JOC Article

One-Pot Syntheses of Dissymmetric Diamides Based on the Chemistry of Cyclic Monothioanhydrides. Scope and Limitations and Application to the Synthesis of Glycodipeptides

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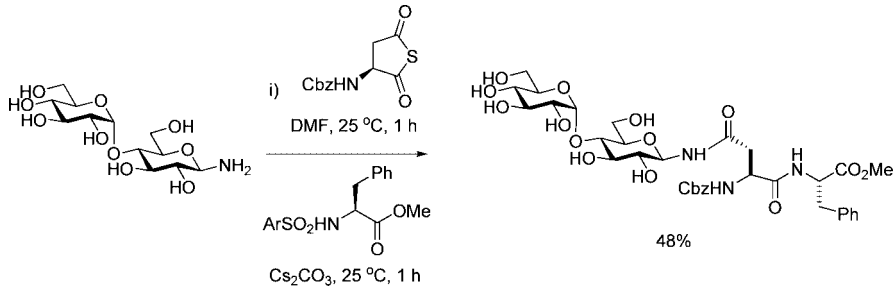

Opening cyclic monothioanhydrides by amines provides a convenient entry into amido thioacids that can be trapped in situ by 2,4-dinitrobenzenesulfonamides, by electron-deficient azides, or by amines in the presence of Sanger's reagent leading, in each case, to dissymmetric diamides in what can be considered a one-pot, three-component coupling sequence. The use of monothiomaleic anhydride and bifunctional nucleophiles such as amino thiols provides access to heterocyclic amides. The low reactivity of cyclic monothioanhydrides toward alcohols enables the use of methanol as solvent and obviates the need for the protection of alcohols in the various reaction components. Reaction of *N*-benzyloxycarbonyl-L-aspartic monothioanhydride with unprotected glycosyl amines, followed by capture of the thioacid intermediate with *N*-sulfonyl amino acid derivatives results in a three-component convergent synthesis of glycosylated peptides.

Introduction

Monothiocarboxylic acids [R−C(═O)−SH][1] have an interesting and varied chemistry,[2] some of the more fascinating aspects of which pertain to their use in amide bond forming reactions. Such amide bond forming reactions include the direct coupling of thioacids with amines,[3] their condensation with azides,[4] their condensation with electron-deficient sulfonamides,

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again leading to amides,[5] their use as precursors to thioesters for native chemical ligation,[6] and their application as components of Ugi-type reactions leading to thioamides.[7] Monoselenocarboxylic acids undergo analogous reactions,[8] as do dithioacids albeit with the provision of thioamides in the latter case.[5a,b,9] Despite the obvious utility of this broad range of chemistry thioacids have found relatively little application in organic synthesis, perhaps due to the very limited range of commercially available thioacids and the consequent need to prepare all but the simplest members of the family.

Cyclic monthioanhydrides are a group of readily prepared thioacid derivatives[10] that exhibit a considerable range of interesting chemistry,[10c,11] but which are also underemployed in organic synthesis. We reasoned that perhaps the simplest of reactions of cyclic monothioanhydrides, their ring-opening with competent nucleophiles, would provide a facile, practical means of generation of thioacids for subsequent use within the one reaction pot, thereby affording a series of multicomponent coupling reactions,[12] by the union of two underappreciated functional groups. Dervan and co-workers had previously studied the ring-opening of monothiosuccinic anhydride with amines, coupled with subsequent alkylation by benzyl bromide to give a thioester for eventual use in native chemical ligation,[13] but as we outlined previously[14] and set out here in full, this simple trick has a much broader scope when the range of easily prepared cyclic monothioanhydrides and the breadth of thioacid chemistry is taken into consideration.

Results and Discussion

Saturated Monothio Anhydrides. We first investigated the reaction of commercially available monothiosuccinic anhydride, studying ring-opening with the relatively modest nucleophile, aniline, and subsequent capture of the resulting thioacid with *N*-benzyl 2,4-dinitrobenzenesulfonamide (Table 1, entries 1 and 2).[15] This reaction sequence worked extremely well at room temperature both in DMF and, more surprisingly at first, in methanol indicating the monothioanhydride to be more reactive toward an approximately stoichiometric amount of aniline than to the bulk solvent, methanol. When aniline was replaced by benzylamine as nucleophile and the *N*-phenyl 2,4-dinitrobenzenesulfonamide employed as a trap for the thioacid, leading overall to the same bisamide **2** (Table 1, entry 3), a notable drop in yield was observed. This is attributed to the weaker nucleophilicity of the aniline released on reaction of the thioacid with the sulfonamide and its consequent slower reaction with the activated thioacid generated in this step. The ability of a relatively modest nucleophile to function in the first step of the protocol is, however, underlined by entry 4 of Table 1, which illustrates how this chemistry may be directed toward glycoconjugate synthesis. With the tetra-*O*-acetyl derivative of glucosamine as the nucleophile the ring-opening is much more difficult, perhaps owing to the electron-withdrawing effect of the esters reducing the nucelophilicity of the already only weakly nucelophilic glucosylamine (Table 1, entry 5).[16] Entry 6 of Table 1 illustrates the employment of 1-glucosamine[17] as the initiating nucleophile, with ultimate capture of the thioacid by an amino acid-based sulfonamide, leading overall to a simple neoglyco conjugate,[18] while entry 7 (Table 1) extends the concept to the use of an amino deoxy sugar as the first nucleophile. Table 1 (entries 8 and 9) serves to illustrate how an aminoglycoside[19]based sulfonamide may be productively employed as the third coupling partner in this three-component sequence, whether in DMF or in methanol as solvent. Self-evidently, given the established compatibility with methanol, the lack of protecting groups on this sulfonamide was not detrimental to the overall process. In entry 10 of Table 1 both the first and third reaction partners are carbohydrate-derived, with the use of 2-acetylamino-2-deoxy-1-glucosamine **13** being particularly noteworthy,[20] while in entry 11 the union between an amino acid and a carbohydrate is again established, this time with the amino acid initiating the cascade and a sugar-based sulfonamide serving to capture the intermediate thioacid. The final two entries of Table 1 demonstrate the extension of this chemistry beyond the commercially available monothiosuccinic anhydride to readily prepared malonic and adipic analogues, giving rise to 1,3- and 1,5-bisamides, respectively. The last two examples of Table 1 also feature the use of an *N*-sulfonyl morpholine derivative, resulting in the inclusion of tertiary amide units in the final three-component coupled products.

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(15) All sulfonamides employed herein were prepared from the amine by reaction with 2,4-dinitrobenzenesulfonyl chloride; see the Supporting Information for details.

(16) In our preliminary communication[14] we reported a yield of 69% for this reaction but we have been unable to reproduce this yield despite considerable effort. Acetylation of the desacetyl compound **4** gave an authentic sample of **6** whose spectra were in every way consistent with those provided in the supporting information to the original communication[14] (see the Supporting Information), forcing us to the conclusion that the original result was obtained with the assistance of an unknown catalyst perhaps present as an impurity in either the nucleophile or the thiosuccinic anhydride employed. Efforts are continuing toward the resolution of this issue.

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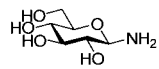
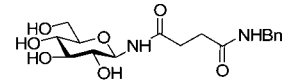
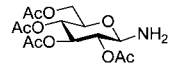
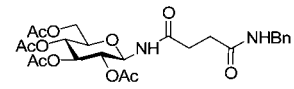
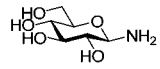
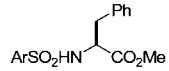
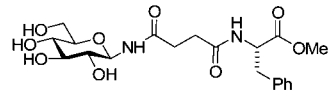
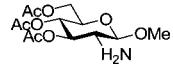
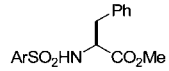
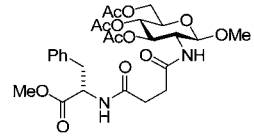
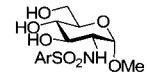
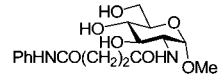
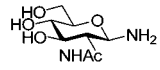
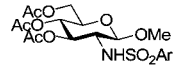
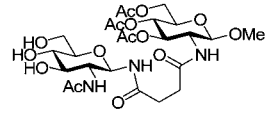
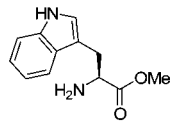
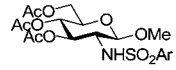
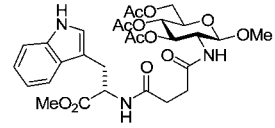
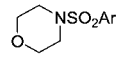
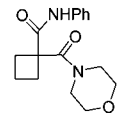
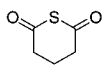
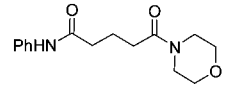
TABLE 1. Three-Component Coupling of Cyclic Thioanhydrides with Amines and 2,4-Dinitrobenzenesulfonamides

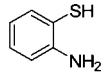
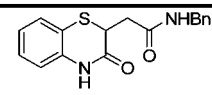
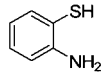
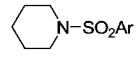
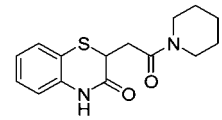
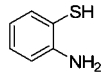
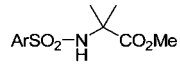
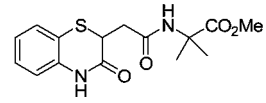
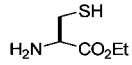
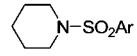
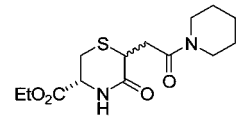
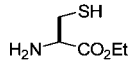
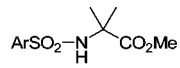
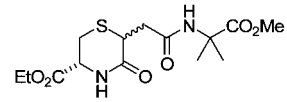
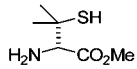
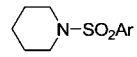
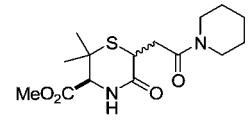
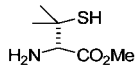
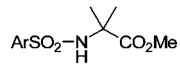
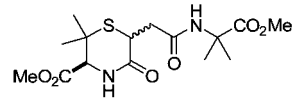
entry	thioanhydride	amine	sulfonamide[a]	product	solvent	yield (%)[b]
1	**1**	$PhNH_2$	$BnNHSO_2Ar$	$PhNHCO(CH_2)_2CONHBn$, **2**	DMF	100
2	**1**	$PhNH_2$	$BnNHSO_2Ar$	**2**	MeOH	85
3	**1**	$BnNH_2$	$PhNHSO_2Ar$	**2**	DMF	42
4[c]	**1**	 **3**	$BnNHSO_2Ar$	 **4**	DMF	63
5	**1**	 **5**	$BnNHSO_2Ar$	 **6**	DMF	5-10
6[c]	**1**	 **3**	 **7**	 **8**	DMF	66
7	**1**	 **9**	 **7**	 **10**	DMF	90
8	**1**	$PhNH_2$	 **11**	 **12**	DMF	77
9	**1**	$PhNH_2$	**11**	**12**	MeOH	84
10[c]	**1**	 **13**	 **14**	 **15**	DMF	43
11	**1**	 **16**	 **14**	 **17**	DMF	58
12	 **18**	$PhNH_2$	 **19**	 **20**	DMF	85
13	 **21**	$PhNH_2$	**19**	 **22**	DMF	90

[a] Ar = 2,4-dinitrophenyl. [b] Conditions: (i) 1−1.2 equiv of thioanhydride, 1 equiv of amine, DMF, 30 min; (ii) 1 equiv of Cs_2CO_3, 1 equiv of sulfonamide, DMF 1 h. [c] $CsHCO_3$ was the base in this reaction.

Thiomaleic Anhydride. Subsequently, we turned our attention to monothiomaleic anhydride, for which several preparations are available with the optimal in our hands being reaction of the maleic anhydride/furan cycloadduct with sodium sulfide,[10b] followed by retro Diels−Alder reaction and concomitant distillation of the product. In extending the basic concept to monothiomaleic anhydride we anticipated that vicinal aminothiols would undergo reaction first by conjugate addition of the softer, more nucelophilic thiol, and that this would be followed up by cyclization of the amine onto the thioanhydride moiety. The viability of this concept is evident from entries 1−3 of Table 2, in which 2-mercaptoaniline is employed as the doubly nucleophilic first reaction component. Particularly noteworthy here is the use of the piperidine sulfonamide **24** and of the α-aminoisobutyric acid-derived sulfonamide **26** (Table 2, entries 2 and 3) leading to the formation of a tertiary and a somewhat hindered amide bond, respectively. The remaining four examples of Table 2 illustrate the use of L-cysteine and D-penicillamine derivates as the initial reaction partner. These four reactions, in which a second stereogenic center was generated, were moderately diastereoselective providing in each case an approximately 3:1 mixture of epimers favoring the cis-isomers as determined by NOE studies.

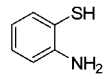
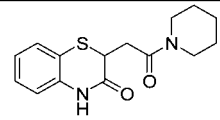
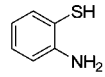
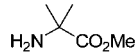
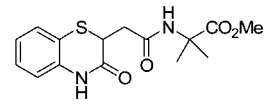
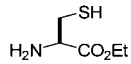
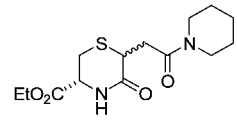
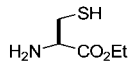
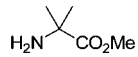
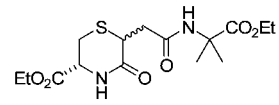
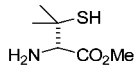
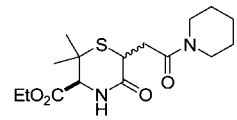
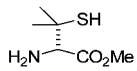
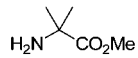
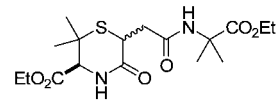
[4+2]-Cycloaddition of thiomaleic anhydride with 2-*tert*-butyloxycarbamoylmethylfuran **34** afforded the cycloadduct **35** in 68% yield, as a single diastereoisomer, after 4 days at room temperature in benzene. Hydrogenation over Raney nickel, as described by Dauben et al. for the adduct with furan itself,[21] afforded the dihydro analogue **36** in 94% yield, whose exo-stereochemistry was readily ascertained by NOE measurements, thereby confirming the stereochemistry of the initial adduct (Scheme 1). Both **35** and **36**, on treatment with trifluoroacetic acid followed by collidine, underwent the anticipated cyclization with generation of a thioacid that was immediately captured

TABLE 2. Three-Component Coupling of Thiomaleic Anhydrides with Aminothiols and 2,4-Dinitrobenzenesulfonamides

entry	aminothiol	sulfonamide[a]	product (% yield, cis:trans)[b]
1		$BnNHSO_2Ar$	 **23** (96)
2		 **24**	 **25** (59)
3		 **26**	 **27** (67)
4	 **28**	 **24**	 **29** (72, 3:1)
5	 **28**	 **26**	 **30** (63, 3:1)
6	 **31**	 **24**	 **32** (53, 3:1)
7	 **31**	 **26**	 **33** (41, 3:1)

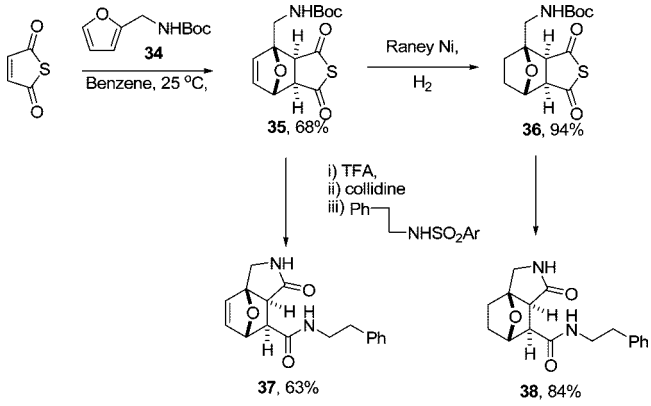
[a] Ar = 2,4-dinitrophenyl. [b] Conditions: (i) 1.2 equiv of thioanhydride, 1 equiv of aminothiol, DMF; (ii) 1.2 equiv of Cs_2CO_3, 1 equiv of sulfonamide, DMF 3 h.

TABLE 3. Three-Component Coupling of Thiomaleic Anhydrides with Aminothiols and Amines Promoted by Sanger's Reagent

entry	aminothiol	amine	product (% yield, cis:trans)[a]
1			 **25** (51)
2			 **27** (53)
3			 **29** (65, 3:1)
4			 **30** (70, 3:1)
5			 **32** (46, 3:1)
6			 **33** (53, 3:1)

[a] Conditions: (i) 1.2 equiv of thioanhydride, 1 equiv of aminothiol, DMF; (ii) 1.2 equiv of Cs_2CO_3, 1 equiv of Sanger's reagent, 1 equiv of amine, DMF 3 h.

SCHEME 1. Intramolecular Ring-Opening of Cyclic Thioanhydrides Generated by Diels−Alder Reaction



with a 2,4-dinitrobenzenesulfonamide leading, overall, to **37** and **38** in 84% and 63% yield, respectively (Scheme 1).

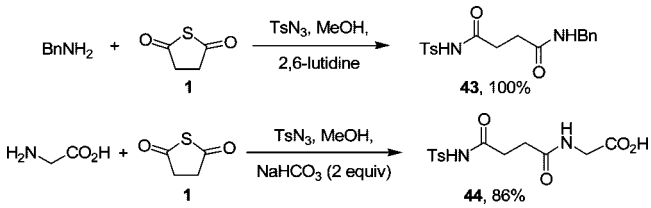
Thioacid Capture by Other Electrophilic Species. The mechanism of the condensation of thioacids with 2,4-dinitrobenzenesulfonamides involves nucleophilic aromatic substitution of the sulfonamide by the thioacid, giving a *S*-(2,4-dinitrophenyl) thioester and a free amine, which then react to give the final amide.[5c,7] On this basis, as we have established elsewhere in the course of work directed at the synthesis of peptides, the sulfonamide may be productively replaced by a simple amine and either Sanger's reagent (2,4-dinitrofluorobenzene), its iodo analogue, or Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide),[22] and doubtless other electron-deficient arenes capable of undergoing nucleophilic aromatic substitution. The proof of this was established by the reaction of vicinal aminothiols with monothiomaleic anhydride followed by the addition of Sanger's reagent and a second amine, as illustrated in Table 3.

Although we have not made an extensive study, the thioacid may also be productively trapped by electron-deficient azides according to the Williams and Liskamp protocol,[4] as illustrated by the two examples of Scheme 2. Particularly noteworthy here is the illustration of the use of an unprotected amino acid as the nucleophile initiating the entire sequence.

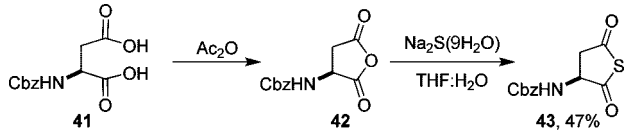
(21) Kawamura, N.; Li, Y. M.; Engel, J. L.; Dauben, W. G.; Casida, J. E. *Chem. Res. Toxicol.* **1990**, *3*, 318–324.

(22) Crich, D.; Sharma, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 2355–2358.

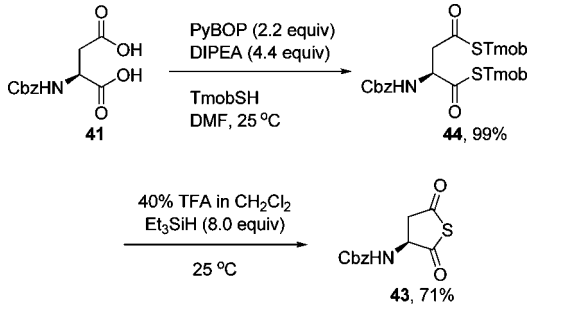
SCHEME 2. Nucleophilic Ring-Opening of Thiosuccinic Anhydride with Subsequent Thioacid Capture by *p*-Toluenesulfonyl Azide



SCHEME 3. First-Generation Synthesis of a Thioaspartic Anhydride



SCHEME 4. Second-Generation Synthesis of a Thioaspartic Anhydride



Glycopeptide Synthesis. An intriguing facet of this chemistry was the possibility of extending it to unsymmetrically substituted monothioanhydrides, particularly those based on aspartic acid. Toward this end, *N*-benzyloxycarbonyl-L-aspartic acid **41** was converted to the known cyclic anhydride **42** by heating with acetic anhydride according to a literature protocol,[23] followed by reaction with sodium sulfide[10b] (Scheme 3). Although this last step results only in an isolated yield of 47% of the cyclic thioanhydride **43**, it has to be remembered that this is close to the theoretical 50% owing to the consumption of half of the initial anhydride as dehydrating reagent for the intermediate monothio diacid.

An improved synthesis of the thioaspartic anhydride **43**, based on the literature observation[24] that aspartic and glutamic monothioesters undergo facile cyclization to anhydrides, involved activation of *N*-benzyloxycarbonyl-L-aspartic acid with the PyBOP reagent, under the Kajihara conditions for nonracemizing synthesis of thioesters at the C-terminus of peptides,[25] in the presence of 2,4,6-trimethyloxybenzylthiol (TmobSH)[26] to give the bisthioester **44** in essentially quantitative yield (Scheme 4). Treatment with trifluoroacetic acid in the presence of triethylsilane as cation scavenger then gave the desired cyclic thioanhydride in 71% isolated yield, by a process involving the liberation of a first thioacid and its cyclization onto the remaining thioester.

Reaction of *N*-Cbz-monothioaspartic anhydride **43** with aniline in DMF followed by addition of the *N*-sulfonyl morpholine derivative **19** led to the isolation of the asparagines derivative **45** in 48% isolated yield as a single regioisomer (Table 4, entry 1). No evidence was found by NMR spectroscopy for the formation of a second regioisomer in the crude reaction mixture. Subsequently, 1-glucosylamine **3** was allowed to react with the monothioaspartic anhydride, followed by trapping of the thioacid with the morpholine-based sulfonamide resulting in the formation of a *N*-glycosyl asparagine derivative **46** in 44% yield (Table 4, entry 2). Gratifyingly, this chemistry could be extended to the use of an amino acid-based sulfonamide **7**, thereby coupling the introduction of the *N*-glycosyl asparagines unit with the formation of a peptide bond (Table 4, entry 3). Moreover, β-cellobiosylamine[27] **48** and β-maltosylamine[28] **50** also served as productive nucleophiles in this chemistry (Table 4, entries 4 and 5). The ability to conduct this chemistry with unprotected glycosylamines is stressed. It should also be noted that the isolation of the various products in this table as single diastereomers indicates not only a very high degree of regioselectivity in the initial ring-opening reaction, but also the absence of racemization both in the formation and the reaction of the monothioaspartic anhydride. Unfortunately, we have been unable so far to translate this chemistry to 2-acetamido-2-deoxyglucosylamine derivates as nucleophiles.

The regioselectivity of the reactions presented in Table 4 was predicted on the basis of the known reactivity of the corresponding carboxylic anhydride, which was known to undergo preferential nucelophilic attack at the γ-carbon in the polar solvent DMSO, but at the α-carbon in the nonpolar solvent benzene, with aniline as nucleophile.[23b] The regiochemistry of the initial attack of aniline on the monothioanhydride is supported by a strong HMBC correlation of the anilide NH to the γ-carbonyl carbon. For proof of the rather more important cases of the formation of the *N*-glycosylasparagine derivatives, we resorted to unambiguous synthesis of authentic samples, as set out in Scheme 5 starting from the known γ-allyl aspartate derivative **52**,[29] passing through the known dipeptide **54**,[30] and resulting in the formation of samples that were chromatographically and spectroscopically homogeneous with those obtained in Table 4. In addition to establishing firmly the regiochemistry of the ring-opening reaction in DMF as solvent the somewhat longer authentic syntheses highlight the efficiency of the monothioanhydride protocol for the preparation of this class of compounds.

In a more general sense unsymmetrically substituted succinic anhydrides frequently undergo preferential attack at the carbonyl group adjacent to the least substituted carbon. Thus, for example, 2,2-dimethylsuccinic anhydride undergoes reaction with organonickel reagents[31] and phosphorus ylides[32] with a significant preference for reaction at the carbonyl group distal to the quaternary center. On the other hand metal hydride reduction of 2,2-dimethylsuccinic anhydride takes place predominantly

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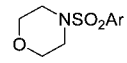
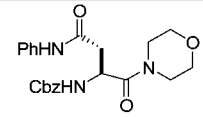
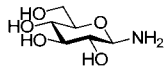
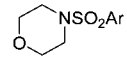
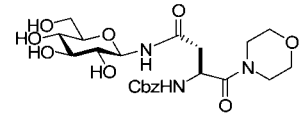
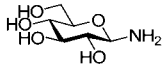
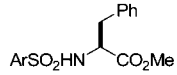
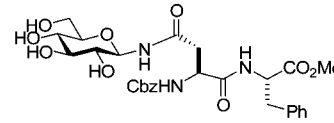
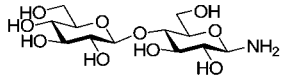
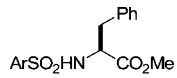
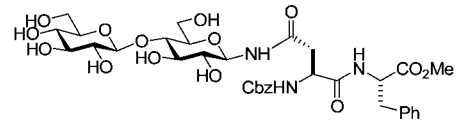
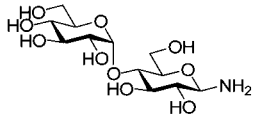
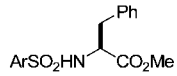
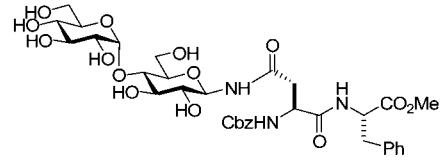
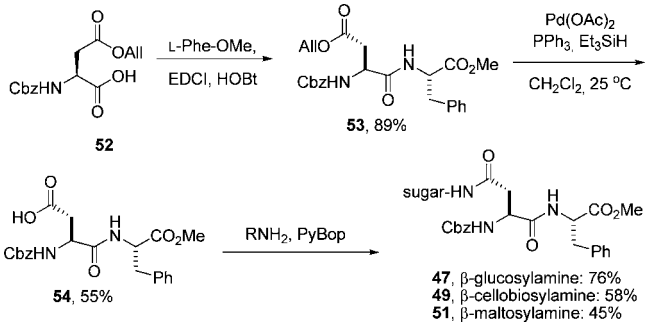
TABLE 4. Three-Component Coupling Centered on Monothioaspartic Anhydride

entry	amine	sulfonamide[a]	product (% yield)[b]
1	$PhNH_2$	 **19**	 **45** (48)
2	 **3**	 **19**	 **46** (44)
3	 **3**	 **7**	 **47** (51)
4	 **48**	 **7**	 **49** (50)
5	 **50**	 **7**	 **51** (48)

[a] Ar = 2,4-dinitrophenyl. [b] Conditions: (i) 1 equiv of thioanhydride, 1 equiv of amine, DMF, 30 min; (ii) 1 equiv of Cs_2CO_3, 1 equiv of sulfonamide, DMF 1 h.

SCHEME 5. Synthesis of Authentic Glycopeptide Samples



α to the quaternary center,[33] something that it has in common with the 2,2-dimethylsuccinimides.[34]

Presumably, the regioselectivity of these reactions for the simple aspartic anhydrides reported in the literature and the monothioanhydride described here, with preferential nucleophilic attack at the γ-center in polar solvents, is due to simple hydrogen bonding of the carbamate group to the solvent thereby significantly hindering access to the α-position. Self-evidently, and unlike the case of 2,2-dimethylsuccinic anhydride and the corresponding succinimdes the Burgi−Dunitz approach vector is only blocked by the solvated carbamate group on a single face of the molecule leaving the second open for productive interaction.

Experimental Section

General Procedure for Multicomponent Coupling Reaction in Table 1. The reactions in Table 1 were carried out as follows unless particular conditions were specified. To a stirred solution of thioanhydride (∼1.0 mmol, 1.2 equiv) in DMF (∼1 mL; ∼1 M in thioanydride) was added 1.0 equiv of amine (∼0.8 mmol) in an equal volume of DMF (∼1 mL) at room temperature. The reaction mixture was allowed to stir for 30 min to 1 h, after which time the color of the reaction had turned a faint yellow. Cs_2CO_3 (1.0 equiv) was added followed immediately by 1.0 equiv of sulfonamide. Upon addition of the sulfonamide the reaction mixture became dark red, which further deepened as the reaction continued. The reaction mixture was allowed to stir ∼1 h, after which the DMF was removed under high vacuum and the crude mixture was dissolved in EtOAc and washed with $NaHCO_3$ and brine and dried over Na_2SO_4. Evaporation of the solvent, followed by column chromatography provided the diamide products in the yields described below. When the products were water-soluble the extraction was omitted and the crude mixture submitted directly to chromatography after the removal of DMF.

Methyl 2-Amino-2-deoxy-*N*-(*N*-phenylsuccinamyl)-α-D-glucopyranoside (12). Pale yellow oil. $[\alpha]^{24}_D$ +64.8 (*c* 0.8, CH_3OH).

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^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 7.51−7.54 (m, 2H), 7.26−7.30 (m, 2H), 7.06 (t, J = 7.0 Hz, 1H), 4.64 (d, J = 3.0 Hz, 1H), 3.90−3.95 (m, 1H), 3.82 (dd, J = 3.0, 12.5 Hz, 1H), 3.64−3.70 (m, 2H), 3.52−3.56 (m, 1H), 3.34−3.37 (m, 4H), 2.65−2.70 (m, 2H), 2.60−2.63 (m, 2H). ^{13}C NMR (125.9 MHz, $CDCl_3/CD_3OD$) δ 173.8, 171.7, 138.5, 128.4, 123.7, 119.8, 98.5, 72.3, 71.7, 70.8, 61.3, 54.2, 54.0, 31.7, 30.5. ESIHRMS: *m/z* calcd for $C_{17}H_{24}N_2O_7$ $(M + Na)^+$ 391.14760, found 391.14741.

Method A: General Procedure for Three-Component Coupling of Thiomaleic Anhydrides with Aminothiols and 2,4-Dinitrobenzenesulfonamides (Table 2). Aminothiol (0.41 mmol, 1.0 equiv) was added to a stirred solution of maleic thioanhydride (0.5 mmol, 1.2 equiv) in 1 mL of DMF at 0 °C. The reaction mixture turned purple and further deepened in color as it was warmed to room temperature. The reaction mixture was allowed to stir for 1 h then cooled to 0 °C and Cs_2CO_3 (0.5 mmol, 1.2 equiv) was added, followed immediately by the sulfonamide (0.4 mmol, 1.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for a further 3 h. The solvent was then removed under vacuum and the crude reaction mixture was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ solution followed by brine, and dried over Na_2SO_4. The product was purified by silica gel column chromatography.

2-(2,3-Dihydrobenzo-1,4-thiazin-3-on-2-yl)acetylpiperidine (25). Chromatographic purification eluting with 70% EtOAc/hexanes afforded a light yellow oil in 59% yield (method A) or 51% yield (method B, which employed 2.0 equiv of Cs_2CO_3 instead of 1.2 equiv to liberate amine from the corresponding hydrochloride salt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 7.29 (dd, J = 1.6, 8 Hz, 1H), 7.15 (dt, J = 1.6, 9 Hz, 1H), 6.99 (dt, J = 1.6, 7.4 Hz, 1H), 6.89 (dd, J = 1.6, 8 Hz, 1H), 4.19 (dd, J = 4.8, 8 Hz, 1H), 3.65−3.50 (m, 2H), 3.41−3.32 (m, 2H), 3.10 (dd, J = 4.8, 16 Hz, 1H), 2.57 (dd, J = 8, 16 Hz, 1H), 1.67−1.58 (m, 2H), 1.58−1.52 (m, 4H). ^{13}C NMR (100 MHz, CDCl3) δ 168.0, 167.3, 136.2, 128.2, 127.4, 124.0, 120.0, 117.3, 46.8, 43.4, 38.5, 32.6, 26.6, 25.7, 24.7. ESIHRMS: *m/z* calcd for $C_{15}H_{18}N_2O_2S$ $(M + Na)^+$ 313.0987, found 313.0995.

Method B: General Procedure for Three-Component Coupling of Thiomaleic Anhydrides with Aminothiols and Amines Promoted by Sanger's Reagent (Table 3). Aminothiol (0.4 mmol, 1.0 equiv) was added to a stirred solution of maleic thioanhydride (0.5 mmol, 1.2 equiv) in 1 mL of DMF at 0 °C. The reaction mixture turned purple, and further deepened in color as it was warmed to room temperature. The reaction mixture was allowed to stir for 1 h and cooled to 0 °C then (0.5 mmol, 1.2 equiv) Cs_2CO_3 was added, followed immediately by Sanger's reagent (1-fluoro-2,4-dinitrobenzene) (0.4 mmol, 1.0 equiv). The reaction mixture was allowed to warm to room temperature and then was stirred for 5 min before the amine (0.4 mmol, 1.0 equiv) was added and stirring continued for 3 h. The solvent was then removed under vacuum and the crude reaction mixture was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ solution followed by brine, and dried over Na_2SO_4. The product was purified by silica gel column chromatography.

***N*-(1-Ethoxycarbonyl-1-methylethyl) 2-(5-Ethoxycarbonyl-2,3,5,6-tetrahydro-1,4-thiazin-3-on-2-yl)acetamide (30).** Chromatographic purification eluting with 3% methanol in dichloromethane afforded a light yellow oil in 63% yield (method A) or 70% yield (method B, with 2.0 equiv of Cs_2CO_3 instead of 1.2 equiv to liberate the amine from the corresponding hydrochloride salt) with 3:1 cis/trans selectivity. Cis: $[\alpha]^{24}_D$ +28.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (br s, 1H), 6.44 (br s, 1H), 4.34−4.24 (m, 3H), 3.94 (t, J = 6.4 Hz, 1H), 3.72 (s, 3H), 3.27 (dd, J = 4, 12 Hz, 1H), 3.00−2.90 (m, 2H), 2.41 (dd, J = 5.6, 15.8 Hz, 1H), 1.53 (s, 6H), 1.30 (t, J = 7.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 169.8, 169.2, 168.9, 62.9, 56.8, 55.4, 52.8, 37.9, 37.6, 29.9, 24.9, 14.3. ESIHRMS: *m/z* calcd for $C_{14}H_{22}N_2O_6S$ $(M + Na)^+$ 369.1096, found 369.1103. Trans: $[\alpha]^{24}_D$ −19.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (br s, 1H), 6.30 (br s, 1H), 4.44−4.40 (m, 1H), 4.26 (q, J = 6.8 Hz, 2H), 3.89 (t, J = 6 Hz, 1H), 3.73 (s, 3H), 3.18 (dd, J = 4, 13.6 Hz, 1H), 3.00 (dd, J = 9, 13.8 Hz, 1H), 2.91 (dd, J = 5.6, 15.6 Hz, 1H), 2.60 (dd, J = 6.4, 14.8 Hz, 1H), 1.54 (s, 6H), 1.30 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 169.0, 62.7, 58.0, 56.8, 52.9, 39.1, 28.2, 24.9, 24.9, 14.3. ESIHRMS: *m/z* calcd for $C_{14}H_{22}N_2O_6S$ (M + Na)$^+$ 369.1096, found 369.1107.

***N*-Benzyloxycarbonyl-L-aspartic Thioanhydride (43).** To a solution of **44** (29.0 mg, 0.044 mmol) in 40% TFA in CH_2Cl_2 (300 μL) was added Et_3SiH (56.2 μL, 0.35 mmol), and the reaction mixture was stirred for 4 h. The volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ (5 mL) and washed with sat. $NaHCO_3$ aq (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from $CHCl_3$/hexanes to give a white solid (8.2 mg, 71%). Mp 87.5−88.4 °C. $[\alpha]^{24}_D$ +3.0 (*c* 1.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.37 (m, 5H), 6.03 (d, J = 6.5 Hz, 1H), 5.08 (s, 2H), 4.66−4.71 (m, 1H), 3.25 (dd, J = 8.5 Hz, 1H), 3.10 (dd, J = 9.0 Hz, 1H). ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 199.2, 195.2, 156.0, 135.7, 128.8, 128.6, 128.4, 128.3, 67.7, 60.4, 45.4. Elemental anal. calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.51; H, 4.10; N, 5.24; S, 12.05.

General Procedure for Table 4. To a solution of *N*-benzyloxycarbonyl-L-aspartic thioanhydride (**43**, 20.0 mg, 0.075 mmol) in DMF (150 μL) was added a suspension or a solution of amine (0.075 mmol) in DMF (150 μL) dropwise. The reaction mixture was stirred for 1 h, then Cs_2CO_3 (24.5 mg, 0.075 mmol) was added, immediately followed by sulfonamide (0.075 mmol). The reaction mixture was stirred for further 1 h. After removal of DMF under high vacuum, the residue was purified by column chromatography to give the corresponding peptide.

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\gamma$-{4-(β-D-glucopyranosyl)-β-D-glucopyranosyl}-L-asparaginyl-L-phenylalanine Methyl Ester (49).** $[\alpha]^{24}_D$ +8.7 (*c* 0.70, DMF); ^{1}H NMR (300 MHz, DMF-d_7 with drops of D_2O) δ 7.37−7.14 (m, 10H), 5.01 (s, 2H), 4.86 (d, J = 9.3 Hz, 1H), 4.60−4.51 (m, 2H), 4.39 (d, J = 7.2 Hz, 1H), 3.83 (dd, J = 11.7, 1.8 Hz, 1H), 3.78−3.72 (m, 2H), 3.61 (s, 3H), 3.54 (dd, J = 12.0, 6.3 Hz, 1H), 3.50−3.42 (m, 2H), 3.42−2.98 (m, 7H), 2.76−2.58 (m, 2H). ^{13}C NMR (75 MHz, DMF-d_7) δ 172.5, 172.4, 170.8, 156.8, 138.0, 138.0, 130.0, 129.0, 129.0, 128.4, 128.3, 127.3, 104.5, 81.7, 80.5, 78.0, 77.8, 77.6, 74.6, 73.4, 71.3, 66.4, 62.3, 61.7, 54.8, 52.2, 38.3, 37.7. ESIHRMS: *m/z* calcd for $C_{34}H_{45}N_3O_{16}Na$ $(M + Na)^+$ 774.2689, found 774.2704.

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Supporting Information Available: Details of the preparation of compounds **2**, **4**, **6**, **8**, **10**−**12**, **14**, **15**, **17**, **19**, **20**, **22**, **24**, **25**, **27**, **29**, **30**, **32**, **33**, **35**−**40**, **43**−**47**, **49**, **51**, **53**, and **54**, and copies of their ^{1}H spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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