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Solid-phase synthesis of 4-aryl-1,4-dihydropyridines via the Hantzsch three component condensation

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Abstract

We report the synthesis of 1,4-dihydropyridines on solid support utilizing the Hantzsch condensation. Unwanted reactive impurities were removed from the desired products, by selective cleavage from solid support. The synthesis of a 272 compound library is reported using the methods described.

Keywords: combinatorial chemistry; solid-phase synthesis; Hantzsch condensation.

The use of combinatorial chemistry techniques have become commonplace to generate compounds for the screening and identification of new drug leads.[1] In attempting to build compounds with the greatest value, it is logical to build libraries on scaffolds which have historically been rich in biological activity. This approach has been taken as far back as the early heterocyclic libraries of benzodiazapines.[2] Compounds containing the 4-aryl-1,4-dihydropyridine (DHP) nucleus comprise a large family of medicinally important compounds. The most prominent of these is the Nifedipine class of Ca^{+2} channel antagonists and second generation analogs.[3] A recent computational analysis of the Comprehensive Medicinal Chemistry Database found the DHP framework to be among the most prolific chemotypes found.[4] However, to date only one group has reported a solid phase method to synthesize libraries of this valuable class of heterocycle.

An impressive paper by Gordeev and co-workers reported Hantzsch condensation of support bound β-aminocrotonates with aldehydes and β-ketoesters to form the DHP nucleus.[5] However, a limitation of linking through the nitrogen of the aminocrotonate was that the cyclization reaction could not be driven to completion on support. Instead, final cyclization occurs upon cleavage with TFA. This would complicate attempts to further functionalize the core scaffold on support, and limit the method's potential scope. Alternatively, our approach was to attach β-ketoesters to

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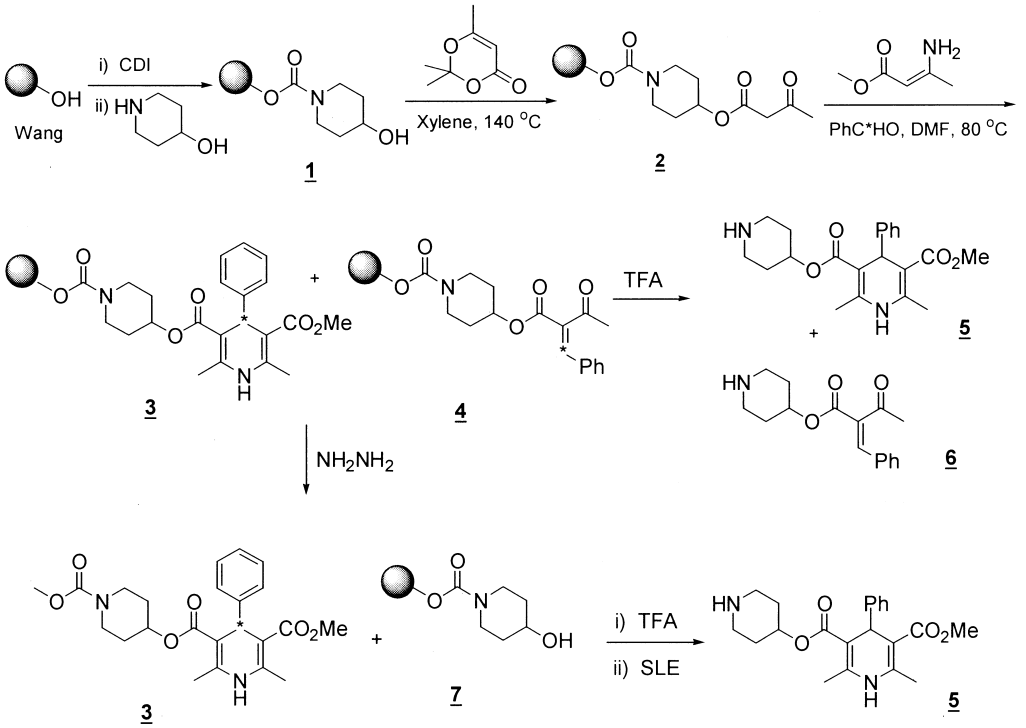
support via diverse aminoalcohol linkers. We expected that by linking through the β-ketoester cyclization would occur on support therefore allowing additional diversity elements to be added to the scaffold prior to cleavage.[6]

We began our method development by attaching 4-hydroxypiperidine to Wang resin using carbonyldiimidazole (Scheme 1). Treatment of **1** with 2,2,6-trimethyl-1,3-dioxanone at 140°C in xylenes provided β-ketoester resin **2** (IR: 1700, 1758 cm^{-1}). Resin **2** was treated with methyl aminocrotonate, and benzaldehyde in DMF to form resin bound DHP **3**. Upon cleavage from resin with TFA (25% in DCM) the desired DHP product **5** was obtained along with by-product **6** (15%). Compound **6** appeared to arise from incomplete crotonate addition to the intermediate Knovenagel product **4**. This was confirmed by performing the above condensation with ^{13}C labeled benzaldehyde. ^{13}C NMR of the resin clearly showed a major peak at 40 ppm consistent with the desired product **3**, along with a minor peak at 141 ppm indicative of resin **4**.

We considered by-products of type **6** to be unacceptable for broad-based biological screening due to their potent electrophilicity. Michael acceptors such as **6** can bind irreversibly to nucleophilic residues in proteins complicating the results of HTS assays.[7] Many variations in solvent, temperature, and stoichiometry failed to eliminate this undesired by-product. Even retreatment of resin **3** with additional aminocrotonate did not eliminate **6**.

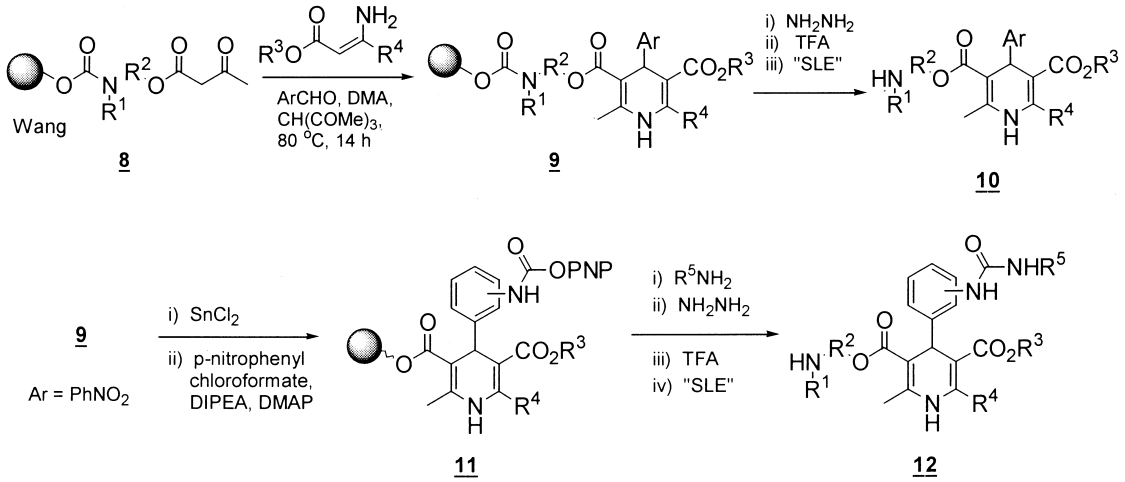


Scheme 1. Solid-phase DHP synthesis

It was recognized that the ester carbonyl of **4** should be more susceptible to nucleophilic attack than the vinylogous urethane of **3**. Thus, washing of the resin with hydrazine (0.5N in 1:1 EtOH:THF) resulted in the complete disappearance of the ^{13}C NMR signal at 141 ppm while the

signal at 40 ppm was unaffected. In addition, monitoring of the effluent solution by LC/MS showed no apparent cleavage of the desired DHP from resin. Treatment of the resin with TFA then afforded the desired product **5** with no evidence of compound **6** by LC/MS. The hydrazine wash did, however, give 4-hydroxy piperidine as an impurity, but this material could be easily removed by Supported Liquid Extraction (SLE)[8] affording DHP **5** in 60% overall yield.

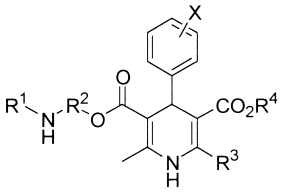
Upon completion of the initial chemistry development, a library of DHPs was synthesised using the following procedures (Scheme 2). Three different resins of type **8** were prepared as outlined above. Hantzsch condensations were then performed in filter-bottomed microtiter plates with eight different aminocrotonates and eight different aryl aldehydes to give 192 separate resins of type **9**. These were then treated with hydrazine, followed by cleavage with TFA to afford crude DHP products **10**.[9] The crude materials were subjected to SLE using 1N NH_4OH as the aqueous phase to afford purified **10**. LC/MS analysis of the library showed an average purity of 81% (AUC, 254 nM). In all cases the product molecular ion was present as the base peak in the mass spectrum. Six of these compounds were further purified by silica gel chromatography, and characterized.[10] The pure compounds were then used as HPLC standards to determine the crude purities for these components of the library (Table 1).

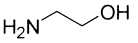
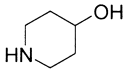
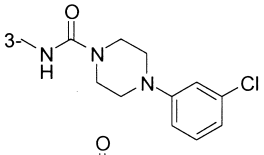
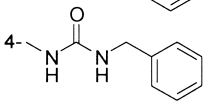
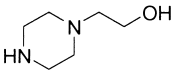
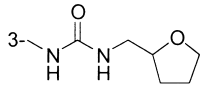
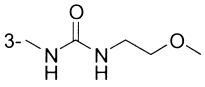


Scheme 2. Library synthesis

Further diversification of resin **9** was performed to show that the DHP scaffold could be further elaborated on support to make additional libraries (Scheme 2). Eight resins of type **9**, which contained a nitro functionality on the aryl group of the DHP, were subjected to reduction with $SnCl_2$ affording the corresponding anilines. Subsequent treatment with *p*-nitrophenyl chloroformate provided the phenyl urethanes **11**. Addition of ten different primary or secondary amines followed by hydrazine wash and TFA cleavage provided 80 DHP analogs. Finally, the amino-alcohol impurities were removed by SLE to provide clean DHPs of structure **12**. The library was then analyzed by LC/MS and showed an average purity of 54% (AUC, 254 nM). Four of the compounds were purified by silica gel chromatography, and characterized. The crude purities of these components were then determined by HPLC (Table 1).

Table 1



Compound	HNR^1R^2OH	R^4	R^3	X	Purity	Yield
10a		Me	Me	4-F	78%	44%
10b	" "	$CH_2CH_2OCH_3$	Me	4-CO_2H	77%	68%
10c		Et	Ph	3-NO_2-4-OH	90%	88%
12a	" "	i-Pr	Me		59%	45%
12b	" "	Bn	Me		40%	60%
10d	" "	Me	Me	H	57%	60%
10e	" "	Bn	Me	4-Cl-3-NO_2	89%	88%
10f		Et	Ph	3-NO_2	89%	57%
12c	" "	Me	Me		51%	41%
12d	" "	Bn	Me		56%	44%

Conclusion: We have demonstrated a novel method for the generation of 4-aryl-1,4-dihydropyridine libraries. Unwanted reactive impurities were removed by a unique method of selective cleavage from solid support. By paying particular attention to the removal of such reactive impurities, we hope to create libraries which will be much more reliable for biological screening.

References

1. For reviews, see: Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235. Nuss, J. M.; Renhowe, P. A. *Curr. Opin. Drug Disc. Dev.* **1999**, *2*, 631.
2. Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA.* **1993**, *90*, 6909.

3. For reviews, see: Gaudio, A. C.; Korolkovas, A.; Takahata, Y.; *J. Pharm. Sci.* **1994**, *83*, 1110. Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Des. Discovery* **1992**, *8*, 273.
4. Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.
5. Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924. Gordeev, M. F.; Patel, D. V.; England, B. P.; Supriya, J.; Combs, J. D.; Gordon, E. M. *Bioorg. Med. Chem. Lett.* **1998**, *6*, 883.
6. Other groups have performed Hantzsch condensations on solid support. However, in these example the DHPs are oxidized during or after cleavage to afford 4-aryl pyridine products. See: Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37*, 4643. Tadesse, S.; Bhandari, A.; Gallop, M. A. *J. Comb. Chem.* **1999**, *1*, 184.
7. Rishton, G. M. *Drug Discovery Today* **1997**, *2*, 382.
8. Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295. Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097.
9. Initially 4-aryl-pyridines were seen as by-products in this library. Oxidation to 4-aryl pyridines was minimized by diluting the products with 1:1 acetonitrile:toluene prior to concentration of the reaction mixture. This allowed for the maintenance of a low concentration of TFA during concentration.
10. Compounds were characterized by: ^{1}H and ^{13}C NMR, MS, and combustion analysis.