Solid-Phase Synthesis

DOI: 10.1002/anie.200901643

Polystyrene Sulfonyl Chloride: A Highly Orthogonal Linker Resin for the Synthesis of Nitrogen-Containing Heterocycles**

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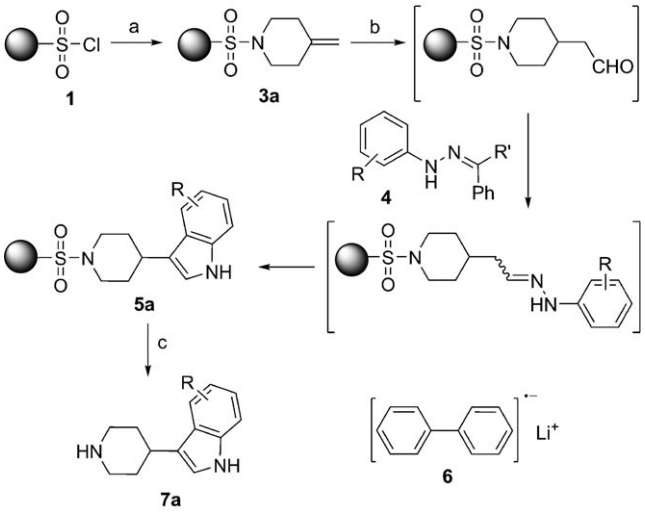
In memory of Peter Welzel

Solid-phase organic synthesis (SPOS) is probably the most efficient tool for the synthesis of large and diverse compound libraries. During the last few years, the focus has shifted towards libraries of more complex and structurally diverse substances (diversity-oriented synthesis; DOS)[1] and natural products (biology-inspired synthesis; BIOS).[2] Concomitantly, the methodological frontiers of SPOS have been redefined. To achieve the highest possible flexibility in synthesis a highly orthogonal linker system is needed, which means that the chemical entity which attaches the substrate to the polymer should not only be stable against a very diverse set of reaction conditions, but also be cleaved quantitatively under very mild conditions at the end of the reaction sequence.[3] Unfortunately, most linker systems used in SPOS exhibit only limited orthogonality. Herein, we report on the use of commercially available polystyrene sulfonyl chloride[4] as an inexpensive support with built-in linker functionality, and its application in the synthesis of amine-based compound libraries of privileged structures.[5] The superior stability of this linker allows the synthesis of scaffold-rearranged libraries of nitrogen-containing heterocycles, which can be cleaved from the resin in a traceless manner under electron transfer mediated by radical anions or according to the "safety catch" principle.

The arenesulfonyl moiety can be regarded as one of the most stable protecting groups for primary and secondary amines.[6,7] Whilst it is stable against most acidic, basic, and oxidative reaction conditions and also common reducing agents, it can be cleaved under electron-transfer conditions, such as Na/NH_3,[8] radical anions,[9] SmI_2,[10] or electrolysis,[11] in a mild fashion. Our interest in the implementation of electron-transfer conditions in SPOS[12] has motivated us to take advantage of these opportunities to establish a reductively cleavable linker system.[13]

Starting from inexpensive polystyrene sulfonyl chloride (**1**; loading 1.5 mmol g^{-1}, 1% DVB, 100–200 mesh), olefinic secondary amines **2** were immobilized on the solid support. The olefinic sulfonamides **3** were transformed on the solid phase using a domino hydroformylation/Fischer indole synthesis[14–17] (Scheme 1, Table 1). The sulfonamide linker was



Scheme 1. Immobilization of olefins and domino hydroformylation/indole synthesis followed by radical-anion-mediated cleavage: a) **2a**, Py/THF 1:1, RT, overnight; b) 20 mol% $[Rh(acac)(CO)_2]$, 50 bar CO, 10 bar H_2, **4a**, PTSA, THF, 80°C, 2 d; c) 10 equiv **6** (1 M in THF), THF, 0°C, 2 h. Py = pyridine, THF = tetrahydrofuran, acac = acetylacetonate, PTSA = *para*-toluenesulfonic acid.

stable under the acidic reaction conditions, whereas the use of a hydroxymethylbenzoic acid (HMBA) linker[18] resulted in cleavage. Both benzhydrylidene- (**4a**,**b**) and benzylidene-protected (**4c**) phenylhydrazines could be successfully

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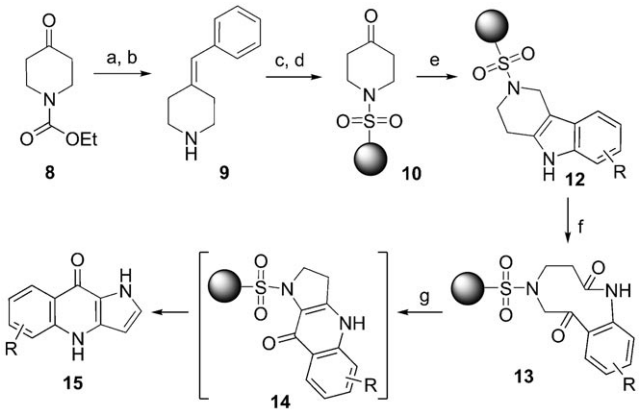
[**] This work was supported by the Max Planck Society, the Fonds der Chemischen Industrie (Liebig scholarship for R.B.), the Deutsche Forschungsgemeinschaft (Br2324/1-1), the State of Northrhine–Westfalia, and the University of Leipzig.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901643.

Table 1: Yields and purities [%] in the synthesis of tryptamine and homotryptamine derivatives from olefins **2a**,**b** and phenylhydrazones **4a**–**c**.[a]

	4a R = H R′ = Ph	**4b** R = *o*-Me R′ = Ph	**4c** R = *p*-OMe R′ = H
2a	**7aa** 36 (96/88)	**7ab** 27 (98/89)	**7ac** 38 (93/75)
2b	**7ba** 34 (73/85)	**7bb** 36 (84/88)	**7bc** 21 (70/83)

[a] Yields after cleavage with lithium biphenyl and aqueous workup. GC-MS/HPLC-UV purities (280 nm) are given in brackets.



Scheme 2. Immobilization of 4-piperidone and synthesis of a pyrrolo-[3,2-*b*]quinolone library: a) $BnPPh_3Br$, *n*BuLi, THF, 0 °C to reflux, 7 h; b) KOH, EtOH, reflux, 19 h, 81 % (2 steps); c) **1**, Py/THF 1:1, RT, 2 d; d) O_3, CH_2Cl_2, −78 °C, 2 h, then PPh_3 or Py, RT, overnight, 85 % (2 steps); e) phenylhydrazine **11**, $ZnCl_2$, THF, MS 4 Å, 70 °C, 18 h; f) O_3, CH_2Cl_2, −78 °C, 15 min, then Py, to RT, 1 h; g) Et_3N/DMF 1:1, 80 °C, overnight. Bn = benzyl, MS = molecular sieves, DMF = *N*,*N*-dimethylformamide.

Table 2: Synthesis of pyrrolo[3,2-*b*]quinolones.

	11 R =	**15** R =	yield of crude material (purity)[a] [%]	isolated yield[b] [%]
a	H	H	59 (84)	15
b	4-Br	7-Br	67 (97)	14
c	4-OMe	7-OMe	30 (90)	8
d	4-Me	7-Me	26 (84)	8
e	4-SO_2NH_2	7-SO_2NH_2	25 (n.d.)	5
f	4-*t*Bu	7-*t*Bu	50 (94)	19
g	4-F	7-F	60 (91)	14
h	4-CN	7-CN	19 (26)	2
i	4-triazolyl	7-triazolyl	41 (82)	5
j	3-F	8-F	38 (27+71)	4
k	–	6-F		15
l	3-Me	8-Me	41 (53+43)	7
m	–	6-Me		13
n	3-NO_2	8-NO_2	21 (25+31)	–
o	–	6-NO_2		2
p	2-Et	5-Et	32 (92)	12
q	2-Br	5-Br	72 (92)	15
r	2-F	5-F	64 (73)	20
s	2,3-Me_2	5,6-Me_2	53 (86)	3
t	2,4-F_2	5,7-F_2	74 (75)	10[c]

[a] HPLC purity at 254 nm. [b] Yields of isolated product after three steps based on the loading of piperidone resin **10**. [c] Yield determined by NMR spectroscopy.

employed as substrates. The generated tryptamine and homotryptamine derivatives **5** were cleaved from the solid phase under electron-transfer conditions by employing lithium biphenyl (**6**) in high purity and good yields (21–38 % over all steps; Scheme 1, Table 1).[19,20]

Limitations of this cleavage method were found in the use of bromine-substituted phenylhydrazones, which delivered the corresponding dehalogenated indoles after cleavage in similar yields. The use of nitro-substituted phenylhydrazones, which are known to be notoriously problematic substrates in Fischer indole synthesis for electronic reasons, was not successful, and delivered only 1,4-phenylenediamine after cleavage. This result can be explained by the reductive cleavage of the corresponding solid-phase-bound nitrophenylhydrazone.

In a further library synthesis of indole-based nitrogen-containing heterocycles, polymer-bound 4-piperidone **10** was synthesized starting from **1** and benzylidene-masked piperidone **9** (after **9** was immobilized on the resin and the ketone moiety was then liberated by ozonolysis; Scheme 2). The success of immobilization was ascertained qualitatively by FTIR spectroscopy (carbonyl stretching frequency at 1730 cm^{-1}) and quantitatively by employing the FmPH method.[21] By this method, piperidone resin **10** with a loading of 1.16 mmol g^{-1} was prepared on 20 g scale. The subsequent conversion of piperidone **10** into indoles under Fischer conditions proved challenging, which was due in part to the high hydrolytic instability of the phenylhydrazone intermediate. Considerable experimentation was required to identify suitable water- and oxygen-free conditions, which were achieved by addition of molecular sieves and "degassing" of the resin by swelling in toluene and evaporation of the solvent. These precautions then allowed Fischer indolization with $ZnCl_2$ catalysis (Table 2). The intended cleavage of indoles **12** under reductive conditions mediated by radical anions was problematic in this case; highly variable yields and purities of the cleavage products were obtained.

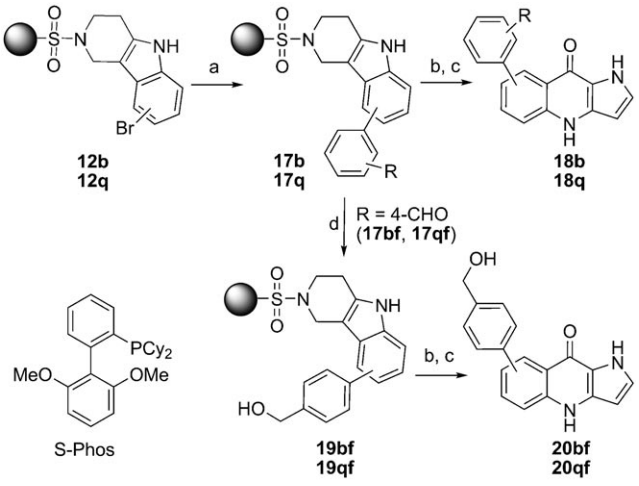
Our intention to increase the diversity of the library by implementing the Witkop–Winterfeldt reaction on a solid phase for the first time was unaffected by these problems, and resulted in the scaffold-rearranging conversion of indoles into quinolones.[22] Indoles **12** were converted by ozonolysis into ketolactam intermediates **13**, which were sequentially condensed selectively under basic conditions into γ-quinolones **14**

and cleaved from the resin as pyrrolo[3,2-*b*]quinolones **15**. Such a simple detosylation reaction has not yet been reported for comparable sulfonamides, and benefits from the formation of an extended aromatic system as the driving force (Scheme 2, Table 2).

The selectivity of the ozonolysis reaction for indoles and the subsequent selective cleavage of the oxidation products are instrumental to the success of the synthesis. Upon using 3-substituted phenylhydrazines **11j**, **11l**, and **11n** in the Fischer indole synthesis, regioisomers are obtained that can be isolated by HPLC after cleavage from the resin. A remarkable result is the successful [3,3]-sigmatropic rearrangement of the phenylhydrazones generated from electron-deficient sulfonamido-, nitrilo-, and nitrophenylhydrazines **11e**, **11h**, and **11n**. In total, we were able to assemble 20 differently substituted pyrrolo[3,2-*b*]quinolones, which is a heterocyclic scaffold that has not been described in the literature to date.[23] The relatively low yields reflect both the ambitious and multi-step reaction sequence and the non-quantitative indole rearrangement for electron-deficient substrates. The desired pyrrolo[3,2-*b*]quinolones were obtained mostly in high purity (>80% from HPLC) without contamination by intermediate phenylhydrazone or unreacted piperidone. For screening purposes, all the compounds were purified by means of semi-preparative RP-HPLC.

To increase the diversity of the library, the derivatization of bromo derivatives **12b** and **12q** by Suzuki coupling was explored (Scheme 3, Table 3). Double coupling with S-Phos–palladium catalyst[24] finally enabled the reaction with these indole derivatives, which are highly unreactive because of their electron-rich nature, with conversions of 85–100%.

Suzuki reaction with 4-formylphenylboronic acid (**16f**) furnished coupling products **17bf** and **17qf**, which were converted on resin with sodium cyanoborohydride into benzylic alcohols **19**. Cleavage and flash chromatographic purification delivered pyrrolo[3,2-*b*]quinolones **20**.



Scheme 3. Suzuki cross-coupling of polymer-bound bromoindoles, aldehyde reduction, and cleavage after Witkop–Winterfeldt oxidation: a) 0.2 equiv $Pd(OAc)_2$, 0.8 equiv S-Phos, $ArB(OH)_2$ (**16**), K_3PO_4, THF, 80°C, 24 h, double coupling; b) O_3, CH_2Cl_2, −78°C, 15 min, then Py, warming to RT, 1 h; c) Et_3N/DMF 1:1, 80°C, overnight; d) 1% AcOH/THF, $NaBH_3CN$, RT, overnight.

Table 3: Yields [%] of phenylpyrrolo[3,2-*b*]quinolones.[a]

	Ar =	**18b** (7-Ar)	**18q** (5-Ar)
16a	3-MeC_6H_4	10	7
16b	4-FC_6H_4	11[b]	16
16c	3-$MeOC_6H_4$	9[c]	13
16d	4-$MeOC_6H_4$	7	13
16e	3-$NO_2C_6H_4$	3	21
16f	4-$CHOC_6H_4$	3[d] (**20bf**)	6[d] (**20qf**)

[a] Yields of isolated product over four steps based on the loading of piperidone resin **10**. [b] Yield determined by NMR spectroscopy. [c] Coupling conditions: toluene/THF/H_2O 1.45:1.45:0.1, 90°C, 40 h (single coupling). [d] Yields over 5 steps.

In conclusion, polystyrene sulfonyl chloride is an inexpensive linker resin for the synthesis of privileged nitrogen-containing heterocycles, such as indoles and quinolones, which can be cleaved under electron-transfer conditions. The extraordinary orthogonality of this linker resin allowed the synthesis of a small library of novel pyrrolo[3,2-*b*]quinolones in which we could employ acidic (Fischer indole synthesis), basic and transition-metal-mediated (Suzuki coupling), oxidative (Witkop–Winterfeldt oxidation), and reductive conditions (borohydride reduction) in a single sequence on a solid phase. We are convinced that with the development of further such highly orthogonal linker system, new opportunities for SPOS will arise.

Received: March 25, 2009
Published online: July 6, 2009

Keywords: domino reactions · quinolones · solid-phase synthesis · sulfonamide linkers · Witkop–Winterfeldt oxidation

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