Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from α,β-Unsaturated Ketones on the Solid Phase

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The value of α,β-unsaturated ketones as key intermediates for the combinatorial assembly of four different templates on the solid phase, namely pyrimidines, dihydropyrimidinones, pyridines, and pyrazoles, was explored with individual syntheses of variably substituted model compounds. Starting from aldehydes grafted on polystyrene support, the Wittig and the Claisen−Schmidt reaction conditions were adapted to efficiently prepare α,β-unsaturated ketones on the solid phase. Further derivatization of the α,β-unsaturated ketones to form pyrimidines succeeded with a number of amidines. In a feasibility study, the potential to obtain, in a modular fashion, other small heterocycles from the same intermediates was assessed. In this solid-phase approach α,β-unsaturated carbonyl intermediates can act as a three-carbon component and a primary enamine is utilized to complement the system for pyridine ring formation. Instead, with *N*-methylurea a dihydropyrimidinone is obtained. As an alternative, substituted hydrazines are incorporated in one orientation, providing pyrazoles with defined regioisomerism. The study indicates that α,β-unsaturated ketones grafted on the solid phase can take a pivotal role as branching points in a number of synthetic diversity schemes and, therefore, represent versatile intermediates for the efficient preparation of combinatorial *small molecule* libraries.

Introduction

The ability to generate large numbers of compounds rapidly in parallel processes, rather than by sequential reiteration of individual syntheses, is one of several factors that contribute to the appeal of combinatorial chemistry for drug discovery.[1] Another consequence of the developments in this area is the growing choice of modular reaction schemes, which provide high molecular diversity with broadly applicable reaction steps, under standardized conditions.[2]

The search for new valuable drug candidates not only demands that numerous structural subunits (building blocks) are combined on a particular backbone or template but also that a rich variety of such scaffolds is provided. This takes into account that the core structure of a compound class contributes to the pharmacological profile, in addition to the effects it mediates by directing the spatial arrangement of the pharmacophoric substituents. Occasionally, reports in the literature have indicated that, from certain intermediate structures grafted on the solid phase, it is possible to derive more than one type of heterocyclic compound libraries, e.g., pyrrolidines,[3] thiazolidines,[4] metathiazanones[4] and β-lactams[5] from immobilized aldimines, or dioxopiperazines and dioxomorpholines from α-bromo-substituted dipeptides,[6] or pyrazoles and isoxazoles from β-diketones.[7]

Here we discuss the value of α,β-unsaturated ketones as key intermediates for the combinatorial assembly of four different templates on the solid phase, namely pyrimidines, dihydropyrimidinones, pyridines, and pyrazoles, indicating that the potential to branch out to an even larger choice of scaffolds is worth exploring.

Results and Discussion

From the various reactions that afford α,β-unsaturated ketones, we chose to concentrate on the Wittig and the Claisen−Schmidt reaction, in view of the expected ease to adapt conditions to the solid-phase format. Aldol condensations, which provide β-ketols on solid support, have been described.[8] One early example reporting the solid-phase synthesis of formylchalcone[9] was not reproducible, under the given conditions, on the support and linkage we worked with, leading in fact exclusively to Michael adducts. A particular advantage of the base-catalyzed Claisen−Schmidt reaction is the large choice of commercially available carbonyl building blocks suitable to react with the aldehydes grafted on the solid support. Such immobilized aldehydes (e.g., **2**) are easily obtained by standard amide coupling protocols,[10] utilizing *N*,*N*′-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) on polystyrene with the Rink linker[11]

(1) For reviews see: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (b) Krchnak, V.; Lebl, M. *Mol. Diversity* **1995**, *1*, 193. (c) Felder, E. R.; Poppinger, D. *Adv. Drug Res.* **1997**, *30*, 111.

(2) For reviews see: (a) Thompson, L. A. and Ellman, J. A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 555. (b) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2436.

(3) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029.

(4) Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328.

(5) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.

(6) Scott, B. O.; Siegmund, A. C.; Marlowe, C. K.; Pei, Y.; Spear, K. L. *Mol. Diversity* **1996**, *1*, 125.

(7) Marzinzik, A. L.; Felder, E. R. *Tetrahedron Lett.* **1996**, *37*, 1003.

(8) (a) Kobayashi, S.; Hachiya, I.; Yasuda, M. *Tetrahedron Lett.* **1996**, *37*, 5569. (b) Kurth, M. J.; Ahlberg Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B. *J. Org. Chem.* **1994**, *59*, 5862. (c) Ruhland, T.; Künzer, H. *Tetrahedron Lett.* **1996**, *37*, 2757.

(9) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756.

(10) Heizmann, G.; Felder, E. R. *Peptide Res.* **1994**, *7*, 328.

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

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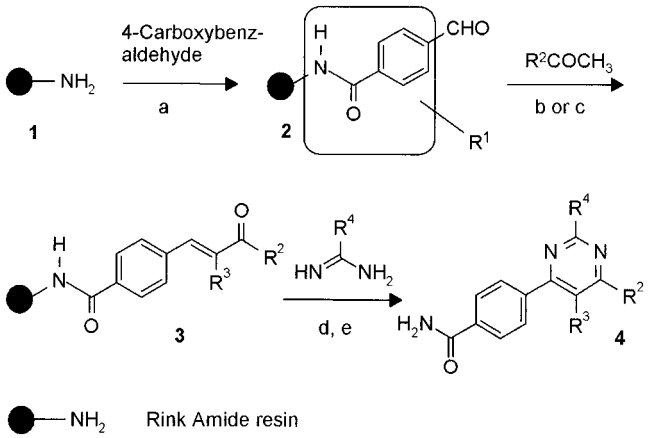

Figure 1. Key: (a) 3 equiv of $HOOCC_6H_4CHO$, 3.3 equiv of DIC, 3.3 equiv of HOBt, DMA, rt, 1 h; (b) 20 equiv of R^2COCH_3, 20 equiv of LiOH, DME, rt, 16 h; (c) 7.5 equiv of $R^2COC(PPh_3)R_3$, DMA, 60 °C, 4 h; (d) 10 equiv of $R^4CNH(NH_2)$, DMA, air, 100 °C, 16 h; (e) 20% TFA/CH_2Cl_2, rt, 15 min.

Table 1. α,β-Unsaturated Ketones 3

entry	R^2	R^3	% purity of crudes[a]	% yield[b]
3a	Ph	H	93	98
3b	2,4-$(CH_3O)_2C_6H_3$	H	94	64
3c	2-pyrrolyl	H	>95	83
3d	CH_3	H	>95	67
3e	Ph	CH_3	>95	71

[a] Purity determined by C-18 RP HPLC. [b] Isolated yields after preparative HPLC.

1. 4-Carboxybenzaldehyde, but also other aldehydes with furan or thiophene moieties, are coupled to the carrier with quantitative yield (data not shown), representing a first variable site R^1 for diversity generation (see Figure 1). Throughout the experiments reported here, we utilized resin-bound benzaldehyde **2** for all downstream derivatizations; the 4-carboxy substituent represented a convenient handle for the reversible attachment to the solid support.

For the following condensation we examined bases with sufficient solubility and aprotic solvents, which would better suit the requirements of solid-phase reaction conditions, than the reagents commonly used for analogous reactions in solution[12] (sodium hydroxide or sodium ethoxide in ethanol). Best results were obtained with LiOH in DME at room temperature. Under these specific conditions no Michael adduct was formed. Variably substituted acetophenones afforded chalcone derivatives **3a**−**c** of satisfactory purity. Table 1 lists purities of crude products, determined by HPLC analysis after cleavage from the resin with 20% TFA in dichloromethane. Even the presence of a weakly acidic heterocycle seems acceptable, since compound **3c** was obtained without detectable side products. On the other hand, the simultaneous introduction of an R^3 residue, namely a methyl substituent by usage of propiophenone instead of acetophenone, was not successful under the same or similar reaction conditions. Rather than attempting to expand the scope of the aldol reaction by applying more stringent conditions, we opted to access R^3-substituted compounds by the Wittig reaction. An advantage of the Wittig reaction in combinatorial chemistry is its broad applicability, being compatible with various functional groups. Entries **3d** and **3e** were obtained in excellent purity by Wittig reaction of the appropriate **2** and the corresponding triphenylphosphonium bromide with NaOEt at 60 °C in dimethylacetamide (DMA). The phosphorus ylides are readily available from α-bromo ketones by the Arbuzov reaction and treatment with a strong base, such as NaOEt.

(12) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 69.

Table 2. Examples of Characterized Products 4−7

entry	R^2	R^3	R^4	% purity of crudes[a]	% yield[b]
4a	Ph	H	4-$MeOC_6H_4$	>95	98
4b	Ph	H	2-thienyl	>95	83
4c	Ph	H	Me	>95	56
4d	Ph	H	4-pyridyl	>95	98
4e	Ph	H	NH_2	>95	94
4f	Me	H	Ph	>95	56
4g	Ph	Me	4-$MeOC_6H_4$	>95	38
4h	2,4-$(MeO)_2C_6H_3$	H	Ph	82	52
4i	2-pyrrolyl	H	Ph	78	60
5				93	46
6				94	84
7				83	73

[a] Purity determined by C-18 RP HPLC. [b] Isolated yields after preparative HPLC.

Initially, our main focus in further derivatizing the α,β-unsaturated ketones was the conversion to pyrimidines by means of a number of amidines with different steric and electronic properties. Resin-bound **3** was treated with a 0.5 M solution of the appropriate amidine in DMA at 100 °C for 16 h under air atmosphere. Subsequent treatment with 20% TFA in dichloromethane, elution from the support, and evaporation of the cleavage reagents gave **4**, which could be analyzed off the resin. At lower temperatures a mixture of a noncyclized, a nonaromatized, and the expected product was obtained. Chalcone **3a** can be cyclized with benzamidines bearing electron-releasing substituents, but also with other amidines carrying aromatic or heteroaromatic residues with electron-rich or electron-withdrawing moieties (Table 2, entries **4a**, **4b**, and **4d**). Pyrimidines with an alkyl group or another functional group, like $-NH_2$ in R^4, can also be synthesized (**4c** and **4e**). Once we had assessed that the substitution pattern of amidines is of minor importance for the cyclization, we were interested in studying the influence of residues other than R^4. Pyrimidines **4f** and **4g** were also prepared successfully from the alkyl-substituted intermediate **3d** and from enone **3e**, with an additional (methyl) substituent in the α-position. In compounds **4h** and **4i**, the electrophilicity of the COAr moiety is varied again by means of more or less electron-rich substituents, which does not noticeably affect the cyclization.

We also moved on to a simple feasibility study, which assessed the potential to obtain, in a modular fashion, other small heterocycles from the α,β-unsaturated ketones.

The "3+3" pyridine synthesis is one of the numerous synthetic sources of the pyridine ring in solution-phase chemistry.[13] In our solid-phase approach α,β-unsaturated carbonyl intermediates **3** can act as the three-carbon component and a primary enamine is utilized to comple-

(13) (a) Robinson, J. M.; Brent, L. W.; Chau, C.; Floyd, K. A.; Gillham, S. L.; McMahan, T. L.; Magda, D. J.; Motycka, T. J.; Pack, M. J.; Roberts, A. L.; Seally, L. A.; Simpson, S. L.; Smith, R. R.; Zalesny, K. N. *J. Org. Chem.* **1992**, *57*, 7352. (b) Shibata, K.; Urano, K.; Matsui, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2199.

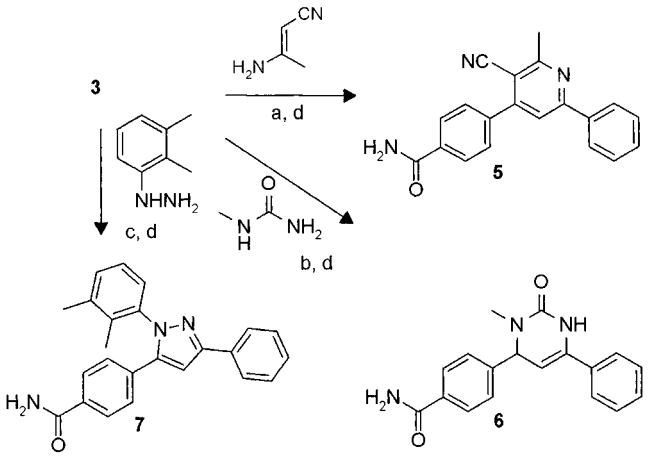

Figure 2. Key: (a) 11 equiv of *t*-BuOK, CH_3CN, rt, 16 h; (b) 10 equiv of $CH_3NHCONH_2$, 10 equiv of NaOEt, DMA, 16 h, rt; (c) 10 equiv of 2,3-$(CH_3)_2C_6H_3NHNH_2$, DMSO, 100 °C, 16 h; (d) 20% TFA/CH_2Cl_2, rt, 15 min.

ment the system for ring formation. Such enamines are, for instance, readily available by Thorpe reaction.[14] Ultrasonic irradiation of acetonitrile with potassium *tert*-butoxide in the presence of **3a** provides 3-cyanopyridine **5** at room temperature (Figure 2). The key intermediate, the imino tautomer of 3-aminocrotononitrile, is easily transformed into a reactive carbanion by potassium *tert*-butoxide. Primary enamine synthons other than nitriles, stabilized by conjugation with various electron-withdrawing groups, are under investigation, especially those that afford annelated heterocycles by preliminary Thorpe−Ziegler reaction.

The prospects to discover compounds with pharmacological activity has prompted combinatorial chemists to synthesize dihydropyrimidines in a combinatorial way. One approach has been reported with the Biginelli multicomponent condensation of immobilized ureas, β-keto esters, and aldehydes.[15] Our stepwise reaction scheme allows us to apply the *split-and-mix*[16] methodology and therefore to generate diversity on dihydropyrimidines with high efficiency. Reaction of *N*-methylurea with **3a** in the presence of NaOEt provided dihydropyrimidine **6** in 84% yield as a single regioisomer, identified by magnetic resonance NOE experiments.

We recently published the synthesis of pyrazoles from 1,3-diketones on solid support.[7] The reaction, although efficient, proceeds without stereoselectivity. The formation of pyrazoles from enones is regiospecific due to the Michael acceptor properties of α,β-unsaturated ketones and due to the difference in reactivity of the two hydrazine nitrogens. Treatment of **3a** with an excess of 2,3-dimethylphenylhydrazine provided only one regioisomer of *N*-phenylpyrazole **7**. The regioisomerism could be elucidated by NMR spectroscopy based on the observed NOE. In a previous experiment, using unsubstituted phenylhydrazine, the assignment was impeded by the overlap of aromatic protons coinciding in two multiplets. Nonaromatized product was also identified as a side product. The purity assessment of crudes (as listed in Tables 1 and 2) is important in view of the fact that in many instances the components of large libraries cannot be purified individually before testing their activity in screening assays.

In summary, we have indicated that α,β-unsaturated ketones grafted on the solid phase can take a pivotal role as branching points in a number of synthetic diversity schemes and, therefore, represent versatile intermediates for the efficient preparation of combinatorial libraries.

Experimental Section

Reagents were purchased from Aldrich, Fluka, and Novabiochem and used without further purification. ^{1}H NMR and ^{13}C chemical shifts are reported in ppm downfield from TMS. NMR spectra were measured on a Varian 300 MHz instrument. Analytical HPLC was performed using a reversed phase Purospher RP-C18 (5 μm) column (4 mm × 125 mm), 215 nm detection, gradient 5−100% B (A = H_2O/0.1% TFA; B = CH_3CN/0.1% TFA) over 20 min, flow = 1 mL/min. Preparative HPLC was performed using a reversed-phase Nucleosil C18 (5 μm) column (20 mm × 250 mm), 215 nm detection, 10−90% B over 90 min, flow = 15 mL/min. The mass spectra of the crude products were recorded on a VG Platform II (Micromass, Manchester, U.K.) equipped with an atmospheric pressure ionization (API) source coupled to a Hewlett-Packard 1050 HPLC system. The mass spectrometer was set up as an open access mass spectrometer running under electrospray conditions (ESI-MS). Samples were injected in flow injection analysis mode. The solvent delivery system was methanol/water 90/10 (% v/v) containing 0.1% ammonia.

Coupling Carboxyaldehydes onto the Solid Support (General Procedure). Fluorenylmethoxycarbonyl (Fmoc)-protected 4-[(2′,4′-dimethoxyphenyl)aminomethyl]phenoxymethyl resin (Rink amide resin[11]) (5 g, 2.25 mol) was subjected to repeated washes with 20% (v/v) piperidine/DMA until the UV absorption at 299 nm in the eluate reached the base-line level. Additional 5 washes (50 mL each) were carried out with pure DMA. Resin **1**, with the deprotected amino group of the linker, was acylated with 22.5 mL of a 0.3 M solution of a carboxyaldehyde (6.75 mmol) at rt (preactivation 40 min with 3.3 equiv of DIC (7.23 mmol) and 3.3 equiv of HOBt (7.23 mmol)) for at least 4 h, until the Kaiser test[17] was negative. The resulting solid-phase grafted aldehydes **2** were utilized for the following derivatizations.

Claisen−Schmidt Reaction on Solid Phase (General Procedure). To a glass vial containing 250.0 mg of aldehyde resin **2** (0.1 mmol) in 5.0 mL anhydrous DME were added 48.0 mg of $LiOH\cdot H_2O$ (2.0 mmol) and 2.0 mmol of the appropriate methyl ketone. The capped vial was shaken for 16 h at rt. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and dried in vacuo.

In our examples, cleavage from the resin with 20% (v/v) TFA/CH_2Cl_2 for 15 min afforded crude **3a**−**c** after evaporation. The products were purified by preparative HPLC.

4-(3-Oxo-3-phenylpropenyl)benzamide (3a). From 250.0 mg of the resin was obtained 24.6 mg (98% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (2H, m), 8.08 (1H, bs), 8.04 (1H, d, J =

(14) Doornbos, T.; Strating, J. *Synth. Commun.* **1971**, *1*, 193.
(15) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819.
(16) (a) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82. (b) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. 1988. *Abstr. 14th Int. Congr. Biochem. Prague* **1988**, *5*, 47 (Abstr FR:013).
(17) Kaiser, E. *Anal. Biochem.* **1970**, *34*, 595.

15.7 Hz), 7.98 (2H, d, J = 8.8 Hz), 7.94 (2H, d, J = 8.7 Hz), 7.78 (1H, d, J = 15.7 Hz), 7.68 (1H, m), 7.58 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 189.1, 167.5, 167.2, 158.0, 142.8, 137.4, 137.2, 135.6 133.3, 128.8, 128.7, 128.6, 127.9, 127.9, 127.0, 123.5; HRMS (FAB$^+$, m/z) calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0945.

4-[3-(2,4-Dimethoxyphenyl)-3-oxopropenyl]benzamide (3b). From 110.0 mg of the resin was obtained 9.0 mg (64% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (1H, bs), 7.92 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.5 Hz), 7.60 (3H, m), 7.42 (1H, bs), 6.66 (2H, m); ^{13}C NMR (75 MHz, DMSO) δ 189.2, 167.2, 164.1 160.3, 140.0, 137.5, 135.3, 132.1, 128.5, 128.1, 128.0, 121.2, 106.1, 98.6, 56.0, 55.6; HRMS (FAB$^+$, m/z) calcd for $C_{18}H_{17}NO_4$ 311.1158, found 311.1158.

4-[3-Oxo-3-(1*H*-pyrrol-2-yl)propenyl]benzamide (3c). From 300 mg of the resin was obtained 24.0 mg (83% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (1H, s), 8.05 (1H,s), 7.92 (4H, m), 7.79 (1H, d, J = 15.7 Hz), 7.66 (1H, d, J = 15.7 Hz) 7.42 (2H, m), 7.18 (1H, m), 6.28 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 178.4, 168.2, 140.5, 138.4, 136.1, 133.9, 129.2, 128.2, 128.8, 127.6, 125.4, 118.6, 111.1; HRMS (FAB$^+$, m/z) calcd for $C_{18}H_{17}NO_4$ 311.1157, found 311.1153.

Preparation of 3d and 3e by Wittig Reaction. A 23.6 mL portion of a 0.25 M solution of the appropriate triphenylphosphorane (5.91 mmol) in DMA was added to 2.0 g (788 μmol) of resin-bound **2**, and the resulting mixture was shaken at 60 °C for 14 h. The resulting mixture was filtered, washed with DMA and *i*-PrOH, and air-dried on the frit. Cleavage of the resin with 20% (v/v) TFA/CH_2Cl_2 for 15 min provided compounds **3d** and **3e**, respectively.

4-(3-Oxobut-1-enyl)benzamide (3d). From 154.0 mg of the resin prepared with 1-(triphenylphosphoranylidene)-2-propanone was obtained 7.7 mg (67% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (1H, bs), 7.91 (2H, d, J = 8.5 Hz), 7.79 (2H, d, J = 8.4 Hz), 7.64 (1H, d, J = 16.5 Hz), 6.89 (1H, d, J = 16.4 Hz), 2.35 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 198.1, 167.2, 142.0, 137.0, 135.5, 128.5, 128.2, 128.0, 27.4; HRMS (FAB$^+$, m/z) calcd for $C_{11}H_{11}NO_2$ 189.0789, found 189.0790.

4-(2-Methyl-3-oxo-3-phenylpropenyl)benzamide (3e). From 300 mg of the resin prepared with 1-phenyl-2-(triphenylphosphoranylidene)-1-propanone[18] was obtained 22.7 mg (71% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz) δ 8.04 (1H, bs), 7.93 (2H, d, J = 8.3 Hz), 7.74 (2H, d, J = 8.3 Hz), 7.56 (5H, m), 7.43 (1H, bs), 7.14 (1H, s), 2.19 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 199.2, 168.2, 140.9, 138.9, 138.6, 138.2, 134.9, 132.9, 130.4, 130.1, 129.5, 129.3, 128.5; HRMS (FAB$^+$, m/z) calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1103.

Cyclization to Pyrimidines 4a−i. To a solution of the corresponding amidine hydrochloride (96 μmol) in 96 μL of DMA was added 96 μL of a 1 M suspension of NaOEt in DMA. Free amidines were used without NaOEt treatment. The suspension was sonicated for 5 min and centrifuged. The resulting solution was added to the resin-bound chalcone derivative **3a** (9.6 μmol) in a vial, and the suspension was vigorously stirred at 100 °C overnight under air atmosphere. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and dried in vacuo. Cleavage with 20% (v/v) TFA/CH_2Cl_2 for 15 min afforded pyrimidines **4a−i**.

4-[2-(4-Methoxyphenyl)-6-phenylpyrimidin-4-yl]benzamide (4a). From 250.0 mg of the resin was obtained 37.3 mg (98% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (7H, m), 8.17 (1H, bs), 8.10 (2H, d, J = 8.7 Hz), 7.61 (3H, m), 7.53 (1H, bs), 7.14 (2H, d, J = 9.0 Hz), 3.87 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 165.1, 164.2, 164.1, 162.5, 140.0, 137.5, 137.2, 132.0, 130.8, 130.6, 129.8, 128.9, 128.3, 128.1, 115.0, 111.0, 56.2; HRMS (FAB$^+$, m/z) calcd for $C_{24}H_{19}N_3O_2$ 381.1477, found 381.1477.

4-(6-Phenyl-2-thien-2-yl-pyrimidin-4-yl)benzamide (4b). From 112.0 mg of the resin was obtained 13.3 mg (83% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (2H, d J = 8.6 Hz), 8.45 (3H, m), 8.21 (1H, d, J = 1.3 Hz), 8.17 (1H, s), 8.09 (2H, d, J = 8.7 Hz), 7.83 (1H, d, J = 5.1), 7.62 (3H, m), 7.55 (1H, bs), 7.29 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 168.2, 165.3, 164.2, 161.5, 144.1, 139.5, 137.4, 137.0, 132.3, 131.8, 130.2, 129.9, 129.5, 128.9, 128.3, 128.1, 111.3; HRMS (FAB$^+$, m/z) calcd for $C_{21}H_{19}N_3OS$ 357.0936, found 357.0933.

4-(2-Methyl-6-phenylpyrimidin-4-yl)benzamide (4c). From 92 mg of the resin was obtained 6.0 mg (56% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (1H, s), 8.42 (2H, d, J = 9.5 Hz), 8.35 (2H, m), 8.12 (1H, bs), 8.04 (2H, d, J = 9.5 Hz), 7.57 (3H, m), 7.48 (1H, bs), 2.77 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 167.7, 167.3, 164.1, 163.0, 138.9, 136.4, 136.2, 131.0, 128.9, 127.9, 127.3, 127.1, 110.0, 26.1; HRMS (FAB$^+$, m/z) calcd for $C_{18}H_{15}N_3O$ 289,1215, found 289,1217.

4-(6-Phenyl-2-pyridin-4-ylpyrimidin-4-yl)benzamide (4d). From 109.0 mg of the resin was obtained 15.0 mg (98% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (2H, m), 8.78 (3H, m), 8.61 (2H, d, J = 8.6 Hz), 8.54 (2H, m), 8.20, (1H, bs), 8.10 (2H, d, J = 8.6 Hz), 7.63 (3H, m), 7.55 (1H, bs); ^{13}C NMR (75 MHz, DMSO) δ 168.1, 165.7, 164.6, 161.1, 149.6, 147.2, 139.0, 137.6, 136.5, 132.5, 129.8, 128.9, 128.4, 128.3, 124.4, 113.7; HRMS (FAB$^+$, m/z) calcd for $C_{22}H_{16}ON_4$ 352.1324, found 352.1324.

4-(2-Amino-6-phenylpyrimidin-4-yl)benzamide (4e). From 125.0 mg of the resin was obtained 13.6 mg (94% yield) of product: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (2H, d, J = 8.7 Hz), 8.24 (2H, m), 8.10 (1H, bs), 8.01 (2H, d, J = 8.6 Hz), 7.80 (1H, s), 7.54 (3H, m), 7.47 (1H, bs); ^{13}C NMR (75 MHz, DMSO) δ 167.3 164.9, 163.9, 163.2, 139.2, 136.6, 136.0, 130.8, 128.7, 127.8, 127.2, 126.9, 102.4; HRMS (FAB$^+$, m/z) calcd for $C_{17}H_{14}N_4O$ 290.1167, found 290.1167.

4-(6-Methyl-2-phenylpyrimidin-4-yl)benzamide (4f). From 81.8 mg of the resin was obtained 6.0 mg (56% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (2H, m), 8.41 (2H, d, J = 8.5 Hz), 8.15 (1H, s), 8.06 (2H, d, J = 8.5 Hz), 8.01 (1H, s), 7.55 (4H, m), 2.63 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 169.4, 168.2, 163.9, 162.8, 139.7, 138.2, 137.2, 131.7, 129.9, 129.5, 128.9, 127.8, 115.7, 25.0; HRMS (FAB$^+$, m/z) calcd for $C_{18}H_{15}N_3O$ 289.1215, found 289.1219.

4-[2-(4-Methoxyphenyl)-5-methyl-6-phenylpyrimidin-4-yl]benzamide (4 g). From 240.0 mg of the resin was obtained 14.3 mg (38% yield) of product after

(18) Dombrovskii, A. V.; Shevchuk, M. I. *Zh. Obshch. Khim.* **1963**, *33*, 1263.

preparative HPLC: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (2H, d, J = 9.1 Hz), 8.05 (2H, d, J = 8.6 Hz), 7.84 (2H, d, J = 8.6 Hz), 7.74 (2H, d, J = 8.0 Hz), 7.53 (3H, m), 7.00 (2H, d, J = 9.1 Hz), 3.86 (3H, s), 2.33 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.4, 167.3, 166.5, 162.2, 161.1, 150.4, 142.2, 139.5, 135.7, 130.6, 130.2, 130.1, 130.0, 129.2, 128.3, 123.8, 114.9, 56.2, 18.1; HRMS (FAB$^+$, m/z) calcd $C_{25}H_{21}N_3O_2$ 395.1634, found 395.1634.

4-[6-(2,4-Dimethoxyphenyl)-2-phenylpyrimidin-4-yl]benzamide (4h). From 94.5 mg of the resin was obtained 9.0 mg (52% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (2H, m), 8.43 (1H, s), 8.37 (2H, d, J = 8.6 Hz), 8.23 (1H, d, J = 9.3 Hz), 8.12 (1H, bs), 8.07 (2H, d, J = 8.6 Hz), 7.58 (3H, m), 7.51 (1H, bs), 6.78 (2H, m), 3.98 (3H, s), 3.89 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 164.0, 163.7, 163.0, 160.6, 140.3, 138.5, 137.1, 132.8, 131.6, 129.5, 129.1, 128.8, 127.9, 119.1, 115.4, 107.1, 99.7; HRMS (FAB$^+$, m/z) calcd for $C_{25}H_{21}N_3O_3$ 411.1583, found 411.1581.

4-[2-Phenyl-6-(1*H*-pyrrol-2-yl)pyrimidin-4-yl]benzamide (4i). From 100 mg of the resin was obtained 10.0 mg (60% yield) of product after preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (2H, m), 8.41 (2H, d, J = 8.7 Hz), 8.06 (2H, d, J = 8.6 Hz), 8.03 (1H, s), 7.51 (3H, m), 7.19 (1H, d, J = 3.7 Hz), 7.08 (1H, d, J = 2.5), 6.33 (1H, dd, J = 3.7, 2.5 Hz); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 164.0, 162.7, 158.9, 140.1, 138.4, 137.0, 131.7, 130.3, 129.3, 129.1, 128.9, 127.7, 124.3, 113.2, 111.2, 109.0; HRMS (FAB$^+$, m/z) calcd for $C_{21}H_{16}N_4O$ 340.1324, found 340.1324.

Synthesis of 3-Cyanopyridine 5. To a vial containing 250 mg of **3a** on Rink amide resin (0.1 mmol) were added 3.7 mL acetonitrile and 125 mg (1.1 mmol) *t*-BuOK. The reaction mixture was sonicated for 50 min at rt under Ar and was allowed to stand for 16 h. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and air-dried. 4-(3-Cyano-2-methyl-6-phenylpyridin-4-yl)benzamide (**5**) was cleaved from the resin with 20% (v/v) TFA/CH_2Cl_2. The crude product was purified by preparative HPLC to obtain 20.5 mg (46% yield) of pure **5**: ^{1}H NMR (300 MHz DMSO-d_6) δ 8.25 (2H, m), 8.13 (1H, s), 8.06 (3H, m), 7.64 (2H, d, J = 8.6 Hz), 7.53 (4H, m), 2.83 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.1, 162.9, 159.0, 153.5, 139.6, 137.8, 136.3, 13.4, 129.8, 129.6, 128.8, 128.4, 118.7, 117.9, 110.0, 106.2; HRMS (FAB$^+$, m/z) calcd for $C_{20}H_{15}N_3O$ 313.1215, found 313.1214.

Synthesis of Dihydropyrimidinone 6. To a vial containing 14.2 mg (0.57 mmol) of NaOEt in 1.14 mL of anhydrous DMA were added 142 mg (57 μmol) of resin loaded with **3a** and 42.0 mg (0.57 mmol) of *N*-methylurea. The reaction mixture was allowed to stand under Ar for 16 h. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and air-dried. 4-(3-Methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydro-pyrimidin-4-yl)-benzamide (**6**) was cleaved from the resin with 20% (v/v) TFA/CH_2Cl_2. The crude product was purified by preparative HPLC to obtain 14.6 mg (84% yield) of pure product: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (1H, d, J = 1.7 Hz), 7.94 (1H, bs), 7.88 (2H, d, J = 8.6 Hz), 7.50 (2H, m), 7.37 (2H, d, J = 8.6), 7.33 (4H, m), 5.19 (1H, dd, J = 1.7, 5.0 Hz), 5.15 (1H, d, J = 5.0 Hz), 2.70 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 153.2, 145.5 135.3, 133.6, 128.7, 128.4, 128.1, 127.9, 126.2, 125.4, 98.2, 61.7, 32.4; HRMS (FAB$^+$, m/z) calcd for $C_{18}H_{17}N_3O_2$ 307.1321, found 307.1321.

Synthesis of Pyrazole 7. To a vial containing 250.0 mg of **3a** on Rink amide resin (0.1 mmol) was added 2 mL of 0.5 M solution of dimethylphenylhydrazine in DMSO. The reaction mixture was shaken for 16 h at rt. The resin was washed with DMA and *i*-PrOH consecutively and air-dried. **7** was cleaved from the resin with 20% (v/v) TFA/CH_2Cl_2. The crude product was purified by preparative HPLC to obtain 26.8 mg (73% yield) of 4-[2-(2,3-dimethylphenyl)-5-phenyl-2*H*-pyrazol-3-yl]benzamide (**7**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (2H, d, J = 8.6 Hz), 7.77 (2H, d, J = 8.6 Hz), 7.43 (2H, m), 7.35 (1H, m), 7.30 (3H, m), 7.19 (2H, m), 7.16 (1H, d, J = 7.5 Hz), 2.30 (3H, s), 1.87 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.0, 151.6, 145.3, 140.1, 139.1, 134.9, 134.6, 133.6, 133.1, 131.4, 129.6, 128.8, 128.5, 128.2, 126.9, 126.6, 126.2, 104.7, 20.7, 14.6; HRMS (FAB$^+$, m/z) calcd for $C_{24}H_{21}N_3O$ 367.1685, found 367.1687.

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Supporting Information Available: ^{1}H NMR spectra of products of type **3** and **4** and of compounds **5**−**7**, including NOE spectra of **6** and **7**. IR spectrum of **3a**, measured by the *single bead* technique (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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