Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

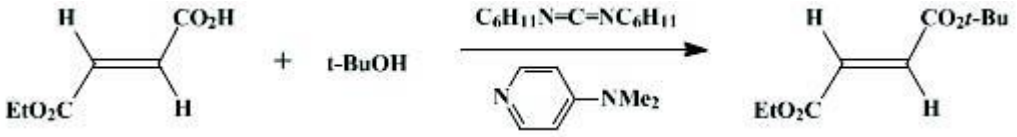
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.063.0183

Organic Syntheses, Coll. Vol. 7, p.93 (1990); Vol. 63, p.183 (1985).

ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYLCARBODIIMIDE/4-DIMETHYLAMINOPYRIDINE: *tert*-BUTYL ETHYL FUMARATE

[(*E*)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester]



Submitted by B. Neises and Wolfgang Steglich[1].
Checked by Cheryl Stubbs and Robert V. Stevens.

1. Procedure

Caution! Dicyclohexylcarbodiimide is a potent allergen and should be handled with gloves.

A 500-mL, one-necked flask equipped with a calcium chloride drying tube is charged with 28.83 g (0.20 mol) of monoethyl fumarate (Note 1), 200 mL of dry dichloromethane (Note 2), 44.47 g (0.60 mol) of *tert*-butyl alcohol (Note 3), and 2.00 g (0.016 mol) of 4-dimethylaminopyridine (Note 4). The solution is stirred and cooled in an ice bath to 0°C while 45.59 g (0.22 mol) of dicyclohexylcarbodiimide (Note 5) is added over a 5-min period. After a further 5 min at 0°C the ice bath is removed and the dark-brown reaction mixture is stirred for 3 hr at room temperature. The dicyclohexylurea that has precipitated is removed by filtration through a fritted Büchner funnel (G3), and the filtrate is washed with two 50-mL portions of 0.5 *N* hydrochloric acid (Note 6) and two 50-mL portions of saturated sodium bicarbonate solution. During this procedure some additional dicyclohexylurea is precipitated, which is removed by filtration of both layers to facilitate their separation. The organic solution is dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure, affording, after a small forerun, 30.5–32.5 (76–81%) of *tert*-butyl ethyl fumarate, bp 105–107°C (12 mm) (Note 7).

2. Notes

1. Monoethyl fumarate was purchased from Ega-Chemie, D-7924 Steinheim, Germany.
2. Dichloromethane was freshly distilled over P_4O_{10}.
3. *tert*-Butyl alcohol was purchased from E. Merck, D-6100 Darmstadt, Germany, and used without further purification.
4. 4-Dimethylaminopyridine was obtained from Schering AG, D-1000 Berlin, Germany. 4-Pyrrolidinopyridine, which is equally well suited as a catalyst in this reaction may be purchased from Ega-Chemie, D-7924 Steinheim, Germany.
5. Dicyclohexylcarbodiimide was freshly distilled with a Kugelrohr apparatus (Büchi GKR-50), bp 135–140°C (0.5 mm). It may be either added in crystalline form or dissolved in 50 mL of dry dichloromethane.
6. For esters more sensitive to acids, the use of concentrated aqueous citric acid solution is advisable.
7. The proton magnetic resonance spectrum of the product in chloroform-d shows the following absorptions: δ 1.30 [t, 3 H, J = 7.5, CH_3CH_2), 1.50 (s, 9 H, $C(CH_3)_3$], 4.23 (q, 2 H, J = 7.5, CH_3CH_2), 6.77 (s, 2 H, CH=CH). *tert*-Butyl ethyl fumarate may be easily converted into ethyl fumarate by alkaline hydrolysis.

3. Discussion

This procedure offers a convenient method for the esterification of carboxylic acids with alcohols[2,3,4] and thiols[2] under mild conditions. Its success depends on the high efficiency of 4-dialkylaminopyridines

as nucleophilic catalysts in group transfer reactions.[5] The esterification proceeds without the need of a preformed, activated carboxylic acid derivative, at room temperature, under nonacidic, mildly basic conditions. In addition to dichloromethane other aprotic solvents of comparable polarity such as diethyl ether, tetrahydrofuran, and acetonitrile can be used. The reaction can be applied to a wide variety of acids and alcohols, including polyols,[2,4,6] α-hydroxycarboxylic acid esters,[7] and even very acid labile alcohols such as vitamin A.[8] It has also been used for the esterification of urethane-protected α-amino acids with polymeric supports carrying hydroxy groups.[9] In this case, however, some racemization of the amino acid is observed because of 2-alkoxyoxazolin-5-one formation.[10] Racemization can be decreased by shortening the coupling time[10] or completely avoided by working with *N*-(*p*-nitrophenylsulfenyl)amino acids.[11]

With increasing steric hindrance, the rate of esterification is decreased and the formation of *N*-acylureas may become a serious side reaction. This is indicated by the decrease in yield in the esterification of 2,5-cyclohexadiene-1-carboxylic acid with different alcohols: MeOH (95%), EtOH (84%), i-PrOH (75%), *c*-$C_6H_{11}OH$ (65%), *t*-BuOH (65%).[12] Diminished acidity because of the influence of electron-donating substituents in aromatic carboxylic acids can also lead to low yields.

The dicyclohexylcarbodiimide/4-dialkylaminopyridine method is also well suited to the synthesis of a wide variety of thiol esters.[2,13]

4-Dimethylaminopyridine also catalyzes the formation of esters and thiol esters in the reaction of mixed carboxylic anhydrides[14] or 2,4,6-trinitrophenyl esters[15] with alcohols and thiols. 1-Acyl-4-benzylidene-1,4-dihydropyridines have been introduced recently as promising reagents for the synthesis of sterically hindered esters.[16] The current methods available for ester and thiol ester formation have been reviewed recently by Haslam.[17]

References and Notes

1. Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Strasse 1. D-5300 Bonn, Germany.
2. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl*. **1978**, *17*, 522; *Angew. Chem*. **1978**, *90*, 556.
3. Hassner, A.; Alexanian, V. *Tetrahedron Lett*. **1978**, 4475.
4. Ziegler, F. E.; Berger, G. D. *Synth. Commun*. **1979**, *9*, 539.
5. Steglich, W.; Höfle, G. *Angew. Chem., Inter. Ed. Engl*. **1969**, *8*, 981; *Angew. Chem*. **1969**, *81*, 1001; Höfle, G.; Steglich, W. *Synthesis* **1972**, 619; Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Inter. Ed. Engl*. **1978**, *17*, 569; *Angew. Chem*. **1978**, *90*, 602; Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.
6. Zinic, M.; Bosnic-Kasnar, B.; Kolbah, D. *Tetrahedron Lett*. **1980**, 1365.
7. Gilon, Ch.; Klausner, Y.; Hassner, A. *Tetrahedron Lett*. **1979**, 3811.
8. Niewöhner, U.; Steglich, W., unpublished results.
9. Wang, S.-S.; Yang, C. C.; Kulesha, I. D.; Sonenberg, M.; Merrifield, R. B. *Int. J. Pept. Protein Res*. **1974**, *6*, 103; Wang, S.-S.; Kulesha, I. D. *J. Org. Chem*. **1975**, *40*, 1227; Chang, C.-D.; Meienhofer, J. *Int. J. Pept. Protein Res*. **1978**, *11*, 246.
10. Atherton, E.; Benoiton, N. L.; Brown, E.; Sheppard, R. C.; Williams, B. J. *J. Chem. Soc., Chem. Commun*. **1981**, 336.
11. Neises, B.; Andries, Th.; Steglich, W., publication in preparation.
12. Neises, B.; Steglich, W., unpublished results.
13. Neises, B.; Steglich, W.; van Ree, T. S. *Afr. J. Chem*. **1981**, *34*, 58.
14. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M.; *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989; Kawanami, Y.; Dainobu, Y.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 943.
15. Kim, S.; Yang, S. *Synth. Commun*. **1981**, *11*, 121; Kim, S.; Yang, S. *Chem. Lett*. **1981**, 133.
16. Anders, E.; Will, W. *Synthesis* **1980**, 485.
17. Haslam, E. *Tetrahedron* **1980**, *36*, 2409.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

P_4O_{10}

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

citric acid (77-92-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

ethyl fumarate,
monoethyl fumarate (2459-05-4)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

2,5-Cyclohexadiene-1-carboxylic acid (4794-04-1)

tert-butyl alcohol (75-65-0)

dicyclohexylcarbodiimide (538-75-0)

dicyclohexylurea (2387-23-7)

4-dimethylaminopyridine (1122-58-3)

4-Pyrrolidinopyridine (2456-81-7)

tert-Butyl ethyl fumarate,
(E)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester (100922-16-5)