Solid Phase Synthesis of Aminopropenones and Aminopropenoates; Efficient and Versatile Synthons for Combinatorial Synthesis of Heterocycles

Jacob Westman,*[a] Ronny Lundin[b]

[a] Actar AB, Franzéngatan 6, 112 51 Stockholm, Sweden
Fax +46(8)54560806; E-mail: jacob.westman@actar.se

[b] Personal Chemistry AB, Kungsgatan 76, 753 18 Uppsala, Sweden
Fax +46(18)4899200

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Abstract: Simple and fast solid phase methods for the synthesis of heterocycles will be described. Two different three-step methods are presented. The first method includes esterifications of *N*-protected glycine derivatives to a solid support (Merrifield resin), formation of aminopropenoates and subsequent reaction with dinucleophiles. The second method includes methylamination of a Merrifield resin, formation of aminopropenones via in-situ formation of an active intermediate in a three-component reaction and finally treatment with dinucleophiles to form heterocycles. These procedures lead not only to the formation of heterocycles but also to simultaneous intramolecular cleavage of the products from the resin giving the product in pure form in the solution. In addition, the use of microwave dielectric heating enhanced the velocity of all reaction steps and was found to be a very efficient complement to the solid phase synthesis.

Key words: solid-phase synthesis, microwave irradiation, combinatorial chemistry, heterocycles

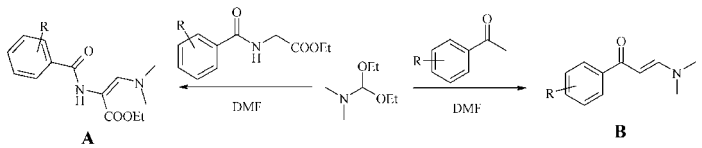
Highly functionalized heterocycles of various ring sizes, with different heteroatoms and substitution patterns are of major interest in the pharmaceutical and agricultural industry due to the their many intrinsic biological properties.

In medicinal chemistry in general, and combinatorial chemistry in particular, the use of versatile synthons or versatile scaffolds which are available after just a few reaction steps are of great interest. One reagent producing such synthons is *N*,*N*-dimethylformamide diethyl acetal (DMFDEA).[1] Condensation reactions between an activated methyl or methylene group adjacent to a keto or ester functionality and DMFDEA form alkylaminopropenones or alkylaminopropenoates (see Scheme 1). These intermediates, in which the dimethylamino moiety acts as a good leaving group, have been used in many applications using conventional heating methods, probably most extensively described by Stanovnik et al.[2] The intermediates could then be reacted with dinucleophiles to form different heterocycles. We have recently reported efficient microwave assisted one-pot methods for the synthesis of a number of small libraries in solution[3] based on alkylaminopropenones or alkylaminopropenoates.

When producing a large number of substances in solution, the subsequent purifications will be time-consuming, and thereby diminish the advantage given by the short reaction times found by the use of microwave heating.

In order to overcome cumbersome purification we found it reasonable to try a solid phase synthesis approach to those reactions. It is well known that the solid phase technique besides allowing for easy automation also could eliminate certain time-consuming purification steps. For example, a large excess of reagent could be used in a reaction with a resin bound substrate and thus drive the reaction to completion. The redundant amount of reagent could then be removed by a simple filtration. On the other hand, one well-known disadvantage of solid phase synthesis is that longer reaction times usually are required compared to reactions performed in a homogeneous solution system. We have however found that also the reaction times in heterogeneous systems could be substantially shortened by the use of microwave heating.[4]

The analysis of the degree of incorporation of a certain compound into the resin is usually performed by cleavage of the compound from the resin and then analyzing the cleavage mixture,[5] by quantitative colorizing methods[6] or by elemental analysis. We chose to adopt a recently devel-



Scheme 1 Examples of the formation of dimethylaminopropenoates (**A**) and dimethylaminopropenones (**B**) from dimethylformamide diethylacetal.

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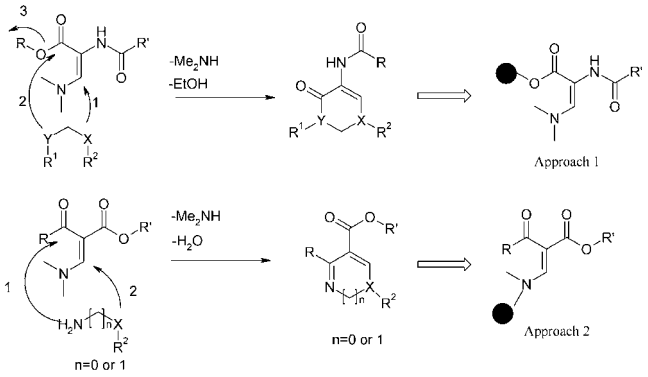
oped NMR-technique, Magic angle spinning ^{1}H NMR (MAS-NMR) analysis. The technology was developed some years ago[7,8] and has shown to work well with resins such as TentaGel and Merrifield resin. We herein describe the efficient combination of microwave heating and solid phase synthesis for reducing both the reaction time and the purification time.

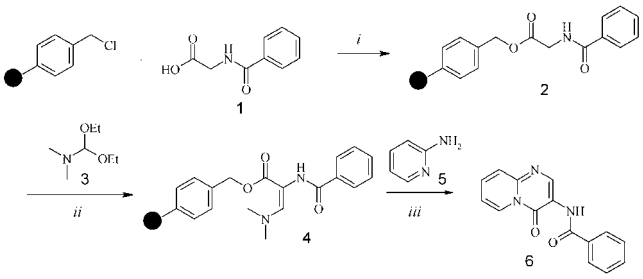
Dialkylamino propenoates react with dinucleophiles in a two-step reaction where substitution of the dimethylamino group is followed by a nucleophilic attack on the ester functionality, which cleaves the ester. Dialkylamino propenones also reacts with dinucleophiles. In this case the reactions proceed differently since a condensation reaction with the keto function is followed by the substitution of the dialkylamino group. Based on the two different reaction pathways, two different solid phase intermediates were proposed as described in Scheme 2. Since the proposed procedures form the heterocycles by an intramolecular cyclization mechanism that simultaneously cleaves the products from the resin it will give the products in pure form in the solution and thus, any reaction step for cleavage from the resin is not needed. Since the heterocycles from dialkylpropenoates are formed after cleavage of the ester (approach 1) the chosen approach was therefore to form the ester bond to the solid phase. For the formation of heterocycles from propenones (approach 2) the chosen approach was to bind the leaving group (the dialkylamino group) to the solid phase.



Scheme 2 Approaches 1 and 2.

Synthesis of Heterocycles from Solid Phase Bound Dialkylaminopropenoates

Formation of heterocycles where one of the substrates is bound to the resin was performed in a 3 step reaction as described in Scheme 3. Magic angle spinning NMR (MAS-NMR) analysis[7,8] was used for the protocol development. NMR analysis of Merrifield resin gives, however, a poorer resolution with respect to line width and spectral purity compared to resins like Tentagel.[8] Merrifield resin was used due to its high loading capacity and high thermal stability. By comparing the peak area from the methylene group in the resin handle ($PhCH_2Cl$) and the peak area from the solid phase benzylester methylene group ($PhCH_2OCO$) the yield could be determined as shown in Figure 1. For the two last steps we applied the same protocols as was developed for solution phase[3] with minor modifications. Formation of an ester linkage between a carboxylic acid substrate and a solid phase resin is a common reaction in the area of peptide synthesis and combinatorial chemistry and is well described in the literature.[5,9] Merrifield resin was treated with 5 equivalents of *N*-benzoylated glycine **1** together with cesium carbonate in 2 mL of DMF at 200 °C for 10 min[10] giving **2**. The analysis (MAS-NMR and elemental analysis) showed a loading of approximately 1 mmol/g (80% yield) (Figure 1), which is in the same range as described in the literature, but approximately within a 100-fold shorter reaction time. After washing, the resin was treated with 5 equivalents DMFDEA in 2.5 ml DMF at 180 °C for 10 min to form the dimethylamino propenoates intermediate **4**.



Scheme 3 Synthesis of 3-(benzoyl)amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one. Reaction conditions: (i) Hippuric acid (5 equiv), $CsCO_3$ (5 equiv), DMF, 200 °C, 10 min. (ii) DMFDEA (5 equiv) in DMF, 180 °C, 10 min (iii) 2-aminopyridine (0.5 equiv) in HOAc, 180 °C, 10 min.

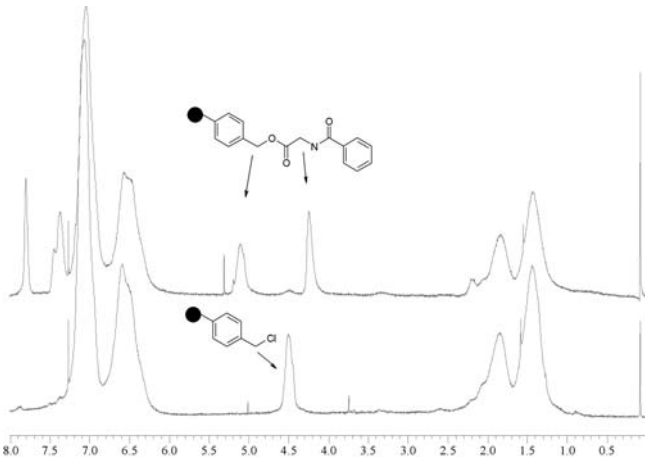


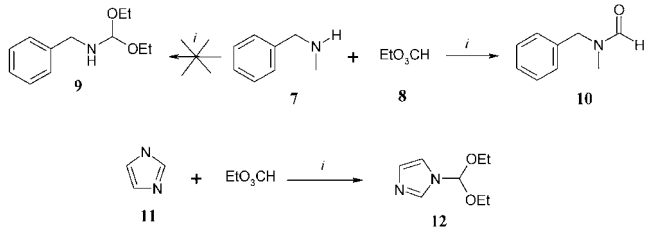
Figure 1 By comparing the peak area of the benzylic methylene group the yield could be determined.

The resin was washed, dried and then swelled in 0.5 mL of HOAc. In order to minimize the amount of unreacted dinucleophiles in the final reaction solution we only added 0.5–0.7 equivalents of dinucleophiles (**5**, **15**, **16**) to the reaction mixtures, based on an assumed 1 mmol/g loading of the intermediate. The reaction mixtures were heated for an additional 10 min at 180 °C. After filtration and wash-

ing of the resin, evaporation of the solvent was performed and the products (**6**, **17**, **18**) were found in high purity (>90%) and in yields between 77–95% (see Table 1).

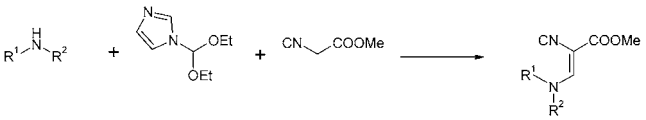
Synthesis of Heterocycles from Solid Phase Bound Dialkylaminopropenones

Approach 2 (Scheme 2) where dialkyl formamide diethyl acetal is bound to the solid phase and where the cleavage from the resin occurs when the dialkyl amino group is cleaved by a nucleophile was not as straightforward as approach 1. The idea was to form the dialkylformamide diethyl acetal on solid phase starting from methylaminated Merrifield resin (benzylchloride handle) and consequently we used benzyl methylamine (**7**) as a model substance in order to develop a protocol in solution which then could be transferred into solid phase conditions (Scheme 4). Benzyl methylamine was treated with 9 equivalents of triethyl orthoformate (**8**) in 2.0 mL of DMF at 200 °C for 5 min. to form benzyl methylformamide diethylacetal (**9**) according to a method described by Gmeiner et al.[11] However, we only found benzyl methylformamide as the product **10**. On the other hand we found, in accordance with the reference, that imidazole **11** forms the imidazolium diethylacetal (**12**) after treatment with triethylorthoformate[12] in 2.0 mL of DMF at 200 °C for 5 min.



Scheme 4 Synthesis of benzyl methylformamide. Reaction conditions: DMF, 200 °C, 5 min.

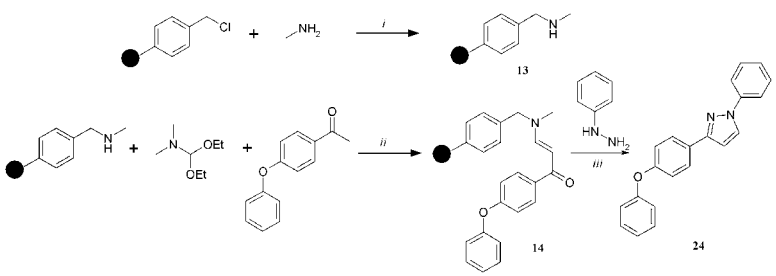
Our plan was then to follow the procedure describe by Meerwein et al.[13] for the synthesis of DMFDEA from DMF. The solid supported benzylmethyl amine could be treated with triethyloxonium tetrafluoroborate to afford a tetrafluoroborate salt. Treatment of the salt with sodium ethoxide should then give the diethylacetal compound. The major drawback with this procedure is the number of reaction steps needed to form the reagent. This strategy was therefore not adopted. Meerwein et al. have also described that when a dialkylamine was reacted with DMFDEA an amine exchange occurs in-situ giving the dialkylformamide diethylacetal. Unfortunately, when trying this method, benzyl methylformamide was formed as the only product. Bienaymé[14] reported recently the formation of substituted isonitriles by treatment of a dialkyl amine, imidazole diethylacetal and methyl isocyanoacetate, which form dialkylamino propenoates by a three-component cascade reaction[15] mechanism (Scheme 5). Since this multi-component approach forms the reagent in-situ it also reduces the number of reaction steps needed for the formation of the reactive intermediate.



Scheme 5 Formation of amino propenoates in a multicomponent approach via amine exchange.

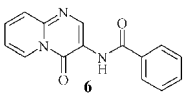
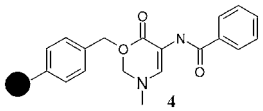
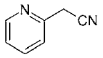
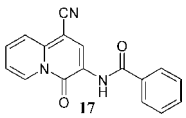
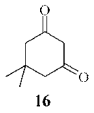
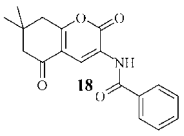
We therefore decided to try this approach to our model synthesis and we found that when reacting benzylmethylamine with DMFDEA and acetophenone in 2.0 mL of DMF at 180 °C for 5 min the desired propenone was formed in good yield based on LC/MS analysis. The outcome of the reaction indicated that this procedure could be successfully applied to our planned strategy with the solid phase linked *N*-methyl benzylamine The following procedure was therefore performed: Merrifield resin was reacted with 2.0 mL methylamine in water at 150 °C for 10 min to form the solid supported benzylmethylamine (**13**) in high yield (86% yield, 1.08 mmol/g based on elemental analysis). The MAS-NMR analysis was in this case difficult to interpret and therefore not used.[16] The resin was, after washing, treated with 5 equivalents DMFDEA together with 5 equivalents of 4-phenoxyacetophenone at 180 °C for 10 min in 2.0 mL of DMF to form the solid supported benzyl methyl aminopropenones **14**. MAS-NMR showed that products were formed but the spectra was not resolved well enough to make a good interpretation.

After washing, the resin was finally treated (the resin bound intermediate in excess) at 180°C for 10 min in 2.0 mL EtOH, DMF, or HOAc with 0.5 equivalents of the dinucleophiles to form the heterocycles in pure form. In



Scheme 6 Example of a solid phase synthesis of 1-Phenyl-5-(4-phenoxyphenyl)-pyrazole. Reaction conditions: (i) $MeNH_2$ in H_2O, 150 °C, 10 min (ii) DMF, 150 °C, 10 min (iii) HOAc, 150 °C, 10 min.

Table 1 Synthesis of Heterocycles via Propenoates[a]

Substrates	Products	Yields	Purity
 **5**	 **6**	77%	96%
 **4** +  **15**	 **17**	92%	95%
 **16**	 **18**	95%	98%

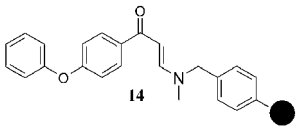
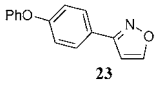
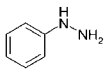
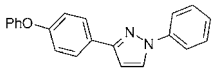
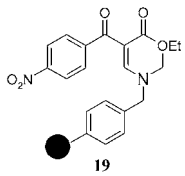
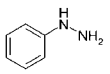
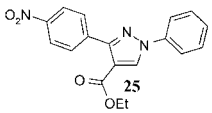
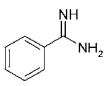
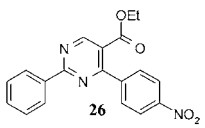
[a] Reaction conditions: 100–200 mg of solid supported propenoates were reacted with 0.5 equiv. of substrate **5**, **15**, **16** in HOAc at 180 °C for 10 min.

order to verify the developed methods described above, we performed a number of syntheses of heterocycles where both approaches 1 and 2 were performed (Scheme 6, Table 2).

In conclusion, we have described two ways to form activated aminopropenones and aminopropenoates on solid phase which in turn could be used in combinatorial syntheses of a large number of different heterocycles with an overall reaction time of approximately 30 min to give products of high purity in good to excellent yields. The major benefit with this approach is that purification is not needed. Our belief is that this approach could be extended further, to construct high libraries with high purity and large degree of diversity.

The microwave-assisted reactions were performed in a SmithSynthesizer™, a single mode microwave cavity, from Personal Chemistry. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 25 °C, using a Bruker at 300 MHz (^{1}H)/75 MHz (^{13}C) or a Varian 600 MHz instrument with a nano probe for the MAS-NMR analysis. All NMR spectra recorded were in agreement with the postulated structures and only selected data are reported. HPLC-MS chromatograms and spectra were obtained with an Agilent 1100 system with a diode array detector and a Agilent MSD. The analytical HPLC column was a HiChrome ACE AQ-5mm, C18. A gradient elution of 10% MeCN in H_2O by an increase to 95% MeCN in 2.5 min was used unless otherwise specified. Retention time for LC/MS is reported with % area of the peak. Elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden. All starting reagents were of the best grade available (Aldrich or Lancaster) and were used without purification. **CAUTION: These reactions are not recommended to be carried out in a multimode domestic microwave oven due to non-uni-**

Table 2 Synthesis of Heterocycles via Propenones[a]

Substrates		Products	Yields	Purity
 **14**	 **20**	 **23**	81%	85%
,,	 **21**	 **24**	81%	93%
 **19**	 **21**	 **25**	92%	91%
,,	 **22**	 **26**	94%	88%

[a] Reaction conditions: 100–200 mg of solid supported propenones were reacted with 0.5 equiv of substrate **20**–**22** at 180 °C for 10 min.

form irradiation and no temperature control (risk of explosion and thermal runaway). Also observe that the reactions are run in a closed vessel and that in several cases the pressure during the reaction is between 5 and 20 bar overpressure.

Coupling of *N*-Benzoyl Glycine to Merrifield Resin (2)
Merrifield resin (200 mg, 1.25 mmol/g loading capacity) was swelled in DMF (2.5 mL, 1.25 mmol, 5 equiv). *N*-Benzoyl glycine (Hippuric acid) (**1**), Cs_2CO_3 (1.25 mmol) were added and the reaction mixture was heated at 200 °C for 10 min. The reaction mixture was then cooled down to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicate compound **2** in a yield of 80% (approx. 1.0 mmol/g loading).

^{1}H NMR ($CDCl_3$): δ = 4.24 ($COCH_2NCO$), 5.11 ($PhCH_2CO$), 7.30–7.40 (4 H, Ar), 7.80 (1 H, Ar).

Elemental analysis: 1.35 weight % giving 0.96 mmol/g loading

Methylamination of Merrifield Resin (13)
Merrifield resin (200 mg, 1.25 mmol/g loading capacity) was treated with methylamine (2.0 mL) in H_2O (40% w/w) (excess) at 150 °C for 5 min. The reaction mixture was then cooled to r.t. by pressurized air. The residue was washed several times with H_2O, CH_2Cl_2 and MeOH to give compound **13**. Elemental analysis gave 1.52-weight% giving ca. 1.08 mmol/g loading.

Dimethyl Amino Propenoates from *N*-Benzoyl Glycine on Solid Support (4)
Solid supported *N*-Benzoyl glycine benzyl ester **2** (250 mg, ca. 0.25 mmol) was swelled in DMF (2.5 mL), DMFDEA (1.57 mmol) was added and the reaction mixture was heated at 180 °C for 10 min. The reaction mixture was then cooled to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicate compound **4** but no yield was determined due to low resolution.

Benzyl Methyl Amino Propenones from 4-Phenoxy Acetophenone on Solid Support (14)
Benzyl methylamine (200 mg) on solid support **13** (ca. 0.2 mmol) was swelled in DMF (2.0 mL), DMFDEA (214 μL), 4-phenoxy acetophenone (155 μL) were added and the reaction mixture was heated at 180 °C for 10 min. The reaction mixture was then cooled down to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicated compound **14** but no yield was determined due to low resolution.

Benzyl Methyl Amino Propenones from Ethyl 4-nitrobenzoylacetate on Solid Support (19)
Benzyl methylamine (200 mg) on solid support **13** was treated with ethyl 4-nitrobenzoylacetate as describe above for the synthesis of compound **19**. MAS-NMR analysis indicated compound **19** but no yield was determined due to low resolution.

3-(Benzoyl)amino-4*H*-pyrido[1,2-a]pyrimidin-4-one (6)[17]
Solid supported compound **4** (100 mg) were added to 2-aminopyridine (**5**) (6.6 mg, 0.07 mmol) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The HOAc was evaporated giving product **6** (14.2 mg), a total yield of 77% and 96% purity based on LC/MS analysis. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (dt, 1 H, ArH), 7.45–7.65 (m, 4 H, ArH), 7,75 (dd, 1 H, ArH), 7.95 (dd, 2 H, ArH), 8.84 (s, 1 H, NH), 8.95 (dd, 1 H, ArH), 9.75 (s, 1 H, pyrimidin-H). The structure was in accordance with the already published data.

3-(Benzoyl)amino-1-cyano-4*H*-quinolizin-4-one (17)[18]
Solid supported compound **4** (100 mg) was added to 2-pyridyl-acetonitrile (**15**) (5.6 μL , 0.05 mmol) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The HOAc was evaporated. The residue was dissolved in CH_2Cl_2 and filtered through a plug of silica. Crude analysis showed a LC/MS purity of 95%. Evaporation of the solvent gave the product **17 (**13.3 mg), a total yield of 92%. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (ddd, 1 H, ArH), 7.32–7.42 (m, 4 H, ArH), 7.77 (m, 2 H, ArH), 7.81 (dt, 1 H, ArH), 8.88 (s, 1 H, NH), 8.92 (dt, 1 H, ArH), 9.11 (s, 1 H, quinolizin-4-one). The structure was in accordance with the already published data.

3-(Benzoyl)amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (18)[19]
Solid supported compound **4** (100 mg) were added to 5,5 dimethyl-1,3-cyclohexanedione (**16**) (7.0 mg) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min. and then cooled to r.t. The HOAc was evaporated giving product **18** (14.8 mg), a total yield of 95% and 98% purity based on LC/MS analysis. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2 (s, 6 H, CH_3) 2.48 (s, 2 H, CH_2), 2.78 (s, 2 H, CH_2), 7.5–7.7 (m, 3 H, ArH), 7.92 (m, 2 H, ArH), 8.59 (s, 1 H, NH), 8.83 (s, 1 H, *C*H). The structure was in accordance with the already published data.

(4-Phenoxy)phenylisoxazole (23)
Solid supported compound **14** (200 mg) was mixed with hydroxylamine hydrochloride (0.5 equiv, 0.1 mmol) (**20**) and EtOH (2 mL). The mixture was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated. The product **23** was isolated in 81% yield and 85% purity based on LC/MS analysis.

HPLC: t_R 2.32 min (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (d, 1 H, *J* = 1.9 Hz, isoxazole), 7.04 (m, 4 H, ArH), 7.17 (dt, 1 H, ArH), 7.38 (m, 2 H, ArH), 7.76 (m, 2 H, ArH), 8.25 (d, 1 H, *J* = 1.9 Hz, isoxazole).

MS (APCI): *m*/*z* = 238.1 $[M + H]^+$.

1-Phenyl-5-(4-phenoxyphenyl)-pyrazole (24)
Solid supported compound **14** (200 mg) was mixed with phenylhydrazine (**21**) (0.5 equiv, 0.1 mmol) and HOAc (2 mL). The mixture was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated.The product **24** was isolated in 81% yield and 93% purity.

HPLC: t_R 2.48 min (93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.48 (d, 1 H, *J* = 1.9 Hz, pyrazole), 6.91 (dd, 2 H, ArH), 7.03 (m, 2 H, ArH), 7.18 (dd, 2 H, ArH), 7.3–7.4 (m, 8 H, ArH), 7.71 (d, 1 H, *J* = 1.9 Hz, pyrazole).

MS (APCI): *m*/*z* = 313.0 $[M + H]^+$.

Ethyl 1-Phenyl-3-(4-nitrophenyl)-pyrazole-4-carboxylate (25)
Solid supported compound **19** (200 mg) was treated as described for compound **24** using EtOH as solvent. The EtOH was evaporated giving product **25** (31.0 mg) in 92% yield and 91% purity. The structure was confirmed by NMR.

HPLC: t_R 2.28 min (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ =1.28 (t, 3 H, CH_3CH_2), 4.25 (q, 2 H, CH_2CH_3), 7.20 (m, 2 H, ArH), 7.35 (m, 3 H, ArH), 7.51(d, 2 H, ArH), 8.21 (d, 2 H, ArH), 8.23(s, 1 H, pyrazole).

MS (APCI): *m*/*z* = 338.0 $[M + H]^+$.

Ethyl 2-Phenyl-4-(4-nitrophenyl)-pyrimidine-5-carboxylate (26)

Solid supported compound **19** (200 mg) in DMF (2 mL) was treated with 4-amidinobenzene hydrochloride (**22**) (0.1 mmol, ca. 0.5 equiv) and KOH (0.15 mmol), exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated. The product (**26**) was isolated in 94% (32.7 mg) in 88% purity.

HPLC: t_R 2.51 min (88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3 H, CH_3CH_2), 4.28 (q, 2 H, CH_2CH_3), 7.54 (m, 3 H, ArH), 7.85 (m, 2 H, ArH), 8.35 (dd, 2 H, NO_2-phenyl), 8.56 (dd, 2 H, NO_2-phenyl), 9.31 (s, 1 H, pyrimidine).

MS (APCI): m/z = 350.0 $[M + H]^+$.

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Solid Phase Synthesis of Aminopropenones and Aminopropenoates; Efficient and Versatile Synthons for Combinatorial Synthesis of Heterocycles

Jacob Westman,*[a] Ronny Lundin[b]

[a] Actar AB, Franzéngatan 6, 112 51 Stockholm, Sweden
Fax +46(8)54560806; E-mail: jacob.westman@actar.se

[b] Personal Chemistry AB, Kungsgatan 76, 753 18 Uppsala, Sweden
Fax +46(18)4899200

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Abstract: Simple and fast solid phase methods for the synthesis of heterocycles will be described. Two different three-step methods are presented. The first method includes esterifications of *N*-protected glycine derivatives to a solid support (Merrifield resin), formation of aminopropenoates and subsequent reaction with dinucleophiles. The second method includes methylamination of a Merrifield resin, formation of aminopropenones via in-situ formation of an active intermediate in a three-component reaction and finally treatment with dinucleophiles to form heterocycles. These procedures lead not only to the formation of heterocycles but also to simultaneous intramolecular cleavage of the products from the resin giving the product in pure form in the solution. In addition, the use of microwave dielectric heating enhanced the velocity of all reaction steps and was found to be a very efficient complement to the solid phase synthesis.

Key words: solid-phase synthesis, microwave irradiation, combinatorial chemistry, heterocycles

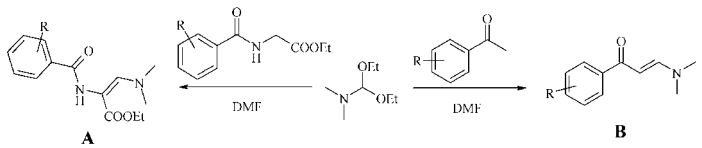
Highly functionalized heterocycles of various ring sizes, with different heteroatoms and substitution patterns are of major interest in the pharmaceutical and agricultural industry due to the their many intrinsic biological properties.

In medicinal chemistry in general, and combinatorial chemistry in particular, the use of versatile synthons or versatile scaffolds which are available after just a few reaction steps are of great interest. One reagent producing such synthons is *N*,*N*-dimethylformamide diethyl acetal (DMFDEA).[1] Condensation reactions between an activated methyl or methylene group adjacent to a keto or ester functionality and DMFDEA form alkylaminopropenones or alkylaminopropenoates (see Scheme 1). These intermediates, in which the dimethylamino moiety acts as a good leaving group, have been used in many applications using conventional heating methods, probably most extensively described by Stanovnik et al.[2] The intermediates could then be reacted with dinucleophiles to form different heterocycles. We have recently reported efficient microwave assisted one-pot methods for the synthesis of a number of small libraries in solution[3] based on alkylaminopropenones or alkylaminopropenoates.

When producing a large number of substances in solution, the subsequent purifications will be time-consuming, and thereby diminish the advantage given by the short reaction times found by the use of microwave heating.

In order to overcome cumbersome purification we found it reasonable to try a solid phase synthesis approach to those reactions. It is well known that the solid phase technique besides allowing for easy automation also could eliminate certain time-consuming purification steps. For example, a large excess of reagent could be used in a reaction with a resin bound substrate and thus drive the reaction to completion. The redundant amount of reagent could then be removed by a simple filtration. On the other hand, one well-known disadvantage of solid phase synthesis is that longer reaction times usually are required compared to reactions performed in a homogeneous solution system. We have however found that also the reaction times in heterogeneous systems could be substantially shortened by the use of microwave heating.[4]

The analysis of the degree of incorporation of a certain compound into the resin is usually performed by cleavage of the compound from the resin and then analyzing the cleavage mixture,[5] by quantitative colorizing methods[6] or by elemental analysis. We chose to adopt a recently devel-



Scheme 1 Examples of the formation of dimethylaminopropenoates (**A**) and dimethylaminopropenones (**B**) from dimethylformamide diethylacetal.

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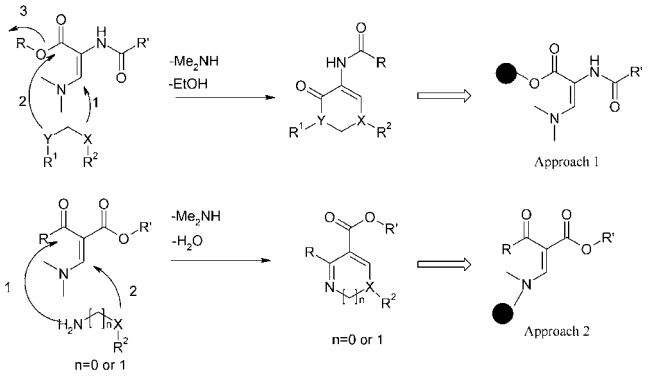
oped NMR-technique, Magic angle spinning ^{1}H NMR (MAS-NMR) analysis. The technology was developed some years ago[7,8] and has shown to work well with resins such as TentaGel and Merrifield resin. We herein describe the efficient combination of microwave heating and solid phase synthesis for reducing both the reaction time and the purification time.

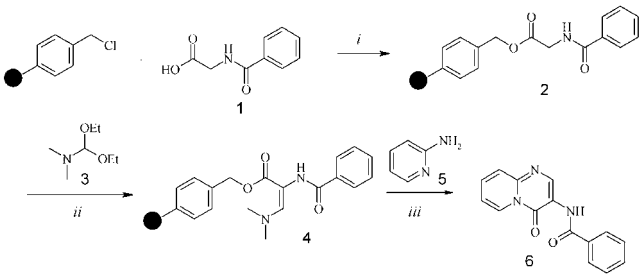
Dialkylamino propenoates react with dinucleophiles in a two-step reaction where substitution of the dimethylamino group is followed by a nucleophilic attack on the ester functionality, which cleaves the ester. Dialkylamino propenones also reacts with dinucleophiles. In this case the reactions proceed differently since a condensation reaction with the keto function is followed by the substitution of the dialkylamino group. Based on the two different reaction pathways, two different solid phase intermediates were proposed as described in Scheme 2. Since the proposed procedures form the heterocycles by an intramolecular cyclization mechanism that simultaneously cleaves the products from the resin it will give the products in pure form in the solution and thus, any reaction step for cleavage from the resin is not needed. Since the heterocycles from dialkylpropenoates are formed after cleavage of the ester (approach 1) the chosen approach was therefore to form the ester bond to the solid phase. For the formation of heterocycles from propenones (approach 2) the chosen approach was to bind the leaving group (the dialkylamino group) to the solid phase.



Scheme 2 Approaches 1 and 2.

Synthesis of Heterocycles from Solid Phase Bound Dialkylaminopropenoates

Formation of heterocycles where one of the substrates is bound to the resin was performed in a 3 step reaction as described in Scheme 3. Magic angle spinning NMR (MAS-NMR) analysis[7,8] was used for the protocol development. NMR analysis of Merrifield resin gives, however, a poorer resolution with respect to line width and spectral purity compared to resins like Tentagel.[8] Merrifield resin was used due to its high loading capacity and high thermal stability. By comparing the peak area from the methylene group in the resin handle ($PhCH_2Cl$) and the peak area from the solid phase benzylester methylene group ($PhCH_2OCO$) the yield could be determined as shown in Figure 1. For the two last steps we applied the same protocols as was developed for solution phase[3] with minor modifications. Formation of an ester linkage between a carboxylic acid substrate and a solid phase resin is a common reaction in the area of peptide synthesis and combinatorial chemistry and is well described in the literature.[5,9] Merrifield resin was treated with 5 equivalents of *N*-benzoylated glycine **1** together with cesium carbonate in 2 mL of DMF at 200 °C for 10 min[10] giving **2**. The analysis (MAS-NMR and elemental analysis) showed a loading of approximately 1 mmol/g (80% yield) (Figure 1), which is in the same range as described in the literature, but approximately within a 100-fold shorter reaction time. After washing, the resin was treated with 5 equivalents DMFDEA in 2.5 ml DMF at 180 °C for 10 min to form the dimethylamino propenoates intermediate **4**.



Scheme 3 Synthesis of 3-(benzoyl)amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one. Reaction conditions: (i) Hippuric acid (5 equiv), $CsCO_3$ (5 equiv), DMF, 200 °C, 10 min. (ii) DMFDEA (5 equiv) in DMF, 180 °C, 10 min (iii) 2-aminopyridine (0.5 equiv) in HOAc, 180 °C, 10 min.

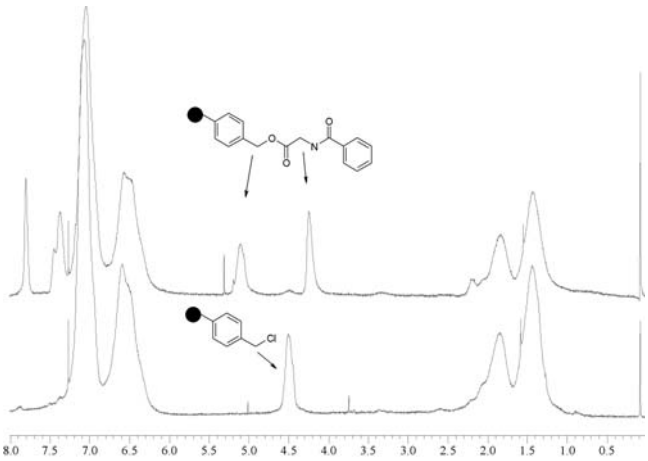


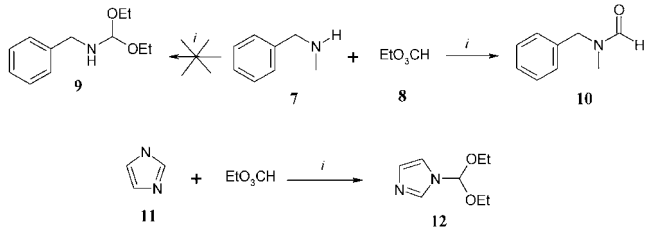
Figure 1 By comparing the peak area of the benzylic methylene group the yield could be determined.

The resin was washed, dried and then swelled in 0.5 mL of HOAc. In order to minimize the amount of unreacted dinucleophiles in the final reaction solution we only added 0.5–0.7 equivalents of dinucleophiles (**5**, **15**, **16**) to the reaction mixtures, based on an assumed 1 mmol/g loading of the intermediate. The reaction mixtures were heated for an additional 10 min at 180 °C. After filtration and wash-

ing of the resin, evaporation of the solvent was performed and the products (**6**, **17**, **18**) were found in high purity (>90%) and in yields between 77–95% (see Table 1).

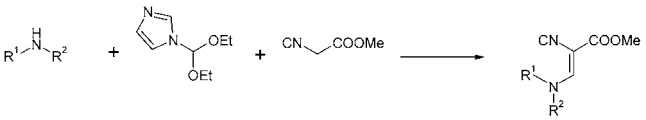
Synthesis of Heterocycles from Solid Phase Bound Dialkylaminopropenones

Approach 2 (Scheme 2) where dialkyl formamide diethyl acetal is bound to the solid phase and where the cleavage from the resin occurs when the dialkyl amino group is cleaved by a nucleophile was not as straightforward as approach 1. The idea was to form the dialkylformamide diethyl acetal on solid phase starting from methylaminated Merrifield resin (benzylchloride handle) and consequently we used benzyl methylamine (**7**) as a model substance in order to develop a protocol in solution which then could be transferred into solid phase conditions (Scheme 4). Benzyl methylamine was treated with 9 equivalents of triethyl orthoformate (**8**) in 2.0 mL of DMF at 200 °C for 5 min. to form benzyl methylformamide diethylacetal (**9**) according to a method described by Gmeiner et al.[11] However, we only found benzyl methylformamide as the product **10**. On the other hand we found, in accordance with the reference, that imidazole **11** forms the imidazolium diethylacetal (**12**) after treatment with triethylorthoformate[12] in 2.0 mL of DMF at 200 °C for 5 min.



Scheme 4 Synthesis of benzyl methylformamide. Reaction conditions: DMF, 200 °C, 5 min.

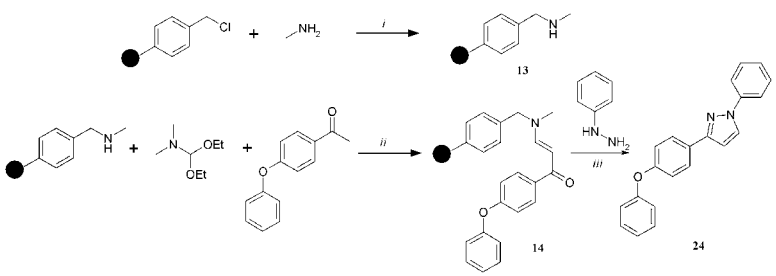
Our plan was then to follow the procedure describe by Meerwein et al.[13] for the synthesis of DMFDEA from DMF. The solid supported benzylmethyl amine could be treated with triethyloxonium tetrafluoroborate to afford a tetrafluoroborate salt. Treatment of the salt with sodium ethoxide should then give the diethylacetal compound. The major drawback with this procedure is the number of reaction steps needed to form the reagent. This strategy was therefore not adopted. Meerwein et al. have also described that when a dialkylamine was reacted with DMFDEA an amine exchange occurs in-situ giving the dialkylformamide diethylacetal. Unfortunately, when trying this method, benzyl methylformamide was formed as the only product. Bienaymé[14] reported recently the formation of substituted isonitriles by treatment of a dialkyl amine, imidazole diethylacetal and methyl isocyanoacetate, which form dialkylamino propenoates by a three-component cascade reaction[15] mechanism (Scheme 5). Since this multi-component approach forms the reagent in-situ it also reduces the number of reaction steps needed for the formation of the reactive intermediate.



Scheme 5 Formation of amino propenoates in a multicomponent approach via amine exchange.

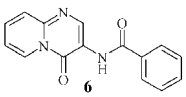
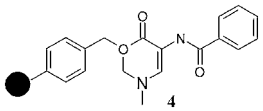
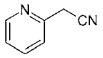
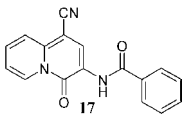
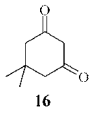
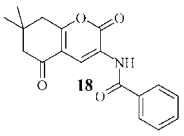
We therefore decided to try this approach to our model synthesis and we found that when reacting benzylmethylamine with DMFDEA and acetophenone in 2.0 mL of DMF at 180 °C for 5 min the desired propenone was formed in good yield based on LC/MS analysis. The outcome of the reaction indicated that this procedure could be successfully applied to our planned strategy with the solid phase linked *N*-methyl benzylamine The following procedure was therefore performed: Merrifield resin was reacted with 2.0 mL methylamine in water at 150 °C for 10 min to form the solid supported benzylmethylamine (**13**) in high yield (86% yield, 1.08 mmol/g based on elemental analysis). The MAS-NMR analysis was in this case difficult to interpret and therefore not used.[16] The resin was, after washing, treated with 5 equivalents DMFDEA together with 5 equivalents of 4-phenoxyacetophenone at 180 °C for 10 min in 2.0 mL of DMF to form the solid supported benzyl methyl aminopropenones **14**. MAS-NMR showed that products were formed but the spectra was not resolved well enough to make a good interpretation.

After washing, the resin was finally treated (the resin bound intermediate in excess) at 180°C for 10 min in 2.0 mL EtOH, DMF, or HOAc with 0.5 equivalents of the dinucleophiles to form the heterocycles in pure form. In



Scheme 6 Example of a solid phase synthesis of 1-Phenyl-5-(4-phenoxyphenyl)-pyrazole. Reaction conditions: (i) $MeNH_2$ in H_2O, 150 °C, 10 min (ii) DMF, 150 °C, 10 min (iii) HOAc, 150 °C, 10 min.

Table 1 Synthesis of Heterocycles via Propenoates[a]

Substrates	Products	Yields	Purity
 **5**	 **6**	77%	96%
 **4** +  **15**	 **17**	92%	95%
 **16**	 **18**	95%	98%

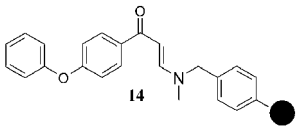
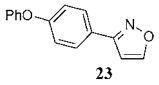
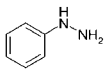
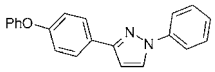
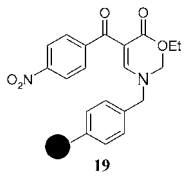
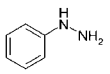
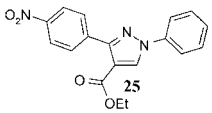
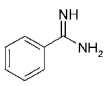
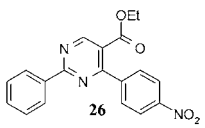
[a] Reaction conditions: 100–200 mg of solid supported propenoates were reacted with 0.5 equiv. of substrate **5**, **15**, **16** in HOAc at 180 °C for 10 min.

order to verify the developed methods described above, we performed a number of syntheses of heterocycles where both approaches 1 and 2 were performed (Scheme 6, Table 2).

In conclusion, we have described two ways to form activated aminopropenones and aminopropenoates on solid phase which in turn could be used in combinatorial syntheses of a large number of different heterocycles with an overall reaction time of approximately 30 min to give products of high purity in good to excellent yields. The major benefit with this approach is that purification is not needed. Our belief is that this approach could be extended further, to construct high libraries with high purity and large degree of diversity.

The microwave-assisted reactions were performed in a SmithSynthesizer™, a single mode microwave cavity, from Personal Chemistry. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 25 °C, using a Bruker at 300 MHz (^{1}H)/75 MHz (^{13}C) or a Varian 600 MHz instrument with a nano probe for the MAS-NMR analysis. All NMR spectra recorded were in agreement with the postulated structures and only selected data are reported. HPLC-MS chromatograms and spectra were obtained with an Agilent 1100 system with a diode array detector and a Agilent MSD. The analytical HPLC column was a HiChrome ACE AQ-5mm, C18. A gradient elution of 10% MeCN in H_2O by an increase to 95% MeCN in 2.5 min was used unless otherwise specified. Retention time for LC/MS is reported with % area of the peak. Elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden. All starting reagents were of the best grade available (Aldrich or Lancaster) and were used without purification. **CAUTION: These reactions are not recommended to be carried out in a multimode domestic microwave oven due to non-uni-**

Table 2 Synthesis of Heterocycles via Propenones[a]

Substrates		Products	Yields	Purity
 **14**	 **20**	 **23**	81%	85%
,,	 **21**	 **24**	81%	93%
 **19**	 **21**	 **25**	92%	91%
,,	 **22**	 **26**	94%	88%

[a] Reaction conditions: 100–200 mg of solid supported propenones were reacted with 0.5 equiv of substrate **20**–**22** at 180 °C for 10 min.

form irradiation and no temperature control (risk of explosion and thermal runaway). Also observe that the reactions are run in a closed vessel and that in several cases the pressure during the reaction is between 5 and 20 bar overpressure.

Coupling of *N*-Benzoyl Glycine to Merrifield Resin (2)
Merrifield resin (200 mg, 1.25 mmol/g loading capacity) was swelled in DMF (2.5 mL, 1.25 mmol, 5 equiv). *N*-Benzoyl glycine (Hippuric acid) (**1**), Cs_2CO_3 (1.25 mmol) were added and the reaction mixture was heated at 200 °C for 10 min. The reaction mixture was then cooled down to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicate compound **2** in a yield of 80% (approx. 1.0 mmol/g loading).

^{1}H NMR ($CDCl_3$): δ = 4.24 ($COCH_2NCO$), 5.11 ($PhCH_2CO$), 7.30–7.40 (4 H, Ar), 7.80 (1 H, Ar).

Elemental analysis: 1.35 weight % giving 0.96 mmol/g loading

Methylamination of Merrifield Resin (13)
Merrifield resin (200 mg, 1.25 mmol/g loading capacity) was treated with methylamine (2.0 mL) in H_2O (40% w/w) (excess) at 150 °C for 5 min. The reaction mixture was then cooled to r.t. by pressurized air. The residue was washed several times with H_2O, CH_2Cl_2 and MeOH to give compound **13**. Elemental analysis gave 1.52-weight% giving ca. 1.08 mmol/g loading.

Dimethyl Amino Propenoates from *N*-Benzoyl Glycine on Solid Support (4)
Solid supported *N*-Benzoyl glycine benzyl ester **2** (250 mg, ca. 0.25 mmol) was swelled in DMF (2.5 mL), DMFDEA (1.57 mmol) was added and the reaction mixture was heated at 180 °C for 10 min. The reaction mixture was then cooled to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicate compound **4** but no yield was determined due to low resolution.

Benzyl Methyl Amino Propenones from 4-Phenoxy Acetophenone on Solid Support (14)
Benzyl methylamine (200 mg) on solid support **13** (ca. 0.2 mmol) was swelled in DMF (2.0 mL), DMFDEA (214 μL), 4-phenoxy acetophenone (155 μL) were added and the reaction mixture was heated at 180 °C for 10 min. The reaction mixture was then cooled down to r.t. by pressurized air. The residue was washed several times with DMF, H_2O, and CH_2Cl_2. The resin was dried under reduce pressure in a desiccator. MAS-NMR analysis indicated compound **14** but no yield was determined due to low resolution.

Benzyl Methyl Amino Propenones from Ethyl 4-nitrobenzoylacetate on Solid Support (19)
Benzyl methylamine (200 mg) on solid support **13** was treated with ethyl 4-nitrobenzoylacetate as describe above for the synthesis of compound **19**. MAS-NMR analysis indicated compound **19** but no yield was determined due to low resolution.

3-(Benzoyl)amino-4*H*-pyrido[1,2-a]pyrimidin-4-one (6)[17]
Solid supported compound **4** (100 mg) were added to 2-aminopyridine (**5**) (6.6 mg, 0.07 mmol) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The HOAc was evaporated giving product **6** (14.2 mg), a total yield of 77% and 96% purity based on LC/MS analysis. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (dt, 1 H, ArH), 7.45–7.65 (m, 4 H, ArH), 7,75 (dd, 1 H, ArH), 7.95 (dd, 2 H, ArH), 8.84 (s, 1 H, NH), 8.95 (dd, 1 H, ArH), 9.75 (s, 1 H, pyrimidin-H). The structure was in accordance with the already published data.

3-(Benzoyl)amino-1-cyano-4*H*-quinolizin-4-one (17)[18]
Solid supported compound **4** (100 mg) was added to 2-pyridyl-acetonitrile (**15**) (5.6 μL , 0.05 mmol) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The HOAc was evaporated. The residue was dissolved in CH_2Cl_2 and filtered through a plug of silica. Crude analysis showed a LC/MS purity of 95%. Evaporation of the solvent gave the product **17 (**13.3 mg), a total yield of 92%. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (ddd, 1 H, ArH), 7.32–7.42 (m, 4 H, ArH), 7.77 (m, 2 H, ArH), 7.81 (dt, 1 H, ArH), 8.88 (s, 1 H, NH), 8.92 (dt, 1 H, ArH), 9.11 (s, 1 H, quinolizin-4-one). The structure was in accordance with the already published data.

3-(Benzoyl)amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (18)[19]
Solid supported compound **4** (100 mg) were added to 5,5 dimethyl-1,3-cyclohexanedione (**16**) (7.0 mg) in HOAc (0.5 mL). The soln was exposed to microwaves at 180 °C for 10 min. and then cooled to r.t. The HOAc was evaporated giving product **18** (14.8 mg), a total yield of 95% and 98% purity based on LC/MS analysis. The structure was confirmed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2 (s, 6 H, CH_3) 2.48 (s, 2 H, CH_2), 2.78 (s, 2 H, CH_2), 7.5–7.7 (m, 3 H, ArH), 7.92 (m, 2 H, ArH), 8.59 (s, 1 H, NH), 8.83 (s, 1 H, *C*H). The structure was in accordance with the already published data.

(4-Phenoxy)phenylisoxazole (23)
Solid supported compound **14** (200 mg) was mixed with hydroxylamine hydrochloride (0.5 equiv, 0.1 mmol) (**20**) and EtOH (2 mL). The mixture was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated. The product **23** was isolated in 81% yield and 85% purity based on LC/MS analysis.

HPLC: t_R 2.32 min (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (d, 1 H, *J* = 1.9 Hz, isoxazole), 7.04 (m, 4 H, ArH), 7.17 (dt, 1 H, ArH), 7.38 (m, 2 H, ArH), 7.76 (m, 2 H, ArH), 8.25 (d, 1 H, *J* = 1.9 Hz, isoxazole).

MS (APCI): *m*/*z* = 238.1 $[M + H]^+$.

1-Phenyl-5-(4-phenoxyphenyl)-pyrazole (24)
Solid supported compound **14** (200 mg) was mixed with phenylhydrazine (**21**) (0.5 equiv, 0.1 mmol) and HOAc (2 mL). The mixture was exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated.The product **24** was isolated in 81% yield and 93% purity.

HPLC: t_R 2.48 min (93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.48 (d, 1 H, *J* = 1.9 Hz, pyrazole), 6.91 (dd, 2 H, ArH), 7.03 (m, 2 H, ArH), 7.18 (dd, 2 H, ArH), 7.3–7.4 (m, 8 H, ArH), 7.71 (d, 1 H, *J* = 1.9 Hz, pyrazole).

MS (APCI): *m*/*z* = 313.0 $[M + H]^+$.

Ethyl 1-Phenyl-3-(4-nitrophenyl)-pyrazole-4-carboxylate (25)
Solid supported compound **19** (200 mg) was treated as described for compound **24** using EtOH as solvent. The EtOH was evaporated giving product **25** (31.0 mg) in 92% yield and 91% purity. The structure was confirmed by NMR.

HPLC: t_R 2.28 min (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ =1.28 (t, 3 H, CH_3CH_2), 4.25 (q, 2 H, CH_2CH_3), 7.20 (m, 2 H, ArH), 7.35 (m, 3 H, ArH), 7.51(d, 2 H, ArH), 8.21 (d, 2 H, ArH), 8.23(s, 1 H, pyrazole).

MS (APCI): *m*/*z* = 338.0 $[M + H]^+$.

Ethyl 2-Phenyl-4-(4-nitrophenyl)-pyrimidine-5-carboxylate (26)

Solid supported compound **19** (200 mg) in DMF (2 mL) was treated with 4-amidinobenzene hydrochloride (**22**) (0.1 mmol, ca. 0.5 equiv) and KOH (0.15 mmol), exposed to microwaves at 180 °C for 10 min and then cooled to r.t. The solvent was evaporated. The product (**26**) was isolated in 94% (32.7 mg) in 88% purity.

HPLC: t_R 2.51 min (88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3 H, CH_3CH_2), 4.28 (q, 2 H, CH_2CH_3), 7.54 (m, 3 H, ArH), 7.85 (m, 2 H, ArH), 8.35 (dd, 2 H, NO_2-phenyl), 8.56 (dd, 2 H, NO_2-phenyl), 9.31 (s, 1 H, pyrimidine).

MS (APCI): m/z = 350.0 $[M + H]^+$.

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