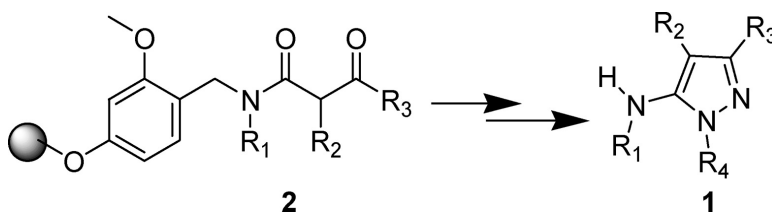Article

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Solid-Phase Synthesis of 5-Substituted Amino Pyrazoles

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An efficient method for the solid-supported synthesis of 5-*N*-alkylamino and 5-*N*-arylamino pyrazoles is described. This method is general and mild and utilizes readily accessible resin-immobilized β-ketoamides **2** as starting materials for the preparation of **1**. Resin-immobilized β-ketoamide, aryl-, or alkylhydazine and Lawesson's reagent are suspended in a mixture of THF/Py and heated at 50−55 °C to give a resin-bound 5-aminopyrazole, that is liberated from the solid support by treatment with TFA.

Introduction

Rapid assembly of small molecules using high-speed synthesis is proving to be a powerful tool in the current resource constrained environment of drug discovery.[1] We have previously described[2] a solution-phase method that allows for the efficient introduction of *N*-mono or *N,N*-disubstituted amino groups at the C-5 position of the pyrazole core. We now present the application of this methodology to the solid-supported synthesis of 5-*N*-alkyl/arylamino pyrazoles **1** (Figure 1). A method for the solid-phase synthesis of 5-*N*-alkylamino pyrazoles has been reported previously,[3] but it is limited to the preparation of 5-*N*-alkylamino pyrazoles with electron-withdrawing groups at the C-3 (R_3) position (**1**, Figure 1). The method presented herein is broader in scope and allows for the efficient introduction of alkyl groups at R_2 and R_3 on 5-amino pyrazoles **1**. Our protocol utilizes readily accessible resin-immobilized β-ketoamides **2** as the key starting material.

Results and Discussion

The resin-immobilized β-ketoamides serve as strategic starting materials for the generation of diverse aminopyrazoles. Three of the four possible points of diversity can be incorporated into this single constituent. For the most part, these resin-immobilized intermediates can be synthesized using techniques analogous to those described in the literature for the formation of β-carboxamides in solution[4,5] and are presented in Scheme 1. Methods A and B were used to introduce C-2-unsubstituted β-ketoamides, where R_2 is an H (**2a**−**d**, Table 1). Method A required reacting the readily accessible acyl adducts of Meldrum's acid[4a] **4** with resin-immobilized primary amines **3**. Method B takes advantage
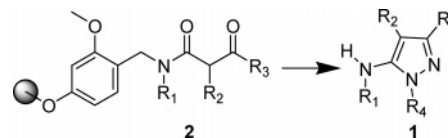

Figure 1. Solid-phase synthesis of 5-aminopyrazoles.

of the reactivity of *tert*-butyl-β-ketoesters[4b] **5** to accomplish this same task. Moreover, aliphatic *tert*-butyl-β-ketoesters **5** (R_3 is alkyl) substituted with alkyl groups R_2 at the C-2 position reacted readily with resin-bound amines to give their corresponding β-ketoamides (e.g., **2e** and **2g**, Table 1).[6] Both methods require heating the β-keto substrates with resin-bound amines **3** in resin-compatible solvents, such as NMP or toluene, in the presence of DMAP. The study presented herein is limited to a small set of representative substrates. Overall, we have found, at least when the substituent at C-2 (R_2) is H, that methods A and B are extremely general. We have examined multiple substrates of the nature **4** and **5** containing various electronically diverse aryl and alkyl R_3 groups. Overwhelming, a majority of these subtrates reacted with resin-bound amines **3** to give β-ketoamides **2** in high loading.

Unfortunately, aryl *tert*-butyl-β-ketoesters **5** (R_3 is aryl) substituted with alkyl R_2 groups at the C-2 position failed to give adequate coupling to the resin-bound amines **3**. To circumvent this issue, Method C was used, wherein the resin-bound amines **3** were first converted to amides **6** to install the required R_2 groups. Subsequent steps involved reacting the enolate of **6** with esters of aryl acids **7** to generate the requisite β-ketoamides (eg. **2f**, **h**). The presence of other ionizable centers is a limitation using this method.

Representative resin-immobilized β-ketoamides used in the study are shown in Table 1. Resin-bound amines (R_1) included aniline (Ph) and benzylamine (Bn). For the substitutents R_2 and R_3 on the β-ketoamides, a phenyl (Ph) was used as a representative aryl group, and the methyl (Me) group, to represent an aliphatic group. Phenylhydrazine and

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Scheme 1. Immobilization of β-Ketoamides on Solid Support
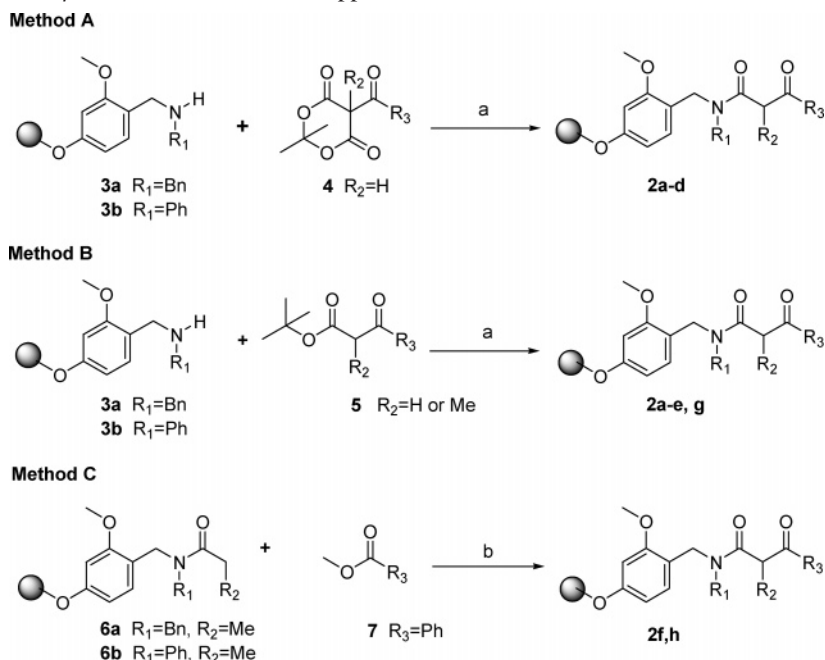
Reagents and conditions: (a) 2.5 equiv of **4** or **5**, DMAP (0.1 equiv), NMP, 85 °C, 10–24 h. (b) 2.5 equiv of **7**, 3 equiv LHMDS, −78 °C, 2 h and then room tmeperature for 2 h.

Table 1. Resin Immobilized β-Ketoamides **2**

resin (2)	R_1	R_2	R_3	resin loading (mmol/g)
2a	Bn	H	Me[a,b]	0.80
2b	Bn	H	Ph[a,b]	0.80
2c	Ph	H	Me[a,b]	0.80
2d	Ph	H	Ph[a,b]	0.75
2e	Bn	Me	Me[b]	0.73
2f	Bn	Me	Ph[c]	0.70
2g	Ph	Me	Me[b]	0.70
2h	Ph	Me	Ph[c]	0.70

[a] Prepared using method A. [b] Prepared using method B. [c] Prepared using method C.

benzylhydrazine were chosen as the representative aryl and alkyl hydrazines, respectively.

Preparation of the resin-bound 5-amino pyrazole intermediate **10** (Scheme 2) was achieved by reacting a mixture of the β-ketoamide resins **2**, monosubstituted hyrazines **8** (free-based or HCl salts), and Lawesson's reagent in THF/pyridine.[7a] Reaction times were variable and depended on the nature of the substrates. Reaction temperature appears to be crucial, particularly for the C-substituted β-ketoamides (**2e**–**h**). Temperatures >60 °C[7a] resulted in a significant decrease in yield. The cyclization presumably proceeds through the formation of hydrazone intemediate **9**. Those substrates that did not react efficiently undergo cyclization to give pyrazolones **11**, which cleave from the resin during the reaction. These could be identified by LC/MS analysis of the reaction media.[7b]

For uniformity, the reactions were heated at 55 °C for 40 h. The excess reagents were washed free from the resin-bound intermediate **10**, and the 5-aminopyrazoles were liberated from the solid support by treatment with 25% TFA in DCE. In all cases, only a single product was identified.[8a,9]

The results of the study are reported in Table 2. These results are in line with those found for the solution-phase

study.[2] The C-2-unsubstitued β-ketoamide intermediates **2a**–**d**, in which R_2 is H, reacted with alacrity when treated with either phenyl- or benzylhydrazine to give **1a**–**h** (Table 2) in yields of 55–91%. Conversely, β-ketoamide intermediates **2e**–**h**, in which R_2 is Me, reacted sluggishly and gave products **1i**–**p** (Table 2) in much lower yields (<55%). In one case, only a trace amount of product **1i** was isolated from the reaction of phenylhydrizine with substrate **2e**, whereas benzylhydrazine reacted with **2e** to give product **1j** in ~45% yield. More interestingly, both phenyl- and benzylhydrazine reacted with substrate **2g** to give **1k** (53%) and **1l** (55%), respectively. The only notable difference between substrates **2e** and **2g** is in the amide substituent R_1. β-Ketoamide **2e** is appended to the resin via an alkyl benzylamine (R_1, Bn), whereas **2g** is bound by an aryl aniline (R_1, Ph). The electronic nature of the aniline (R_1) group appears to have played a role in the outcome of the reaction. Thus, at least for these specific C-2 and C-3 dialkyl-substituted β-ketoamides (**2e** and **2g**), the aryl R_1 group in **2g** appears to offer greater stability to its corresponding intermediate phenylhydrazone **9** relative to that generated from β-ketoamide **2e**. The electronic nature of the R_1 appears to be less important in the fate of the reaction involving β-ketoamides **2e** and **2g** with benzylhydrazine.

As was found in the solution-phase[2] study, β-ketoamides in which R_3 is phenyl (intermediates **2b, d, f,** and **h**) required longer reaction times and gave lower yields in comparison to their β-ketoamide counterparts (**2a, c, e,** and **g**), where R_3 is Me (see Table 2). In this study, β-ketoamides generated from aniline (**2c, d, g, h**) appeared to give slightly better yields of the respective 5-aminopyrazoles than the benzyl-β-ketoamides **2a, b, e, f**. As mentioned previously, this was most dramatically demonstrated in the isolation of **1k** (R_1 = Ph) in 53% yield relative to **1i** (R_1 = Bn), which was isolated in only a trace amount.

Scheme 2. Solid-Phase Synthesis of 5-Aminopyrazoles
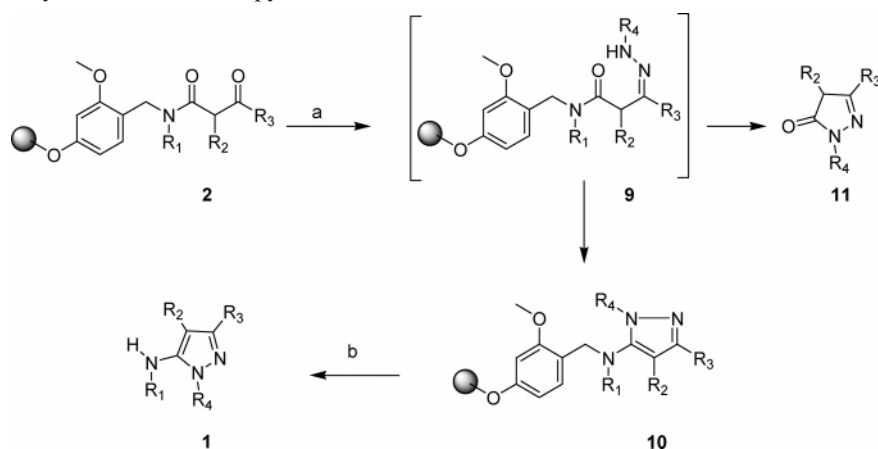
Reagents and conditions: (a) 2.5 equiv of R₄NHNH₂·xHCl (**8**), 2.5 equiv of Lawesson's reagent, THF/Py (95/5), 55 °C, 40 h. (b) 25% TFA/DCE, room temperature for 1 h.

Table 2. Representative Yields of **1**

products (**1**)	R₁	R₂	R₃	R₄	crude purity (%)[a]	yield (%)[c]
1a	Bn	H	Me	Ph	>90	85
1b	Bn	H	Me	Bn	>90	80
1c	Ph	H	Me	Ph	>90	90
1d	Ph	H	Me	Bn	>90	90
1e	Bn	H	Ph	Ph	>90	70
1f	Bn	H	Ph	Bn	>90	63
1g	Ph	H	Ph	Ph	>90	68
1h	Ph	H	Ph	Bn	>90	55
1i	Bn	Me	Me	Ph		trace amount[d]
1j	Bn	Me	Me	Bn	>90	45
1k	Ph	Me	Me	Ph	>90	53
1l	Ph	Me	Me	Bn	>90	55
1m	Bn	Me	Ph	Ph	90[b]	20
1n	Bn	Me	Ph	Bn	90[b]	18
1o	Ph	Me	Ph	Ph	85[b]	15
1p	Ph	Me	Ph	Bn	90[b]	15

[a] Purity assessed by HPLC prior to purification. [b] Remaining material was identified as unreacted β-ketoamide. [c] Purified using preparative HPLC; averaged yield of two runs (from 50 mg of resin **2**) and based on the loading of resins **2**. [d] Apparent by LC/MS.

In summary, we have extended the scope of our previously described methodolgy[2] to include solid-supported synthesis of 5-*N*-alkylamino and 5-*N*-arylamino pyrazoles. The use of a solid support allows for the expansion of this methodology[2] for diversity generation,[9] as well as high-speed analoging and ease of product isolation. The 5-pyrazolone side product **11** that was identified in solution-phase reactions[2] is no longer an issue, because it undergoes cyclative cleavage from the resin prior to product isolation. Most importantly, the excess of noxious Lawesson's reagent and its waste are easily removed.

Experimental Section

General Methods. (4-Formyl-3-methyoxyphenoxy)methyl-polystyrene (FMP) resin (100−200 mesh, 1.4 mmol/g loading) was purchased from Polymer Laboratories. Solvents were purchased from EM Science or Aldrich. All reagents were purchased from Sigma-Aldrich and were used without further purification. Compounds were analyzed by LC/MS with a Shimadzu SCL-10A HPLC coupled to a Waters Micromass ZQ electrospray mass spectrometer using a Phenomenex-prime S5 C-18, 4.6 × 30 mm column, gradient elution 0−100% B/A over 2 min, hold 100% B for 1 min (solvent A = 10% MeOH/H₂O containing 0.1% TFA, solvent B = 90% MeOH/H₂O containing 0.1% TFA), flow rate 5 mL/min, and UV detection at 220 nm. Preparative HPLC was run on Shimadzu VP-ODS 20 × 50 mm column eluting with a mixture of solvents A and B (same as above), elution gradient 0−100% B over 10 min and hold at 100% B for 2 min, flow rate 20 mL/min, and UV detection at 220 nm. Prepacked silica columns (Part no. CUSIL15R3) were purchased from United Chemical Technologies, Inc., Bristol, PA 19007. ¹H NMR spectra were obtained on a Bruker Advance 400 MHz.

Procedure for Reductive Amination of Amines to Formyl Resin. Typical Reaction Conditions. 4-Formyl-3-methoxyphenoxy-derivatized polystyrene resin (5g, 7 mmol, 1.4 mmol/g loading) was suspended in DMF (65 mL) and trimethyl orthoformate (5 mL), then treated with benzylamine (2.25 g, 21 mmol), followed by sodium triacetoxyboro-hydride (3.7 g, 17.5 mmol) and acetic acid (0.65 mL). The mixture was shaken for 14 h at room temperature. The resin slurry was poured into a peptide vessel, filtered, and washed thoroughly with 10% H₂O/DMF (3 × 75 mL), THF (3 × 75 mL), THF/MeOH/Et₃N (50/48/2) (2 × 75 mL), THF (3 × 75 mL) and DCM (3 × 75 mL), then dried under reduced pressure to give **3a**. The loading of the amine was determined by benzoylating (benzoyl chloride, Et₃N in DCE, 4 h) a known amount of resin and establishing the amount of benzyl benzoate liberated from the resin upon treatment with 25% TFA in DCM. Loading of **3a** was established to be approximately 1.1 mmol/g.

Immobilization of β-Ketoamides to Resin. Methods A and B. For example, amine resin **3a** (1 g, 1.1 mmol, 1.1 mmol/g loading), Meldrum's adducts **4** (R₂ = H, R₃ = alkyl or aryl), or *tert*-butyl-β-keto esters **5** (R₂ = H or alkyl, R₃ = alkyl or aryl) (2.75 mmol, 2.5 equiv), and DMAP (33 mg, 0.28 mmol) were suspended in NMP (12 mL) and heated at 85 °C for 20 h. The resins were filtered and washed thoroughly with THF (3 × 20 mL), MeOH (3 × 20 mL), and DCE (3 × 20 mL), then dried to give resins **2a−e** and **g**. The loading of β-ketoamides was established by cleaving

a known amount of resin with 25% TFA in DCE. Purity was established by LC/MS and ^{1}H NMR. In all cases, only the corresponding β-ketoamides were isolated. Resin loading ranged from 0.7 to 0.8 mmol/g.

Method C. For example, resin **2a** (1 g, 1.1 mmol, 1.1 mmol/g loading) was suspended in 15 mL of DCM and treated sequentially with $(i\text{-Pr})_2$EtN (580 μL, 3.3 mmol) and propionyl chloride (240 μL, 2.75 mmol). The mixture was shaken for 10 h. The resin was filtered and washed with THF (4 × 10 mL) and DCM (3 × 10 mL), then dried under vacuum to give **6a**. Loading was established to be 0.92 mmol/g. Resin **6a** (0.5 g, 0.46 mmol) and methyl benzoate (155 mg, 1.15 mmol) were suspended in dry THF (6 mL) under nitrogen atmosphere. The mixture was cooled to −78 °C and treated with LHMDS (1.4 mL, 1.4 mmol, 1 M in THF). The mixture was stirred gently at −78 °C for 2 h, then allowed to warm to 0 °C and stirred for an additional 2 h. The resin was treated with 250 μL of water and 50 μL of acetic acid, filtered, and washed thoroughly with THF (2 × 10 mL), 1% AcOH in THF (3 × 10 ML), THF (4 × 10 mL), and DCM (3 × 10 mL), then dried under reduced pressure. The loading of resins **2f** and **2h** was established to be ~0.7 mmol/g. The method is limited to reagents that contain no other reactive or ionizable centers (R$_1$, R$_2$, or R$_3$) that are also capable of reacting under the these conditions.

General Procedure of the Synthesis of 5-Amino-pyrazoles. Typical Reaction Conditions. For example, a mixture of the β-ketoamide resin **2a** (50 mg, 0.04 mmol, 0.8 mmol/loading)), phenylhydrazine hydrochloride (15 mg, 0.1 mmol), and Lawesson's reagent (41 mg, 0.1 mmol) were suspended in 950 μL of THF and 50 μL of pyridine in a 1-dram vial. The reaction was heated at 55 °C with shaking for 40 h. The slurry was transferred to a fritted polypropylene tube and washed free of the excess reagents using the following sequence of solvents, with intermittent shaking (2−5 min): DMF (3 × 1 mL), DMF/AcOH/H$_2$O (90/5/5) (3 × 1 mL), MeOH/THF (1/1) (3 × 1 mL), THF/NH$_4$OH(aq) (9/1) (3 × 1 mL), DCM/MeOH (1/1) (3 × 1 mL), and DCM (3 × 1 mL). The resin was air-dried and treated with 1 mL of 25% TFA in DCM for 1 h to liberate the compound. The TFA cleavage cocktail was collected, and the resin was rinsed with DCM (2 mL). The filtrates were combined, concentrated in vacuo, suspended in 0.150 mL of toluene, and filtered through a prepacked silica column (500 mg) with diethyl ether/heptane (1/4, 5−7 mL) to give **1a** (9 mg, 86%) in >90% purity by HPLC. The crude products were purified to homogeneity using Prep-HPLC or silica gel chromatography.

N-Benzyl-3-methyl-1-phenyl-1H-pyrazol-5-amine (1a). Yield, 9 mg (85%, from 50 mg of **2a**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.65 (m, 3H), 7.60 (m, 2H), 7.33 (m, 4H), 4.39 (s, 2H), 2.30 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 264/265; t_R = 1.27 min.

N,1-Dibenzyl-3-methyl-1H-pyrazol-5-amine (1b). Yield, 9 mg (80%, from 50 mg of **2a**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.42 (m, 3H), 7.33 (m, 5H), 7.20 (m, 2H), 5.33 (s, 2H), 4.47 (s, 2H), 2.27 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 278/279; t_R = 1.40 min.

3-Methyl-N,1-diphenyl-1H-pyrazol-5-amine (1c). Yield, 9 mg (90%, from 50 mg of **2c**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.56 (m, 2H), 7.50 (t, J = 13 Hz, 2H), 7.40 (m, 1H), 7.20 (td, J = 7.7, 1.8 Hz, 2H), 6.93 (d, J = 7.7 Hz, 2H), 6.85 (t, 7.3 Hz), 2.31 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 250/251; t_R = 1.49 min.

1-Benzyl-3-methyl-N-phenyl-1H-pyrazol-5-amine (1d). Yield, 9.5 mg (90%, from 50 mg of **2c**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.36−7.24 (m, 5H), 7.20 (d, J = 7.2 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.96 (t, J = 8.0 Hz, 1H), 5.29 (s, 2H), 2.27 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 264/265; t_R = 1.49 min.

N-Benzyl-1,3-diphenyl-1H-pyrazol-5-amine (1e). Yield, 9 mg (70%, from 50 mg of **2b**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.74 (dd, J = 7.6 Hz, 1.6 Hz, 2H), 7.70−7.55 (m, 4H), 7.50 (m, 1H), 7.45−7.30 (m, 7H), 7.25 (1H, m), 4.39 (s, 2H). LC/MS (ESI) m/z (M + H)$^+$ 326/327; t_R = 1.83 min.

N,1-Dibenzyl-3-phenyl-1H-pyrazol-5-amine (1f). Yield, 8.5 mg (63%, from 50 mg of **2b**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.72 (dd, J = 8.0 Hz, 2.0 Hz, 2H), 7.50−7.23 (m, 11H), 7.20 (dm, J = 8 Hz, 2H), 5.39 (s, 2H), 4.47 (s, 2H). LC/MS (ESI) m/z (M + H)$^+$ 340/341; t_R = 1.77 min.

N,1,3-Triphenyl-1H-pyrazol-5-amine (1g). Yield, 8 mg (68%, from 50 mg of **2d**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.86 (dd, J = 4 Hz, 1.2 Hz, 2H), 7.66 (d, J = 4 Hz, 2H), 7.64 (t, J = 7.2 Hz, 2H), 7.48−7.30 (m, 4H), 7.20 (m, 2H), 7.00 (m, 2H), 6.82 (m, 1H), 6.60 (s, 1H). LC/MS (ESI) m/z (M + H)$^+$ 312/313; t_R = 2.00 min.

1-Benzyl-N,3-diphenyl-1H-pyrazol-5-amine (1h). Yield, 6.7 mg (55%, from 50 mg of **2d**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.77 (d, J = 8.5 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.38−7.20 (m, 8H), 6.93 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 6.85 (t, J = 7.6 Hz, 1H), 5.35 (s, 2H). LC/MS (ESI) m/z (M + H)$^+$ 326/327; t_R = 2.00 min.

N,1-Dibenzyl-3,4-dimethyl-1H-pyrazol-5-amine (1j). Yield, 4.7 mg (45%, from 50 mg of **2e**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.40 (m, 3H), 7.30 (m, 3H), 7.22 (m, 2H), 7.14 (m, 2H), 5.32 (s, 2H), 4.57 (s, 2H), 2.23 (s, 3H), 2.00 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 292/293; t_R = 1.45 min.

3,4-Dimethyl-N,1-diphenyl-1H-pyrazol-5-amine (1k). Yield, 4.9 mg (53%, from 50 mg of **2g**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.47 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.30 (m, 1H), 7.12 (t, J = 7.6 Hz, 2H), 6.72 (t, J = 7.0 Hz), 6.57 (dd, J = 8.5, 1.2 Hz, 2H), 2.29 (s, 3H), 1.89 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 264/265; t_R = 1.68 min.

1-Benzyl-3,4-dimethyl-N-phenyl-1H-pyrazol-5-amine (1l). Yield, 5.3 mg (55%, from 50 mg of **2g**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.25 (m, 3H), 7.14 (m, 4H), 6.80 (t, J = 7.6 Hz, 1H), 6.62 (d, J = 7.6 Hz, 2H), 5.15 (s, 2H), 2.23 (s, 3H), 1.82 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 278/279; t_R = 1.63 min.

N-Benzyl-4-methyl-1,3-diphenyl-1H-pyrazol-5-amine (1m). Yield, 2.4 mg (20%, from 50 mg of **2f**); ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.60 (m, 4H), 7.55 (t, J = 8.0 Hz, 1H), 7.50−7.48 (m, 4H), 7.25 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 4.04 (s, 2H), 2.05 (s, 3H). LC/MS (ESI) m/z (M + H)$^+$ 340/341; t_R = 1.83 min.

N,1-Dibenzyl-4-methyl-3-phenyl-1*H*-pyrazol-5-amine
(**1n**). Yield, 2.2 mg (18%, from 50 mg of **2f**); ^{1}H NMR (400
MHz, CD$_3$OD) δ 7.56 (d, J = 8.0 Hz, 2H), 7.50−7.15 (bm,
13H), 5.31 (s, 2H), 4.90 (s, 2H), 2.02 (s, 3H). LC/MS (ESI)
m/z (M + H)$^+$ 354/355; t_R = 1.843 min.

4-Methyl-*N*,1,3-triphenyl-1*H*-pyrazol-5-amine (1o). Yield,
1.7 mg (15%, from 50 mg of **2h**); ^{1}H NMR (400 MHz,
CD$_3$OD) δ 7.65 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz,
2H), 7.37 (t, 2H, J = 8.0 Hz, 2H), 7.30 (m, 3H), 7.25 (m,
1H), 7.05 (t, J = 8.0 Hz, 2H), 6.63 (t, J = 8.0 Hz, 1H), 6.55
(d, J = 8.0 Hz, 2H), 1.98 (s, 3H). LC/MS (ESI) *m/z* (M +
H)$^+$ 326/327; t_R = 1.99 min.

**1-Benzyl-4-methyl-*N*,3-diphenyl-1*H*-pyrazol-5-amine
(1p).** Yield, 1.8 mg (15%, from 50 mg of **2h**); ^{1}H NMR
(400 MHz, CD$_3$OD) δ 7.67 (d, J = 8.0 Hz, 2H), 7.46 (t, J
= 8.0 Hz, 2H), 7.40 (m, 1H), 7.25 (m, 3H), 7.15 (m, 4H),
6.77 (t, J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 2H), 5.26 (s,
2H), 2.02 (s, 3H). LC/MS (ESI) *m/z* (M + H)$^+$ 340/341; t_R
= 2.00 min.

Supporting Information Available. Spectroscopic char-
acterization for compounds **1a**−**1h** and **1j**−**1p**. This material
is available free of charge via the Internet at http://
pubs.acs.org.

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of pyrazoles with electron-withdrawing groups at the C-3
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(6) β-Ketoamides **2** substituted with aryl R$_2$ were not prepared.
From our previous solution-phase study, we had found that
ketoamides of this type were not very reactive in the
subsequent 5-aminopyrazole synthesis step (see ref 2).
(7) (a) THF can be substituted for 1,4-dioxane. Pyridine is not
necessary for all substrates. Reactions involving a C-2-
unsubstituted β-ketoamide (i.e., **2a**−**d**, Table 1), intermedi-
ates proceed equally well without pyridine. Pyridine appears
to be necessary in reactions involving hindered, C-2-
substituted β-ketoamide intermediates (i.e., **2e**−**h**, Table 1)
for decent product recovery. Reaction temperature (50−55
°C) also appears to be critical, again more so for the C-2-
substituted β-ketoamide intermediates. Reaction temperatures
>60 °C are detrimental and result in lower yields, presum-
ably due to the premature formation of the corresponding
5-pyrazolone **11**, which undergoes cyclative cleavage from
the resin. The rates for the sluggish reactions could not be
enhanced by heating at higher temperatures without com-
promising yields. (b) Intermediates of type **9** were also
identified when the reactions were carried out in solution
phase (see ref 2).
(8) The regiochemistry of the R$_4$ group was established using
(2D) ^{1}H/^{13}C HMQC/HMBC and ^{1}H/^{15}N HMQC/HMBC, as
well as COSY and PSNOESY NMR experiments.
(9) The reactivity of both electron-rich and electron-deficient
hydrazines and R$_3$ on β-ketoamides were examined in library
format. Though there were some combinations of hydrazines
and β-ketoamides that were not compatible, on the whole,
many electronically diverse reagents were tolerated, giving
reasonable yields and purities. For example, simple hydrazine
is incompatible under these reaction conditions. We also
noticed that certain heteroarylhydrazines, as an example,
2-hydrazinopyridine, failed to give appreciable products with
2. We also observed that sterically hindered substrates also
played a role in reaction rates and product recovery.
β-Ketoamides **2** containing sterically encumbered groups at
the C-3 position generally required longer reaction times
(>36 h) for complete reaction. In some instances, the
reactions could not be pushed to completion. Similar trends
were seen with ortho-substituted arylhydrazines, but to a
much lesser extent. The combination of sterically encum-
bered C-3-substituted β-ketoamides and ortho-substituted
arylhydrazines gave poor recovery of pyrazoles **1**, and mostly
starting β-ketoamides were isolated after TFA-mediated
cleavage from the resin. In all cases, the regioselectivity was
independent of the electronic nature of the reactants.

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