Pyrazole, Pyridine and Pyridone Synthesis on Solid Support

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Abstract: Versatile solid-phase syntheses of trisubstituted pyrazole carboxylic acids, trisubstituted pyridines and disubstituted pyridones are presented. Pyrazoles are prepared by reaction of polymer bound arylidene- or alkylidene-ß-oxo esters with phenylhydrazines. Pyridines result from the Kröhnke reaction of immobilised enones with 1-(2-oxo-2-arylethyl)pyridinium salts and ammonium acetate. Pyridones are obtained from polymer bound enones, 1-(methoxycarbonylmethyl)pyridinium bromide and ammonium acetate.

Key words: pyrazoles, pyridines, pyridones, solid-phase synthesis, combinatorial chemistry

Introduction

Combinatorial chemistry, high-throughput synthesis and screening have been established as key technologies in the lead discovery and lead optimisation process.[1] Recently the combinatorial approach has also received increasing attention in topics outside medicinal chemistry. For example, it has been successfully applied in material science,[2] heterogeneous[3] and homogeneous catalysis. [4]

The most advanced synthetic technique for preparing compound libraries is solid-phase synthesis.[1d,5] Working on a solid support facilitates the multiple parallel synthesis of both single compounds and compound collections in the format of defined mixtures.

Due to their conformational constraints and their wide range of properties, heterocyclic systems play an essential role as scaffolds of potentially active compounds. Enones represent important educts in this field since they can be converted into a wide range of heterocycles. Therefore we decided to use polymer bound enones as substrates for the preparation of pyrazoles, pyridines and pyridones. Two structurally different types of enones were used (Figure 1).

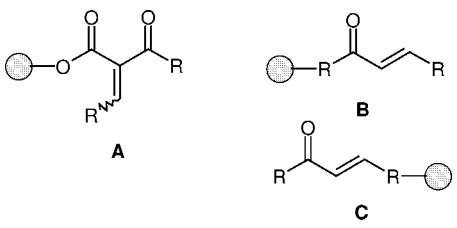


Figure 1

Starting from arylidene- or alkylidene-β-oxo esters **A**, trisubstituted pyrazole carboxylic acids were formed upon treatment with phenylhydrazines. Diaryl substituted enones **B** and **C** served as educts for the pyridine and pyridone syntheses.

Pyrazoles

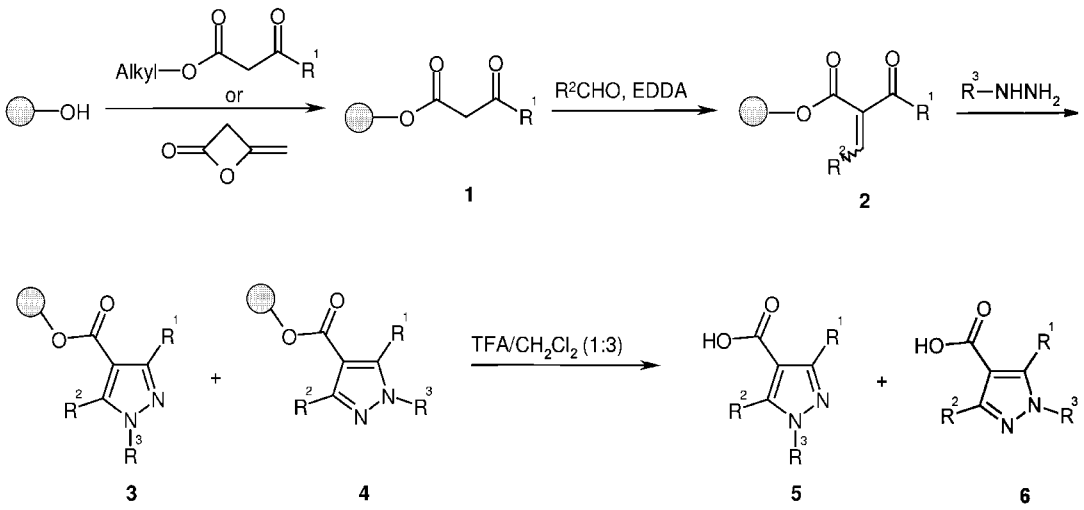
The pyrazole scaffold occurs in several biologically active compounds, for example COX-2 inhibitors[6] and antimicrobial pyrrolnitrin analogues[7] and therefore represents an interesting target for combinatorial chemistry.

Several solid-phase pyrazole syntheses have been previously reported.[8] However, in none of these pathways are pyrazole carboxylic acids formed, which are potential synthons for convergent combinatorial strategies.

In our approach these scaffolds were obtained by starting from alkylidene- and arylidene-β-oxo esters **2** (Scheme 1). In the first step resin bound β-oxo esters **1** were prepared either by transesterification of methyl or ethyl β-oxo carboxylates with Wang resin in NMP under DMAP catalysis or in the case of acetoacetic acid ester via acetoacetylation with diketene in CH_2Cl_2 under DMAP catalysis. The following Knoevenagel reaction with aliphatic and aromatic aldehydes resulted in the formation of 2-alkylidene- and 2-arylidene-β-oxo esters **2**. In the case of aromatic aldehydes catalytic amounts of ethylenediamine diacetate (EDDA) in DMF/pyridine (4:1) were used for the condensation step. Milder conditions were applied for aliphatic aldehydes, which were reacted following a protocol of Tietze et al.[9] (cat. EDDA in CH_2Cl_2 at room temperature). Cyclisation with phenylhydrazine hydrochlorides and subsequent cleavage with TFA/CH_2Cl_2 (1:3) led to trisubstituted pyrazole-4-carboxylic acids **5** and **6**.

The cyclisation step can result in the formation of two regioisomers. This is due to two mechanistic pathways (Scheme 2). Under basic conditions Michael addition of the phenylhydrazine to the enone is favoured, followed by a condensation and subsequent aromatisation step (**4**). Basic conditions (DIEA in NMP, 70 °C) were used in the standard procedure for the regioselective synthesis of one hundred pyrazoles **6**. Some representative examples are shown in Table 1. Figure 2 shows the structures of two pyrazole carboxylic acids.

For comparative NMR studies of the two regioisomers we also established a synthesis of regioisomer **5**. A two step procedure was used. Acidic treatment of the polymer bound enone **2** with a phenylhydrazine hydrochloride pro-



Scheme 1

Table 1 Solid-Phase Synthesis of Pyrazole Carboxylic Acids

Entry	R^1	R^2	R^3	Method	Purity[a] (%)	Yield[b] (%)
6a	CH_3-	4-CF_3-C_6H_4-	C_6H_5-	A	77	41
6b	CH_3-	4-NO_2-C_6H_4-	C_6H_5-	A	90	49
6c	CH_3-	4-NO_2-C_6H_4-	4-MeO-C_6H_4-	A	73[c]	52
6d	CH_3-	3-OH-4-NO_2-C_6H_3-	C_6H_4-	A	84	52
6e	CH_3-	3-MeO-C_6H_4-	4-MeO-C_6H_5-	B	64[d]	43
6f	CH_3-	EtOOC-	C_6H_5-	A	83	57
6g	CH_3-	$C_6H_5CH_2CH_2$-	C_6H_5-	B	75	61
6h	C_2H_5-	4-Pyridyl-	4-Cl-C_6H_4-	B	88	41
6i	$CH_3CH_2CH_2$-	3-OH-4-NO_2-C_6H_3-	C_6H_5-	A	91	44
6j	$(CH_3)_2CH$-	4-Br-C_6H_4-	4-MeO-C_6H_4-	A	87	40
6k	$(CH_3)_2CH$-	4-CF_3-C_6H_4-	3,4-Me_2-C_6H_3-	A	91	42
6l	C_6H_5-	4-CF_3-C_6H_4-	C_6H_5-	A	89	32
6m	C_6H_5-	3-Pyridyl-	4-Br-C_6H_4-	A	79	48

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin
[c] 16 % of regioisomer **5c**
[d] 9 % of regioisomer **5e**

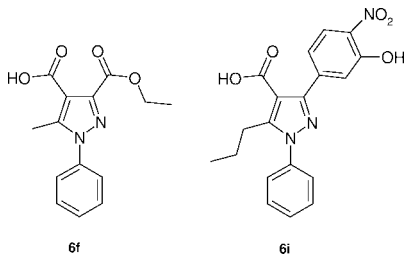


Figure 2

vided the hydrazone. Cyclisation and aromatisation were achieved by heating the hydrazone with DBU in DMF (Scheme 2). This pathway has not been fully optimised yet. Therefore only the data of those pyrazoles **5** which were synthesised for the NOE experiments are shown in Table 3.

The identity of the regioisomers **5** and **6** was proven by NOE difference spectroscopy for compounds **5a**, **5b**, **6a**, and **6b**. Irradiation of the resonance frequency of the protons H-2' led to the enhancement of the signal of the pro-

Table 2 High Resolution ES-FT-ICR-MS Analysis of Pyrazole Carboxylic Acids

Entry	Molecular Formula	m $(M+H)_{calculated}$	m $(M+H)_{measured}$	Δm	ppm	Hits
6a	$C_{18}H_{13}F_3N_2O_2$	347.100180	347.100934	0.000754	2.172	1
6b	$C_{17}H_{13}N_3O_5$	324.097872	324.098406	0.000534	1.648	1
6c	$C_{18}H_{15}N_3O_5$	354.108435	354.108835	0.000400	1.130	1
6d	$C_{17}H_{13}N_3O_5$	340.092786	340.093374	0.000588	1.729	1
6e	$C_{19}H_{18}N_2O_4$	339.133922	339.134232	0.000310	0.914	1
6f	$C_{14}H_{14}N_2O_4$	275.102623	275.102657	0.000034	0.124	1
6g	$C_{19}H_{18}N_2O_2$	307.144093	307.144086	0.000007	0.023	2
6h	$C_{17}H_{14}ClN_3O_2$	328.084721	328.084668	0.000053	0.162	2
6i	$C_{19}H_{17}N_3O_5$	368.124084	368.124820	0.000736	1.999	1
6j	$C_{20}H_{19}BrN_2O_3$	415.065168	415.064605	0.000563	1.356	9
6k	$C_{22}H_{21}N_2O_2$	403.162777	403.161771	0.001030	2.495	2
6l	$C_{23}H_{15}F_3N_2O_2$	409.115829	409.115941	0.000112	0.274	2
6m	$C_{21}H_{14}BrN_3O_2$	420.034204	420.033174	0.001030	2.452	8

Table 3 Selective Formation of Regioisomers **5**

Entry	R^1	R^2	R^3	Purity[a] (%)	Regioisomer **6** (%)	Yield[b] (%)
5a	CH_3-	4-CF_3-C_6H_4-	C_6H_5-	62	3	71
5b	CH_3-	4-NO_2-C_6H_4-	C_6H_5-	64	9	67

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin

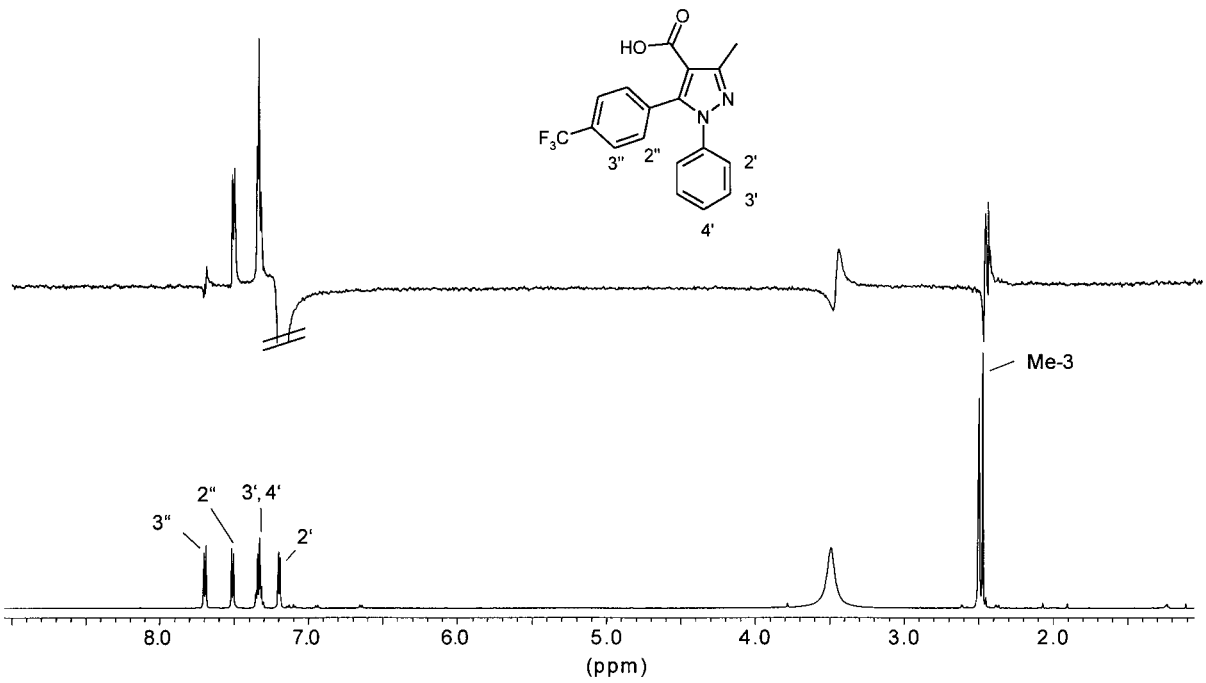


Figure 3a

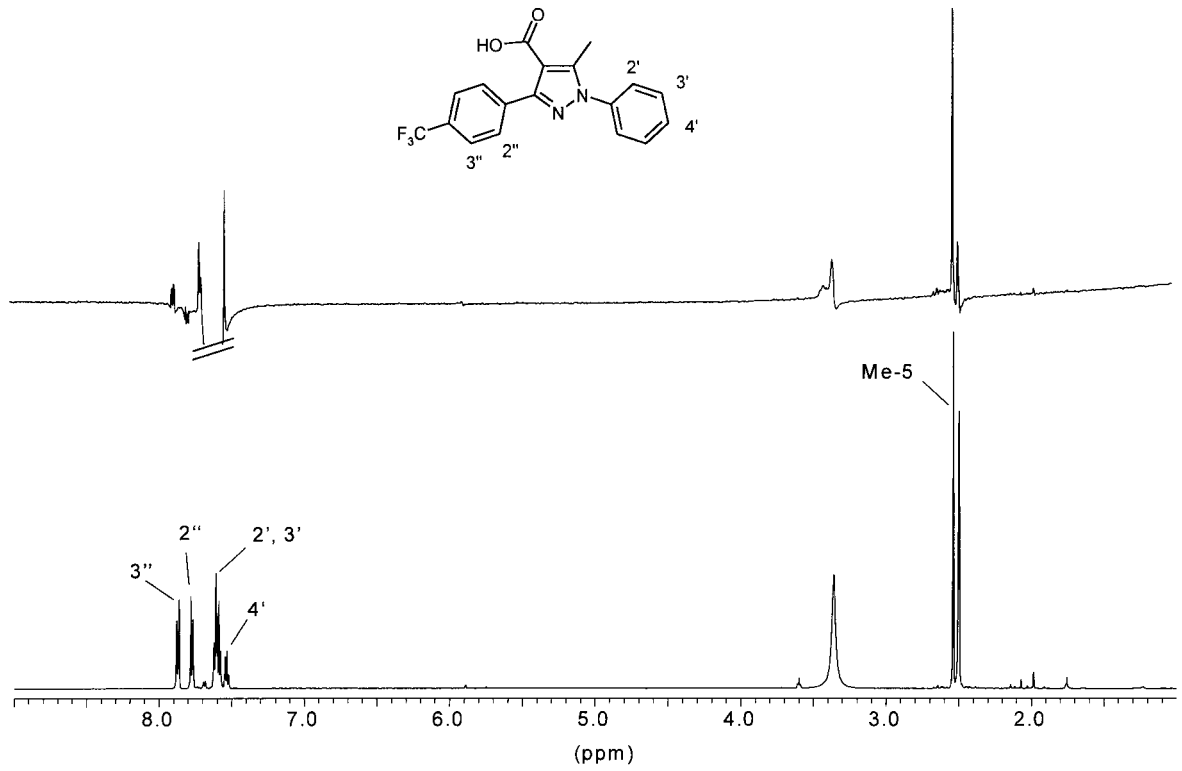
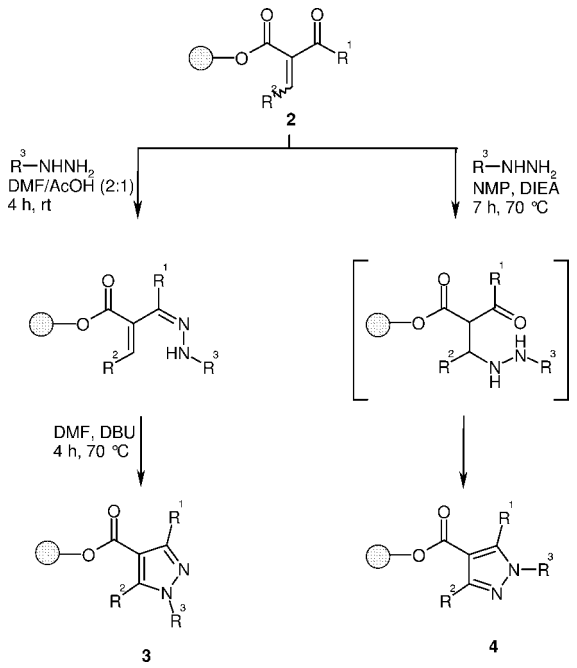


Figure 3b

tons H-2" in the case of regioisomers **5** (Figure 3a), whereas for regioisomers **6** an enhancement of the signal of the methyl protons Me-5 was observed (Figure 3b).

All compounds were analysed by analytical HPLC and ES-FT-ICR-MS. ES-FT-ICR-MS offers the advantages of very low sample consumption, high throughput analysis, high resolution, high mass accuracy and the possibility to determine the molecular formula of the analysed compound.[10] A further advantage is that the elemental composition of crude products can be determined, so that a time consuming purification step is not necessary. In the case of the pyrazoles **6** the proof of the elemental composition by FT-ICR-MS data was exemplified. The results are summarised in Table 2. The hits represent the number of possible molecular formulae by taking the exclusion rules (nitrogen rule, double bound rule, valences) into account.

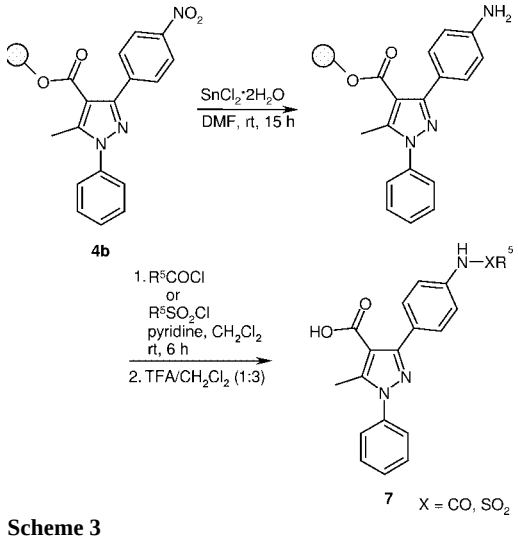


Scheme 2

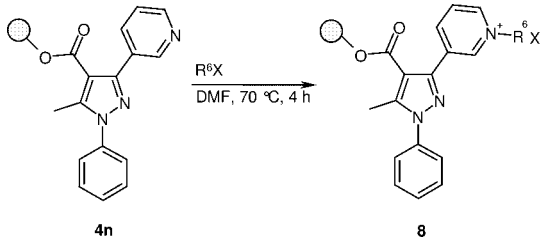
Postmodification of Immobilised Pyrazoles

Additional structural diversity was introduced via acylation, sulphonylation or alkylation of suitable polymer bound pyrazoles. For this purpose nitrophenyl or pyridyl substituted pyrazoles are applicable. The nitro group was reduced with 2 M $SnCl_2 \cdot 2H_2O$ in DMF and the resulting amino function was acylated or sulfonylated with carboxylic acid chlorides or sulfonyl chlorides, respectively, at room temperature in dichloromethane in the presence of pyridine as base. As an example the reduction and acylation of polymer bound 5-methyl-3-(4'-nitrophenyl)-1-phenylpyrazole-4-carboxylic acid **4b** is shown (Scheme 3).

Pyridinium substituted pyrazoles **8** were obtained by treatment of **4n** with alkylating reagents in DMF at 70 °C



Scheme 3



Scheme 4

(Scheme 4). To demonstrate the possibility of this modification we used polymer bound acetoacetic acid, pyridine-3-carboxaldehyde and phenylhydrazine hydrochloride for the pyrazole formation and ethyl iodide, methyl bromoacetate and 4-nitrobenzyl bromide for the pyridine *N*-alkylation.

The results of the postmodifications are presented in Table 4.

Table 4 Alkylation and Acylation/Sulfonylation of Pyrazole Derivatives

Entry	Educt	Acylation/Sulfonylation/ Alkylating reagent	Purity[a] (%)	Yield[b] (%)
7a	**4b**	pivaloyl chloride	83	58
7b	**4b**	benzoyl chloride	70	52
7c	**4b**	methanesulfonyl chloride	82	63
8a	**4n**	ethyl iodide	83	44[c]
8b	**4n**	methyl bromoacetate	85	44[c]
8c	**4n**	4-nitrobenzyl bromide	74	47[c]

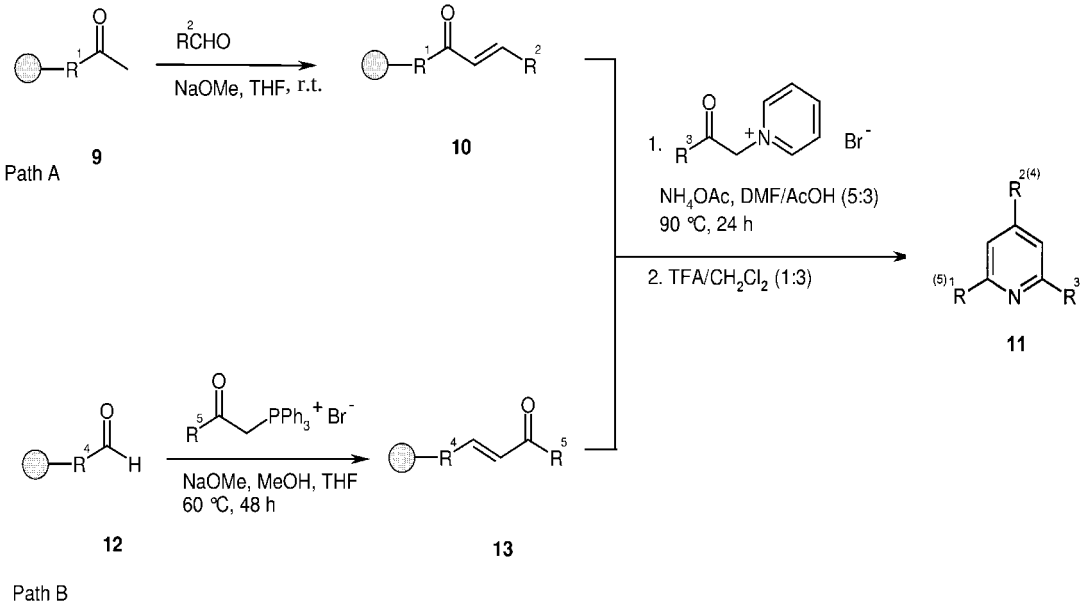
[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin
[c] trifluoroacetate as anion

Pyridines

Dihydropyridines and pyridines have recently attracted the attention of solid-phase chemists.[11] In the second part of our contribution we present a novel three step solid-phase pyridine synthesis following the route first described by Kröhnke,[12] which includes the Michael type addition of 1-(2-oxo-2-arylethyl)pyridinium salts to enones followed by cyclisation with ammonium acetate under formation of the pyridine ring. In each reaction step a variable substituent is introduced via commercially available or easily accessible building blocks. From a combinatorial point of view, this reaction allows the preparation of a complex and diverse pyridine library. Furthermore, diaryl substituted pyridones[13] were obtained by treatment of polymer bound enones with 1-(methoxycarbonylmethyl)pyridinium bromide and ammonium acetate.

The synthesis was performed using Wang Bromo PS in the case of hydroxy functionalised educts or Rink Amide PS in the case of carboxy functionalised educts. In order to increase the diversity of the enones two pathways were followed (Scheme 5). Path A uses polymer bound acetophenones **9** which were condensed with aromatic and heteroaromatic aldehydes to afford enones **10**. The Knoevenagel condensation was performed in THF using NaOMe (0.5 M in MeOH) as base at room temperature.[14] Reaction time and base concentration were adapted to the electronic properties of the corresponding building blocks. Path B utilises immobilised aldehydes **12** which were converted in a Wittig reaction into enones **13** upon treatment with 1-(2-oxo-2-arylethyl)triphenylphosphonium bromide and sodium methylate. The phosphonium bromides were obtained by reaction of α-bromo ketones with triphenylphosphane according to a literature procedure.[15] Enones **10** and **13** were then reacted with pyridinium salts (Scheme 5: R^3 = aryl, heteroaryl) and ammonium acetate to form pyridines **11**. The pyridinium salts were obtained by reaction of the respective α-bromo ketones with pyridine. The pyridinium salts may also be generated by treatment of the corresponding acetyl compounds with iodine and pyridine.[16]

The cyclisation conditions were optimised by using resin bound 4**'**-hydroxychalcone and phenacylpyridinium bromide. The choice of solvent is of particular importance. In solution phase cyclisation is commonly performed in glacial acetic acid. When we performed the solid-phase reaction in this solvent almost no product was formed, even after heating for 24 h at 90 °C. Changing to neat DMF as solvent led to nearly complete conversion of the intermediate Michael adduct **14** to a byproduct **15** which is formed through cleavage of the benzoyl residue (Scheme 6). The best results were obtained with a mixture of DMF and acetic acid (5:3) (Table 5). After cleavage from the resin with TFA/CH_2Cl_2 2,4,6-trisubstituted pyridines were obtained in good purity. Table 6 shows some representative results of the solid-phase Kröhnke reaction.



Scheme 5

Table 5 Influence of the Solvent in the Solid-Phase Kröhnke Pyridine Synthesis

Solvent	Educt (%)	Pyridine **11** (%)	By-product **15** (%)
HOAc	79	9	–
HOAc/DMF 3:1	54	36	–
HOAc/DMF 5:3	38	54	–
HOAc/DMF 1:1	10	82	1
HOAc/DMF 3:5	2	91	1
HOAc/DMF 1:3	1	88	2
DMF	–	11	65

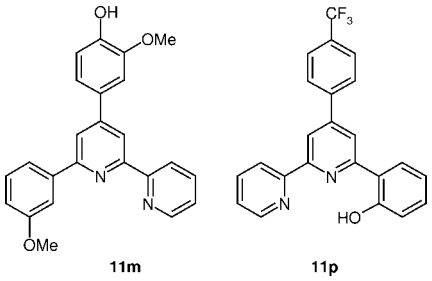
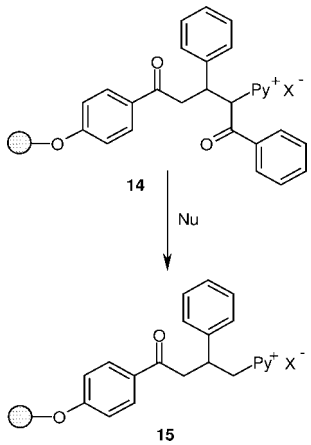


Figure 4



Scheme 6

Bipyridines and Terpyridines

Bipyridines and terpyridines are well known as ligands of metal ions.[17] Both classes of compounds can be obtained via our solid-phase pyridine synthesis described above. Bipyridines are accessible via two pathways. The first pathway starts from polymer bound enones **10** which are then converted to bipyridines upon treatment with 1-[2-oxo-2-(pyrid-2'-yl)ethyl]pyridinium iodide. This compound was synthesised in an Ortoleva-King reaction[16] of 2-acetylpyridine.

In a second approach resin bound aldehydes were treated with 1-[2-oxo-2-(pyrid-2'-yl)ethyl]phosphonium bromide in a Wittig reaction resulting in pyridyl substituted enones. This phosphonium bromide was synthesised by bromination of 2-acetylpyridine[18] and subsequent substitution with triphenylphosphane. The following Kröhnke reaction with 1-(2-oxo-2-arylethyl)pyridinium salts provided bipyridines. Figure 4 shows two representative structures of the bipyridine syntheses. The use of 1-[2-oxo-2-(pyrid-2'-yl)ethyl]pyridinium iodide led to the formation of terpyridines. Two examples are shown in Figure 5.

Table 7 shows representative results of the bi- and terpyridine synthesis.

We also applied the Kröhnke pyridine synthesis to the modification of polymer bound amino acids. Fmoc-amino

Table 6 Solid-Phase Synthesis of Pyridines

Entry	R^1, R^5	R^2, R^4	R^3	Path	Purity[a]	Yield[b]
11a	4-OH-3-MeO-C_6H_3-	2-Thienyl-	3,4-Cl_2-C_6H_3-	A	77	74
11b	4-OH-C_6H_4-	4-NO_2-C_6H_4-	4-F-C_6H_4-	A	89	78
11c	3-OH-C_6H_4-	3,4,5-$(MeO)_3$-C_6H_2-	2,5-$(MeO)_2$-C_6H_3-	A	78	74
11d	4-NO_2-C_6H_4-	4-$(CONH_2)$-C_6H_4-	C_6H_5-	B	92	82
11e	4-Cl-C_6H_4-	3-$(CONH_2)$-C_6H_4-	C_6H_5-	B	97	78
11f	4-Cl-C_6H_4-	3-OH-C_6H_4-	C_6H_5-	B	96	72
11g	3-MeO-C_6H_4-	2-OH-3-MeO-C_6H_3-	C_6H_5-	B	87	85
11h	C_6H_5-	3,5-Cl_2-2-OH-C_6H_2-	C_6H_5-	B	88	72
11i	2-Naphthyl-	4-OH-3,5-$(MeO)_2$-C_6H_2-	C_6H_5-	B	89	68

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin

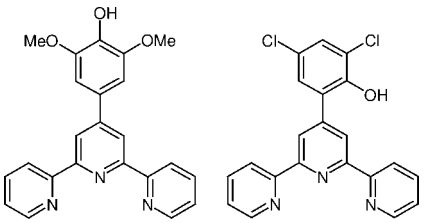


Figure 5

acids were coupled to Rink Amide PS resin using DIC, HOBt in DMF. After cleavage of the Fmoc-group the amino function was acylated with 3- or 4-carboxybenzaldehyde. The following steps were performed as described above. Table 8 shows the corresponding results. Figure 6 shows a lysine based bis(bipyridine).

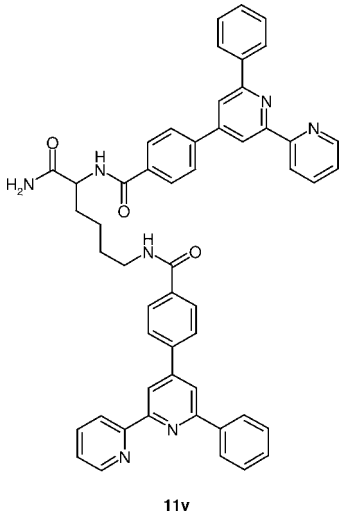


Figure 6

Table 7 Solid-Phase Synthesis of Bipyridines and Terpyridines

Entry	R^1	R^2	R^3	Path	Purity[a]	Yield[b]
11j	2-Pyridyl-	4-OH-3,5$(MeO)_2$-C_6H_2-	2-Pyridyl-	B	85	69
11k	2-Pyridyl-	2-OH-3,5-Cl_2-C_6H_2-	2-Pyridyl-	B	95	54
11l	2-Pyridyl-	3-$CONH_2$-C_6H_4-	2-Pyridyl-	B	95	81
11m	2-Pyridyl-	4-OH-3-MeO-C_6H_3-	3-MeO-C_6H_4-	B	88	64
11n	2-Pyridyl-	3-OH-C_6H_4-	C_6H_5-	B	94	71
11o	2-Pyridyl -	2-OH-3,5-Cl_2-C_6H_2-	C_6H_5-	B	98	79
11p	2-OH-C_6H_4-	4-CF_3-C_6H_4-	2-Pyridyl-	A	90	71
11q	2-OH-C_6H_4-	4-MeO-C_6H_4-	2-Pyridyl-	A	91	71
11r	4-OH-3-MeO-C_6H_3-	2-Thienyl-	2-Pyridyl-	A	76	65

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin

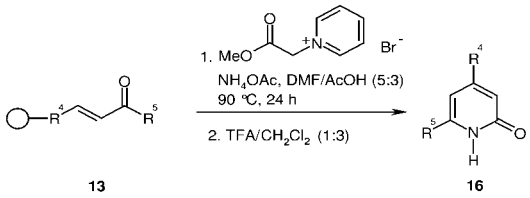
Table 8 Solid-Phase Pyridine Synthesis Based on Immobilized Amino Acids

Entry	Amino Acid	R^1	R^2	R^3	Purity[a]	Yield[b]
11s	Phe	3-OC-C_6H_4-	C_6H_5-	C_6H_5-	91	75
11t	Ile	3-OC-C_6H_4-	4-Cl-C_6H_4-	4-MeO-C_6H_4-	90	70
11u	ε-Ahx	4-OC-C_6H_4-	3-MeO-C_6H_4-	4-Cl-C_6H_4-	92	85
11v	Lys[c]	4-OC-C_6H_4-	C_6H_5-	2-Pyridyl-	88	84

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin
[c] both amino functions were modified

Pyridones

Enones **13** were also used for the solid-phase synthesis of 4,6-disubstituted pyridones. Treatment of enones **13** with 1-(methoxycarbonylmethyl)pyridinium bromide and ammonium acetate in DMF/acetic acid (5:3) afforded pyridones **16** (Scheme 7). Repetition of the reaction was necessary for a satisfying conversion of the educt. The reaction conditions were applied to a range of enones. Table 9 shows some representative results of the pyridone synthesis.



Scheme 7

Conclusions

In summary we have established the solid-phase syntheses of three heterocyclic systems. The common feature of these strategies is the use of enones as versatile polymer bound educts. Pyrazole-4-carboxylic acids were obtained in good regioselectivity and purity from the reaction of phenylhydrazines with alkylidene- or arylidene-β-oxo esters. This synthetic strategy allows the production of large libraries of a pharmacologically interesting scaffold. Pyridines and pyridones were synthesised according to the Kröhnke procedure starting from immobilised diaryl substituted enones. Our procedures also offer access to bi- and terpyridines which possess interesting metal chelating properties.

Table 9 Representative Results of the Pyridone Synthesis

Entry	R^1	R^2	Purity[a]	Yield[b]
16a	4-OH-C_6H_4-	C_6H_5-	73	75
16b	4-OH-3-MeO-C_6H_3-	C_6H_5-	75	78
16c	4-OH-3,5-$(MeO)_2$-C_6H_2-	4-Cl-C_6H_4-	69	74
16d	3-OH-C_6H_4-	4-Cl-C_6H_4-	75	76
16e	3-OH-C_6H_4-	3-MeO-C_6H_4-	76	71
16f	2-OH-3-MeO-C_6H_3-	2-Naphthyl-	67	73

[a] determined by C18 RP HPLC at λ=214 nm
[b] yield of the crude products based on the initial loading of the resin

^{1}H and ^{13}C NMR spectra of all compounds except **5a**, **5b**, **6a**, and **6b** were recorded on a Bruker AC250 spectrometer at 297 K. ^{1}H NMR and NOE difference spectra of compounds **5a**, **5b**, **6a**, and **6b** were acquired on a Bruker AMX2-600 spectrometer at 300 K. NMR samples were solutions of the compounds in DMSO-d_6. Chemical shifts were measured in δ (ppm) and coupling constants *J* in Hz. The spectra were referenced to the signal of the solvent at δ(^{1}H) = 2.50 and δ(^{13}C) = 39.5.

Reagents were purchased from Aldrich, Fluka, Lancaster, Novabiochem and Rapp Polymere and used without further purification. Analytical HPLC was performed using a reversed phase Nucleosil C18 (5 μm) column (250 x 2 mm) (Grom, Herrenberg, Germany), 214 nm detection, gradient 10–100% B (A = Water/0.1% TFA; B = ACN/0.1% TFA) over 45 min, flow = 0.3 ml/min. ES-FT-ICR-MS measurements were performed on a Bruker-Daltonic Apex II spectrometer which was connected to a Hewlett Packard HP 1100 HPLC.

Polymer Bound β-Oxo Esters 1; General Procedure
Wang PS (1% DVB) resin (100 mg, capacity:1.13 mmol/g) was suspended in NMP (800 μL). DMAP (4.4 mg, 0.045 mmol) and β-oxo ester (1.13 mmol) were added and the mixture was stirred for 20 h at 105 °C. The resin was washed with DMF, MeOH, CH_2Cl_2 and Et_2O and dried under vacuum.

Polymer Bound Acetoacetic Ester 1
Wang PS (1% DVB) resin (100 mg, capacity:1.13 mmol/g) was suspended in CH_2Cl_2 (1000 μL). DMAP (4.4 mg, 0.045 mmol) was added and the suspension was cooled to –21 °C. A solution of diketene (60 μL, 0.791 mmol) in CH_2Cl_2 (500 μL) was added in small portions over a period of 15 min. After shaking at r.t. for 2 h the resin was washed with DMF, MeOH, CH_2Cl_2 and Et_2O and dried under vacuum.

Polymer Bound Arylidene-β-oxo Ester 2; General Procedure
Polymer bound β-oxo ester **1** (0.113 mmol) was suspended in DMF/pyridine (4:1) (800 μL). Ethylenediamine diacetate (4.1 mg, 0.023

mmol) and aldehyde (0.226 mmol) were added and the mixture was stirred for 16 h at 70 °C. The resin was washed and dried as described above. Ethyl glyoxylate was also reacted following this procedure.

Polymer Bound Alkylidene-β-oxo Ester 2; General Procedure
Polymer bound β-oxo ester **1** (0.113 mmol) was suspended in CH_2Cl_2 (1000 µL). Ethylenediamine diacetate (8.2 mg, 0.046 mmol) and aldehyde (0.565 mmol) were added and the mixture was shaken for 3 h at r.t. The resin was washed and dried as described above.

Trisubstituted Pyrazole Carboxylic Acids 6; General Procedure
Method A: Polymer bound arylidene-β-oxo ester **2** (0.113 mmol) was treated with a solution of phenylhydrazine hydrochloride (0.226 mmol) and DIEA (34.8 µL, 0.203 mmol) in NMP(2mL). After stirring the mixture at 70 °C for 7 h the resin was washed with DMF, MeOH and CH_2Cl_2. The resin was then treated with CH_2Cl_2/HOAc for 0.5 h and washed with CH_2Cl_2. Cleavage was performed with TFA/CH_2Cl_2 (1:3) for 45 min. This step was repeated once. The solution was concentrated to dryness to provide the crude pyrazole which was then lyophilised twice from *t*-BuOH/H_2O (4:1).

Method B: Method B follows the procedure described under Method A with the difference that 1.2 equiv phenylhydrazine hydrochloride (0.136 mmol) and 1.1 equiv DIEA (21.2 µL, 0.124 mmol) were used.

5-methyl-1-phenyl-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazole-4-carboxylic Acid (6a)
^{1}H NMR (600.13 MHz): δ = 2.54 (s, 3H, Me-5), 7.53 (t, 1H, J_{bc} = 7.2 Hz, H-4'), 7.59 (dd, 2H, J_{bc} = 7.2 Hz, J_{ab} = 8.3 Hz, H-3'), 7.62 (d, 2H, J_{ab} = 8.3 Hz, H-2'), 7.77 (d, 2H, J_{ab} = 8.3 Hz, H-2''), 7.87 (d, 2H, J_{ab} = 8.3 Hz, H-3''), 12.60 (br, 1H, COOH).

5-Methyl-3-(4'-(nitrophenyl)-1-phenylpyrazole-4-carboxylic Acid (6b)
^{1}H NMR (600.13 MHz): δ = 2.54 (s, 3H, Me-5), 7.54 (t, 1H, J_{bc} = 7.2 Hz, H-4'), 7.59 (dd, 2H, J_{bc} = 7.2 Hz, J_{ab} = 8.3 Hz, H-3'), 7.62 (d, 2H, J_{ab} = 8.3 Hz, H-2'), 7.94 (d, 2H, J_{ab} = 8.8 Hz, H-2''), 8.27 (d, 2H, J_{ab} = 8.8 Hz, H-3''), 12.68 (br, 1H, COOH).

Trisubstituted Pyrazole Carboxylic Acid (5); General Procedure
Polymer bound arylidene-β-oxo ester **2** (0.113 mmol) was treated with a solution of phenylhydrazine hydrochloride (32.6 mg, 0.226 mmol) in DMF/HOAc (2:1) (1500 µL). After shaking for 4 h at r.t. the resin was washed. A solution of DBU (50 µL) in DMF (1000 µL) was added and the mixture was stirred at 70 °C for 4 h. The resin was washed and cleavage was performed as described above.

3-Methyl-1-phenyl-5-[4'-(trifluoromethyl)phenyl]pyrazole-4-carboxylic Acid (5a)
^{1}H NMR (600.13 MHz): δ = 2.48 (s, 3H, Me-3), 7.20 (d, 2H, J_{ab} = 6.5 Hz, H-2'), 7.33 (m, 3H, H-3' and H-4'), 7.51 (d, 2H, J_{ab} = 8.3 Hz, H-2''), 7.70 (d, 2H, J_{ab} = 8.3 Hz, H-3''), 12.30 (broad, 1H, COOH).

3-Methyl-5-(4'-nitrophenyl)-1-phenylpyrazole-4-carboxylic Acid (5b)
^{1}H NMR (600.13 MHz): δ = 2.48 (s, 3H, Me-3), 7.21 (d, 2H, J_{ab} = 6.5 Hz, H-2'), 7.34 (m, 3H, H-3' and H-4'), 7.59 (d, 2H, J_{ab} = 8.8 Hz, H-2''), 8.17 (d, 2H, J_{ab} = 8.8 Hz, H-3''), 12.39 (broad, 1H, COOH).

5-Methyl-1-phenyl-3-(*N*-acyl (or sulfonyl)-4-aminophenyl)pyrazol-4-carboxylic Acid (7); General Procedure
Polymer bound **4b** (0.113 mmol) was shaken with 2 M $SnCl_2 \cdot 2\,H_2O$ in DMF (1000 µL) at r.t.. for 15 h. After washing the resin was suspended in CH_2Cl_2 (1000 µL). Pyridine (73 µL, 0.904 mmol) and acid chloride (0.565 mmol) were added and the mixture was shaken for 6 h at r.t. The resin was washed and cleavage was performed as described above (**6**).

3-(*N*-Alkylpyridyl)-5-methyl-1-phenylpyrazole-4-carboxylic Acid (8); General Procedure
Polymer bound **4n** (0.113 mmol) was shaken with a solution of DIEA (50 µL) in DMF (1000 µL) for 20 min at r.t. and then washed with DMF. The resin was suspended in DMF (1000 µL) and the alkylating reagent (0.452 mmol) was added. The mixture was stirred for 4 h at 70 °C. The resin was washed and cleavage was performed as described above (**6**).

Loading of Wang Bromo PS with Hydroxyacetophenones and Hydroxybenzaldehydes 9/12; General Procedure
Wang Bromo PS (1% DVB) resin (50 mg, capacity: 1.1 mmol/g) was treated with the hydroxy component (0.275 mmol), Cs_2CO_3 (35.8 mg, 0.11 mmol) and DMF (500 µL). After stirring for 3 h at 80 °C the resin was washed and dried.

Loading of Rink Amide PS with Carboxylic acids; General Procedure
Fmoc Rink Amide PS (1% DVB) resin (50 mg, capacity: 0.78 mmol/g) was deprotected by treatment with piperidine/DMF (1:1) (2x). After washing with DMF a solution of carboxylic acid (0.117 mmol), HOBt (17.9 mg, 0.117 mmol) in DMF (800 µL) was added followed by DIC (18.1 µL, 0.117 mmol). The mixture was shaken at r.t. until the Kaiser test was negative, followed by a washing and deprotection step.

In the case of carboxybenzaldehyde, the mixture of aldehyde, HOBt and DIC in DMF was shaken for 30 min at r.t. before adding to the resin.

Enone 10 Synthesis by Condensation of Acetophenones with Aldehydes
Resin **9** was suspended in THF (650 µL). 0.5 M NaOMe in MeOH (650 µL) and aldehyde (0.55 mmol) were added and the mixture was stirred at r.t. for 72 h. After washing the resin was dried.

The enone used for the synthesis of pyridine **11b** was synthesised via a slightly modified procedure:

The resin was suspended in THF (890 µL). 0.5 M NaOMe in MeOH (110 µL) and aldehyde (0.55 mmol) were added and the mixture was stirred at r.t. for 24 h. After washing, the resin was dried.

Enone 13 Synthesis by Wittig Reaction
Resin bound aldehydes **12** were treated with 1-(2-aryl-2-oxoethyl)triphenylphosphonium bromide (0.385 mmol), THF (650 µL) and 0.5 M NaOMe in MeOH (650 µL). After stirring for 2 d at 60 °C the resin was washed and dried.

2,4,6-Trisubstituted Pyridines (11); General Procedure
Resin bound enone **10/13** (0.055 mmol) was treated with 1-(2-aryl-2-oxoethyl)pyridinium salt (0.22 mmol) and a solution of NH_4OAc (84.7 mg, 1.1mmol) in DMF/HOAc (5:3) (1000 µL) was added. After 24 h at 90 °C the resin was washed and cleavage was performed as described above. The solution was concentrated to dryness to provide the crude pyridine which was then lyophilised twice from *t*-BuOH/H_2O (4:1).

2-(3',4'-Dichlorophenyl)-6-(4''-hydroxy-3''-methoxyphenyl)-4-(thien-2'''-yl)pyridine (11a)
^{1}H NMR (250.13 MHz): δ = 3.92 (s, 3H), 6.94 (d, 1H, *J* = 8.4 Hz), 7.28 (dd, 1H, *J* = 5.0 Hz, *J* = 3.7 Hz), 7.74 (dd, 1H, *J* = 8.4 Hz, *J* = 2.1 Hz), 7.77 to 7.84 (m, 3H), 8.04 (d, 1H, *J* = 1.2 Hz), 8.11 (dd, 1H, *J* = 3.7 Hz, *J* = 1.1 Hz), 8.14 (d, 1H, *J* = 1.2 Hz), 8.31 (dd, 1H, *J* = 8.4 Hz, *J* = 2.1 Hz), 8.54 (d, 1H, *J* = 2.1 Hz), 9.44 (br, 1H).

^{13}C NMR (62.90 MHz): δ = 55.84, 110.95, 114.09, 114.56, 115.68, 120.15, 126.93, 127.29, 128.38, 128.47, 128.69, 129.52, 130.87, 131.66, 131.86, 139.16, 140.59, 143.07, 147.83, 148.38, 153.65, 156.91.

2-(4'-Fluorophenyl)-6-(4'-hydroxyphenyl)-4-(4'-nitrophenyl)-pyridine (11b)

^{1}H NMR (250.13 MHz): δ = 6.93 (d, 2H, *J* = 8.7 Hz), 7.37 (t, 2H, *J* = 8.9 Hz), 8.12 to 8.24 (m, 4H), 8.28 to 8.44 (m, 6H), 9.84 (br, 1H).

13C NMR (62.90 MHz): δ = 115.34, 115.50, 115.67, 123.93, 128.44, 128.73, 129.07, 129.19, 129.28, 135.10, 144.23, 147.12, 147.78, 155.40, 156.82, 158.91, 163.03.

4-(3'-Carboxamidophenyl)-2-(4'-chlorophenyl)-6-phenylpyridine (11e)

^{1}H NMR (250.13 MHz): δ = 7.45 to 7.72 (m, 7H), 8.02 (d, 1H, *J* = 7.9 Hz), 8.23 (d, 2H, *J* = 7.9 Hz), 8.30 (d, 2H, *J* = 2.0 Hz), 8.34 (dd, 2H, *J* = 7.9 Hz, *J* = 1.5 Hz), 8.40 (d, 2H, *J* = 8.6 Hz), 8.46 (t, 1H, *J* = 1.5 Hz).

^{13}C NMR (62.90 MHz): δ = 116.62, 116.91, 125.93, 126.94, 128.59, 128.72, 129.14, 129.32, 130.11, 134.11, 135.07, 137.48, 138.56, 149.11, 155.27, 156.67, 167.47.

Pyridones (16); General Procedure

Resin bound enone **13** (0.055 mmol) was treated with a solution of 1-(methoxycarbonylmethyl)pyridinium bromide (54.5 mg, 0.22 mmol) and NH_4OAc (84.7 mg, 1.1 mmol) in DMF/HOAc (5:3) (1000 µL). After 24 h at 90 °C, the resin was washed and the reaction step was repeated once. Cleavage was performed as described above. The solution was concentrated to dryness to provide the crude pyridone which was then lyophilised twice from *t*-BuOH/H_2O (4:1).

4-(3'-Hydroxyphenyl)-6-(3'-methoxyphenyl)pyrid-2-one (16e)

^{1}H NMR (250.13 MHz): δ = 3.85 (s, 3H), 6.55 (d, 1H, *J* = 1.4 Hz), 6.87 (ddd, 1H, *J* = 7.9 Hz, *J* = 2.3 Hz, *J* = 1.1 Hz), 6.91 (s, br, 1H), 7.03 (ddd, 1H, *J* = 7.8 Hz, *J* = 2.4 Hz, *J* = 1.4 Hz), 7.12 (t, 1H, *J* = 1.8 Hz), 7.20 (dt, 1H, *J* = 7.9 Hz, *J* = 1.4 Hz), 7.28 (t, 1H, *J* = 7.8 Hz), 7.35 to 7.49 (m, 3H), 9.66 (br, 1H).

^{13}C NMR (62.90 MHz): δ = 56.22, 104.66, 105.38, 111.16, 127.29, 128.59, 128.86, 133.93, 134.17, 137.22, 147.43, 148.22, 152.05, 163.70.

6-(4'-Chlorophenyl)-4-(4'-hydroxy-3',5'-dimethoxyphenyl)-pyrid-2-one (16c)

^{1}H NMR (250.13 MHz): δ = 3.86 (s, 6H), 6.72 (d, 1H, *J* = 1.4 Hz), 7.05 (s, 2H), 7.09 (s, br, 1H), 7.56 (d, 2H, *J* = 8.6 Hz), 7.95 (d, 2H, *J* = 8.6 Hz), 8.75 (very br, 1H).

^{13}C NMR (62.90 MHz): δ = 55.25, 104.59, 111.95, 112.61, 113.51, 115.72, 116.31, 117.58, 119.23, 129.79, 129.99, 135.82, 138.84, 148.03, 151.96, 157.78, 159.44, 163.55.

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