

Catalysis by 4-dialkylaminopyridines

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Abstract

Representative experimental procedures are given for the most important types of reactions catalyzed by 4-dimethylaminopyridine (DMAP).

Keywords: 4-Dimethylaminopyridine synthetic procedures, DMAP, acylations, acetylations, esterification, benzylation, lactonization, silylation, sulphonylation, Baylis-Hillman reaction

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1. Introduction

The treatment of substrates such as alcohols, phenols and amines with acetic anhydride (or acetyl chloride) in the presence of pyridine has provided a general acetylation method since the turn of the 20th century. However, this approach often proves to be unsatisfactory for the acetylation of deactivated substrates. It was not until the late 1960's that certain 4-dialkylaminopyridines were found (independently by two research groups)¹ to be much superior to pyridine as catalysts for difficult acetylations or acylations, in general.

4-Dialkylaminopyridines were soon found to have general applicability for catalysis of a wide variety of reactions. 4-dimethylaminopyridine's (DMAP) wide applicability has been frequently reviewed since the first review appeared in 1978.² The accelerating pace of reported applications for DMAP and the availability of DMAP in commercial quantities, at modest prices, has continued to stimulate great interest in its use as a catalyst in the fields of organic, polymer, analytical and biochemistry. Today there are thousands of examples of the use of DMAP in far ranging fields of chemistry in both patents and the research literature. Many full-scale production processes utilizing DMAP have been and are being operated. Several pharmaceutical and agricultural products that rely on DMAP's superior catalytic properties in their synthetic sequences have been produced for years. Since 1976 more than 11,000 US patents have been granted which mention DMAP or dimethylaminopyridine.

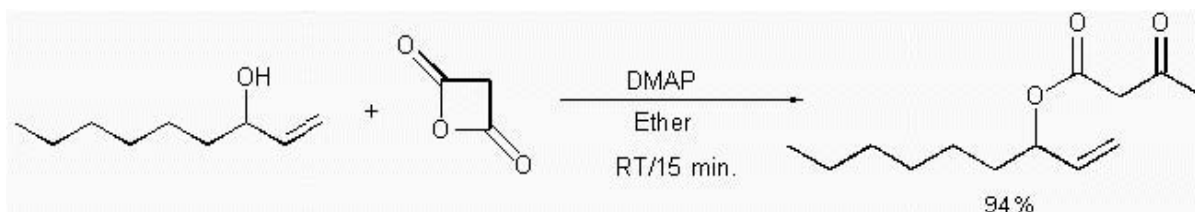
The functional groups and class of compounds that are involved in the reactions with DMAP include alcohols, amines, arenes, azides, carbenes, enols, epoxides, hydrazines, hydroxylamines, phenols, thiols, lipids, sugars, aminoacids, peptides, alkaloids, steroids, terpenes, and others. Reactions that have been published in the literature using DMAP fall into, but are not limited to, the following types of reactions: Acylation; Acetylation; Alkylation; Benzoylation; Bischler-Napieralski cyclization, Carbonylation; Carbo-diimidation; Cyclization; Dehydration; Esterification; Indole Synthesis; Nucleophilic Substitution; Rearrangement; Silylation;

Sulfonamidation; Sulfonation; Tritylation; Formylation; Carbamoylation; Phosphorylation; Lactonization; Pivaloylation; Dakin-West Reaction; Baylis-Hillman Reaction.

The following is a collection of samples of reactions with reaction conditions from the literature in which DMAP has been used effectively to improve, and in some cases make possible, transformations in organic chemistry. It is our hope that collecting these procedures and presenting them in this easily accessible format will make your job easier and more effective as you search for ways to synthesize new products or for ways to improve existing processes.

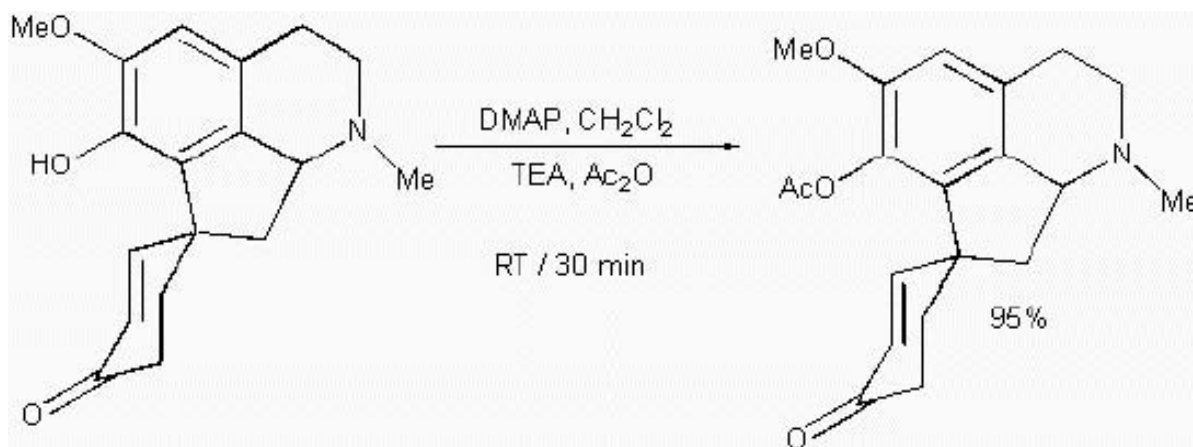
2. Acetylation

2.1. Acetoacetylation: synthesis of (1-ethenyl)heptanyl 3-ketobutanoate from 3-hydroxy-1-nonene³



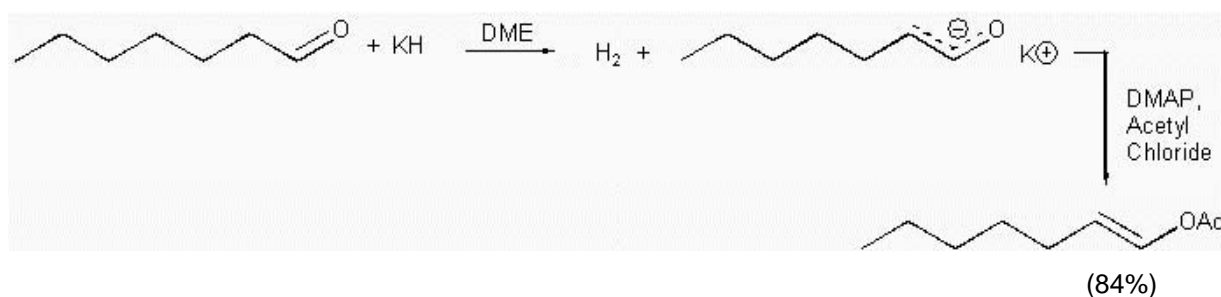
1. A solution of 3-hydroxy-1-nonene (7.5 g, 0.053 mol) in anhydrous ether (250 mL) is stirred under a nitrogen atmosphere. To this solution, diketene (5.04 g, 0.060 mol) is added using a syringe followed by DMAP (0.591 g, 0.0049 mol).
2. The reaction mixture slightly exotherms and stirring is continued for a further 15 min.
3. The reaction mixture is quenched by the addition of 0.1% sodium hydroxide solution (100 mL) followed by ether (100 mL). The layers are separated and the organic layer washed with 0.1% sodium hydroxide solution (50 mL) followed by brine. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure to afford (1-ethenyl)heptanyl 3-ketobutanoate (11.3 g, 94%) as a pale yellow oil. Further purification can be accomplished by distillation (b.p. 113-114°C at 1.4 mm) to afford a colorless oil.

2.2. Acylation of a phenolic group in 11,12-dihydroglaziovine⁴



1. A solution of (+/-)-11,12-dihydroglaziovine (0.168 g, 0.56 mmol) in dichloromethane (10 mL) is stirred at ambient temperature under a nitrogen atmosphere. To this solution is added triethylamine (0.75 mL), DMAP (0.07 g), and acetic anhydride (0.05 mL).
2. The reaction mixture is stirred for a further 30 min.
3. To the solution is added dichloromethane (20 mL), and then the solution is washed with water (3 x 5 mL) followed by saturated sodium bicarbonate solution (1 x 5 mL). The organic layer is dried (anhydrous magnesium sulfate), filtered, and concentrated to give a foam (0.234 g) which is crystallized from ether to afford (+/-)-1-O-acetyl-11,12-dihydroglaziovine (0.18 g, 95%, m.p. 176-178°C).

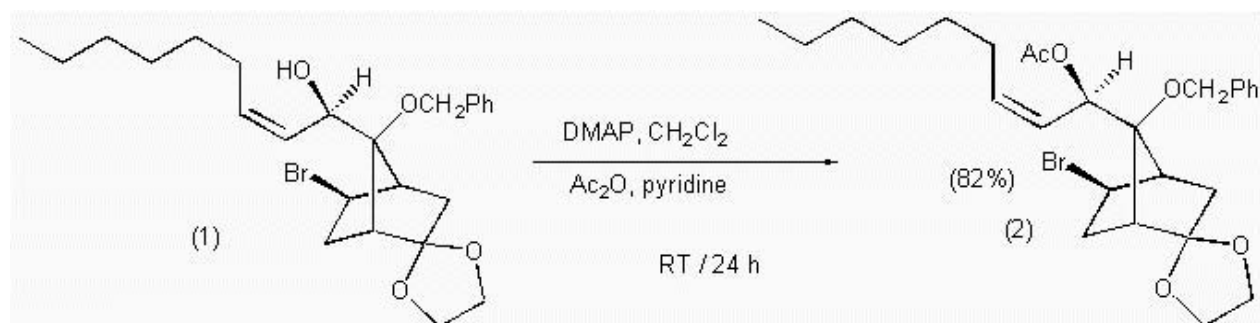
2.3. Synthesis of 1-acetoxy-1-heptene⁵



1. To a stirred suspension of potassium hydride (4.4 g, 0.11 mol) in dry 1,2-dimethoxyethane (50 mL), at -5° C under nitrogen, is added heptanal (11.4 g, 0.1 mol) in dry 1,2-dimethoxyethane (10 mL). Hydrogen evolution is quantitative within 10-12 min.

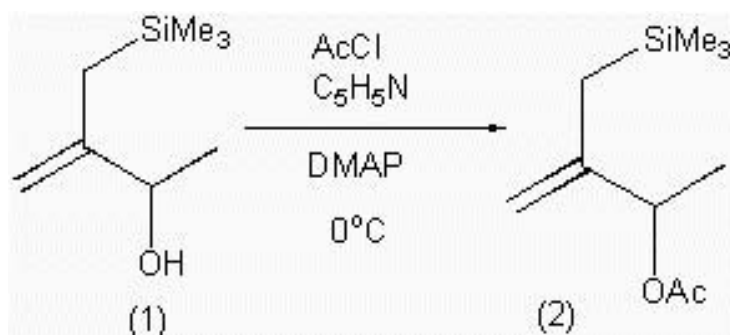
2. The enolate in solution is added by syringe to a solution of excess acetyl chloride (15.7 g, 0.2 mol), DMAP (0.6 g, 5 mmol), and 1,2-dimethoxyethane (30 mL) and stirred at room temperature for 15 min.
3. The reaction mixture is slurried into a two-phase ice-water/pentane system. After separation, the organic phase is washed twice with a saturated aqueous sodium hydrogen carbonate solution then with water, and dried with magnesium sulfate.
4. The solvent is evaporated in vacuum, and the residual product is distilled in vacuo to give a mixture of *cis*- and *trans*-1-acetoxy-1-heptene (13.1 g, 84%); b.p. 83-85°/15 torr.

2.4. Acetylation of *cis*-allylic alcohols⁶



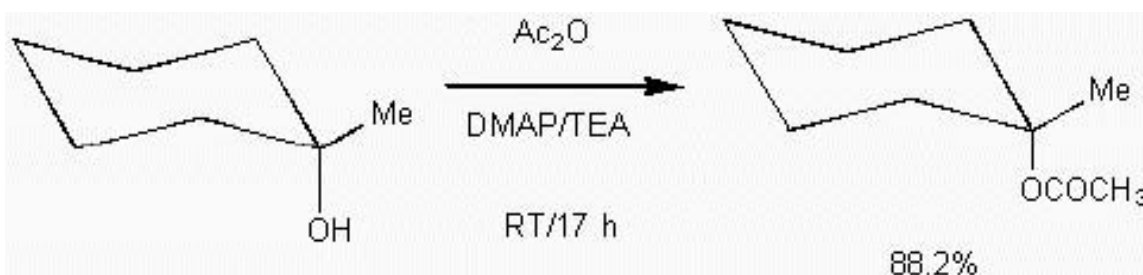
1. A solution of the alcohol (1) (220 mg, 0.473 mmol), acetic anhydride (1.0 mL), and pyridine (0.5 mL) in dry dichloromethane (5.0 mL) is prepared.
2. DMAP (catalytic amount) is added and the reaction mixture stirred at ambient temperature for 24 h.
3. The reaction mixture is diluted with ether (50 mL) and then is washed successively with copper sulfate solution, water, sodium bicarbonate solution, and brine. The organic phase is dried (anhydrous magnesium sulfate), filtered, and evaporated to afford a residue (210 mg). The residue is purified on silica gel (40 g) eluting with hexane:ethyl acetate (15:1) to give, after solvent evaporation, the pure acetate (2) (196 mg, 82%) as a colorless oil.

2.5. Acetylation of alcohols using acetyl chloride⁷



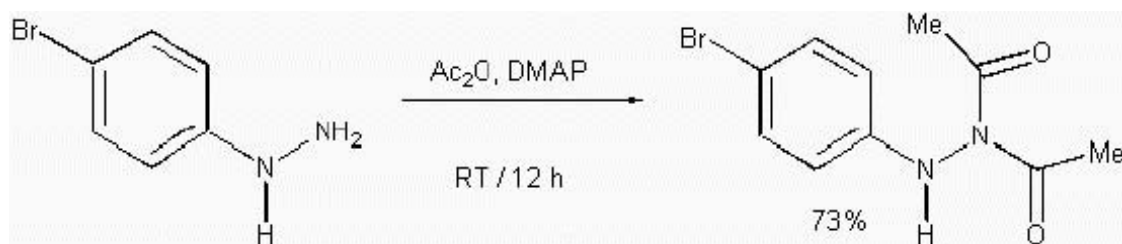
Compound (1), acetyl chloride, pyridine, and DMAP (catalytic amount) are stirred at 0 °C to give the acetylated product (2).

2.6. Acetylation of 1-methylcyclohexanol⁸



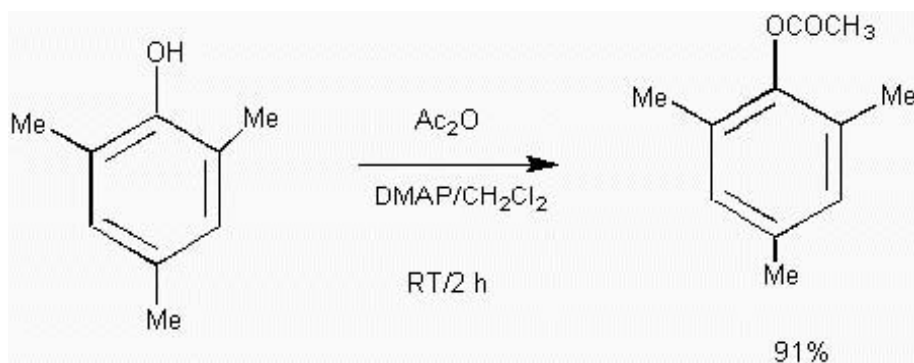
1. Acetic anhydride (20 mL, 0.21 mol) is added with stirring to 1-methylcyclohexanol (11.4 g, 0.1 mol), DMAP (0.5 g, 4.1 mmol), and triethylamine (20 mL, 0.15 mol).
2. The mixture is allowed to stand at room temperature for 17 h.
3. The reaction mixture is worked-up by initially adding water, followed by sodium carbonate until carbon dioxide evolution ceases and the aqueous layer remains basic. The organic layer is extracted with chloroform, dried over anhydrous sodium carbonate, and the solvent removed to give the crude product. Distillation at atmospheric pressure (b.p. 176°C) affords 1-methylcyclohexyl acetate (13.7 g, 88% yield).

2.7. (Arylhydrazines - N,N-diacetylation) : N,N-diacetylation of arylhydrazines⁹

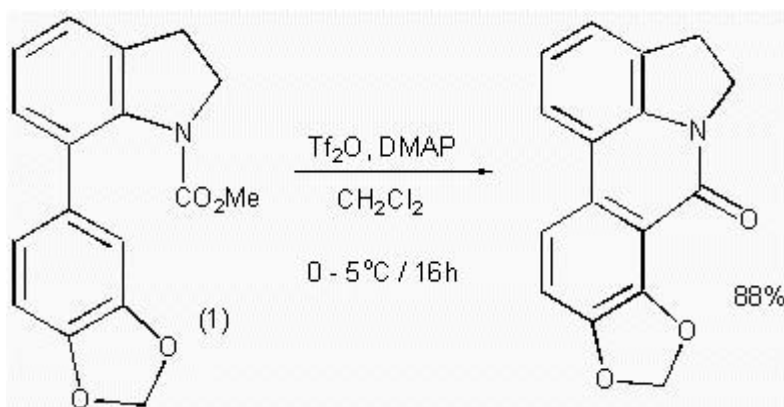


1. A stirred solution of 4-bromophenylhydrazine (0.01 mol) and DMAP (0.001 mol) in dry pyridine (10 mL) is prepared and cooled to 0°C. Acetic anhydride (0.02 mol) is added; the solution is allowed to warm to ambient temperature and is stirred for a further 12 h.
2. The reaction mixture is poured into 2 N hydrochloric acid (100 mL) and extracted with dichloromethane (3 x 50 mL). The combined methylene chloride solution is evaporated to yield an oily residue which is purified by preparative medium pressure liquid chromatography on silica (eluent ether) to afford *N,N*-diacetyl-2-(4-bromophenyl)hydrazide (1.98 g, 73%, m.p. 101°C).

2.8. Acetylation of mesitol¹⁰

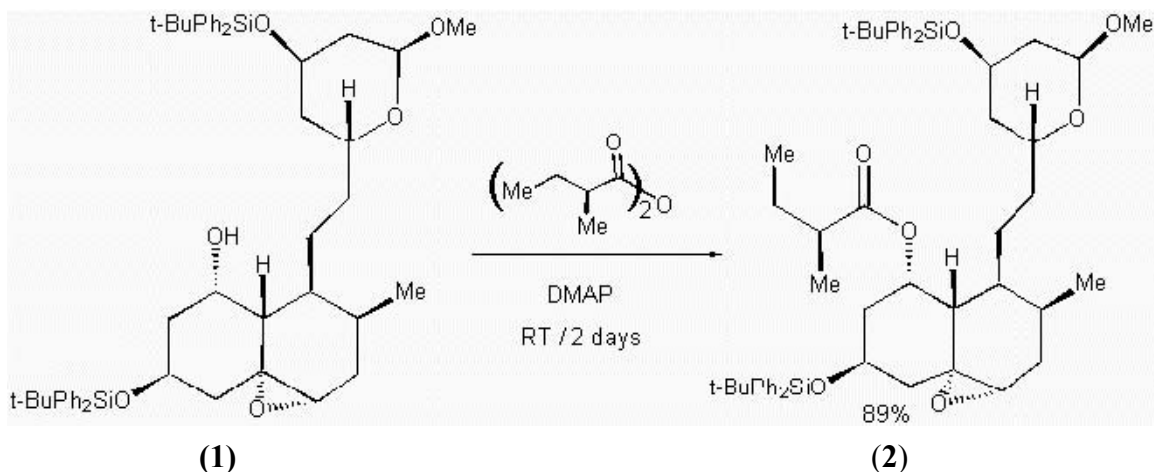


1. To a solution of mesitol (1.36 g, 10 mmol), and DMAP (1.5 g, 12 mmol) in dichloromethane (10 mL) is added acetic anhydride (1.3 g, 13 mmol).
2. An exothermic reaction ensues, and after 2 h, addition of methanol and evaporation of the solvents gives an oily residue.
3. The residue is suspended in ether and successively washed with 2 N hydrochloric acid and aqueous sodium bicarbonate solution. The ether layer is dried (anhydrous magnesium sulfate), filtered, and evaporated to afford 2,4,6-trimethylphenyl acetate (1.75 g, 98%).

2.9. Intramolecular: Bischler – Napieralski cyclization¹¹

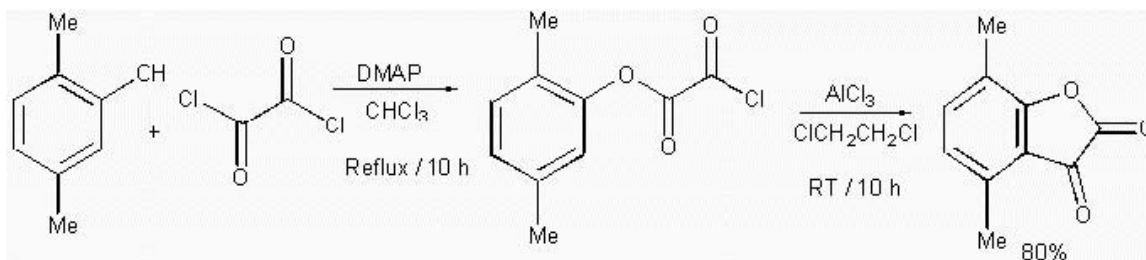
1. A solution of the carbamate (1) (69 mg, 0.23 mmol) and DMAP (85 mg, 0.69 mol), in anhydrous dichloromethane (6 mL) is stirred at 0-5 C. A 1.10 mol/dm³ solution of triflic anhydride (1.05 mL, 1.16 mmol) in anhydrous dichloromethane is prepared and this triflic anhydride solution (1.05 mL, 1.16 mmol) is added to this reaction mixture over 15 min.
2. The reaction mixture is stirred for a further 16 h, allowing the flask contents to warm to room temperature over this time period.
3. Dichloromethane (10 mL) is added to the reaction mixture and the mixture is successively washed with saturated sodium carbonate solution (1 x 5 mL), aqueous acetic acid (20% v/v) (1 x 5 mL) and saturated sodium carbonate solution (1 x 5 mL). The organic phase is dried (sodium sulfate), filtered and concentrated under reduced pressure to give a light brown solid. Recrystallization (twice from methanol) affords anhydrocorinone (40 mg) as fine white needles, m.p. 236 -238°C. The mother liquors were subject to preparative thin layer chromatography (silica, benzene:acetone, 8:2 elution) to produce additional anhydrocorinone (13 mg, 88% combined yield).

2.10. Synthesis of an intermediate leading to Pravastatin¹²



1. A solution of the epoxide (1) (1.30 g, 0.00156 mmol), DMAP (0.08 g), and (S)-(+)-2-methylbutyric anhydride (1.3 mL) in pyridine (5 mL) is prepared.
2. The reaction mixture is stirred for 2 days at ambient temperature.
3. The reaction mixture is quenched by the addition of water (1 mL) and stirred for a further 15 min. A mixture of hexane/ethyl acetate (4:1) (25 mL) is added, and the reaction mixture is washed with saturated potassium bicarbonate solution. Chromatography of the crude product (eluent hexane/ethyl acetate 4:1) affords the 2-methylbutyrate ester (1.30 g, 89%) (2).

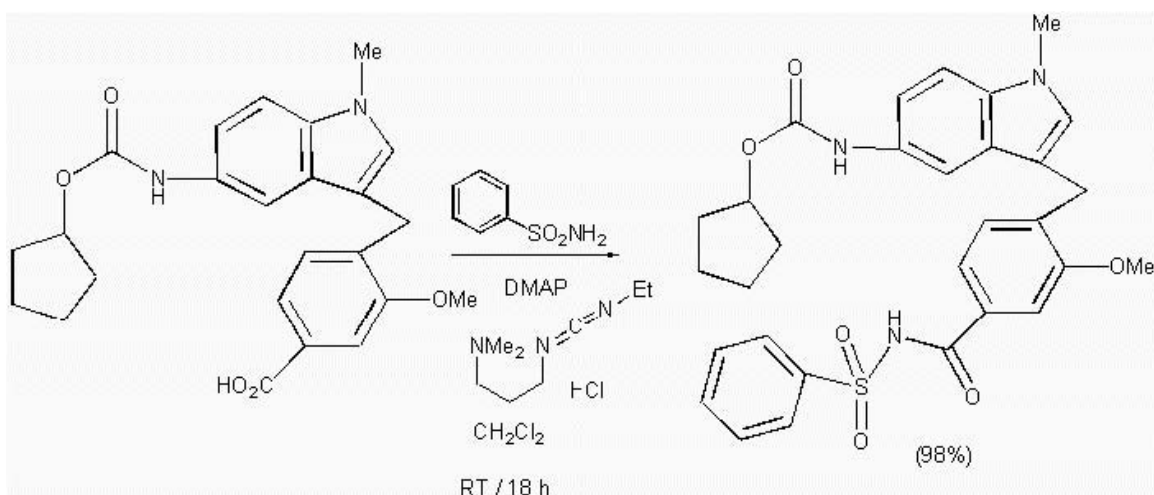
2.11. Synthesis of 2,3-dioxo-2,3-dihydrobenzofurans¹³



1. A solution of 2,5-dimethylphenol (12.2 g, 0.1 mol), oxalyl chloride (27.94 g, 0.22 mol), DMAP (0.5 g, 4.1 mmol) in chloroform (300 mL) are heated under reflux for 10 h (no 2,5-dimethylphenol detected by glc).
2. The reaction mixture is concentrated, the oily residue dissolved in 1,2-dichloroethane (100 mL) and dropped into a stirred suspension of aluminum chloride (40 g, 0.3 mol) in 1,2-dichloroethane (300 mL) at room temperature.
3. After 10 h the reaction mixture is hydrolyzed with water (100 mL), extracted with 1,2-

dichloroethane, dried (molecular sieves, 4 Å) and concentrated. The yellow-red residue is purified by column chromatography (silica 0.05 - 0.2 mm, eluent: chloroform). Appropriate fractions are combined, evaporated and the residue crystallized from petroleum ether to give 4,7-dimethyl-2,3-dioxo-2,3-dihydrobenzofuran (b.p. 40-60°C). Yield 80%.

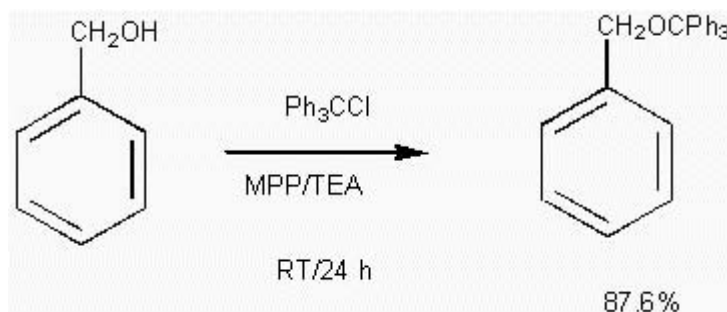
2.12. N-Acylation of sulfonamides: N-acylation of sulfonamide¹⁴



1. A solution of [5-(cyclopentyloxycarbonyl)amino-1-methylindol-3-ylmethyl]-3-methoxybenzoic acid (6.0 g), benzene sulfonamide (2.34 g), DMAP (1.84 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.86 g) in dichloromethane (100 mL) is prepared under a nitrogen atmosphere.
2. The solution is stirred at room temperature for 18 h.
3. The reaction mixture is quenched by pouring into 1 M hydrochloric acid (100 mL), the aqueous layer separated and extracted with dichloromethane (2 x 100 mL). The combined organic extracts are washed with water, brine, then dried with anhydrous magnesium sulfate and the filtered solution evaporated. The residual oil is purified by flash chromatography on silica gel (700 mL) eluting with hexane:dichloromethane:ethyl acetate (45:50:5 v/v/v) to give *N*-[4-[5-(cyclopentyloxycarbonyl)amino-1-methylindol-3-ylmethyl]-3-methoxybenzoyl]benzenesulfonamide (7.82 g, 98%).

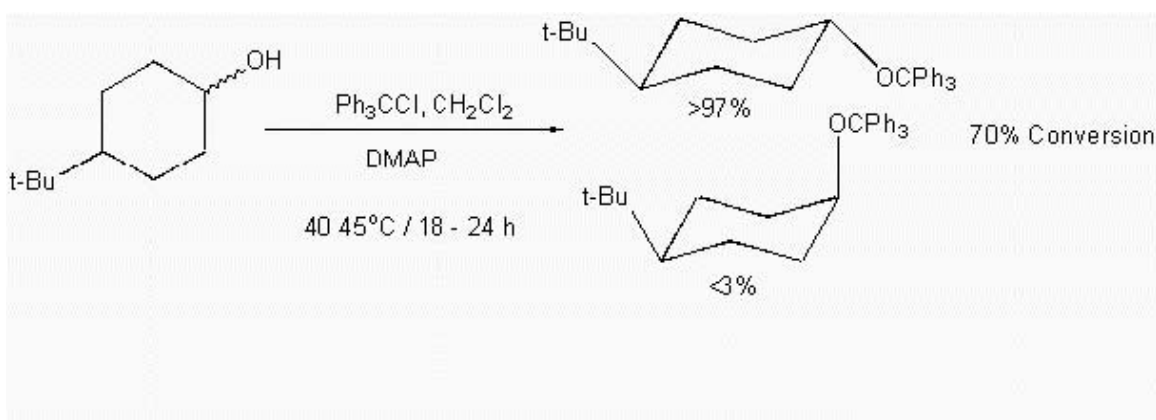
3. Alkylation

3.1. Tritylation of benzyl alcohol --- 4-(4'-methyl-1-piperidinyl)pyridine (MPP) as catalyst



- 1 To a solution of benzyl alcohol (2.17 g, 0.02 mol), MPP (0.15 g, 0.86 mmol), and triethylamine (7 mL, 0.05 mol) in dichloromethane (40 mL) is added trityl chloride (5.85 g, 0.021 mol).
- 2 The reaction mixture is allowed to stand at ambient temperature overnight.
- 3 The solvent is removed and the residue crystallized from ethanol (80 mL). Recrystallization from ethanol affords triphenylmethylbenzyl ether (6.2 g, 87.6%, m.p. 105-106°C).

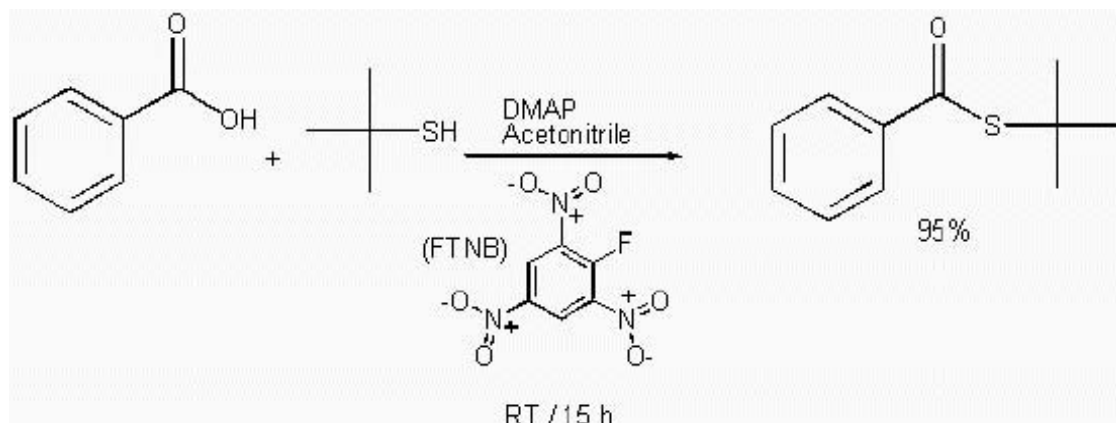
3.2. Tritylation of a *cis-trans* mixture of 4-*t*-butylcyclohexanols¹⁵



A mixture of 4-*t*-butylcyclohexanol, triphenylmethylchloride, and DMAP in dichloromethane are stirred and heated under reflux for 24 hours to give a 97:3 mixture of the tritylethers (70% conversion).

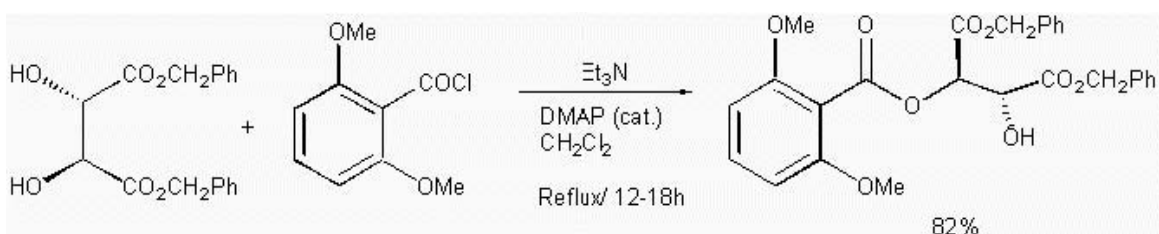
4. Benzoylation

4.1. Preparation of thiol esters¹⁶



1. To a solution of benzoic acid (123 mg, 1.0 mmol), 1-fluoro-2,4,6-trinitrobenzene (235 mg, 1.0 mmol), and DMAP (249 mg, 2.0 mmol) in acetonitrile (4 mL) is added *tert*-butanethiol (98 mg, 1.1 mmol).
2. The reaction mixture is stirred at ambient temperature for 4 h.
3. The precipitated salts are filtered off, the solution concentrated, the residue purified by filtration through a short column of silica gel (eluent dichloromethane) followed by evaporation of the solvent to afford the thiol ester (184 mg, 95%).

4.2. Synthesis of dibenzyl mono(2,6-dimethoxybenzoyl)tartrate from dibenzyl tartrate and 2,6-dimethoxybenzoyl chloride¹⁷



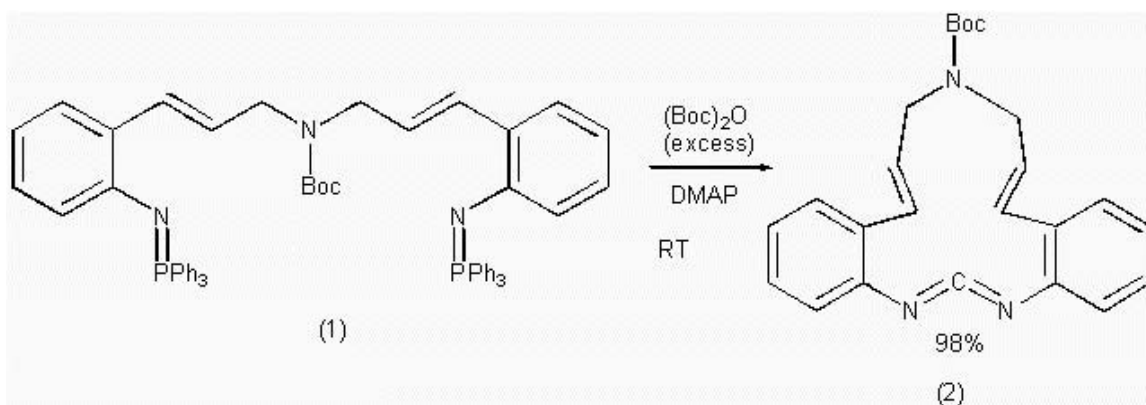
1. A mixture of dibenzyl tartrate (6.1 g, 18.5 mmol), triethylamine (4 mL, 28.8 mmol), DMAP (50 mg, 0.4 mmol) and dry dichloromethane (100 mL) is stirred and cooled to 0 C under a nitrogen atmosphere. To this mixture is added 2,6-dimethoxybenzoyl chloride (3.65 g, 18.2 mmol) over 1 h. The reaction mixture is allowed to warm to ambient temperature and

then heated under reflux for 12-18 h (monitored by TLC).

- The reaction mixture is allowed to cool to ambient temperature and is poured into water (100 mL). The aqueous phase is extracted with dichloromethane (2 x 75 mL); the organic phases are combined, dried over sodium sulfate, filtered, and concentrated to a viscous oil.
- This oil is purified by column chromatography on silica gel (eluent hexane, ether, dichloromethane 3:1:5) to afford dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (7.1-7.5 g, 78%-82%) as a clear oil.

5. Carbodiimide formation

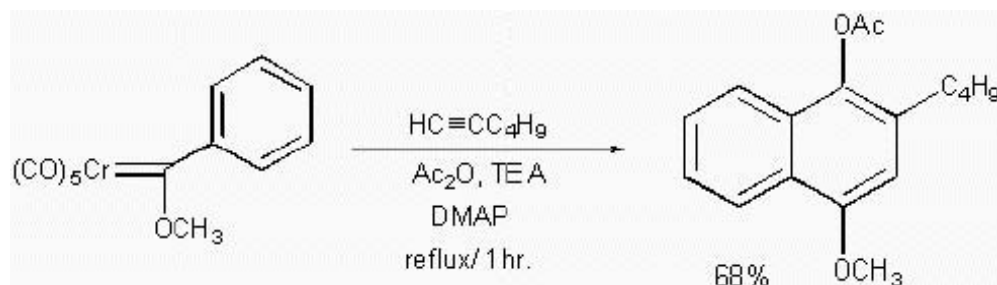
5.1. Carbodiimide preparation : preparation of cyclic carbodiimides¹⁸



The bis(iminophosphorane) (1), DMAP, dry dichloromethane, and a slight excess of di-*tert*-butyldicarbonate (Boc₂O) are stirred at room temperature to afford the cyclic carbodiimide (2) in 98% yield.

6. Carbonylation

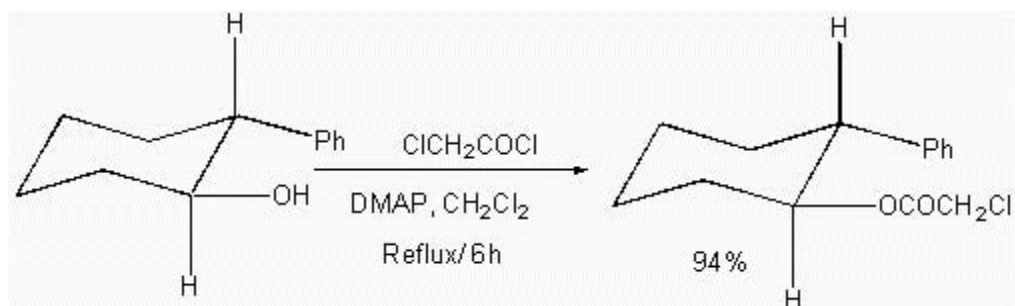
6.1. Synthesis of 1-Acetoxy-2-butyl-4-methoxynaphthalene using chromium carbene complexes¹⁹



- 1 A solution of DMAP (1.22 g, 10 mmol), tetrahydrofuran (500 mL), 1-hexyne (11.0 mL, 95.7 mmol), acetic anhydride (13.2 mL, 140 mmol), triethylamine (9.8 mL, 70 mmol), pentacarbonyl[phenyl(methoxy)chromium]carbene (20.0 g, 64.0 mmol), and tetrahydrofuran (100 mL) is heated under reflux in a nitrogen atmosphere.
- 2 Heating is maintained until TLC indicates the chromium complex is totally consumed, ~45-60min.
- 3 The solution is cooled to ambient temperature and silica gel (30 g) is added. Volatile organic material is removed under reduced pressure. The green solids are transferred to a filter funnel and washed with hexane until TLC indicates all products have been removed (5 x 100 mL). The hexane filtrate is concentrated under reduced pressure to give crude product contaminated with chromium hexacarbonyl. To this mixture is added isopropyl alcohol (20 mL) and the insoluble chromium hexacarbonyl removed by filtration. The isopropyl alcohol filtrate is concentrated under reduced pressure and the crude product purified by silica gel chromatography. Appropriate fractions are combined and the solvent removed under reduced pressure to give 1-acetoxy-2-butyl-4-methoxynaphthalene (11.8 g, 68% yield) as a light yellow oil which crystallizes on standing. NOTE: All operations should be conducted in a well-ventilated hood with breathing protection. The chromium carbene complex generally is contaminated with the very volatile and toxic chromium hexacarbonyl, which is also generated as a by-product of the reaction. NOTE: All solvents and liquid reagents were routinely deoxygenated prior to use with a slow stream of nitrogen.

7. Chloroacetylation

7.1. Chloroacetylation of *trans*-2-phenylcyclohexanol²⁰



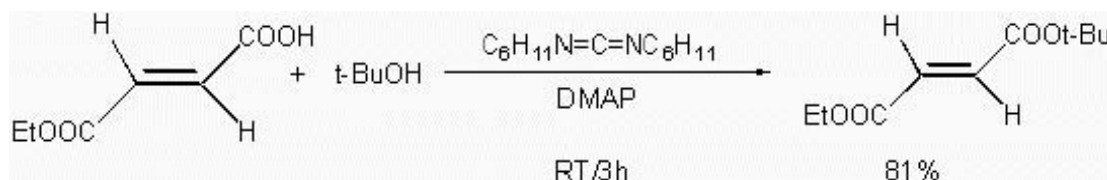
1. A solution of racemic *trans*-2-phenylcyclohexanol (100 g, 0.567 mol), chloroacetyl chloride (50 mL, 0.625 mol), and DMAP (300 mg, 0.0025 mol) in dichloromethane (250 mL) is

rapidly stirred and heated under reflux for 6 h. The reaction mixture is cooled, saturated sodium bicarbonate solution (350 mL) added, and the reaction mixture stirred for a further 3 h.

- The organic layer is separated, dried over anhydrous potassium carbonate, filtered, and the filtrate concentrated under reduced pressure to afford a dark brown oil.
- The oil is distilled through a 2-inch or 4-inch column packed with beads to give the racemic *trans*-2-phenylcyclohexyl chloroacetate (135 g, 94%) as a colorless liquid, b.p. 118-122°C at 0.3 mm.

8. Esterification

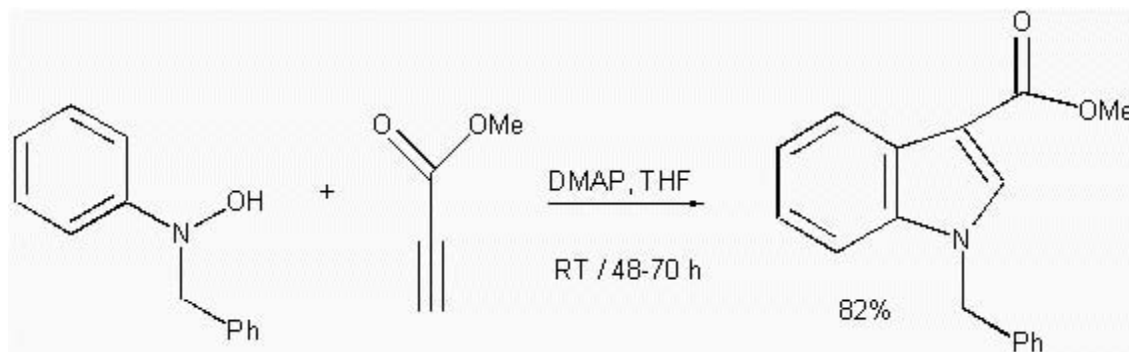
8.1. Esterification of monoethyl fumarate²¹



- A solution of monoethyl fumarate (28.83 g, 0.20 mol), dry dichloromethane (200 mL), *tert*-butyl alcohol (44.47 g, 0.60 mol), and DMAP (2.00 g, 0.16 mol) is prepared. Keeping the reaction mixture dry, the stirred solution is cooled to 0°C and dicyclohexylcarbodiimide (45.59 g, 0.22 mol) is added over 5 min.
- After stirring for a further 5 min. at 0°C, the reaction mixture is allowed to warm to ambient temperature and stirred for a further 3 h.
- The precipitated dicyclohexylurea is removed by filtration and the filtrate is washed with 0.5 N hydrochloric acid (2 x 50 mL) and saturated sodium bicarbonate solution (2 x 50 mL). Additional dicyclohexylurea is precipitated and removed by filtration of both layers to facilitate their separation. The organic phase is dried over anhydrous sodium sulfate, filtered and concentrated. The concentrate is distilled under reduced pressure affording *tert*-butyl ethyl fumarate (30.5-32.5 g, 76-81%, b.p. 105-107°C at 12 mm).

9. Indole synthesis

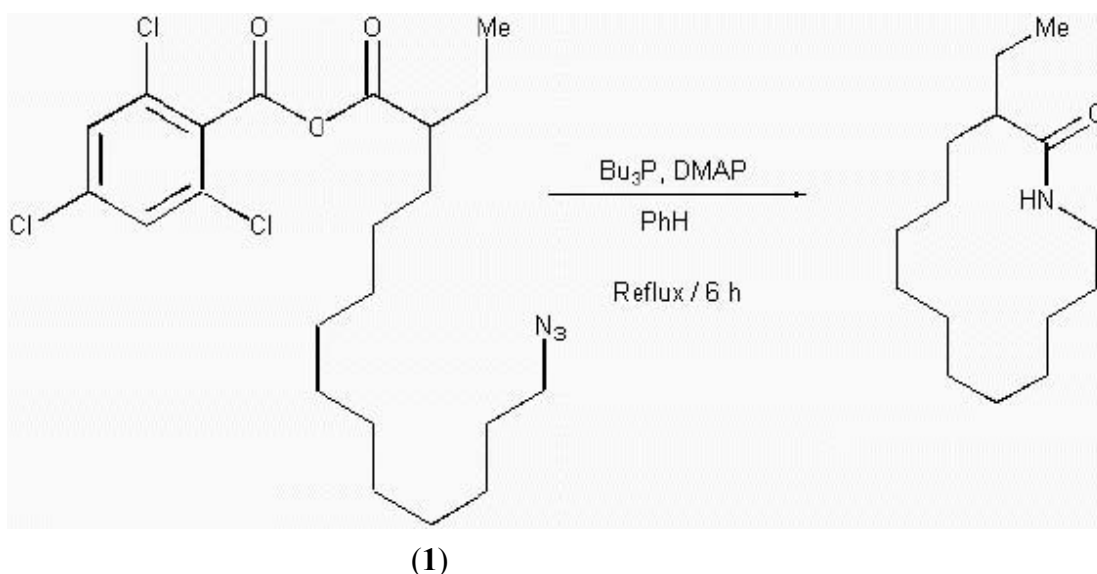
9.1. Synthesis of 1-benzyl-1*H*-indole-3-carboxylic acid methyl ester from *N*-benzyl-*N*-phenylhydroxylamine and methyl propiolate²²



- 1 To a solution of *N*-benzyl-*N*-phenylhydroxylamine (86.2 mg, 0.426 mmol), in THF (15.0 mL), is added 4A molecular sieves. The reaction mixture is cooled to 0 °C; DMAP (6.0 mg, 0.049 mmol) and methyl propiolate (54 mg, 0.562 mmol) are added.
- 2 Reaction mixture is stirred at 0 C for 1 h, then at room temperature for 48 h.
- 3 Ethyl acetate (5.0 mL) is added, and after filtration, the organic solution is washed with water (3 x 20 mL), brine, and then dried over magnesium sulfate. Following filtration, the organics are concentrated under reduced pressure and the resultant oil purified by use of a chromatotron (hexanes:ethyl acetate, 7:3 as eluent) to give 1-benzyl-1*H*-indole-3-carboxylic acid methyl ester (95.6 mg; 82% yield) as a white solid (m.p. 67.0-67.5°C).

10. Lactamization

10.1. Lactamization of 11-azidoundecanoic acid derivatives²³



A solution of tributylphosphine (10 mmol), DMAP (6 mmol) in benzene (200 mL) is heated under reflux. To this solution is added the azido acid (1) (1 mmol) dissolved in THF (5 mL) and benzene (50 mL) via a syringe pump over 6 h. Reflux is maintained for a further 1 h; the solution cooled, washed, dried, and concentrated. The residue is subject to "flash" chromatography (eluent dichloromethane/methanol), and the lactam is obtained in 51% yield.

11. Nucleophilic substitution

11.1. Synthesis of diethyl (2S,3R)-2-azido-3-hydroxysuccinate from diethyl (2R,3R)-2,3-epoxysuccinate²⁴



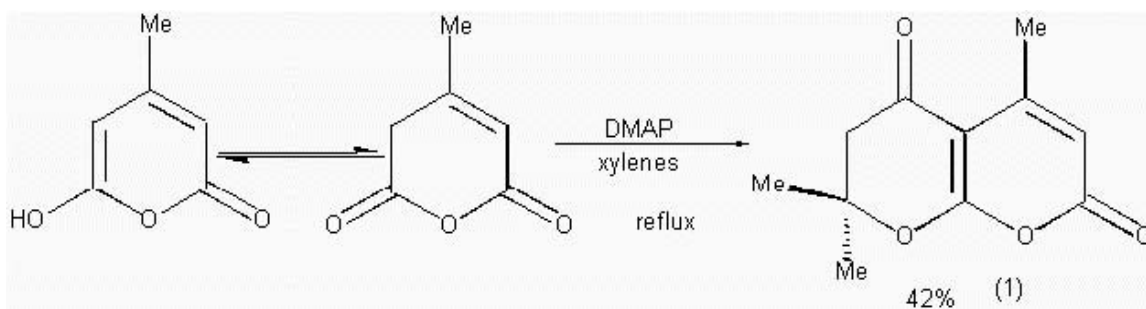
1. A solution of DMAP (3.45 g, 0.0282 mol), dry DMF (17 mL), and dry ethanol (1.93 mL, 0.0329 mol) is stirred under a nitrogen atmosphere and cooled in an ice-water bath. Azidothiomethylsilane (17.1 mL, 0.122 mol) is added dropwise by means of a syringe. A

heterogeneous mixture is formed which is allowed to warm to ambient temperature.

2. Stirring is continued for a further 15 min. at ambient temperature and a solution of diethyl (2R,3R)-2,3-epoxysuccinate (17.7 g, 0.0940 mol) in dry chloroform (50 mL) is rapidly added. Stirring is continued until the epoxide can no longer be detected in the reaction mixture (TLC) (approximately 40 h).
3. Water (300 mL) is added, the organic phase separated, and the aqueous phase extracted with a hexane-ether mixture (1:1 v/v) (60 mL x 4). The combined organic phases are added to a stirred 2.3 N solution of hydrogen chloride in ethanol (20 mL). (This solution is prepared by carefully mixing acetyl chloride (3.28 mL) with ethanol to give a total volume of 20 mL). A further quantity of ethanol (50 mL) is added and stirring continued for a further 30 min. at ambient temperature. The reaction mixture is transferred to a separating funnel and successively washed with water (4 x 50 mL), saturated sodium bicarbonate solution (1 x 50 mL), and saturated brine (1 x 50 mL). The organic phase is dried over sodium sulfate, filtered, concentrated, and then exposed to high vacuum affording 96-98% pure diethyl (2S, 3R)-2-azido-3-hydroxysuccinate (18.6 g, 86%) as a pale yellow oil.

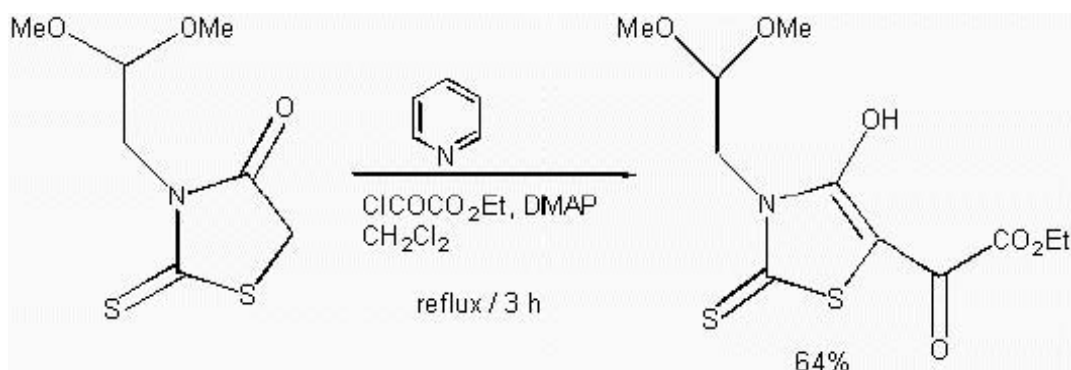
12. Rearrangement

12.1. Synthesis of intermediate in the two-step transformation of pyrone to 4-chromanone²⁵



4-Methyl-6-hydroxy-2-pyrone in xylenes is heated under reflux in the presence of DMAP to afford the coumarochromanone (1) (42%, m.p. 153°C).

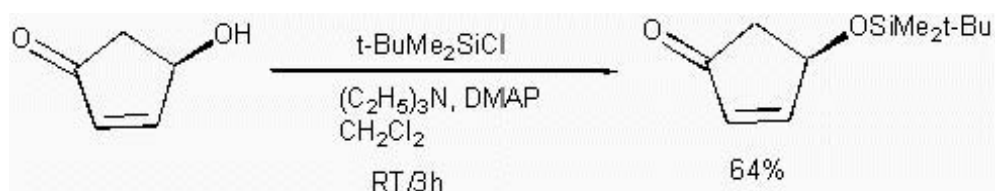
12.2. Synthesis of ethyl 3-(2,2-dimethoxyethyl)-4-oxo-2-thioxothiazolidin-5-yl-glyoxylate²⁶



- 1 A solution of 3-(2,2-dimethoxyethyl)-2-thioxothiazolidin-4-one (4.21 g), pyridine (3.16 g), DMAP (122 mg), ethoxalyl chloride (4.7 mL), in anhydrous dichloromethane (50 mL) is heated under reflux for 3 h.
- 2 Dichloromethane (50 mL) is added to the reaction mixture which is then repeatedly washed with water, dried, and evaporated. The residue is taken up with ether, and after 15 h a small amount of solid filtered off. The rhodanine salt is precipitated by the addition of saturated aqueous potassium hydrogen carbonate, filtered, washed with ether and then with a small amount of hydrogen carbonate solution.
- 3 The crude salt (5.5 g, 78%) is suspended in water and acidified with citric acid (10 g). Chloroform is added to dissolve the precipitate; the chloroform solution is dried and evaporated. Titration of the residue with light petroleum and crystallization from ether-light petroleum affords ethyl 3-(2,2-dimethoxyethyl)-4-oxo-2-thioxothiazolidin-5-yl-glyoxylate (4.11 g, 64%) as yellow needles, m.p. 80-81°C.

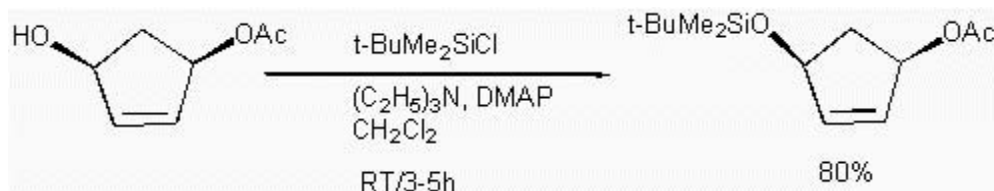
13. Silylation

13.1. Synthesis of (4R)-(+)-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one from (4R)-(+)-Hydroxy-2-cyclopenten-1-one²⁷



- 1 A solution of (4R)-(+)-hydroxy-2-cyclopenten-1-one (7.7 g, 78 mmol), DMAP (0.96 g, 7.8 mmol) and triethylamine (20 g, 200 mmol), in dry dichloromethane (150 mL) is prepared, under nitrogen, and cooled with an ice-water bath.
- 2 A solution of *tert*-butyldimethylsilylchloride (14.2 g, 94 mmol) in dry dichloromethane (50 mL) is added over 10 min. The ice-water bath is removed, and the reaction mixture is stirred at room temperature for 3 h.
- 3 Water (100 mL) is added, the organic layer separated and the aqueous phase extracted with dichloromethane (3 x 50 mL). The combined organic solutions are dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue is passed down a short silica column (eluent 5% ethyl acetate in petroleum ether, b.p. 35-60°C). Appropriate fractions are combined, evaporated and the resulting oil distilled in a short path distillation apparatus (b.p. 60°C at 0.1 mm) to give a colorless oil (13.2 g). Crystallization of this material from pentane gave the product (10.6 g, 64%) as colorless needles.

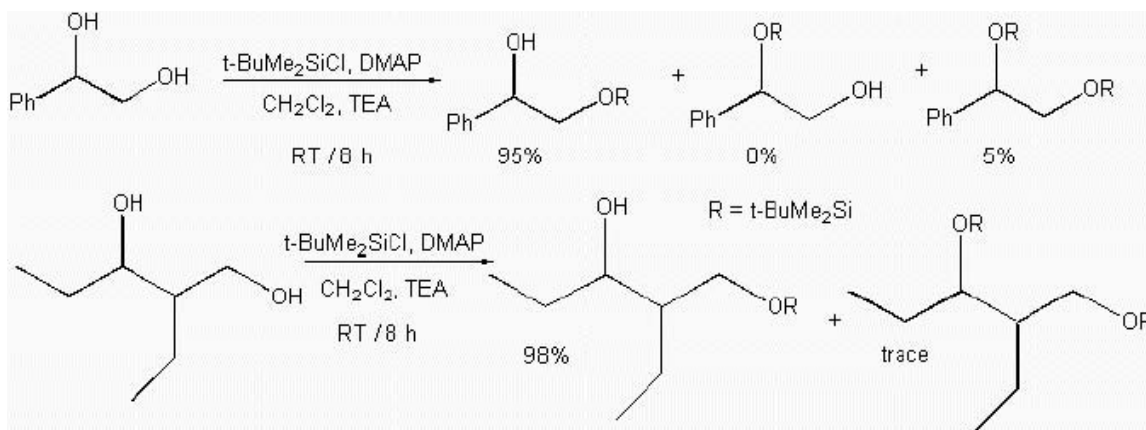
13.2. Synthesis of (1R,4S)-(-)-4-*tert*-butyldimethylsiloxy-2-cyclopentenyl acetate from (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate²⁸



- 1 To (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate (7.67 g, 54 mmol), DMAP (660 mg, 5.4 mmol), triethylamine (17 mL, 122 mmol), and dichloromethane (175 mL), cooled to 0°C with an ice-water bath under a nitrogen atmosphere, *tert*butyldimethylsilyl chloride (10.24 g, 68 mmol) is added in one portion.
- 2 The ice-water bath is removed and the mixture is allowed to warm to room temperature and is stirred for 3 h. At this point, more silyl chloride is added if necessary and stirred for another 2 h. (The progress of the reaction is easily monitored by TLC analysis. Silyl chloride is added until the starting hydroxy-acetate is no longer detected.)
- 3 After 5 h, water (200 mL) is added, the mixture transferred to a separating funnel, and the organic phase separated. The aqueous phase is extracted with dichloromethane (3 x 100 mL) and the combined organic layers are washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL) prior to drying over anhydrous magnesium sulfate. After filtration and solvent removal, the resulting yellow oil is purified by bulb-to-bulb distillation at 0.4 -0.6 mm (pot temperature 80-100°C) to give (1R,4S)-(-)-4-*tert*-butyldimethylsiloxy-2-

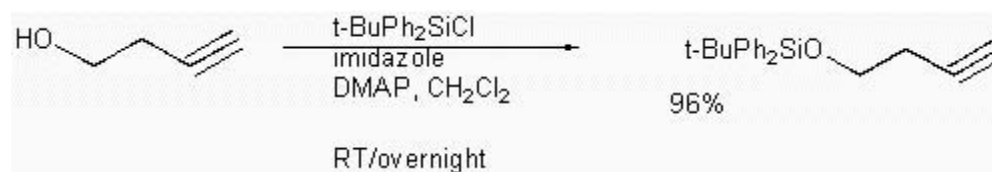
cyclopentenyl acetate (10.67-11.08 g, 77-80% yield) as a colorless liquid.

13.3. Silylation of alcohols²⁹



A solution of the diol (1 eq.), triethylamine (1.1 eq.), and DMAP (0.04 eq.) in dichloromethane is stirred at room temperature to produce the silylated alcohols as shown above.

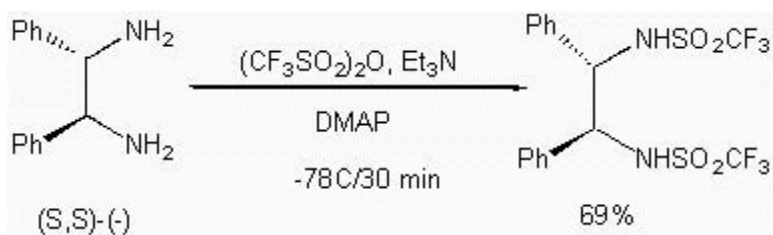
13.4. *t*-Butyldiphenylsilylation of 3-butyn-1-ol³⁰



- 1 To a stirred solution of butyn-1-ol (2.1 g, 30 mmol) in dry dichloromethane (60 mL) is added *tert*-butyldiphenylchlorosilane (8.5 g, 31 mmol) and the resultant reaction mixture is immersed in a water bath. Imidazole (2.86 g, 42 mmol) and DMAP (0.37 g, 3 mmol) are added and the reaction flask removed from the water bath.
- 2 The reaction mixture is stirred at room temperature overnight.
- 3 The white precipitate is removed by filtration through a sintered glass funnel and the precipitate is washed with cold dichloromethane (50 mL). The combined filtrates are washed successively with 1 M hydrochloric acid (50 mL), and water (100 mL); the organic layer is dried (anhydrous magnesium sulfate), filtered and concentrated. Bulb to bulb distillation of the residue affords *tert*-butyl(but-3-ynyloxy)diphenylsilane (8.90 g, 96%, b.p. 150-151°C at 1 mm.)

14. Sulfonylation

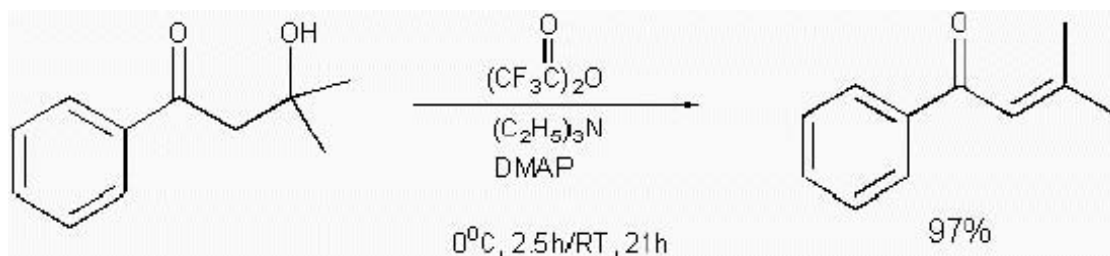
14.1. Bistriflamide of (1*S*,2*S*)-1,2-diphenylethylenediamine³¹



- 1 A solution of (1*S*,2*S*)-1,2-diphenylethylenediamine (1.06 g, 5 mmol), triethylamine (2.1 mL, 15 mmol), and DMAP (12.2 mg, 0.1 mmol) in methylene chloride (25 mL) is cooled to -78°C .
- 2 To this stirred solution is added trifluoromethanesulfonic anhydride (3.39 g, 12 mmol) dropwise. The cooling bath is removed and flask contents allowed to reach ambient temperature (30 min).
- 3 The reaction mixture is poured into a 4% sodium bicarbonate solution, the phases separated and the aqueous phase extracted with dichloromethane (15 mL). The combined organic phases are successively washed with hydrochloric acid (1*N*) and brine before being dried over anhydrous sodium sulfate. After filtration, the filtrate is concentrated under reduced pressure and the residue subjected to flash chromatography on silica gel (100 g, eluent ethyl acetate-hexane 15% v/v) to afford the bistriflamide of (1*S*,2*S*)-1,2-diphenylethylenediamine (1.64 g, 69%), as colorless crystals, m.p. $213\text{--}214^\circ\text{C}$.

15. Trifluoroacetylation

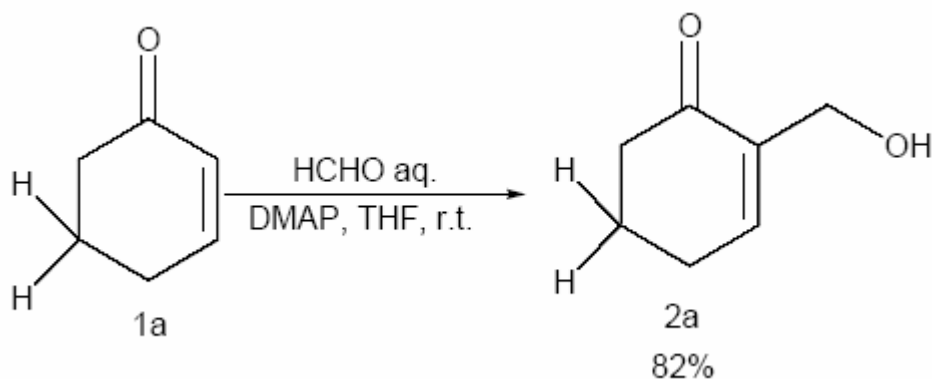
15.1. Synthesis of isopropylideneacetophenone from 3-hydroxy-3-methyl-1-phenyl-1-butanone³²



- 1 A solution of 3-hydroxy-3-methyl-1-phenyl-1-butanone in dry dichloromethane (60 mL) is stirred under an inert atmosphere and cooled in an ice bath. To this cooled solution is added triethylamine (28.5 g), DMAP (catalytic amount), and dichloromethane (20 mL). A solution of trifluoroacetic acid (25.8 g) in dichloromethane (40 mL) is added dropwise over 15 min. and the reaction mixture is stirred for a further 2.5 h. The ice bath is removed and stirring is continued for a further 21 h at room temperature (approximately 30°C).
- 2 The rate of stirring is increased and saturated sodium carbonate (100 mL), water (100 mL), and ether (300 mL) are added to the reaction mixture. The organic layer is separated and the water layer is extracted with ether (1 x 100 mL). The combined organic phases are washed with brine, dried over magnesium sulfate, and filtered.
- 3 The ether solution is condensed and the residue is distilled under vacuum to afford isopropylideneacetophenone (14.5-16.0 g, 88-97% yield, b.p. 73-75°C at 0.4 mm).

16. Baylis-Hillman reaction

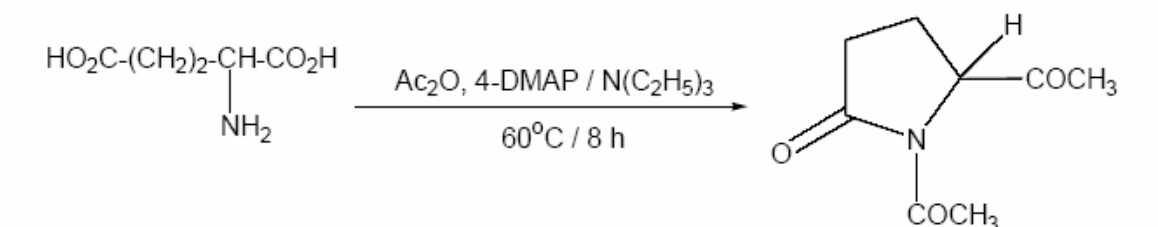
16.1. DMAP-Catalyzed hydroxymethylation of 2-cyclohexenones in aqueous medium through Baylis-Hillman reaction³³



- 1 A solution of compound (1a) (24 g, 0.25 mol), 30% aqueous formaldehyde (50 mL, 0.5 mol), THF (50 mL) and DMAP (3.05 g, 25 mmol), is stirred at room temperature for 15 hours. The solution is then acidified dropwise with aqueous HCl (1.5 N).
- 2 The reaction mixture is extracted with methylene chloride and washed successively with sodium bicarbonate and brine. Chromatography of the crude product (ether-methylene chloride (3:1) eluent) gave 82% yield of pure 2a as a yellow oil.

17. Dakin-West Reaction reaction

17.1 α -amino dicarboxylic acids with carboxylic acid anhydrides - Dakin-West reaction³⁴



- 1 To glutamic acid (7.3 g) and acetic anhydride (25 mL) is added DMAP (50 mg) and triethylamine (25 mL).
- 2 The solution is stirred at 60 C for 8 h.
- 3 The resulting product is distilled under vacuum to give 1,5-diacetyl-2-pyrrolidone (5.8 g, 78%).

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