

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/8087266>

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

ARTICLE in JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · FEBRUARY 2005

Impact Factor: 12.11 · DOI: 10.1021/ja0455446 · Source: PubMed

---

CITATIONS

9

---

READS

41

4 AUTHORS, INCLUDING:



Robert P. Hammer

Ra Pharmaceuticals, Inc.

113 PUBLICATIONS 2,609 CITATIONS

SEE PROFILE



George Barany

University of Minnesota Twin Cities

245 PUBLICATIONS 6,565 CITATIONS

SEE PROFILE

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

Michael J. Barany,<sup>†,§</sup> Robert P. Hammer,<sup>†,||</sup> R. B. Merrifield,<sup>‡</sup> and George Barany<sup>\*,†,‡</sup>

University of Minnesota, Department of Chemistry, 207 Pleasant Street S.E., Minneapolis, Minnesota 55455, and  
The Rockefeller University, 1230 York Avenue, New York, New York 10021

Received July 24, 2004; E-mail: barany@umn.edu

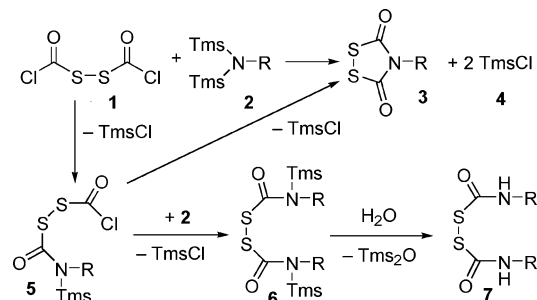
The 1,2,4-dithiazolidine-3,5-dione heterocycle **3** [alternatively, a dithiasuccinoyl (Dts)-amine]<sup>1</sup> was first described in the German patent literature, as summarized in a seminal review by Zumach and Kühle.<sup>2</sup> The realization in 1977 that heterocycle **3** constituted an orthogonal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

Methods described to date for transformation of amines to Dts-amines<sup>2,3,4d–h</sup> involve multiple operations, with concomitant reductions in overall yield and increases in formation of byproducts. It seemed plausible that bis(chlorocarbonyl)disulfane (**1**),<sup>3,11</sup> the two-sulfur analogue of succinyl chloride,<sup>1</sup> might be used in facile single-step elaborations of Dts-heterocycles **3** from primary amines. This seemingly straightforward approach failed for reasons sketched elsewhere.<sup>3,4h</sup> Inspired by precedents from organosilicon chemistry,<sup>12</sup> reactions of **1** with bis(trimethylsilyl)amines **2**,<sup>13</sup> 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**].<sup>14</sup> The same decomposition is observed when the intermediate is generated by alternative approaches.<sup>3,4h</sup> 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<sub>3</sub> 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 <sup>1</sup>H and <sup>13</sup>C NMR [a *p*-xylene internal

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



standard facilitated molar estimation of all reaction species by NMR integration]. Product **3** [R = Me; <sup>1</sup>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<sub>2</sub>O 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**)<sup>11</sup> to form monoadduct CCl<sub>3</sub>SS-(C=O)N(Tms)Me [**11**; δ 2.99, 0.32], which after aqueous workup gave the known trichloromethyl *N*-methylcarbamoyl disulfane (**12**)<sup>3a,4h,15</sup> 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**.

**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<sub>2</sub>, 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<sub>3</sub> 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).<sup>16</sup> The corresponding reaction of **10** with **2** (R = H) gave CCl<sub>3</sub>SS(C=O)NHTms (**13**) plus TmsCl (**4**).

<sup>†</sup> University of Minnesota.

<sup>‡</sup> The Rockefeller University.

<sup>§</sup> Current Address: Roseville Area High School, 1240 W County Rd B2, Roseville, MN 55113.

<sup>||</sup> Permanent Address: Department of Chemistry, 232 Choppin Hall, Louisiana State University, Baton Rouge, LA 70803.

Alternatively, when starting with nonamethyltrisilazane (**2**, R = Tms), the reaction with **1** failed to progress appreciably in CDCl<sub>3</sub> at reflux, whereas in tetrachloroethylene at reflux a similar decomposition to TmsCl (2 equiv), COS, S, and HNCO-related products<sup>16</sup> 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),<sup>17</sup> which readily produced DtsGlyOEt<sup>3,4e</sup> along with 1,2-bis(chlorodimethylsilyl)ethane.<sup>17</sup>

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**)<sup>13</sup> were studied. Reactions of **14** with **10** smoothly gave CCl<sub>3</sub>SS(C=O)NHBn (**15**) plus TmsCl (**4**), establishing the highly selective net replacement of Tms instead of a proton.<sup>18</sup> 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<sup>1</sup>R<sup>2</sup>, is preceded, <sup>4c,e,12</sup> and even bis(acylation) of Tms<sub>2</sub>NR [requiring heat and Lewis acid catalysis] has been described.<sup>19</sup> Evidence provided herein, as well as previously,<sup>3a,4h</sup> 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 Tsehay, James W. Wollack, Abeyayeu 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>.

## References

- (1) The name dithiasuccinoyl-amine derives from the conceit that the heterocycle is the sulfurized analogue of a succinimide that represents a protected amine derivative. The present contribution introduces the first synthesis of Dts-amines that follows the intuitive notion that an analogue of succinyl chloride could be used to establish amino protection.
- (2) Zumach, G.; Kühle, E. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 54–63.
- (3) (a) Barany, G. Ph.D. Thesis, The Rockefeller University, 1977, *Dissertation Abstr.* **38**, 5893-B. (b) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363–7365.
- (4) (a) Barany, G.; Merrifield, R. B. *Anal. Biochem.* **1979**, *95*, 160–170. (b) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3084–3095. (c) Barany, G. *Int. J. Pept. Protein Res.* **1982**, *19*, 321–324. (d) Słomczyńska, U.; Barany, G. *Heterocyclic Chem.* **1984**, *21*, 241–246. (e) Zalipsky, S.; Albericio, F.; Słomczyńska, U.; Barany, G. *Int. J. Pept. Protein Res.* **1987**, *30*, 740–783. (f) Hammer, R. P.; Albericio, F.; Gera, L.; Barany, G. *Int. J. Pept. Protein Res.* **1991**, *36*, 31–45. (g) Chen, L.; Thompson, T. R.; Hammer, R. P.; Barany, G. *J. Org. Chem.* **1996**, *61*, 6639–6645. (h) Barany, G.; Barany, M. J.; Chen, L.; Eastep, S. J.; Hammer, R. P.; Hanson, M. C.; Majerle, R. S.; Mott, A. W.; Słomczyńska, U. (alphabetical), currently being readied for publication.
- (5) (a) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936–4942. (b) Albericio, F.; Barany, G. *Int. J. Pept. Protein Res.* **1987**, *30*, 177–205.
- (6) (a) Meinjohanns, E.; Vargas-Berenguel, A.; Meldal, M.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2165–2175 and follow-up papers by this group. (b) Jensen, K. J.; Hansen, P. R.; Venugopal, D.; Barany, G. *J. Am. Chem. Soc.* **1996**, *118*, 3148–3155.
- (7) Planas, M.; Bardaji, E.; Jensen, K. J.; Barany, G. *J. Org. Chem.* **1999**, *64*, 7281–7289.
- (8) (a) Xu, Q.; Musier-Forsyth, K.; Hammer, R. P.; Barany, G. In *Peptides: Chemistry, Structure and Biology. Proceedings of the Fourteenth American Peptide Symposium*; Kaumaya, P. T. P., Hodges, R. S., Eds.; Mayflower Scientific Ltd.: Kingswinford, U.K., 1996; pp 123–124. (b) Xu, Q.; Musier-Forsyth, K.; Hammer, R. P.; Barany, G. *Nucleic Acids Res.* **1996**, *24*, 1602–1607 and references therein.
- (9) Wood, M. E.; Cane-Honeysett, D. J.; Dowle, M. D.; Coles, S. J.; Hursthouse, M. B. *Org. Biomol. Chem.* **2003**, *1*, 3015–3023 and two earlier communications by this group.
- (10) For a review of Gabriel synthesis of amines [alkylation of phthalimide salts, followed by dephthaloylation], see: Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919–930.
- (11) (a) Kobayashi, N.; Osawa, A.; Fujisawa, T. *Chem. Lett.* **1973**, 1315–1318. (b) Haas, A.; Helmbrecht, J.; Klug, W.; Koch, B.; Reinke, H.; Sommerhoff, J. *J. Fluorine Chem.* **1973/74**, *3*, 383–395. (c) Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 8, 4750–4761.
- (12) Silylated amines can be acylated, in some cases more selectively and in higher yield than the corresponding free amines: (a) Birkofer, L.; Ritter, A. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 417–429. (b) Klebe, J. F. *Adv. Org. Chem.* **1972**, *8*, 98–178. (c) Kricheldorf, H. R. *Liebigs Ann. Chem.* **1972**, *763*, 17–38. (d) Mironov, V. F.; Sheludyakov, V. D.; Kozyukov, V. P. *Russ. Chem. Rev.* **1979**, *48*, 473–489 (Engl. trans.).
- (13) Substrates **2** are made either by exhaustive silylation of the corresponding primary amine or by silylation of an isolated monosilylamine intermediate, which is in turn made readily from amine plus TmsCl, or by S<sub>N</sub>2 reaction of alkyl/aryl halides/tosylates with metal bis(trimethylsilyl)amides. General review: Tamao, K.; Kawachi, A. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: New York, 2001; Vol. 4, pp 451–472.
- (14) Byproducts **8** and/or **9** may be transformed further to ureas or are hydrolyzed back to the parent amines upon aqueous workup.
- (15) Harris, J. F., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 155–158.
- (16) These results are not surprising, given the difficulty, discussed in refs 2 and 4g, in preparing **3** (R = H) by methods that suffice to elaborate **3** for most other substituents R. In the case under consideration, initial nitrogen/silicon-containing products could be Tms-N=C=O [matches authentic standard] and/or TmsNH(C=O)Cl.
- (17) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787–1790.
- (18) Reference 12d shows that reaction of Tms-NH-R with R'(C=O)Cl (but not COCl<sub>2</sub>) gives predominantly R'(C=O)NH-R + TmsCl. Thus, while it was conceivable that reaction of Tms-NH-Bzl with **1** could lead to **5** + HCl (if **1** reacted like COCl<sub>2</sub>), in fact, **1** reacts exclusively via N-Tms bond cleavage to give **16** + HCl, and heterocyclization does not occur.
- (19) Rühlmann, K. *Chem. Ber.* **1961**, *94*, 2311–2313.

JA0455446