

# SYNLETT Spotlight 156

## *tert*-Butoxy Bis(dimethyl-amino)methane (Bredereck's Reagent)

Compiled by Giovanni Bernardi Rosso



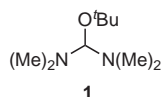
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Giovanni B. Rosso was born in Uruguaiana, RS (South of Brazil) in 1973. Giovanni received his B.Sc. from Universidade Federal de Santa Maria (Santa Maria, RS) in 1998. His masters degree was carried out in the same institution (1998–2000) under the supervision of Professor Mara E. F. Braibante, exploring the reactivity of  $\beta$ -enamino compounds under solid support (Montmorillonite/K-10). In 2000, he moved to Campinas, SP to work at Universidade Estadual de Campinas (UNICAMP) under supervision of Professor Ronaldo A. Pilli. His Ph.D. work concerns studies toward the synthesis and structural elucidation of *Stemona* alkaloid Parvistemoamide by a Michael addition reaction sequence. He has had a long-standing interest in the total synthesis of natural products, especially those of marine flora and fauna.

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### Introduction

*tert*-Butoxy-bis(dimethylamino)methane [Bredereck's reagent, *t*-BuOCH(NMe<sub>2</sub>)<sub>2</sub>] (Figure 1) is a useful reagent for  $\alpha$ -methylation,  $\alpha$ -methylenation, and  $\alpha$ -amination of several carbonyl systems or compounds with an active CH group.



**Figure 1** Bredereck's reagent (1).

Compared to the conventional methods to insert a methyl, methylene or amine groups at the position  $\alpha$  to a carbonyl group, Bredereck's reagent has the advantage of generating a strong basic alkoxide (*t*-BuO<sup>-</sup>) in situ and the corresponding iminium ion by thermal decomposition. After the Mannich reaction between the carbonyl substrate and the iminium

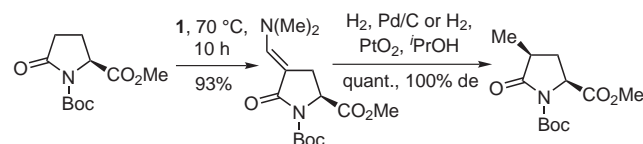
ion formed in situ,  $\beta$ -elimination of dimethylamine from the adduct in the final step affords the condensation product which can be transformed into various types of compounds as shown below. These factors combine to make Bredereck's reagent the reagent of choice for  $\alpha$ -methylation,  $\alpha$ -methylenation, and  $\alpha$ -amination of carbonyl compounds.

### Preparation

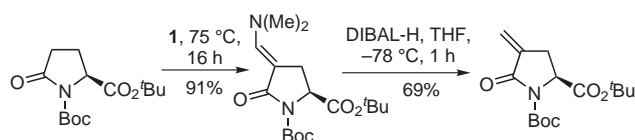
Bredereck's reagent is commercially available in pure form and can be used either in solution (e.g. DMF, benzene, toluene) or as a solvent and reagent. The reagent can also be prepared from the reaction of alcohol-free alkoxides and secondary amines, or from the reaction of Villsmeier reagent with sodium alkoxides.<sup>1</sup>

### Abstract

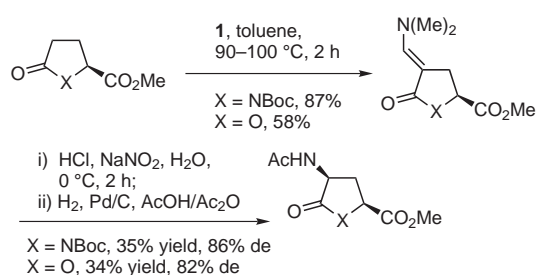
(A)  *$\alpha$ -Methylation of  $\gamma$ -lactams and  $\gamma$ -lactones*: The Bredereck reagent has been employed in the preparation of 4-methylglutamic acids, non-proteinogenic amino acids and analogues with high optical purity and total diastereoselectivity 3,5-*cis* after hydrogenolysis of enamino lactam intermediate.<sup>2</sup>



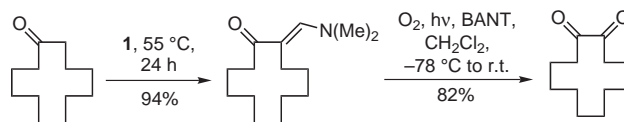
(B)  *$\alpha$ -Methylenation of  $\gamma$ -lactams*: After preparing the corresponding  $\beta$ -enamino carboxylic system by reaction of a pyroglutamic acid derivative with Bredereck's reagent, its reduction with DIBAL-H afforded the corresponding  $\alpha$ -methylene  $\gamma$ -butyrolactam.<sup>3</sup>



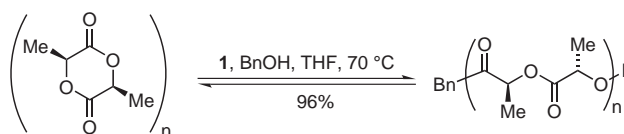
(C)  $\alpha$ -Amination: Bredereck's reagent has been used as an intermediate for the nitrosation of active methylene groups, followed by reduction of the resulting oxime to afford  $\alpha$ -amino lactones and lactams.<sup>4</sup>



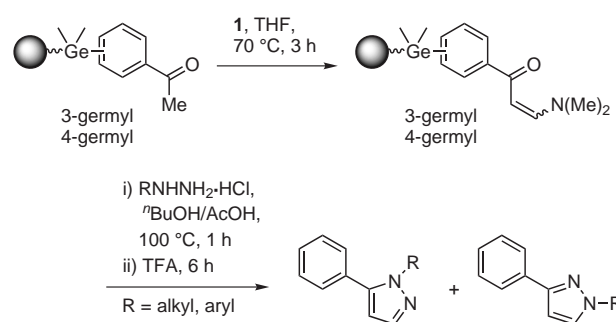
(D) Introduction of a ketone group  $\alpha$  to the carbonyl group: Bredereck's reagent has been employed in the preparation of  $\beta$ -enamino ketones, lactones, esters, substituted amides, or lactams, which after treatment with singlet oxygen using a sensitizer (BANT – bisacenaphthalenethiophene) afford the corresponding  $\alpha$ -keto derivatives.<sup>5</sup>



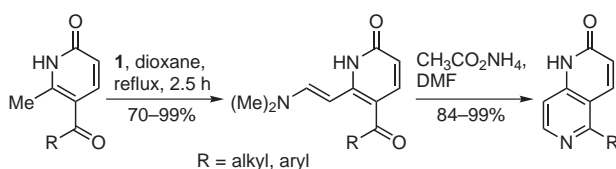
(E) Ring-opening polymerization: Recently, Waymouth, Hedrick and co-workers have described the use of Bredereck's reagent as an organic catalyst for the ring-opening polymerization of strained cyclic esters for the synthesis of polylactides.<sup>6</sup>



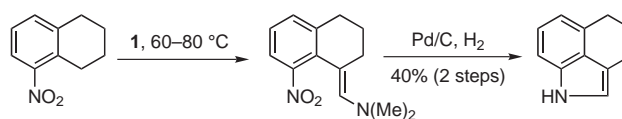
(F) Solid-phase synthesis: The usefulness of the Bredereck's reagent was extended to the solid-phase synthesis of a library of pyrazoles, employing a germanium-based linker, via the formation of enamionones from aromatic ketones.<sup>7</sup>



(G) Enamine formation from active methylene compounds: 5-Acyl-6-methyl-2-pyridinones were converted to the corresponding enamines upon treatment with Bredereck's reagent. 1,6-Naphthyridones were obtained in good yields upon treatment of the enamines with ammonium acetate.<sup>8</sup>



(H) Indole synthesis: Indoles can be obtained from tetrahydronaphthalenes and Bredereck's reagent via enamine formation assisted by the nitro group in the benzene ring under mild conditions.<sup>9</sup>



## References

- (1) (a) Bredereck, H.; Simchen, G.; Rebsdats, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41. (b) Kantlehner, W.; Speh, P. *Chem. Ber.* **1972**, *105*, 1340. (c) For another procedure, see: Blank, H. U.; Kraus, H.; Marzolph, G.; Müller, N. Patent EP 525536A2, **1993**; *Chem. Abstr.* **1993**, *118*, 212507.
- (2) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863.
- (3) (a) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617. (b) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 507.
- (4) Skof, M.; Svete, J.; Kmetec, M.; Golic-Grdadolnik, S.; Stanovick, B. *Eur. J. Org. Chem.* **1999**, *64*, 1581.
- (5) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573 and references cited therein.
- (6) Csihony, S.; Beaudette, T. T.; Sentam, A. C.; Nyce, G. W.; Waymouth, R. M.; Hedrick, J. L. *Adv. Synth. Catal.* **2004**, *346*, 1081.
- (7) Spivey, A. C.; Diaper, C. M.; Adams, H.; Rudge, A. J. *J. Org. Chem.* **2000**, *65*, 5253.
- (8) (a) Singh, B.; Leshner, G. *J. Heterocycl. Chem.* **1990**, *27*, 2085. (b) Singh, B.; Leshner, G.; Brundage, R. P. *Synthesis* **1991**, 894.
- (9) Haefliger, W.; Knecht, H. *Tetrahedron Lett.* **1983**, *25*, 285.