Diastereoselective Enolsilane Coupling Reactions

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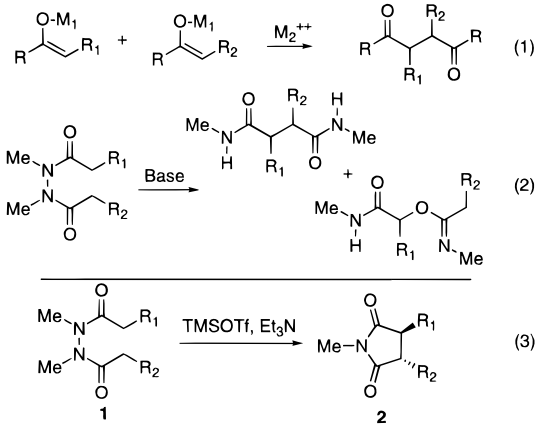
Reliable C−C bond forming processes that proceed under mild conditions are of significance in organic synthesis. Diastereoselective bond constructions are particularly important, as they allow for efficient synthesis of stereochemically complex molecules. Coupling of enolates is a conceptually attractive process for these goals because their generation is reasonably well understood (eq 1).[1] However, traditional approaches to enolate coupling involve formation of enolates with a strong base, followed by oxidative dimerization induced by high valent metal salts (*e.g.*, $Cu(OAc)_2$ or $TiCl_4$).[2] As a result of the harsh conditions, yields and diastereoselectivities often suffer, and the substrate scope is frequently limited. Alternatively, enolates have been coupled by sigmatropic rearrangement. Magedov[3] and Endo[4] independently reported that under anionic conditions diacyl hydrazines and hydroxylamines rearrange to afford succinic diamides (eq 2); rearrangement is apparently driven by the cleavage of a weak N−N bond. Yet, yields and diastereoselectivities are generally poor, and various byproducts are formed under these conditions. Herein, we report a mild intramolecular coupling of bis(enolsilanes) that leads to succinimide heterocycles (eq 3). In the present study, use of a Lewis acid and a mild base not only renders the rearrangement of unactivated substrates feasible, but also introduces an alternative reactivity pattern wherein a different product is obtained.



As illustrated in Scheme 1, treatment of *N,N′*-dialkyl-*N,N′*-diacylhydrazines (**1**) with 4 equiv of TMSOTf and 4 equivalents of Et_3N results in the formation of *N*-methyl-2,3-disubstituted succinimides **2**. It is plausible that hydrazide **1** is first converted to the bis(enolsilane) **3**, which undergoes diastereoselective bond formation through a neutral [3,3]-sigmatropic rearrangement to afford bis(imine) **4**.[5] Cyclization and expulsion of a methylamine equivalent then lead to the formation of succinimide **2**.[6]

Scheme 1

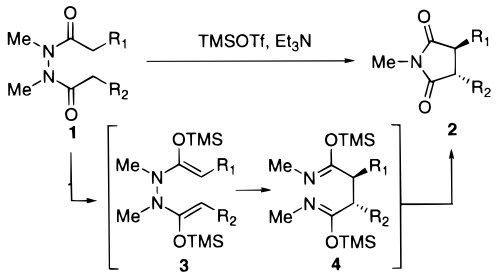
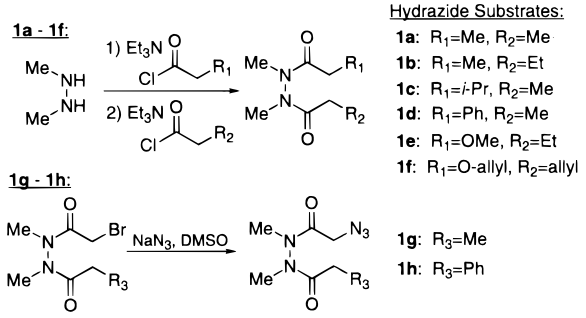


Chart 1. Preparation of Hydrazide Substrates



An attractive feature of the present process is that hydrazide preparation is straightforward. Thus, symmetrical and unsymmetrical *N,N′*-diacylhydrazines (**1a**−**h**) are readily made by sequential acylation of *N,N′*-dimethylhydrazine (Chart 1). In cases where one of the substituents is an azide, the bromoacetate derivative serves as the precursor; azide displacement subsequently produces the hydrazide in good yield. (See Supporting Information for details.)

Table 1 illustrates a wide range of substrates that undergo efficient rearrangement with moderate to excellent selectivity (2:1 to >20:1). Both symmetrical and unsymmetrical hydrazides rearrange efficiently, supporting the notion that the reaction is intramolecular. Rearrangement of both aliphatic- (**1a**−**c**) and aryl-substituted substrates (**1d**) demonstrates that activating groups are not required to enhance substrate acidity. In addition, α-alkoxy-substituted substrates rearrange to form the

(1) (a) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Syntheis:Additions to C-X π-Bonds*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Part 2, pp 99−131. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; vol. 3, Chap. 2. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115.

(2) For representative examples, see: (a) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912−2914. For more recent representative contributions, see (b) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809−2812. (c) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277−7283. (d) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457−4460.

(3) Magedov, I. V.; Smushkevich, Y. I. *J. Chem. Soc., Chem. Commun.* **1990**, 1686−1687.

(4) (a) Endo, Y.; Shudo, K. *Tetrahedron Lett.* **1991**, *32*, 4517−4520. (b) Endo, Y.; Shudo, K. *Heterocycles* **1992**, *33*, 91−95. (c) Uchida, T.; Endo, Y.; Hizazate, S.; Shudo, K. *Chem. Pharm. Bull.* **1994**, *42*, 419−421. (d) Endo, Y.; Uchida, T.; Hizazate, K.; Shudo, K. *Synthesis* **1994**, 1096−1105.

(5) For reviews of hetero-[3,3]-rearrangements, see: (a) Blechert, S. *Synthesis* **1989**, 71−82. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452. (c) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579−586.

(6) Representative procedure (substrates **1a**−**f**): To a cold (−78 °C) solution of the *N,N′*-diacylhydrazine in dichloromethane (0.2 M) is added TMSOTf (4.0 equiv) followed by Et_3N (4.0 equiv). The reaction mixture is then warmed to room temperature and stirred for 12−24 h. The reaction mixture is then applied directly to a silica gel column, which is eluted with the appropriate EtOAc/hexane solvent system. Modification for substrates **1g** and **1h**: The reactions were quenched by addition of saturated $NaHCO_3$ solution. The organic layer was then vigorously stirred for 10 min in the presence of 1 N HCl. Concentration of the aqueous layer then afforded the pure cyclic hydrazide salt (**5a** and **5b**). See Supporting Information for details.

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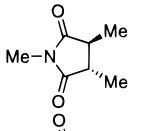
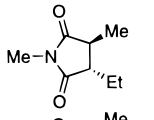
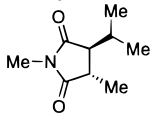
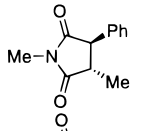
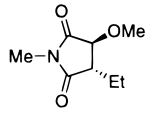
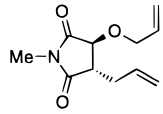
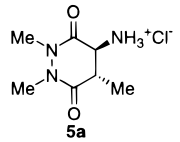
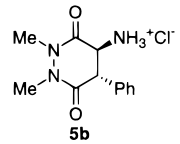
Table 1. Substrates Prepared by [3,3]-Rearrangement

substrate	major product	trans/cis ratio[a]	isolated yield (%)[c]
1a		6:1	66
1b		3:1 (7:1 at -30°C)	93
1c[b]		>20:1	77
1d		2:1	70
1e		6:1	60
1f		5:1	53

a) Ratios determined by 400 MHz ^{1}H NMR spectroscopy. b) Treatment of the reaction mixture with trifluoroacetic acid was required to induce cyclization. c) Isolated yield after silica gel chromatography.

Table 2. Formation of Cyclic Hydrazides

substrate	major product	trans/cis ratio[a]	isolated yield (%)[b]
1g	 **5a**	>20:1	80
1h	 **5b**	>20:1	58

a) Ratios determined by 400 MHz ^{1}H NMR spectroscopy. b) Isolated yield after aqueous work-up.

corresponding heterocycles (**1e** and **1f**). In all cases, the *trans*-disubstituted product constitutes the major diastereomer.[7,8]

To extend the utility of the present method to the preparation of N-substituted heterocycles, we examined the rearrangement of azide-substituted hydrazides (**1g** and **1h**). These substrates exhibit a different reactivity pattern wherein C−C bond formation occurs without rupture of the hydrazide N−N bond to afford the derived six-membered ring product (**5a** and **5b**, Table 2). In these cases, the *trans*-substituted products are obtained exclusively.[9] With the azide-substituted compounds, we postulate that formation of the bis(enolsilane) is followed by

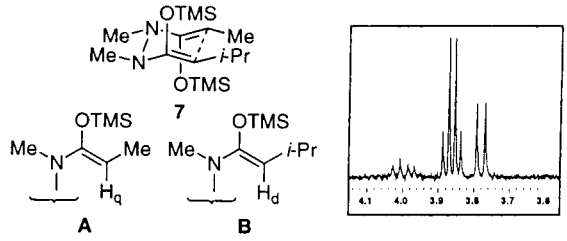
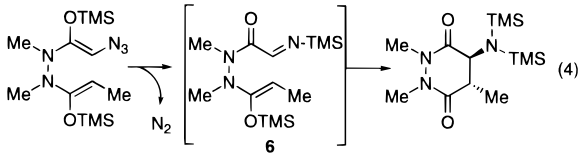


Figure 1. 400 MHz ^{1}H NMR spectrum of reaction mixture after 10 min (25 °C).

β-elimination of N_2 to afford a silylated glyoxalate−imine intermediate **6** (eq 4).[10] This scenario suggests that intramolecular aldol addition is responsible for C−C bond formation to provide the β-substituted aspartic acid derivative.



The origin of the observed diastereoselectivity is not certain at the present time and must await further studies to be completely understood. Nonetheless, in cases where we observe high *trans* selectivity, we expect that the [3,3]-rearrangement proceeds through a chair-like transition state.[11] In these instances, enolsilane geometries are projected to be mutually *Z*, as shown for structure **7**. Attempts to observe this intermediate in the reaction by ^{1}H NMR spectroscopy have yielded the following information (Figure 1). Exposure of **1c** to the reaction conditions yields a reaction mixture in which two dominant enol protons can be observed in approximately a 2:1 ratio. While the multiplicity of each proton allows a definitive assignment of each to the coupling moieties **A** and **B**, we have not been able to establish rigorously the individual enolate geometries. These and other mechanistic studies are in progress.

In summary, we have described a facile coupling of enol silanes linked through a N−N bond. Attractive features of the reaction include the following: (i) facile synthesis of substrates for the coupling process; (ii) diastereoselective C−C bond formation under the influence of TMSOTf and Et_3N; (iii) *in situ* cyclization to form *trans*-disubstituted succinimide products. In addition, a new reaction of azidoacetate derivatives is presented that results in a stereochemically defined β-substituted cyclic aspartic acid-derived hydrazide. Studies directed toward the development of enantioselective variants of this process and their application in natural products synthesis are underway.

Acknowledgment. The National Science Foundation is acknowledged for financial support (CHE-9612563).

Supporting Information Available: Characterization data for all compounds and experimental details for their preparation (10 pages).

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(7) For a review highlighting selectivity issues in [3,3]-sigmatropic rearrangements, see: Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882.

(8) The relative stereochemical relationships were established on the basis of the characteristically smaller coupling constant between the C3 and C4 methine protons in the *trans*-products. For example, see: Tschappat, K. D.; Crider, A. M.; Hassan, M. N.; Fahn, S. *J. Heterocycl. Chem.* **1987**, *24*, 673−676.

(9) In this case, stereochemical assignment was made based on the large coupling constants observed for the vicinal protons. See Supporting Information for details.

(10) Conversion of α-azido carbonyl compounds to the corresponding diketones by a related mechanism has been reported. See: (a) Edwards, O. E.; Purushothaman, K. K. *Can. J. Chem.* **1964**, *42*, 712−716. (b) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952−4954.

(11) (a) Doering, W. v. E.; Roth, W. R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115−122. (b) Reference 7 and references cited therein.