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Solution Phase Synthesis of a Spiro[pyrrolidine-2,3'-oxindole] Library via a Three Component 1,3-Dipolar Cycloaddition Reaction

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Abstract: A combinatorial library of 26,500 spiro[pyrrolidine-2,3'-oxindoles] was prepared in a single-compound format by a facile intermolecular 1,3-dipolar cycloaddition. An azomethine ylide, generated by the decarboxylative condensation of an isatin **1** with an α-amino acid **2**, was trapped by a *trans*-chalcone **3** to afford heterocycles of the general structure **4**. The regio- and stereochemistry of a representative product was determined by single crystal X-ray structure.

In recent years the synthesis of combinatorial libraries has emerged as a valuable tool for the discovery[1] of biologically active compounds. Solution phase parallel synthesis of small molecule libraries offers certain advantages over the better established solid phase methodology and is gaining increasing acceptance in the pharmaceutical industry for accelerated lead generation, compound optimization and process chemistry.

Multicomponent reactions continue to be the center of attention for the preparation of combinatorial libraries[2] since three or more molecular building blocks can be combined in one step yielding large numbers of compounds. However, many multi-component assembly strategies result in linear strings of modular components with a high degree of conformational freedom, molecules which rarely mimic the well defined secondary structure characteristics that are frequently associated with bioactive oligomers.

Library assembly of polycyclic molecules poses a greater challenge than that of acyclic or oligomeric compounds but such targets provide more opportunity for the development of synthetic strategies and methods. We have undertaken a systematic exploration of the polycyclic compound library opportunities presented by chemistries involving chalcone analogs[3] and have discovered within this area a particularly productive expression of these ideas.

Pyrrolidine, pyrrolizidine and oxindole alkaloids constitute classes of compounds with significant biological activity and the spiro[pyrrolidine/oxindole] ring system is common to most oxindole alkaloids.[4] Solid phase synthesis of pyrrolidine libraries by the azomethine ylide dipolar cycloaddition strategy has been described.[5]

Solution phase azomethine ylides resulting from the condensation of 1,2-dicarbonyl compounds with α-amino acids or amines and their cycloaddition reactions with acrylate esters or maleimides were studied by Grigg.[6] We envisioned that planar electron deficient π-systems such as chalcones[7] would capture as cycloadducts the intermediate ylide generated from an isatin and an α-amino acid. Indeed, when isatin **1** was treated with an acyclic or cyclic amino acid **2** and chalcone **3** in a MeOH-H_2O, CH_3CN-H_2O or dioxane-H_2O solution, spiropyrrolidine **4** (Scheme 1) was obtained as the sole product in good yield and high purity (Table 1).

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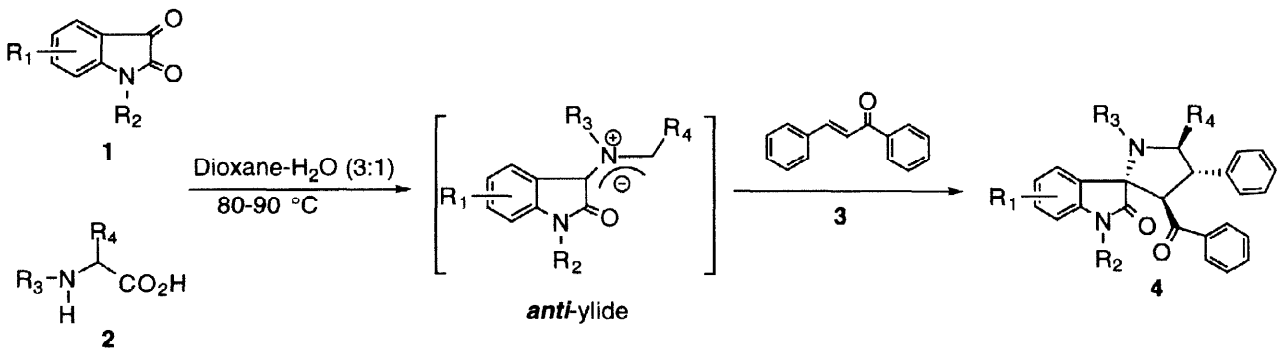


Scheme 1

Table 1

Isatin	Amino acid	Product	Yield[a] (%)	Purity[b] (%)
R_1, R_2=H	Sarcosine, R_3 = Me, R_4 = H	**4a**	65	89
R_1, R_2=H	L-Phenylalanine, R_3 = H, R_4 = -CH_2Ph	**4b**	87	87
R_1, R_2=H	L-Leucine, R_3 = H, R_4 = -$CH_2CH(CH_3)_2$	**4c**	75	91
R_1, R_2=H	L-Proline, R_3-R_4 = -$(CH_2)_3$-	**4d**	83	98
R_1=5-Br, R_2=H	L-Proline	**4e**	85	90
R_1=H, R_2=Ph	L-Proline	**4f**	88	96[c]
R_1, R_2=H	L-Thiaproline, R_3-R_4 = -CH_2SCH_2-	**4g**	79	81
R_1=H, R_2=Me	L-Proline	**4h**	73	81[c]

a) Isolated yields. All compounds gave satisfactory ^{1}H NMR and Mass Spectra. b) Determined on crude products by HPLC (UV detector, λ=254 nm). c) ^{1}H NMR spectra of some cycloadducts showed the presence of a minor product, the regioisomer of **4**. The structure of a representative product (**5**), the regioisomer of **4h**, was determined by X-ray analysis.[9] The ratio of regioisomers (e.g. 4h:5=6) was determined by ^{1}H NMR analysis.

However, substitution of proline with pipecolinic acid (R_3-R_4 = -$(CH_2)_4$-) gave only 26% yield of the corresponding cycloadduct while no product was observed with the α,α-disubstituted 1-aminocyclohexanecarboxylic acid under the same reaction conditions.

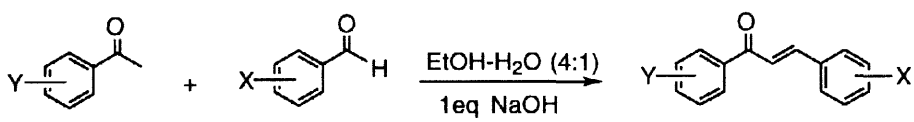
The cycloaddition proceeds in a regio- and stereocontrolled fashion. Control of relative stereochemistry at chiral center bearing side chain R_4 is realized for both cyclic and acyclic amino acids. Presumably, an *anti*-ylide[8] is involved in the transition state where *exo* addition of the chalcone to the W-periphery of the ylide prevails. Formation of the *syn*-ylide is not observed due to unfavorable steric repulsions between the carbonyl oxygen of the oxindole ring and substituent R_4. The regio- and stereochemical outcome of the cycloaddition was determined by a single X-ray crystal structure of the 5-bromoisatin cycloadduct **4e**.[9] The crystal structure of **4e** reflects the *trans*-geometry of chalcone, clearly defines the relative configurations at all four chiral centers, and establishes the (counterintuitive) regiochemistry of the chalcone addition, a result which supports a concerted bond forming process.

The high purity and the good yields of the cycloadducts, prompted us to investigate the synthesis of a spiropyrrolidine library in a parallel fashion. Combination of 16 readily available isatins,[10] 20 amino acids (Table 2) and 1280 different available chalcones could afford 409,600 functionalized pyrrolidines. However, 80 different *trans*-chalcones were selected and easily prepared from commercially available acetophenones and arylaldehydes (Table 3).[11]

Table 2. List of Isatins and Amino Acids

5-Fluoroisatin	5,7-Dimethylisatin	Sarcosine	L-Leucine
Isatin	5-Bromoisatin	L-Valine	O-Benzyl-(D,L)-serine
1-Methylisatin	5-Chloroisatin	L-Methionine	O-Methyl-L-tyrosine
5-Methylisatin	5-(Trifluoromethoxy)isatin	L-Methionine Sulfoxide	L-Isoleucine
5-Nitroisatin	1-Benzylisatin	L-Methionine Sulfone	L-Proline
5-Iodoisatin	1-(3-Chlorobenzyl)isatin	L-Alanine	4-Hydroxy-L-proline
1-Phenylisatin	1-(4-Methoxybenzyl)isatin	L-Glutamine	L-Thiaproline
5-Chloro-7-methylisatin	1-Allylisatin	L-Threonine	L-Tryptophan
		D-Serine	L-Phenylglycine
		L-Phenylalanine	Glycine

Table 3. Set of 80 Chalcones[a]



A. Acetophenone	4-Methoxybenzaldehyde (A, E, O)
B. 3,4-Dimethylacetophenone	3-Thiophenecarboxaldehyde (A, C, F, H, I, J, L)
C. 4-Cyclohexylacetophenone	1,4-Benzodioxan-6-carboxaldehyde (A, C, E, F, H, I, J, K, M)
D. 3-Methoxyacetophenone	Benzaldehyde (A, N, O)
E. 4-Methoxyacetophenone	4-Bromobenzaldehyde (A, F, I, J, L)
F. 4-Ethoxyacetophenone	3-Fluoro-4-methoxybenzaldehyde (A,C, E, F, H, I, J, K, L)
G. 3,4-Dimethoxyacetophenone	4-Phenoxybenzaldehyde (A, E, F, H, I, L)
H. 2-Fluoro-4-methoxyacetophenone	p-Tolualdehyde (A, F, H, I, J, L)
I. 4-Chloroacetophenone	4-Propoxybenzaldehyde (B, D, G)
J. 1,4-Benzodioxane-6-yl methyl ketone	4-t-Butylbenzaldehyde (B)
K. 4-N-Piperidinoacetophenone	2-Thiophenecarboxaldehyde (C, F, H, I, J, K, L)
L. 3,4-Methylenedioxyacetophenone	4-Butoxybenzaldehyde (K)
M. 3-Acetyl-1-methylpyrrole	2,4-Dichlorobenzaldehyde (K)
N. 2-Chloroacetophenone	5-Bromo-3-thiophenecarboxaldehyde (K)
O. 4-Fluoroacetophenone	3-Trifluoromethylbenzaldehyde (A, E)
	2-Chlorobenzaldehyde (A, E, O, N)
	4-Methylthiobenzaldehyde (B, D, G)
	3,5-Difluorobenzaldehyde (B, D, G)
	3,5-Dimethoxybenzaldehyde (C, E, F, J, K, M)

a) Acetophenones used with each arylaldehyde designated by letters in parenthesis.

The realization of this plan afforded a 25,600 compound library of spiropyrrolidines with the general structure **4** in 50 μM quantities in a single compound per well format using the three component strategy depicted in Scheme 1. Isatins and chalcones were dispensed in perfume vials as 0.25 M solutions in dioxane while amino acids were added as 0.25 M aqueous solutions (including 1 equivalent of NaOH for L-phenylalanine, L-leucine, O-benzyl-D,L-serine, L-tryptophan, L-isoleucine and O-methyl-L-tyrosine). The reaction vials were heated at 80 ° C overnight and the solvent was next evaporated. The products were isolated as single racemates in good purity as determined by HPLC and mass spectrometry.[12]

Further exploration of cycloadditions with other classes of dipolarophiles that would provide us with more complex heterocyclic ring systems is currently under investigation.

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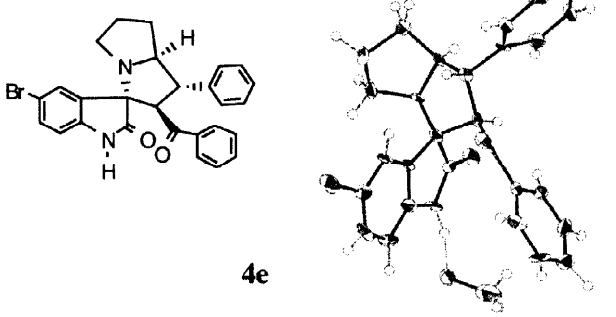
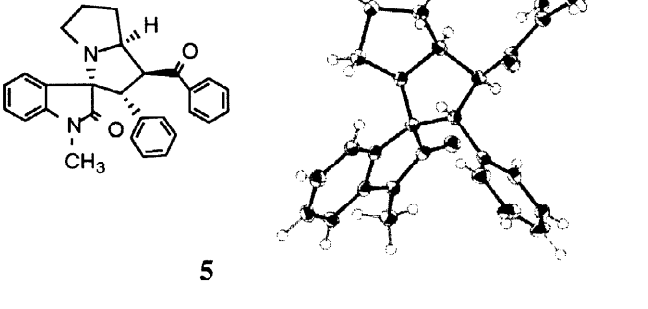
9. Crystals were grown from methanol and a molecule of methanol was located in the crystal of **4e**. We are pleased to acknowledge the contribution to this project provided by Dr. John Huffman and the X-ray crystallography laboratory of Indiana University.



4e



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10. Twelve isatins were commercially available. Four other substrates were easily made by alkylation of isatin with benzyl/allyl halides in the presence of DMF and NaH.
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