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Amino Acid and Peptide Synthesis and Functionalization by the Reaction of Thioacids with 2,4-Dinitrobenzenesulfonamides

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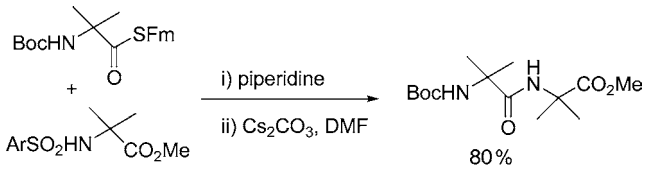
ABSTRACT



Fm = 9-fluorenylmethyl, Ar = 2,4-dinitrophenyl

Readily prepared amino thioacids react at room temperature in DMF in the presence of cesium carbonate with 2,4-dinitrobenzenesulfonamides to give amides. When the sulfonamide is derived from an amino acid the method results in peptide bond formation, whereas the use of carbohydrate derived sulfonamides gives neoglycoconjugates.

The development of new methods for amide and peptide bond formation is an area of considerable current interest.[1] Azides have played a prominent role in this burgeoning and important field,[2] as key starting materials in the Staudinger ligation,[3] the traceless Staudinger ligation,[4] and in couplings with thio-[5] and selenoacids.[6] These excellent azide-based coupling methods, however, are not without limitations, chief among which are the need to prepare azides and the obligate restriction to the formation of secondary amides. In this respect, as we report here, we have investigated the application of the reaction of thioacids with 2,4-dinitrobenzenesulfonamides[7] to the formation of peptide bonds and neoglycoconjugates.

As developed and demonstrated by Fukuyama the mono- and dinitrobenzenesulfonamides are excellent protecting groups for amines. They are introduced in high yield directly to the amines themselves, may be alkylated on nitrogen because of the acidity of the N−H bond, are stable to many reaction conditions, and are cleaved under very mild conditions by nucleophilic aromatic substitution with a thiol.[8] When the nucleophilic thiol is replaced by a thioacid, as described by Tomkinson and co-workers for simple substrates,[7] the product is an amide (Scheme 1). The mild reaction conditions and high yields observed suggested to

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(1) (a) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765−775. (b) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447−2467.
(2) Agard, M. J.; Bashkin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *ACS Chem. Biol.* **2006**, *1*, 644−648.
(3) (a) Hang, H. C.; Bertozzi, C. R. *Acc. Chem. Res.* **2001**, *34*, 727−736. (b) Köhn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106−3116. (c) Kim, H.; Cho, J. K.; Aimoto, S.; Lee, Y.-S. *Org. Lett.* **2006**, *8*, 1149−1151. (d) Lin, L. F.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686−2695.
(4) (a) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141−2143. (b) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2001**, *3*, 9−12. (c) Bianchi, A.; Bernardi, A. *J. Org. Chem.* **2006**, *71*, 4565−4577. (d) Soellner, M. B.; Tam, A.; Raines, R. T. *J. Org. Chem.* **2006**, *71*, 9824−9830. (e) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Am. Chem. Soc.* **2006**, *128*, 8820−8828. (f) Grandjean, C.; Boutonnier, A.; Guerreiro, C.; Fournier, J.-M.; Mulard, L. A. *J. Org. Chem.* **2005**, *70*, 7123−7132. (g) He, Y.; Hinklin, R. J.; Chang, J.; Kiessling, L. L. *Org. Lett.* **2004**, *6*, 4479−4482. (h) Liu, L.; Hong, Z.-Y. *ChemBioChem* **2006**, *7*, 429−432.

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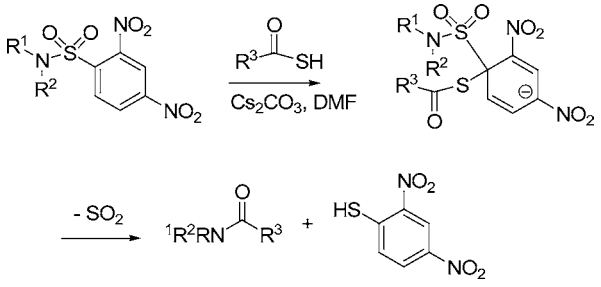
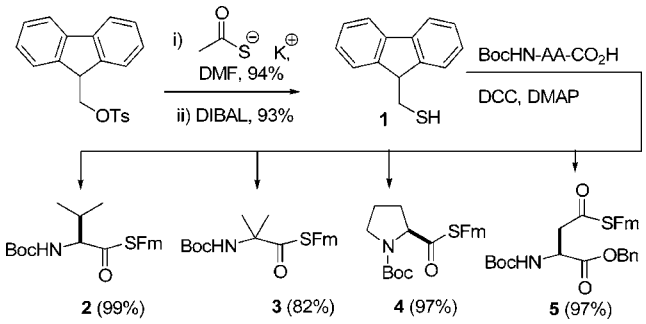
Scheme 1. Amide Forming Reaction



us that this protocol could have considerable use in peptide chemistry provided a suitable method for thioacid synthesis could be developed.[9]

Displacement of 9-fluorenylmethyl *p*-toluenesulfonate with potassium thioacetate followed by DIBAL reduction gave 9-fluorenylmethanethiol **1**, which was then coupled with a series of *N*-Boc protected amino acids under standard carbodiimide conditions to give the thioesters **2**−**5**, each of which were obtained in excellent yield (Scheme 2).[10]

Scheme 2. Preparation of 9-Fluorenylmethyl (Fm) Thioesters



Reaction of a set of amino ester hydrochlorides with 2,4-dinitrobenzenesulfonamide in dichloromethane in the presence of pyridine gave the sulfonamides **6**−**10** (Figure 1).

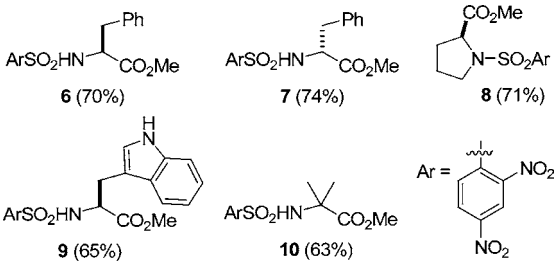
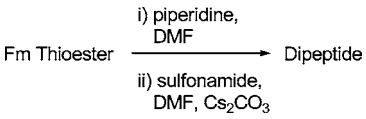


Figure 1. 2,4-Dinitrobenzenesulfonamides.

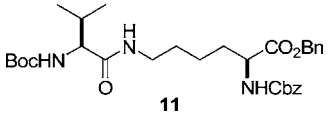
Treatment of the 9-fluorenylmethyl thioesters with piperidine in DMF at room temperature gave the corresponding thioacids, which were immediately coupled to the sulfonamides in the presence of cesium carbonate, also in DMF at room temperature, resulting in the formation of dipeptides (Table 1). These reactions, which were conducted with

Table 1. Dipeptides from Thioesters and Sulfonamides



no.	thioester	sulfonamide	dipeptide[a]	yield, %
1	**2**	**6**	Boc-L-V-L-F-OMe	81
2	**2**	**7**	Boc-L-V-D-F-OMe	82
3	**2**	**9**	Boc-L-V-L-W-OMe	82
4	**4**	**8**	Boc-L-P-L-P-OMe	78
5	**4**	**9**	Boc-L-P-L-W-OMe	77
6	**5**	**8**	Boc-L-β-D-L-P-OMe	75
7	**5**	**8**	Boc-L-β-D-Aib-OMe	79
8	**5**	**6**	Boc-L-β-D-L-F-OMe	82
9	**3**	**9**	Boc-Aib-L-W-OMe	80
10	**3**	**10**	Boc-Aib-Aib-OMe	80
11	**3**	**6**	Boc-Aib-L-F-OMe	82
12[b]	**2**	**6**	Boc-L-V-L-F-OMe	51
13[c]	**2**	**6**	Boc-L-V-L-F-OMe	62
14[d,e]	**2**	**6**	Boc-L-V-L-F-OMe	59

[a] V = valine, F = phenylalanine, W = tryptophan, P = proline, Aib = α-aminoisobutyrate, D = γ-aspartic acid α-benzyl ester. [b] Reaction conducted in methanol as solvent. [c] Reaction conducted in the presence of an equimolar amount of Boc-L-Asp-α-O-Bn. [d] Reaction conducted in the presence of an equimolar amount of N-α-Cbz-L-Lys-O-Bn. [e] 23% of the side chain functionalized lysine derivative **11** was also isolated from this experiment.



11

approximately 1:1 ratios of the thioacid and the sulfonamide, serve to illustrate the scope of this peptide bond forming methodology.[11] In particular attention is drawn to entries 1 and 2 of Table 1 in which diastereomeric products were obtained, ruling out the possibility of racemization in the course of the thioester deprotection or the coupling.[12] It is

(5) (a) Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580−1582. (b) Rakotomanomana, N.; Lacombe, J.-M.; Pavia, A. *Carbohydr. Res.* **1990**, *197*, 318−323. (c) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 77554−7755. (d) Merkx, R.; Brouwer, A. R.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125−1128. (e) Kolakowski, R. V.; Shangguan, N.; Williams, L. J. *Tetrahedron Lett.* **2006**, *47*, 1163−1166. (f) Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006**, *8*, 823−826. (g) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695−5702. (h) Crich, D.; Dudkin, V. Y. *Tetrahedron Lett.* **2003**, *44*, 1787−1789. (i) Zhu, X. M.; Pachamuthu, K.; Schmidt, R. R. *Org. Lett.* **2004**, *6*, 1083−1085. (j) Merkx, R.; van Haren, M. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2007**, *72*, 4574−4577.

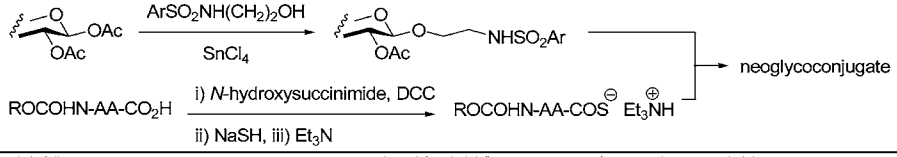
(6) (a) Knapp, S.; Darout, E. *Org. Lett.* **2005**, *7*, 203−206. (b) Wu, X.; Hu, L. *J. Org. Chem.* **2007**, *72*, 765−774.

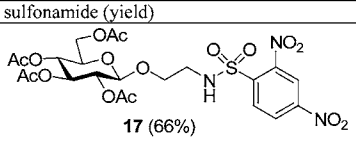
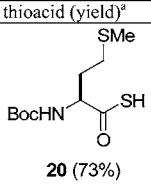
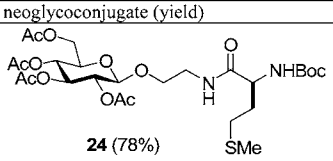
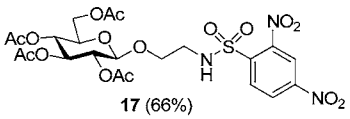
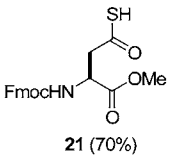
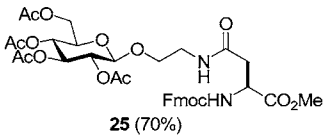
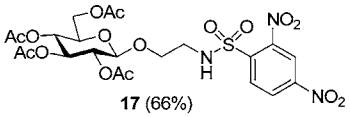
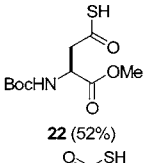
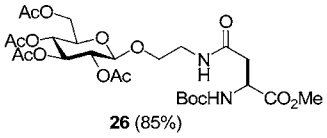
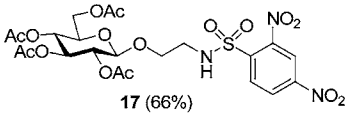
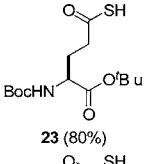
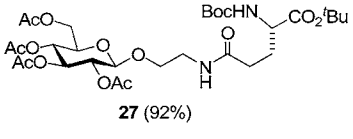
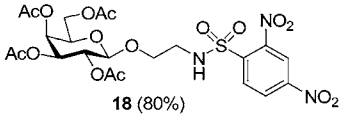
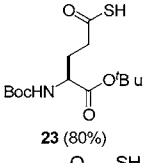
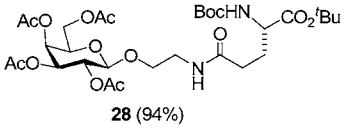
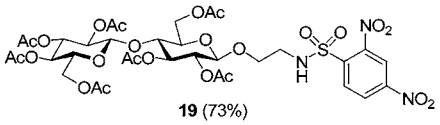
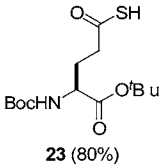
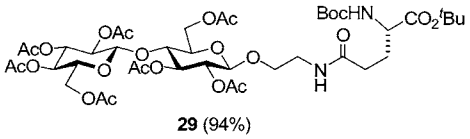
(7) (a) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1669−1672. (b) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1673−1676.

(8) (a) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831−5834. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353−359.

(9) Previous applications of amino thioacids in peptide synthesis: (a) Yamashiro, D.; Blake, J. *Int. J. Peptide Protein Res.* **1981**, *18*, 383−392. (b) Mitin, Y. V.; Zapevalova, N. P. *Int. J. Peptide Protein Res.* **1990**, *35*, 352−356.

Table 2. Neoglycoconjugates from Thioacids and Sulfonamides



entry	sulfonamide (yield)	thioacid (yield)[a]	neoglycoconjugate (yield)
1	 **17** (66%)	 **20** (73%)	 **24** (78%)
2	 **17** (66%)	 **21** (70%)	 **25** (70%)
3	 **17** (66%)	 **22** (52%)	 **26** (85%)
4	 **17** (66%)	 **23** (80%)	 **27** (92%)
5	 **18** (80%)	 **23** (80%)	 **28** (94%)
6	 **19** (73%)	 **23** (80%)	 **29** (94%)

[a] Isolated in the form of a triethylammonium salt and carried forward to the next step without purification

especially noteworthy that the protocol is applicable to hindered amino acids such as proline and aminoisobutyric acid, whichever side of the nascent peptide bond they occupy.

Comparison of entries 1 and 12 in Table 1 indicates that the coupling reaction is compatible with the presence of alcohols, and that methanol may even be employed as solvent, albeit with a slight loss of yield. When the reaction was conducted in the presence of a Boc-L-Asp-α-OBn (Table 1, entry 13) some loss of yield was recorded but no coupling was observed to the spectator acid. Finally, the inclusion of *N*-α-Cbz-L-Lys-*O*-Bn in the reaction mixture also resulted in some loss of yield (Table 1, entry 14) accompanied by some amidation of the free amine group. The interference of unprotected amines in the peptide bond forming reactions is, of course, common to most such reactions. In this case it suggests that the reaction proceeds, at least in part, by decomposition of the intermediate Meisenheimer complex (Scheme 1) to a 2,4-dinitrophenyl thioester that subsequently captures the nucleophilic amine.

As outlined in Scheme 3, we have also applied the method to the synthesis of a model tetrapeptide by the segment coupling of two dipeptides.

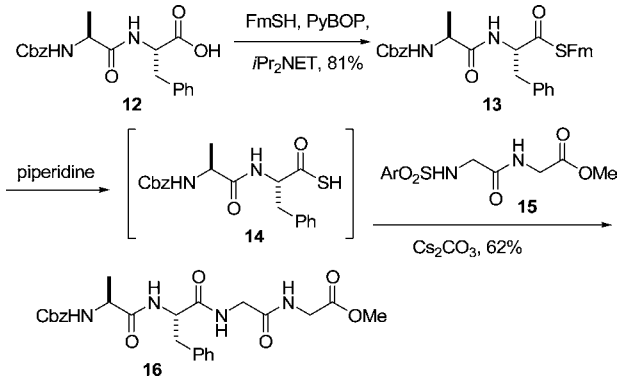
The method is also adaptable to neoglycoconjugate[5i,13] synthesis. Thus, reaction of *N*-(2,4-dinitrobenzenesulfonyl)-ethanolamine[14] with peracetyl glucopyranose, galactopyra-

(10) Protection of thiols as 9-fluorenylmethyl ethers: (a) Garcia-Echeverria, C.; Molins, M. A.; Albericio, F.; Pons, M.; Giralt, E. *Int. J. Peptide Protein Res.* **1990**, *35*, 434−440. (b) Gu, X.; Ying, J.; Agnes, R. S.; Navratilova, E.; Davis, P.; Stahl, G.; Porreca, F.; Yamamura, H. I.; Hruby, V. J. *Org. Lett.* **2004**, *6*, 3285−3288.

(11) Consistent with the early literature[9] on the reaction of amino thioacids with amino acids no coupling was observed when the thioacid obtained by deprotection of thioester **2** was stirred in DMF at room temperature with phenylalanine methyl ester in the presence of cesium carbonate, clearly indicating the need for the sulfonamide in this chemistry.

(12) Within the limits of detection by 500 MHz NMR spectroscopy.

Scheme 3. Tetrapeptide Formation



nose, and cellobiose in the presence of tin(IV) chloride gave the functionalized sulfonamides **17**−**19** in good yield as the β-anomers (Table 2). A further series of amino acid-based thioacids **20**−**22** were prepared from the corresponding *N*-hydroxysuccinimide esters by reaction with sodium hydrogen sulfide (Table 2).[15] Coupling of sulfonamides **17**−**19** with thioacids **20**−**22** under the standard conditions then gave the neoglycoconjugates **24**−**29** (Table 2).

In summary, we present a facile method for the formation of peptide bonds and amide-derived neoglycoconjugates that is based on the reaction of thioacids with readily available 2,4-dinitrobenzenesulfonamides. The precursors are easy to prepare, and the coupling reaction takes place under mild conditions at room temperature and is compatible with typical amino acid protecting groups. The further investigation of this methodology is currently under investigation in our laboratory.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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