

Scale-Up of the Synthesis of a Pyrimidine Derivative Directly on Solid Support

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Abstract:

The solid-phase synthesis of 4-(2-amino-6-phenylpyrimidin-4-yl)benzamide, a compound obtained through combinatorial chemistry and parallel synthesis, can be scaled up directly on solid support in excellent yields and high purity. By applying highly loaded aminomethyl polystyrene as solid support, a good ratio between the product and the starting resin is achieved. For comparison, the synthesis was also performed in solution. The solid-phase synthesis approach has the advantage that the desired compound is easily and quickly accessible in sufficient quantities for early development demands.

Introduction

Research departments in industry and academia increasingly apply combinatorial chemistry for lead finding and lead optimisation. One of the practical approaches is solid-phase-supported parallel synthesis which generates libraries for high-throughput screening. The number of hits from this approach may increase dramatically, and consequently, numerous compounds as potential drug candidates are entering development. Process chemists are then faced with the problem of rapidly delivering the first amounts necessary for early preclinical and clinical studies. If the compounds were obtained by a solid-phase approach, solution-phase procedures for their synthesis might not be readily available. To tackle this problem we were interested in gaining experience of scaling up the solid-phase syntheses directly, without investing resources, for the search of solution-phase alternatives. In addition, solid-phase syntheses may be inherently time saving by allowing multistep procedures to be conducted without the need for isolation and purification of intermediates. Similar ideas have already been expressed and verified by Raillard¹ and are illustrated by additional examples in the present paper.

Starting from α,β -unsaturated ketones **A** (Figure 1) a library of different heterocycles was prepared in research.² From that library we choose the pyrimidine **1** as an example to study the following items: (1) scale-up phenomena of different solid-phase reactions and the necessary on-bead analytics, (2) effect of loading (an equivalent to concentration in solution-phase chemistry), (3) selection of appropriate

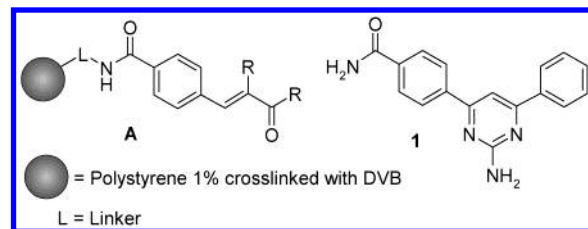


Figure 1.

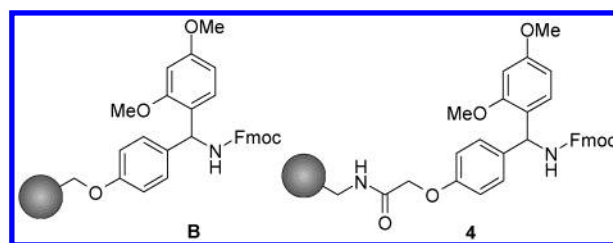


Figure 2.

equipment and investment, (4) comparison with the solution-phase alternative.

Results and Discussion

(1) Scale-Up Phenomena and On-Bead Analytics. The availability of starting materials is an obvious and self-explanatory issue during scale-up.³ For the anticipated large-scale solid-phase synthesis of pyrimidine **1** we had to replace Rink amide resin **B**⁴ which was used by our colleagues in research, because it is not readily available in larger amounts (see Figure 2). Therefore, we used the Rink amide acetamido resin **4**, which is well established in peptide amide synthesis⁵ and easily accessible.

Thus (see Scheme 1), 1.5 equiv of the acetic acid derivative **3** was coupled to aminomethyl polystyrene (AMPS **2a**, 1.54 mmol/g) by standard amide-forming conditions. After complete acylation as indicated by a negative Kaiser-test⁶ for unreacted amino functions, resin **4a** was checked for its loading by well elaborated UV techniques.⁷ After cleaving the Fmoc group with 20% diethylamine in DMF, 4-carboxybenzaldehyde **5** was coupled (diisopropyl carbodiimide, HOBt). Prolonged reaction time allowed the reduction of the amount of building block **5** by a factor of 10 as

(3) Lee, S.; Robinson, G. *Process Development: Fine Chemicals from Grams to Kilograms*; Oxford University Press: Oxford, 1995.

(4) Rink, H. *Tetrahedron Lett.* **1987**, 28, 3787.

(5) Bernatowicz, M. S.; Daniels, S. B.; Köster, H. *Tetrahedron Lett.* **1989**, 30, 4645.

(6) Kaiser, E.; Collescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, 34, 595.

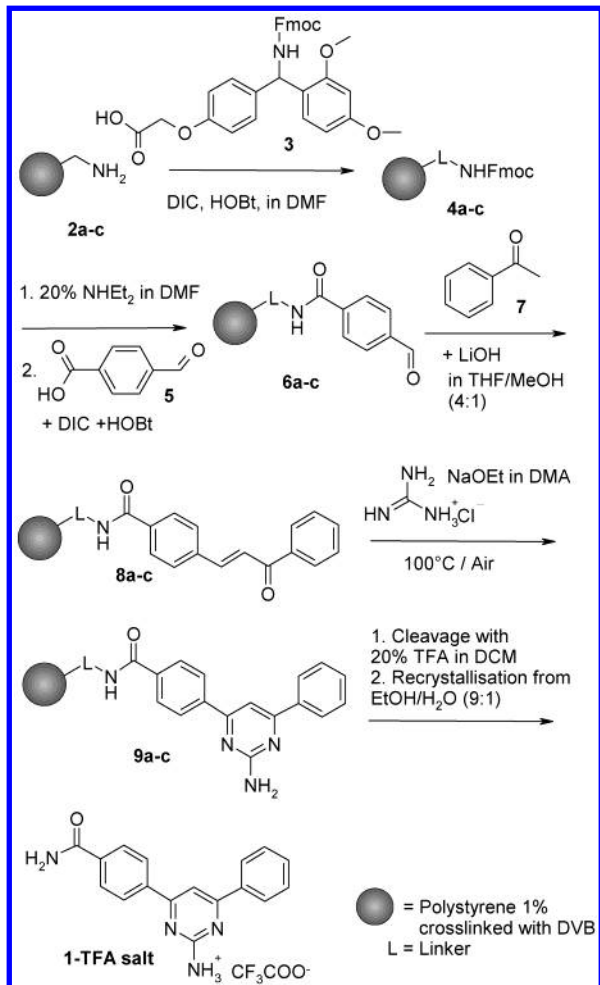
(7) Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makofske, R. C.; Chang, C. D. *Int. J. Pep. Protein Res.* **1979**, 13, 35.

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(1) (a) Raillard, S. P.; Ji, G.; Mann, A. D.; Baer, T. A. *Org. Process Res. Dev.* **1999**, 3, 177. (b) Raillard, S. P.; Ji, G.; Mann, A. D.; Baer, T. A. U.S. Pat. Appl. Publ. U.S. 2002/028466, March 7, 2002.

(2) Felder, E. R.; Marzinzik, A. L. *J. Org. Chem.* **1998**, 63, 723.

Scheme 1



compared to the original protocol. The structure of the resulting solid-phase-supported aldehyde **6a** was confirmed by IR spectroscopy⁸ which showed a strong C=O band at 1710 cm⁻¹ and the characteristic C-H band at 2730 cm⁻¹.

The subsequent Claisen–Schmidt reaction was originally performed on a 10 μmol scale using 20-fold excess of both acetophenone and LiOH to achieve complete formation of the chalcone **8**. This result could be verified; however, by employing the same conditions on a 35 mmol scale, no conversion was observed even after 22 h, as shown by IR spectroscopy. By cleaving a resin sample with 20% TFA in dichloromethane, only *p*-formylbenzamide **11** was detected by HPLC. This result may be rationalised by the low solubility of LiOH in DME under dry/aprotic conditions. Therefore, a small amount of EtOH was added, which initiated a fast reaction⁹ and the formation of the desired chalcone **8** together with 20% of the Michael adduct **10**. This was confirmed by sample cleavage from the resin and LC–MS analysis (Figure 3). Short reaction screening resulted in considerable improvements: using less acetophenone **7** and LiOH (1.5 and 0.5 equiv, respectively) and a mixed-solvent system of THF and methanol gave complete conversion within only 1 h, forming only 5% of Michael adduct as

(8) Yan, B.; Gremlich, H.-U.; Moss, S.; Coppola, G. M.; Sun, Q.; Liu, L. *J. Comb. Chem.* **1999**, *1*, 46.

(9) Chiu, C.; Tang, Z.; Ellingboe, J. W. *J. Comb. Chem.* **1999**, *1*, 73.

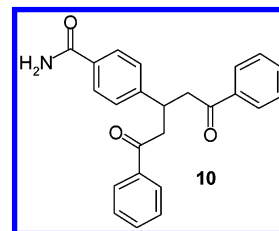
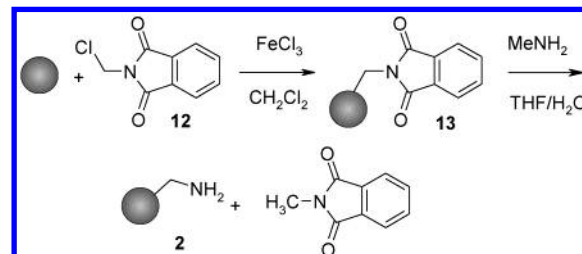


Figure 3.

Scheme 2



byproduct. An online Raman spectroscopic method was established to monitor the conversion of this Claisen–Schmidt reaction (see Supporting Information).¹⁰

The final reaction could be scaled up without any problems: chalcone **8a** and guanidine (liberated from its hydrochloride with sodium ethoxide) were heated in dimethyl acetamide while bubbling air through the mixture to form pyrimidine **9a**. After complete conversion (16 h) the product was cleaved from the support (20% trifluoroacetic acid in DCM). Pure 4-(2-amino-6-phenyl-pyrimidin-4-yl)benzamide **1** was obtained as its trifluoroacetate salt upon evaporation of the filtrate and recrystallisation of the residue from ethanol/water in 56% overall yield based on the solid-phase attached 4-carboxybenzaldehyde **6a**.

(2) Effect of Different Loading. After isolating the product of a solid-phase synthesis, the support (resin + linker) is usually discarded as waste, although successful examples of its reuse in further synthetic cycles are known.¹¹ To reduce both volume of operation and amount of waste, the loading of the resin, quantified as mmol of functionality per g, has to be increased. In addition to theoretical limitations (for polystyrene this is reached when every phenyl ring is substituted by the linker) there may be practical boundaries for the use of highly loaded resins in solid-phase-supported synthesis. For the preparation of **1** we verified the effect of this resin loading on operability, yield, and costs. This was also another reason to switch from the ether bonded Rink-linker **B** to the acetic acid derivative **4**, which can be assembled from **3** and differently loaded aminomethylated polystyrenes resins (AMPS, **2**). AMPS is commercially available with loading up to 2.9 mmol/g **2b** (NovaBiochem, Switzerland). By adapting and optimising the procedure of Adams¹² higher-loaded resins were prepared. Thus, polystyrene cross-linked with 1% divinylbenzene was reacted with *N*-chloromethyl phthalimide **12** in dichloromethane

(10) Dyson, R. M.; Helg, A. G.; Meisenbach, M.; Allmendinger, T. *11th International Symposium on Pharmaceutical and Biomedical Analysis*; Basle May 14–18 2000; P 007.

(11) Frechet, J. M. J.; Haque K. E. *Tetrahedron Lett.* **1975**, *16*, 3055.

(12) Adams, J. H.; Cook, R. M.; Hudson, D.; Jammalamadaka, V.; Lyttle, M. H.; Songster, M. F. *J. Org. Chem.* **1998**, *63*, 3706.

Table 1. Solid-phase synthesis of pyrimidine 1-TFA salt starting with resins of different loading

loading of AMPS, scale of synthesis	mass of 9 (g)	yield of crude 1-TFA salt		purity (area%) ^a	overall yield and purity after recrystallization of 1-TFA salt	
		in (g)	in (%)		in (%)	in (area%) ^a
2a , 1.54 mmol/g, 40 mmol, 26 g	49	14.9	92	84	56	>98
2b , 2.86 mmol/g, 70 mmol, 24.5 g	61.3	17.8	66	80	47	>97
2c , 4.48 mmol/g, 100 mmol, 22.3 g	74.9	31.8	82	86	55	>98

^a RP-HPLC.

using iron (III) chloride as Friedel–Crafts catalyst. If the reaction is performed at 25 °C, a colourless product **13** is obtained (Scheme 2) in contrast to dark-yellow resins obtained when working under reflux. The phthaloyl protective group was removed by means of aminolysis using methylamine in water/THF to avoid the common but toxic hydrazine and dioxane, respectively. The desired loading can be obtained by adjusting the ratio of PS, chloromethyl phthalimide, and FeCl₃. We synthesised AMPS with up to 4.48 mmol/g (**2c**), corresponding to two out of three phenyl rings being aminomethylated. We have not extended the investigation to the highest possible loading of AMPS. A resin with up to 7.3 mmol/g (96% of phenyl rings on polystyrene are substituted) has been described previously,¹³ but its application has not been reported thus far.

To study the effect of loading we repeated the synthesis depicted in Scheme 1 using different loaded resins. The conditions during reactions on higher-loaded resins (**2b** and **2c**) as compared to the initially used **2a** did not need any adjustments. The quality of the product was comparable, and the ratio of product to solid support was increased. The results are summarised in Table 1.

(3) Equipment Needed. Simple overhead mechanically stirred glass vessels immersed in an oil bath can be used to run on-bead reactions; however, filtration and washing of the whole mixture may be cumbersome. As pointed out by Raillard,¹ the use of reactors employed for scaling up solid-phase peptide synthesis is advantageous. These consist essentially of stirred suction filters with different volumes¹⁴ (if not, continuous flow reactors are employed).¹⁵ As peptide coupling and deprotection reactions are highly optimised, they usually run at room temperature; therefore, these suction filters do not have heating/cooling jackets. We therefore designed reactors capable of temperature adjustments by incorporating sintered filter plates into multiple necked double-wall reactors with volumes up to 4 L.¹⁶ The outer compartment can be connected to a heating/cooling circuit (thermostat). For single-wall sintered-bottom reaction vessels a simple cooling finger was designed. Figure 4 depicts two such vessels used throughout the investigations.

(4) Comparison with Solution-Phase Chemistry. Without the experience and the equipment to perform solid-phase-



Figure 4. Reactors with coarse fritted filter plates: (A) 250 mL, equipped with three-necks, jacket, and mechanical glass stirrer with Teflon paddle and (B) 1.5 L, equipped with jacket, glass anchor stirrer, and a five-necked clamped top.

supported syntheses on larger scale, chemists need to explore alternative routes utilising solution chemistry. To evaluate advantages and disadvantages of both approaches, we prepared pyrimidine **1** in solution phase as well. For this relatively small and simple molecule, similar chemistry was applied (see Scheme 3). Some interesting results arose.

Heating 4-carboxybenzaldehyde **5** in excess thionyl chloride, which is described to form acid chloride **14**,¹⁷ actually afforded the trichloro compound **15** instead. Therefore, the milder Vilsmeier reagent was used followed by aminolysis to obtain **11**. Due to its solubility in water the variable yield of **11** depended on the workup procedure. The Aldol condensation with acetophenone under standard conditions gave chalcone **17** containing 10% of the intermediate **16**. Its structure was revealed by independent synthesis¹⁸ to compare the NMR data and chromatographic properties.

(13) Zikos, C. C.; Ferderigos, N. G. *Tetrahedron Lett.* **1995**, 36, 3741.

(14) Edelstein, M.; Scott, P. E.; Sherlund, M.; Hansen, A. L.; Hughes, J. L. *Chem. Eng. Sci.* **1986**, 41, 617.

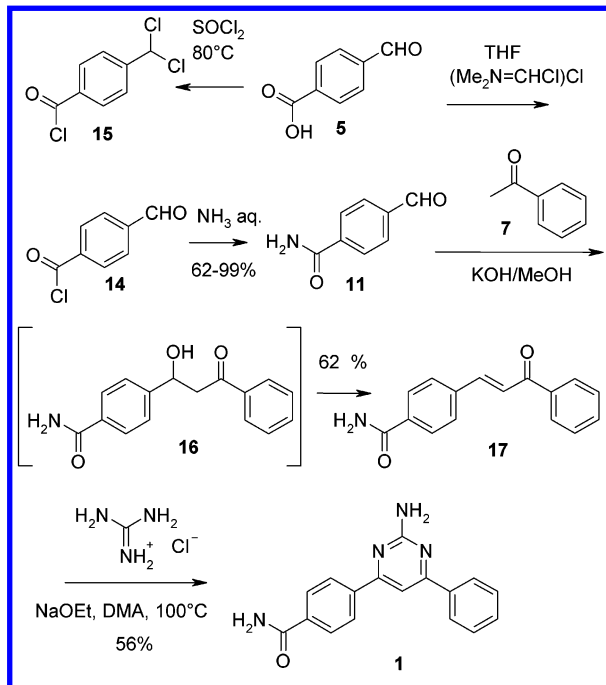
(15) Caciagli, V.; Cardinali, F.; Hansicke, A.; Tuchalski, G.; Lombardi, P. J. *Pept. Sci.* **1997**, 3, 224.

(16) These are made on request by AMSI-Glas AG, CH-4317 Wegenstetten, Switzerland.

(17) Graffner-Nordberg, M.; Sjödin, K.; Tunek, A.; Hallberg, A. *Chem. Pharm. Bull.* **1998**, 46, 591.

(18) Aldol reaction of silylenol ethers with aldehydes catalysed with bismuth trichloride according to Ohki, H.; Wada, M.; Akiba, K. *Tetrahedron Lett.* **1988**, 29, 4719.

Scheme 3



Hydroxyketone **16** thus prepared (see Experimental Section) turned out to be hardly soluble (even in dimethyl sulfoxide), the reason for its precipitation. This phenomena indicates the advantage of solid-phase-supported synthesis when intermediates have only low solubility. Finally the condensation with guanidine and the subsequent oxidation afforded pyrimidine **1** in moderate yield.

Conclusions

In summary, we demonstrated that a fast scale-up of the synthesis of the desired pyrimidine derivative was possible on the solid support. The research protocols could be used directly with only minor modifications. This saves time, which is one of the most important factors in the early stage of drug development. Highly loaded AMPS resin shifts the ratio of support/product in the desired direction and provides higher volume productivity. Thus, it makes this support attractive for the fast scale-up of small molecules. The production time of the solid-phase synthesis is comparable with the synthesis in solution due to the few reaction steps, but the overall yield (47–56%) exceeds the yield obtained by solution-phase synthesis (21–34%). Sure enough, process development would find conditions or routes to overcome drawbacks of the solution-phase synthesis and to improve the yield; however, we could show the relative ease of scaling up synthesis on solid support.

Experimental Section

All reagents and solvents were obtained from commercial suppliers and used without further purification. The 4-[(*R,S*)-1-[1-(9*H*-fluoren-9-yl)methoxycarbonylamino]-(2',4'-dimethoxybenzyl)]phenoxyacetic acid (**3**) was purchased from Senn Chemicals (Dielsdorf, Switzerland). The following aminomethylated polystyrene resins were used: 1.54 mmol/g 100–200 mesh from Senn Chemicals (Dielsdorf, Switzer-

land), 2.86 mmol/g 200–400 mesh from NovaBiochem (Läufelfingen, Switzerland). Polystyrene 100–400 mesh from Purolite (Pontyclun, UK) was used for the synthesis of highly loaded resin. All resins are 1% cross-linked with divinylbenzene. Melting points are uncorrected. ¹H- and ¹³C NMR spectra were recorded on a Bruker AC-300. IS-MS was carried out on a Varian MAT-711. FT-IR spectra (KBr) were recorded with a Bruker IFS66. The extinction in UV was determined on a Hewlett-Packard 3453 spectrophotometer. Thin-layer chromatography was performed on Merck silica gel 60 F₂₅₄ plates. RP-HPLC was carried out with an Agilent 1100 system at 50 °C using a Macherey-Nagel CC 125/4 Nucleosil 100-5 C18 column. Synthesis sequences were performed in reaction vessels containing a jacket, a frit Por. 2, and multiple necks. The reactions were carried out under N₂ atmosphere.

Highly Loaded Aminomethylated Polystyrene (2c). Underivatized 1% cross-linked 100–400 mesh polystyrene (26 g 0.25 mol) was washed twice with DCM. In 250 mL of DCM were suspended *N*-chloromethyl phthalimide (29.35 g, 0.15 mol) and anhydrous ferric chloride (12.17 g, 0.075 mol) for 15 min and then added to the pre-swollen resin. After stirring the suspension for 1 day at 23 °C, the resin was filtered and washed with DCM (100 mL), THF/H₂O (4:1, 100 mL), THF (150 mL), MeOH (100 mL), DMF (2 × 100 mL), MeOH (2 × 100 mL), THF (2 × 150 mL). A sample for IR was withdrawn. Then the resin was suspended in 500 mL of THF, aqueous methylamine (40%, 167 mL) was added, and the reaction mixture was stirred for 16 h at 55 °C. The resin was filtered and washed with THF (150 mL), alternating MeOH and DMF (2 × 100 mL), DCM (2 × 150 mL), and MeOH (3 × 100 mL). The colourless product **2c** was dried in vacuo at 45 °C for 16 h, providing 29.3 g of aminomethylated polystyrene. Elemental analysis showed 6.53% N, corresponding to a loading of 4.66 mmol/g. Titration with HCl gave 4.48 mmol/g (87.5% yield from chloromethyl phthalimide), and in the IR-spectrum the characteristic bands of the phthalylated intermediate at 1772 and 1712 cm⁻¹ had disappeared.

Loading of the Aminomethylated Resins 2 with the Fmoc-Protected Rink-Linker (3). The aminomethylated resins were swollen in DMF. To a 0.33 M solution of 1.5 equiv of Fmoc-protected Rink-linker and HOBt in DMF, was added dropwise 1.8 equiv of DIC over 15 min. This solution was stirred for an additional 15 min at 23 °C, and then the solution of the activated linker was added to the drained resins; the suspension was stirred for at least 16 h until the Kaiser test was negative. The resins were washed with 5 mL/g portions alternating DMF and MeOH (3 ×), DCM (2 ×), and MeOH (3 ×). The colourless products (**4a–c**) were dried in vacuo at 45 °C for 16 h. The loading efficiency was determined via quantitative monitoring of the Fmoc deprotection by UV spectroscopy² (Table 2).

Coupling of the 4-Carboxybenzaldehyde (5) onto the Solid Support. The Fmoc protecting group was cleaved from the resin **4a–c** with 20% diethylamine in DMF (4 mL/g) within 2 × 15 min. The resins were washed with 5 mL/g portions of alternating DMF and MeOH (2 ×) and DMF

Table 2: Loading of the AMPS resin with the Rink-linker

starting material	product	loading (Z, mmol/g)
32.5 g 2a Z = 1.54 mmol/g	59.73 g, 4a	0.87
24.5 g 2b Z = 2.86 mmol/g	59.08 g, 4b	1.17
22.3 g 2c Z = 4.48 mmol/g	70.72 g, 4c	1.45

(3 ×). 4-Carboxybenzaldehyde **5** (1.3 equiv) and 1.3 equiv of HOBt were dissolved in DMF (0.23 M solution including DMF on the swollen resin), and 1.5 equiv of DIC was added dropwise. After 15 min activation the solution was added to the resin. The suspension was stirred for at least 16 h until the Kaiser test⁶ was negative. The resins were washed with 5 mL/g portions of alternating DMF and MeOH (3 ×), DCM (2 ×), MeOH (3 ×). The product stemming from resin **4a** was dried in vacuo at 25 °C for 48 h, resulting in 54.96 g of colourless aldehyde resin **6a** (Z = 0.91 mmol/g according to weight decrease). Resins **6b–c** were directly used after 3 × washing with THF for the next step.

IR (cm⁻¹) 3400 (N–H), 3080–2850 (C–H), 2730 (C–H, aldehyde), 1710 (C=O, aldehyde), 1660 (C=O, amide), 1610 (C=C).

4-(3-Oxo-3-phenylpropenyl)benzamide (8a–c) via Claisen–Schmidt Reaction. The aldehyde resins were treated at 23 °C with a 0.25 M solution of 1.5 equiv of acetophenone **7** and 0.5 equiv of LiOH in THF/MeOH (4:1). At various times samples were withdrawn, washed, and treated with 20% TFA in DCM. The solvent was removed in vacuo, and the residue was analysed by RP-HPLC and TLC. (*R*_f = 0.56, *R*_f = 0.41 Michael-adduct, EtOAc/MeOH/TEA (9:1.5:0.5)). When the aldehyde had almost completely disappeared (RP-HPLC < 1%), within about 1.5 h, the resins were isolated by filtration. The resins were washed with 5 mL/g portions of THF, HOAc, DCM (2 ×), DMF (2 ×), and MeOH (3 ×). After taking a sample for IR, the resins were directly used for the next step.

IR (cm⁻¹) 3400 (N–H), 3070–2849 (C–H), 1660 (C=O, amide), 1607 (C=C).

4-(2-Amino-6-phenylpyrimidin-4-yl)benzamide Tri-fluoroacetate (1-TFA Salt). The chalcone resins **8a–c** were washed three times with DMA. Guanidine hydrochloride (6 equiv) was solubilised in DMA and treated with 6 equiv of NaOEt in DMA. The precipitate was filtered off, and the resulting 1 M solution of the free guanidine was added to the solid-supported chalcone. The reaction mixture was stirred at 100 °C for 16 h under an air atmosphere. The resins were washed with 5 mL/g portions of DMA, HOAc, DCM (2 ×), MeOH (2 ×), DMF (2 ×), DCM (2 ×), MeOH (3 ×). The products were dried in vacuo at 40 °C for 48 h (Table 1).

IR (cm⁻¹) 3420 (N–H), 3070–2850 (C–H), 1670 (C=O, amide), 1610 (C=C)

The final cleavage of the product was performed with 20% TFA in DCM (10 mL/g), the resin was filtered off, and the resulting solutions were evaporated to dryness yielding slightly coloured solids, which were recrystallised from EtOH/H₂O (9:1). Yields and purity are shown in Table

1. All products gave the expected results in IS-MS and identical IR and NMR spectra.

IS-MS (*m/z*) 291 [MH]⁺.

IR (cm⁻¹) 3421 (N–H), 3320 (N–H), 3050–3170 (C–H), 1674 (C=O), 1613 (C=C).

¹H NMR (DMSO-*d*₆) δ 8.31 (d, 2 H, 8.7 Hz); 8.23 (m, 2H); 8.12 (bs, 1H); 8.02 (d, 2 H, 8.6 Hz); 7.82 (s, 1H); 7.55 (m, 3H); 7.49 (bs, 1H).

¹³C NMR (DMSO-*d*₆) δ 168.2, 165.6, 164.7, 163.3, 139.6, 137.1, 137, 132, 129.6, 128.7, 128.2, 128, 103.5.

Microanalysis, found (calculated) C: 56.44 (56.45); H: 3.74 (3.79); N: 13.86 (13.92); F: 14.1 (13.87).

4-Formylbenzamide (11). The solution of 14.65 g (0.145 mol) of Vilsmeier reagent in 100 mL of dry THF was cooled under argon to –5 °C, and 17.0 g (0.113 mol) of 4-carboxybenzaldehyde **5** was added at once. The suspension was warmed to 0 °C and stirred for 16 h at this temperature and then poured onto 30 mL of cold aqueous ammonia. The mixture was concentrated by distillation at reduced pressure and the solid product obtained was filtered, washed with small amounts of cold water, and dried in vacuo to yield 10.23 g of 4-formylbenzamide. A second crop may be obtained from the mother liquor by extraction using ethyl acetate.

¹H NMR (300 MHz, DMSO-*d*₆) δ 9.85 (s, 1H); 7.95 (bs, 1H); 7.83 (d, 2H, 7.9 Hz); 7.74 (d, 2H, 7.9 Hz); 7.30 (bs, 1H).

Microanalysis, found (calculated) C: 64.42 (64.31); H: 4.73 (4.69); N: 9.39 (9.37).

1-Phenyl-3-(4-aminocarbonyl-phenyl)-2-propen-1-one (17). The solution of 4 g (26.8 mmol) of **11** and 4.83 g (40.2 mmol) of acetophenone **7** in 40 mL of methanol was treated with 0.47 g of a 15% aqueous solution of potassium hydroxide (1.24 mmol) and stirred at room-temperature overnight. The thick suspension obtained was diluted with methanol (10 mL) and water (50 mL). The solid was isolated by filtration, washed with methanol/water, and dried in vacuo to yield 4.2 g (17 mmol, 62%) of **17**, containing about 10% of the aldol addition product **16** according to ¹H NMR-spectroscopy, HPLC and elemental analysis. The aldol addition product was prepared independently (see below). A second crop obtained from the mother liquor was contaminated by the Michael-adduct **10**.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 8.12 (d, 2H, 7.5 Hz); 7.97 (d, 1H, 15 Hz); 7.91 (m, 4H); 7.88 (bs, 1H); 7.73 (d, 1H, 15 Hz); 7.61 (d, 1H, 7.5 Hz); 7.52 (t, 2H, 7.5 Hz); 7.42 (bs, 1H).

4-(2-Amino-6-phenylpyrimidin-4-yl)benzamide (1). The solution of guanidine hydrochloride (1.53 g, 16 mmol) in *N,N*-dimethylacetamide (10 mL) was treated with sodium ethoxide (1.1 g, 16.1 mmol), stirred for 15 min, and filtered. The filtrate was added to a solution of **17** (2.0 g, 7.95 mmol) in DMA (10 mL), and the resulting mixture was heated with stirring to 100 °C for 18 h. The reaction mixture was cooled to room temperature, and water (30 mL) was added slowly. The precipitate was filtered, washed with water, and dried in vacuo at 45 °C to obtain **1** (1.3 g, 56.4%) as a slightly yellow solid.

4-(1-Hydroxy-3-oxo-3-phenyl-propyl)benzamide 16 (Prepared for Structure Elucidation and Comparison). A mixture of 0.36 g (1.14 mmol) of bismuth trichloride, 10 mL of dichloromethane, 0.58 g (3.9 mmol) of **11** and 2.2 mL of 1-phenyl-1-trimethylsilyloxy ethylene (silylenolether of acetophenone) are stirred under nitrogen for 22 h at room temperature. Upon addition of methanol (0.5 mL) and concentrated aqueous HCl (20 μ L) the product precipitates. Isolation by filtration, washing with dichloromethane and water, and drying in vacuo afforded 588 mg of **16**. ^1H NMR (300 MHz, DMSO- d_6) δ : 7.90 (d, 2H, 7.6 Hz); 7.87 (bs, 1H); 7.78 (d, 2H, 7.6 Hz); 7.58 (t, 1H, 7.6 Hz); 7.4–7.5 (m,

4H); 7.23 (bs, 1H); 5.42 (d, 1H, 6 Hz); 5.1–5.2 (m, 1H); 3.38 (dd, 1 H, 16 Hz, 7.6 Hz); 3.12 (dd, 1H, 16 Hz, 5 Hz).

Supporting Information Available

Description of an online Raman spectroscopic method established to monitor the conversion of this Claisen–Schmidt reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>

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