Solid-Phase Synthesis of 1,2,3,4-Tetrahydro-2-pyridones via Aza-Annulation of Enamines

K. Paulvannan* and Tao Chen

Affymax Research Institute, 3410 Central Expressway, Santa Clara, California 95051
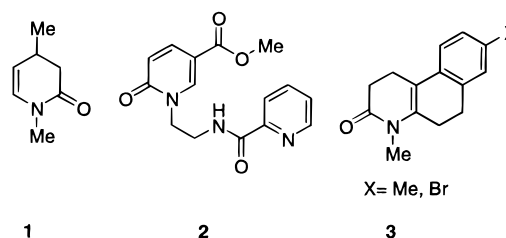
kumar_paulvannan@affymax.com

An efficient solid-phase approach has been developed to prepare nitrogen heterocycles with a 1,2,3,4-tetrahydro-2-pyridone core via aza-annulation of enamines. Immobilized enamines were prepared from the reaction of primary amines with propynoic acid derivatives or ketones. Aza-annulation reactions were carried out by reacting resin-bound enamines with symmetrical α,β-unsaturated acid anhydrides or α,β-unsaturated acids in the presence of DPPA and TEA. The annulation products were isolated in good to high crude yields. Influence of sterically hindered amines as well as α- and β-substituted acrylic acid derivatives on the annulation reaction was also investigated.

Introduction

Substituted six-membered lactams, 2-pyridones and their dihydro and tetrahydro derivatives, have attracted the attention of synthetic organic chemists for many years because these structural features are found in a wide variety of naturally occurring alkaloids.[1] Since compounds with these scaffolds have been shown to exhibit significant pharmacological properties, medicinal chemists often incorporate these motifs in the design of novel biologically active molecules. For example, compounds **1**, **2**, and **3** have been found to display hypolipidemic, antihypertensive and 5α-reductase inhibitory activities, respectively.[2] Development of a general and efficient synthetic strategy that could provide access to a wide range of nitrogen heterocycles with six-membered lactam core is therefore highly desired. Several novel synthetic methodologies directed toward the preparation of six-membered nitrogen heterocycles have been reported.[3]

The aza-annulation methodology, initially studied by Hickmott, is one of the simple and efficient synthetic routes to prepare mono- and polycyclic nitrogen heterocycles from the reaction of imines (Scheme 1)[4a] or enamines (Scheme 2)[4b] with α,β-unsaturated acid chlorides. The aza-annulation reaction is believed to proceed via an initial Michael addition of the imine−enamine tautomer to an α,β-unsaturated acid derivative followed by an intramolecular N-acylation. In this approach, a

carbon−carbon and a carbon−nitrogen bond are efficiently formed in a two-step, one-pot procedure. Several research groups have studied the aza-annulation reaction and successfully utilized it in the preparation of various nitrogen heterocycles.[5,6] Generally, the reaction of imines with α,β-unsaturated acid chlorides provided the annulation products in low yields due to the formation of an uncyclized enamide derived from an initial N-acylation, a potential competing reaction.[4a] Recently, Stille et al. have successfully investigated the reaction of imines with α,β-unsaturated acids in the presence of various acid-activating reagents to increase the yields of the annula-

(1) (a) Jones, T. H.; Blum, M. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, pp 33−84. (b) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1−90. (c) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, p 89. (d) Daly, J. W. *J. Nat. Prod.* **1998,** *61,* 162. (e) Plunkett, A. O. *Nat. Prod. Rep.* **1994,** *11,* 581. (f) Balasubramanian, M.; Keay, J. G. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: 1996, 5, p 245. (g) Rubiralta, M.; Giralt, E.; Diez, A. In *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.
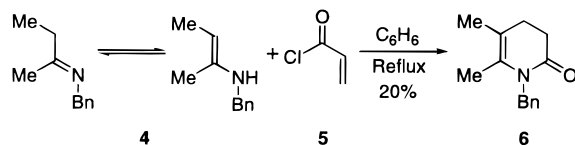
(2) Source: MDL Drug Data Registry, by MDL information Systems, Inc.; San Leandro, CA .

(3) (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999,** *1,* 261. (b) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998,** *54,* 6191. (c) Citterio, A.; Carnevali, E.; Farina, A.; Meille, V.; Alini, S.; Cotarca, L. *Org. Prep. Proced. Int.* **1997,** *29,* 465. (d) Marson, C. M.; Grabowska, U.; Fallah, A.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994,** *59,* 291. (e) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993,** *49,* 8805. (f) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993,** *34,* 6329. (g) Furukawa, I.; Fujisawa, H.; Kawazome, M.; Nakai, Y.; Ohta, T. *Synthesis* **1998,** 1715. (h) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Heterocycles* **1997,** *45,* 1589. (i) Katritzky, A. P.; Rachwal, S.; Smith, T. P. *J. Heterocyclic Chem.* **1995,** *32,* 1007. (j) Elgemeie, G. E. H.; El-Ezbawy, S. R.; Ali, H. A.; Mansour, A. K. *Org. Prep. Proced. Int.* **1994,** *26,* 465. (k) Ito, K.; Miyajima, S. *J. Heterocyclic Chem.* **1992,** *29,* 1037. (l) Okano T.; Sakaida, T.; Eguchi, S. *J. Org. Chem.* **1996,** *61,* 8826. (m) Caballero, E.; Puebla, P.; Medarde, M.; Honores, Z.; Sastre, P.; Lopez, J. L.; Feliciano, A. S. *Tetrtahedron Lett.* **1998,** *39,* 455. (n) Chung, K. H.; Cho, K. Y.; Asami, Y.; Takahashi, N.; Yoshida, S. *Heterocycles* **1991,** *32,* 99. (o) Okano, T.; Sakaida, T.; Eguchi, S. *J. Org. Chem.* **1996,** *61,* 8826. (p) Tokuda, M.; Fujita, H.; Nitta, M.; Suginome, H. *Heterocycles* **1996,** *42,* 385. (q) Herdeis, C.; Schiffer, T. *Tetrahedron* **1999,** *55,* 1043. (r) Aranda, V. G.; Barluenga, J.; Gotor, V. *Tetrahedron Lett.* **1974,** 977. (s) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **1999,** *64,* 2038.
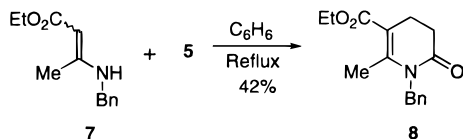
(4) (a) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971,** 1358. (b) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971,** 2112.

(5) For an excellent review on aza-annulation, see: Stille, J. R.; Barta, N. S. *Stud. Nat. Prod. Chem.* **1996,** *18,* 315.

Scheme 1

Scheme 2

tion products by suppressing the uncyclized enamide formation.[6g] In the case of enamines, the annulation reaction proceeded smoothly with α,β-unsaturated acid chlorides and led to the isolation of the annulation products in moderate to good yields.[4b,6c,j] The aza-annulation strategy has also been extended to the preparation of five-membered lactams[7] and 2-pyridones[8] by reacting enamines with maleic anhydride and α,β-acetylenic esters, respectively.

Although the aza-annulation methodology has been successfully employed for the preparation of various nitrogen heterocycles, the feasibility of this chemistry to prepare combinatorial libraries of small molecules on solid support has not been explored. In addition, influence of the sterically hindered amines and substituted acrylic acid derivatives on the aza-annulation product formation

has not been fully investigated. Preparation of small molecules on solid support is a rapidly growing area of research and has received much attention recently as evidenced by an abundance of literature on solid-phase organic synthesis (SPOS).[9] Due to the ease of workup and isolation, and the ability to drive reactions to completion, SPOS allows rapid synthesis of large number of structurally diverse molecules in a short period of time, which could accelerate the lead generation and lead optimization processes in the pharmaceutical industry. As a part of our drug discovery program directed toward the identification of new families of biologically active compounds from diverse combinatorial libraries of small molecules, we were interested in the construction of tetrahydro-2-pyridone libraries on solid support using the aza-annulation methodology. Herein we describe solid-phase synthesis of various nitrogen heterocycles with 1,2,3,4-tetrahydro-2-pyridone moiety via aza-annulation of enamines.[10,11] The influence of sterically hindered amines as well as α- and β- substituted acrylic acid derivatives on the annulation reaction has also been addressed.

Results and Discussion

Acid-labile Sieber amide resin was selected to perform our solid-phase study because of its loading (0.58 mmol/g, Nova Biochem), stability at higher temperatures, and mild cleavage condition (2−3% TFA in CH_2Cl_2). Our resin-bound enamine synthesis took advantage of the ability of propynoic acid derivatives to serve as Michael acceptors (Scheme 3). Accordingly, addition of a primary amine to a propynoic amide or ester would undergo a facile conjugate addition to provide the corresponding enamino amide and enamino ester, respectively.[12] Acylation of the resin-bound amine **9** with propynoic acid under standard coupling conditions (HOAt/ DIC/ DMF) provided the desired immobilized Michael acceptor **10**. It was interesting to note that, irrespective of the resin used, the color of the resin-bound propynoic amide **10** became dark brown. To find optimal conditions, the resin-bound propynoic amide **10** was initially treated with an excess (20 equiv) of simple unhindered isobutylamine (**11a**) in DMSO to furnish the isobutyl enamino amide **12a**, which was then subjected to the aza-annulation reaction with α,β-unsaturated acid derivatives. Transformation of the propynoic amide **10** to the enamino amide **12a** changed the resin color from dark brown to

(6) (a) Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433. (b) Shono, T.; Matsumura, Y.; Kashimura, S. *J. Org. Chem.* **1981**, *46*, 3719. (c) Brunerie, P.; Celerier, J. P.; Huche, M.; Lhommet, G. *Synthesis* **1985**, 735. (d) Capps, N. K.; Davies, G. M.; Loakes, D.; McCabe, R. W.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3077. (e) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (f) Hua, D. H.; Park, J. G.; Katasuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144. (g) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (h) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (i) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (j) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197. (k) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (l) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575. (m) Beholz, L. G.; Benovsky, P.; Ward, D. L.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1997**, *62*, 1033. (n) Benovsky, P.; Stille, J. R. *Tetrahedron Lett.* **1997**, *38*, 8475. (o) Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493. (p) Agami, C.; Kadouri-Puchot, C.; Guen, V. L.; Vaissermann, J. *Tetrahedron Lett.* **1995**, *36*, 1657. (q) Audia, J. E.; Lawhorn, D. E.; Deeter, J. B. *Tetrahedron Lett.* **1993**, *34*, 7001. (r) Audia, J. E.; Droste, J. J.; Dunigan, J. M.; Bowers, J.; Heath, P. C.; Holme, D. W.; Eifert, J. H.; Kay, H. A.; Miller, R. D.; Olivares, J. M.; Rainey, T. F.; Weigel, L. O. *Tetrahedron Lett.* **1996**, *37*, 4121. (s) Astleford, B. A.; Audia, J. E.; Deeter, J.; Heath, P. C.; Janisse, S. K.; Kress, T. J.; Wepsiec, J. P.; Weigel, L. O. *J. Org. Chem.* **1996**, *61*, 4450. (t) Kozikowski, A. P.; Campiani, G.; Sun, L.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357. (u) Agami, C.; Hamon, L.; Kadouri-Puchot, C.; Guen, V.; L. *J. Org. Chem.* **1996**, *61*, 5736. (v) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Silvani, A. *J. Org. Chem.* **1997**, *62*, 6519.

(7) (a) Cave, C.; Desmaele, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361. (b) d'Angelo, J.; Cave, C.; Desmaele, D.; Gassama, A.; Thominiaux, C.; Riche, C. *Heterocycles* **1998**, *47*, 725. (c) Cave, C.; Gassama, A.; Mahuteau, J.; d'Angelo, J.; Riche, C. *Tetrahedron Lett.* **1997**, *38*, 4773. (d) Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3437. (e) Nagasaka, T.; Inoue, H.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 1099. (f) Nagasaka, T.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848.
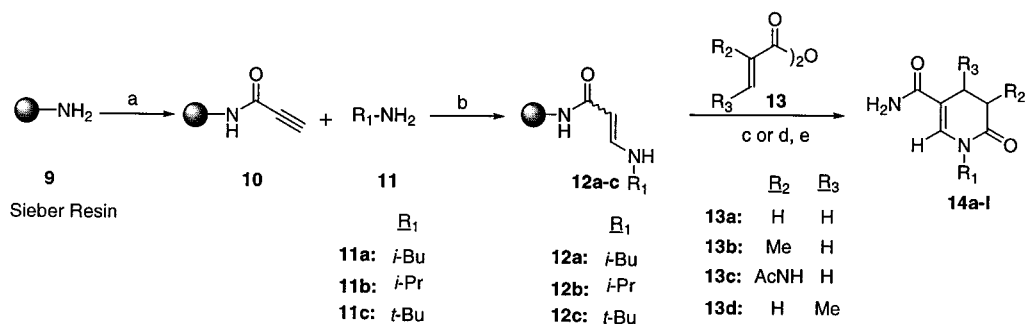
(8) (a) Wang, L.; Huang, Z. *Synth. Commun.* **1997**, *27*, 409. (b) Cocco, M. T.; Congiu, C.; Maccioni, A.; Onnis, V. *Synthesis* **1992**, 371. (c) Singh, B.; Lesher, G. Y.; Brundage, R. P. *Synthesis* **1991**, 894. (d) Huang, Z.; Zhang, P.; *Chem. Ber.* **1989**, *122*, 2011. (e) Huang, Z.; Wang, X. *Tetrahedron Lett.* **1987**, *28*, 1527. (f) Huang, Z.; Wang, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1085. (g) Singh B.; Lesher, G. Y. *J. Heterocycl. Chem.* **1990**, *27*, 2085.

(9) Recent Reviews on SPOS: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. (c) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (d) Corbett, J. W. *Org. Prep. Proced. Int.* **1998**, *30*, 491. (e) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon Press: Oxford, 1998. (f) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M.; Kerwin, J. F., Jr., Eds.; Wiley-Liss: New York, 1998. (g) *Combinatorial Chemistry and Technology*; Miertus, S., Fassina, G., Eds.; Marcel Dekker: New York, 1999.

(10) Initial results were presented at: (a) The Seventh International Kyoto Coference on New Aspects of Organic Chemistry (IKCOC-7), Kyoto, Japan; November 1997, OP-51. (b) The 217th ACS National Meeting, Anaheim, CA.; March 1999, ORGN 331.

(11) Aza-annulation of enamines on solid support approach was independently presented by the Parke-Davis Research Group at the 217th ACS National Meeting, Anaheim, CA.; March 1999, ORGN 226.

(12) (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1−67. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (c) Birnberg, G. H.; Fanshawe, W. J.; Francisco, G. D.; Epstein, J. W. *J. Heterocyclic Chem.* **1995**, *32*, 1293.

Scheme 3[a]

	R$_2$	R$_3$
13a:	H	H
13b:	Me	H
13c:	AcNH	H
13d:	H	Me

[a] Key: (a) 10 equiv of propynoic acid, 10 equiv of HOAt, 10 equiv of DIC, DMF, rt, 12 h; (b) 20 equiv of **11**, DMSO, rt, 12 h; (c) 10−25 equiv of **13**; (d) 10 equiv of α,β-unsaturated acid, 10 equiv of DPPA, 10 equiv of TEA, rt, 12 h; (e) 3% TFA in CH$_2$Cl$_2$, 2 h.

Table 1. Aza-Annulation of Enamino Amides

entry	product	R$_1$	R$_2$	R$_3$	T (°C)	crude yield[a] (%)
1	**14a**	i-Bu	H	H	23	95
2	**14b**	i-Bu	CH$_3$	H	80	94
3	**14c**	i-Bu	NHAc	H	23	87
4	**14d**	i-Bu	H	CH$_3$	80	62
5	**14e**	i-Pr	H	H	23	95
6	**14f**	i-Pr	CH$_3$	H	80	87
7	**14g**	i-Pr	NHAc	H	23	69[b]
8	**14h**	i-Pr	H	CH$_3$	80	77
9	**14i**	t-Bu	H	H	23	NP
10	**14j**	t-Bu	CH$_3$	H	80	81
11	**14k**	t-Bu	NHAc	H	80	NP
12	**14l**	t-Bu	H	CH$_3$	80	52[b]

[a] Yields are based on the initial loading of the resin-bound starting material. [b] Purified by column chromatography. NP = no desired product was detected.

bright yellow color. Given the efficiency of the reaction sequence and commercial availability of a large selection of primary amines, highly diverse arrays of enamines can be readily prepared.

Following the literature procedure[6j] enamino amide **12a** was treated with acryloyl chloride (**5**) in refluxing THF to effect the annulation. However, under these conditions, no desired annulation product was isolated after cleavage with TFA. Instead, an unidentified impurity was isolated and no further optimization study was carried out. Reaction of **12a** with symmetrical acrylic anhydride (**13a**) was then investigated. The anhydride **13a** was readily prepared by stirring a 2:1 mixture of acrylic acid and 1,3-diisopropylcarbodiimide (DIC) in CH$_2$Cl$_2$ for 45 min at room temperature.[13] Gratifyingly, treatment of **12a** with 10 equiv of **13a** in CH$_2$Cl$_2$ at room temperature effected the annulation and the desired product **14a** was isolated in 95% yield and good purity (>90%), after cleavage with 3% TFA in CH$_2$Cl$_2$ (Table 1, entry 1).[14] The yield represents the crude yield and was determined based on the weight of the annulation product in reference to the initial loading of the resin and the purity was determined by LCMS. The aza-annulation reaction was very clean and the final product **14a** did not require purification. Compound **14a** was fully char-

acterized by LCMS, HRMS, ^{1}H and ^{13}C NMR. Reaction of **12a** with **13a** at room temperature in the presence of N,N-diisopropylethylamine (DIEA) or 4-(dimethylamino)-pyridine (DMAP) also provided **14a** in high crude yields.

To find an alternative facile annulation condition, reaction of **12a** with acrylic acid in the presence of an acid activating reagent was examined. Accordingly, treatment of **12a** with 10 equiv of acrylic acid in the presence of 10 equiv of diphenylphosphoryl azide (DP-PA)[15] and 10 equiv of triethylamine (TEA) at room temperature smoothly effected the annulation and provided the desired product **14a** in 90% yield. Use of α,β-unsaturated acids in the presence of an acid activating reagent would eliminate the necessity to preform the requisite symmetrical anhydrides. Since this route utilizes lesser amounts of acid than the symmetrical anhydride method, this approach is highly preferred in the case of expensive α,β-unsaturated acids and in large-scale synthesis. Although only DPPA was used in our study, based on the literature precedence other acid activating agents such as 2-chloro-1-methylpyridinium iodide[16] and 2,2'-dipyridyl disulfide[17] would also be expected to show similar results. In our study, unless otherwise mentioned, primarily symmetrical anhydrides were used to promote the annulation.

The influence of α- and β-substituted acrylic acid derivatives on the product formation was then investigated by subjecting **12a** to aza-annulation with methacrylic, 2-acetamidoacrylic and crotonic anhydrides (Scheme 3, Table 1, **13b−d**). Since the α-carbon of an α, β-unsaturated acid derivative is not directly involved in the carbon−carbon or carbon−nitrogen bond forming step, a substituent on the α-carbon was not expected to exert any major impact on the product formation. Hence, anhydrides with a α-substituent (**13b** and **13c**) were expected to behave similar to the unsubstituted acrylic anhydride (**13a**) in the annulation reaction. As expected, treatment of **12a** with **13b** in CH$_2$Cl$_2$ at room temperature yielded the product **14b** in 85% yield with moderate purity (>80%). The purity of **14b** was improved (>90%) when the reaction was carried out at 80 °C in DMF, and the product **14b** was isolated in 94% yield (Table 1, entry 2).
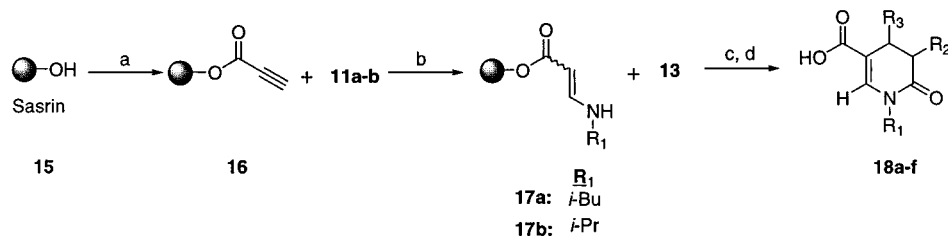
(13) (a) Paulvannan, K.; Jacobs, J. W. *Tetrahedron* **1999**, *55*, 7433. (b) Atuegbu, A.; Maclean, D.; Nguyen, C.; Gordon, E. M.; Jacobs, J. W. *Bioorg. Med. Chem.* **1996**, *4*, 1097. (c) Tartar, A.; Gesquiere, J. C. *J. Org. Chem.* **1979**, *44*, 5000.

(14) Treatment of the enamino amide **12a** with 4 equiv of **13a** or **13b** under the annulation reaction conditions provided the corresponding aza-annulation products **14a** and **14b** in good yields and purity. In this study, the enamino amide **12a** was prepared by treating **10** with 4 equiv of **11a**.

(15) Shiori, T.; Ninomiya, K.; Yamada, S. J. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *Synthesis* **1984**, 353. (c) Qian, L.; Sun, Z.; Deffo, T.; Mertes, K. B. *Tetrahedron Lett.* **1990**, *31*, 6469.

(16) (a) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem Lett.* **1975**, 1163. (b) Mazon, A.; Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1455.

(17) Kobayashi, S.; Limori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406.

Scheme 4[a]

[a] Key: (a) 10 equiv of propynoic acid, 10 equiv of DIC, 2 equiv of DMAP, DMF, rt, 12 h; (b) 20 equiv of **11**, DMSO, rt, 12 h; (c) 15 equiv of **13**, **13b**, and **13d**, CH_2Cl_2 at room temperature or DMF at 80 °C; (d) 5% TFA in CH_2Cl_2, 2 h.

Treatment of **12a** with **13c**, prepared from 2-acetami-doacrylic acid (Aldrich) and DIC, at room temperature smoothly effected the annulation and provided **14c** in 87% yield (Table 1, entry 3). In contrast, the presence of a substituent on the β-carbon of the acrylate derivative was expected to show steric hindrance during the initial Michael addition of the enamine to the α, β-unsaturated acid derivative, which would obstruct the annulation reaction. As predicted, treatment of **12a** with crotonic anhydride (**13d**) at room temperature did not yield the desired product, as determined by MS and ¹H NMR of the crude reaction mixture. However, heating a mixture of **13d** and **12a** at 80 °C in DMF smoothly effected the annulation to yield **14d** in 62% yield (Table 1, entry 4). These results clearly indicate that the annulation of enamines with β-substituted acrylic acid derivatives hinders the annulation reaction at room temperature, and higher temperature is required to overcome the steric effect.

The influence of sterically congested amines on the annulation reaction was investigated by subjecting the enamino amides **12b** and **12c**, prepared from *i*-propyl and *tert*-butylamines **11b** and **11c** respectively, to aza-annu-lation with anhydrides **13a**−**d** (Scheme 3, Table 1, entries 5−12). Reaction of *i*-propyl enamino amide **12b** with anhydrides **13a**−**d** under the annulation conditions readily furnished the corresponding products **14e**−**h** in good yields (entries 5−8). Isolation of the annulation products **14e**−**h** in good yields suggested that moderately bulky *i*-propylamine did not have any significant impact on the product formation. Next, sterically hindered *tert*-butyl enamino amide **12c** was treated with anhydrides **13a**−**d** (Table 1, entries 9−12). To our surprise, reaction of **12c** with **13a** at room temperature did not give the desired annulation product (entry 9).[18] Instead, an uni-dentified complex mixture was isolated. Unfortunately, even modification of the reaction conditions such as the temperature (0 °C, rt, and 80 °C) and the acylation conditions (acrylic acid/ DPPA/ TEA or sodium acrylate/ acryloyl chloride) failed to promote the annulation reac-tion. Although these results clearly illustrate the influ-ence of the bulky *tert*-butylamine on the annulation reaction, no possible explanation could be provided at this time. However, treatment of **12c** with **13b** or **13d** at 80 °C in DMF smoothly effected the annulation reaction and furnished the corresponding annulation products **14j** and **14l** in 81% yield and 52% yield (Table 1, entries 10 and 12), respectively. To our disappointment, treatment of **12c** with **13c** under various reaction conditions failed to

Table 2. Aza-Annulation of Enamino Esters

entry	product	R_1	R_2	R_3	T (°C)	crude yield[a] (%)
1	**18a**	*i*-Bu	H	H	23	98
2	**18b**	*i*-Bu	CH_3	H	80	92
3	**18c**	*i*-Bu	H	CH_3	80	45
4	**18d**	*i*-Pr	H	H	23	98
5	**18e**	*i*-Pr	CH_3	H	80	88
6	**18f**	*i*-Pr	H	CH_3	80	79

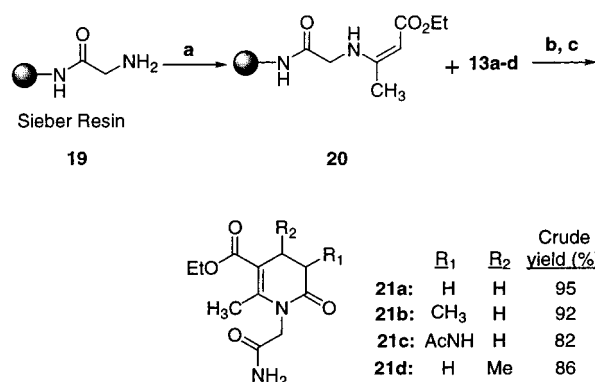[a] Yields are based on the initial loading of the resin-bound starting material.

effect the annulation. Isolation of the annulation products **14j** and **14l** clearly showed the formation of the enamino amide **12c** from **10** and **11c**. Further study is required to explain why enamino amide **12c** provided the annu-lation products with anhydrides **13b** and **13d** but not with anhydrides **13a** and **13c**.

To prepare 1,2,3,4-tetrahydro-2-pyridone acids, the reaction of resin-bound enamino esters with anhydrides **13a**, **13b**, and **13d** was then examined (Scheme 4, Table 2, entries 1−6). The requisite enamino esters **17a,b** were readily prepared as shown in Scheme 4. Acylation of the resin-bound OH **15** (Sasrin, Bachem, loading 1.02 mmol/ g) with propynoic acid under standard coupling condi-tions (DIC/ DMAP) furnished the Michael acceptor **16**. As before, treatment of **16** with 20 equiv of amine **11a** or **11b** in DMSO provided the enamino esters **17a** and **17b**, respectively, which were then subjected to the annulation reaction. As shown in Table 2, reaction of enamino esters **17a** and **17b** with anhydrides **13a**, **13b**, and **13d**, readily effected the annulation and provided the desired acids **18a**−**f** in high yields and purity, after cleavage with 5% TFA in CH_2Cl_2 (Table 2, entries 1−6). Isolation of the products in high yields showed that the addition of excess primary amine during the enamino ester formation did not cleave the ester linkage. Fur-thermore, these results also show that the enamino esters behave similarly to the enamino amides under the aza-annulation conditions.
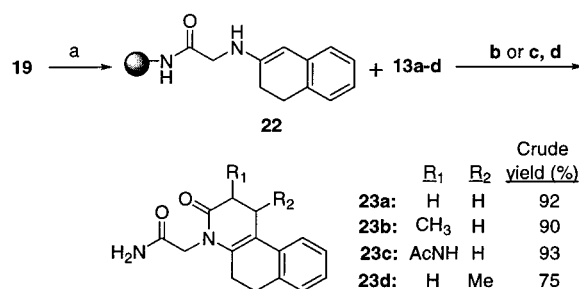
To increase the synthetic scope of our solid-phase approach, the study was extended to enamino ester **20** and enamino ketone **22** (Schemes 5 and 6). The enamines **20** and **22** were readily prepared from condensation of the resin-bound amine **19**, prepared in two steps from **9**, with ethyl acetoacetate and β-tetralone, respectively, using trimethyl orthoformate (TMOF) or a 1:1 mixture of CH_2Cl_2 and TMOF (Schemes 5 and 6).[19] Treatment of the enamino ester **20** with the anhydrides **13a**−**d** at 80

(18) In a solution phase study, reaction of *tert*-butyl enamino amide, prepared from *N*-benzylpropynoic amide and 25 equiv of *tert*-buty-lamine, with **13a** provided the corresponding aza-annulation product only in 28% yield.

(19) (a) Trautwein, A. W.; Submuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. (b) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263. (c) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

Scheme 5[a]

21a: R₁ = H, R₂ = H, Crude yield (%) 95
21b: R₁ = CH₃, R₂ = H, 92
21c: R₁ = AcNH, R₂ = H, 82
21d: R₁ = H, R₂ = Me, 86

	R_1	R_2	Crude yield (%)
21a:	H	H	95
21b:	CH₃	H	92
21c:	AcNH	H	82
21d:	H	Me	86

[a] Key: (a) 27 equiv of ethyl acetoacetate, TMOF:CH₂Cl₂ (1:1), rt, 12 h, (2×); (b) 10 to 25 equiv of **13a**−**d**, DMF, 80 °C; (c) 3% TFA, 2 h.

Scheme 6[a]

	R_1	R_2	Crude yield (%)
23a:	H	H	92
23b:	CH₃	H	90
23c:	AcNH	H	93
23d:	H	Me	75

[a] Key: (a) 15 equiv of β-tetralone TMOF, rt, 12 h; (b) 10 to 25 equiv of **13a**−**d**, DMF 80 °C; (c) 10 equiv of acrylic acid, 10 equiv of DPPA, 10 equiv of TEA, DMF, 80 °C; (d) 3% TFA, 2 h.

°C in DMF provided the corresponding aza-annulation products **21a**−**d**, 1,2,3,4-tetrahydro-2-pyridones with an additional substitutent at C-6 position, in high yields (Scheme 5). Commercial availability of large numbers of diverse β-keto acid derivatives and amino acids makes this approach more attractive to prepare a wide range of functionalized 1,2,3,4-tetrahydro-2-pyridones.

Reaction of the enamine **22** with anhydride **13a** in DMF at 80 °C provided the aza-steroid like tricyclic lactam **23a** in 85% yield with moderate purity (>80%). When the enamine **22** was treated with acrylic acid in the presence of DPPA/ TEA in DMF at 80 °C, the annulation product **23a** was isolated in 92% yield and good purity. Anhydrides **13b**−**d** also smoothly effected the annulation and provided the corresponding tricyclic lactams **23b**−**d** in good to high yields (Scheme 6). This solid phase synthetic strategy could be used to prepare a large number of structurally diverse analogues of compound **3** in short period of time.

Conclusions

An efficient solid-phase synthesis of various nitrogen heterocycles with 1,2,3,4-tetrahydro-2-pyridone core via aza-annulation of enamines has been described. The annulation reaction was efficient and yielded the desired products in good yields and purity.[20] The influence of sterically hindered amines as well as α- and β-substituted acrylic acid derivatives on the product formation has also

(20) All compounds, except **14g** and **14j**, gave satisfactory ¹H and ¹³C NMR data without purification.

been investigated. Currently, aza-annulation of enamines with cinnamic, fumaric, and maleic acid derivatives is being investigated, and the results will be reported in due course.

Experimental Section

General Methods. All solvents and reagents were purchased from commercial sources and used without further purification. Sasrin-OH resin (1.02 mmol/g) was purchased from Bachem. Sieber amide resin (0.58 mmol/g) and HOBt (N-hydroxybenzotriazole) were purchased from NovaBiochem. HOAt (1-Hydroxy-7-azabenzotriazole) was purchased from PerSeptive Biosystems. Propynoic acid (propiolic acid), methacrylic anhydride, crotonic anhydride, DPPA, DIC and 2-acetamidoacrylic acid were purchased from Aldrich. Column chromatography was performed on silica gel column using an ethyl acetate−hexane mixture as the eluent. ¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in the δ scale in ppm using the solvent as the internal standard.

General Procedure for Enamine Preparation. Enamino Amide 12. To a suspension of **9** (1 g, 0.58 mmol, 1 equiv) in DMF (15 mL) were added propynoic acid (406 mg, 5.8 mmol, 10 equiv), HOAt (789 mg, 5.8 mmol, 10 equiv), and DIC (732 mg, 5.8 mmol, 10 equiv), and the reaction mixture was agitated at room temperature for 12 h. Excess reagents were drained, and the resin was washed (3 × 20 mL of DMF) to provide **10**. To a suspension of **10** in DMSO (10 mL) was added **11** (11.6 mmol, 20 equiv), and the reaction mixture was agitated at room temperature for 12 h. Excess amine was drained and the resin was washed (3 × 20 mL of DMF) to yield **12**.

Enamino Ester 17. To a suspension of **15** (1 g, 1.02 mmol, 1 equiv) in DMF (20 mL) were added propynoic acid (715 mg, 10.2 mmol, 10 equiv), DIC (1.29 g, 10.2 mmol, 10 equiv) and DMAP (250 mg, 2.04 mmol, 2 equiv), and the reaction mixture was agitated at room temperature for 12 h. Excess reagents were drained, and the resin was washed (3 × 20 mL of DMF) to provide **16**. To a suspension of **16** in DMSO (10 mL) was added **11** (20.4 mmol, 20 equiv), and the reaction mixture was agitated at room temperature for 12 h. Excess amine was drained and the resin was washed (3 × 20 mL of DMF) to yield **17**.

Preparation of 19. To a suspension of **9** (1 g, 0.58 mmol, 1 equiv) in DMF (20 mL) were added Fmoc-glycine-OH (1.21 g, 4.06 mmol, 7 equiv), HOBt (624 mg, 4.06 mmol, 7 equiv), and DIC (512 mg, 4.06 mmol, 7 equiv), and the reaction mixture was agitated at room temperature for 12 h. Excess reagents were drained, and the resin was washed (3 × 20 mL of DMF) and then treated with 20 mL of 20% piperidine in DMF (v/v). After 2 h, the reagent was drained and the resin was washed (3 × 20 mL of DMF) to yield **19** (0.58 mmol).

Enamino Ester 20. To a suspension of **19** (0.58 mmol, 1 equiv) in a 1:1 mixture of CH₂Cl₂/TMOF (16 mL) was added ethyl acetoacetate (2.0 mL, 15.66 mmol, 27 equiv) and the reaction mixture was agitated at room temperature for 12 h. Excess reagent was drained and the reaction sequence was repeated one more time to drive enamine formation to completion. Excess reagent was drained and the resin was washed (3 × 20 mL DMF) to give the enamino ester **20**.

Enamine 22. To a suspension of **19** (0.58 mmol, 1 equiv) in a 1:1 mixture of CH₂Cl₂/TMOF (16 mL) was added β-tetralone (1.27 g, 8.7 mmol, 15 equiv) and the reaction mixture was agitated at room temperature for 12 h. Excess reagent was drained and the resin was washed (3 × 20 mL of DMF) to give the enamine **22**.

General Procedure for Aza-Annulation. Symmetrical Anhydride Method at 25 °C. To a solution of α, β-unsaturated acid (8.6 mmol, 20 equiv) in CH₂Cl₂ (15 mL) was added DIC (540 mg, 4.3 mmol, 10 equiv), and the reaction mixture was stirred at room temperature for 45 min. After filtering the insoluble urea, the anhydride **13** (4.3 mmol, 10 equiv) was directly added to the resin-bound enamine (0.43 mmol, 1 equiv) and the suspension was agitated at room temperature for 12

h. Excess anhydride was drained and the resin was washed (3 × 15 mL of DMF, 3 × 15 mL of MeOH, and 2 × 15 mL of CH$_2$Cl$_2$). Treatment of the resin with 3 or 5% TFA in CH$_2$Cl$_2$ (30 mL) at room temperature for 2 h and removal of the volatile provided the annulation product.

Symmetrical Anhydride Method at 80 °C. The Symmetrical anhydride **13** (4.3 mmol, 10 equiv) was prepared as above. The solvent (CH$_2$Cl$_2$) was removed under vacuum to provide the crude anhydride, which was then taken in DMF (15 mL) and added to the resin-bound enamine (0.43 mmol, 1 equiv). The reaction mixture was heated at 80 °C for 12 h. Excess anhydride was drained and the resin was washed (3 × 20 mL of DMF, 3 × 20 mL of MeOH, and 2 × 20 mL of CH$_2$Cl$_2$). Treatment of the resin with 3% TFA in CH$_2$Cl$_2$ (30 mL) at room temperature for 2 h and removal of the volatile provided the annulation product.

DPPA/TEA Activation Method. To a suspension of resin-bound enamine (0.34 mmol) in DMF (12 mL) were added α, β-unsaturated acid (3.4 mmol, 10 equiv), TEA (0.35 g, 3.4 mmol, 10 equiv) and DPPA (0.94 g, 3.4 mmol, 10 equiv). The reaction mixture was stirred at room temperature or 80 °C for 12 h. Excess reagents were drained and the resin was washed (3 × 15 mL of DMF, 3 × 15 mL of MeOH, and 2 × 15 mL of CH$_2$Cl$_2$). Treatment of the resin with 3% TFA in CH$_2$-Cl$_2$ (25 mL) at room temperature for 2 h, and removal of the volatile provided the annulation product.

Methacrylic and Crotonic Anhydrides. To a suspension of resin-bound enamine (0.58 mmol, 1 equiv) in DMF (20 mL) was added methacrylic or crotonic anhydride (2.24 g, 14.5 mmol, 25 equiv) and the reaction mixture was heated at 80 °C for 12 h. Excess reagents were drained and the resin was washed with 3 × 20 mL of DMF 3 × 20 mL of MeOH, and 2 × 20 mL of CH$_2$Cl$_2$. Treatment of the resin with 3 or 5% TFA in CH$_2$Cl$_2$ (30 mL) at room temperature for 2 h and removal of the volatile provided the annulation product.

1-Isobutyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14a). Compound **14a** (108 mg, 95%) was obtained as a viscous oil (91% purity): ^{1}H NMR (CDCl$_3$) δ 0.86 (d, J = 6.6 Hz, 6H), 1.92 (m, 1H), 2.53 (m, 2H), 2.60 (m, 2H), 3.32 (d, J = 7.3 Hz, 2H), 7.17 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 20.0, 20.2, 28.3, 30.7, 54.6 108.2, 139.8, 169.4, 170.2; HRMS (FAB) calcd for C$_{10}$H$_{16}$N$_2$O$_2$ (M + H) 197.1291, found 197.1284.

1-Isobutyl-3-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14b). Compound **14b** (115 mg, 94%) was isolated as viscous oil (90% purity): ^{1}H NMR (DMSO-d_6) δ 0.81 (d, J = 6.6 Hz, 6H), 1.08 (d, J = 7.0 Hz, 3H), 1.86 (m, 1H), 2.13 (ddd, J = 16.1, 11.6, 1.6 Hz, 1H), 2.47 (m, 1H), 2.62 (dd, J = 16.1, 6.6 Hz, 1H), 3.20 (dd, J = 13.6, 7.4 Hz, 1H), 3.34 (dd, J = 13.6, 7.4 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 15.9, 19.7, 19.8, 27.6, 27.7, 34.5, 53.1, 110.4, 135.7, 167.4, 171.8; HRMS (FAB) calcd for C$_{11}$H$_{18}$N$_2$O$_2$ (M + H) 211.1447, found 211.1442.

N1-(5-Carbamoyl-1-isobutyl-2-oxo-1,2,3,4-tetrahydro-3-pyridinyl)acetamide (14c). Compound **14c** (127 mg, 87%) was isolated as an amorphous solid (85% purity): ^{1}H NMR (DMSO-d_6) δ 0.82 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 1.87 (s, 3H), 2.30 (m, 1H), 2.75 (dd, J = 16.0, 7.0 Hz, 1H), 3.21 (dd, J = 13.6, 7.3 Hz, 1H), 3.39 (dd, J = 13.6, 7.3 Hz, 1H), 4.43 (m, 1H), 8.22 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 19.7, 22.7, 26.6, 27.7, 48.0, 53.4, 110.1, 135.6, 166.8, 168.1, 169.0; HRMS (FAB) calcd for C$_{12}$H$_{19}$N$_3$O$_3$ (M + H) 254.1505, found 254.1499.

1-Isobutyl-4-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14d). Compound **14d** (76 mg, 62%) was isolated as a viscous oil (82% purity): ^{1}H NMR (CDCl$_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 7.3 Hz, 3H), 1.98 (m, 1H), 2.48 (d, J = 14.3 Hz, 1H), 2.75 (m, 2H), 3.12 (dd, J = 13.6, 7.3 Hz, 1H), 3.62 (dd, J = 13.6, 7.3 Hz, 1H), 7.18 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.1, 20.2, 20.3, 27.3, 28.6, 38.7, 54.4, 115.1, 136.9, 168.0, 168.9; HRMS (FAB) calcd for C$_{11}$H$_{18}$N$_2$O$_2$ (M + H) 211.1447, found 211.1448.

1-Isopropyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14e). Compound **14e** (100 mg, 95%) was isolated as an oil (93% purity): ^{1}H NMR (DMSO-d_6) δ 1.12 (d, J = 7.0 Hz, 6H), 2.41 (s, 4 H), 4.70 (m, 1H), 7.23 (s, 1H); ^{13}C NMR

(DMSO-d_6) δ 19.5, 20.6, 31.0, 43.6, 112.2, 130.6, 167.4, 168.1; HRMS (FAB) calcd for C$_9$H$_{14}$N$_2$O$_2$ (M + H) 183.1134, found 183.1139.

1-Isopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14f). Compound **14f** (99 mg, 87%) was isolated as a viscous oil (82% purity): ^{1}H NMR (DMSO-d_6) δ 1.07 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H) 1.13 (d, J = 7.0 Hz, 3H), 2.08 (ddd, J = 16.5, 11.7, 1.8 Hz, 1H), 2.42 (m, 1H), 2.60 (dd, J = 16.5, 7.0 Hz, 1H), 4.69 (m, 1H), 7.23 (d, J = 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 15.9, 20.5, 20.9, 27.4, 34.8, 44.1, 111.4, 130.6, 167.7, 171.2; HRMS (FAB) calcd for C$_{10}$H$_{16}$N$_2$O$_2$ (M + H) 197.1291, found 197.1286.

N1-(5-Carbamoyl-1-isopropyl-2-oxo-1,2,3,4-tetrahydro-3-pyridinyl)acetamide (14g). Compound **14g** (96 mg, 69%) was isolated as an amorphous solid: R_f (85:15 EtOAc/ MeOH) 0.31; ^{1}H NMR (DMSO-d_6) δ 1.14 (d, J = 6.6 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H) 1.88 (s, 3H), 2.24 (dd, J = 16.1, 2.6 Hz, 1H), 2.74 (dd, J = 16.1, 7.3 Hz, 1H), 4.36 (m, 1H), 4.64 (m, 1H), 7.22 (d, J = 2.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 20.1, 20.9, 22.6, 26.2, 44.8, 48.1, 111.1, 130.2, 166.7, 167.3, 168.8; HRMS (FAB) calcd for C$_{11}$H$_{17}$N$_3$O$_3$ (M + H) 240.1349, found 240.1348.

1-Isopropyl-4-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14h). Compound **14h** (97 mg, 77%) was isolated as a viscous oil (82% purity): ^{1}H NMR (DMSO-d_6) δ 0.88 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 2.22 (dd, J = 16.0, 1.8 Hz, 1H), 2.59 (dd, J = 16.0, 7.0 Hz, 1H), 2.81 (m, 1H), 4.71 (m, 1H), 7.18 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.7, 19.9, 21.0, 25.2, 38.4, 43.5, 117.6, 129.2, 166.9, 167.5; HRMS (FAB) calcd for C$_{10}$H$_{16}$N$_2$O$_2$ (M + H) 197.1291, found 197.1291.

1-*tert*-Butyl-3-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14j). Compound **14j** (99 mg, 81%) was isolated as an oil (88% purity): ^{1}H NMR (DMSO-d_6) δ 1.04 (d, J = 7.0 Hz, 3H), 1.46 (s, 9H), 2.04 (ddd, J = 16.1, 11.4, 1.5 Hz, 1H), 2.38 (m, 1H), 2.52 (dd, J = 16.1, 6.7 Hz, 1H), 7.33 (d, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 15.8, 27.1, 28.6, 36.5, 58.0, 110.6, 132.9, 167.7, 172.8; HRMS (FAB) calcd for C$_{11}$H$_{18}$N$_2$O$_2$ (M + H) 211.1447, found 211.1446.

1-*tert*-Butyl-4-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxamide (14l). Compound **14l** (63 mg, 52%) was isolated as a viscous oil (88% purity): R_f (EtOAc) 0.26; ^{1}H NMR (CDCl$_3$) δ 1.11 (d, J = 7.3 Hz, 3H),1.52 (s, 9H), 2.48 (dd, J = 15.8, 1.8 Hz, 1H), 2.63 (m, 1H), 2.76 (dd, J = 15.8, 7.0 Hz, 1H), 7.72 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 18.6, 26.4, 29.0, 41.2, 59.4, 114.3, 135.7, 169.0, 170.0; HRMS (FAB) calcd for C$_{11}$H$_{18}$N$_2$O$_2$ (M + H) 211.1447, found 211.1446.

1-Isobutyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic Acid (18a). Compound **18a** (197 mg, 98%) was isolated as a solid (87% purity): ^{1}H NMR (CDCl$_3$) δ 0.92 (d, J = 6.6 Hz, 6H), 1.97 (m, 1H), 2.64 (s, 4H), 3.39 (d, J = 7.3 Hz, 2H), 7.39 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.5, 20.0, 28.4, 30.9, 54.7, 107.4, 142.1, 170.2, 171.2; HRMS (FAB) calcd for C$_{10}$H$_{15}$NO$_3$ (M + H) 198.1131, found 198.1131.

1-Isobutyl-3-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic Acid (18b). Compound **18b** (198 mg, 92%) was isolated as a solid (84% purity): ^{1}H NMR (CDCl$_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.96 (m, 1H), 2.31 (ddd, J = 16.5, 11.0, 1.5 Hz, 1H), 2.62 (m, 1H), 2.77 (dd, J = 16.5, 7.0 Hz, 1H), 3.29 (dd, J = 13.6, 7.3 Hz, 1H), 3.46 (dd, J = 13.6, 7.3 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 16.1, 20.0, 20.1, 27.2, 28.4, 35.3, 55.0, 106.5, 142.1, 171.8, 173.8; HRMS (FAB) calcd for C$_{12}$H$_{12}$-NO (M + H) 212.1287, found 212.1290.

1-Isobutyl-4-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic Acid (18c). Compound **18c** (92 mg, 45%) was isolated as a solid (95% purity): ^{1}H NMR (CDCl$_3$) δ 0.91 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.99 (m, 1H), 2.49 (dd, J = 16.5, 1.8 Hz, 1H), 2.72 (dd, J = 16.5, 7.3 Hz, 1H), 2.98 (m, 1H), 3.14 (dd, J = 13.6, 7.3 Hz, 1H), 3.64 (dd, J = 13.6, 7.3 Hz, 1H), 7.34 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.0, 20.0, 26.1, 28.6, 38.5, 54.8, 112.5, 141.5, 170.0, 172.0; HRMS (FAB) calcd for C$_{12}$H$_{12}$NO (M + H) 212.1287, found 212.1282.

1-Isopropyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic acid (18d). Compound **18d** (182 mg, 98%) was isolated as a solid (80% purity). ^{1}H NMR (CDCl$_3$) δ 1.23 (d, J = 7.0 Hz, 6H), 2.62 (m, 4H), 4.88 (m, 1H), 7.52 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.2, 21.2, 31.2, 45.1, 108.3, 137.1, 169.7, 171.2; HRMS (FAB) calcd for C$_{12}$H$_{12}$NO (M + H) 184.0974, found 184.0976.

1-Isopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic Acid (18e). Compound **18e** (177 mg, 88%) was isolated as a solid (79% purity): ^{1}H NMR (CDCl$_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H) 1.25 (d, J = 7.0 Hz, 3H) 2.30 (dd, J = 16.5, 10.6 Hz, 1H), 2.63 (m, 1H), 2.75 (dd, J = 16.5, 7.0 Hz, 1H), 4.86 (m, 1H) 7.53 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 16.1, 21.1, 21.5, 27.0, 35.5, 45.2, 107.2, 137.1, 171.7, 172.8; HRMS (FAB) calcd for C$_{10}$H$_{15}$NO$_3$ (M + H) 198.1131, found 198.1129.

1-Isopropyl-4-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylic Acid (18f). Compound **18f** (159 mg, 79%) was isolated as a solid (83% purity): ^{1}H NMR (CDCl$_3$) δ 1.08 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.28 (d, J = 7.3 Hz, 3H), 2.54 (d, J = 15.0 Hz, 1H), 2.74 (dd, J = 16.5, 7.3 Hz, 1H), 2.95 (m, 1H), 4.89 (m, 1H), 7.48 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 18.9, 20.6, 21.8, 25.7, 38.8, 45.0, 113.8, 136.0, 169.3, 171.3; HRMS (FAB) calcd for C$_{10}$H$_{15}$NO$_3$ (M + H) 198.1131, found 198.1129.

Ethyl 1-Carbamoylmethyl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylate (21a). Compound **21a** (132 mg, 95%) was isolated as a viscous oil (85% purity): ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 2.41 (m, 2H), 2.47 (m, 2H), 4.09 (q, J = 7.0 Hz, 2H), 4.25 (s, 2H), 7.12 (bs, 1H), 7.50 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 14.3, 15.9, 20.9, 30.5, 44.3, 59.8, 106.9, 148.4, 166.8, 169.6, 170.0; HRMS (FAB) calcd for C$_{11}$H$_{16}$N$_2$O$_4$ (M + H) 241.1189, found 241.1191.

Ethyl 1-Carbamoylmethyl-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylate (21b). Compound **21b** (136 mg, 92%) was isolated as an amorphous solid (90% purity): ^{1}H NMR (CDCl$_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 2.29 (m, 1H), 2.43 (s, 3H), 2.55 (m, 1H), 2.80 (dd, J = 16.2, 6.1 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 4.36 (d, J = 16.5 Hz, 1H), 4.44 (d, J = 16.5 Hz, 1H), 6.38 (bs, 1H), 6.61 (bs, 1H); ^{13}C NMR (CDCl$_3$) δ 14.7, 15.4, 16.8, 29.2, 34.9, 45.9, 60.9, 109.5, 146.9, 167.5, 172.5, 175.0; HRMS (FAB) calcd for C$_{12}$H$_{18}$N$_2$O$_4$ (M + H) 255.1346, found 255.1340.

Ethyl 1-Carbamoylmethyl-6-methyl-3-methylcarboxamido-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylate (21c). Compound **21c** (141 mg, 82%) was isolated as a solid (91% purity): ^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.0 Hz, 3H), 1.88 (s, 3H), 2.30 (s, 3H), 2.37 (dd, J = 15.4, 2.2 Hz, 1H), 2.76 (dd, J = 15.4, 6.6 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.24 (d, J = 17.3 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 4.47 (m, 1H), 7.19 (bs, 1H), 7.56 (bs, 1H), 8.21 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 14.6, 16.2, 22.9, 27.6, 45.2, 47.9, 60.5, 106.0, 148.6, 166.7, 169.6, 169.9, 170.0; HRMS (FAB) calcd for C$_{13}$H$_{19}$N$_3$O$_5$ (M + H) 298.1404, found 298.1404.

Ethyl 1-Carbamoylmethyl-4,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyridinecarboxylate (21d). Compound **21d**

(127 mg, 86%) was isolated as a viscous oil (90% purity): ^{1}H NMR (CDCl$_3$) δ 1.08 (d, J = 7.0 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 2.41 (s, 3H), 2.47 (dd, J = 15.8, 2.2 Hz, 1H), 2.71 (dd, J = 15.8, 6.6 Hz, 1H), 3.04 (m, 1H), 4.22 (m, 2H), 4.43 (s, 2H), 6.35 (bs, 1H), 6.68 (bs, 1H); ^{13}C NMR (CDCl$_3$) δ 14.6, 16.9, 18.1, 27.3, 38.0, 45.3, 60.8, 115.1, 145.7, 167.3, 171.4, 172.5; HRMS (FAB) calcd for C$_{12}$H$_{18}$N$_2$O$_4$ (M + H) 255.1346, found 255.1340.

2-(3-Oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinolin-4-yl)acetamide (23a). Compound **23a** (137 mg, 92%) was isolated as an amorphous solid (85% purity): ^{1}H NMR (DMSO-d_6) δ 2.34 (t, J = 8.0 Hz, 2H), 2.57 (s, 4H), 2.79 (t, J = 8.0 Hz, 2H), 4.19 (s, 2H), 7.02−7.19 (m, 4H), 7.47 (bs, 2H); ^{13}C NMR (DMSO-d_3) δ 20.6, 23.3, 27.8, 31.0, 43.6, 111.6, 120.9, 125.1, 126.5, 126.7, 132.0, 134.8, 136.6, 169.1, 169.9; HRMS (FAB) calcd for C$_{15}$H$_{16}$N$_2$O$_2$ (M$^+$) 256.1212, found 256.1211.

2-(2-Methyl-3-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinolin-4-yl)acetamide (23b). Compound **23b** (141 mg, 90%) was isolated as an amorphous solid (88% purity): ^{1}H NMR (DMSO-d_6) δ 1.17 (d, J = 6.8 Hz, 3H), 2.31−2.36 (m, 3 H), 2.56−2.72 (m, 2 H), 2.79 (t, J = 7.9 Hz, 2H), 4.14 (d, J = 16.8 Hz, 1H), 4.25 (d, J = 16.8 Hz, 1H), 7.01−7.19 (m, 4H), 7.45 (bs, 1H); ^{13}C NMR (DMSO-d_3) δ 15.7, 23.3, 27.9, 28.6, 34.6, 43.8, 111.1, 120.9, 125.0, 126.5, 126.7, 132.0, 134.9, 136.3, 169.9, 172.0; HRMS (FAB) calcd for C$_{16}$H$_{18}$N$_2$O$_2$ (M$^+$) 270.1368, found 270.1372.

2-(2-Methylcarboxamido-3-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinolin-4-yl)acetamide (23c). Compound **23c** (169 mg, 93%) was isolated as an amorphous solid (81% purity): ^{1}H NMR (DMSO-d_6) δ 1.91 (s, 3H), 2.33−2.37 (m, 2H), 2.48−2.52 (m, 1H), 2.72−2.85 (m, 3H), 4.16 (d, J = 17.2 Hz, 1H), 4.24 (d, J = 17.2 Hz, 1H), 4.62−4.70 (m, 1H), 7.04−7.19 (m, 4H), 7.53 (bs, 1H), 8.29 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_3) δ 22.7, 23.2, 27.6, 27.8, 44.2, 48.3, 110.8, 121.1, 125.4, 126.6, 126.8, 132.2, 134.4, 136.4, 168.5, 169.2, 169.6; HRMS (FAB) calcd for C$_{17}$H$_{19}$N$_3$O$_3$ (M + H) 314.1505, found 314.1497.

2-(1-Methyl-3-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinolin-4-yl)acetamide (23d). Compound **23d** (117 mg, 75%) was isolated as an amorphous solid (88% purity): ^{1}H NMR (CDCl$_3$) δ 1.20 (d, J = 7.2 Hz, 3H), 2.47−2.59 (m, 3 H), 2.81−2.89 (m, 2H), 2.91−3.01 (m, 2H), 4.22 (d, J = 16.0 Hz, 1H), 4.49 (d, J = 16.0 Hz, 1H), 7.11−7.15 (m, 2H), 7.21−7.24 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 17.9, 23.9, 27.1, 28.6, 39.0, 45.2, 119.0, 121.3, 126.0, 126.9, 127.4, 132.8, 133.7, 134.0, 170.5, 171.2; HRMS (FAB) calcd for C$_{16}$H$_{18}$N$_2$O$_4$ (M$^+$) 270.1368, found 270.1365.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000676C