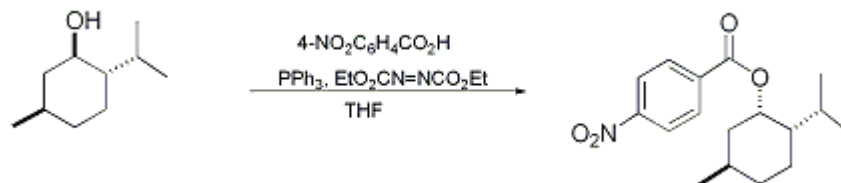


A GENERAL PROCEDURE FOR MITSUNOBU INVERSION OF STERICALLY HINDERED ALCOHOLS: INVERSION OF MENTHOL. (1S,2S,5R)-5-METHYL-2-(1-METHYLETHYL)CYCLOHEXYL 4-NITROBENZOATE

[Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 4-nitrobenzoate, [1S-(1 α ,2 α ,5 β)]-]



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1. Procedure

(1S,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate. A 250-mL, three-necked, round-bottomed flask is equipped with a stirring bar, nitrogen inlet, rubber septum, and thermometer. The flask is charged with 3.00 g of (1R,2S,5R)-(-)-menthol (19.2 mmol), 12.9 g of 4-nitrobenzoic acid (77.2 mmol), 20.1 g of triphenylphosphine (PPh₃) (76.6 mmol) (Note 1), and 150 mL of tetrahydrofuran (Note 2). The flask is immersed in an ice bath, and 12.1 mL of diethyl azodicarboxylate (77 mmol) is added dropwise at a rate such that the temperature of the reaction mixture is maintained below 10°C (Note 3). Upon completion of the addition (Note 4), the flask is removed from the ice bath and the solution is allowed to stir at room temperature overnight (14 hr) and subsequently at 40°C for 3 hr (Note 5). The reaction mixture is cooled to room temperature, diluted with 150 mL of ether, and washed twice with 100 mL portions of saturated aqueous sodium bicarbonate solution. The aqueous layers are combined and back-extracted with 100 mL of ether. The combined organic layers are dried over sodium sulfate. Excess solvent and other volatile reaction components are completely removed under reduced pressure initially on a rotary evaporator and then under high vacuum (approximately 0.2 mm for 3 hr at 30°C) (Note 6). The resulting semi-solid is suspended in 40 mL of ether and the suspension is allowed to stand at room temperature overnight (Note 7). The mixture is stirred while 20 mL of hexanes is slowly added (Note 8). The resulting white solid is filtered under vacuum and the filter cake is washed with 200 mL of 50% (v/v) ether-hexanes. The solvent is removed from the filtrate on a rotary evaporator under reduced pressure to give a yellow oil that is dissolved in 10 mL of methylene chloride (Note 9) and diluted with 40 mL of 8% ether-hexanes. The solution is applied to a flash chromatography column (Note 10) and eluted with 8% ether-hexanes to give 5.03 g (85.6%) of pure nitrobenzoate ester as a white crystalline solid (Note 11).

2. Notes

1. (1R,2S,5R)-(-)-Menthol, 4-nitrobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate were purchased from Aldrich Chemical Company, Inc., and used without further purification.
2. Anhydrous tetrahydrofuran (THF) was purchased from Aldrich Chemical Company, Inc. (Sure/SealTM bottle). The checkers used a freshly opened bottle of certified grade THF from Fisher Scientific Company.
3. Since diethyl azodicarboxylate decomposes when warmed, the reaction temperature is maintained at < 10°C during the addition of this reagent at which time a slight exothermic reaction occurs. [See Hazard Index, p. 837.]
4. 4-Nitrobenzoic acid is not entirely soluble in the tetrahydrofuran solution, resulting in a heterogeneous mixture. Upon addition of diethyl azodicarboxylate the reaction becomes homogeneous within several minutes and turns yellow-orange.

5. Shorter reaction times (2–5 hr) result in slightly decreased yields (65–75%) of inverted product. Lower yields (73–75%) were realized by the checkers when stirring at 40°C was omitted.
6. Removal of all residual [tetrahydrofuran](#) is critical to the success of the subsequent precipitation. The submitters recommend high vacuum removal of the solvent. Use of "house vacuum" (4–10 mm) also proved effective if applied to the crude sample for several hours.
7. Precipitation of the undesired reaction by-products (reduced [diethyl azodicarboxylate](#), [triphenylphosphine oxide](#)) occurs after the product mixture is suspended in [ether](#).
8. Extractive workup can be deleted, in which case sonication is required at this stage. Sonication appears to initiate further crystallization of by-products, as well as minimizing the amount of oil formed during the addition of hexanes.
9. The yellow oil is not sufficiently soluble in the chromatographic eluant (8% [ether](#) in hexanes) to provide efficient loading of the sample on the column. Thus, the crude material is initially dissolved in a small amount of [dichloromethane](#).
10. Chromatography was performed via the method of Still² using an 80-mm i.d. column of 300 g of silica gel (230–400 mesh).
11. The physical properties are as follows: mp 93–95°C; ¹H NMR (300 MHz, CDCl₃) δ: 0.87–1.23 (m, 12 H), 1.44–1.56 (m, 2 H), 1.64–1.70 (m, 1 H), 1.71–1.90 (m, 2 H), 2.05–2.13 (m, 1 H), 5.50 (s, 1 H), 8.20 (d, 2 H, J = 8.5), 8.29 (d, 2 H, J = 8.9); ¹³C NMR (75 MHz, CDCl₃) δ: 20.0, 20.8, 22.0, 25.3, 26.7, 29.0, 29.3, 34.6, 46.8, 73.0, 123.4, 130.5, 136.3, 150.3, 163.8; IR (CDCl₃) cm⁻¹: 1726, 1540, 1293.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since its introduction in 1967,³ the Mitsunobu reaction has been widely used in the refunctionalization of alcohols, in particular, for inversion. However, Mitsunobu inversions of hindered alcohols have been problematic resulting in low yields or unused starting material. A simple modification of the standard Mitsunobu procedure using [4-nitrobenzoic acid](#) (instead of [benzoic acid](#) or [acetic acid](#)) results in significantly improved yields of inverted product for sterically hindered alcohols.⁴ The procedure outlined here provides experimental details for the inversion of [menthol](#), a representative, hindered, secondary alcohol, using [4-nitrobenzoic acid](#) as the acidic coupling partner in the Mitsunobu process. The experimental procedure is a modification of that reported by Martin and Dodge.⁴ Improvements in the solvent ([tetrahydrofuran](#) rather than [benzene](#)) and a practical method for the removal of undesired by-products (e.g., EtCO₂NHNHCO₂Et and [triphenylphosphine oxide](#)) have led to optimization of reaction conditions.

Previously documented methods for [menthol](#) inversion under standard Mitsunobu conditions ([benzoic acid](#), PPh₃, [diethyl azodicarboxylate](#)) result in low yields⁴ (27%). More effective methods have been reported using extended reaction periods in refluxing [toluene](#) via a [formic acid](#)/[N,N'-dicyclohexylcarbodiimide](#)-mediated transformation⁵ (20–92 hr, 80%). For hindered alcohols in general, representative methods for inverting alcohol stereochemistry necessitate conversion of the alcohol to a leaving group such as a mesylate or triflate, followed by S_N2 displacement with a carboxylate nucleophile (typically [cesium acetate](#) or [propionate](#)).⁶ Other prevalent methods include (a) oxidation followed by stereoselective reduction and (b) intramolecular delivery (for suitably functionalized substrates) of the requisite oxygen functionality. One inherent advantage of the Mitsunobu reaction is compatibility with a diverse array of functional groups, due in large part to the mild, essentially neutral reaction conditions.

References and Notes

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 5. Kaulen, J. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 773; Kaulen, J. Ger. Offen. DE 3 511 210, 1986; *Chem. Abstr.* **1987**, 106, 32087g.
 6. For example, Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.
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Appendix

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

silica gel

hexanes

Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 4-nitrobenzoate, [1S-(1 α ,2 α ,5 β)]-

(1R,2S,5R)-(-)-menthol

EtCO₂NHNHCO₂Et

PPh₃

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

Benzoic acid (65-85-0)

toluene (108-88-3)

menthol (15356-60-2)

methylene chloride,
dichloromethane (75-09-2)

Tetrahydrofuran,
THF (109-99-9)

diethyl azodicarboxylate (1972-28-7)

triphenylphosphine (603-35-0)

[N,N'-dicyclohexylcarbodiimide \(538-75-0\)](#)

[triphenylphosphine oxide \(791-28-6\)](#)

[4-nitrobenzoic acid \(62-23-7\)](#)

[cesium acetate](#)

[\(1S,2S,5R\)-5-Methyl-2-\(1-methylethyl\)cyclohexyl 4-nitrobenzoate \(27374-00-1\)](#)

[cesium propionate](#)