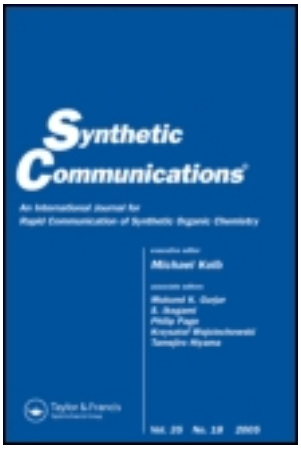

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Improved Procedure for the Preparation of cis-2,4-Dimethylglutaranhydride

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Version of record first published: 27 Oct 2006.

To cite this article: Radomir N. Saicic (2006): Improved Procedure for the Preparation of cis-2,4-Dimethylglutaranhydride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:17, 2559-2562

To link to this article: http://dx.doi.org/10.1080/00397910600781497

*Synthetic Communications*®, 36: 2559–2562, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600781497



# Improved Procedure for the Preparation of *cis*-2,4-Dimethylglutaranhydride

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**Abstract:** Addition of 2.5 mol% DBU to a mixture of isomeric 2,4-dimethylglutaric anhydrides in ethyl acetate promotes crystallization-induced transformation, affording the pure *cis*-2,4-dimethylglutaric anhydride in 87% yield.

**Keywords:** Crystallization, DBU, 2,4-dimethylglutaric anhydride, isomerization

*Meso*-2,4-glutaric anhydride **1** (i.e., *cis*-2,4-glutaric anhydride) is a valuable building block in the synthesis of natural products and biologically active compounds. Some synthetic applications of this compound involve its desymmetrization and conversion, by various methods,[1,2] into Prelog–Djerassi lactonic acid, the constituent of several macrolide antibiotics (e.g., methymycin,[3] erythromycin,[4] etc.), as well as useful synthetic intermediate (e.g., 6-deoxyerythronolide B).[5] Other variants include the conversion of the *meso*-anhydride **1** into advanced intermediates in syntheses of a number of complex antibiotics, such as Monensin-A,[6] Maduramicin,[6] Mucinolide V,[7] Salynomycin,[8] Okilactomycin,[9] and pheromone Multistriatin,[10] to mention just a few examples. Amino-derivatives have also been prepared.[11] Various methods have been developped for the desymmetrization of **1**, which include fractional crystallization of the corresponding diastereoisomeric salts with chiral amines,[6] enzymatic resolutions,[12,13] as well as catalytic asymmetric solvolyses of **1**,[14] the latter being recently achieved

Received in Poland February 3, 2006
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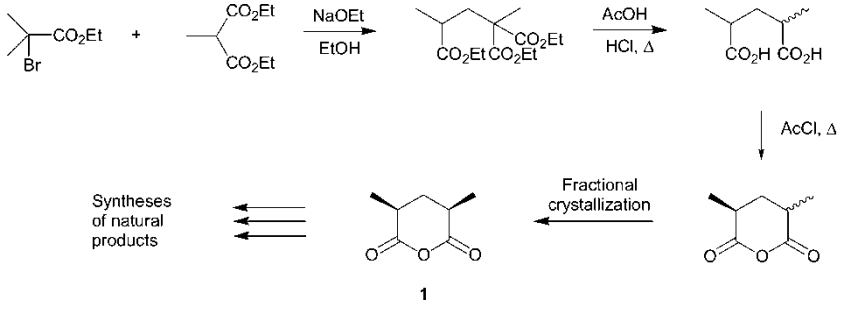
with high selectivity.[15] However, the known methods of preparation of **1** are not very efficient. This compound is still obtained by a modification[4,16] of von Auwers method,[17] as delineated in Scheme 1. The problematic step in this sequence is the last one, that is, the formation of the anhydride. This compound is obtained as a mixture of diastereoisomers, from which the required *meso*-derivative **1** is isolated by multiple fractional crystallizations, and the yield of the pure compound does not exceed 35%. Although the original von Auwers procedure has been recently improved,[9,13] this issue was not addressed. The compound is commercially available, though only in small quantities and at a very high price. (Sigma-Aldrich, Catalog No. S494208; 25 mg/101.1 euro, on January 13, 2006.)

Recently, in the context of our project directed toward the total synthesis of Abyssomicin,[18] we needed **1**. We found it both inconvenient and uneconomical to isolate only ~30% of **1** by multiple crystallizations, while rejecting the most of the crude, diastereoisomeric product mixture. Therefore, we considered the possibility of isomerizing the anhydride. Given the higher crystallinity of the required *meso*-isomer, we hoped that, under the appropriate conditions, isomerization could be followed by crystallization, resulting in a crystallization-induced transformation. The reactive nature of acyl anhydride imposed the nonnucleophilic nature of the basic catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) appeared as a suitable choice. The crude anhydride mixture was prepared as previously described, by treatment of stereoisomeric acids with acetyl chloride. The $^1$H NMR analysis showed this material to be ~1 : 1 mixture of *cis* and *trans*-isomers. Without distillation, or any other preliminary purification, the crude mixture was dissolved in ethyl acetate and treated with 2.5 mol% of DBU. To our pleasure, crystallization afforded the pure **1** in 87%, mp 91.8–92.3 °C (mp lit.[9] 89.5–92.5 °C; mp lit.[16] 91.4–92.8 °C; mp lit.[4] 91.4–92.8 °C). $^1$H NMR analysis showed this product to contain less than 3% of the *trans*-isomer. This compares favorably with the product obtained by repeated crystallizations, as described earlier, which was found to contain up to 7% of the *trans*-diastereoisomer. The product was stable in




***Scheme 1.***

solution, which indicates that no DBU occluded in the crystals (which could induce subsequent isomerization in solution).

The described modification affords the product of superior purity in 85% yield (as compared to 35% previously described), simplifies the isolation procedure, and lowers considerably the cost of preparation of this valuable and expensive synthetic intermediate.



## EXPERIMENTAL

### α,α′-Dimethylglutaric Acid

This mixture of stereoisomers was obtained from methyl diethylmalonate and ethyl α-bromopropanoate, as described elsewhere.[4,9,13,16]

### *cis*-2,4-Dimethylglutaranhydride 1

A mixture of α,α′-dimethylglutaric acid (mixture of stereoisomers from the previous step; 73 g; 0.456 mol) and acetyl chloride (204.7 g; 186 mL) was stirred at rt for 20 h, and then heated to reflux for 1 h. The excess acetyl chloride was removed under reduced pressure, and the residue (69 g) was dissolved in hot ethyl acetate (33 mL). To this solution, DBU (1.6 g; 10 mmol; 2.3 mol%) was added, and the mixture was left at 4 °C for a few hours. The crystals were filtered, washed with cold (−20 °C) ethyl acetate, and dried under reduced pressure (0.02 mmHg) to give 46 g of **1**. The mother liquor was concentrated under reduced pressure, the residue (20.8 g) was dissolved in hot ethyl acetate (9.3 mL), and the procedure was repeated (no additional DBU is added) to give an additional 7.6 g of crystals. Repetition of the procedure with the concentrated mother liquor (dissolved in 3.5 mL of ethyl acetate) gave an additional 3.13 g of crystalline material. The combined, white crystalline material (56.7 g; 87.6%) has mp 91.8–92.3 °C and $^{1}$H and $^{13}$C NMR data identical to those previously reported.[13] The purity of the sample, that is, the content of the *d,l*-isomer, was determined by integration of peaks at 2.05 ppm (1 H from the methylene group in **1**) and at 1.90 ppm (2 H, methylene group in the *d,l*-isomer).

## ACKNOWLEDGMENT

The author is grateful to Professor Pierre Potier (deceased on February 3, 2006), Professor Jean-Yves Lallemand and Dr. Jean Boivin (Institut de Chimie des Substances Naturelles) for their kind hospitality, and to Dr. Mikhail Ermolensko and Dr. Emmanuel Roulland for stimulating discussions.

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