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Cyclic Thioanhydrides: Linchpins for Multicomponent Coupling Reactions Based on the Reaction of Thioacids with Electron-Deficient Sulfonamides and Azides

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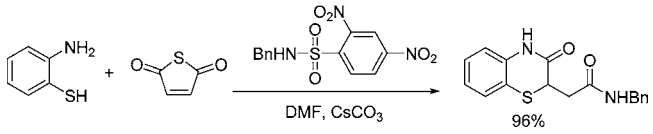
ABSTRACT



Reaction of cyclic thioanhydrides with amines affords amides functionalized with thioacids, which can be trapped in situ with electron-deficient azides or, preferably, 2,4-dinitrobenzenesulfonamides. In this manner the cyclic thioanhydride serves as a linchpin in a three-component coupling sequence. The use of thiomaleic anhydride and a bifunctional nucleophile extends the process to heterocycle synthesis, while a cyclic thioanhydride prepared from aspartic acid directly provides N-functionalized asparagine derivatives.

Thioacids are useful intermediates in organic synthesis,[1] having found application in peptide synthesis,[2] and as precursors to thioesters for native chemical ligation.[3] Their long-established reaction with azides yields secondary amides and has recently come to the fore as a versatile ligation reaction,[4] while their complementary reaction with 2,4-dinitrobenzenesulfonamides[5] has been much less widely applied. The relatively limited application of these useful coupling reactions can be ascribed, at least in part, to the need to prepare all but the simplest thioacids. We conceived that this hurdle could be overcome through the nucleophilic ring-opening of cyclic thioanhydrides with the in situ

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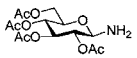
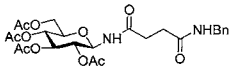
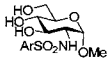
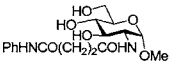
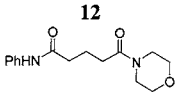
Table 1. Three-Component Coupling of Cyclic Thioanhydrides with Amines and 2,4-Dinitrobenzenesulfonamides

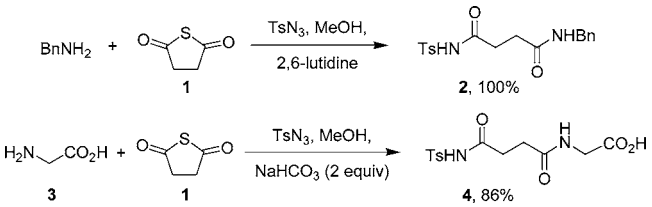
entry	thioanhydride	amine	sulfonamide[a]	product	solvent	Yield (%)[b]
1	**1**	$PhNH_2$	$BnNHSO_2Ar$	$PhNHCO(CH_2)_2CONHBn$, **5**	DMF	100
2	**1**	$PhNH_2$	$BnNHSO_2Ar$	**5**	MeOH	85
3	**1**	$BnNH_2$	$PhNHSO_2Ar$	**5**	DMF	42
4	**1**	 **6**	$BnNHSO_2Ar$	 **7**	DMF	69
5	**1**	$PhNH_2$	 **8**	 **9**	DMF	77
6	**1**	$PhNH_2$	**8**	**9**	MeOH	84
7	 **10**	$PhNH_2$	 **11**	 **12**	DMF	85
8	 **13**	$PhNH_2$	**11**	 **14**	DMF	90

[a] Ar = 2,4-dinitrophenyl. [b] Conditions: i) 1.2 equiv thioanhydride, 1 equiv amine, DMF, 30 min; ii) 1 equiv $CsCO_3$, 1 equiv sulfonamide, DMF 1 h.

generation of a thioacid for use in a coupling reaction. Limited precedent is provided by the opening of thiosuccinic anhydride with amines with subsequent trapping of the thioacid with benzyl bromide, providing a thiolester for later use in native chemical ligation.[6] Success, coupled with the facile synthesis and stability of cyclic thioanhydrides, should provide a new entry into multicomponent coupling reactions.[7]

In a first demonstration of this type commercial thiosuccinic anhydride[8] was treated with benzylamine in methanol at room temperature, followed by the addition of tosyl azide and 2,6-lutidine, leading to the isolation of the dissymmetric succinamide **2** in quantitative yield (Scheme 1). A second

Scheme 1. Three-Component Coupling of Amines, Cyclic Thioanhydrides, and Sulfonyl Azides



example employed free glycine as the initiating nucleophile and also proceeded in excellent yield (Scheme 1).

In general, however, we have preferred to complete our sequences by trapping the thioacids with the versatile 2,4-dinitrobenzenesulfonamides due to their greater versatility,[9] and the potential for synthesis of tertiary amides. Table 1 presents a series of examples conducted in this three-component manner, each of which afforded excellent yields of the products. All reactions in Table 1 were conducted under ambient temperature conditions by addition of the nucleophilic amine to the cyclic thioanhydride, followed by addition of the sulfonamide and a mild base; the overall reaction time, including workup, is less than 2 h. The reaction sequence is not restricted to the opening of five-membered cyclic thioanhydrides but is also suitable for thiomalonic anhydride and thioglutaric anhydride (Table 1, entries 7 and 8) and presumably larger ring sizes, many of which are very readily prepared.[8] The functional group compatibility of the method is highlighted by the use of carbohydrate-based amines either as the nucleophile (Table 1, entry 4) or in the form of the sequence-terminating sulfonamide (Table 1, entries 5 and 6). In particular the absence of protecting groups in the latter example is stressed; compatibility with alcohols is further highlighted by the use of methanol as solvent. The use of the morpholine sulfonamide in entries 7 and 8 of Table 1 leads to the formation of tertiary amides, marking the clear difference between the azide-based chemistry and the sulfonamide route.

A further extension of this new multicomponent-coupling sequence is highlighted by the reaction of thiomaleic anhydride with a bifunctional nucleophile. In this chemistry the softer thiol first undergoes Michael addition to the electrophile, and this is followed by cyclization of the amine onto the thioanhydride moiety. The overall sequence, which results in the formation of a functionalized benzothiazinone, is completed by trapping the thioacid with a sulfonamide (Scheme 2), and the only byproduct is 2,4-dinitrobenzenethiol. We anticipate that similar heterocycle-forming

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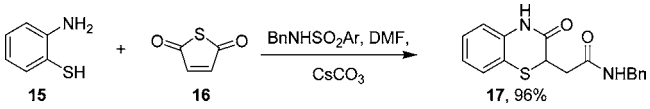
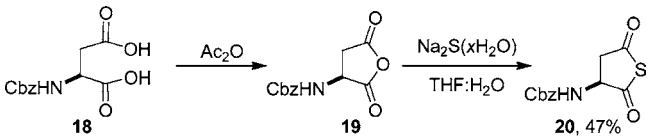
Scheme 2. Three-Component Heterocycle Synthesis



systems will be available from the employment of other bifunctional nucleophiles in this sequence.

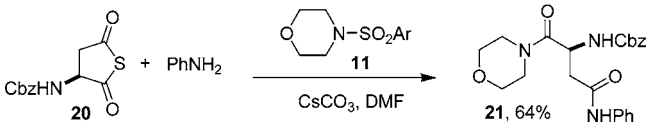
Next, we turned to the potential of more highly functionalized cyclic thioanhydrides and, in particular, ones derived from aspartic acid. Treatment of *N*-Cbz-L-aspartic anhydride with Na_2S, according to the procedure of Kates and Schauble, gave **20** in 47% yield (Scheme 3).

Scheme 3. Synthesis of *N*-Cbz-Thioaspartic Anhydride



Treatment of **20** with aniline in DMF followed by trapping of the intermediate thioacid with the morpholine sulfonamide gave the fully functionalized aspartamide **21** in 63% yield as a single regioisomer (Scheme 4), which was confirmed

Scheme 4. Synthesis of a Fully Functionalized Asparagine Amide



on the basis of HMBC correlations. When the reaction was conducted in benzene as solvent, a regioisomeric mixture of products was formed in the ratio of 2.5:1 favoring **21**.[10]

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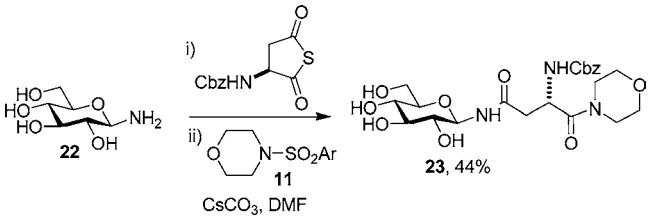
Reaction of **20** with 1-glucosamine followed by trapping with the morpholine sulfonamide gave the *N*-glucosyl asparagine derivative **23** in 44% yield (Scheme 5). The

Scheme 5. Synthesis of a *N*-Glucosyl Asparagine Derivative



isolation of a single diastereomer confirms the enantiomeric purity of the thioaspartic anhydride starting material. This last example opens the way to a new method for glycopeptide synthesis with minimal use of protecting groups; further investigations, aimed at optimization of the reaction substrates and conditions, are in progress.[11,12]

In conclusion, the reaction of readily available cyclic thioanhydrides with amines and then 2,4-dinitrobenzenesulfonamides represents a very efficient multicomponent-coupling sequence employing the cyclic thioanhydride as linchpin. The use of unsaturated cyclic thioanhydrides and bifunctional nucleophiles opens up the possibility of multicomponent-heterocycle synthesis, while amino acid-based cyclic thioanhydrides have the potential to serve as linchpins in the convergent synthesis of glycopeptides.

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

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