

# Solid-Phase Synthesis of *N*-Alkyl-*N*-( $\beta$ -keto)amides and 1,2,4,5-Tetrasubstituted Imidazoles Using a Traceless Cleavage Strategy

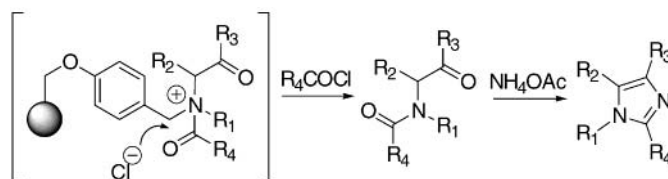
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Received November 23, 1999

## ABSTRACT

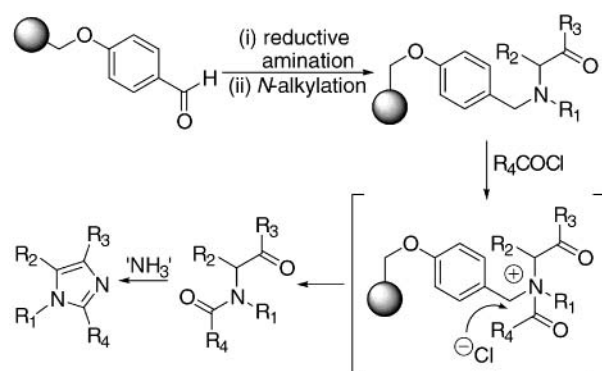


The solid-phase synthesis of *N*-alkyl-*N*-( $\beta$ -keto)amides and 1,2,4,5-tetrasubstituted imidazoles was demonstrated using a traceless cleavage strategy based on benzylic acylammonium chloride reactivity. The approach enables the assembly of diverse compounds in a minimal number of steps in moderate to excellent yield (23–88%) and high purity (64–100%).

Tertiary amides are an important class of compounds for drug discovery. More than 20 000 compounds with known biological activity contain tertiary amides.<sup>1</sup> In particular, the *N*-alkyl-*N*-( $\beta$ -keto)amide skeleton is also a synthetic precursor to imidazoles.<sup>2</sup> The imidazole pharmacophore is of therapeutic interest due to its hydrogen bond donor–acceptor capability.<sup>3</sup> There has recently been considerable development in the solid-phase synthesis of small molecule libraries for lead generation and drug discovery.<sup>4</sup> Despite the importance of tertiary amides, very few methodologies exist for the solid-phase preparation of this class of molecules.<sup>5</sup> To address this, a method for the solid-phase synthesis of tertiary amides was explored using a traceless linker strategy<sup>6</sup> based

on benzylic acylammonium chloride reactivity. This approach involves the formation of an *N*-benzyl tertiary amine on resin followed by *N*-acylation to release in situ a tertiary amide (Scheme 1). The chemistry of debenzylating tertiary amines

Scheme 1. Synthetic Strategy



(1) This estimate was obtained by searching the Molecular Design Limited Drug Data Report.

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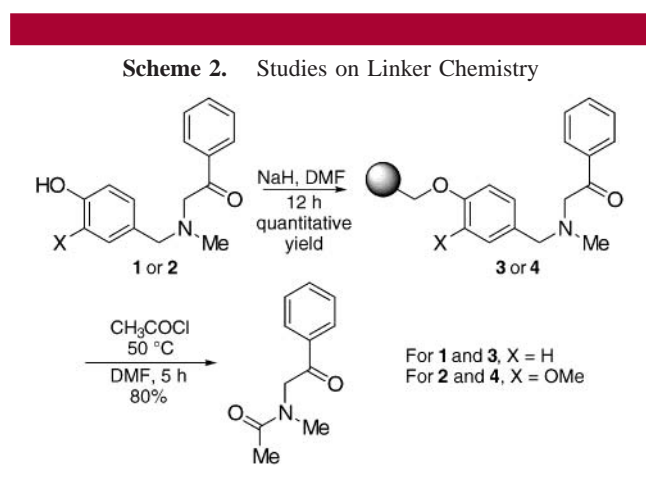
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by acylative dealkylation has been described.<sup>7</sup> Using this chemistry, Coskun and Tirli have synthesized a range of

*N*-alkyl-*N*-phenacylamides in solution.<sup>8</sup> Miller et al. have provided the only exemplification of this solid-phase linker strategy by the preparation of a small range of *N*-benzylpiperazine amides.<sup>9</sup>

This Letter describes the preparation of an array of *N*-alkyl-*N*-( $\beta$ -keto)amides (Scheme 1). The strategy is efficient as it introduces functional diversity in three out of the four synthetic steps, including the cleavage reaction. Since only the correctly assembled tertiary amines should quaternize and cleave, pure product would be expected. Prior assembly of the tertiary amines on resin by reductive amination and *N*-alkylation of the resultant secondary amines permits independent variation of each substituent of the tertiary amide core. Excess acid chloride from the cleavage step could be removed using a scavenger resin.<sup>10</sup> Cyclization of the cleaved ketoamides with ammonia to the corresponding 1,2,4,5-tetrasubstituted imidazoles allows the option of a second, distinct compound library from the synthetic sequence.

To study the linker chemistry, two tertiary amines, **1** and **2**, were first synthesized in solution following a literature procedure<sup>11</sup> and loaded onto Merrifield resin (Aldrich, 1.05 mmol/g) by alkylation to give resins **3** and **4** (Scheme 2).



Both resins were treated with 5 equiv of acetyl chloride at 50 °C for 5 h to generate the desired tertiary amide in each case in 80% crude yield with 95% purity by HPLC UV analysis. Cleavage efficiency was comparable in anhydrous THF, DMF, DCE, or TMOF, and the use of additives such as potassium carbonate,<sup>12</sup> potassium iodide,<sup>8</sup> and lithium chloride<sup>13</sup> showed only marginal improvement in yield

(<5%). Lowering the temperature to ambient reduced the efficiency considerably, suggesting that the milder cleavage conditions reported by Miller et al. for unconstrained tertiary amines are not general.<sup>9</sup> It was also observed that the methoxy substitution present in **2** resulted in cleavage efficiency comparable to that of **1**, in contrast with the studies of Coskun and Tirli.<sup>8</sup> This suggests that a single alkoxy substitution (i.e., resin **3**) is necessary and sufficient to activate the nitrogen–benzyl carbon bond scission by acid chloride. The simple monoalkoxybenzyl system **3** was the preferred linker for the subsequent library synthesis.

The reaction sequence for *N*-alkyl-*N*-( $\beta$ -keto)amides synthesis is shown in Scheme 3. 4-Hydroxybenzaldehyde was immobilized on chloromethylpolystyrene resin (Polymer Lab, 3.75 mmol/g) by alkylation using sodium hydride. The alkylation was monitored by FTIR spectroscopic analysis of the intensity of the aryl aldehyde peak at 1695 cm<sup>-1</sup> relative to a polystyrene backbone peak at 1600 cm<sup>-1</sup>. An “average” set of reagents considered to have moderate electronic and steric properties were chosen for optimization of all subsequent reactions to test the generality of the chemistry. The reagents selected were *n*-butylamine, 4-chlorophenacyl bromide, and benzoyl chloride. Selection of 4-chlorophenacyl bromide also facilitated quantitation of yields by chlorine elemental analysis of the *N*-alkylated product. Resin **5** was treated with 5 equiv of *n*-butylamine in THF/TMOF and the imine reduced using LiBH<sub>4</sub>. The reaction was monitored by gel phase FTIR spectroscopy which detected the disappearance of the aldehyde band at 1695 cm<sup>-1</sup> and the appearance of the imine band at 1645 cm<sup>-1</sup>, followed by the loss of the latter band; gel phase <sup>13</sup>C NMR spectra of **5** and **6a** clearly resolved all the substrate signals. The loading was determined to be 2.30 mmol/g by N-analysis (94% yield from Merrifield resin). The resin-bound secondary amine **6a** was alkylated using 2 equiv of 4-chlorophenacyl bromide in the presence of 1.9 equiv of diisopropylamine at 45 °C for 16 h to generate  $\beta$ -keto amine **7a** on resin. Overalkylation of the tertiary amine occurred when excess bromoketone was used. Owing to its apparent instability, the resin-bound keto–amine **7a** was promptly subjected to cleavage by acylation.

To explore the acylation–cleavage step the reaction between resin-bound tertiary amine **7a** and benzoyl chloride was studied. This reaction proved to be sensitive to both solvent and the added base. Treatment of **7a** with 5 equiv of benzoyl chloride in DCM, THF, or DCE resulted in a low yield of the corresponding tertiary amide **8q** (typically 23%) and detectable formation of side products that included *N*-butylbenzoylamide, presumably formed by benzoylation and cleavage of the unreacted secondary amine. No side products were detected in the more basic solvent DMF. Inclusion of triethylamine base further improved the cleavage reaction, increasing the yield dramatically from 23% to 67%. However the product contained detectable contaminants including *N,N*-dimethylbenzoylamide,<sup>14</sup> plus 10–15% yield of the overbenzoylated tertiary amide *N*-(*n*-butyl)-*N*-(4-

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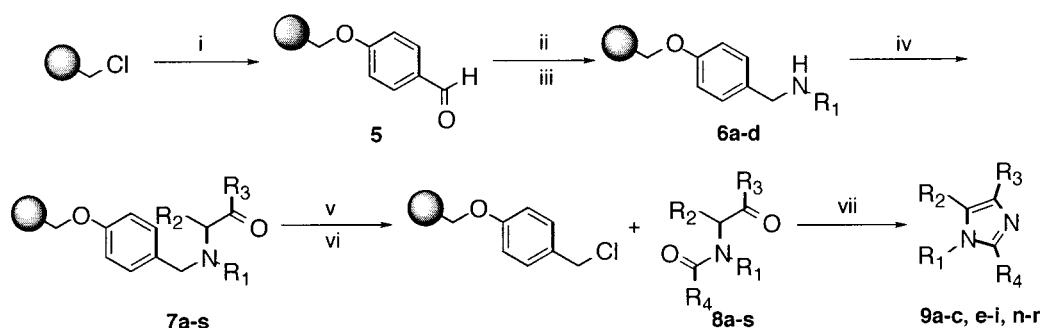
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**Scheme 3.** Solid Phase Synthesis of *N*-Alkyl-*N*-( $\beta$ -keto)amides and 1,2,4,5-Tetrasubstituted Imidazoles<sup>a</sup>



For	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
<b>6a - 9a</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	Me
<b>6b - 9b</b>	<i>i</i> -Pr	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	Me
<b>6c - 9c</b>	Bn	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	Me
<b>6d - 9d</b>	Ph	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	Me
<b>7e - 9e</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-OMe)	Me
<b>7f - 9f</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	Me
<b>7g - 9g</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	Et	Me
<b>7h - 9h</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-pyr) where pyr = (1-pyrrolidino)	Me
<b>7i - 9i</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Me	Ph	Me
<b>7j - 9j</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Ph	Ph	Me
<b>7k - 9k</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	COOEt	Me
<b>7l - 9l</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	-(CH <sub>2</sub> ) <sub>3</sub> -		Me
<b>7m - 9m</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Ac	N(Me) <sub>2</sub>	Me
<b>7n - 9n</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	CH <sub>2</sub> OAc
<b>7o - 9o</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	COOEt
<b>7p - 9p</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	<i>c</i> -C <sub>6</sub> H <sub>11</sub>
<b>7q - 9q</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	Ph
<b>7r - 9r</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	C <sub>6</sub> H <sub>4</sub> (4-CN)
<b>7s - 9s</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	C <sub>6</sub> H <sub>4</sub> (4-Cl)	C <sub>6</sub> H <sub>4</sub> (4-OMe)

<sup>a</sup> (i) 4-Hydroxybenzaldehyde (2.2 equiv), NaH (2.1 equiv), DMF, 12 h, 25 °C; (ii) R<sub>1</sub>NH<sub>2</sub> (5 equiv), 1 h, rt, 2:1 THF/TMOF, (iii) LiBH<sub>4</sub> (2.5 equiv), 24 h, rt, 87–97% yields from Merrifield resin; (iv)  $\alpha$ -haloketone (2 equiv.), DIPEA (1.9 equiv), 45 °C, 16 h, DMF; (v) R<sub>4</sub>COCl (6 equiv), NMM (1.5 equiv), 45 °C, 6 h, DMF; (vi) aminomethylpolystyrene (10 equiv), DCM, 1 h, 25–88% yields from **6a–d**; (vii) NH<sub>4</sub>OAc (100 equiv), AcOH, residual DMF, 90 °C, 24 h, 23–84% yields from **6a–c**.

chlorophenacyl- $\alpha$ -benzoyl)phenamide. The latter side product probably results from the deprotonation of the acidic proton  $\alpha$  to the nitrogen in the resin-bound acylammonium intermediate<sup>15</sup> and was not formed when a less basic amine such as *N*-methylmorpholine (NMM) was employed. The optimized conditions for the benzoylation reaction used 6 equiv of acid chloride and 1.5 equiv of NMM at 50 °C for 6 h in DMF. Excess benzoyl chloride and the majority of the benzoic acid (from hydrolyzed benzoyl chloride) were removed by stirring with high capacity aminomethylpolystyrene resin (1.8 mmol/g, Polymer Lab, 10 molar equiv of amine) for 30 min at room temperature. TLC of the filtrate indicated a base-line contaminant<sup>16</sup> which was easily removed by filtration through a pad of silica to furnish a single product (**8q**) in 82% yield and 97% purity.

To form the corresponding imidazole **9q**, the tertiary amide **8q** was stirred in DMF at 90 °C with NH<sub>4</sub>OAc and glacial acetic acid. Quantitative conversion of the amide to the imidazole was observed in 24 h according to HPLC, TLC,

(15) The pK<sub>a</sub> of the methylene protons sandwiched between a tertiary amine and a ketone functionality is estimated to be 6.4 and will be lower if the nitrogen is quaternized/positively charged.

(16) Confirmed by <sup>1</sup>H NMR spectroscopy to contain NMM-benzoate salt.

and LCMS. The crude product was filtered through a pad of silica<sup>17</sup> to furnish material in 96% purity (81% overall yield in three steps from **6a**).

To test the generality of the chemistry optimized for single compounds, the synthesis of a carefully selected array of 19 tertiary amides and 13 imidazoles (Scheme 3 and Table 1) was attempted in parallel under identical conditions. The reagents selected for each step were chemically diverse to explore structure–reactivity relationships.

To explore the effect of varying the primary amine, benzaldehyde resin **5** was reacted with *n*-butylamine, isopropylamine, benzylamine, and aniline to furnish secondary amines **6a–d** respectively in good yields (**6a**, 94%; **6b**, 87%; **6c**, 92%; **6d**, 97%). *N*-Alkylation of resins **6a–d** with 4-chlorophenacyl bromide to furnish **7a–d** was followed by cleavage with acetyl chloride to yield tertiary amides **8a–d**. Of all the primary amines utilized, only aniline failed to yield any tertiary amide (**8d**). Chlorine analysis of resin **7d** showed a high level of alkylated material, suggesting that the acylation of unreactive *N,N*-disubstituted aniline **7d** was

(17) As an alternative workup procedure, a simple evaporation under high vacuum can also be carried out as the excess NH<sub>4</sub>OAc, HOAc, and DMF solvents are all volatile materials.

**Table 1.** Yield and Purity for Samples **8a–s** and **9a–c,e–i,n–r**

entry	% yield <sup>a</sup>	% purity <sup>b</sup>	entry	% yield <sup>a</sup>	% purity <sup>b</sup>
<b>8a</b>	87	98	<b>9a</b>	84	95
<b>8b</b>	33	86	<b>9b</b>	26	68
<b>8c</b>	58	93	<b>9c</b>	54	87
<b>8d</b>	0		NA <sup>d</sup>		
<b>8e</b>	88	96	<b>9e</b>	79	86
<b>8f</b>	82	<sup>c</sup>	<b>9f</b>	80	100
<b>8g</b>	81	<sup>c</sup>	<b>9g</b>	78	96
<b>8h</b>	28	71	<b>9h</b>	19	49
<b>8i</b>	30	98	<b>9i</b>	27	89
<b>8j</b>	10	100	NA <sup>d</sup>		
<b>8k</b>	0		NA <sup>d</sup>		
<b>8l</b>	0		NA <sup>d</sup>		
<b>8m</b>	0		NA <sup>d</sup>		
<b>8n</b>	51	94	<b>9n</b>	40	73
<b>8o</b>	65	91	<b>9o</b>	54 <sup>e</sup>	76 <sup>e</sup>
<b>8p</b>	26	71	<b>9p</b>	23	64
<b>8q</b>	82	97	<b>9q</b>	81	96
<b>8r</b>	84	90	<b>9r</b>	80	86
<b>8s</b>	25	71	NA <sup>d</sup>		

<sup>a</sup> Isolated yields were calculated on the basis of the loading of resin-bound secondary amines **6a–d**. All compounds were characterized by HPLC, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, HRMS, and FTIR spectroscopy. <sup>b</sup> % purity was measured from HPLC UV spectra (at 254 nm for **8a–s** and 220 nm for **9a–c,e–i,n–r**). <sup>c</sup> % purity could not be determined by HPLC UV analysis due to the low extinction coefficient of the product. <sup>d</sup> Synthesis of these compounds from low-yielding precursors were not attempted. <sup>e</sup> Figures for the unexpected product 2,3-diketo-5-(4-chlorophenyl)-5,6-dehydropiperidine.

the problematic step. To study the effect of varying the  $\alpha$ -haloketones, the resin-bound secondary amine **6a** was *N*-alkylated with the nine  $\alpha$ -haloketones: 2-bromo-4'-methoxyacetophenone, 1-bromopinacolone, 1-bromo-2-butanone,  $\alpha$ -bromo-4-(1-pyrrolidino)acetophenone,  $\alpha$ -bromopropiophenone, desyl bromide, ethyl bromopyruvate, 2-chlorocyclopentanone, and 2-chloro-*N,N*-dimethylacetoacetamide. Cleavage of the resultant tertiary amines **7e–m** with acetyl chloride yielded the corresponding tertiary amides **8e–m** with varying degrees of success. However purity levels were high (>71%)

even for the cases where yields were relatively low. In general lower alkylation efficiencies were observed for  $\alpha$ -branched haloketones with the  $\alpha$ -branched chloroketones and bromopyruvate failing to yield any tertiary amide product. The acylation of resin **7a** was explored using six reagents: acetoxyacetyl chloride, ethyl oxalyl chloride, cyclohexanecarbonyl chloride, benzoyl chloride, 4-cyanobenzoyl chloride, 4-methoxybenzoyl chloride. Here the overall yields of tertiary amides **8n–s** from the common precursor is a direct reflection of the acylation–cleavage efficiency. In general the acylations afforded tertiary amides in reasonably high purity (>70%) but with a range of overall yields (25–84%). The cyclization efficiency for 13 of the  $\beta$ -ketoamides was subsequently studied. Quantitative conversions were observed for all but two cases. Cyclization of crude **8h** was poor, probably due to the impurities from the preceding step. LCMS of the reaction mixture of **8o** revealed relatively clean formation of a diketopiperidine compound (details in Supporting Information).

To summarize, the traceless linker strategy was employed to synthesize a diverse array of *N*-alkyl-*N*-( $\beta$ -keto)amides. Of the 19 cases studied, 15 lead to product in varying yields (25–88%) but always in high purity (71–100%). Cyclization of the amides gave the corresponding substituted imidazoles in most cases. The results of these studies have enabled the design of a much larger library. Indeed, the automated synthesis of libraries of *N*-alkyl-*N*-( $\beta$ -keto)amides and substituted imidazoles for biological screening is now underway.

**Acknowledgment.** We thank Brian G. Main for useful discussions and Zeneca for a studentship to H.B.L.

**Supporting Information Available:** Experimental procedures and characterization details for samples **1–5**, **6a–d**, **8a–s**, **9a–c**, **9e–i**, **9n–r**, *N*-(*n*-butyl)-*N*-(4-chlorophenacyl- $\alpha$ -benzoyl)phenamide, and 2,3-diketo-5-(4-chlorophenyl)-5,6-dehydropiperidine, <sup>1</sup>H NMR spectra for **8a** and **9a**, <sup>13</sup>C NMR spectra for **5**, **6a** and **7a**, FTIR spectra for **5**, **6a**, **7a**, and HPLC traces for **8q** and **9q**. This material is available free of charge via the Internet at <http://pub.acs.org>.

OL991271L