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Synthesis of 4-Amino-3,4-dihydro-2(*1H*)-Quinolinones *via* β-Lactam Intermediates on The Solid-Phase

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Abstract: The synthesis of 3,4-dihydro-2(*1H*)-quinolinones has been accomplished through the rearrangement of β-lactam intermediates on the solid-phase. The β-lactam intermediates were constructed through [2+2] cycloadditions between ketenes and imines on the solid-phase. A library of 4,140 dihydroquinolinones has been produced using this synthetic process. © 1997 Elsevier Science Ltd.

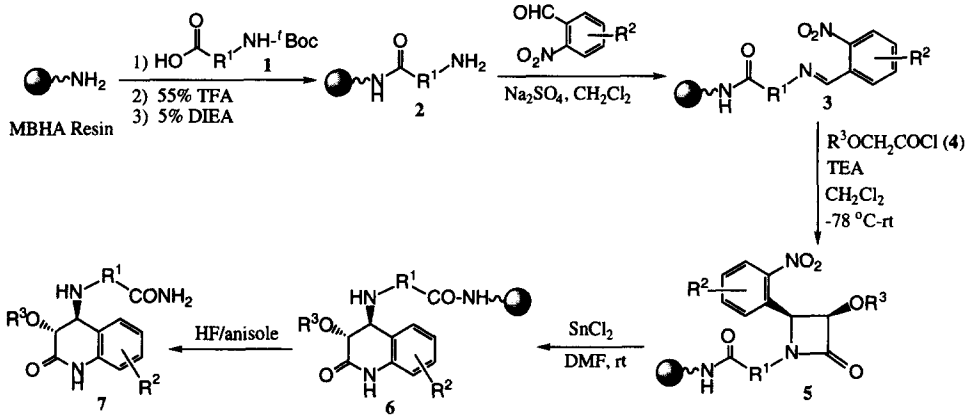
Recent advances in solid-phase organic synthesis (SPOS) has demonstrated this technology as a powerful tool for the rapid generation of large numbers of organic compounds. Lead compounds in various research areas have been identified through this approach.[1] For the past several years, the focus of this field of research, in addition to synthesizing peptides and oligonucleotides, has been exploring the possibility of synthesizing small organic molecules on the solid-phase. To this end, many classical solution-phase organic reactions have been successfully carried out on the solid-phase.[2]

Mono-cyclic β-lactams have been shown to be versatile intermediates in organic synthesis.[3] They can be constructed from readily available starting materials using well-established chemistry.[4] The high strain energy of this 4-membered ring makes its amide bond relatively labile towards nucleophilic attacks. Through this mechanism, β-lactams have been used as intermediates in the syntheses of heterocycles, amino acids and their derivatives.[5] They have also been reported to serve as acylating agents in the total syntheses of taxol and taxol analogs.[6] From a combinatorial point of view, the β-lactam template allows us to bring together several different types of building blocks. In addition, the reported reaction conditions involved in the syntheses of β-lactams in solution-phase are mild enough to tolerate a large variety of functional groups. Therefore, it is possible to incorporate various substituents into the final products through β-lactam intermediates. In this report, we wish to describe the synthesis of 4-amino-3,4-dihydro-2(*1H*)-quinolinones from amino acids, aldehydes and acid chlorides, through the rearrangement of β-lactam intermediates on the solid-phase.

The synthesis of 4-amino-3,4-dihydro-2(*1H*)-quinolinones was carried out on the solid-phase using the tea-bag technology.[7] The reaction sequence is illustrated in Scheme 1. Polystyrene MBHA resin was chosen because of its chemical stability to the conditions used in this synthesis.[8] We initially examined the feasibility of this synthetic route with three amino acids: ᵗBoc-Gly-OH (**1a**), *L*-ᵗBoc-Ala-OH (**1b**) and ᵗBoc-aminomethybenzoic acid (**1c**). They were separately attached onto the polystyrene MBHA resin using normal peptide coupling conditions (DIC/HOBT/DIEA) in dichloromethane or dimethylformamide depending on the solubility of the amino acids. The complete coupling with each amino acid was confirmed by negative result from ninhydrin test. The ᵗBoc-protecting group was removed by treatment with 55% TFA in dichloromethane for 30 minutes at room temperature to give **2**. Resin bound amines **2** were condensed with *ortho*-nitrobenzaldehyde in dichloromethane in the presence of anhydrous sodium sulfate as drying agent to furnish imines **3**. After washing with dichloromethane (3x) and drying under high vacuum over phosphorus pentaoxide, [2+2] cycloaddition of **3** with ketene was carried out in dichloromethane at -78 °C. The ketene was generated *in situ* from corresponding phenoxyacetyl chloride in the presence of triethylamine. To monitor the reaction sequence up to this point, β-lactam intermediates **5** from each amino acid were cleaved from the resin

using HF/anisole (95/5) and analyzed using ^{1}H NMR. In all cases, *cis*-β-lactams were obtained as single products in almost quantitative yield. From *L*-^{t}Boc-Ala-OH (**1b**), a mixture of two diastereomers of the *cis*-β-lactam **5b** was obtained in about 1 : 1 ratio (by ^{1}H NMR). The nitro groups of the β-lactam intermediate **5** were reduced to amines using tin(II) chloride (2.0 M) in DMF at room temperature.[9] Under this reaction condition, the β-lactam ring underwent rearrangement to give the *trans*-3,4-dihydro-2(*1H*)-quinolinones **6**, through intramolecular nucleophilic attack of the β-lactam amide moiety by the newly generated amino groups. Dihydroquinolinones **7a-c** (Table 1) were obtained in excellent yield after cleavage using HF/anisole (95/5). They were analyzed using ^{1}H NMR and LC-MS.[10] In the case of **7b** derived from *L*-^{t}Boc-Ala-OH (**1b**), the diastereomeric ratio remained at 1:1 (by ^{1}H NMR) after the reduction with tin(II) chloride and HF cleavage. Similar results were observed later with other chiral amino acids. To simplify, only one diastereomer from each chiral amino acids was shown in Scheme 1 at both β-lactam and dihydroquinolinone stages. Having validated this synthetic route, we also examined the applicability of a larger selection of amino acids, *ortho*-nitrobenzaldehydes, acid chlorides and various combinations. As shown in Table 1, dihydroquinolinones **7** were obtained in good yield in all cases. Under the LC-MS conditions, one major peak was observed in each case which represented >85% purity. In some cases, separations of diastereomers were observed for dihydroquinolinones **7** derived from chiral amino acids.

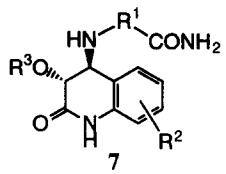
Scheme 1: **Syntheses of Dihydroquinolinones on MBHA Resin.**



Using the process illustrated in Scheme 1 and in combination with the divide-couple-recombine resin method,[12] a library of dihydroquinolinones was produced. This library contains 4,140 dihydroquinolinones (2,070 pairs of enantiomers) which were derived from 69 amino acids (R^1), 6 *ortho*-nitro-benzaldehydes (R^2) and 5 acid chlorides (R^3). These dihydroquinolinones were distributed into 30(R^2 x R^3) pools, each consisting of 138 compounds [69 (R^1) pairs of enantiomers], i.e. R^1 position is in mixture format and R^2 and R^3 are formatted as two-dimensional array. In this format, both R^2 and R^3 substituents were defined for an individual pool. In the event active pools have been identified in a given biological assay, this unique library format expedites the process of deconvoluting the active pools to give individual compounds in one iteration.

In summary, an efficient route for the solid-phase syntheses of dihydroquinolinones through β-lactam intermediates has been developed. This route allows us to bring together three different types of building blocks to construct a dihydroquinolinone template with a set of diverse substituents at various positions. A library of dihydroquinolinones has been produced.

Table 1: 4-Amino-3,4-dihydro-2(*1h*)-quinolinones



7

Entry	R^1	R^2	R^3	Yield[a]	MW	MH^+, found[b]
a	←CH_2→	H	Ph	96%	311.1	312.2 (238.5)
b	CH_3CH	H	Ph	100%	325.1	326.3 (238.6)
c		H	Ph	100%	387.1	383.3 (238.5)
d	$PhCH$	6,7-methylendioxy	4'-Cl-Ph	100%	465.1	466.0 (316.5)
e		6-chloro	CH_3CO-	85%	373.1	374.4
f		6-chloro	CH_3	75%	345.1	346.2 (210.5)
g		6-chloro	Ph	87%	407.1	408.2 (272.5)
h		6-chloro	H[c]	68%	331.1	332.2
i		6-chloro	4'-Cl-Ph	80%	441.1	442.5 (306.5)
j	CH_3CH	H	4'-Cl-Ph	100%	359.1	360.3 (272.5)
k	$(CH_3)_2CHCH$	8-methoxy	Ph	92%	383.2	384.1 (268.6)
l	$(CH_3)_2CHCH$	8-methoxy	CH_3CO-	80%	349.2	350.0 (234.4)
m	$(CH_3)_2CHCH$	8-methoxy	4'-Cl-Ph	100%	417.2	418.4 (302.6)
n		6,7-dimethoxy	Ph	92%	447.2	448.0 (298.3)
o		6,7-dimethoxy	4'-Cl-Ph	90%	481.1	481.8 (332.5)
p	HO_2CCH_2CH [d]	6-hydroxy	4'-Cl-Ph	91%	419.1	419.8 (288.4)

[a] Yield of crude product based on resin substitution. [b] The number in brackets is the major peak in the mass spectrum, resulted from the fragmentation of the parent molecular ion.[11] [c] Derived from corresponding benzyl ether which is removed during HF cleavage. [d] Derived from corresponding benzyl ester which is removed during HF cleavage.

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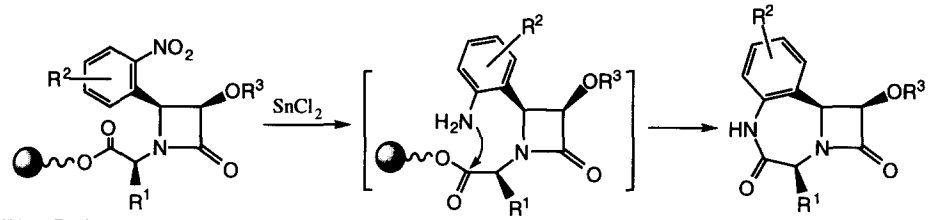
References and Notes:

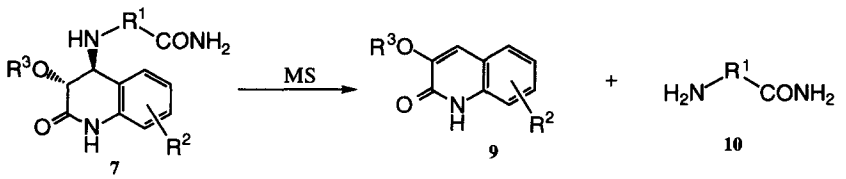
1. a) Zuckermann, R.N.; Martin, E.J.; Spellmeyer, D.C.; Stauber, G.B.; Shoemaker, K.R.; Kerr, J.M.; Figliozzi, G.M.; Goff, D.A.; Siani, M.A.; Simon, R.J.; Banville, S.C.; Brown, E.G.; Wang, L.; Richter, L.S.; Moos, W.H. *J. Med. Chem.* **1994**, *37*, 2678. b) Murphy, M.M.; Schullek, J.R.; Gordon, E.M.; Gallop, M.A. *J. Org.Chem*, **1995**, *117*, 7029.

2. For reviews see: a) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2289. b) Thompson, L.A.; Ellman, J.A. *Chem. Rev*, **1996**, *96*, 555.
3. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383 and references cited therein.
4. a) Ruhland, B.; Bhandari, A.; Gordorn, E.M.; Gallop, M.A. *J. Am. Chem. Soc.* **1996**, *118*, 253. b) For a review see: Mukerjee, A.K.; Singh, A.K. *Tetrahedron* **1978**, *34*, 1731.
5. a) Manhas, M.S.; Amin, S.G.; Bose, A.K. *Heterocycles*, **1976**, *5*, 669. b) Kano, S.; Ebata, T.; Shibuya, S. *Chem. Pharm. Bull.* **1979**, *27*, 2450. c) Kano, S.; Ebata, T.; Denta, Y.; Hibino, S. Shibuya, S. *Heterocycles*, **1977**, *8*, 411. c) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1992**, *33*, 887-890. d) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977-982 and references cited therein.
6. a) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.I.; Jayasinghe, R. *J. Med. Chem.* **1991**, *56*, 1681. b) Georg, G.I.; Cheruvallath, Z.S.; Himes, R.H.; Mejillano, M.R.; Burke, C.T. *J. Med. Chem.* **1992**, *35*, 4230. c) Ojima, I.; Kuduk, S.D.; Pera, P.; Veith, J.M.; Bernacki, R.J. *J. Med. Chem.* **1997**, *40*, 279.
7. Houghten, R.A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.
8. The syntheses of 4-amino-dihydroquinolinones was initially carried out on polystyrene Wang resin. Low yields were observed with some amino acids, especially glycine (0%). This observation could be attributed to the intramolecular cyclization-cleavage pathway as shown below. However, we were unable to recover the tricyclic-lactam **8** from a 2 M solution of $SnCl_2$ in DMF. The low yield also could result from the premature cleavage of the Wang linker in the presence of $SnCl_2$ and HCl generated *in situ* during the reduction.



Wang Resin **8**

9. Meyers, H.V.; Dilley, G.J.; Durgin, T.L.; Powers, T.S.; Winssinger, N.A.; Zhu, H.; Pavia, M.R. *Molecular Diversity*, **1995**, *1*, 13.
10. LC-MS analyses were carried out on a Hewlett-Packard 1050 HPLC system coupled to a Finnigan LCQ mass spectrometer equipped with atmospheric pressure chemical ionization (APCI).
11. Under MS analytical conditions, dihydroquinolinones **7** undergo β-eliminations to give quinolinone **9** (as shown below). In some cases, the quinolinone fragment **9** is the major peak in mass spectrum.



7 **9** **10**

12. a) Houghten, R.A.; Pinilla, C.; Blondelle, S.E.; Appel, J.R.; Dooley, C.T.; Cuervo, J.H. *Nature*, **1991**, *354*, 84. b) Lam, K.S.; Salmon, S.E.; Hersh, E.M.; Hruby, V.J.; Kazmiersks, W.M.; Knapp, R.J. *Nature*. **1991**, *354*, 82.

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