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Efficient solid-phase synthesis of 2,3-substituted indoles

Dean A. Wacker* and Padmaja Kasireddy

Bristol-Myers Squibb Company, Experimental Station, PO Box 80336, Wilmington, DE 19880-0336, USA

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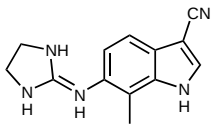
Abstract—The development of the solid-phase version of the modified Madelung indole synthesis is reported. The chemistry was initiated with the reductive amination of Bal resin using an *ortho* substituted aniline. The resin bound aniline was acylated with a variety of acid chlorides followed by cyclization with base to provide the desired indole after TFA-promoted cleavage from the resin.

Combinatorial chemistry has played an ever-increasing role in drug discovery and provided impetus for the continued development of new solid-phase synthetic methodology. Of particular interest is the synthesis of heterocyclic compounds because of their application to a variety of pharmaceutical targets. Our interests were focused on indole containing molecules because of the wide range of G-protein coupled receptors (GPCRs) that interact with these molecules; examples include an adrenergic (alpha 2) agonist **1**,[1] a substance P antagonist **2**,[2] a serotonin antagonist **3**,[3] and an angiotensin II antagonist **4**.[4] Although a number of synthetic methodologies are available for the synthesis of indoles, only four have been applied to solid-phase libraries: the Fisher indole synthesis,[5] palladium-catalyzed cyclizations,[6] intramolecular Wittig reaction,[7] and the Nenitzescu indole synthesis.[8] The modified Madelung indole synthesis, which can be used to synthesize the GPCR examples below, provides an excellent methodology for the synthesis of 2,3-disubstituted indoles and has not been utilized in a solid-phase library.



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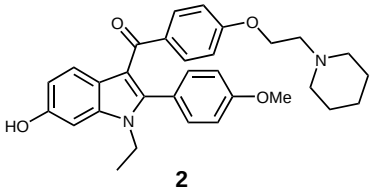

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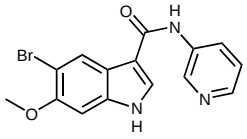

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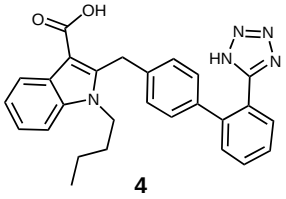

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We believed there were several reasons why the modified Madelung synthesis would be an excellent methodology to use in solid-phase synthesis. First, the reaction provides a structural motif that has led to many biologically active compounds against GPCRs. Second, the reaction is very modular and therefore allows the incorporation of multiple diversity points. Third, Orlemans et al. have modified the Madelung synthesis,[9] which originally involved the intramolecular cyclization of acylated *ortho*-alkylanilines with strong base at temperatures between 200 and 400°, by using milder conditions that incorporate an electron withdrawing group on the *ortho*-alkyl group of the aniline. This modification also allows for greater diversity during the library synthesis.

Our initial efforts focused on determining the appropriate conditions to effect the intramolecular cyclization on solid support (Scheme 1). Aniline **5** was loaded onto Bal-resin (Perseptive Biosystems) by using 2 equiv. of aniline in trimethylorthoformate overnight to form the imine, which was then reduced to secondary amine **6** with $NaBH(OAc)_3$ in CH_2Cl_2. The resin **6** was then treated with 5 equiv. of benzoyl chloride and 5 equiv. of Hunig's base in DMF overnight to form the acylated resin **7**. The cyclization of resin **7** was then attempted with several different bases under a variety of conditions. The final products were cleaved from resin **8** with a 95:5 mixture of trifluoroacetic acid:triethylsilane over 30 min.

We began our efforts to identify cyclization conditions by following the conditions that Orlemans et al. had devised for solution phase indole cyclization (entry 1,

* Corresponding author. Fax: 1-302-467-6913; e-mail: dean.wacker@bms.com

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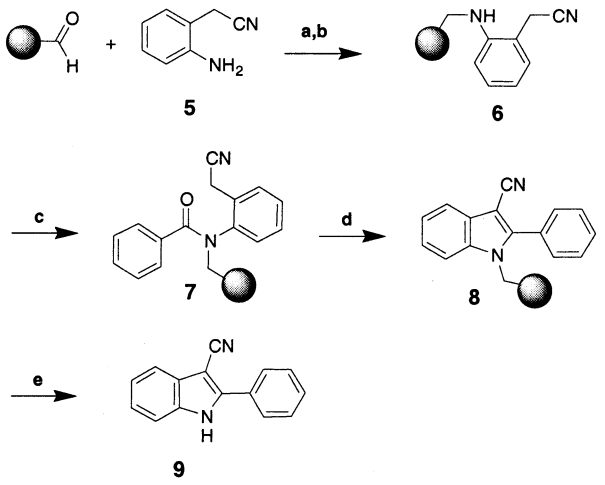


Scheme 1. *Reagents and conditions*: (a) trimethylorthoformate, rt, 16 h; (b) $NaBH(OAc)_3$, CH_2Cl_2, rt, 5 h; (c) benzoyl chloride (5 equiv.), Hunig's base (5 equiv.), rt, 16 h; (d) cyclization conditions (see Table 1); (e) 95:5 TFA:Et_3SiH, rt, 30 min.

Table 1).[9] In the solid-phase reaction there was very little conversion to the indole as the majority of the isolated material was the uncyclized precursor **7**. Increasing both the amount of base (entries 2 and 3) and reaction time (entry 4) dramatically increased the desired indole yield to 75%, but the product was still contaminated with about 20% of precursor **7**. We believed the poor reaction rate was due to the resin failing to swell in the THF solvent and therefore not allowing the reagents to reach the reaction sites inside the resin. To improve the yield, we tried several different solvents (entries 5–7) which provided conditions that not only swelled the resin but also retained the solubility of the base. Although all of the reactions showed complete conversion of the starting material to the desired product, DMF provided the best combination of yield and purity. Attempts were also made to improve the reaction by changing the base (entries 8–11), however, only phosphazene base P_1-*t*-Bu provided the yield and purity equivalent to potassium *tert*-butoxide. Finally, reduction of the amount of base and reaction time (entry 12) provided the mildest reaction conditions (2 equiv. of base for 2 h) providing comparable product yield but superior purity. This provided the appropriate conditions to test the diversity of amides, which could be used in the cyclization reaction.

In order to determine the diversity of acceptable amides that could be used in the solid-phase Madelung reaction, we set up a small validation library (see Table 2). The reaction worked extremely well for almost all phenyl substitutions tested (entries 1–5). Both electron rich (entry 2) and electron poor phenyls (entry 3) gave excellent yields and purity with the exception of the nitro-substituted phenyl (entry 4) which had lower yields and purity. We were concerned that steric hindrance would inhibit the cyclization reaction but 2-ethylphenyl (entry 5) cyclized well. Heterocycles worked just as well as phenyl groups in the cyclization reaction with pyridine (entry 6) and isoxazole (entry 7) producing good yields and purities. The cyclization reaction also worked with alkyl groups (entries 8 and 9) and saturated heterocycles (entry 10). However, the phenylacetyl group (entry 11) provided poor results because deprotonization of the phenylacetyl was competitive with deprotonization alpha to the nitrile functionality. Cyclization of α,β-unsaturated amides (entries 12 and 13) also provided less than desirable results. The cyclization can also be accomplished with ester (entry 14) and amide (entry 15) functional groups in place of the nitrile group. The yields and purities were excellent with both functional groups with the *t*-butyl ester providing the acid product upon cleavage from the resin.

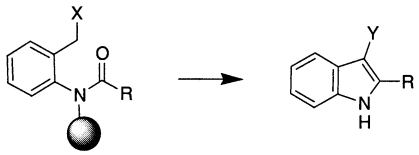
In summary, we have demonstrated the first solid-phase version of the modified Madelung indole synthesis. This initial study defined the optimal cyclization conditions and provided an early understanding of the limitations to the diversity that can be used on solid-phase in a library format. We are currently investigating other resin attachment points and synthesizing a large library using this technology.

Table 1. Optimization of solid-phase Madelung reaction conditions

Entry	Base	Equiv.	Solvent	Time (h)	Yield (%)[a]	Purity (%)[b]
1	*t*-BuOK	1	THF	0.5	8	15
2	*t*-BuOK	2	THF	5	22	31
3	*t*-BuOK	5	THF	5	51	69
4	*t*-BuOK	5	THF	24	75	81
5	*t*-BuOK	5	DMF	24	86	90
6	*t*-BuOK	5	NMP	24	85	88
7	*t*-BuOK	5	DMSO	24	80	82
8	DBU	5	DMF	24	5	7
9	NaHMDS	5	DMF	24	81	91
10	Phosphazene base P_1-*t*-Bu	5	DMF	24	84	89
11	Phosphazene base P_2-*t*-Bu	5	DMF	24	69	73
12	*t*-BuOK	2	DMF	2	88	95

[a] Isolated yield based on theoretical resin loading.
[b] Based on HPLC analysis (UV Auc @ 254 nM) of crude product.

Table 2. Substitution diversity of the solid-phase Madelung reaction



Entry	X	Y	R	Yield (%)[a]	Purity (%)[b]
1	CN	CN	Phenyl	88	95
2	CN	CN	4-MeOphenyl	84	95
3	CN	CN	4-CF_3phenyl	83	94
4	CN	CN	4-Nitrophenyl	75	87
5	CN	CN	2-Ethylphenyl	87	94
6	CN	CN	3-Pyridine	85	93
7	CN	CN	5-Isoxazole	86	96
8	CN	CN	Ethyl	86	95
9	CN	CN	*t*-Butyl	84	95
10	CN	CN	4-*N*-Acetylpiperidine	87	93
11	CN	CN	$PhCH_2$	43	51
12	CN	CN	CH_2CH	0	0
13	CN	CN	PhCHCH	65	71
14	CO_2t-bu	CO_2H	Phenyl	81	92
15	$CON(Me)_2$	$CON(Me)_2$	Phenyl	78	90

[a] Isolated yield based on theoretical resin loading.
[b] Based on HPLC analysis (UV Auc @ 254 nM) of crude product.

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