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Solid-phase synthesis of unsymmetrical ureas through the use of Kenner safety-catch linker

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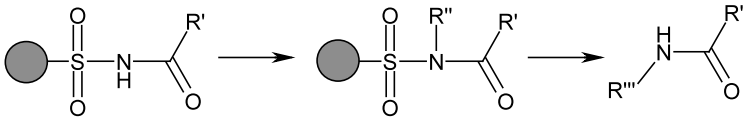
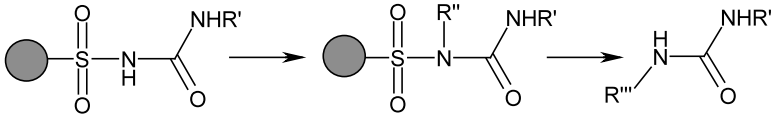
Abstract—A new strategy for the solid-phase synthesis of unsymmetrical ureas is described. Upon treatment of Kenner safety-catch linker with an isocyanate, followed by $TMSCHN_2$ or iodoacetonitrile and an amine, the corresponding unsymmetrical ureas are released in solution.

Ureas are often found in biologically active compounds[1] and a number of methods have been published for their solid-phase synthesis.[2] To the best of our knowledge, none of these methods takes advantage of the safety-catch linkers chemical versatility. Considering our interest in the solid-phase synthesis of drug-like compounds and on the basis of our previous experience in the use of the Kenner safety-catch linker,[3] we developed a novel method for producing unsymmetrical ureas which exploits this linker and it is easy applicable on combinatorial libraries.



Kenner safety-catch linker for amide synthesis



Kenner safety-catch linker for urea synthesis

The Kenner acylsulfonamide safety-catch linker[4] (or its Ellman modification)[5] is largely used for the solid-phase preparation of amides[4] and thioesters.[3a] The acylsulfonamido bond is completely stable to basic and acidic conditions and a large variety of chemical manipulations can be performed 'prior activation'. Activation is accomplished with $TMSCHN_2$ or iodoacetonitrile to provide the corresponding *N*-alkylacylsulfonamide, which is sensitive to nucleophiles and can then be cleaved with amines or thiols.

We reasoned that building on the Kenner sulfonamide resin a sulfonyl urea could allow the preparation of ureas rather than amides or thioesters, following activation and fragment release. To confirm our hypothesis two batches of sulfonyl urea resins **3** and **4** were prepared from commercial 4-carboxyphenylsulfonamide and 4-sulfonamido butyric polystyrene resins[6] **1** and **2** by treatment with phenylisocyanate.[7] A series of experiments was set-up to establish optimal cleavage conditions (Table 1 and Scheme 1).

Resins **3** and **4** were activated both with $TMSCHN_2$ and iodoacetonitrile. Cleavages were performed with 1.2 equiv. of *p*-methoxybenzylamine in 1.5 mL of solvent for 12 h and amine excess was scavenged with isocyanate resin. In vacuo distillation of the solvents afforded crude products that were analyzed by HPLC, MS and ^1H NMR. Resin **3** gave the best results through activation with $TMSCHN_2$ and the use of DMF as cleavage solvent (Fig. 1). Result of entry 4 can

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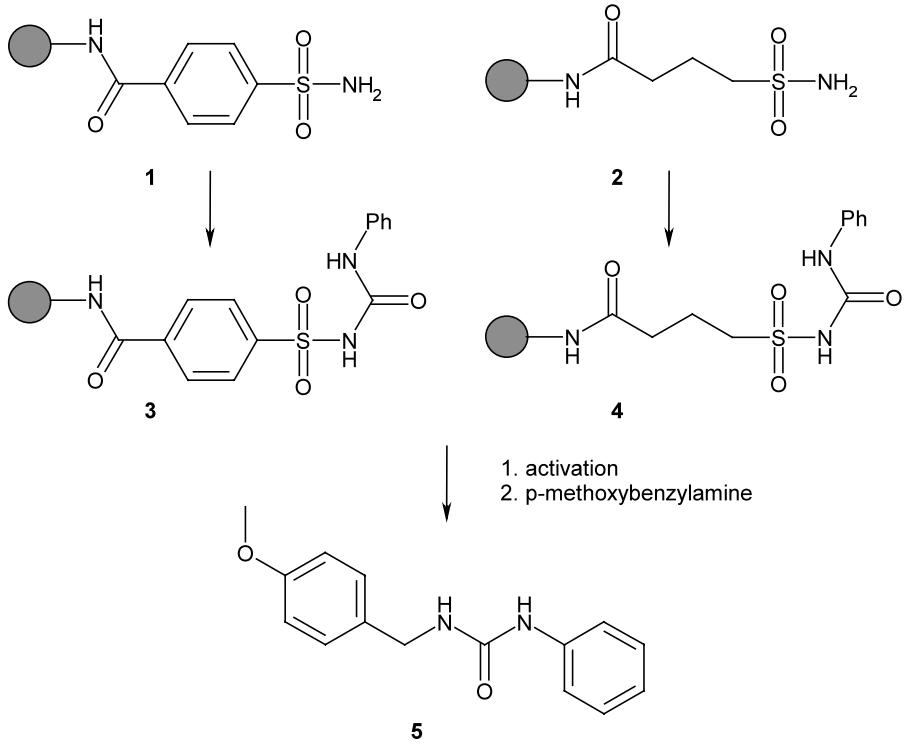
Table 1. Optimization of cleavage conditions[8]

Entry	Resin	Solvent	T (°C)	Activating group	Yield(%)[a]	Purity(%)[b]
1	**3**	THF	rt	Me	60	90
2	**3**	DMF	rt	Me	89	97
3	**3**	THF	60	Me	66	95
4	**3**	THF	rt	CH_2CN	69	77
5	**4**	DMF	rt	Me	42	74
6	**4**	THF	rt	CH_2CN	55	91
7	**4**	DMF	rt	Me	60	87

[a] Effective yield.[9]
[b] HPLC trace 220 nm.[10]



Scheme 1.

be explained as deriving from an incomplete alkylation of the resin, as happens in the acylsulfonamides case. Differences in between DMF and THF were less enhanced when activating with the cyanomethyl group (entries 6 and 7). In the same conditions the unalkylated precursors **3** and **4** released no material.

In order to explore the limits of this methodology, the set of amines **6**–**12** was submitted to the cleaving conditions of entry 2 and the resulting products were analyzed. Primary and secondary amines reacted equally well and crude product were of good to excellent quality (Table 2).

Aniline was much less reactive: with both resins **3** and **4** activated either with $TMSCHN_2$ or iodoacetonitrile and cleaved at rt or 60°C in both DMF and THF, yields were very poor. The best result was obtained heating resin **3** in DMF for 3 h at 60°C (42% yield, 73% purity) in the presence of 1.2 equiv. of aniline, followed by aqueous acidic work-up. Contrary from what was

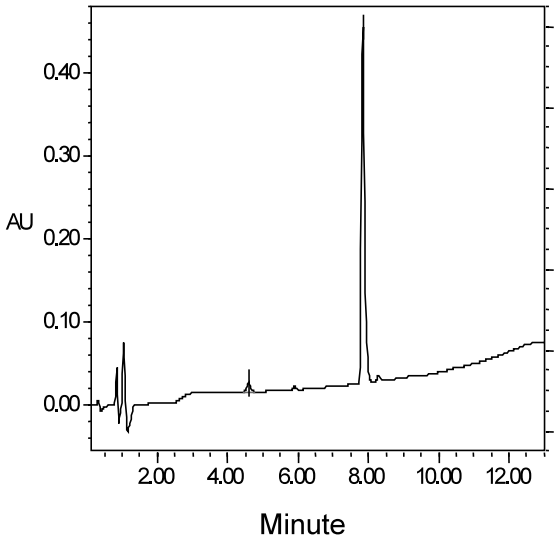


Figure 1. HPLC trace (220 nm) of the crude **5** obtained in entry 2 (Table 1).

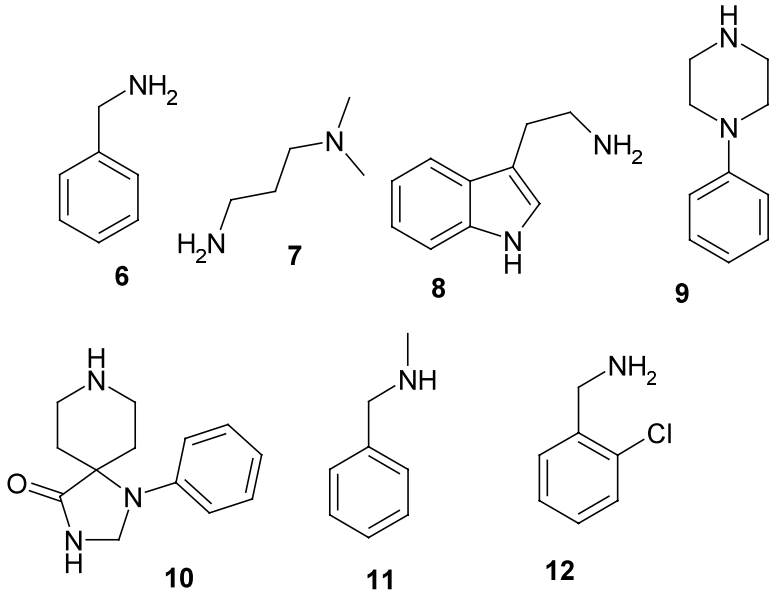
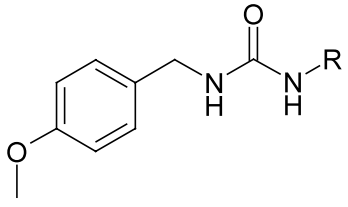


Table 2. Phenyl ureas from amines **6–12**

Amine	Urea	Yield (%)[a]	Purity (%)[b]
6	**6a**	78	97
7	**7a**	100	90
8	**8a**	100	93
9	**9a**	77	92
10	**10a**	91	93
11	**11a**	90	82
12	**12a**	83	91

[a] Effective yield.[9]
[b] HPLC trace 220 nm.[10]

Table 3. Aliphatic and *o*-phenylsubstituted isocyanates



13 R = Bn[11]
14 R = isopropyl[11]
15 R = o-*t*-butylphenyl
16 R = o-trifluoromethylphenyl
17 R = o-bromophenyl

Urea	Yield (%)[a]	Purity (%)[b]
13	42	92
14	62	69
15	62	87
16	100	91
17	74	98

[a] Effective yield.[9]
[b] HPLC trace 220 nm.[10]

observed in the case of acylsulfonamides, with sulfonylureas the cyanomethyl group is not very efficient in enhancing reactivity.

The method was also applicable to the less reactive alkyl isocyanates or to the hindered *ortho* substituted phenyl isocyanates. When resin **1** was reacted with benzyl, isopropyl or orthophenyl substituted isocyanates and then submitted to optimized cleavage conditions, the corresponding ureas (**13–17**) were obtained in good to moderate yields (Table 3).

In conclusion, we have demonstrated that the Kenner safety-catch linker can be used for the preparation of unsymmetrical di- and trisubstituted ureas. Isocyanate loading on the resin seems to be a crucial point: the more acidic resin **1**[12] gives better yields than resin **2**; aliphatic isocyanates require longer loading times and give low yields. This method is especially interesting for the preparation of libraries, since it allows chemical elaboration of the molecule prior to urea release, does not need any further work-up and does not require particularly sensitive or harsh conditions.

Loading methods alternative to the isocyanate one, which would avoid non-commercial isocyanates preparation and allow the synthesis of tetrasubstituted unsymmetrical ureas, are under study and will be reported in due time.

Supplementary material

HPLC chromatograms, MS and ^{1}H NMR for compounds **5**, **6a–12a**, **13–17** are available from the author.

Acknowledgements

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6. Fluka 08559 (**1**) and Novabiochem (**2**).
7. A batch of resin swelled in 1:1 THF/DCM was treated with phenyl isocyanate (10 equiv.) and DIPEA (10 equiv.) and shaken at rt for 12 h. Then it was washed with THF, DCM, THF, diethyl ether and dried in vacuo.
8. A batch of activated resin was treated with 1.2 equiv. of *p*-methoxybenzylamine in 1.5 mL of solvent for 12 h. Then, 2 equiv. of isocyanate resin were added together with 2 mL of THF and the resulting mixture was shaken for an additional 2 h. Filtration and concentration in vacuo (Genevac HT-4 apparatus) afforded the desired crude compounds.
9. Effective yield: a weighted batch of sulfonamido resin was loaded with 3-(3,4,5-trimethoxyphenyl)propionic acid in standard conditions,[5] treated with a THF–benzylamine solution, washed with 1% AcOH in THF, DMC, DMF, DCM and THF and then activated with $TMSCHN_2$ (resin **1**) or iodoacetonitrile (resin **2**). The quantity of *p*-methoxyphenyl amide obtained following cleavage with *p*-methoxybenzyl-amine and treatment with isocyanate resin, was used to evaluate the starting resin loading.
10. HPLC was carried out on a 50×4.6 mm, 3 μm LUNA RPC18 column (Phenomenex) or on a Symmetry RPC18, 100×4.6 mm column (Waters) using Water Alliance 2695 equipment with a gradient of acetonitrile in water (1 mL/min, 0.1% TFA acid buffer, gradient 10–80 over 12 min) and UV detection at 220 nm.
11. Loading of the isocyanate was prolonged for 5 days instead of 12 h.
12. Benzene sulfonamide pK_a (DMSO) 16.1, methane–sulfonamide pK_a (DMSO) 17.5; data from http://daeiris.harvard.edu/pKa/pKa.html.