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# An Efficient High-Speed Synthetic Route to Amino-Substituted Thiazolidinone Libraries

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**Abstract:** An efficient solid-phase synthesis of amino-substituted thiazolidinones using an acid-labile carbamate linkage is reported. In this approach, excess *unprotected* symmetrical diamine is incorporated directly onto a carbonylimidazole activated Wang support followed by imine formation on the remaining free primary amine, cyclization and amide bond expansion. 

*Keywords: solid-phase, thiazolidinone, carbamate linker, high-speed synthesis*

Our high-speed synthesis program has been in the process of constructing a series of substituted heterocyclic libraries as a means to increase the molecular diversity within our corporate sample bank and provide a diverse pool of structures for our high-speed screening program. From the literature and a recent review of the top selling 100 pharmaceuticals, we were struck by the frequency with which a diamine fragment is incorporated into the heterocyclic core of a variety of drug classes (e.g. Cardizem,[1] calcium channel blocker; Ciprofloxacin,[2] antibacterial; Clozapine,[3] antipsychotic). We chose to explore diamine derived thiazolidinones[4] as a heterocyclic scaffold which: (a) resembles an important recurring drug-like motif (b) incorporates a diverse set of inputs into a multi-component system (c) can be assembled on a number of resin bound diamines and (d) can be expanded quickly to explore molecular space (Figure 1). Herein we report our findings in the development of symmetrical diamine functionalized solid supports and the assembly and expansion of thiazolidinones.

Our initial interest was in the development of diamine functionalized solid supports upon which heterocyclic systems could be assembled. We found the commercially available diamine functionalized trityl-based[5] resins unsuitable for our needs.[6] We next turned our attention to carbonylimidazole functionalized Wang resin.[7] In the case of symmetrical diamines, coupling of excess *unprotected* diamine (~4 fold) in NMP at 60 °C resulted in efficient loading of a variety of diamines with less than 5% resin crosslinking (Scheme 1). This process obviated the tedious selective solution phase mono-protection of the symmetrical diamines.[8,9]

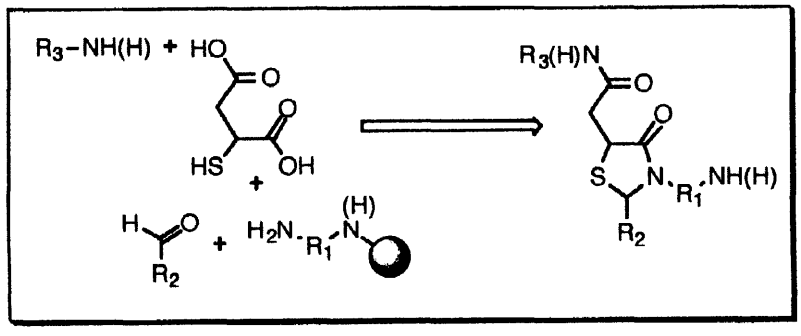


Figure 1

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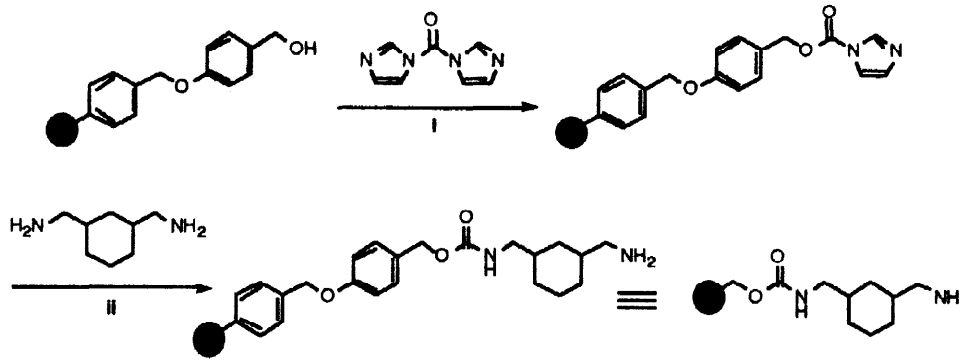
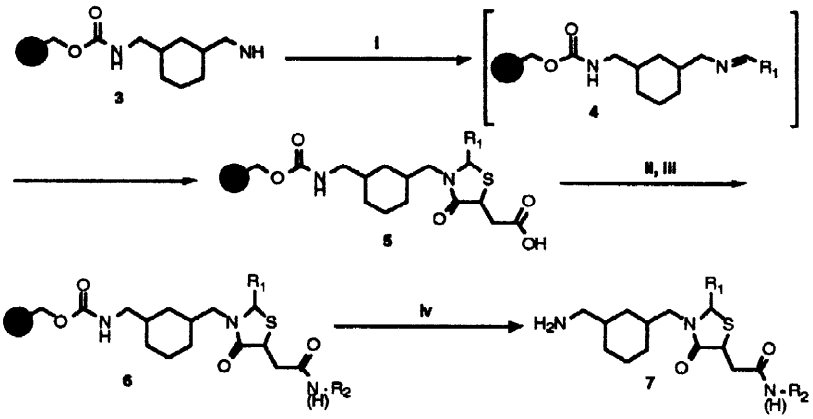


**Scheme 1:** (i) carbonyldiimidazole (4 eq) , $CH_2Cl_2$, 2 h; (ii) 1,3-cyclohexanebis(methylamine) (4 eq), NMP, 60 °C, 4 h. Resins were pre-swelled before each step in reaction solvent. After each step, resins were rinsed with 2 cycles of reaction solvent, then 3 x DMF, 2 x $CH_2Cl_2$ and 3 x MeOH and dried.

We next turned our attention to the scope and limitation of thiazolidinone formation on solid support. While a vast number of aldehydes have been examined for imine formation on solid phase,[10] we concerned ourselves with evaluating aldehydes which would undergo imine formation and subsequent cyclization (Scheme 2). Benzylic aldehydes (electron rich or electron deficient) were found to react cleanly in the imine/cyclization step with mercaptosuccinic acid. Some problems were observed with thiophene and furan based aldehydes (unidentified side-reactions), pyridyl-containing precursors (tertiary amine substitution worked well, however) and poor results were seen when aliphatic aldehydes were used (especially sterically encumbered groups which were unreactive in many cases).

Mercaptosuccinic acid was used to allow for the incorporation of a third diversity point (Figure 1). Amide formation on the resulting free acid worked for most primary or secondary amines evaluated, as well as some highly activated anilines (most aniline couplings, however, required overnight heating at 75 °C) (Scheme 2). We have demonstrated the general utility of this two step approach on a series of 8 different symmetrical diamines reacted with several aldehydes, mercaptosuccinic acid and 80 amines (>1000 compounds synthesized and characterized). Table 1 outlines nine representative examples where initial cyclization proceeded efficiently. On average, purities for the library as a whole were greater than 65% (some methyl esterification of the pendant thiazolidinone acid occurred during dehydration/cyclization). All 1000 compounds were characterized by mass spectrometry in a 96-well plate sampling mode (positive and negative). A general resin-based thiazolidinone cyclization strategy has been previously reported in a recent patent[11] using amino acid-based supports, but to date, this approach has not been used to synthesize the class of molecules we report herein.



**Scheme 2**: (i) a) $R_1CHO$ (3 eq), $(MeO)_3CH$ 1 h, b) mercaptosuccinic acid (6 eq as a solid) 80 °C, 18 (mercaptosuccinic acid does not fully dissolve until after prolonged heating); (ii) pentafluorophenyl trifluoroacetate eq), pyridine/DMF (1:10) 1 h: (iii) RN(H)H (6 eq), DMF, 18 h (iv) TFA/$CH_2Cl_2$ (1:1), 1 hr. Resins were pre-swelled befo each step in reaction solvent. After each solid phase step, resins were rinsed with 2 cycles of reaction solvent, then x DMF, 2 x $CH_2Cl_2$ and 3 x MeOH and dried.

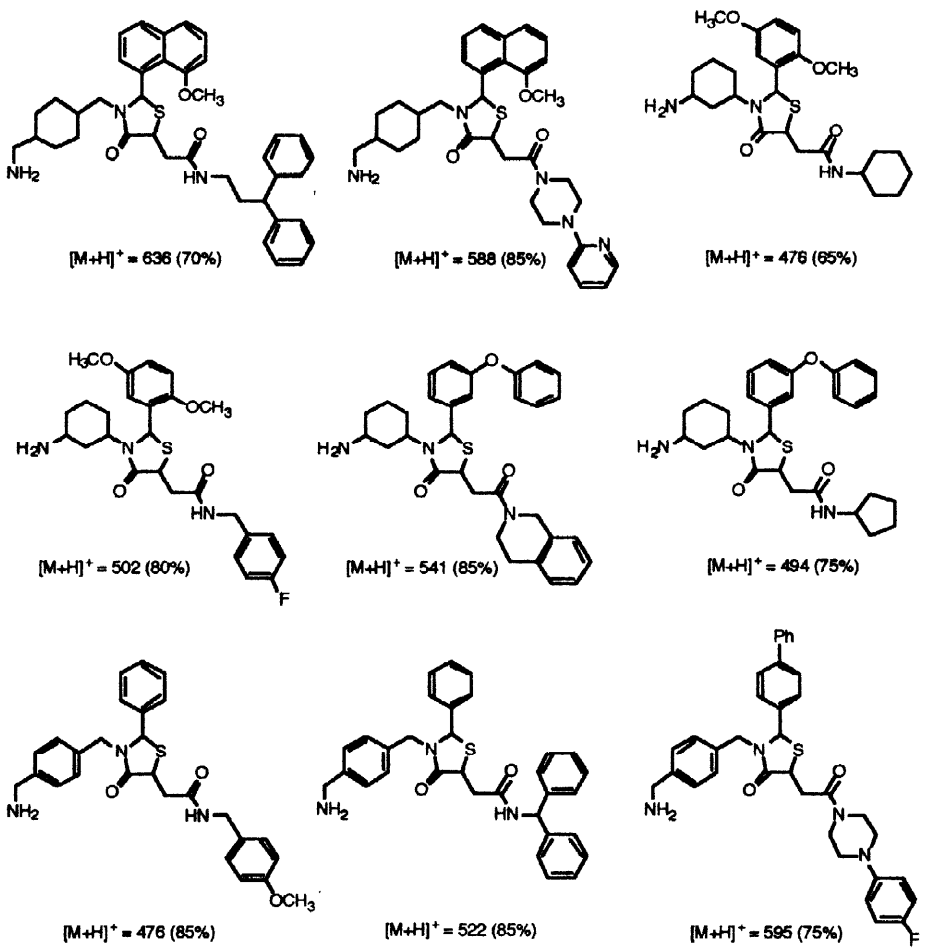



**Table 1.** Representative products and results. Crude yield based on average HPLC purity at 254.0 and 220.0 nm is given in parenthesis (continuous diode array scan HPLC). Expected $[M+H]^+$ was found for each compound and represented between 60-85% of overall ion count. Both positive and negative modes were run on all compounds. Verification of product is based on exact mass calculations for expected versus found weights. The remaining impurity

component was primarily a methyl ester by-product which formed during dehydration/cyclization in TMOF. The ratio of product to methyl ester varied based on aldehyde component. HPLC in some cases showed partial separation of the diastereomers. Isomeric compositions of final ring structures, however, were not determined. Peripheral experiments not reported herein confirmed that closure to the five membered ring was much preferred over six member ring formation (the latter was not observed at all under the conditions reported in this paper). Input diamine linkers are as follows: 1,3-cyclohexanediamine, p-xylyldiamine, 1,4-cyclohexanebis(methylamine). Input aldehydes are as follows: 3-phenoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, benzaldehyde, 4-biphenylcarboxaldehyde, 2-methoxy-1-naphthaldehyde. Amines are as follows: 1,2,3,4-tetrahydroisoquinoline, 4-fluorobenzylamine, cyclopentylamine, cyclohexylamine, 4-methoxybenzylamine, 1-(4-fluorophenyl)piperazine, 1,2-diphenylethylamine, 3,3-diphenylpropylamine, 1-(2-pyridyl)piperazine.

In conclusion, we have reported an efficient two phase approach for the high-speed synthesis of novel amino-substituted thiazolidinones using a simple procedure to construct the precursor diamine carbamate resin. This straightforward method may be generalized to other molecules requiring a pendant primary amine for scaffold construction.

## Acknowledgment

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### References and Notes

[1] Tanaka, T.; Inoue, H.; Date, T.; Okamura, K.; Aoe, K.; Takeda, M.; Kugita, H.; Murata, S.; Yamaguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 1476-1480.
[2] Li, H.; Jiang, T.; *Huaxue Yanjiu Yu Yingyong* **1996**, *8*, 292-294.
[3] Liao, Y.; DeBoer, P.; Meier, E.; Wikstroem, H. *J. Med. Chem.* **1997**, *40*, 4146-4153.
[4] Singh, S.; Parmar, S.; Raman, K.; Stenberg, V. *Chem. Rev.* **1981**, *81*, 175-203.
[5] Barlos, K.; Gatos, D.; Kapolos, S.; Papaphotiu, G.; Schaefer, W.; Yau, W. *Tetrahedron Lett.* **1989**, *30*, 3947-3950.
[6] The trityl based resins showed poor swelling properties in trimethylorthoformate, the solvent of choice for imine formation.
[7] Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589-1592.
[8] Brady, S.; Stauffer, K.; Lumma, W.; Smith, G.; Ramjit, H.; Lewis, S. D.; Lucas, B.; Gardell, S.; Lyle, E.; Appleby, S.; Cook, J.; Holahan, M.; Stranieri, M.; Lynch, J.; Lin, J.; I.-Wu C.; Vastag, K.; Naylor-Olsen, A.; Vacca, J. *J. Med. Chem.* **1998**, *41*, 401-406.
[9] We have employed selective silyl amine protection of primary amines in the presence secondary amines to effect the incorporation of nonsymmetrical diamines in this system. See: Overman, L. E.; Okazaki, M. E.; Mishra, P. *Tetrahedron Lett.* **1986**, *27*, 4391-4394.
[10] Szardenings, A.; Burkoth, T.; Look, G.; Cambell, D. *J. Org. Chem.* **1996**, *61*, 6720-6722.
[11] Holmes, C., PCT Int. Appl., 117 pp. Coden:PIXXD2, WO 9600148 A1 960104.