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The Reversed Kenner Linker: A New Safety-Catch Linker for the Preparation of *N*-Alkyl Sulfonamides

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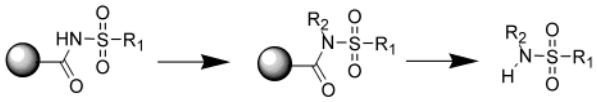
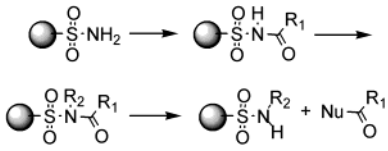
ABSTRACT



A new strategy for the solid-phase synthesis of sulfonamides is described. The Kenner safety-catch strategy has been modified such that the carboxylic acid component remains attached to the solid support while the sulfonamide portion is released into solution. An initial demonstration of the scope of this strategy is presented, along with an analysis of the cleavage characteristics and extension to more elaborate products via Suzuki reaction and thiazolidinone synthesis.

The development of novel linkages for tethering compounds to solid supports is an area of active investigation. Choice of linker is a key consideration in planning a solid-phase chemical route[1,2] since the lability of the linker limits the chemistry which may be carried out on it. In addition, cleavage conditions often dictate the requirements for workup and purification of the released compound prior to bioassay. In the "safety-catch" strategy the linker is maintained in a stable form throughout the chemical manipulation of the resin and is then activated by a specific modification immediately prior to cleavage. This has the advantage of releasing only those resin-bound materials which are competent to both of the cleavage steps. The first such linker to be reported was that of Kenner,[3] employing an *N*-acyl sulfonamide as the linkage for peptide synthesis (Scheme 1). This linker was stable toward the acidic and basic conditions required for peptide assembly but readily cleaved by nucleophilic attack following treatment with diazomethane. The modifications of Backes and Ellman[4−6] have contributed to the further utility of this linker which has become widely used for the assembly of peptides and other compounds.[7−9] Several other safety-catch linkers have been developed more recently for a variety of compound classes in which compound release is achieved by different two-step procedures.[10−15]

Scheme 1. Kenner Safety-Catch Linker Strategy



† Dedicated to Professor Robert Ramage on the occasion of his 65th birthday.

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(2) James, I. W. *Tetrahedron* **1999**, *55*, 4855−4946. Linkers for Solid Phase Organic Synthesis.

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(6) Backes, B. J.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 2322−2330. An Alkanesulfonamide "Safety-Catch" Linker for Solid-Phase Synthesis.

(7) Link, A.; van Calenbergh, S.; Herdewijn, P. *Tetrahedron Lett.* **1998**, *39*, 5175−5176. Practical Method for the Parallel Synthesis of 2′-Amido-2′Deoxyadenosines.

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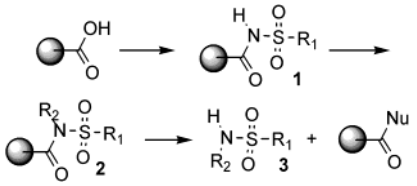
The Kenner linker leaves a resin-bound sulfonamide residue following cleavage (Scheme 1). We reasoned that a "reverse Kenner" strategy could enable a safety-catch process whereby instead of the acids and amides being released from the standard Kenner linker, *N*-alkyl sulfonamides would be cleaved following treatment with a nucleophile (Scheme 2).

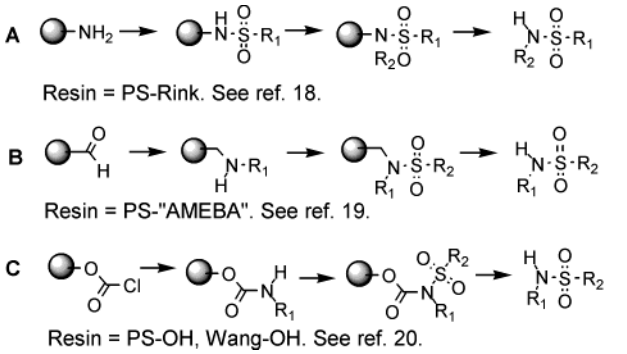
Scheme 2. Proposed "Reverse Kenner" Linker



Sulfonamides have a long history of usage as drugs, from the early sulfa antibiotics such as sulfathiazole[16] to selective serotonin antagonists such as the antimigraine Sumatriptan.[17] More recent reports disclose sulfonamides as inhibitors of cell division.[18] We were interested in developing a preparation of sulfonamides as part of our program for solid-phase synthesis of drug-like compounds.

Several solid-phase routes have already been reported for sulfonamide production (Scheme 3).[19−21] The envisaged route is similar to that of Raju and Kogan (Scheme 3, route C) but employs an amide rather than carbamate link between sulfonamide and resin. We expected that the cleavage conditions for the reverse Kenner linkage would more closely follow those required for Kenner-type linker rather than the significantly harsher conditions required to cleave the carbamate link.[20] Further, it was anticipated that the safety-catch

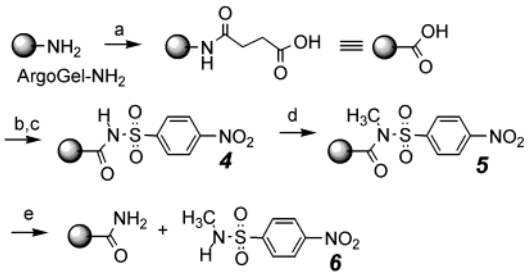
Scheme 3. Reported Strategies for Solid-Phase Sulfonamide Synthesis



properties of the new linker may be advantageous in comparison to the acid cleavable strategies (Scheme 3, routes A and B).

Initial demonstration of this approach proceeded according to Scheme 4. ArgoGel-NH_2 was treated with succinic

Scheme 4[a]



[a] (a) Succinic anhydride (10 equiv), DIEA (10 equiv), NMP, rt, 30 min; (b) pentafluorophenyl trifluoroacetate, pyridine, NMP (1:1:1), rt, 30 min; (c) *p*-nitrobenzenesulfonamide (10 equiv), DIEA (10 equiv), DMAP (10 equiv), NMP, rt, 18 h; (d) MeI (20 equiv), DIEA (10 equiv), DMF, rt, 2 h; (e) 2 M NH_3/MeOH, rt, 2 h.

anhydride and the resulting resin-bound acid activated with pentafluorophenyl trifluoroacetate. Addition of 4-nitrobenzenesulfonamide proceeded smoothly in the presence of DMAP to give resin **4**. Treatment with methyl iodide gave resin **5** and cleavage with methanolic ammonia gave the desired sulfonamide **6**. In contrast, ammonia treatment of unalkylated precursor resin **4** did not result in the release of any material. This was expected by analogy to Kenner's results and effectively illustrates the safety-catch nature of this linker.

Backes and Ellman[5] found that the cyanomethyl derivative of the Kenner linker was significantly more susceptible to nucleophilic cleavage than the corresponding methyl derivative. We prepared the analogous cyanomethyl resin **7** and evaluated its release under the cleavage conditions tried by the Ellman group. In agreement with the results on the Kenner linker, the cyanomethyl resin was more rapidly cleaved under all conditions, although the relative difference

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(21) Raju, A.; Kogan, T. P. *Tetrahedron Lett.* **1997**, *38*, 3373−3376. Solid Phase Synthesis of Sulfonamides Using a Carbamate Linker.

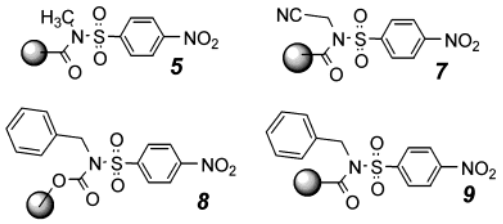
Table 1. Sulfonamide Cleavage Kinetics

	$t_{1/2}$ (min)[a]		
resin	**A**	**B**	**C**
5	1.5	15	>200
7	0.5	3	120
8	>200	n.d.[b]	n.d.
9	<5	n.d.	n.d.

[a] **A**: 2 M ammonia/MeOH. **B**: 0.007 M benzylamine/DMSO. **C**: 20% aniline/CH_2Cl_2. [b] n.d. = not determined; >200 indicates that no product was released after 200 min.

in rate was smaller than was found in the previous study (see Table 1). No product was obtained on treatment of resin **5** with a 20% solution of aniline in CH_2Cl_2, in agreement with previous observations on the Kenner resin.[5]

Carbamate-linked sulfonamide **8** was prepared by the method of Raju and Kogan, along with the analogous reversed Kenner resin **9**. This allowed direct comparison of cleavage from the two resins. As expected, no material was released from resin **8** under conditions which gave quantitative release from resin **9**. A number of different sulfonamides



and alkylating agents were evaluated for compatibility with this strategy (Table 2[22]). Assembling sulfonamides on ArgoGel-Rink allowed acidic release of both unalkylated and alkylated products as their succinate analogues **13** (Scheme 5), providing a further method of assessing reaction progress in addition to nucleophilic release of sulfonamide **12**. The results are shown in Table 2 and demonstrate that the

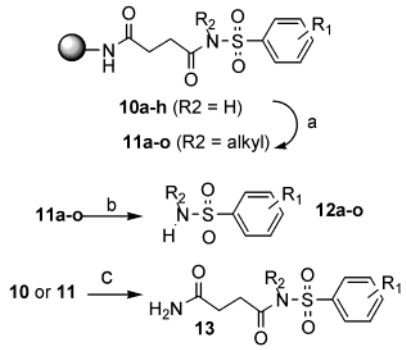
Table 2. Yield of Sulfonamide Products **12**[a] (Scheme 5)

entry	R1	R2-X	yield, %	entry	R1	R2-X	yield, %
12a	H	Me-I	92	**12i**	4-NO_2	ICH_2CN	48
12b	4-CN	Me-I	75	**12j**	4-NO_2	BnBr	56
12c	4-Cl	Me-I	95	**12k**	4-NO_2	4-NO_2BnBr	59
12d	4-tBu	Me-I	65	**12l**	4-NO_2	3-MeOBnBr	54
12e	4-MeO	Me-I	74	**12m**	4-NO_2	Et-I	46
12f	2-Me	Me-I	81	**12n**	4-NO_2	2-Pr−I	10
12g	4-NO_2	Me-I	91				
12h	4-Br	Me-I	82				

[a] Yields are for five steps from amine resin and are based on the manufacturer's stated loading of the initial resin.

procedure is compatible with a range of building blocks. Crude products were of good to excellent quality, and a simple workup gave products of analytical purity.[23] Yield was most sensitive to steric and electronic factors for the alkylating agent, with best yields being obtained for methyl iodide.

Scheme 5[a]



[a] R2-X (20 equiv), DIEA (10 equiv), NMP, rt, 18 h; (b) 2 M NH_3/MeOH, rt, 2 h; (c) TFA/CH_2Cl_2 (1:1), rt, 30 min.

To further demonstrate the synthetic utility of this linker system, several further modified products were prepared. 4-Bromobenzenesulfonamide resin **10h** was used as a substrate for Suzuki coupling[24] with a short series of boronic acids (Scheme 6). The expected products were obtained in high yield and purity on heating for 45 h at 80 °C (some starting material was observed if reaction was stopped at 24 h). No release of product from the resin was observed under these conditions, further illustrating the stability of this resin prior to alkylation.

An additional route to increased diversity was explored with anilino resin **15** obtained via tin chloride mediated

(22) **Representative procedure:** ArgoGel-Rink-NH-Fmoc resin (Argonaut Technologies, San Carlos, CA; 500 mg, 0.36 mmol/g, 0.18 mmol) was treated with a 20% (v/v) piperidine/*N*-methylpyrrolidine (NMP) solution (2 mL) for 20 min and then drained and washed with NMP (5 × 5 mL). To the resin were added a mixture of succinic anhydride (360 mg, 3.6 mmol, 20 equiv) and DIEA (630 μL, 3.6 mmol, 20 equiv) in 2 mL of NMP. After shaking for 30 min, the resin was filtered and washed with NMP (5×) and then further treated with a 1:1:1 mixture of pentafluorophenyl trifluoroacetate, pyridine, and NMP (2 mL) for 20 min followed by a brief wash with NMP (2×). To the resin was immediately added a solution of 4-nitrobenzylsulfonamide (364 mg, 1.8 mmol, 10 equiv), pyridine (730 μL, 90 mmol, 50 equiv), and (dimethylamino)pyridine (2 mg, 0.018 mmol, 0.1 equiv) in NMP (2 mL). The reaction was shaken for 16 h before being drained and washed with NMP (5×), MeOH (3×), dichloromethane (DCM; 3×), and anhydrous NMP (3×). The resin was treated with methyl iodide (112 μL, 1.8 mmol, 10 equiv) and DIEA (157 μL, 0.9 mmol, 5 equiv) in anhydrous NMP (2 mL) for 18 h and then washed well with NMP (3×), DCM (3×), and MeOH (3×). The resin was treated with methanolic ammonia (1.0 M; 3 mL) for 5 min and then drained and washed with further methanolic ammonia (2 × 2 mL). Combined filtrates were concentrated and then dissolved in DCM and passed through a short plug of silica gel. Concentration gave *N*-methyl-4-nitrobenzylsulfonamide **12g** as an off-white solid (35.3 mg; 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 2H, J = 9.1 Hz), 8.06 (d, 2H, J = 9.1 Hz), 4.47 (bs, 1H), 2.75 (d, 3H, J = 5.2 Hz); LC/MS *m*/*z* calcd for $(M - H)^-$ ($C_7H_7N_2O_4S$) 215.22, obsd 215.

(23) The safety-catch nature of the resin means that the products of incomplete reaction are generally retained on the solid support. Passage through silica plug removed plasticizers arising from reaction vessels.

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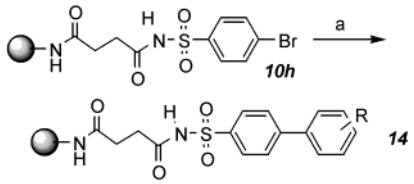
Scheme 6[a]



[a] R−Ph−$B(OH)_2$ (8 equiv), $Pd(PPh_3)_4$ (0.1 equiv), Na_2CO_3 (8 equiv), DMF/H_2O (15:1), 80 °C, 45 h; R = H (97% conversion), 2-Me (88%), 4-CF_3 (94%).

reduction of 4-nitrosulfonamide resin **10g** (Scheme 7). This was subjected to one-pot condensation with benzaldehyde and mercaptosuccinic acid followed by amide formation to give thiazolidinone **17**[25] in good yield and purity. The availability of resin-bound amine **15** allows access to a range of possible derivatives.

In conclusion, we have demonstrated the novel application of the widely used Kenner safety-catch linker for the production of *N*-alkyl sulfonamides. The new "reverse Kenner" linker has good compatibility with a range of starting materials and is of sufficient stability to allow the assembly of more elaborate products by a variety of reaction

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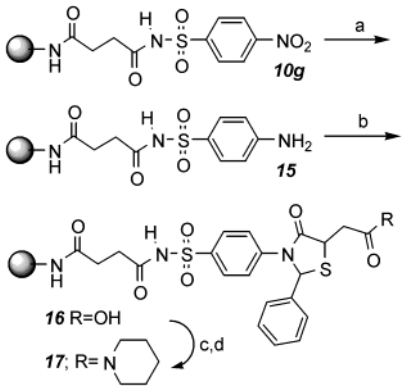
Scheme 7[a]



[a] (a) $SnCl_2$ (50 equiv), DMF, rt, 24 h; (b) Ph-CHO (40 equiv), mercaptosuccinic acid (20 equiv), 4 Å molecular sieves, THF, 70 °C, 18 h; (c) pentafluorophenyl trifluoroacetate, pyridine, DMF (1:1:1), rt, 30 min; (d) 20% piperidine/DMF, rt, 30 min.

conditions. The further application of this linker to the production of drug-like compounds and combinatorial libraries is ongoing and will be described in due course.

Supporting Information Available: ^1H NMR spectra, HPLC chromatograms, and LC-MS data for sulfonamides **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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