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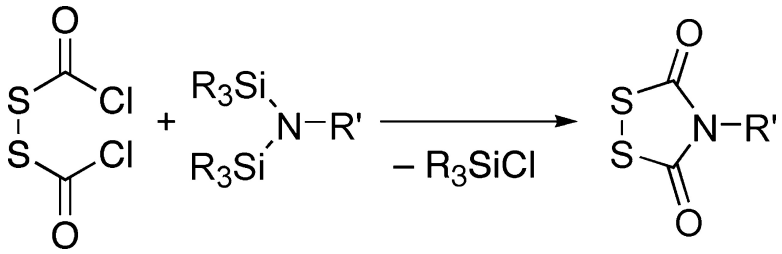
J. Am. Chem. Soc., **2005**, 127 (2), 508-509• DOI: 10.1021/ja0455446 • Publication Date (Web): 23 December 2004



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Published on Web 12/23/2004

Efficient Synthesis of 1,2,4-Dithiazolidine-3,5-diones [Dithiasuccinoyl-Amines] from Bis(chlorocarbonyl)disulfane Plus Bis(trimethylsilyl)amines

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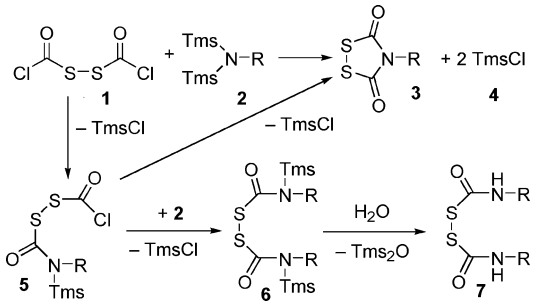
The 1,2,4-dithiazolidine-3,5-dione heterocycle **3** [alternatively, a *dit*hiasuccinoyl (Dts)-amine][1] was first described in the German patent literature, as summarized in a seminal review by Zumach and Kühle.[2] The realization in 1977 that heterocycle **3** constituted an orthogonal amino protecting group,[3] readily removable by thiols and other reducing agents, was followed by extensive mechanistic work,[4] as well as the development of applications to the syntheses of peptides,[3,5] amino-sugars in glycopeptides,[6] and PNA.[7] The Dts heterocycle has also proved useful as a masked isocyanate[5b,8,9] and (inversely) as a sulfurization reagent for trivalent phosphorus, particularly for synthesis of phosphorothioate DNA.[8] Finally, the parent heterocycle (R = H) and its salts can be alkylated[4h,9] in an analogue of the Gabriel synthesis,[10] with further entries to amines and isocyanates.

Methods described to date for transformation of amines to Dts-amines[2,3,4d−h] involve multiple operations, with concomitant reductions in overall yield and increases in formation of byproducts. It seemed plausible that bis(chlorocarbonyl)disulfane (**1**),[3,11] the two-sulfur analogue of succinyl chloride,[1] might be used in facile single-step elaborations of Dts-heterocycles **3** from primary amines. This seemingly straightforward approach failed for reasons sketched elsewhere.[3,4h] Inspired by precedents from organosilicon chemistry,[12] reactions of **1** with bis(trimethylsilyl)amines **2**,[13] instead of primary amines, have been investigated. The present paper reports the successful development of a high-yield, direct synthesis of Dts-amines based on this plan (Scheme 1).

Concept. Several decades of intermittent studies exploring reactions of bis(chlorocarbonyl)disulfane (**1**) with primary amines, under a wide range of acidic, neutral, and basic conditions, never gave characterizable levels of the desired heterocycles **3**. Initial monoacylation does occur to form a chlorocarbonyl carbamoyl disulfane [like **5**, but with H in place of Tms], but this decomposes to carbonyl sulfide (COS), elemental sulfur, and either a carbamoyl chloride [Cl(C═O)NHR, **8**] or an isocyanate [O═C═N−R, **9**].[14] The same decomposition is observed when the intermediate is generated by alternative approaches.[3,4h] We hypothesize that this decomposition is related, directly or indirectly, to the formation of coproduct HCl. Were this premise correct, reaction of **1** with a bis-(Tms)-protected amine would yield the benign TmsCl, together with intermediate **5**; this might be sufficiently stable to allow cyclization to **3** without decomposition to isocyanate-type byproducts.

Pilot Studies. A model compound, heptamethyldisilazane (**2**, R = Me), was combined with **1** in $CDCl_3$ solution at various ratios [2:1, 1:1, and 1:2, sum of concentrations = 1.0 M], and reactions at 25 °C were monitored by ^{1}H and ^{13}C NMR [a *p*-xylene internal standard facilitated molar estimation of all reaction species by NMR integration]. Product **3** [R = Me; ^{1}H NMR δ 3.28] was evident within 30 min, as was the presumed intermediate **5** [R = Me; δ 2.92, 0.32]. The expected coproduct TmsCl (**4**; δ 0.42) was in evidence throughout; it hydrolyzed to HCl plus Tms_2O upon aqueous workup. In addition, the diacylated, disilylated adduct **6** [R = Me; δ 3.01, 0.29] was detected, especially when **2** was in excess. Byproduct **6** hydrolyzed to **7** (R = Me) upon aqueous workup. Endpoints were reached after overnight reaction, giving product **3** in yields of 69−93%. Modeling the first step of the title process, **2** (R = Me) reacted smoothly with ((trichloromethyl)-dithio)carbonyl chloride (**10**)[11] to form monoadduct CCl_3SS-(C═O)N(Tms)Me [**11**; δ 2.99, 0.32], which after aqueous workup gave the known trichloromethyl *N*-methylcarbamoyl disulfane (**12**)[3a,4h,15] quantitatively. The rate of reaction of **2** plus **10** to form stable **11** was substantially slower than the rate of **2** plus **1** to form intermediate **5**.

Scheme 1. Bis(silyl)amine Route to Dts-Amines



Generalizations. An array of parallel studies was carried out to test the effects of various parameters on the reactions of **1** plus **2** (R = Me). With the thought that silylated and/or acyl halide compounds might be sensitive to hydrolysis, one set of trials was carried out under N_2, with outcomes comparable to those of trials carried out open to atmosphere. Further, scrupulously dry solvents were unnecessary. NMR monitoring demonstrated that reactions performed in $CDCl_3$ under reflux were complete within 15 min. On the scales examined, at several temperatures, rates and orders of addition of reactants did not affect yields. Preliminary kinetics experiments which followed by NMR the reaction course at various concentrations of starting reactants were consistent with rate-limiting unimolecular cyclization of intermediate **5** to product **3**.

Generalization to different R groups (in **2**) showed the reaction of R = allyl, Bn, or Ph to be as straightforward as R = Me. However, reaction of the ammonia derivative hexamethyldisilazane (**2**, R = H) failed. A rapid exothermic reaction gave TmsCl (1 equiv), COS, S, and a mixture of products (total 1 equiv) related to cyanic acid (H−N═C═O).[16] The corresponding reaction of **10** with **2** (R = H) gave CCl_3SS(C═O)NHTms (**13**) plus TmsCl (**4**).

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10.1021/ja0455446 CCC: $30.25

Alternatively, when starting with nonamethyltrisilazane (**2**, R = Tms), the reaction with **1** failed to progress appreciably in $CDCl_3$ at reflux, whereas in tetrachloroethylene at reflux a similar decomposition to TmsCl (2 equiv), COS, S, and HNCO-related products[16] occurred *without* evidence of cyclization to the hoped-for **3** (R = Tms).

Another generalization involved reaction of **1** with the "tethered" *N*,*N*-bis(silylated) amino acid derivative ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate (STABASE-GlyOEt),[17] which readily produced DtsGlyOEt[3,4e] along with 1,2-bis(chlorodimethylsilyl)ethane.[17]

To achieve Dts formation by the aforementioned chemistry, it was important that *both* free valences of nitrogen be silylated. To reinforce results already cited for **2** (R = H), the rapid, exothermic reactions of **1** or **10** with *N*-trimethylsilyl *N*-benzylamine (**14**)[13] were studied. Reactions of **14** with **10** smoothly gave $CCl_3SS(C{=}O)NHBn$ (**15**) plus TmsCl (**4**), establishing the highly selective net replacement of Tms instead of a proton.[18] In the same vein, reactions of **14** with **1** gave TmsCl (**4**) plus chlorocarbonyl carbamoyl disulfane $Cl(C{=}O)SS(C{=}O)NHBn$ (**16**), which *did not progress* to Dts derivative **3** (R = Bn).

Mechanisms of Silylamine Acylation and Dts Heterocyclization. The central finding of this work is that whereas simple primary amines upon reaction with bis(chlorocarbonyl)disulfane (**1**) form isocyanates **9** and related derivatives rather than the anticipated Dts-amines **3**, the same chemistry carried out on bis(silyl)amine substrates [e.g., **2**, STABASE] indeed provides **3** in respectable yields and purities, with negligible amounts of **9** and related compounds.

Two separate stages of the process must be considered. Acylation of mono(trimethylsilyl)amines, i.e., TmsNHR or Tms-NR^1R^2, is precedented,[4c,e,12] and even bis(acylation) of Tms_2NR [requiring heat and Lewis acid catalysis] has been described.[19] Evidence provided herein, as well as previously,[3a,4h] suggests that chlorocarbonyl carbamoyl disulfane intermediates (like **5** and **16**) are indeed generated from **1** plus amine derivatives and are surprisingly stable; yet the success or failure of cyclization to Dts is contingent on whether the carbamoyl nitrogen bears a trimethylsilyl group [TmsCl (**4**) formed as final coproduct] or a proton [HCl produced, but *no* cyclization]. We now conclude that when there is a proton on the amino nitrogen, its removal (either spontaneous or promoted intentionally) initiates a cascade of nonproductive side reactions. Formation of these byproducts is precluded when the proton is replaced by a bulky Tms group; in this case, the *only* accessible pathway for loss of TmsCl is coupled to the heterocyclization that gives Dts-amines **3**.

Summary and Conclusions. Dts-amines can be synthesized *directly* in a simple and robust reaction that uses the trimethylsilyl group as a "large proton" to circumvent extant synthetic problems. This simplification and improvement in the synthesis of 1,2,4-dithiazolidine-3,5-diones promises to open up new avenues for the application of Dts-based protection strategies to meet a wide spectrum of goals in synthetic organic and biological chemistry research.

Acknowledgment. We thank Lori J. Enloe and Drs. Alayne L. Schroll and Fernando Albericio (1982), and Dana M. Baas, Megan M. Corey, Eric P. Gillis, Michael C. Hanson, Isaac D. Mitchell, Abraham Tsehaye, James W. Wollack, Abehayeu Yilma, and Dr. Mian Liu (2004) for assistance in preparing key starting materials, Drs. Paul C. Ewbank, Jed Fisher, Craig J. Forsyth, Rita S. Majerle, and Simon K. Shannon for valuable discussions and critical reading of the manuscript, and Drs. Kate and Michael Bárány for long-standing encouragement. Supported by NIH Grants AM 01260, GM 28934, GM 42722, and GM 43552.

Supporting Information Available: Experimental procedures, NMR characterization, representative kinetics (8 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0455446