Abstract: A novel linker for the solid-phase synthesis of substituted 1-methylindoles has been developed. The linker is stable under strong basic conditions and compatible with a broad range of chemical transformations as demonstrated by electrophilic and nucleophilic substitution reactions in the 2-position of the indole nucleus. Indoles are cleaved under reductive conditions by use of alane resulting in 1-methylindole derivatives. Sensitive functional groups in the indole moiety such as aldehydes, ketones, esters, imines, and amides are reduced simultaneously.

Key words: combinatorial chemistry, solid phase synthesis, derivatisation of indoles, nucleophilic aromatic substitution, reductive cleavage

During the last decade combinatorial chemistry and parallel synthesis have emerged as key methodologies for the discovery of novel drugs. The palette of strategies, technologies and chemical methods for the synthesis of combinatorial libraries is rapidly expanding and has been extensively reviewed. Solid-phase organic synthesis has become an established and powerful method in particular for the synthesis of larger libraries involving multi-step synthesis.

The choice of linker for the attachment of substrates to the solid support is one of the key issues for a successful solid-phase synthesis. The linker has to be stable to all reaction conditions during the entire synthesis before cleavage. In particular, traceless linking strategies have become very attractive since the final target molecules after cleavage do not possess any memory of their former attachment point. Therefore these target molecules exclusively bear only those functional groups that have been chosen, for example, for biological activity. The most prominent examples of traceless linking methods are the REM linkers for the synthesis of tertiary amines, linking strategies involving simultaneous intramolecular cyclisation and cleavage and linking methods involving C–H bond forming cleavages such as silicon- or germanium-linkers, and selenium-linkers for the linking via aromatic groups and alkyl groups, respectively.

The indole nucleus is present in numerous pharmacologically and biologically important compounds. These include classes of compounds acting in the central nervous system (CNS) such as the antiemetic ondansetron and the antimigraine agent sumatriptan. Consequently, we have explored the use of the indole nucleus as a scaffold in combinatorial libraries within our ongoing CNS drug discovery projects and developed methods for traceless solid-phase synthesis of indole derivatives.

Recently, linking strategies for indoles using the indole nitrogen as attachment point have been described. Indoles are attached under mild conditions either to a resin bound tetrahydropyran (THP) linker or as carbamates using the p-nitrophenylcarbonate derivative of the Wang resin. After derivatisation the indoles are smoothly cleaved under acidic conditions yielding 1-unsubstituted indoles.

In the present paper, we describe a new method for immobilisation of 1H-indoles to a polystyrene based resin. The indole derivatives are attached to polystyrene bound ethoxymethyl chloride (PEOM–Cl) resin by direct loading using the indole nitrogen as attachment point. After completion of the reaction sequence the final products are released from the resin as 1-methyl indoles by reduction of the C–O bond of the N,O-acetal linkage to a C–H bond with alane.

The starting polymer (PEOM–Cl) 3 was used for the direct loading of 1-unsubstituted indole derivatives. Polymer 3 was prepared in a two-step procedure starting from commercially available 2-hydroxyethyl polystyrene (Scheme 1). The method applied is analogous to the solution-phase procedure described by Benneche et al. Deprotonation of 2-hydroxyethyl polystyrene with potassium tert-butoxide followed by alkylation with chloromethyl methyl sulfide afforded the intermediate methylsulfanylmethoxy substituted resin 2, which subsequently was converted into the desired resin 3 by treatment with sulfuryl chloride.

The synthesis of chloromethoxymethyl polystyrene by reaction of hydroxymethyl polystyrene with formaldehyde and hydrochloric acid has been described in a recent patent application. In the above patent application, the use of the resin in the immobilisation of substrates via carboxylic acids as linking functional group and the release of the final products by acid-mediated cleavages are described.

2-Chloro-3-formyl-1H-indole (4) was prepared according to Schulte et al. and immobilised on resin 3 by alkylation after deprotonation with sodium hydride in dimethyl sulfoxide (Scheme 1). The resulting resin-bound indole 5
was reacted with selected nucleophiles at 80 °C in N,N-dimethylacetamide. The nucleophiles 8b and 8c were deprotonated with sodium hydride prior to the reaction whereas the reaction with the piperazine derivative 8a was performed using disopropylethyl amine (DIEA) as base. The reaction of 1-substituted and unsubstituted 2-chloro-3-formylindoles with a variety of nucleophiles in solution has been described in the literature for a number of applications.14

The final products 7a–c were cleaved from the resin by reacting the resins 6a–c with alane in diethyl ether. In the cleavage step the ethoxymethyl group (linking the indole to the resin) and the 3-formyl group are reduced to methyl groups, simultaneously. The reduction of the ethoxymethyl group to a methyl group is in analogy with the solution-phase reduction of N,O-acetals to methyamines using alane or lithium aluminium hydride15 and with the reduction of 8-methoxymethyl pyrroloindole to its 8-methyl analogue using borane.16 The reduction of the 3-formyl group to a methyl group is analogous to literature procedures.17 After purification of the cleaved products by solid phase extraction using silica gel the final products 7a–c were isolated in 7–23% overall yield (5 steps) and with UV-purities higher than 90%. All attempts to cleave under acid conditions in order to obtain 1H-indole derivatives failed due to the formation of undefined side products.

The entire reaction sequence was monitored by gel-phase 13C NMR in standard 5 mm probe heads. Selected spectra are shown in Figure 1. Since the success of gel phase NMR is highly dependent on the swelling properties of the resin in a particular solvent, the spectra in Figure 1 were recorded in the optimal solvent for each resin. The progress of the reaction sequence is easily monitored by the appearance and disappearance of characteristic carbon signals as shown in Figure 1.

In order to show the stability of the linker towards extreme basic conditions, PEOM-bound indole (10) was treated with tert-butyllithium. The intermediate 2-lithiated PEOM-bound indole was subsequently trapped with benzonitrile to PEOM-bound imine 11 (Scheme 3), in ano-
gy with similar reaction in solution.\textsuperscript{18} The reaction was quenched with saturated ammonium chloride in THF, but on the solid support the imine was not hydrolysed to the corresponding ketone, as expected from similar solution phase reactions. Resin \textsuperscript{11} was treated with alane in diethyl ether resulting in simultaneous reductive cleavage and reduction of the imine group to the corresponding amine. The resulting α-indolylbenzylamine \textsuperscript{12} was obtained in 2\% overall yield (5 steps) after solid-phase extraction and with NMR-purity of \textsuperscript{>90\%}. The identity of \textsuperscript{12} was confirmed via its chemical transformation into the corresponding methyl urea \textsuperscript{13} by reaction with methyl isocyanate. Despite the low yield obtained, the chemical stability of the linker has been demonstrated even under the forced basic conditions used.

In conclusion, we have developed a novel linker for the solid-phase synthesis of substituted 1-methylindoles. The indole derivatives are attached to the PEOM resin by direct loading, and the final products are cleaved using reductive conditions resulting in simultaneous reduction of sensitive functional groups such as aldehydes, ketones, esters, imines and amides. The linker is stable even under forced basic conditions and is expected to be compatible with a broad range of chemical transformations as demonstrated by electrophilic and nucleophilic substitution reactions in the 2-position of the indole nucleus. Limitations for the application of the linker are chemical transformations requiring strong acidic conditions since undefined products are cleaved from the resin.

All reactions were carried out under positive pressure of nitrogen. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under \textsubscript{N$_2$} from sodium/benzophenone immediately prior to use. Et\textsubscript{2}O was stored over sodium and CH\textsubscript{2}Cl\textsubscript{2} over 4 Å molecular sieves. For solid-phase extraction, Scharlabi 60 (230–400 mesh) silica gel (sorbil) was used. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded at 500.13 MHz and 124.67 MHz, respectively, on a Bruker Avance DRX 500 instrument. Gel-phase \textsuperscript{13}C NMR spectra of polymer-bound substances were recorded at 62.9 MHz on a Bruker AC 250 instruments. Unless otherwise noted, compounds were measured in CDCl\textsubscript{3} (99.8%). Chemical shifts of deuterated solvents. Coupling constants (\textit{J} values) are in Hz. LC-MS data were obtained on a Sciex API 150 EX using a YMC C-18 column (4.6 × 50 mm, 5 µm). HRMS were performed at the University of Vienna, Department of Physical chemistry (Vienna, Austria), with a Perkin-Elmer 2.400 CHN elemental analyser. Hydroxyethylpolystyrene (200–400 mesh, cross-linked with 1\% divinylbenzene, capacity 1.15 mmol/g) was commercially available.

\textbf{2-(Methylsulfonylimethoxy)ethylpolystyrene (2)}

A slurry of 2-hydroxyethylpolystyrene (1) (25.0 g, 28.8 mmol) and t-BuOK (30.0 g, 268 mmol) in THF (250 mL) was stirred at r.t. for 12 h. After filtration and washing with THF (3 × 200 mL), the resin was suspended in THF (250 mL) and treated once more with t-BuOK (3.8 g, 33.9 mmol) at r.t. After stirring for 12 h, neat chloromethyl methyl sulfide (25 mL, 299 mmol) was added slowly at r.t. and stirring continued for a further 12 h. The yellow resin was filtered off, washed with THF (3 × 200 mL), water (3 × 200 mL), THF (3 × 200 mL), CH\textsubscript{3}Cl\textsubscript{2} (3 × 200 mL) and dried in vacuum for 48 h at r.t. The resin \textsuperscript{2} thus obtained was calculated to have a loading of 1.07 mmol/g under the assumption that the coupling reaction went to completion.

\textbf{Attachment of 2-Chloro-3-formyl-1H-indole (4) to 2-(Chloromethoxy)ethylpolystyrene (3)}

To a solution of 2-chloro-3-formyl-1H-indole (4) (1.5 g, 8.4 mmol) in THF (30 mL) was added NaH (60\% dispersion in mineral oil, 404 mg, 10.1 mmol) at r.t. After 30 min 2-(chloromethoxy)ethoxypoly-styrene (3) (2.1 g, 2.3 mmol) was added, and the mixture was stirred for 3 d. The almost colourless resin was filtered under nitrogen, washed with CH\textsubscript{3}Cl\textsubscript{2} (5 × 20 mL), dried in vacuum for 3 h at 40 °C and used immediately in the coupling reaction described below. Resin \textsuperscript{3} thus obtained was calculated to have a loading of 0.94 mmol/g under the assumption that the coupling reaction went to completion.

\textbf{Attachment of 1H-Indole to 2-(Chloromethoxy)ethylpolystyrene (3)}

NaH (60\% dispersion in mineral oil, 1.5 g, 38 mmol) in anhyd DMSO (20 mL) was heated at 70 °C for 45 min. After cooling to 0 °C, a solution of 1H-indole (4.8 g, 40.9 mmol) in THF (20 mL) was added, and the solution was allowed to warm up to r.t. After 1 h, the mixture was cooled to 0 °C, and 2-(chloromethoxy)ethylpolystyrene (3) (2.5 g, 2.73 mmol) was added. After complete addition, the mixture was stirred for 2 d at r.t. The resin was filtered off and washed with DMSO (2 × 20 mL), water (3 × 20 mL), THF (3 × 30 mL), THF–water (1:1, 2 × 20 mL), EtOH (2 × 50 mL), acetone (3 × 50 mL), CH\textsubscript{3}Cl\textsubscript{2} (3 × 50 mL) and dried in vacuum at r.t.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme3}
\caption{Scheme 3 \textsuperscript{3} Lithiation of PEOM bound indole \textsuperscript{10} with t-BuLi and subsequent introduction of an electrophile in the 2-position. 1. NaH, DMF; 2. \textsuperscript{9} THF; (ii) 1. t-BuLi, PhCH\textsubscript{2}Cl; 2. PhCN, Et\textsubscript{2}O, NH\textsubscript{4}Cl, THF/H\textsubscript{2}O; (iii) AlH\textsubscript{3}, Et\textsubscript{2}O, 20 °C, 12 h; (iv) CH\textsubscript{3}NCO, CH\textsubscript{3}Cl; \textsuperscript{11} Ph.}
\end{figure}
PEOM bound \(1H\)-indole (10) thus obtained was calculated to have a loading of 0.38 mmol/g under the assumption that the reaction went to completion.

### Nucleophilic Aromatic Substitution of PEOM-bound 2-chloro-3-formyl-1H-indole (5) with 1-(2-Methoxyphenyl)piperazine

A mixture of PEOM-bound 2-chloro-3-formyl-1H-indole (5) (1.00 g, 0.94 mmol), 1-(2-methoxyphenyl)piperazine (903 mg, 4.7 mmol), DIPEA (0.82 mL, 4.7 mmol) in \(\text{NaOH-dimethylethamide}\) (5 mL) was heated to 80 °C for 12 h. The mixture was filtered, washed with DMF (3 × 25 mL), water (3 × 25 mL), THF (3 × 25 mL), EtOH (3 × 25 mL), \(\text{CH}_2\text{Cl}_2\) (3 × 25 mL), and dried in vacuum at 40 °C for 12 h. The resin 6a thus obtained was calculated to have a loading of 0.82 mmol/g under the assumption that the reaction went to completion.

### Nucleophilic Aromatic Substitution of PEOM-bound 2-chloro-3-formyl-1H-indole (5) with 3-Dimethylaminophenol (8b)

\(\text{NaH}\) (60% dispersion in mineral oil, 151 mg, 3.76 mmol) was added to a solution of 3-dimethylaminophenol (8b) (645 mg, 4.7 mmol) in \(\text{N,N-dimethylacetamide}\) (5 mL) at r.t. After hydrogen generation ceased, the mixture was stirred for further 30 min and subsequently treated with resin PEOM-bound 2-chloro-3-formyl-1H-indole (5) (1.00 g, 0.94 mmol) at 80 °C for 12 h. The mixture was allowed to warm to r.t., and EtOAc (3 mL) was added. After hydrogen generation ceased, the mixture was stirred for further 30 min and subsequently filtered, washed with \(\text{DMF–EtOH–sat. aq \text{Na}_2\text{SO}_4}\) (5:1:1, 25 mL), and dried in vacuum at 40 °C for 12 h. The resin 6b thus obtained was calculated to have a loading of 0.86 mmol/g under the assumption that the reaction went to completion.

### Nucleophilic Aromatic Substitution of PEOM-bound 2-chloro-3-formyl-1H-indole (5) with 3-Chloro-2-methoxy-thiophenol (8c)

Resin 6c was synthesised from PEOM bound 2-chloro-3-formyl-1H-indole (5) (1.00 g, 0.94 mmol) and 3-chloro-2-methoxythiophenol (8c) (820 g, 4.7 mmol) by a procedure analogous to that for resin 6b. The resin was calculated to have a loading of 0.83 mmol/g under the assumption that the reaction went to completion.

### Treatment of PEOM-bound 1H-indole (10) with tert-Butyllithium and Subsequently with Benzonitrile

A solution of t-BuLi (1.7 M in pentane) (0.9 mL, 1.5 mmol) was slowly added to a slurry of PEOM-bound 1H-indole (10) (500 mg, 0.50 mmol) in anhyd toluene (3 mL) at −10 °C. After complete addition, the mixture was allowed to warm to r.t. and stirred for 3.5 h. The resin was added to the solvent decanted and a solution of benzonitrile (0.5 mL, 4.9 mmol) in anhyd Et\(_2\)O (2 mL) was added at r.t. After stirring at r.t. for 12 h, the resin was filtered, stirred sat. aq \(\text{NaOH}\)−THF (1:2, 3 × 50 mL), THF (3 × 50 mL), \(\text{N aq \text{NaOH–THF (1:2, 3 × 50 mL)}}, \text{THF (3 × 50 mL), \text{acetone (3 × 50 mL), \text{CH}_2\text{Cl}_2 (3 × 50 mL)} and dried in vacuum at 40 °C for 12 h. The resin 6b thus obtained was calculated to have a loading of 0.86 mmol/g under the assumption that the reaction went to completion.

### Preparation of Alane

Alane\(^{59}\) was prepared by a modified method of Schlesinger. Et\(_2\)O (150 mL) was added carefully (!) under intensive stirring and cooling to neat \(\text{AlCl}_3\) (6.3 g, 46.8 mmol) at 0 °C. After warming to r.t., LiAlH\(_4\) (5.4 g, 141.0 mmol) was added carefully in small portions. After stirring at r.t. for 45 min the solution (approximately 1.2 M alane in Et\(_2\)O) was separated from the voluminous precipitate by decanting and used immediately. Caution: The remaining precipitate is highly flammable in contact with moisture. Prior to disposal it was either treated carefully with i-PrOH or slowly added to ice.

---

**Solid-Phase Synthesis of Substituted 1-Methyl-1H-Indoles**

2-(3-Chloro-2-methoxy-phenylsulfanyl)-1,3-dimethyl-1H-indole (1c)

The title compound was synthesised from resin 6c (980 mg, 0.84 mmol) by a procedure analogous to that for 7a. Solid-phase extraction (toluene–hexane, 1:1) gave 17 mg (7%) of the desired product as a solid; LC-MS: 95% (UV-purity), \(t_{RZ}\) 2.5 min; recrystallisation from (heptane–Et\(_2\)O, 3:1) gave colourless crystals; mp 105–106 °C.

---

**Reactive Cleavage of Final Products from the PEOM Resin 2-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-1,3-dimethyl-1H-indole (7a)**

**Typical Procedure**

Resin 6a (1.0 g, 0.82 mmol) was treated with anile (8 mL, 9.6 mmol; \(c ≤ 1.2 \text{ M, Et}_2\text{O}\)) at r.t. for 12 h. Water (0.5 mL, 28 mmol) was carefully added at −10 °C. After hydrogen generation ceased, the mixture was allowed to warm to r.t., and EtOAc (3 mL) was added. After stirring for 10 min, the resin and precipitated salts were filtered and extracted with EtOAc (3 mL). The combined filtrates were dried over MgSO\(_4\), and the volatile solvent evaporated in vacuo. Solid-phase extraction (toluene) gave 63 mg (23%) of the desired product 7a as a solid; LC-MS: 91% (UV-purity), \(t_{RZ}\) 5.9 min; recrystallisation (heptane–Et\(_2\)O, 3:1) of the solid gave colourless crystals; mp 110–111 °C.

---

**Synthesis 2003, No. 14, 2236–2240 © Thieme Stuttgart · New York**
C-[1-(1-Methyl-1H-indol-2-yl)-1-phenyl]-methylamine (12)

This compound was synthesised from resin 11 (7.0 g, 6.3 mmol) by cleavage with alane. Solid-phase extraction (EtOAc–hexane, 2:1) gave 28 mg (2%) of the desired product as a slightly coloured oil; NMR-purity: 90%.

$^1$H NMR: $\delta = 3.45$ (s, 3 H), 5.24 (s, 1 H), 6.31 (s, 1 H), 6.95 (t, $J = 7.5$, 1 H), 7.05 (t, $J = 7.6$, 1 H), 7.15 (d, $J = 8.2$, 1 H), 7.18 (m, 1 H), 7.24 (m, 4 H), 7.44 (d, $J = 7.8$, 1 H).

$^{13}$C NMR: $\delta = 29.3$, 52.9, 98.9, 101.8, 118.5, 120.4, 126.5, 126.6, 127.9, 137.3, 143.2, 143.4.

HRMS: $m/z$ calc'd for C$_{18}$H$_{19}$N$_3$O, 293.1528; found, 293.153.

Acknowledgement

The excellent technical assistance by Mr. Peter Brøsen and Mr. Jens Schiott as well as Ms. Vibeke Nielsen and Annick Somerville for typing the manuscript is highly appreciated.

References


(c) Baldino, C. M. J. Comb. Chem. 2000, 2, 89.


(13) Schulte, K. E.; Reisch, J.; Stoess, U. Arch. Pharm. (Weinheim, Ger.) 1972, 305, 523.


