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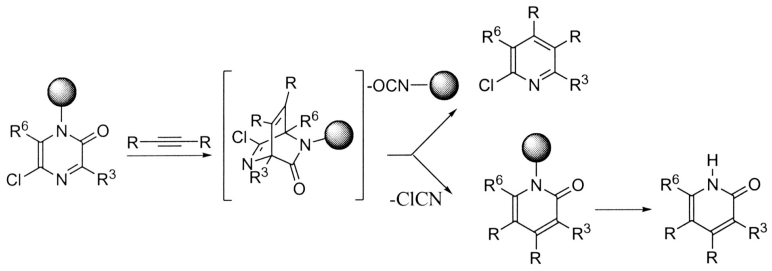

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An Exploratory Study on Microwave-Assisted Solid-Phase Diels−Alder Reactions of 2(1*H*)-Pyrazinones: the Elaboration of a New Tailor-Made Acid-Labile Linker

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Microwave-assisted solid-phase Diels−Alder cycloaddition reactions of 2(1*H*)-pyrazinones with dienophiles are discussed. Separation of the resulting pyridines from the pyridinone byproducts was achieved by applying a traceless-linking concept, whereby the pyridinones remain on the solid support with concomitant release of the pyridine products to solution. As a model study, Wang linker was mimicked in solution using a 4-methoxybenzyl group at the N1 position of the 2(1*H*)-pyrazinone. The sequence was successfully carried out in solution under conventional thermal heating conditions as well as utilizing high-speed microwave irradiation. The results were adapted to polystyrene supports, using various different acid labile linkers, such as Wang resin, HMPB-AM resin, and a novel, tailor-made acid-labile linker based on syringaldehyde, which has been proven in terms of cleavage rates to be superior to both the standard Wang and HMPB-AM linkers. All steps in the solid-phase protocol (linking, cycloaddition, cleavage) were carried out under both thermal and controlled microwave irradiation conditions. In general, significant rate enhancements were found for reactions carried out under high-temperature microwave conditions, reducing reaction times from hours or days to minutes.

Introduction

In the course of the last two decades, our laboratory has explored 3,5-dichloro-2(1*H*)-pyrazinones as interesting starting materials for the elaboration of different types of skeletons of biologically active compounds.[1] A versatile synthesis for these scaffolds has been developed starting from suitable aldehyde and amine building blocks, which upon consecutive treatment with cyanide and oxalyl chloride furnish the desired 2(1*H*)-pyrazinones in moderate to good yields (Scheme 1).[2] This approach allows a wide variation of the substitution pattern of the pyrazinones at the N1- and the C6-position. Various substituents can easily be introduced at the C3-position upon addition/elimination reactions involving the sensitive imidoyl chloride moiety.[1] In addition, we have demonstrated that the Stille cross-coupling procedure constitutes a very mild method to introduce different alkyl and aryl groups at the 3-position.[3,4] The multifunctionalized 2-azadiene system of these heterocycles was used in cycloaddition reactions with electron-rich and electron-poor dienophiles. They easily undergo inter- and intramolecular cycloaddition−elimination reaction with acetylenes (Scheme 1), generating for example, pyridines and pyridinones (ratio dependent on the substitution pattern of the starting 2(1*H*)-pyrazinone),[5] α-carbolines and β-carbolinones,[6] (benzo)furo/pyranopyridines and -pyridinones,[7] pyrrolopyridin(on)es and naphthyridin(on)es.[4] 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 that have been shown to be valuable building blocks for the synthesis of, for example, β-turn mimics[8] and the tricyclic core skeleton of the brevianamide class of natural products.[9]

Therefore, it is apparent that the application of a solid-phase approach to the diverse and rich 2(1*H*)-pyrazinone chemistry outlined above would allow us to take full advantage of combinatorial principles, paving the way for the generation of libraries of many biologically interesting structures. Upon Diels−Alder reaction of a resin-linked 2(1*H*)-pyrazinone **1** with an acetylenic dienophile (Scheme 2), a labile bicyclic adduct **2** would be formed, which could not be isolated[5] and would directly undergo retro-Diels−Alder fragmentation, yielding pyridine **3** upon loss of the resin-linked isocyanate, providing the resin-bound 2(1*H*)-pyridinone **4** upon loss of cyanogen chloride, or both. In comparison with the synthesis in solution, two advantages emerge. From the point of view of the generated pyridine, we are dealing with the concept of "traceless-linking",

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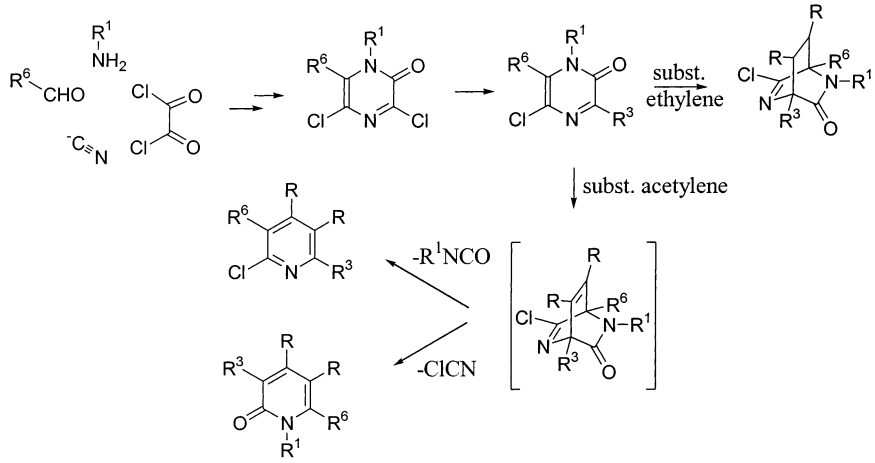
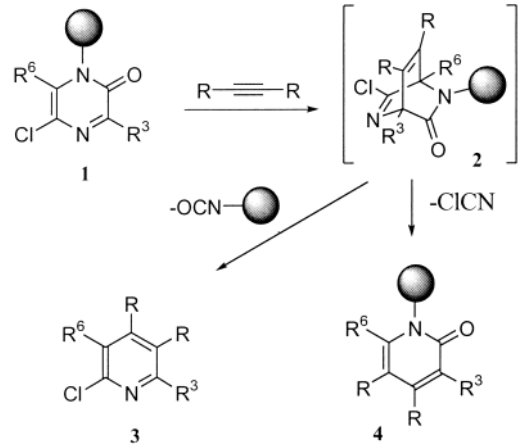
Scheme 1. General Synthesis and Cycloaddition Chemistry of 2(1*H*)-Pyrazinones



Scheme 2. Traceless-Linking Concept for 2(1*H*)-Pyrazinone Diels−Alder Cycloadditions with Acetylenic Dienophiles

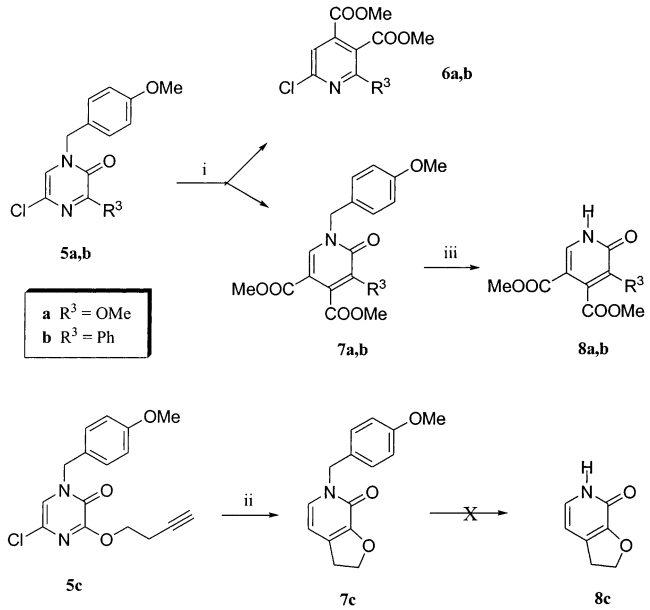


resulting in an easy separation of the pyridine **3** from the 2(1*H*)-pyridinone **4**, which remains linked to the resin. Moreover, the resin-bound 2(1*H*)-pyridinone **4** could easily be purified from the excess of dienophile through simple washing. Although the separation of excess and polymerized dienophile from pyridine **3** could be performed by column chromatography over silica gel, the 2(1*H*)-pyridinones obtained via solution-phase chemistry cannot be purified from the polymerized dienophile via column chromatography.

However, the comparatively long reaction times that are usually required in solid-phase synthesis, owing to the heterogeneous reaction conditions involving insoluble polymer supports, still represent a severe shortcoming as compared to solution-phase synthesis. Since speed is generally recognized as an important factor in high-throughput synthesis and combinatorial chemistry, any technique capable of accelerating the process of solid-phase organic synthesis is of considerable interest. In recent years, an increasing number of reports have been published that advocate the advantages and the use of microwave irradiation for speeding up resin-bound chemistry.[10−14] Therefore we decided to investigate the application of controlled microwave irradiation for our strategy.

Here we present the first successful solid-phase chemistry (linking, Diels−Alder reaction, and cleavage) involving the 2(1*H*)-pyrazinone scaffold. A very detailed comparison for every single step is given between microwave irradiation and conventional heating conditions. Because of the peculiarities of the 2(1*H*)-pyrazinone scaffold and our linking strategy (Scheme 2), we designed a novel, tailor-made, and readily available linker, derived from inexpensive syringaldehyde.

Scheme 3. Solution-Phase Diels−Alder Cycloaddition Reactions of N1-(4-Methoxybenzyl)-2(1*H*)-pyrazinones **5a**−**c**[a]

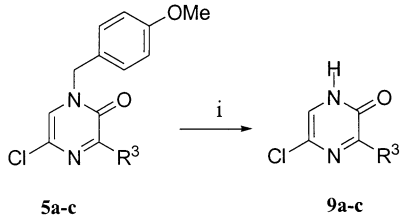


[a] Reagents and conditions: (i) DMAD, chlorobenzene, reflux (132 °C), 17−21 h or DMAD, 1,2-dichlorobenzene, MW, 200 °C, 5−10 min; (ii) bromobenzene, reflux (156 °C), 2 h or 1,2-dichlorobenzene, MW, 220 °C, 8 min; (iii) TFA, reflux (72 °C), 18 h or TFA-DCM (1:2), MW, 120 °C, 20 min.

Results and Discussion

Diels−Alder Reactions of 2(1*H*)-Pyrazinones in Solution Phase. For solid-phase synthesis, 2(1*H*)-pyrazinones can be linked to the acid-labile Wang resin via the amide nitrogen atom (N1), as will be discussed below. For an initial model study, as a "proof-of-concept", we decided to mimic the Wang linker with a 4-methoxybenzyl group at the N1 position, as illustrated for the pyrazinones **5a**−**c** (Scheme 3). At the same time, as will be illustrated below, this would solve the problem of accessing (N1)-unsubstituted 2(1*H*)-

Scheme 4. Deprotection of N1-Benzylated 2(1*H*)-Pyrazinones[a]



5a-c **9a-c**

a R^3 = OMe
b R^3 = Ph
c R^3 = O (CH) CCH

[a] Reagents and conditions: (i) TFA, reflux (72 °C), 6−12 h or TFA/DCM [(1:2) or (1:1)], MW, 120 °C, 10−20 min.

Table 1. Cycloaddition/Retro-Cycloaddition Reaction of the 2(1*H*)-Pyrazinones 5A−c under Conventional Heating and Microwave Irradiation Conditions.

	conventional heating[a]		microwave irradiation[b]	
pyrazinone	temp (°C)/ time (h)	product (% yield)[c]	temp (°C)/ time (min)	product (% yield)[c]
5a	132/17	**6a** (∼2)	200/5	**6a** (∼2)
		7a (44)		**7a** (52)
5b	132/21	**6b** (50)	200/10	**6b** (52)
		7b (30)		**7b** (32)
5c	156/2	**7c** (65)	220/8	**7c** (91)

[a] The intermolecular cycloaddition/retrocycloaddition reactions of **5a,b** with an excess of DMAD under conventional heating conditions were performed in chlorobenzene, and the intramolecular cycloaddition/retro-cycloaddition reaction of **5c** was run in bromobenzene. [b] Microwave irradiation experiments were performed in 1,2-dichlorobenzene. [c] All yields are isolated yields after purification (for details, see the Experimental Section).

pyrazinones **9a**−**c** (Scheme 4) required for coupling to the resin: indeed, although (N1)-substituted derivatives are readily accessible, it is not possible to prepare (N1)-unsubstituted 2(1*H*)-pyrazinones directly via the general strategy outlined in Scheme 1.[1]

(N1)-4-Methoxybenzylated compounds **5a**−**c** can easily be synthesized applying our previously described general procedure for the synthesis of 2(1*H*)-pyrazinones starting from 4-methoxybenzylamine and formaldehyde.[2] The substituents in the 3-position are introduced in an addition−elimination sequence with the appropriate alkoxide[1,15] for **5a** and **5c** or via a Stille coupling reaction[16] for **5b**. Diels−Alder reactions were performed upon heating to reflux (132 °C) of a solution of **5a** or **5b** in chlorobenzene [5,6] and an excess (5 equiv) of dimethyl acetylenedicarboxylate (DMAD) for 17−21 h (Table 1). The intramolecular Diels−Alder reaction of compound **5c** requires the higher boiling solvent bromobenzene[15] (156 °C) and takes 2 h for completion. In the case of **5a** and **5b**, a mixture of pyridines **6a** or **6b** and pyridinones **7a** or **7b**, respectively, is obtained in moderate to good yields, whereas for **5c**, only the dihydrofuropyridinone **7c** is isolated.

For the investigation of the reactions under microwave irradiation conditions, both solvents were replaced with 1,2-dichlorobenzene, because it couples very effectively with microwaves (loss-tangent (tan δ) at 20 °C: 1,2-dichlorobenzene 0.280, as compared to 0.101 for chlorobenzene).[17] Reactions were run in a monomode microwave reactor enabling the rapid and safe irradiation of reaction mixtures in sealed vials under controlled conditions with on-line temperature and pressure monitoring.[18] Using a preselected maximum temperature of 200 °C (observed pressure value is 1.7−1.8 bar), solutions of **5a** and **5b** in 1,2-dichlorobenzene containing an excess of DMAD (5.0 equiv), were irradiated for 5−10 min, resulting in complete conversion of the starting material (Table 1), as indicated by HPLC monitoring. The intramolecular reaction of **5c** was performed at a slightly higher temperature (220 °C; observed pressure value is 1.7−1.8 bar), and completion was reached after 8 min of irradiation. This represents a dramatic reduction of the reaction time, as compared to conventional reflux conditions (Table 1). The yields obtained after microwave irradiation are comparable with those reached after thermal heating for compounds **6a**,**b** and **7a**,**b**, whereas for the dihydrofuropyridinone **7c**, the yield is markedly improved from 65 to 91%. In all cases, a comparable product distribution was observed with and without microwave irradiation (Table 1). Finally, we tried to deprotect the amide nitrogen of pyridinones **7a** and **7b** upon reflux in neat trifluoroacetic acid (TFA) for 18 h. Products **8a** and **8b** were isolated in 73 and 79% yield, respectively. In contrast, upon microwave irradiation at 120 °C for only 20 min, a 1:2 TFA/DCM mixture suffices to deprotect **7a**−**b** (isolated yields 75 and 73%, respectively). Surprisingly, deprotection with either refluxing neat TFA (18 h) or microwave irradiation in neat TFA with a catalytic amount of methanesulfonic acid (20 min) did not work for dihydrofuropyridinone **7c**.

Deprotection of the 2(1*H*)-Pyrazinones. As mentioned above, our planned strategy involved attaching the 2(1*H*)-pyrazinones to the resin via the amide nitrogen atom (N1). Because it is not possible to synthesize directly the required 2(1*H*)-pyrazinones **9a**−**c** bearing a hydrogen at the N1-position,[1] these derivatives have to be prepared by deprotection of the corresponding 2(1*H*)-pyrazinones **5a**−**c** upon reflux in neat TFA for 6−12 h (Scheme 4).[16] Yields vary between 69 and 96% (Table 2). All attempts to use milder conditions, such as, for example, TFA (95%) in dichloromethane (DCM) at room temperature as well as DDQ,[19] failed. In contrast, upon microwave irradiation at 120 °C for 10−20 min, a 1:1 or 1:2 TFA/DCM mixture suffices to deprotect **5a**−**c** (Table 2). The yields are comparable with those obtained under conventional heating conditions. Apart from the milder reaction conditions, this also represents a considerable shortening of the reaction time.

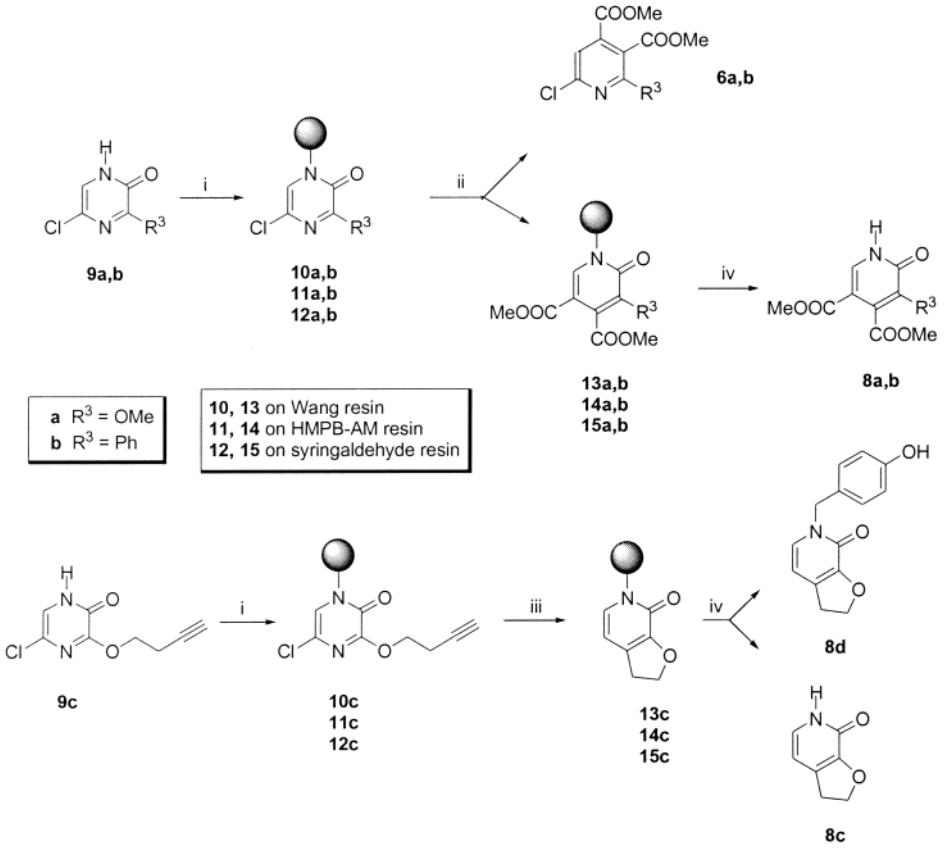
Diels−Alder Reactions of Wang Resin-Bound 2(1*H*)-Pyrazinones. Loading of the Resin. To perform the sequence on a solid phase, our first choice was the commercially available brominated Wang resin. Complete loading (1.2 mmol/g resin; determined by weight upon cleavage) could be obtained upon treatment of the resin with the corresponding 2(1*H*)-pyrazinones **9a**−**c** (3 equiv) and Cs_2CO_3 (4 equiv) in DMF for 6 h at ambient temperature (Scheme 5). The reaction time for complete loading could be shortened to only 5 min upon microwave irradiation at a

Table 2. Deprotection of the 2(1*H*)-Pyrazinones **5a**−**c**

	conventional heating in TFA at reflux (72 °C)		microwave irradiation in TFA/DCM at 120 °C		
pyrazinone	time (h)	product (% yield)[a]	ratio TFA/DCM	time (min)	product (% yield)[a]
5a	12	**9a** (88)	1:2	20	**9a** (87)
5b	12	**9b** (96)	1:2	20	**9b** (93)
5c	6	**9c** (69)	1:1	10	**9c** (62)

[a] All yields are isolated yields after purification (for details, see the Experimental Section).

Scheme 5. Inter- and Intramolecular 2(1*H*)-Pyrazinone Diels−Alder Reactions on Solid Support[a]



[a] Reagents and conditions: (i) resin, Cs_2CO_3, DMF, rt, 6 h or MW, 70 °C, 5 min; (ii) DMAD, chlorobenzene, reflux (132 °C), 1−2 days or 1,2-dichlorobenzene, MW, 220 °C, 20−40 min; (iii) bromobenzene, reflux (156 °C), 2 h or 1,2-dichlorobenzene, MW, 220 °C, 10 min; (iv) for **13a**−**c**: TFA, reflux (72 °C), 20−24 h or for **13a**−**c**, **14a**−**c**, and **15a**−**c**: TFA-DCM (for the ratio see Table 4), MW, 120 °C, 10−40 min.

preselected maximum temperature of 70 °C (150 W maximum power).

Diels−Alder/Retro-Diels−Alder Reactions. To drive the cycloaddition/retrocycloaddition reaction of the resin-bound pyrazinones **10a**−**c** to completion, an excess of the DMAD (5.0 equiv) in chlorobenzene was necessary, and the reaction mixture was heated under reflux (132 °C) for 1−2 days. Microwave-assisted cycloaddition/retrocycloaddition reaction of these substrates was performed in 1,2-dichlorobenzene at higher temperatures (220 °C) but in significantly shorter reaction times (**10a**, 20 min; **10b**, 40 min; **10c**, 10 min) (Scheme 5). Unfortunately, as was the case in solution phase, both upon conventional heating as well as upon microwave irradiation, the thermal polymerization of DMAD is inevitable. However, pyridines **6a**,**b** were easily separated from the polymeric byproducts by passing their dichloromethane solution through a plug of silica gel (see the Experimental Section), and the resin-bound pyridinones **13a**−**c** were washed with TFA (5%) in DCM to remove the polymerized DMAD prior to cleavage.

Cleavage from the Resin. The pyridinones **8a**−**c** could not be released from the resin applying the general standard conditions TFA (95%) in DCM at room temperature. Instead, the corresponding *N*-*p*-hydroxybenzylated pyridinones were obtained. Therefore, the final cleavage of compounds **13a**,**b** was effected with neat TFA under reflux instead of room temperature conditions, affording pyridinones **8a**,**b** in 40 and 28% yield, respectively (Table 3). However, even under these conditions, compound **13c** still yielded only the *N*-*p*-hydroxybenzylated pyridinone **8d** in 55% yield. The product distribution and the yields of the cycloaddition/retrocycloaddition reaction in solution phase and on solid support are comparable (Table 3) (in the case of the intramolecular reaction, we compare **7c** with **8d**). We next tried to perform the cleavage by microwave irradiation. In a mixture of TFA in dichloromethane (1:2) at 120 °C, the reaction was complete after 40 min for pyridinones **8a**,**b**. In the case of **13c**, a mixture of pyridinones **8c** and **8d** was obtained (see Table 4 for an overview). Attempts to use more concentrated

Table 3. Product Distribution after Cycloaddition/Retrocycloaddition Reactions in Solution Phase[a] Compared to Solid Phase[b]

solution phase			solid phase (Wang resin)		
pyrazinone	pyridine yield (%)	pyridinone yield (%)	pyrazinone	pyridine yield (%)	pyridinone yield (%)[c]
5a	**6a** (2)	**8a** (32)	**9a**	**6a** (2)	**8a** (40)
5b	**6b** (50)	**8b** (24)	**9b**	**6b** (49)	**8b** (28)
5c		**7c** (65)	**9c**		**8d** (55)

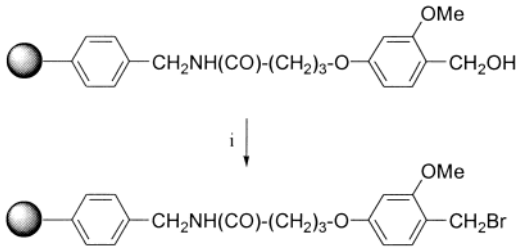
[a] 132 °C, 17−21 h. [b]132 °C, 24−48 h; Wang resin; all yields are isolated yields after purification. [c] Yields are given after cleavage from the resin upon reflux in neat TFA for 20−24 h.

Table 4. Product Distribution and Microwave Cleavage Conditions of Pyridinones from the Three Different Types of Resin at 120 °C

	Wang resin			HMPB-AM resin			Syringaldehyde resin		
	ratio[a]	min	yield (%)[b]	ratio[a]	min	yield (%)[b]	ratio[a]	min	yield (%)[b]
9a	1:2	40	**6a** (~2) **8a** (45)	1:9	10	**6a** (2) **8a** (42)	5:95	10	**6a** (2) **8a** (41)
9b	1:2	40	**6b** (53) **8b** (27)	1:9	10	**6b** (52) **8b** (25)	5:95	10	**6b** (49) **8b** (25)
9c	1:2	40	**8c** (31) **8d** (16)	1:4	20	**8c** (77)	1:9	20	**8c** (67)

[a] Ratio of TFA/DCM. [b] All yields are isolated yields after purification (for details, see the Experimental Section). Diels−Alder/retro-Diels−Alder reactions were performed by microwave irradiation as described.

Scheme 6. Preparation of Brominated HMPB-AM Resin[a]



[a] Reagents and conditions: (i) $SOBr_2$, THF, rt, 6 h.

TFA solutions or longer reaction times resulted in complex reaction mixtures.

Diels−Alder Reactions of HMPB-AM Resin-Bound 2(1*H*)-Pyrazinones. Bromination of the Resin. Because of its *o*-methoxy group, the commercially available HMPB-AM resin is more sensitive toward acidic cleavage conditions than Wang resin. The brominated form of this resin is not commercially available and has to be prepared from the corresponding benzylic alcohol to allow coupling of the 2(1*H*)-pyrazinones with the resin. Although this bromination is described under neutral conditions applying triphenylphosphine and carbon tetrabromide,[20] in our hands, this procedure afforded varying and irreproducible results. Therefore, an alternative procedure was elaborated, applying a large excess of thionyl bromide (10 equiv)[21] in dry tetrahydrofuran for 6 h at room temperature (Scheme 6). Upon treatment of the brominated resin with 2-naphthoic acid diisopropylammonium salt and consecutive cleavage with TFA,[22] it was shown by weight determination of the released compound that the conversion for bromination was >95%.

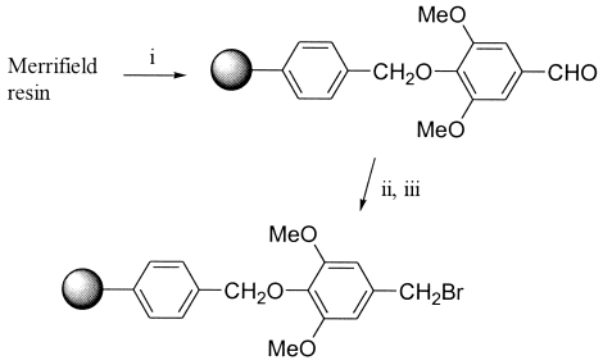
Loading of the Resin. The 2(1*H*)-pyrazinones **9a−c** were coupled with the brominated HMPB-AM resin upon reaction with Cs_2CO_3 in DMF, either at room temperature for 6 h or upon microwave irradiation at 70 °C for 5 min, (150 W maximum power), as described for the brominated Wang resin (Scheme 5). The loading was complete, as determined by weight of the released 2(1*H*)-pyrazinone upon microwave irradiation of a TFA/DCM (1:9) suspension of the derivatized resin at 120°C for 10 min.

Diels−Alder/Retro-Diels−Alder Reactions. The conventional heating conditions as well as the microwave irradiation conditions for the cycloaddition/retrocycloaddition of resin bound compounds **11a−c** with DMAD were the same as described for the sequence using Wang resin. The yields of the pyridines, due to "traceless-linking" directly released in solution, were 2% for **6a** and 52% for **6b** (Table 4). Again, no pyridine is formed upon reaction of **11c**.

Cleavage from the Resin. Attempts to cleave the polymer-bound pyridinones **14a−c** from the resin using different mixtures of TFA in dichloromethane resulted in the formation of several byproducts. In contrast, the microwave-assisted cleavage of pyridinones **14a**,**b** at 120 °C for 10 min proceeded well and required significantly less acidic conditions (TFA/DCM 1:9), as compared to the case of the Wang resin (TFA/DCM 1:2) (Table 4). To our surprise, microwave irradiation of the dihydrofuropyridinone **14c** in a mixture of TFA in DCM (1:4) at 120 °C for 20 min furnished exclusively the desired compound **8c** in 77% yield, without any trace of the hydroxybenzylated pyridinone **8d**. These cleavage conditions are considerably milder, as compared to those applied for the Wang resin, although cleavage of the pyridinone **14c**, resulting from the intramolecular reaction, still requires a significant concentration of TFA.

Diels−Alder Reactions of 2(1*H*)-Pyrazinones Utilizing a "Syringaldehyde-Based Resin" as the Solid Phase. Elaboration of the Resin. To obtain an even more acid labile linker, we decided to develop a tailor-made acid-labile linker based on Merrifield resin derivatized with syringaldehyde. Most commercial acid-sensitive benzylic linkers possess one or two methoxy groups in ortho-position of benzyl group. For steric reasons, this could be disadvantageous for linking the 2(1*H*)-pyrazinones to the resin. We reasoned that this could be circumvented by applying commercially readily available syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) for the construction of the linker. A mixture of Merrifield resin, syringaldehyde (3.0 equiv), Cs_2CO_3, and KI in DMF was heated for 24 h at 60 °C (Scheme 7). The reaction time could be dramatically reduced to 5 min upon microwave irradiation at 200 °C (observed pressure value is 5−6 bar). After workup, the aldehyde moiety was reduced with $NaBH_4$ in THF-methanol (1:1) at room temperature for 12 h. All transformations on the solid-phase were monitored by FTIR analysis, weight determination, or both after cleavage. Finally, the benzylic position was brominated upon treatment with thionyl bromide, as described for the HMPB-

Scheme 7. Preparation of Brominated Syringealdehyde-Based Resin[a]



[a] Reagents and conditions: (i) syringaldehyde, Cs_2CO_3, KI, DMF, 60 °C, 24 h or MW, 200 °C, 5 min; (ii) $NaBH_4$, THF-MeOH, r.t., 12 h; (iii) $SOBr_2$, THF, rt, 6 h.

AM resin (vide supra). The loading of the new resin was determined upon coupling with 2-naphthoic acid diisopropylammonium salt and consecutive cleavage upon reaction with TFA, as described for the brominated HMPB-AM resin.[22] The loading was established to be 0.85 mmol/g resin starting from Merrifield resin.

Loading of the Resin and Diels−Alder/Retro-Diels−Alder Reactions. The coupling of the pyrazinones **9a−c** to this novel support as well as the Diels−Alder/retro-Diels−Alder reactions of resin-bound compounds **12a−c** were performed using analogous conventional and microwave conditions, as described for the Wang resin (Scheme 5). The yields of the pyridines that are directly released in solution were 2% for **6a** and 49% for **6b** (Table 4), with no pyridine being formed upon reaction of **12c**.

Cleavage from the Resin. Here conventional cleavage of the resin-bound pyridinones **15a−c** using different ratios of TFA in dichloromethane gave unsatisfactory results. In contrast, a smooth release from the support could be performed upon microwave irradiation of a suspension of resin-bound **15a**,**b** in TFA/DCM (5:95) at 120 °C for only 10 min (Table 4). For resin-bound pyridinone **15c**, a slightly higher concentration of TFA in DCM (1:9) and an irradiation time of 20 min are required. The very mild cleavage conditions for this new linker (even for compound **15c**), as well as its stability toward different reaction conditions and its easy accessibility from low cost, commercially available Merrifield resin, and syringaldehyde, make this a highly suited linker for our pyrazinone chemistry.

Concluding Remarks

In conclusion, it has been demonstrated that controlled microwave irradiation is very effective in speeding up both the coupling of 2(1*H*)-pyrazinones with an appropriate resin as well as in accelerating the rate of the subsequent solid-phase cycloaddition/retrocycloaddition reactions and the following cleavage processes from the resin. A detailed comparison between conventional heating and microwave irradiation for every reaction step reveals that the microwave technique seems to be advantageous not only to speed up reactions, but also to perform transformations that did not work under conventional heating. It has to be noted that temperatures up to 220 °C were involved in the transformations on polystyrene-based supports, without affecting resin stability.[12] To the best of our knowledge, this sequence is the first case described in the literature in which microwave irradiation has been used for each reaction step in a solid-phase protocol.[23] We assume that here the observed rate enhancements are a consequence of the rapid direct heating of the solvents to high temperatures, and are not due to any nonthermal microwave effect.[11] In addition, on the basis of the concept of "traceless-linking" of the pyridines, the procedure was also proven to be useful for separating the resulting pyridines from the pyridinone products. Moreover, the synthesis on solid supports has been shown to offer an excellent solution to the problem of contamination of the final products with polymeric DMAD. Although the commercially available Wang resin is well suited to perform the cycloaddition/retrocycloaddition reactions of the coupled 2(1*H*)-pyrazinones, the required cleavage conditions are rather harsh, even upon microwave irradiation. We have demonstrated that our novel tailor-made linker derived from Merrifield resin and syringaldehyde is very well suited for the disclosed pyrazinone chemistry. It combines an appropriate chemical stability with very mild cleavage conditions. This "proof-of-concept" study opens the way for further multistep sequences toward the synthesis of biologically interesting compounds starting from polymer-bound 2(1*H*)-pyrazinones. We are currently evaluating Diels−Alder reactions of resin-bound pyrazinones with alkenes as dienophiles, as well as the direct construction of the pyrazinone scaffold on solid support.

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. On-bead FTIR spectra were recorded on an Unicam Galaxy series FTIR 7000 (Mattson Instruments, Inc.) using mashed resin beads in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker WM 250, a Bruker Avance 300, or a Bruker AMX 400 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.

HPLC Analysis. For reaction monitoring and purity control of the synthesized compounds, a Shimadzu LC-10 system was used, including LC10−VT(AP) pumps, an autosampler (Sil-10AXL), and a dual-wavelength UV detector set at 215 and 280 nm. The separations were carried out using a C18 reversed-phase analytical column, LiChrospher

100 (E. Merck, 119 × 3 mm, particle size 5 μm) at 25 °C and a mobile phase composed of (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradients (A/B) were applied at a flow rate of 0.5 mL/min: linear increase from 30 to 100% B in 7 min, and held at 100% solution B for 1 min. Sample preparation was done by diluting ~5 μL of the solution with 0.5 mL of MeCN. Five-microliter portions of the solutions were injected onto the HPLC system.

Microwave Irradiation Experiments. The EmrysSynthesizer (PersonalChemistry AB)[24] was used in the standard configuration as delivered, including proprietary Workflow Manager software (version 2.1).[18] All experiments were carried out in sealed large (10 mL) microwave process vials utilizing the standard absorbance level (300 W maximum power), except where otherwise stated.

General Procedure for the Synthesis of the 2(1*H*)-Pyrazinones 5a−c. The (N1)-4-methoxybenzylated compounds **5a−c** were synthesized according to our previously described general procedure for the synthesis of 2(1*H*)-pyrazinones starting from 4-methoxybenzylamine and formaldehyde.[2] The substituents in the 3-position were introduced in an addition−elimination sequence with the appropriate alcoholate[1,15] for **5a** and **5c** or via a Stille coupling reaction[16] for **5b**.

5-Chloro-3-methoxy-1-paramethoxybenzyl-2(1*H*)-pyrazinone (5a). mp 125 °C (EtOAc). IR (KBr) ν 1659 (CO lactam) cm^{-1}. ^{1}H NMR: δ 3.78 (s, 3H), 3.97 (s, 3H), 4.98 (s, 2H), 6.81 (s, 1H), 6.86 (d, ^3J = 8.8 Hz, 2H), 7.26 (d, ^3J = 8.8 Hz, 2H). ^{13}C NMR: 51.9, 55.7, 55.7, 114.9, 119.0, 123.4, 127.0, 130.6, 150.7, 155.8, 160.3. HR-MS (EI): $C_{13}H_{13}N_2O_3Cl$ calcd. 280.061 47; found 280.061 70.

Spectral data of **5b** were reported earlier.[16]

General Procedure for the Diels−Alder Reactions of the 2(1*H*)-Pyrazinones 5a−c in Solution Phase. (A) Conventional Heating. A mixture of the appropriate 2(1*H*)-pyrazinone **5a**,**b** (0.14 mmol) and DMAD (0.7 mmol) was heated under reflux in chlorobenzene (5 mL) for 17−21 h according to the previously described procedure.[5] The 2(1*H*)-pyrazinone **5c** (0.16 mmol) was heated under reflux in bromobenzene (2 mL) for 2 h.[15] After cooling to ambient temperature, the solvent was evaporated, and the residue was subjected to column chromatography over silica gel (DCM/EtOAc mixtures as eluents) to afford pyridines **6a**,**b** and pyridinones **7a−c**. For the yields and ratios, see Table 1.

(B) Microwave Irradiation. A mixture of the appropriate 2(1*H*)-pyrazinone **5a**,**b** (0.5 mmol) and DMAD (2.5 mmol) in 1,2-dichlorobenzene (2 mL) was irradiated for 5−10 min at 200 °C. The 2(1*H*)-pyrazinone **5c** (0.3 mmol) in 1,2-dichlorobenzene (2 mL) was irradiated for 8 min at 220 °C. After removal of the solvent, the crude reaction mixtures were treated as described under (A). For the yields and ratios, see Table 1.

Dimethyl 6-Chloro-2-phenyl-pyridine-3,4-dicarboxylate (6b). mp 124−125 °C (EtOAc). IR (KBr): ν 1738 (CO ester) cm^{-1}. ^{1}H NMR: δ 3.76 (s, 3H), 3.96 (s, 3H), 7.43−7.45 (m, 3H), 7.58−7.63 (m, 2H), 7.80 (s, 1H). ^{13}C NMR: 52.9, 53.4, 122.1, 127.1, 128.4, 128.5, 129.6, 137.3, 139.2, 152.1, 158.0, 163.8, 167.5. HR-MS(EI): $C_{15}H_{12}NO_4Cl$ calcd. 305.045 49; found 305.045 92.

Spectral data of **6a** were reported earlier.[5]

Dimethyl 3-Methoxy-1-paramethoxybenzyl-2(1*H*)-pyridinone-4,5-dicarboxylate (7a). mp 142−143 °C (EtOAc). IR (KBr): ν 1740 (CO ester), 1663 (CO lactam) cm^{-1}. ^{1}H NMR: δ 3.67 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 5.01 (s, 2H), 6.77 (d, ^3J = 8.8 Hz, 2H), 7.18 (d, ^3J = 8.8 Hz, 2H), 7.97 (s, 1H). ^{13}C NMR: 52.6, 52.7, 53.1, 55.6, 60.7, 106.3, 114.7, 127.5, 130.2, 132.2, 138.4, 145.5, 159.1, 160.1, 163.6, 165.7. HR-MS (EI): $C_{18}H_{20}NO_7$ calcd. 362.123 98; found 362.120 23.

General Procedure for the Diels−Alder Reactions of the Polymer-Bound 2(1*H*)-Pyrazinones 10−12a−c and Consecutive Cleavage of the Pyridinones 13−15a−c from the Resin. (A) Conventional Heating. The procedure was carried out analogously to the previously described procedure for solution phase[5,15] by heating a chlorobenzene suspension (5 mL) of the appropriate 2(1*H*)-pyrazinone **10a**,**b** (0.24 mmol) with DMAD (1.2 mmol, relative to the loading of the resin) under reflux for 24 (**10a**) or 48 h (**10b**) or a bromobenzene suspension (2 mL) of 2(1*H*)-pyrazinone **10c** (0.24 mmol) for 2 h. After cooling to ambient temperature, the resin was filtered off and washed with DCM (5 × 5 mL). The solvents were evaporated, the residue was dissolved in DCM, and the resulting solution was passed through a silica gel plug, affording pure pyridines **6a**,**b**. The resin was washed with TFA/DCM mixture (5:95, 3 × 5 mL) and then with DCM (3 × 5 mL). After drying under vacuum, the resin was suspended in neat TFA (2 mL) and heated under reflux for 20 (**13c**) or 24 h (**13a**,**b**). After cooling, the resin was filtered off and washed with DCM (5 × 5 mL). The solvent was evaporated and coevaporated with acetonitrile, affording **8a** (purity 73%), **8b** (purity 57%), and **8d** (purity 75%). The crude products were recrystallized from EtOAc/DCM mixtures, affording pure pyridones **8a**,**b**,**d**. For the yields and ratios, see Table 3.

(B) Microwave Irradiation. The procedure was carried out analogously to the one described for solution phase, by irradiation of 1,2-dichlorobenzene suspensions of the 2(1*H*)-pyrazinones **10−12a**,**b** with DMAD (5 equiv, relative to resin loading) for 20−40 min at 220 °C or bromobenzene suspensions of pyrazinones **10−12c** for 10 min. Workup and isolation of pure pyridines **6a**,**b** was performed as described under (A). After drying under vacuum, the resin was suspended in a TFA/DCM mixture (ratio indicated in Table 4) and irradiated for 10−40 min at 120 °C, affording **8a−d** (purities after cleavage: **8a**: 75% (Wang), 85% (HMPB-AM), 83% (syringaldehyde); **8b**: 81% (Wang), 79% (HMPB-AM), 84% (syringaldehyde); **8c**: 96% (HMPB-AM), 98% (syringaldehyde)). Workup and purification were performed as described under (A). The yields are indicated in Table 4. The crude mixture of **8c** and **8d** was subjected to column chromatography using MeOH/DCM (1:9) mixture as the eluent.

Dimethyl 3-Methoxy-2(1*H*)-pyridinone-4,5-dicarboxylate (8a). mp 174 °C (MeOH). IR (KBr) ν 1742 (CO ester), 1651 (CO lactam) cm^{-1}.^{1}H NMR ($CDCl_3$−CD_3OD, 3:1): δ 3.75 (br s, 1H), 3.84 (s, 3H), 3.97 (s, 6H), 8.00 (s, 1H). ^{13}C

NMR ($CDCl_3$−CD_3OD, 3:1): 52.1, 52.7, 60.2, 107.1, 133.7, 135.1, 145.1, 160.1, 163.3, 165.4. HR-MS (EI): $C_{10}H_{11}NO_6$ calcd. 241.058 64; found 241.059 28.

General Procedure for the Deprotection of the 2(1*H*)-Pyrazinones 5a−c and the Pyridinones 7a−c. (A). Conventional Heating. A mixture of the appropriate 2(1*H*)-pyrazinone **5a−c** or pyridinone **7a**,**b** (1 mmol) and neat TFA (2 mL) was heated under reflux for 6 (**5c**, Table 2), 12 (**5a**,**b**, Table 2), or 18 h (**7a**,**b**). After cooling to ambient temperature, the solvent was evaporated and coevaporated with acetonitrile. The crude product was subjected to column chromatography over silica gel (EtOAc/DCM mixtures as eluents) to give the deprotected 2(1*H*)-pyrazinone **9a−c** or the pyridinone **8a−b**, respectively. The yields are indicated in Tables 2 and 3. It was not possible to deprotect **7c** applying this procedure; only starting material was recovered.

(B) Microwave Irradiation. To 1 mmol of the appropriate 2(1*H*)-pyrazinone **5a−c** or pyridinone **7a−c** was added 2 mL of TFA/DCM mixture (1:2 for pyrazinones **5a**,**b** and pyridinones **7a−c** and 1:1 for pyrazinone **5c**). The capped process vial was irradiated for 20 min (10 min for **5c**) at 120 °C. After cooling to ambient temperature, the solvent was evaporated, and the crude reaction mixture was treated as described under (A) to afford pyridinones **8a** and **8b** in 75 and 73% yields, respectively. It was not possible to deprotect **7c** applying this procedure; only starting material was recovered. The yields of the pyrazinones **9a−c** are indicated in Table 2.

5-Chloro-3-methoxy-2(1*H*)-pyrazinone (9a). mp 159−160 °C (EtOAc/DCM). IR (KBr) ν 1694 (CO lactam) cm^{-1}. ^1H NMR ($CDCl_3$−CD_3OD, 3:1): δ 4.00 (s, 3H), 6.95 (s, 1H). ^{13}C NMR ($CDCl_3$−CD_3OD): 54.0, 115.9, 123.3, 150.5, 154.7. HR-MS (EI): $C_5H_5N_2O_2Cl$ calcd. 160.003 96; found 160.000 03.

General Procedure for the Preparation of the Resin-Bound 2(1*H*)-Pyrazinones 10−12a−c. (A). Conventional Conditions. Typical Procedure Illustrated for the Brominated Wang Resin. The brominated Wang resin (0.3 g, 0.36 mmol, Novabiochem, loading 1.2 mmol/g, product no. 01-64-0186, lot no. A265254) was swollen in dry DMF (5 mL) for 15 min. Cs_2CO_3 (0.47 g, 1.44 mmol) and the appropriate 2(1*H*)-pyrazinone **9a−c** (1.08 mmol) were added to the suspension, and the mixture was shaken for 6 h at room temperature. The resin was filtered off and washed with DMF−H_2O (1:1, 3 × 5 mL), DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL) and dried under vacuum. The loading was established by weight determination of the released pyrazinone upon heating of the resin in neat TFA for 6 h (conventional conditions) or by microwave irradiation in a TFA/DCM mixture (1:2) at 120 °C for 20 min.

(B) Microwave Irradiation. Typical Procedure Illustrated for the Brominated Wang Resin. A suspension of the brominated Wang resin (0.24 mmol) in dry DMF (2 mL) was stirred for 15 min at room temperature to allow complete swelling of the resin. Cs_2CO_3 (0.96 mmol) and the appropriate 2(1*H*)-pyrazinone **9a−c** (0.72 mmol) were added to the suspension, and the mixture was exposed to microwave irradiation for 5 min at 70 °C. The reaction vessel was allowed to reach ambient temperature. The resin was collected on a filter and treated as described under (A).

General Procedure for the Bromination of the HMPB-AM Resin and the Syringaldehyde-Based Resin.[21] Typical Procedure Illustrated for the HMPB-AM Resin. The HMPB-AM resin (0.30 g, 0.162 mmol; Novabiochem, loading 0.54 mmol/g, product no 01−64−0362, lot no A23459) was suspended in dry THF (3 mL). The slurry was cooled under argon to 0 °C, and thionyl bromide (0.125 mL, 1.6 mmol) was added dropwise. The resulting suspension was shaken for 6 h at room temperature. The resin was filtered off and successively washed with dry THF (5 × 5 mL) and DCM (5 × 5 mL) to give the brominated resin ready to use. Determination of loading was performed by treatment of the brominated resin with 2-naphthoic acid diisopropylammonium salt and consecutive cleavage with TFA as described.[22] It appeared to be 0.52 mmol/g for HMPB-AM resin and 0.85 mmol/g for syringaldehyde-based resin.

Preparation of the Syringladehyde-Based Resin. Merrifield resin (0.3 g, 0.51 mmol; Fluka, loading 1.7 mmol/g, product no. 63866-506-F, lot no. 0100657843) in dry DMF (3 mL) was stirred with 0.279 g (1.53 mmol) of syringaldehyde and 0.665 g (2.04 mmol) of Cs_2CO_3 in the presence of KI (8.5 mg, 0.051 mmol) for 24 h at 60 °C. The resin was filtered off and washed consecutively with DMF−H_2O (1:1, 3 × 5 mL), DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL). The reaction was followed by FTIR. The loading was established by weight determination of the released pyrazinone upon microwave irradiation of the resin in a mixture of TFA/DCM (1:1) at 120 °C for 30 min and appeared to be quantitative. After drying under vacuum, the resin was suspended in a mixture of THF-MeOH (1:1, 3 mL) and treated with $NaBH_4$ (0.12 g, 3.17 mmol) for 12 h at room temperature. The reaction was followed by FTIR. The resin was filtered off and washed carefully with THF−H_2O (1:1, 3 × 5 mL) and THF (3 × 5 mL), then suspended in a THF−1 M HCl mixture (1:1, 2 mL) and gently stirred for 40 min. The white product was filtered off, washed with THF−H_2O (1:1, 3 × 5 mL) and THF (3 × 5 mL) and brominated with 0.2 mL of thionyl bromide, as described for HMPB-AM resin.

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Supporting Information Available. Spectroscopic data are available for the following compounds: the 2(1*H*)-pyrazinones **5c**, **9b−c**, the substituted pyridinones **7b−c**,

8b−**d**, and the intermediates in the synthesis of the syringaldehyde-based resin. This material is available free of charge via the Internet at http://pubs.acs.org.

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