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O,N,N′-Trialkylisoureas as Mild Activating Reagents for *N*-Acylsulfonamide Anchors

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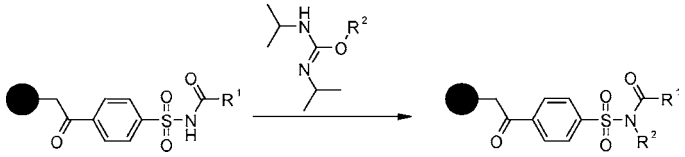
ABSTRACT



Prior to detachment of compounds synthesized on sulfonamide based safety-catch linkers, the molecular anchor has to be activated. This is achieved by alkylation of the nitrogen atom of the *N*-acylsulfonamide using different established protocols. As an addition to the existing repertoire of activating reagents, we suggest the use of *O,N,N′*-trialkylisoureas. Besides the demonstration of the feasibility of these mild alkylating agents for this purpose, custom-tailored novel *O,N,N′*-trialkylisoureas prepared from electron-deficient alcohols are reported.

Polymer-bound *N*-acylsulfonamides conceptually related to Kenner's safety-catch linker experienced a renaissance during the past decades.[1] One prominent driving force was the invention of chemical ligation of proteins and the resulting high demand for straightforward access to thioester peptide fragments. A key step in utilizing the family of *N*-acylsulfonamide linkers is the activation of a stable and safe *N*-acylsulfonamide link through alkylation, yielding the corresponding reactive *N*-acyl-*N*-alkylsulfonamides.[2] The latter allow for nucleophilic displacement of the acyl moiety. In this context, several activation methods have been described. Kenner initially applied freshly generated diazomethane that can be replaced by commercially available trimethylsilyldiazomethane solutions. For a reversed Kenner linker according to Maclean et al., the use of inexpensive methyl iodide as activating reagent has been reported.[3] However, the alkylated species thus obtained demonstrate only moderate activity toward attack by nucleophiles. This changes considerably, when bromo- and iodoacetonitrile are applied as alkylating agents leading to cyanomethylated *N*-acylsulfonamides.[4] The electron-withdrawing properties of the cyanomethyl residue raises the lability of the *N*-acyl-*N*-alkylsulfonamides toward nucleophilic attack considerably. The transfer of acyl residues onto very weak nucleophiles such as anilines thus became achievable in many cases. However, sometimes the nitrile group thus introduced gave rise to side reactions, e.g., transcyanomethylation of methionine substituents as reported by Flavell et al.[5] Polystyrene beads treated with haloacetonitriles turn brownish, indicating the occurrence of unknown transformations. In addition, it is known that the weaker activation introducing methyl groups can lead to higher yields in comparison to the use of the stronger activating haloacetonitriles, most

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(1) Heidler, P.; Link, A. *Bioorg. Med. Chem.* **2005**, *13* (3), 585−99.
(2) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636−637.
(3) Maclean, D.; Hale, R.; Chen, M. *Org. Lett.* **2001**, *3* (19), 2977−2980.
(4) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116* (24), 11171−11172.
(5) Flavell, R. R.; Huse, M.; Goger, M.; Trester-Zedlitz, M.; Kuriyan, J.; Muir, T. W. *Org. Lett.* **2002**, *4* (2), 165−168.

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probably due to a higher ratio of activated polymer bound linker. Last but not least, the handling of bromoacetonitrile solutions in DMF or NMP is hazardous. The solution penetrates gloves and leads to severe skin damage upon exposure. Diazomethane is unstable and might cause explosions; trimethylsilyldiazomethane in hexane is stable but volatile. Therefore, reagents with a better safety profile would be advantageous. Thus, alkylation of the acylsulfonamide group using Mitsunobu chemistry introduced by Willoughby et al. and recently modified to synthesize peptide thioesters by an intramolecular *S*-acyl shift is an elegant alternative route.[6,7]

In our ongoing efforts to broaden the applicability of *N*-acyl-*N*-alkylsulfonamides as polymer-bound acylating reagents, we decided to use *O*,*N*,*N*′-trialkylisoureas as alkylating species to achieve the desired activated intermediates. Syntheses and reactions of *O*,*N*,*N*′-trisubstituted isoureas have been studied already 40 years ago, thus the desired *O*,*N*,*N*′-trialkylisoureas were prepared according to Schmidt et al. using *N*,*N*′-diisopropylcarbodiimde, copper(I/II) chloride, and the adequate alcohol.[8,9] To raise the activity of the gained *N*-acyl-*N*-alkylsulfonamides toward nucleophiles, we mainly focused on the use of alcohols with electronegative substituents. Four known *O*,*N*,*N*′-trisubstituted isoureas **1a**,**c**,**e**,**h**[10] and five novel derivatives **1b**,**d**,**f**,**g**,**i** were thus prepared and fully characterized (Figure 1).

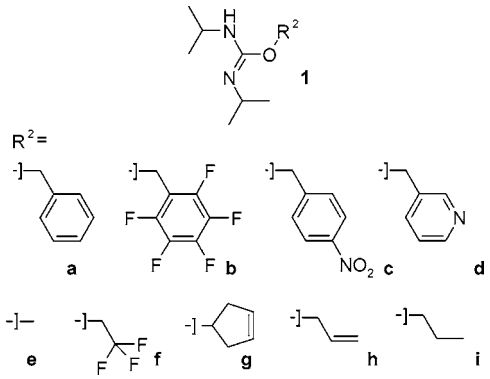
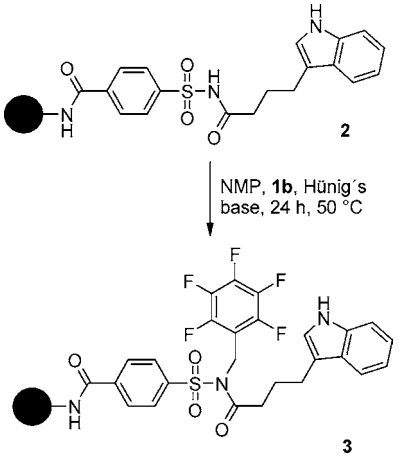


Figure 1.

Initially, we investigated whether *O*,*N*,*N*′-trisubstituted isoureas are suited to transfer their *O*-alkyl residue onto the acylsulfonamide group. Reagent **1b** was selected for ease of detection, and the reaction on the polymer-bound linker was monitored by means of gel phase ^{19}F NMR. The experiments effortlessly proved that the desired alkylation of a model construct **2** to the activated construct **3** could be achieved in the presence of Hünig's base (Scheme 1). The

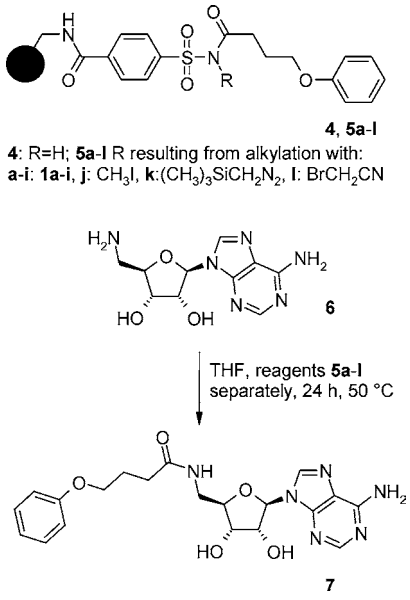
Scheme 1



activated linker construct **3** can be obtained using the Mitsunobu protocol suggested by Willoughby et al.[7] as well, but the use of a preformed *O*,*N*,*N*′-trialkylisourea **1b** for this purpose is cheaper and easier.

Subsequently, all isoureas **1a**−**i** were reacted with polymer-bound 4-phenoxybutyric acid (**4**), attached to the Kenner linker modified by Ellman et al.[4] At the same time, resin **4** was activated with the standard activation reagents bromo acetonitrile, methyl iodide, and trimethylsilyldiazomethane, respectively, to enable comparison of the reactivity of the intermediates **5** obtained (Scheme 2). The progress of the conversion to identical model amides **7** using the 12 different *N*-acyl-*N*-alkylsulfonamides **5** bearing the same acyl residue in different vessels was monitored by means of HPLC.

Scheme 2



(6) Ollivier, N.; Behr, J. B.; El-Mahdi, O.; Blanpain, A.; Melnyk, O. *Org. Lett.* **2005**, *7* (13), 2647−50.
(7) Willoughby, C. A.; Hutchins, S. M.; Rosauer, K. G.; Dhar, M. J.; Chapman, K. T.; Chicchi, G. G.; Sadowski, S.; Weinberg, D. H.; Patel, S.; Malkowitz, L.; Di Salvo, J.; Pacholok, S. G.; Cheng, K. *Bioorg. Med. Chem. Lett.* **2002**, *12* (1), 93−96.
(8) Däbritz, E. *Angew. Chem., Int. Ed. Engl.* **1966**, *5* (5), 470−477.
(9) Schmidt, E.; Däbritz, E.; Thulke, K.; Grassmann, E. *Justus Liebigs Ann. Chem.* **1965**, *685*, 161−166.
(10) Badache, L.; Rahal, S.; Ghosez, L. *J. Soc. Alger. Chim.* **2002**, *12* (1), 1−19.

As main result of this initial experiment, the use of *O*-alkylisoureas prepared using pentafluorobenzyl and 4-nitrobenzyl alcohol **1b** and **1c**, respectively, yielded activated linkers **5b** and **5c** that showed intermediate reactivity with respect to the standards: Conversion of **6**[11] to the model amide **7** proceeded faster than observed with the construct **5k** activated using trimethylsilyldiazomethane and slower in comparison to **5l**, the one where bromoacetonitrile had been applied. Interestingly, the introduction of a methyl substituent by different methods (A) using methyl iodide or (B) *O*-methylisourea **1e** leads to dissimilar resin properties that are macroscopically visible. In direct comparison, the performance of the polystyrene beads activated with the comparatively mild alkylating reagent **1e** was superior in our hands. This topic might justify further investigations in the future.

To show that *O*,*N*,*N*′-trialkylisoureas are synthetically useful for our purpose, a proof of principle synthesis of amides in parallel format was performed. The desired compounds shown in Figure 2 could be obtained as anticipated.

In conclusion, custom-tailored *O*,*N*,*N*′-trialkylisoureas are a useful addition to the repertoire of activation protocols for Kenner's safety-catch linker and might be the best selection, when the highly reactive cyanomethylation leads to side -products and the activation resulting from the alkylation using trimethylsilyldiazomethane is insufficient.

(11) Kolb, M.; Danzin, C.; Barth, J.; Claverie, N. *J. Med. Chem.* **1982**, *25* (5), 550−556.

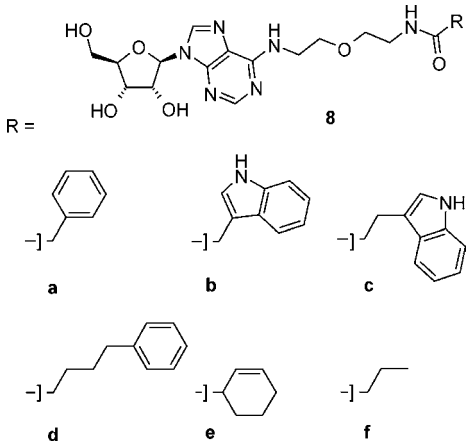


Figure 2.

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Supporting Information Available: A graphical representation of the progress of conversion, NMR data of novel derivatives **1b**,**d**,**f**,**g**,**i** and resin **3**, and a description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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