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Working with Hazardous Chemicals

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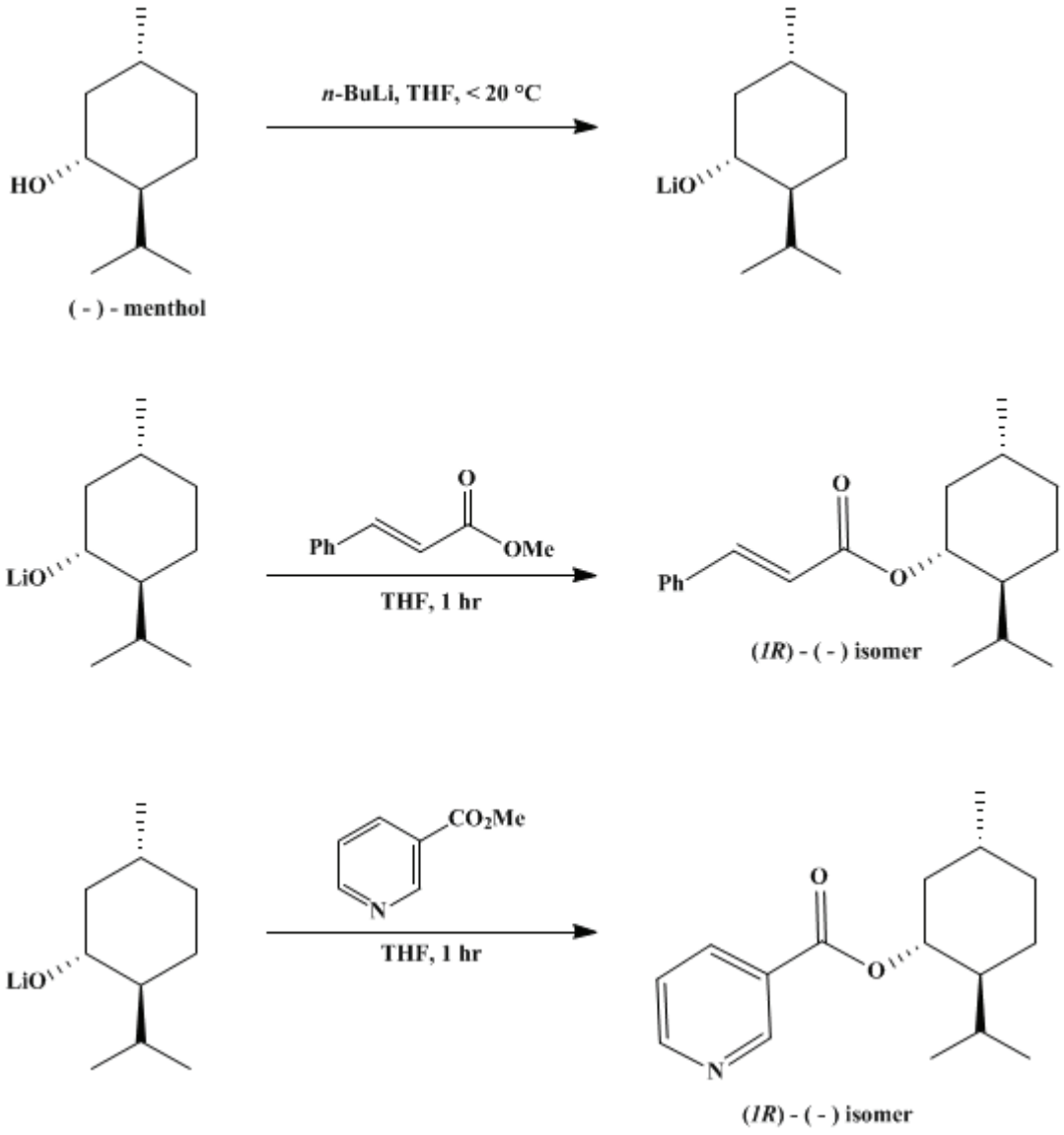
TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND α,β-UNSATURATED ACIDS WITH BULKY ALCOHOLS: (−)-MENTHYL CINNAMATE AND (−)-MENTHYL NICOTINATE

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



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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 (Note 7) 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 (1*R*)-(−)-menthyl ester is collected. (1*R*)-(−)-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%). (1*R*)-(−)-Menthyl 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 R_f 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: R_f 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); menthyl nicotinate 20.2 min (programmed 150–240°C, 5°C/min). The products showed the following properties. Menthyl cinnamate: $[\alpha]_D^{20}$ −57.8° ($CHCl_3$, *c* 0.20) [lit.[2] $[\alpha]_D^{25}$ −59.5° ($CHCl_3$, *c* 7.5)]; ^{1}H NMR ($CDCl_3$) 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). Menthyl nicotinate: $[\alpha]_D^{20}$ −86.8° ($CHCl_3$, *c* 0.11); ^{1}H NMR ($CDCl_3$) 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 $[\alpha]_D^{20}$ −60.7° ($CHCl_3$, *c* 0.11) for menthyl cinnamate and $[\alpha]_D^{20}$ −87.9° ($CHCl_3$, *c* 0.11) for menthyl 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.[4] Potassium *tert*-butoxide in the presence of Linde 4A molecular sieves converts certain dimethyl malonates into methyl *tert*-butyl malonates.[5] 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[6] or *p*-toluenesulfonic acid,[7] Lewis acids such as boron tribromide,[8] or bases such as alkoxides.[4,9] Neutral catalysts, in particular titanates,[10] and potassium cyanide[11] have also been used.

References and Notes

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

(−)-MENTHYL CINNAMATE

(−)-MENTHYL NICOTINATE

(1R)-(−)-Menthyl cinnamate

(1R)-(−)-Menthyl 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)]-