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Fischer Indole Synthesis on a Solid Support

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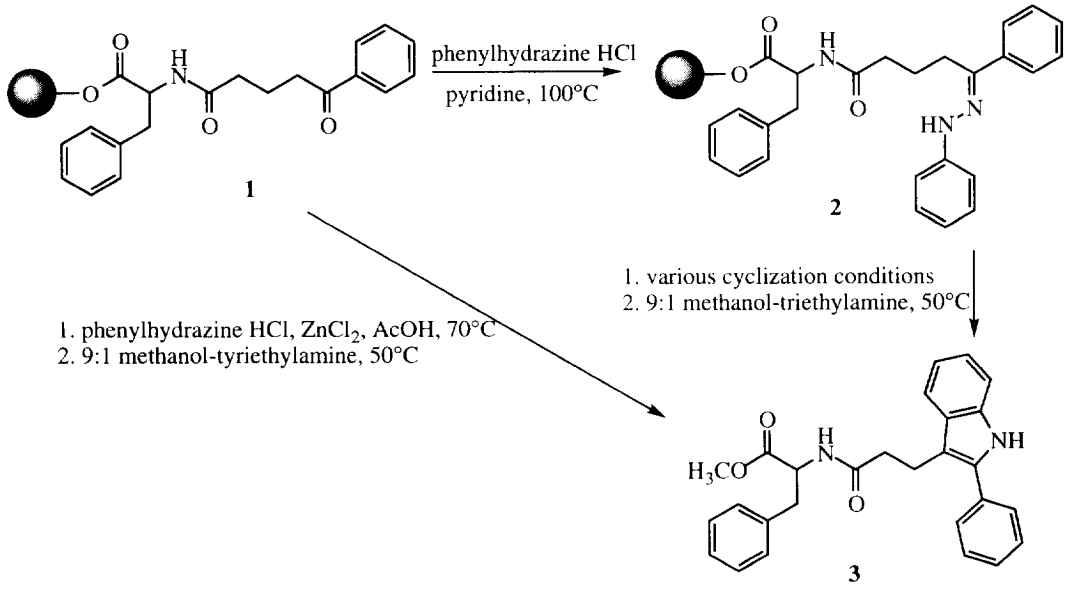
Abstract: *The preparation of 2-arylindoles on a solid support has been developed utilizing the Fischer indole synthesis. This route uses support bound 4-benzoylbutyric acid and variously substituted phenylhydrazine hydrochlorides as the synthetic building blocks.* Copyright © 1996 Elsevier Science Ltd

As part of an ongoing research effort in the area of combinatorial chemistry, we required a flexible solid phase synthetic protocol for the preparation of 2-arylindoles from commercially available starting materials. The Fischer indole synthesis[1] has proven to be an efficient and flexible solution phase preparation of the indole nucleus. We now report the adaptation of the Fischer indole synthesis to the solid phase.

Scheme:



The system we chose to study is illustrated in the above scheme. Our starting point for the Fischer indole synthesis was resin bound ketone **1**. Since the indole cyclization required acid catalysis, the 4-hydroxymethylbenzoic acid (HMB) linker was chosen. Resin bound hydrazone (**2**) could then be formed by

heating the ketone (**1**) in pyridine with phenylhydrazine hydrochloride and zinc chloride. Table 1 shows the conditions attempted for cyclization of the hydrazone (**2**). Glacial acetic acid alone did not produce any appreciable amount of the desired indole (**3**). However, optimal cyclization conditions were found in acetic acid with either trifluoroacetic acid or zinc chloride producing 52% and 65% indole respectively. It was then determined that treatment of ketone (**1**) with phenylhydrazine hydrochloride and zinc chloride in glacial acetic acid at 50°C for 18 hours, produced the desired indole (**3**) in excellent purity.

Table 1

Reaction Conditions for Hydrazone Cyclization	% Ketone (**1**)	% Hydrazone (**2**)	% Indole (**3a**)
glacial acetic acid, 50°C	91%	-	7%
1:1 glacial acetic acid-trifluoroacetic acid, 50°C	48%	-	52%
2M HCl in dioxane, 50°C	73%	-	27%
water, H_2SO_4, 50°C	100%	-	-
glacial acetic acid, 0.5 M $ZnCl_2$, 50°C	35%	-	65%
toluene, 0.5 M $ZnCl_2$, 50°C	81%	17%	3%

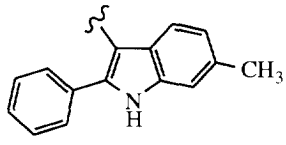
Balancing reaction temperature, reaction time and resin type proved to be a significant synthetic challenge. Phenylhydrazine hydrochloride underwent the Fischer indole reaction with **1** at 50°C for 18 hours. However, reactions employing electron deficient hydrazines (e.g. 2,4-dichlorophenylhydrazine hydrochloride) did not proceed to completion at that temperature even after 64 hours. Table 2 illustrates the various cyclization conditions investigated for the reaction between 2,4-dichlorophenylhydrazine hydrochloride and ketone (**1**). When the temperature was increased to 70°C, even the electron deficient hydrazines proceeded cleanly to completion (i.e. no detected ketone or hydrazone intermediate by HPLC or ^{1}H NMR).

Attention was now focused upon the solid support. At the higher temperatures necessary for complete indole formation, the yields began to decline and impurities related to the PEG-PS[2] solid support became problematic. Table 2 illustrates the different reaction conditions and resin used for the indole cyclization. Using a polystyrene resin,[3] the desired 5,7-dichloroindole was prepared from 2,4-dichlorophenylhydrazine hydrochloride and **1** at 70°C in 18 hours. The purity is excellent, the mass and ^{1}H NMR spectra are free of the impurity peaks and the yield is modestly improved.

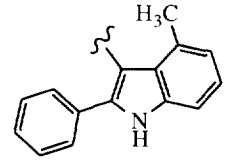
Table 2

Resin	Reaction Temperature (°C)	Reaction Time (hours)	Purity[4]	Yield
PEG-PS	50	18	50%	-
PEG-PS	50	64	91%	76%
PEG-PS	70	18	99%	52%
PEG-PS	110	18	-	no product
PS	70	18	98%	70%

Table 3 illustrates the variety of phenylhydrazine hydrochlorides that were utilized in this reaction. Monosubstitution with alkyl (**3b**, **3c**, **3d**, **3h** & **3i**) and halo (**3e** & **3f**) groups was well tolerated yielding cleaved product purities >96%. 2,4-dichlorophenylhydrazine (**3g**) also afforded the desired product in high chemical purity. Even 2,5-disubstituted hydrazines (**3m** & **3 n**) which produced sterically hindered 4,7-disubstituted indoles work moderately well yielding final products in 74% purity. Electron deficient 4-substituted hydrazines (**3p** & **3q**) did not yield any of the desired indole products. However, 3-nitrophenylhydrazine hydrochloride (**3o**) produced the desired indole in moderate purity.



6-methylindole



4-methylindole

Meta-substituted phenylhydrazines (**3c**, **3f**, **3j**, **3k** &**3o**) produced both 6- and 4-substituted indoles (shown above). After careful investigation of the ^{1}H NMR spectra of these compounds, the average ratio of 6- to 4-substituted indoles was 7:3 respectively.

Table 3

Entry	Hydrazine HCl	% Indole[4]	% Hydrazone[4]	% Ketone[4]
3a	phenyl	100%	-	-
3b	2-methylphenyl	97%	-	-
3c	3-methylphenyl	97%	-	-
3d	4-methylphenyl	100%	-	-
3e	2-bromophenyl	98%	-	-
3f	3-bromophenyl	96%	-	-
3g	2,4-dichlorophenyl	96%	-	-
3h	4-(t-butyl)phenyl	97%	-	-
3i	4-(isopropyl)phenyl	98%	-	-
3j	3-fluorophenyl	97%	-	-
3k	3-chlorophenyl	97%	-	-
3l	1-naphthyl	80%	5%	-
3m	2,5-dimethylphenyl	74%	26%	-
3n	2,5-dichlorophenyl	74%	8%	16%
3o	3-nitrophenyl	74%	20%	4%
3p	4-nitrophenyl	-	35%	60%
3q	4-carboxyphenyl	-	58%	40%

In summary, we have demonstrated the preparation of substituted 2-arylindoles *via* the Fischer indole synthesis on a solid support. The cleaved products obtained are of high chemical purity and can be screened in biological assays with no further purification. There are numerous commercially available ketoacids and arylhydrazine hydrochlorides making this scheme compatible with the preparation of combinatorial libraries.

Acknowledgements: Special thanks to Ms. Amy Bernick for performing mass spectral analyses.

Typical Procedure (**3a**): A double coupling was performed on 50 mg of PS-HMB resin using 4 equivalents of Fmoc-Phe-OH and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide plus catalytic 4-dimethylaminopyridine in 2 mL of 1:1 THF-methylene chloride for 2 hours each time. The resin was washed with 1:1 THF-methylene chloride (4 x 2 mL) and DMF (4 x 2 mL). Then added 2 mL of 1:1 piperidine-DMF to the resin. After 25 minutes the resin was washed with DMF (8 x 2 mL). Another double coupling was performed using 4 equivalents of 4-benzoylbutyric acid, PyBOP and HOBt along with 10 equivalents of diisopropylethylamine in 2 mL of DMF for 1 hour each time. The resin was then washed with DMF (4 x 2 mL) methylene chloride (4 x 2 mL) and glacial acetic acid (4 x 2 mL). Then, 2 mL of phenylhydrazine hydrochloride (0.5 M) and zinc chloride (0.5 M) in glacial acetic acid is added and the reaction heated to 70°C. After mixing for 18-20 hours at 70°C the resin was allowed to cool to ambient temperature and washed with glacial acetic acid (4 x 2 mL), 1:1 tetrahydrofuran-methylene chloride (4 x 2 mL), DMF (4 x 2 mL), methylene chloride (4 x 2 mL) and methanol (4 x 2 mL). Then, 2 mL of 9:1 methanol-triethylamine was added and the reaction heated to 50°C. After mixing for 20 hours, the sample was allowed to cool to ambient temperature. The reaction was filtered and the filtrate was concentrated to dryness and lyophilized from acetonitrile-water to yield 11.6 mg of **3a** (98%). ^{1}H NMR (400 MHz, DMSO-d6) δ 2.41-2.46 (m, 2), 2.83-3.02 (m, 4), 3.57 (s, 3), 4.45-4.51 (m, 1), 7.00 (t, 1, J=7Hz), 7.08 (t, 1, J=7Hz), 7.15-7.24 (m, 5), 7.34 (d, 1, J=8Hz), 7.39 (d, 1, J=7Hz), 7.50 (t, 2, J =8Hz), 7.55 (d, 1, J=8Hz), 7.61 (d, 2, J=7Hz), 8.43 (d, 1, J=8Hz). Mass Spec (ESI) $[M+H]^+ = 427$.

References and Notes:

1. Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: New York, **1982**
2. The resin used was purchased from Rapp Polymere (Polyethyleneglycol spacer on a polystyrene bead (130 micron, 0.23 mmol/g) - TentaGel S HMB - cat. # S30014).
3. The resin used was purchased from Advanced ChemTech (Aminomethylated Polystyrene Resin, 200-400 mesh, catalog #SA5002). The HMB handle was loaded using PyBOP.
4. Purity determined by HPLC. HPLC Conditions: 10 - 100% acetonitrile in water + 0.1% trifluoroacetic acid, linear gradient over 10 minutes, flow rate: 1.5 mL/min, Zorbax SB C8 column (4.6 mm x 7.5 cm), 254 nm.

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