alder Reaction of the Triazole-Functionalized 2(1*H*)-Pyrazinones 5a**−**d,h**−**k and 8a,c,d,h.** We have previously reported the inter- and intramolecular cycloaddition−elimination reaction of the 2-azadiene system of the 2(1*H*)-pyrazinones with various kinds of acetylenes, generating pyridines and pyridinones (ratio dependent on the

Scheme 6. Microwave-Enhanced Diels−Alder Reaction of the 2(1*H*)-Pyrazinones **5a**−**d**,**h**−**k** with DMAD



substitution pattern of the starting 2(1*H*)-pyrazinone).[9] This reaction allows further diversification of the generated compounds. As a proof of concept, we first investigated the Diels−Alder reaction of the triazole-functionalized 2(1*H*)-pyrazinones **5a**−**d** with dimethyl acetylenedicarboxylate (DMAD) (Scheme 6). A mixture of one of the compounds **5a**−**d** and DMAD (3.5 equiv) was irradiated in 1,2-dichlorobenzene for 6−20 min at a preselected maximum temperature of 180 °C (Table 3) and 200 W maximum power.

After spontaneous elimination of cyanogen chloride or isocyanate, the pyridinones **9a**−**d** and pyridines **10a**−**d** were isolated in good combined yields. In a similar fashion, the triazole functionalized pyrazinones **5h**−**k** were reacted with DMAD, and the resulting pyridones **9h**,**j** and pyridines **10h**−

Table 3. Microwave-EnhancedDiels−Alder Reaction of the 2(1*H*)-Pyrazinones **5a**−**d**,**h**−**k** with DMAD[a]

entry	2(1*H*)-pyrazinone	*t* (min)	pyridinone **9** yield (%)[b]	pyridine **10** yield (%)[b]
1	**5a**	06	**a**, 89	**a**, 10
2	**5b**	20	**b,** 60	**b**, 22
3	**5c**	20	**c**, 62	**c**, 18
4	**5d**	20	**d**, 64	**d**, 21
5	**5h**	20	**h**, 74	**h**, 16
6	**5i**	20	**i**, traces	**I**, 73
7	**5j**	20	**j**, 71	**j**, traces
8	**5k**	20	**k**, traces	**k**, 76

[a] 3.5 equiv of DMAD was used in 2 mL of 1,2-dichlorobenzene; irradiations were performed at 200 W maximum power at a ceiling temperature of 180 °C. [b] Yields are isolated yields

Scheme 7. Microwave-Enhanced Diels−Alder Reaction of the 2(1*H*)-Pyrazinones **8a**,**c**,**d**,**h** with DMAD

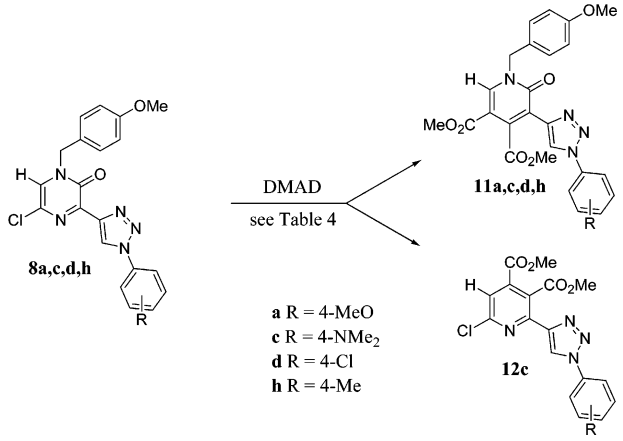


Table 4. Microwave-Enhanced Diels−Alder Reaction of the 2(1*H*)-Pyrazinones **8a**,**c**,**d**,**h** with DMAD[a]

entry	2(1*H*)-pyrazinone	*t* (min)	pyridinone **11** yield (%)[b]	pyridine **12** yield (%)[b]
1	**8a**	10	**a**, 88	**a**, 0
2	**8c**	10	**c**, 38	**c**, 14
3	**8d**	20	**d**, 84	**d**, 0
4	**8h**	20	**h**, 81	**h**, 0

[a] All reactions were run at a 0.18-mmol scale; 3.5 equiv of DMAD were used in 1 mL of 1,2-dichlorobenzene; irradiations were performed at 200 W maximum power at a ceiling temperature of 190 °C. [b] Yields are isolated yields

i,**k** were isolated in excellent combined yields. Contrary to the pyrazinones **5h**,**j** with a 1-alkyl substitution pattern, for which the pyridones **9h**,**j** were the major products, the corresponding 1-phenyl analogues **5i**,**k** gave a completely opposite selectivity, as the pyridines **10i**,**k** were isolated as the major products (Table 3).

Similarly, compounds **8a**,**c**,**d**,**h** were reacted with DMAD (3.5 equiv) under microwave irradiation at a preselected maximum temperature of 190 °C, resulting in the exclusive formation of the pyridones **11a**,**d**,**h** (entries 1, 3 and 4) and a mixture of the pyridone **11c** and the pyridine **12c** (entry 2) (Scheme 7, Table 4).

1,3-Dipolar Cycloadditions with "Azide-Functionalized" 2(1*H*)-Pyrazinones. The 1,2,3-triazole ring was introduced at the C3-position of the 2(1*H*)-pyrazinone system following a different approach. The imidoyl chloride moiety of the 2(1*H*)-pyrazinone underwent addition elimination reaction with sodium azide, and the 1,2,3-triazole unit was constructed via 1,3-dipolar cycloaddition reaction with a suitable acetylene (Scheme 8). This finally resulted in the formation of a 1,2,3-triazole ring linked via the N1-position with the 2(1*H*)-pyrazinone core. Thus, upon addition−elimination reaction of the pyrazinones **1a**−**d** with an excess of sodium azide in acetonitrile at 60 °C, the tetrazoles **13a**−**d** were isolated in excellent yields (77−90%).

Indeed, as could be deduced from their IR-spectra,[19] the initially formed azides directly cyclize to the tetrazoles, due to a higher stability of the ring-closed products. We then investigated the 1,3-dipolar cycloaddition of the various tetrazoles **13a**−**d** with the commercially available phenylacetylene (Scheme 8). We expected that upon heating, the equilibrium should be shifted to the open azide form. Due to the 1,3-dipolar cycloaddition with phenylacetylene, the equilibrium should be continuously shifted to the right side until the reaction should reach completion. We therefore decided to investigate the course of the reaction under microwave irradiation. A mixture of copper wire, $CuSO_4$, and ligand **6** (Figure 1) was used as the catalyst system in a solvent mixture of *t*-BuOH/water/THF (3:2:5); however, no reaction took place upon microwave irradiation at moderate temperature (100 °C), whereas at elevated temperature (160 °C), the starting material started to decompose. Only very minor amounts of the desired cycloadducts **14a**−**d**, together with traces of the C3-amino substituted pyrazinone, were indicated by LC/MS. To our surprise, upon stirring at room temperature, all of the reactions reached completion within 30 h, yielding the 1,2,3-triazoles **14a**−**d** in reasonable to excellent yields (Table 5, 49−92%).

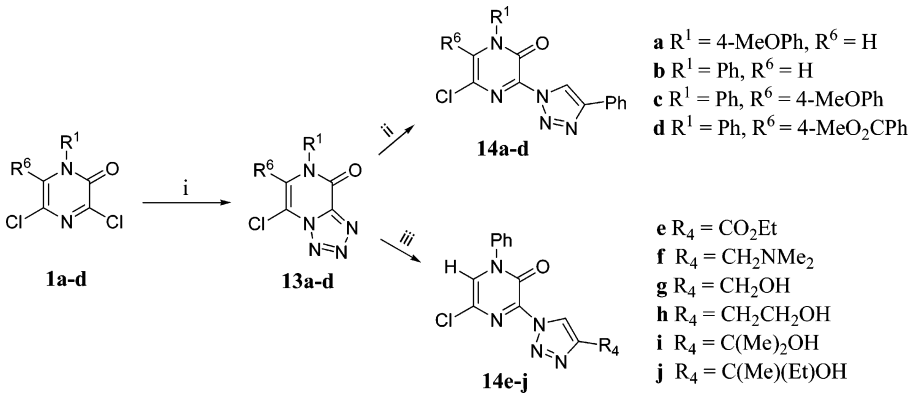
To demonstrate the versatility of this approach, we carried out the 1,3-dipolar cycloaddition of the tetrazoles with a variety of terminal acetylenes (Scheme 8). Thus, the tetrazole **13b** was reacted with the corresponding terminal acetylenes (2.5 equiv) in a 5:3:1 ratio of *t*-BuOH, DMF, and H_2O in the presence of Cu wire (2.5 equiv) and aq $CuSO_4$ solution. In anology with previous cases, stirring at room temperature was found to be efficient to perform the reactions, as the required tetrazoles **14e**−**j** were isolated (Table 5) in moderate to good yields (33−88%) after a reaction time of 48 h.

Diels−Alder Reaction of the "Triazole-Functionalized" 2(1*H*)-Pyrazinones 14a−c. The intermolecular cycloaddition−elimination reaction of the 2-azadiene system of the 2(1*H*)-pyrazinones **14a**−**c** with various kinds of acetylenes should generate interesting triazole linked pyridines and pyridinones (ratio depends on the substitution pattern of the starting 2(1*H*)-pyrazinone).[9] As a proof of concept, we investigated the Diels−Alder reactions of these systems **14a**−**c** with DMAD (Scheme 9, Table 6). A mixture of one of the compounds **14a**−**c**, DMAD (3.5 equiv) was irradiated in 1,2-dichlorobenzene for 15 min at a preselected maximum temperature of 200 °C. This resulted in the exclusive formation of pyridines **15a**−**c**, whereas no traces of the corresponding pyridinones were formed.

Conclusion

In conclusion, we have demonstrated that the application of "click chemistry" for the decoration of the 2(1*H*)-

Scheme 8. Synthesis of the Tetrazoles **13a**−**d**, Followed by Microwave-Enhanced 1,3-Dipolar Cycloaddition, Resulting in the Formation of the 1,2,3-Triazoles **14a**−**d**



(i) NaN_3, CH_3CN, reflux, 6 h; (ii) phenylacetylene (2.2 equiv), Cu wire (5 equiv), $CuSO_4 \cdot 5H_2O$ (0.12 equiv), ligand **6** (0.067 equiv), *t*-BuOH/H_2O/THF (3:2:5), r.t., 30 h; (iii) RCCH (2.5 equiv), Cu wire (2.5 equiv), aq $CuSO_4 \cdot 5H_2O$ (0.12 equiv), ligand **6** (0.067 equiv), *t*-BuOH/DMF/H_2O (5:3:1), r.t., 48 h.

Scheme 9. Microwave-Enhanced Diels−Alder Reaction of the 2(1*H*)-Pyrazinones **14a**−**c** with DMAD

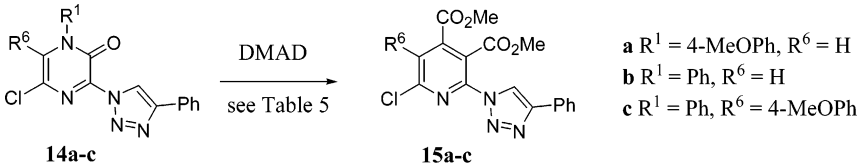


Table 5. Synthesis of the Triazoles **14a**−**j** via 1,3-Dipolar Cycloaddition of the Tetrazole **13a**−**d** with Various Terminal Acetylenes

entry	compound	yield, %
1	**14a**	88
2	**14b**	49
3	**14c**	92
4	**14d**	68
5	**14e**	33
6	**14f**	88
7	**14g**	45
8	**14h**	67
9	**14i**	54
10	**14j**	69

Table 6. Microwave-Enhanced Diels−Alder Reaction of the 2(1*H*)-Pyrazinones **14a**−**c** with DMAD[a]

entry	2(1*H*)-pyrazinone	pyridine **15** yield (%)[b]
1	**14a**	**a**, 55
2	**14b**	**b**, 39
3	**14c**	**c**, 68

[a] All reactions were run at a 0.2-mmol scale; 3.5 equiv of DMAD were used in 1 mL of 1,2-dichlorobenzene; irradiations were performed at 250 W maximum power at a ceiling temperature of 200 °C for 15 min. [b] Yields are isolated yields.

pyrazinone scaffold gives an easy access to the generation of small libraries of interesting compounds with hitherto unexplored structures. Two different routes were evaluated. In the first approach, an acetylene unit was introduced at the C3-position of the 2(1*H*)-pyrazinones **1a**−**c** via addition−elimination reaction or via Sonogashira cross-coupling reaction. We demonstrated that the subsequent Huisgen 1,3-dipolar cycloaddition reaction highly benefits from microwave irradiation. Reaction times were reduced from 1.5 days to minutes, providing the compounds **5a**−**k** and **8a**−**d**,**h** in good yields. Starting from the 2(1*H*)-pyrazinone **2**, it was possible to perform the reactions in water as the sole solvent, although this was accompanied by a substantial increase of the reaction time and a lower yield for the compounds **5e**−**g**. Moreover, the addition of the Cu(I)-complexing ligands **6** or **7** seems to be highly beneficial because the reaction times were dramatically reduced. In the second approach, an addition elimination reaction at the C3-position of the 2(1*H*)-pyrazinones **1a**−**d** was performed with sodium azide, resulting in the formation of the tetrazoles **13a**−**d**. Consecutively, the Huisgen 1,3-dipolar cycloaddition reaction was explored. This reaction was found to be slow at room temperature, and we were unable to speed up this cycloaddition upon microwave irradiation, probably due to the thermal instability of the resulting 1,2,3-triazoles **14a**−**j**. Subsequently, the triazole-functionalized pyrazinones **5a**−**d**,**h**−**k**, **8a**,**c**,**d**,**h**, and **14a**−**c**, obtained via "click chemistry", were investigated for their Diels−Alder reactivity toward dimethyl acetylenedicarboxylate (DMAD). Depending on the substrate, a mixture of the pyridinone/pyridine was formed. We demonstrated that all of these Diels−Alder reactions could dramatically be sped up upon microwave irradiation, resulting in the formation of a small library of hitherto unexplored compounds.

Experimental Section

General Methods. Melting points were determined using a Reichert-Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1720 Fourier transform spectrometer and a Perkin-Elmer 297 grating IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance 300 instrument using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos

MS50TC and a Kratos Mach III data system. The ion source temperature was 150−250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10 000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70−230 mesh silicagel (E. M. Merck)) were used.

Microwave Irradiation Experiments. A monomode SmithSynthesizer (Biotage) or CEM-Discover microwave reactor (CEM Corporation, P.O. Box 200, Matthews, NC 28106) were used in the standard configuration as delivered, including proprietary software.[20] All experiments were carried out in microwave process vials (5 or 10 mL) sealed with an aluminum-Teflon crimp top at the maximum power and temperature, as indicated in the Tables. After the completion of the reaction, the vial was cooled to 50 °C via air jet cooling before the vial was opened.

General Procedure for the Preparation of 3-(4-aryl-[1,2,3]Triazol-1-ylmethoxy)-1*H*-pyrazin-2-ones 5a−g. Pyrazinone **2**[21] (0.03 g, 0.1 mmol), azide **4 a**−**f** (0.11 mmol, 1.1 equiv) or **4g** (0.22 mmol, 2.2 equiv), Cu turnings (0.02 g), and $CuSO_4$ (1 M solution, 2 μL) were irradiated at 100 °C at 100 W power for the time indicated in Table 1 (A) in water (2 mL); (B) in water (2 mL) in the presence of ligand **6** (0.002 g, 0.16 μmol) or **7** (0.75 μg, 0. 8 μmol); (C) in water/*t*-BuOH (1:1, 2 mL); or (D) in water/*t*-BuOH (1:1, 2 mL) in the presence of ligand **6** or (0.002 g, 0.0016 mmol) or **7** (0.75 μg, 0.8 μmol). The reaction mixture was extracted with DCM (10 mL × 3) and washed with water. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated in vacuo, and the crude mixture was purified by column chromatography on silica gel. The products were recrystallized from suitable solvents to afford analytically pure samples of pyrazinones **5 a**−**f**.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-methoxyphenyl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-2(1*H*)-pyrazinone (**5a**) was synthesized following the general procedure, starting from azide **4a** (0.016 g, 0.11 mmol), irradiating the sample for (A) 20 min, (B) 10 min, (C) 15 min, or (D) 5 min to obtain after the recrystallization from ethanol (A); (B) 0.037 g, 82%; (C); (D) 0.038 g, 84% of pyrazinone **5a**. mp 70−71 °C. ^{1}H NMR: δ 8.08 (s, 1H), 7.61 (d, 2H, J = 9 Hz), 7.27 (d, 2H, J = 8 Hz), 7.01 (d, 2H, J = 8 Hz), 6.88 (d, 2H, J = 9 Hz), 6.87 (s, 1H), 5.56 (s, 2H), 4.98 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR: 160.4, 160.3, 154.6, 150.4, 143.0, 130.7 (×2), 126.9, 123.0 (×2), 122.7, 119.6, 115.2, 114.9, 61.8, 56.0, 55.7, 52.1. HR-MS (EI): $C_{22}H_{20}N_5O_4Cl$ calcd 453.1204, found 453.1218.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-nitrophenyl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-2(1*H*)-pyrazinone (**5b**) was synthesized following the general procedure, starting from azide **4b** (0.018 g, 0.11 mmol) irradiating the sample for (A) 40 min, (B) 25 min, (C) 20 min, (D) 10 min to obtain after the recrystallization from ethanol (A); (B) 0.038 g, 83%; (C); (D) 0.037 g, 80% of pyrazinone **5b**. mp 232−233 °C. ^{1}H NMR (DMSO-d_6): δ 9.10 (s, 1H), 8.45 (d, 2H, J = 9 Hz), 8.23 (d, 2H, J = 9 Hz), 7.71 (s, 1H), 7.33 (d, 2H, J = 9 Hz), 6.90 (d, 2H, J = 9 Hz), 5.44 (s, 2H), 4.97 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6): 159.9, 154.6, 150.1, 147.7, 144.0, 141.6, 130.7, 128.7, 126.5, 124.8, 122.1, 121.7, 121.3, 114.9, 60.9, 55.7, 51.7. HR-MS (EI): $C_{21}H_{17}N_6O_5Cl$ calcd 468.0949, found 468.0955.

5-Chloro-3-[1-(4-dimethylaminophenyl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (**5c**) was synthesized following the general procedure, starting from azide **4c** (0.018 g, 0.11 mmol) irradiating the sample for (A) 20 min, (B) 10 min, (C) 5 min, (D) 2.5 min to obtain after the recrystallization from ethanol (A); (B) 0.038 g, 82%; (C) 0.034 g, 72%; (D) 0.035 g, 76% of pyrazinone **5c**. mp 146−147 °C. ^{1}H NMR: δ 8.04 (s, 1H), 7.53 (d, 2H, J = 9 Hz), 7.28 (d, 2H, J = 8 Hz), 6.89 (d, 2H, J = 8 Hz), 6.86 (s, 1H), 6.77 (d, 2H, J = 9 Hz), 5.58 (s, 2H), 4.99 (s, 2H), 3.80 (s, 3H), 3.02 (s, 6H). ^{13}C NMR: 160.3, 154.7, 151.0, 150.5, 130.7, 127.0, 122.4, 119.5, 114.9, 112.7, 61.9, 55.7, 52.0, 40.9, 32.3, 30.1, 29.8, 23.1, 14.5. HR-MS (EI): $C_{23}H_{23}N_6O_3Cl$ calcd 466.1520, found 466.1529.

5-Chloro-3-[1-(4-chlorophenyl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-1-(4-methoxy- benzyl)-2(1*H*)-pyrazinone (**5d**) was synthesized following the general procedure, starting from azide **4d** (0.017 g, 0.11 mmol), irradiating the sample for (A) 60 min, (B) 30 min, (C) 25 min, (D) 15 min to obtain after the recrystallization from ethanol (A) 0.027 g, 60%; (B) 0.036 g, 80%; (C); (D) 0.037 g, 81% of pyrazinone **5d**. mp 148−149 °C. ^{1}H NMR: δ 8.17 (s, 1H), 7.68 (d, 2H, J = 9 Hz), 7.49 (d, 2H, J = 9 Hz), 7.28 (d, 2H, J = 9 Hz), 6.88 (s, 1H), 6.87 (d, 2H, J = 9 Hz), 5.57 (s, 2H), 4.99 (s, 2H), 3.79 (s, 3H). ^{13}C NMR: 160.4 (×2), 154.6, 150.4, 135.8, 135.1, 130.7 (×2), 130.4, 126.9, 122.9, 122.2, 119.7, 114.9, 61.7, 55.7, 52.1. HR-MS (EI): $C_{21}H_{17}N_5O_3Cl_3$ calcd 457.0708, found 457.0719.

5-{4-[6-Chloro-4-(4-methoxybenzyl)-3-oxo-3,4-dihydro-pyrazin-2-yloxymethyl]-[1,2,3]triazol-1-yl}-isophthalic acid dimethyl ester (**5e**) was synthesized following the general procedure, starting from azide **4e** (0.026 g, 0.11 mmol), irradiating the sample for (A) 60 min, (B) 35 min, (C) 15 min, (D) 5 min to obtain after the purification by column chromatography (eluent: hexanes−ethyl acetate 1:1) and recrystallization from ethanol (A) 0.016 g, 30%; (B) 0.019 g, 36%; (C) 0.024 g, 45%; (D) 0.028 g, 53% of pyrazinone **5e**. mp 217−218 °C. ^{1}H NMR: δ 8.75 (s, 1H), 8.62 (s, 2H), 8.31 (s, 1H), 7.28 (d, 2H, J = 9 Hz), 6.88 (d, 2H, J = 9 Hz), 6.88 (s, 1H), 5.62 (s, 2H), 5.02 (s, 2H), 4.01 (s, 6H), 3.81 (s, 3H). ^{13}C NMR: 165.3, 160.4, 154.5, 150.4, 144.0, 137.7, 132.9, 131.8, 130.9, 130.7, 126.8, 125.5, 123.0, 122.6, 119.7, 115.0, 61.7, 55.7, 53.2, 52.9, 52.2. HR-MS (EI): $C_{25}H_{22}N_5O_7Cl$ calcd 539.1208, found 539.1200.

4-{4-[6-Chloro-4-(4-methoxybenzyl)-3-oxo-3,4-dihydro-pyrazin-2-yloxymethyl]-[1,2,3]triazol-1-yl}-benzamide (**5f**) was synthesized following the general procedure, starting from azide **4f** (0.018 g, 0.11 mmol), irradiating the sample for (A) 25 min, (B) 15 min, (C) 5 min, (D) 2.5 min to obtain after the purification by column chromatography (eluent: hexanes−ethyl acetate 1:1) and recrystallization from petroleum ether/ethyl acetate (2:1) (A); (B) 0.019 g, 40%; (C) 0.033 g, 72%; (D) 0.036 g, 78% of pyrazinone **5f**. mp 208−210 °C. ^{1}H NMR (DMSO-d_6): δ 8.98 (s, 1H), 8.14 (bs, 1H), 8.09 (d, 2H, J = 9 Hz), 8.01 (d, 2H, J = 9 Hz), 7.70 (s, 1H), 7.55 (bs, 1H), 7.33 (d, 2H, J = 9 Hz), 6.90 (d, 1H, J

= 9 Hz), 5.43 (s, 2H), 4.97 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6): 167.6, 159.9, 154.6, 150.1, 143.5, 139.2, 135.1, 130.7, 130.1, 128.7, 124.5, 122.0, 121.3, 120.6, 114.9, 61.1, 56.0, 51.7. HR-MS (EI): $C_{22}H_{19}N_6O_4Cl$ calcd 466.1156, found 466.1168.

2,2-Bis-(4-[6-Chloro-4-(4-methoxybenzyl)-3-oxo-3,4-dihydropyrazin-2-yloxymethyl]-[1,2,3]triazol-1-methyl)-propane-1,3-diol (**5g**) was synthesized following the general procedure, starting from azide **4 g** (aqueous solution (0.23 g in 1 g), 0.046 g, 0.22 mmol), irradiating the sample for (A), (B) 60 min, (C), (D) 3 min. The reaction mixture was extracted with chloroform (10 mL × 3) and washed with water. The combined organic layers were dried over $MgSO_4$, the solvent was under reduced pressure, and the residue was purified by column chromatography (eluent: DCM/MeOH 93:7 and 1% of ammonia) to give pyrazinone **5h** (A) 0.017 g, 21%; (B) 0.021 g, 27%; (C); (D) 0.032 g, 40%. mp 100−102 °C. ^{1}H NMR: δ 8.16 (s, 1H), 7.25 (d, 2H, J = 9 Hz), 6.88 (s, 1H), 6.86 (d, 2H, J = 9 Hz), 5.46 (s, 2H), 4.97 (s, 2H), 4.38 (s, 2H), 3.58 (s, 3H), 3.38 (s, 2H), 2.61 (bs, 2H). ^{13}C NMR: 160.3, 154.5, 150.5, 130.6, 127.5, 126.7, 123.4, 119.7, 114.9, 63.2, 61.6, 60.7, 55.7, 49.4, 47.2, 45.5. MS (ES): m/z (%) = 795 (2) [M^+ + 1].

General Procedure for the Synthesis of Triazoles 5h−i. Compounds **5h−i** were synthesized accoding to the general procedure, starting from the corresponding pyrazinone **1b** or **1c** (0.25 mmol), 4-methoxyphenyl azide (0.275 mmol, 1.1 equiv), Cu turnings (0.05 g), and $CuSO_4$ (1 M solution, 5 μL) in a 1:1 mixture of *t*-BuOH and H_2O (3 mL) in 10 min at 100 °C, using a maximum irradiation power of 100 W. Column chromatography (silica gel, gradient elusion from 100% DCM to 8:2 DCM/ethyl acetate) afforded the analytically pure products **5h−i** as colorless solids.

Ethyl [5-Chloro-3-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-6-methyl-2-oxopyrazin-1(2*H*)-yl]acetate (5h). Yield 0.082 g, 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29(t, 3H, J = 7.3 Hz), 2.33 (s, 3H), 3.86 (s, 3H), 4.25 (q, 2H, J = 7.3 Hz), 4.80 (s, 2H), 5.57 (s, 2H), 7.01 (d, 2H, J = 8.8 Hz), 7.61 (d, 2H, J = 8.8 Hz), 8.10 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 15.9, 46.3, 55.5, 60.3, 61.0, 62.2, 114.7, 121.4, 122.2, 122.6, 126.9, 130.3, 156.7, 157.6, 159.8, 166.6 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 14.0, 15.9, 46.3, 55.5, 61.0, 62.2, 114.7, 122.2, 122.6 ppm. LR−MS (EI) $[M]^+$: 433.

Ethyl [3-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-chloro-6-methyl-2-oxopyrazin-1(2*H*)-yl]acetate 5i. Yield 0.075 g, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.3 Hz), 2.30 (s, 3H), 4.23 (q, 2H, J = 7.3 Hz), 4.77 (s, 2H), 5.45 (s, 2H), 5.50 (s, 2H), 7.26−7.29 (m, 2H), 7.34−7.36 (m, 3H), 7.65 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.8, 46.2, 54.0, 60.9, 62.1, 121.3, 123.9, 126.8, 128.0, 128.6, 128.9, 134.3, 142.5, 150.6, 151.6, 166.5 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 14.0.0, 15.9, 46.2, 54.0, 61.0, 62.2, 124.0, 128.1, 128.6, 129.0 ppm. LR−MS (EI) $[M]^+$: 417.

5-Chloro-3-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-1-phenylpyrazin-2(1*H*)-one 5j. Yield 0.088 g, 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (s, 3H), 5.63 (s, 2H), 7.01 (d, 3H, J = 8.1 Hz), 7.37−7.62 (m, 5H), 7.62 (d, 2H, J = 9.5 Hz), 8.12 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 61.4, 114.7, 120.3, 122.2, 122.5, 112.6, 125.6, 129.2, 129.5, 130.3, 138.6, 142.5, 149.5, 154.5, 159.8 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 56.0, 61.9, 115.2, 120.8, 122.7, 123.1, 126.1, 129.7, 130.0 ppm. LR−MS (EI) $[M]^+$: 409.

3-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-chloro-1-phenyl-2(1*H*)-pyrazinone 5k. Yield 0.087 g, 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (s, 2H), 5.40 (s, 2H), 7.24−7.36 (m, 7H), 7.45−7.56 (m, 4H), 8.22 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.8, 58.0, 119.0, 122.4, 126.4, 126.7, 127.3, 128.4, 129.1, 129.3, 133.2, 141.5, 142.9, 146.9, 149.9, 153.9 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 54.8, 58.0, 119.0, 122.4, 126.4, 126.7, 127.3, 128.4, 129.1, 129.3 ppm. EI-MS: 393 (M^+).

Diels−Alder Reaction of 2-(1*H*)-Pyrazinones 5 a−d: General Procedure. Pyrazinones **5 a−d** (1 equiv) and DMAD (3.5 equiv) were suspended in 2 mL of *ortho*-dichlorobenzene in a 10-mL glass vial containing a small magnetic stirrer. The sample was irradiated at 180 °C for the time specified in Table **3**, using a power level of 200 W. The reaction mixture was cooled to room temperature. Solvents were removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel. The products thus obtained were recrystallized from suitable solvents to obtain analytically pure samples of the corresponding pyridinones **9a−d** and pyridines **10a−d**.

Pyridinone **9a** and pyridine **10a** were synthesized following the general procedure, starting from pyrazinone **5a** (0.091 g, 0.2 mmol) and DMAD (85 μL, 0.70 mmol), irradiating the sample for 6 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the products, which were recrystallized from suitable solvents to obtain analytically pure samples of **9b** (ethanol, 0.097 g, 89%) and **10b** (ethyl acetate, 0.008 g, 10%).

Dimethyl 1-(4-Methoxybenzyl)-5-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-6-oxo-1,6-dihydropyridine-3,4-dicarboxylate (9a). mp 109−111°C. ^{1}H NMR: δ 3.77 (s, 3H), 3.79 (s, 3H), 3.85 (s, 6H), 5.13 (s, 2H), 5.50 (s, 2H), 6.87 (d, 2H, J = 8.0 Hz), 7.0 (d, 2H, J = 8.8 Hz), 7.26 (d, 2H, J = 8.7 Hz), 7.60 (d, 2H, J = 8.8 Hz), 8.01 (s, 1H), 8.06 (s, 1H). ^{13}C NMR: δ 52.8, 53.0, 53.3, 55.7, 56.0, 65.8, 106.7, 114.9 (×2), 115.2 (×2), 122.5, 122.6 (×2), 127.4, 130.2 (×2), 130.9, 132.8, 138.4, 144.0, 144.6, 159.2, 160.2 (×2), 163.6, 165.5. HR-MS (EI): $C_{27}H_{26}N_4O_8$ calcd 534.17506, found 534.17712.

Dimethyl 6-Chloro-2-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}pyridine-3,4-dicarboxylate (10a). mp 69−72 °C. ^{1}H NMR: δ 3.88 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.65 (s, 2H), 7.01 (d, 2H, J = 8 Hz), 7.44 (s, 1H), 7.62 (d, 2H, J = 8 Hz), 8.35 (s, 1H). ^{13}C NMR: δ 50.1, 52.5, 55.6, 60.0, 114.0 (×2), 115.6, 119.3, 122.1 (×2), 122.3, 127.7, 138.5, 154.3, 158.4, 158.7, 158.8, 159.8, 167.0. HR-MS (EI): $C_{19}H_{17}ClN_4O_6$ calcd 432.08366, found 432.08362.

Pyridinone **9b** and pyridine **10b** were synthesized following the general procedure, starting from pyrazinone **5b** (0.085 g, 0.18 mmol) and DMAD (78 μL, 0.64 mmol), irradiating the sample for 20 min. Purification by column chromatog-

raphy (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the products, which were recrystallized from suitable solvents to obtain analytically pure samples of **9b** (ethanol, 0.07 g, 60%) and **10b** (ethyl acetate, 0.018 g, 22%).

Dimethyl 1-(4-Methoxybenzyl)-6-oxo-5-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1,6-dihydropyridine-3,4-dicarboxylate (9b). ^{1}H NMR: δ 3.78 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 5.14 (s, 2H), 5.54 (s, 2H), 6.89 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.97 (d, 2H, J = 8.8 Hz), 8.03 (s, 1H), 8.31 (s, 1H), 8.40 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 52.8, 53.1, 53.4, 53.7, 65.5, 106.7, 114.9, 120.9, 122.3, 125.9, 127.3, 130.2, 130.7, 132.8, 138.5, 141.6, 143.7, 147.6, 159.2, 160.3, 163.6, 165.6. LR−MS (EI) $[M]^+$: 549, 121 (100%).

Dimethyl 6-Chloro-2({1-[4-nitrophenyl]-1*H*-1,2,3-triazol-4-yl}methoxy)pyridine-3,4-dicarboxylate (10b). ^{1}H NMR: δ 3.93 (s, 3H), 3.94 (s, 3H), 5.69 (s, 2H), 7.47 (s, 1H), 7.99 (d, 2H, J = 8.8 Hz), 8.25 (s, 1H), 8.44 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 53.6, 53.8, 61.2, 117.0 (×2), 121.0, 122.4, 126.0, 141.0, 141.4, 145.0, 147.7, 150.1, 159.9, 163.8, 165.7. LR−MS (EI) $[M]^+$: 447 (100%).

Pyridinone **9c** and pyridine **10c** were synthesized following the general procedure, starting from pyrazinone **5c** (0.080 g, 0.17 mmol) and DMAD (74 μL, 0.6 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the products, which were recrystallized from suitable solvents to obtain analytically pure samples of **9c** (ethanol, 0.058 g, 62%) and **10c** (ethyl acetate, 0.014 g, 18%).

Dimethyl 1-(4-Methoxybenzyl)-6-oxo-5-((1-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol 4-yl)methoxy)-1,6-dihydropyridine-3,4-dicarboxylate (9c). ^{1}H NMR: δ 2.98 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 5.13 (s, 2H), 5.32 (s, 2H), 6.84 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.8 Hz), 8.10 (s, 1H), 8.18 (s, 1H). ^{13}C NMR: δ 40.8, 52.2, 52.5, 52.9, 55.4, 64.4, 107.6, 114.6, 118.7, 121.9, 127.1, 128.5, 129.6, 129.8, 130.5, 132.4, 138.2, 138.9, 140.3, 141.5, 158.9, 159.6, 167.8. LR−MS (EI) $[M]^+$: 547, 121 (100%).

Dimethyl 6-Chloro-2({1-[4-(dimethylamino)phenyl]-1*H*-1,2,3-triazol-4-yl}methoxy) pyridine-3,4-dicarboxylate (10c). ^{1}H NMR: δ 3.02 (s, 6H), 3.91 (s, 3H), 3.92 (s, 3H), 5.63 (s, 2H), 6.77 (d, 2H, J = 8.8 Hz), 7.42 (s, 1H), 7.53 (d, 2H, J = 8.8 Hz), 7.98 (s, 1H). ^{13}C NMR: δ 40.4, 53.1, 53.3, 61.3, 112.3, 116.2, 116.6, 122.0, 122.2, 126.6, 140.3, 142.9, 149.7, 150.6, 159.7, 163.5, 165.4. LR−MS (EI) $[M]^+$: 445 (100%).

Pyridinone **9d** and pyridine **10d** were synthesized following the general procedure, starting from pyrazinone **5d** (0.091 g, 0.2 mmol) and DMAD (86 μL, 0.7 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the products, which were recrystallized from suitable solvents to obtain analytically pure samples of **9d** (ethanol, 0.069 g, 64%) and **10d** (ethyl acetate, 0.018 g, 21%).

Dimethyl 1-(4-Methoxybenzyl)-6-oxo-5-((1-(4-(chloro)-phenyl)-1*H*-1,2,3-triazol-4-yl) methoxy)-1,6-dihydropyridine-3,4-dicarboxylate (9d). ^{1}H NMR: δ 3.78 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 5.13 (s, 2H), 5.52 (s, 2H), 6.89 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.68 (d, 2H, J = 8.8 Hz), 8.01 (s, 1H), 8.14 (s, 1H). ^{13}C NMR: δ 52.4, 52.6, 52.9, 55.3, 64.3, 107.6, 114.5, 118.4, 121.7, 126.9, 128.8, 129.8, 129.9, 130.9, 132.3, 138.0, 138.9, 140.5, 141.7, 158.8, 159.7, 167.7 ppm. LR−MS (EI) $[M]^+$: 538, 121 (100%).

Dimethyl 6-Chloro-2({1-[4-(chloro)phenyl]-1*H*-1,2,3-triazol-4-yl}methoxy)pyridine-3,4-dicarboxylate (10d) ^{1}H NMR: δ 3.80 (s, 3H), 3.82 (s, 3H), 5.47 (s, 2H), 6.91 (d, 2H, J = 8.8 Hz), 7.38 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.84 (s, 1H). ^{13}C NMR: δ 52.8, 53.0, 61.2, 112.1, 115.9, 116.2, 122.2, 122.4, 126.3, 140.6, 142.4, 149.5, 150.8, 159.5, 163.2, 165.1. LR−MS (EI) $[M]^+$: 436 (100%).

Pyridinone **9h** and pyridine **10h** were synthesized following the general procedure, starting from pyrazinone **5h** (0.043 g, 0.1 mmol) and DMAD (43 μL, 0.35 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded analytically pure samples of **9h** (0.038 g, 74%) and **10h** (0.007 g, 16%).

Dimethyl 1-[Ethoxy(oxo)ethyl]-5-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-2-methyl-6-oxo-1,6-dihydro-3,4-pyridinedicarboxylate (9h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.3 Hz), 2.34 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 4.20 (q, 2H, J = 7.3 Hz), 4.84 (s, 2H), 5.28 (s, 2H), 7.40 (d, 2H, J = 8.9 Hz), 7.73 (d, 2H, J = 8.9 Hz), 8.81 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 24.3, 46.4, 52.2, 52.3, 55.6, 58.8, 61.5, 61.5, 113.5, 113.9, 120.9, 121.4, 122.1, 127.9, 145.1, 145.9, 149.3, 159.8, 160.6, 166.0, 168.1 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 14.0, 24.3, 46.4, 52.2, 52.3, 55.6, 58.8, 61.5, 61.5, 113.9, 120.9, 122.1 ppm. LR−MS (EI) [M514.

Dimethyl 6-Chloro-2-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-5-methyl-3,4-pyridinedicarboxylate (10h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 5.40 (s, 2H), 7.29 (d, 2H, J = 8.9 Hz), 7.74 (d, 2H, J = 8.9 Hz), 8.60 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 50.0, 52.2, 55.6, 60.0, 113.9, 118.7, 120.4, 122.1, 122.3, 127.7, 140.5, 155.5, 158.7, 159.8, 160.3, 166.5, 166.6 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 17.9, 50.0, 52.2, 55.6, 60.0, 113.9, 122.1, 122.3 ppm. LR−MS (EI) $[M]^+$: 446.

Pyridine **10i** was synthesized following the general procedure, starting from pyrazinone **5i** (0.041 g, 0.1 mmol) and DMAD (43 μL, 0.35 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the analytically pure sample of **10i** (0.032 g, 73%).

Dimethyl 6-Chloro-2-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}pyridine-3,4-dicarboxylate (10i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.64 (s, 2H), 7.02 (d, 2H, J = 8.8 Hz), 7.43 (s, 1H), 7.62 (d, 2H, J = 8.8 Hz), 8.03 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 53.3, 55.6, 61.1, 114.7, 116.3, 116.6, 122.2, 122.3, 130.3, 140.4, 143.2, 149.6, 159.6, 159.9, 163.4,

165.3 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 53.0, 53.2, 55.5, 61.0, 114.7, 116.2, 122.1, 122.5 ppm. LR−MS (EI) $[M]^+$: 432.

Pyridinone **9j** was synthesized following the general procedure, starting from pyrazinone **5j** (0.042 g, 0.1 mmol) and DMAD (43 μL, 0.35 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the analytically pure sample of **9j** (0.035 g, 71%).

Dimethyl 5-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]-1-[ethoxy-(oxo)ethyl]-2-methyl-6-oxo-1,6-dihydro-3,4-pyridinedicarboxylate (9j). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 2.30 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 4.23 (q, 2H, J = 7.3 Hz), 4.84 (s, 2H), 5.10 (s, 2H), 5.45 (s, 2H), 7.27−7.36 (m, 5H), 7.67 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 24.3, 46.4, 52.2, 52.4, 59.2, 61.5, 113.5, 121.3, 121.6, 127.3, 129.2, 129.3, 133.2, 143.0, 145.1, 160.1, 166.0, 166.6, 168.1 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 14.0, 24.3, 46.4, 52.2, 52.4, 59.2, 61.5, 121.6, 127.3, 129.2, 129.3 ppm. LR−MS (EI) $[M]^+$: 498.

Pyridine **10k** was synthesized following the general procedure, starting from pyrazinone **5k** (0.091 g, 0.1 mmol) and DMAD (43 μL, 0.35 mmol), irradiating the sample for 20 min. Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded the analytically pure sample of **10k** (0.032 g, 76%).

Dimethyl 2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-6-chloropyridine-3,4-dicarboxylate (10k). Yield g, %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 3H), 5.23 (s, 2H), 5.45 (s, 2H), 6.98 (d, 2H, J = 8.8 Hz), 7.26−7.37 (m, 5H), 7.43 (s, 1H), 7.62 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.0, 52.5, 54.8, 59.9, 115.6, 119.3, 123.1, 127.3, 129.2, 129.3, 133.2, 138.5, 154.6, 154.8, 158.4, 158.9, 167.2 ppm. DEPT NMR (75 MHz, $CDCl_3$) δ 50.0, 52.5, 54.8, 59.9, 115.6, 123.1, 127.3, 129.3 ppm. EI-MS: 416 (M^+).

5-Chloro-3-ethynyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (3). 3,5-Dichloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one **1a** (0.285 g, 1 mmol), TMSA (0.180 g, 1.9 mmol), palladium bis(triphenylphosphino)dichloride (0.035 g, 0.05 mmol), copper (I) iodide (0.095 g, 0.05 mmol), and TEA/DMF mixture (1:1, 2 mL) were placed in a MW tube and irradiated at a power level of 50 W for 10 min at 82 °C. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with dichloromethane (50 mL × 3) and dried over Na_2SO_4 overnight. After removal of the solvent, the residue was subjected to column chromatography over silica gel (EtOAc/hexane 1:2 mixture as eluent) to afford the intermediate compound (0.325 g, 94%). mp 84−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.23 (s, 9H), 3.82 (s, 3H), 5.01 (s, 2H), 6.92 (d, 2H, J = 8 Hz), 7.16 (s, 1H), 7.29 (d, 2H, J = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1, 52.9, 55.8, 94.7, 102.5, 115.1 (×2), 125.9, 130.9 (×2), 132.4, 149.4, 151.8, 152.9, 156.7. LR−MS (EI) $[M]^+$: 347.

The 5-chloro-1-(4-methoxybenzyl)-3-[(trimethylsilyl)ethynyl]pyrazin-2(1*H*)-one (0.325 g, 0.94 mmol) was dissolved in solvent mixture (MeOH/THF/DCM, 1:1:1, 15 mL) and stirred with tetrabutylammonium fluoride trihydrate (0.442 g, 1.4 mmol, 1.5 equiv) for 15 min at room temperature. The solvent was then partially evaporated, and the residue was partitioned between DCM and water. The aqueous layer was further extracted with DCM (×3), the combined organic layers were dried on $MgSO_4$, and the dry extract was then passed through a short silica gel column. Removal of solvent under reduced pressure furnished an analytically pure sample of **3** as yellowish needles. Yield 0.228 g (89%). mp 52−54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 1H), 3.80 (s, 3H), 4.98 (s, 2H), 6.47 (d, 2H, J = 8.0 Hz), 7.25 (s, 1H), 7.35 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.7, 55.8, 77.7, 79.2, 115.2 (×2), 126.4, 129.5 (×2), 132.5, 146.9, 149.8, 154.3, 159.7. LR−MS (EI) $[M]^+$: 375.

General Procedure for the Preparation of 8a−d,h. 5-Chloro-3-ethynyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one **3** (0.055 g, 0.2 mmol), 4-substituted phenyl azide (0.4−0.5 mmol), *N*,*N*,*N*-tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)-methyl]amine ligand **6** (0.005 g, 4 mol %), copper turnings (0.032 g, 0.5 mmol), and 1 M $CuSO_4$ solution (30 μL) in *t*-BuOH/water/THF mixture (1:1:1, 3 mL) were sealed in a MW tube and irradiated for 8−14 min at 100 °C using a power level of 100 W. After the completion of the reaction, the mixture was treated with water (50 mL) and extracted by DCM (100 mL × 2). Combined organic phases were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography over silica gel (EtOAc/hexane 1:1 mixture as eluent) to afford compounds **8a**−**d**,**h**.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]pyrazin-2(1*H*)-one (8a). Yield 68%. mp 112−114 °C. (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.88 (s, 3H), 5.13 (s, 2H), 7.28 (s, 1H), 7.30 (d, 2H, J = 8.6 Hz), 7.71 (d, 2H, J = 8.5 Hz), 9.09 (s, 1H). ^{13}C (75 MHz, $CDCl_3$): δ 52.7, 55.2, 57.5, 114.8 (×2), 115.9 (×2), 120.1, 121.9 (×2), 127.1 (×2), 127.2, 129.0, 130.5, 143.2, 143.5, 154.8, 158.6, 159.5. LR−MS (EI) $[M]^+$: 424.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]pyrazin-2(1*H*)-one (8b). Yield 27%. mp 189−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 4.8 (s, 2H), 6.47 (d, 2H, J = 8.3 Hz), 7.12 (s, 1H), 7.39 (d, 2H, J = 8.3 Hz), 8.26 (d, 2H, J = 9.2 Hz), 8.43 (d, 2H, J = 9.2 Hz), 8.56 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.7, 55.4, 114.1 (×2), 120.2, 120.9 (×2), 125.4 (×2), 126.1 (×2), 127.3, 129.8 (×2), 130.4, 140.7, 143.2, 143.5, 146.9, 155.8, 156.9, 158.7. LR−MS (EI) $[M]^+$: 428.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-dimethylaminophenyl)-1*H*-1,2,3-triazol-4-yl]pyrazin-2(1*H*)-one (8c). Yield 59%. mp 233−234 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93 (s, 6H), 3.80 (s, 3H), 4.81 (s, 2H), 6.47 (d, 2H, J = 8.3 Hz), 7.11 (m, 3H), 7.37 (d, 2H, J = 8.2 Hz), 8.35 (s, 1H), 8.67 (d, 2H, J = 9.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.4, 52.7, 55.2, 114.1 (×2), 115.4 (×2), 120.2, 122.9 (×2), 126.1 (×2), 127.3, 130.5, 131.7, 143.2, 143.5, 150.2, 155.8, 156.8, 158.7. LR−MS (EI) $[M]^+$: 437.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]pyrazin-2(1*H*)-one (8d). Yield 64%. mp 171−173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 5.01 (s, 2H), 6.42 (d, 2H, J = 8.3 Hz), 7.12 (s, 1H), 7.37 (d, 2H, J = 8.3 Hz), 7.60 (d, 2H, J = 8.4 Hz), 8.26 (d, 2H, J = 8.3 Hz), 8.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.7, 55.3, 114.0 (×2), 120.2, 122.0 (×2), 126.1 (×2),

127.3, 129.8 (×2), 130.5, 133.4, 135.3, 143.2, 143.5, 155.7, 156.7, 158.6. LR−MS (EI) $[M]^+$: 428.

5-Chloro-1-(4-methoxybenzyl)-3-[1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl]pyrazin-2(1*H*)-one (8h). Yield 71%. mp 171−174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.79 (s, 3H), 5.13 (s, 2H), 6.92 (d, 2H, J = 8.3 Hz), 7.12 (s, 1H), 7.40 (m, 4H), 7.86 (d, 2H, J = 8.4 Hz), 8.33 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.7, 55.2, 114.1 (×2), 120.2, 123.5 (×2), 126.1 (×2), 127.2, 132.1 (×2), 137.8, 143.2, 143.5, 155.7, 156.7, 158.6. LR−MS (EI) $[M]^+$: 409.

General Procedure for the Diels−Alder Reaction of 2-(1*H*)-Pyrazinones 8 a,c,d,h. Pyrazinones **8a**,**c**,**d**,**h** (1 equiv) and DMAD (3.5 equiv) were suspended in *ortho*-dichlorobenzene (2 mL) in a 10-mL glass vial containing a small magnetic stirrer. The sample was irradiated for the time as specified in Table 4 using a power level of 200 W and a ceiling temperature of 190 °C. The reaction mixture was cooled to room temperature, solvents were removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel. The products thus obtained were recrystallized from suitable solvents to obtain analytically pure samples of the corresponding pyridinones **11a**,**c**,**d**,**h** and pyridine **12c**.

Dimethyl 1-(4-Methoxybenzyl)-5-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-6-oxo-1,6-dihydropyridine-3,4-dicarboxylate (11a). Pyridinone **11a** was synthesized following the general procedure, starting from pyrazinone **8a** (0.076 g, 0.18 mmol) and DMAD (77 μL, 0.63 mmol). Purification by column chromatography (silica gel, gradient elution from DCM to (8:2) DCM/ethyl acetate) afforded **11a**, which was further recrystallized from ethyl acetate to obtain an analytically pure sample. Yield 0.080 g (88%). mp 72−74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 5.22 (s, 2H), 6.90 (d, 2H, J = 8.3 Hz), 7.01 (d, 2H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.71 (d, 2H, J = 8.2 Hz), 8.29 (s, 1H), 8.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.9, 53.3, 53.7, 55.8, 56.0, 108.1, 115.0 (×2), 115.2 (×2), 118.4, 122.7 (×2), 124.0, 129.8 (×2), 130.0, 130.8, 149.9, 140.8, 142.0, 160.2, 160.3, 160.4, 163.7, 167.4. LR−MS (EI) $[M]^+$: 505.

Dimethyl 5-{1-[4-(Dimethylamino)phenyl]-1*H*-1,2,3-triazol-4-yl}-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridine-3,4-dicarboxylate (11c). Pyridinone **11c** was synthesized following the general procedure, starting from pyrazinone **8c** (0.079 g, 0.18 mmol) and DMAD (77 μL, 0.63 mmol). Purification by column chromatography (silica gel, gradient elution from DCM to (8:2) DCM/ethyl acetate) afforded **11c**, which was further recrystallized from ethyl acetate to obtain an analytically pure sample. Yield 0.035 g (38%). mp 195−197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.07 (s, 3H), 5.02 (s, 2H), 6.90 (d, 2H, J = 9.22 Hz), 7.07 (d, 2H, J = 8.2 Hz), 7.47 (d, 2H, J = 8.2 Hz), 8.13 (s, 1H), 8.56 (d, 2H, J = 9.2 Hz), 8.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.4 (×2), 52.4, 55.2, 55.9, 104.9, 114.3 (×2), 114.7 (×2), 121.6, 122.2 (×2), 126.1, 129.9 (×2), 131.3, 131.7, 139.8, 143.0, 144.9, 150.2, 159.2, 159.2, 161.0, 167.5. LR−MS (EI) $[M]^+$: 518.

Dimethyl 1-(4-Methoxybenzyl)-6-oxo-5-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1,6-dihydropyridine-3,4-dicarboxylate (11d). Pyridinone **11d** was synthesized following the general procedure, starting from pyrazinone **8d** (0.077 g, 0.18 mmol) and DMAD (77 μL, 0.63 mmol). Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded **11d**, which was further recrystallized from ethyl acetate to obtain an analytically pure sample. Yield 0.077 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.75 (s, 3H), 4.12 (s, 3H), 5.24 (s, 2H), 6.89 (d, 2H, J = 8.8 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.8 Hz), 8.12 (s, 1H), 8.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1, 52.3, 53.2, 55.3, 107.1, 114.2, 117.7, 120.6, 123.2, 128.0, 129.7, 130.4, 134.8, 138.9, 139.3, 140.1, 141.4, 159.5, 159.2, 163.1, 166.8. LR−MS (EI) $[M]^+$: 508, 121 (100%).

Dimethyl 1-(4-Methoxybenzyl)-6-oxo-5-[1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl]-1,6-dihydropyridine-3,4-dicarboxylate (11h). Pyridinone **11h** was synthesized following the general procedure, starting from pyrazinone **8h** (0.073 g, 0.18 mmol) and DMAD (77 μL, 0.63 mmol). Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM/ethyl acetate) afforded **11h**, which was further recrystallized from ethyl acetate to obtain an analytically pure sample. Yield 0.071 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 4.07 (s, 3H), 5.20 (s, 2H), 6.89 (d, 2H, J = 8.8 Hz), 7.29 (t, 4H, J = 7.7 Hz), 7.66 (d, 2H, J = 8.8 Hz), 8.29 (s, 1H), 8.96 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.4, 52.8, 53.2, 55.3, 107.6, 114.5, 117.9, 120.3, 123.3, 126.8, 129.5, 130.1, 134.6, 138.7, 139.5, 140.4, 141.6, 159.8, 159.9, 163.3,167.0. LR−MS (EI) $[M]^+$: 488, 121 (100%).

Dimethyl 6-Chloro-2-{1-[4-(dimethylamino)phenyl]-1*H*-1,2,3-triazol-4-yl}pyridine-3,4-dicarboxylate (12c). Pyridine **12c** was synthesized following the general procedure, starting from pyrazinone **8c** (0.079 g, 0.18 mmol) and DMAD (77 μL, 0.63 mmol). Purification by column chromatography (silica gel, gradient elusion from DCM to (8:2) DCM-ethyl acetate) afforded **12c**, which was further recrystallized from ethanol to obtain an analytically pure sample. Yield 0.010 g (14%). mp 195−197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 (s, 6H), 3.87 (s, 3H), 3.93 (s, 3H), 7.02 (d, 2H, J = 9.2 Hz), 8.01 (s, 1H), 8.35 (s, 1H), 8.70 (d, 2H, J = 9.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.4 (×2), 52.4, 52.5, 114.1 (×2), 120.8, 122.5 (×2), 127.6, 129.1, 144.0, 147.1 156.0, 159.9, 159.2, 160.5. LR−MS (EI) $[M]^+$: 416.

General Procedure for the Preparation of 14a−d. Pyrazinone azides **13a**−**d**[18] (0.4 mmol), phenylacetylene (0.1 g, 0.9 mmol), Cu turnings (0.064 g, 1.0 mmol), $CuSO_4$ (1 M solution, 20 μL), and ligand **6** (0.015 g, 6.7 mol %) were dissolved in a *t*-BuOH/THF/water mixture (3:5:2, 2 mL) and stirred at room temperature. After 30 h, the reactions were completed. The reactions mixtures were diluted with water (15 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic phases were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the solid residue was subjected to column chromatography over silica

gel (EtOAc/hexane 1:3 mixture as eluent) to afford compounds **14a**−**d**.

5-Chloro-1-(4-methoxybenzyl)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrazin-2(1*H*)-one (14a). Yield 88%. mp 64−65 °C. ^{1}H NMR(300 MHz, $CDCl_3$): δ 3.84 (s, 3H), 5.18 (s, 2H), 6.95 (d, 2H, J = 8.0 Hz), 7.37 (m, 9H), 7.27 (s, 1H), 7.94 (d, 2H, J = 7.7 Hz), 9.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.3 (×2), 121.2, 127.1 (×2), 127.4 (×2), 129.1, 129.4, 129.4, 129.8 (×2), 130.2, 130.9, 131.1, 140.6, 149.7, 155.4, 157.0. LR−MS (EI) $[M]^+$: 394.

5-Chloro-1-phenyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-pyrazin-2(1*H*)-one (14b). Yield 49%. mp 198−201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.54 (m, 8H), 7.94 (m, 2H), 9.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.2, 124.9 (×2), 126.2 (×2), 126.6 (×2), 127.7, 128.1, 128.6, 129.4 (×2), 134.8, 146.1, 148.2, 148.4, 151.2. LR−MS (EI) $[M]^+$: 350.

5-Chloro-6-(4-methoxyphenyl)-1-phenyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrazin-2(1*H*)-one (14c). Yield 92%. mp 213−216 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 6.80 (d, 2H, J = 8.25 Hz), 7.09 (m, 4H), 7.57 (m, 7H), 7.86 (d, 2H, J = 8.1 Hz), 9.19 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 115.6 (×2), 116.1, 117.9 (×2), 119.8, 126.6 (×2), 128.0 (×2), 128.5, 129.3 (×2), 131.7 (×2), 134.0, 136.6, 143.4, 147.7, 148.5, 152.7, 159.3. LR−MS (EI) $[M]^+$: 456.

Methyl 4-[3-Chloro-6-oxo-1-phenyl-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,6-dihydropyrazin-2-yl]-benzoate (14d). Yield 68%. mp 242−246 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.12 (m, 2H), 7.39 (m, 9H), 7.94 (m, 4H), 9.20 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.9, 116.1, 118.9 (×2), 121.2, 128.1 (×2), 129.0 (×2), 129.3, 130.2 (×2), 130.5 (×2), 131.7 (×2), 133.9, 136.6, 136.8, 143.4, 148.4, 149.0, 152.7, 166.5. LR−MS (EI) $[M]^+$: 484.

General Procedure for the Synthesis of Triazoles 14e−j. 5-Chloro-7-phenyltetrazolo[1,5-*a*]pyrazin-8(7*H*)-one **13b** (100 mg, 0.4 mmol), acetylene (1 mmol, 2.5 eq), Cu turnings (64 mg, 1.0 mmol), $CuSO_4$ (1 M solution, 20 μL), and ligand **6** (0.015 g, 6.7 mol %) were dissolved in a *t*-BuOH/DMF/water mixture (5:3:1, 3 mL) and stirred at room temperature in the sealed tube. After 48 h, the reactions were completed, as indicated by TLC and CI-MS. The reactions mixtures were diluted with water (25 mL) and extracted with dichloromethane (2 × 50 mL), and the combined organic phases were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the solid residue was subjected to column chromatography over silica gel (10% MeOH in EtOAc mixture as eluent) to afford the analytically pure compounds **14e**−**j**.

Ethyl 1-(6-Chloro-3-oxo-4-phenyl-3,4-dihydropyrazin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (14e). mp 89−91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 6.7 Hz), 4.20 (q, 2H, J = 6.8 Hz), 7.06 (s, 1H), 7.47 (m, 5H), 9.62 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.1, 120.9, 125.2, 125.9 (×2), 129.4 (×2), 129.4, 129.5, 130.1, 138.7, 145.3, 149.9, 170.0 ppm. LR−MS (EI) $[M]^+$: 345.

5-Chloro-3-(4-((dimethylamino)methyl)-1*H*-1,2,3-triazol-1-yl)-1-phenylpyrazin-2(1*H*)-one (14f). mp 185−186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 6H), 3.71 (s, 2H), 7.46 (m, 2H), 7.55 (m, 4H), 8.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.4 (×2), 54.3, 124.6, 125.2, 126.0 (×2), 128.0, 130.3 (×2), 130.6, 138.5, 141.5, 145.2, 149.4. LR−MS (EI) $[M]^+$: 330.

5-Chloro-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-1-phenylpyrazin-2(1*H*)-one (14g). mp 138−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (s, 1H), 4.72 (s, 2H), 7.42 (m, 6H), 8.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.1, 56.6, 123.9, 125.1, 126.1 (×2), 128.4, 130.3 (×2), 130.6, 138.5, 141.3, 148.2, 149.5. LR−MS (EI) $[M]^+$: 303.

5-Chloro-3-(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)-1-phenylpyrazin-2(1*H*)-one (14h). mp 175−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (t, 2H, J = 6.9 Hz), 3.30 (br, 1H), 3.80 (t, 2H, J = 6.8 Hz), 7.67 (m, 5H), 8.31 (s, 1H), 9.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 36.8, 123.1, 127.2 (×2), 130.1, 130.3 (×2), 130.3, 130.7, 139.4, 141.8, 150.5, 155.5. LR−MS (EI) $[M]^+$: 317.

5-Chloro-3-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-1-phenylpyrazin-2(1*H*)-one (14i). mp 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (s, 6H), 2.35 (br, 1H), 7.42 (m, 6H), 8.76 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.6 (×2), 68.8, 115.9, 125.3 (×2), 126.1, 128.0, 130.4 (×2), 130.7, 138.5, 146.1, 151.2, 156.7. LR−MS (EI) $[M]^+$: 331.

5-Chloro-3-(4-(2-hydroxybutan-2-yl)-1*H*-1,2,3-triazol-1-yl)-1-phenylpyrazin-2(1*H*)-one (14j). mp 162−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 6.5 Hz), 1.65 (m, 3H), 1.80 (m, 2H), 4.87 (br, 1H), 7.50 (m, 5H), 8.17 (s, 1H), 8.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.7, 29.7, 36.8, 85.32, 123.0, 123.1, 127.4 (×2), 130.1 (×2), 130.3, 130.7, 139.4, 141.8, 150.6, 155.5. LR−MS (EI) $[M]^+$: 345.

General Procedure for Hetero Diels−Alder Reaction of Compounds 14a−c (Scheme 8). Triazolylpyrazinones **14a**−**c** (0.2 mmol), DMAD (0.1 g, 0.7 mmol), and 1,2-dichlorobenzene (2 mL) were placed in a MW tube, and that was sealed. The mixture was irradiated for 15 min at 200 °C and 250 W power. After the removal of 1,2-dichlorobenzene under reduced pressure, the residue was subjected to column chromatography over silica gel (EtOAc/hexane 1:2 mixture as eluent) to afford analytically pure samples of compounds **15a**−**c**.

Dimethyl 6-Chloro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-pyridine-3,4-dicarboxylate (15a). Yield 55% mp 164−165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (s, 3H), 4.05 (s, 3H), 7.46 (m, 3H), 7.96 (m, 3H), 9.11 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 52.5, 109.6, 118.7, 122.2, 126.3 (×2), 127.9 (×2), 128.5, 144.0, 150.2, 155.6, 158.2, 161.9, 162.1. LR−MS (EI) $[M]^+$: 373.

Dimethyl 6-Chloro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-pyridine-3,4-dicarboxylate (15b). Yield 39%. mp 166−167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (s, 3H), 4.05 (s, 3H), 7.46 (m, 3H), 7.96 (m, 3H), 9.11 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 52. 5, 109.6, 118.7, 122.2, 126.3 (×2), 127.9 (×2), 128.5, 144.0, 150.2, 155.6, 158.2, 161.9, 162.1. LR−MS (EI) $[M]^+$: 373.

Dimethyl 6-Chloro-5-(4-methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine-3,4-dicarboxylate (15c). Yield 68%. mp 152−153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 7.56 (m, 6H), 9.01 (s,

1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9 (×2), 55.0, 103.0, 111.4 (×2), 118.7, 119.2, 126.2 (×2), 127.9 (×2), 128.5, 130.7 (×2), 137.1, 140.0, 150.2, 159.6, 163.5, 166.1. LR−MS (EI) $[M]^+$: 479.

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References and Notes

(1) (a) Bourne, Y.; Kolb, H. C.; Radić, Z.; Sharpless, K. B.; Taylor, P.; Marchot, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 1449. (b) Cunha, A. C.; Figueiredo, J. M.; Tributino, J. L. M.; Miranda, A. L. P.; Castro, H. C.; Zingali, R. B.; Fraga, C. A. M.; de Souza, M. C. B. V.; Ferreira, V. F.; Barreiro, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2051. (c) Tullis, J. S.; VanRens, J. C.; Natchus, M. G.; Clark, M. P.; De, B.; Hsieh, L. C.; Janusz, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1665. (d) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053. (e) Al-Masoudi, N. A.; Al-Soud, Y. A. *Tetrahedron Lett.* **2002**, *43*, 4021. (f) Dabak, K.; Akar, A. *Heterocycl. Comm.* **2002**, *8*, 385. (g) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. (h) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9707.

(2) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 4, pp 1−126.

(3) (a) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613. (b) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494. (c) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol 1, Chapter 5. (d) Bastide, J.; Hamelin, J.; Texier, F.; Ven, V. Q. *Bull. Soc. Chim. Fr.* **1973**, 2555. (e) Bastide, J.; Hamelin, J.; Texier, F.; Ven, V. Q. *Bull. Soc. Chim. Fr.* **1973**, 2871.

(4) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Punna, S.; Diaz, D. D.; Li, C.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2004**, *45*, 778. (d) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588. (e) Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609. (f) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113; *Angew. Chem.* **2002**, *114*, 2214. (g) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (h) Löber, S.; Rodriguez, P.-L.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753. (i) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884.

(5) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(6) Hoornaert, G. *Bull. Soc. Chim. Belg.* **1994**, 583.

(7) Vekemans, J.; Pollers-Wieërs, C.; Hoornaert, G. *J. Heterocycl. Chem.* **1983**, *20*, 919.

(8) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125.

(9) Kaval, N.; Van der Eycken, J.; Caroen, J.; Kappe, O.; Dehaen, W.; Strohmeier, G. A.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560.

(10) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211.

(11) Tahri, A.; De Borggraeve, W.; Buysens, K.; Van Meervelt, L.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1999**, *55*, 14675.

(12) Buysens, K. J.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1996**, *52*, 9161.

(13) De Borggraeve, W. M.; Rombouts, F. J. R.; Van der Eycken, E. V.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron Lett.* **2001**, *42*, 5693.

(14) De Borggraeve, W. M.; Rombouts, F. J. R.; Verbist, B. M. P.; Van der Eycken, E. V.; Hoornaert, G. J. *Tetrahedron Lett.* **2002**, *43*, 447.

(15) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951 and references therein.

(16) CEM Corporation. P. O. Box 200 Matthews, NC 28106; Biotage, Hamnesplanaden 5, SH-753 19 Uppsala, Sweden.

(17) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(18) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.

(19) Medaer, B.; Vanaken, K.; Hoornaert, G. *Tetrahedron Lett.* **1994**, *52*, 9767.

(20) For a detailed description of the monomode microwave apparatus, see: Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.

(21) Buysens, K. J.; Vandenberghe, D. M.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron* **1995**, *51*, 12463.

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