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.
TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND $\alpha,\beta$-UNSATURATED ACIDS WITH BULKY ALCOHOLS: (−)-MENTHYL CINNAMATE AND (−)-MENTHYL NICOTINATE

[2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]-] and [3-pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]-]

Submitted by Otto Meth-Cohn

Checked by Gladys Zenchoff, Hubert Maehr, and David Coffen.

1. Procedure

An oven-dried, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum inlet, an alcohol thermometer, and, through the center neck, a pressure-equalizing dropping funnel bearing a calcium chloride drying tube. The apparatus is flushed with argon (Note 1) and the flask is placed in an ice water bath. To the flask are added (−)-menthol (Note 2) (15.63 g, 100
mmol) and 150 mL of dry tetrahydrofuran (THF) (Note 3). To this stirred solution is added dropwise through the dropping funnel butyllithium in hexane (Note 4) (1.60 M, 55 mL, 88 mmol), transferred by syringe, at such a rate that the temperature does not rise above 20°C (about 10 min). When the addition is complete, the methyl ester [either methyl cinnamate (Note 5) (16.21 g, 100 mmol) or methyl nicotinate (Note 5) (13.71 g, 100 mmol)], dissolved in 30 mL of tetrahydrofuran, is added in one lot to the solution and washed in with an additional 20 mL of tetrahydrofuran. The resulting solution, which slowly becomes cloudy, is stirred for another hour (Note 6) and then poured into 200 mL of water in a 1-L separatory funnel; the flask is washed out with 100 mL of diethyl ether. The aqueous layer is separated and the organic phase is washed twice with 200 mL of water. After the organic phase is dried with magnesium sulfate, the solvent is removed on a rotary evaporator and the residue is distilled from a 100-mL flask bearing a Vigreux column (Note 8) under reduced pressure (0.1–0.5 mm). After a forerun of 2–3 g (Note 9) the (1R)-(−)-menthyl ester is collected. (1R)-(−)-Menthyl cinnamate distills at 145–147°C (0.2 mm) and is greater than 99% pure by GLC (Note 10). The yield is 22.6–23.9 g (79–83%). (1R)-(−)-Methyl nicotinate boils at 141–143°C (0.5 mm) and is greater than 99% pure by GLC (Note 10). The yield is 20.1–21.7 g (77–83%).

2. Notes

1. The submitter used a balloon attached by 1 in. of rubber pressure tubing to the barrel of a plastic disposable syringe bearing a 2-in. needle through the septum.
2. (−)-Menthol was obtained from Fluka Chemical Corporation (>99%, puriss. grade) and used directly.
3. Tetrahydrofuran was obtained from BDH Chemicals Ltd. and was distilled from sodium and benzophenone.
4. Butyllithium in hexane was purchased from Lithium Corporation of Europe. The checkers used material supplied by the Aldrich Chemical Company, Inc.
5. Methyl cinnamate (>99%) and methyl nicotinate (>99%) were used as supplied by Fluka Chemical Corporation.
6. The reactions may be monitored by TLC. The submitter used Merck Silica gel precoated plates, Silica gel 60 F-254, employing diethyl ether : hexane (1 : 5) for the cinnamate and (1 : 1) for the nicotinate transesterifications. After 5 min the reactions are already largely complete. On a small scale, purification by flash chromatography is most effective. Retardation factor Rf times of the reactants are as follows: methyl cinnamate, 0.47; menthyl cinnamate, 0.73; methyl nicotinate, 0.26; menthyl nicotinate, 0.47. Menthol was not visible under ultraviolet light as were the esters, but may be visualized with iodine or phosphomolybdic acid and heat: Rf 0.22 (1 : 4 ether : hexane).
7. The ice bath may be left in place after all of the reactants are added since the transesterifications are rapid, even below 10°C. If the reaction time is prolonged, only a small difference in product yields results.
8. The submitter used a 120 × 20-mm Vigreux column; the checkers used a 120 × 10-mm column.
9. The forerun contained a mixture of menthol and the methyl ester.
10. Capillary GLC analysis (50 m, OV17, He) gave the following retention times: Menthyl cinnamate 17.5 min (programmed 100–240°C, 5°C/min); methyl nicotinate 20.2 min (programmed 150–240°C, 5°C/min). The products showed the following properties. Menthyl cinnamate: [α]D20 = −57.8° (CHCl3, c 0.20) [lit.2 [α]D25 = −59.5° (CHCl3, c 7.5)]; 1H NMR (CDCl3) δ: 0.6–2.25 (m, 18 H, aliphatic), 4.74 (dt, 1 H, J = 9.5 and 5, O-CH), 6.35 (d, 1 H, J = 17, olefinic), 7.2–7.6 (m, 5 H, aromatic), 7.83 (d, 1 H, J = 17, olefinic). Methyl nicotinate: [α]D20 = −86.8° (CHCl3, c 0.11); 1H NMR (CDCl3) δ: 0.6–2.35 (m, 18 H, aliphatic), 5.01 (dt, 1 H, J = 4.5 and 10.0, O-CH), 7.40 (ddd, 1 H, J = 0.8, 4.8 and 7.8, H-5), 8.32 (dt, 1 H, J = 1.8 and 7.8, H-4), 8.81 (dd, 1 H, J = 1.8 and 4.8, H-6), 9.30 (dd, 1 H, J = 0.8 and 2.1, H-2). The optical rotations of the products showed a marked dependence on concentration. The submitters found [α]D20 = −60.7° (CHCl3, c 0.11) for menthyl cinnamate and [α]D20 = −87.9° (CHCl3, c 0.11) for methyl nicotinate.

3. Discussion

The method described here is based on the general method for such transesterifications.3 The best alcohol is bulky or tertiary, a feature disfavored by most other methods. Thus tert-butyl alcohol, tert-amyl alcohol, lanosterol, cholesterol, fenchol, and borneol are highly effective. If primary alcohols,
(e.g., allyl alcohol) are used, it is better to employ 3–5 equiv for an efficient reaction. Alcohols bearing other hetero atoms that form complexes with lithium (e.g., carbohydrate derivatives) prove ineffective in the transesterification.

Methyl esters are always the preferred substrates, as conversions are lower with, for example, ethyl esters. Functional groups such as nitro, methoxy, alkenyl, and pyridyl are compatible with the reaction conditions. Diesters can be effective only if bistransesterification is desired, when an excess of the alcohol (e.g., 3–5 equiv) is necessary. Methyl acrylate tends to polymerize under the reaction conditions, but the use of an excess of the ester (3–5 equiv) and lower temperatures (−10°C) allows efficient isolation of the required ester.

Organolithium compounds other than butyllithium can be used with no change in the reaction efficiency; reduction of the molar ratio of organolithium to alcohol merely slows the transesterification. Even when one-sixth (0.166) of an equivalent is used, efficient but slow transesterification occurs. In no case has it been found necessary to leave reactions longer than 18 hr or to use temperatures higher than ambient. Ether solvents are far more effective than hydrocarbons, in which slower reactions occur.

There are very few known methods for transesterifications using bulky alcohols. Thiol esters undergo ready mercury(II) trifluoroacetate-catalyzed transesterifications with tert-butyl alcohol. Potassium tert-butoxide in the presence of Linde 4A molecular sieves converts certain dimethyl malonates into methyl tert-butyl malonates. The majority of published transesterification methods involve the use of primary or occasionally secondary alcohols and a catalyst, and either require a large excess of one reactant or continuous removal of a low-boiling component in the equilibrium. Catalysts include acids such as sulfuric or p-toluenesulfonic acid, Lewis acids such as boron tribromide, or bases such as alkoxides. Neutral catalysts, in particular titanates, and potassium cyanide have also been used.

References and Notes

1. National Chemical Research Laboratories, CSIR, P. O. Box 395, Pretoria 0001, South Africa. Present address: School of Pharmaceutical and Medical Sciences, Sunderland Polytechnic, Langham Tower, Ryhope Road, Sunderland SR2 7EE, England.

Appendix

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

(−)-MENTHYL CINNAMATE
(−)-MENTHYL NICOTINATE

(1R)-(−)-Mentyl cinnamate

(1R)-(−)-Mentyl nicotinate

(−)-Menthol

ether, diethyl ether (60-29-7)

Allyl alcohol (107-18-6)

potassium cyanide (151-50-8)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

menthol (15356-60-2)

methyl acrylate (96-33-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

tert-amyl alcohol (75-85-4)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron tribromide (10294-33-4)

argon (7440-37-1)

tert-butyl alcohol (75-65-0)

p-toluenesulfonic acid (104-15-4)

phosphomolybdic acid (51429-74-4)

borneol (6627-72-1)
methyl cinnamate (103-26-4)
mercury(II) trifluoroacetate (13257-51-7)
methyl nicotinate (93-60-7)
menthyl cinnamate
menthyl nicotinate
fenchol
potassium tert-butoxide (865-47-4)
lanosterol

2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]- (16205-99-5)

3-pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]-