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Traceless Solid Phase Synthesis of 2,3-Disubstituted Indoles

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Abstract: An efficient method for the traceless solid phase synthesis of 2,3-disubstituted indoles using a THP linker and a Pd(0)-mediated annulation of 2-iodoaniline and acetylenes is reported.

Recent years have witnessed an explosion of interest in the solid phase synthesis of small organic molecules as a tool for medicinal chemists interested in accelerating the drug discovery process through combinatorial chemistry and automated high speed parallel synthesis.[1] Much of the published work has relied upon direct conversion of known solution phase chemistry using resin-tethering substituents such as amines and carboxylic acids which appear in some form as extraneous polar substituents in the final molecules after cleavage. This limits the usefulness of the methodology when investigating structure-activity relationships where these extraneous tethering substituents may not be wanted. Additionally, most of our work relies upon getting the drug candidate across the lipophilic blood-brain barrier for which polar substituents are a positive disadvantage. A number of approaches have been developed to circumvent this problem resulting in so-called traceless solid phase linkers. These include cyclization / cleavage strategies such as the pioneering benzodiazepine synthesis[2] and our own 1,3-disubstituted quinazolinedione synthesis;[3] tethering substituents such as silicon which are replaced by hydrogen (or halogen) during resin-cleavage;[4] and safety-catch linkers,[5] which are useful when the desired molecules contain an amide bond.

Indoles probably represent the most important of all structural classes in drug discovery – high affinity indole ligands have been identified for a variety of G-protein coupled receptors and a large number of drugs are indole based. Several reports have appeared recently describing solid phase synthetic approaches to indoles.[6] However, these have relied upon the use of extraneous resin-tethering polar substituents limiting their use for our needs. We therefore wish to report our own studies which have identified a highly efficient traceless linkage route to 2,3-

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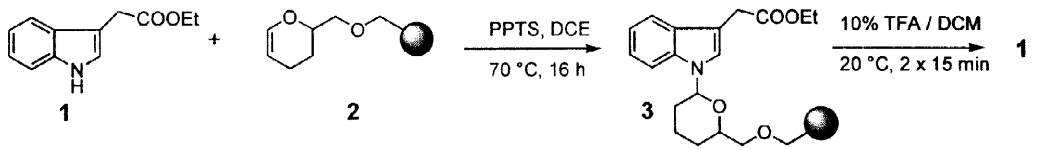
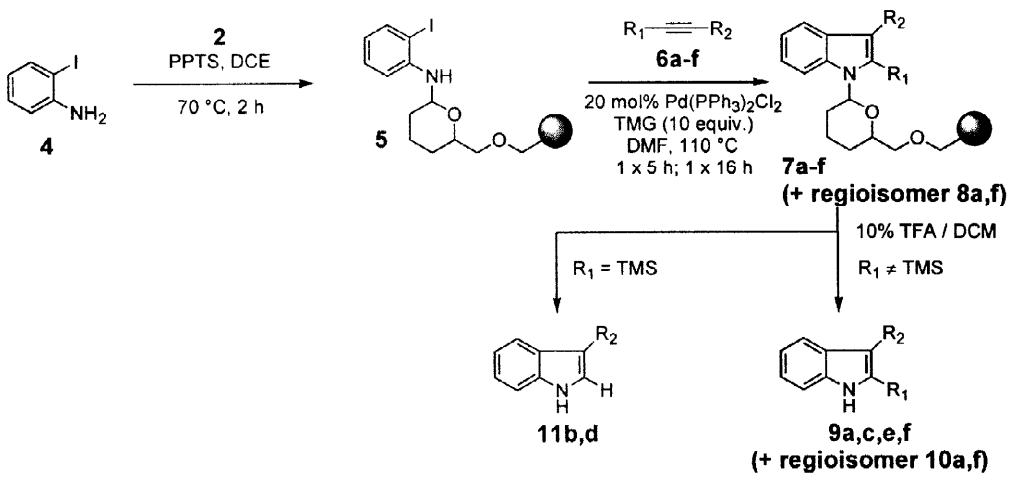
disubstituted (and 3-monosubstituted) indoles amenable to automated high speed parallel synthesis and which could be used as the basis of a split-mix combinatorial strategy.

The most obvious approach for carrying out a traceless solid phase indole synthesis would be to use the indole N-*H* as a resin attachment point which could be cleaved to give the free indole. There have, however, been no reports in the literature of such a strategy being successfully accomplished. We therefore surveyed a number of resin-bound forms of standard indole N-*H* protecting groups.[7] However, none were totally satisfactory in terms of withstanding the reaction conditions we were anticipating using (e.g. strong nucleophiles, bases, mild acids) and yet being cleaved under relatively mild conditions to provide pure products with a minimum of post-cleavage workup (preferably just solvent removal). However, during the course of our work we made the chance observation that THP protection of tryptophol also resulted in the facile formation of an aminal linkage between 3,4-dihydro-2*H*-pyran and the indole nitrogen which is remarkably robust, prompting us to explore its use as a resin linker.[8]



Scheme I

Indoles such as **1** cleanly couple to Ellman's THP resin (**2**)[9] under mildly acidic conditions (**Scheme I**). Complete loading of the resin was achieved using a small excess of the indole (1.4 equiv.).[10] The resulting resin is stable to brief treatment with cold acetic acid and 2 M aqueous HCl, but is readily cleaved with 10% TFA to give back pure **1**.



Scheme II

We next turned our attention to constructing the indole nucleus on the resin. One of the most efficient solution phase methods of indole synthesis is the Pd(0)-mediated reaction of 2-iodoaniline with acetylenes in the presence of base as developed by Larock.[11] 2-Iodoaniline (**4**) was

successfully loaded onto the THP resin **2** through an aminal linkage using PPTS to give **5** (**Scheme II**).[10,12] Attempted indole synthesis (**5**→ **7**) using the various solution phase conditions described by Larock (e.g. $Pd(OAc)_2$, PPh_3, LiCl, Na_2CO_3, DMF, 100 °C, 24 h) were not particularly successful, with incomplete reaction and large quantities of multiple acetylene insertion reaction products being observed, reflecting the poor solubility of the inorganic base. However, replacing the catalyst system with $Pd(PPh_3)_2Cl_2$ and the base with tetramethylguanidine (TMG)[13] completely eliminated multiple acetylene insertion reactions, and double couplings were found beneficial in pushing reactions to completion. Resin cleavage with 10% TFA then gave the free indole products **9-11**. **Table I** illustrates the scope of the chemistry with a range of acetylenes. It was found that TMS-substituted acetylenes such as **6b** readily went to completion at 80 °C with complete regioselectivity. By contrast, **6a** only achieved 20% conversion at 80 °C but went to completion at 110 °C. Regioselectivity was approximately 5:1 at both temperatures, with the more bulky phenyl substituent preferentially ending up at the 2-position of the indole. The more sterically demanding *tert*-butyl acetylene **6f** only achieved 48% conversion under these conditions, although regioselectivity was complete. Clean proto-desilylation of the 2-trimethylsilyl indoles **7b,d** was observed during cleavage giving rise to the pure 3-substituted indoles **11b,d**.

Table I.[a]

Acetylene	R_1	R_2	Conversion (%)[b]	Isomeric Ratio[b,c]	Mass Recovery (%)[d]
6a	Ph	Et	100	84:15	63
6b	TMS	$-CH_2CH_2OH$	100	100:0	82[e]
6c	Ph	Ph	93	-	97
6d	TMS	Ph	100	100:0	73
6e	^{n}Pr	^{n}Pr	100	-	53
6f	^{t}Bu	Me	48	100:0	55

[a] Reactions were carried out at 110 °C (1 x 5 h; 1 x 16 h) on 0.07 mmol scale (100 mg resin). [b] Determined by HPLC analysis of crude cleavage products **4,9-11** (230 nm UV detection). [c] Determined after cleavage by comparison with authentic samples. [d] After cleavage and solvent removal, based upon theoretical. [e] Variable amounts of the corresponding TFA ester were isolated. This was readily hydrolyzed to **11b** with NaOMe / MeOH.

In conclusion, we have identified an efficient resin linkage for indoles which should be compatible with a wide range of chemistries, and utilized it in developing a highly efficient solid phase synthesis of 2,3-disubstituted and 3-monosubstituted indoles. The 2-trimethylsilyl indole substituent is readily introduced with complete regioselectivity, and the chemistry is suitable for automated high speed parallel synthesis and the pursuit of structure-activity investigations as part of a drug discovery program.

References and Footnotes

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