

Koichi Tanaka

Solvent-free Organic Synthesis



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Solvent-free Organic Synthesis

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Koichi Tanaka

Solvent-free Organic Synthesis



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Foreword

Waste prevention and environmental protection are major requirements in an overcrowded world of increasing demands. Synthetic chemistry continues to develop various techniques for obtaining better products with less environmental impact. One of the more promising approaches is solvent-free organic synthesis; this book of Koichi Tanaka collects recent examples in this field in a concise way so that their performance and merits can be easily judged. This endeavor is very welcome, as most recent syntheses and educational textbooks largely neglect solvent-free techniques.

The field of solvent-free organic synthesis covers all branches of organic chemistry. It includes stoichiometric solid–solid reactions and gas–solid reactions without auxiliaries yielding single products in pure form that do not require solvent-consuming purification steps after the actual reaction. It also includes some stoichiometric melt reactions that occur without auxiliaries and with quantitative yield due to direct crystallization of the product. Although such reactions are by far the best choices for application of solvent-free chemistry, the advantages of avoiding solvents should not be restricted to them. Solvent-free conversions can be profitably applied even when unfavorable crystal packing and low melting points impede solid-state reaction and when melt reactions without direct crystallization do not provide 100% yield of one product. The higher concentration of reactants in the absence of solvents usually leads to more favorable kinetics than in solution. In some cases auxiliaries such as catalysts or solid supports may be required. Solid supports and microwave heating, instead of cooling or convection heating, are frequently used in solvent-free reaction steps. However, costly procedures should always be compared with inexpensive, waste-free techniques that do not require steps such as recrystallization, extraction, chromatography, or disposal of distillation residues.

The attitude implied in most current publications restricts (or extends) the term ‘solvent-free’ to the stoichiometric application of solid or liquid reagents, with less than a 10% excess of a liquid or soluble reagent and/or less than 10% of a liquid or soluble catalyst. It seems widely accepted in the field that solvents used for pre-adsorption of reagents to a support or for desorption, purification, and isolation of the products are not counted in ‘solvent-free’ syntheses. On the other hand, photolysis of insoluble solids in (usually aqueous) suspensions undoubtedly qualifies for inclusion as a solvent-free technique, but not the taking up of reagents from a liquid for reaction with a suspended solid.

Reacting gases may be in excess if they react with solids and do not condense in liquid phases, but supercritical media are clearly not the subject of solvent-free chemistry and deserve their own treatment. For practical reasons, this book does not deal with homogeneous or contact-catalyzed gas-phase reactions. Furthermore, very common polymerizations (except for solid-state polymerizations), protonations, solvations, complexations, racemizations, and other stereoisomerizations are not covered, to concentrate on more complex chemical con-

versions. This strategy allowed for presenting diverse reaction types and techniques, including those that proceed only in the absence of liquid phases, in one convenient volume.

The performance and scalability of the various techniques is most easily compared in a side-by-side format. With respect to experimental procedures, it is now recognized that many chemical conversions (e.g., formation of C–N or C–C bonds) that were reported to require solid supports with catalytic activity and microwave irradiation (and thus introduced environmental concerns) do not require such auxiliaries or irradiation. They occur exothermally at low temperatures with quantitative yields and without solvent-consuming workups even on a large scale.

This valuable compilation will become a useful resource for the development of improved, environmentally benign syntheses in industry and academia with the aims of avoiding catalysts and saving resources wherever possible and of preventing all the waste that is produced by using auxiliaries and by unnecessarily creating nonuniform reactions with less than 100% yield. This clearly designed and structured book on solvent-free organic synthesis will be of great value for the broader application of better synthetic techniques and thus for a better environment.

Gerd Kaupp
University of Oldenburg

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Preface

The elimination of volatile organic solvents in organic syntheses is a most important goal in 'green' chemistry. Solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards, and toxicity.

The development of solvent-free organic synthetic methods has thus become an important and popular research area. Reports on solvent-free reactions between solids, between gases and solids, between solids and liquid, between liquids, and on solid inorganic supports have become increasingly frequent in recent years.

This volume is a compilation of solvent-free organic reactions, covering important papers published during the past two decades. It contains graphical summaries of 537 examples of solvent-free organic reactions and is divided into 14 chapters:

1. Reduction,
2. Oxidation,
3. Carbon–Carbon Bond Formation,
4. Carbon–Nitrogen Bond Formation,
5. Carbon–Oxygen Bond Formation,
6. Carbon–Sulfur Bond Formation,
7. Carbon–Phosphorus Bond Formation,
8. Carbon–Halogen Bond Formation,
9. Nitrogen–Nitrogen Bond Formation,
10. Rearrangement,
11. Elimination,
12. Hydrolysis,
13. Protection,
14. Deprotection.

Each summary includes a structure scheme, an outline of the experimental procedure, and references to help the reader.

I hope that this volume will contribute to the studies of organic chemists in industry and academia and will encourage the pursuit of further research into solvent-free organic synthesis.

Koichi Tanaka
Ehime University

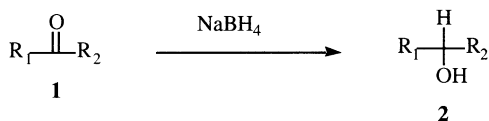
1 Reduction

1.1 Solvent-Free Reduction

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, NaBH₄, alcohol



- a: R₁; R₂ = Ph
- b: R₁=*trans*-PhCH=CH; R₂=Ph
- c: R₁=2-naphthyl; R₂=Me
- d: R₁=PhCH(OH); R₂=Ph
- e: R₁=PhCH₂; R₂=Ph
- f: R₁, R₂=4-*t*-Bu-cyclohexyl

Exerimental procedures:

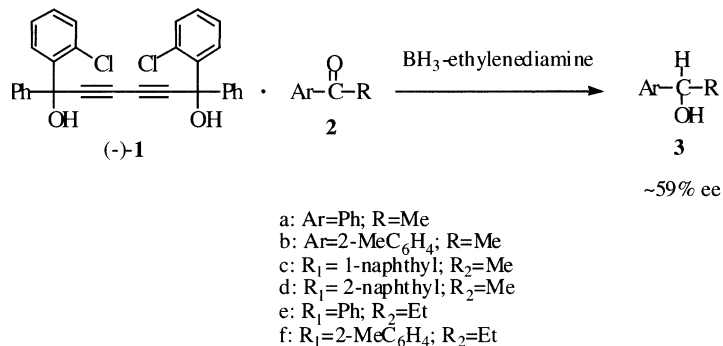
When a mixture of the powdered ketones and a ten-fold molar amount of NaBH₄ was kept in a dry box at room temperature with occasional mixing and grinding using an agate mortar and pestle for 5 days, the corresponding alcohols were obtained in good yields.

References: F. Toda, K. Kiyoshige, M. Yagi, *Angew. Chem. Int. Ed. Engl.*, **28**, 320 (1989).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, enantioselective reduction, BH₃-ethylenediamin complex, inclusion complex, alcohol

**Exerimental procedures:**

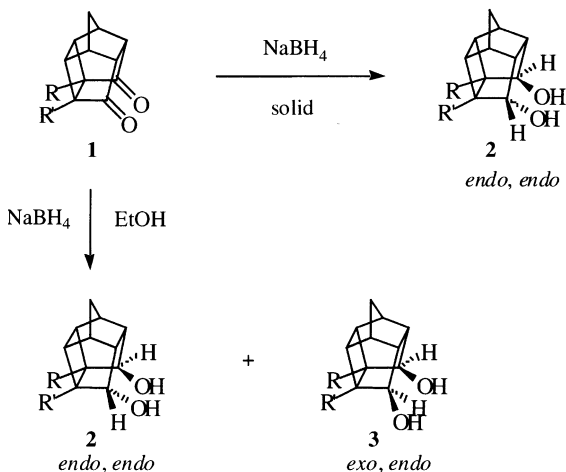
A mixture of finely powdered inclusion complex of (-)-**1** with **2** was kept under N₂ at room temperature for 24 h by occasional stirring. The reaction mixture was decomposed with water and extracted with ether. The ether solution was washed with dilute HCl, dried, and evaporated to give crude alcohols. Distillation of the crude alcohols in vacuo gave pure alcohols.

References: F. Toda, K. Mori, *Chem. Commun.*, **1245** (1989).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: cage diketone, sodium borohydride, alcohol



a: R=R'=H; b: R,R'=-CH₂CH₂-; c: R,R'=-CH=CH-

Exerimental procedures:

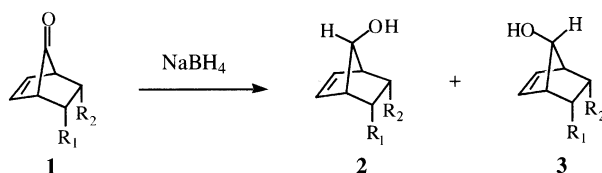
Cage diketone **1a** (87 mg, 0.50 mmol) and NaBH₄ (400 mg, excess) were ground together under an argon atmosphere into a fine powder, thereby producing an intimate solid mixture. The resulting powdery mixture was agitated under argon at room temperature for 7 days. Water (15 mL) then was added, and the resulting mixture was extracted with CHCl₃ (3×20 mL). The combined extracts were washed with water (30 mL), dried (Na₂SO₄), and filtered, and the filtrate was concentrated in vacuo to afford pure *endo,endo*-diol **2a** (89 mg, 100%) as a colorless microcrystalline solid: mp 275–276 °C.

References: A. P. Marchand, G. M. Reddy, *Tetrahedron*, **47**, 6571 (1991).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: 7-norbornenone, NaBH₄, π -face selectivity, alcohol



- a: R₁=R₂=COOCH₃
 b: R₁=H; R₂=COOCH₃
 c: R₁=H; R₂=CN
 d: R₁=R₂=CH₂OCH₃

Exerimental procedures:

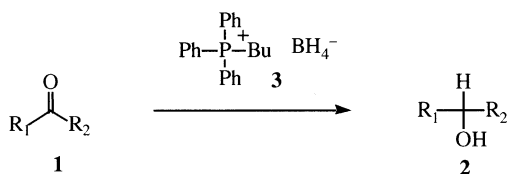
A mixture of **1a** and NaBH₄ (excess) was fully ground and left aside in a sample vial (1–2 days, sonication reduces the reaction time to a few hours). Usual work-up led to the formation (80%) of **2a** and **3a** in 87:13 ratio.

References: G. Mehta, F. A. Khan, K. A. Lakshmi, *Tetrahedron Lett.*, **33**, 7977 (1992).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: ketone, aldehyde, carboxylic acid chloride, butyltriphenylphosphonium tetraborate, alcohol



- | | |
|--|---|
| a: R ₁ =Ph; R ₂ =H | o: R ₁ =2,5-(MeO) ₂ C ₆ H ₃ ; R ₂ =H |
| b: R ₁ =2-MeOC ₆ H ₄ ; R ₂ =H | p: R ₁ =3,4-(MeO) ₂ C ₆ H ₃ ; R ₂ =H |
| c: R ₁ =3-MeOC ₆ H ₄ ; R ₂ =H | q: R ₁ =3,5-(MeO) ₂ C ₆ H ₃ ; R ₂ =H |
| d: R ₁ =4-MeOC ₆ H ₄ ; R ₂ =H | r: R ₁ ,R ₂ =(CH ₂) ₅ ⁻ |
| e: R ₁ =2-BrC ₆ H ₄ ; R ₂ =H | s: R ₁ ,R ₂ =(CH ₂) ₄ ⁻ |
| f: R ₁ =4-BrC ₆ H ₄ ; R ₂ =H | t: R ₁ =Ph; R ₂ =Me |
| g: R ₁ =2-MeC ₆ H ₄ ; R ₂ =H | u: R ₁ =(CH ₂) ₆ ⁻ ; R ₂ =H |
| h: R ₁ =4-MeC ₆ H ₄ ; R ₂ =H | v: R ₁ =PhCH=CH; R ₂ =H |
| i: R ₁ =2-ClC ₆ H ₄ ; R ₂ =H | w: R ₁ =PhCH=CH; R ₂ =Me |
| j: R ₁ =3-ClC ₆ H ₄ ; R ₂ =H | x: R ₁ =Ph; R ₂ =Cl |
| k: R ₁ =4-ClC ₆ H ₄ ; R ₂ =H | y: R ₁ =PhCH ₂ ; R ₂ =Cl |
| l: R ₁ =2-NO ₂ C ₆ H ₄ ; R ₂ =H | z: R ₁ =4-NO ₂ C ₆ H ₄ ; R ₂ =Cl |
| m: R ₁ =3-NO ₂ C ₆ H ₄ ; R ₂ =H | |
| n: R ₁ =4-NO ₂ C ₆ H ₄ ; R ₂ =H | |

Experimental procedures:

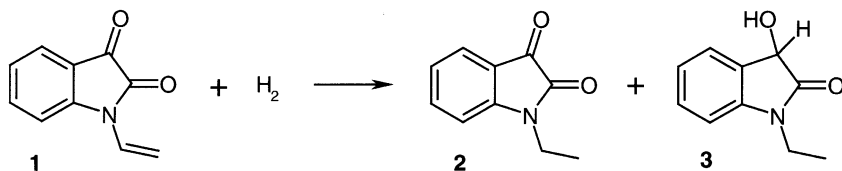
A mortar was charged with aldehyde, ketone, or carboxylic acid chloride and reducing reagent **3**. The mixture was ground at room temperature with a pestle until TLC showed complete disappearance of the starting material. The mixture was then extracted with CCl₄ (2×10 mL). Evaporation of the solvent gave the corresponding alcohols. The product was purified by column chromatography on silica gel using a mixture of ethyl acetate/n-hexane (10:90) as eluent.

References: A. R. Hajipour, S. E. Mallakpour, *Synth. Commun.*, **31**, 1177 (2001).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: N-vinylisatin, hydrogenation, gas-solid reaction, N-ethylidioxindole, N-ethylisatin



Experimental procedure:

Powdered crystals of **1** (670 mg, 3.9 mmol) that were recrystallized from *n*-hexane were evacuated in a 1 L flask and heated to 45 °C. Hydrogen gas was fed in from a steel cylinder (1 bar, 45 mmol) and the system kept at 45 °C for 2 days. The crystals changed their appearance and contained 67 mg (10%) unreacted **1**, 502 mg (74%) **2** and 110 mg (16%) **3**. The products were separated by preparative TLC on 200 g SiO₂ with dichloromethane.

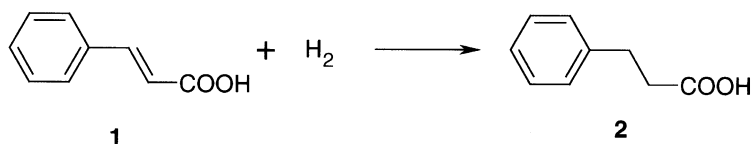
If sublimed **1** was equally treated with H₂, no hydrogenation occurred. Thus, residual Pd impurities from the synthesis of **1** appear to activate the hydrogen in these solid-state reactions.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: cinnamic acid, hydrogenation, gas-solid reaction, 3-phenylpropionic acid

**Experimental procedure:**

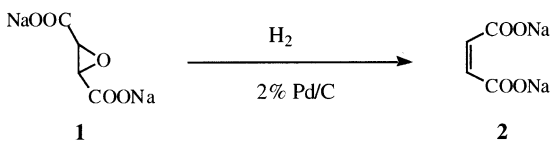
Cinnamic acid crystals **1** were doped by inclusion of some Pd (compound) upon recrystallization from methanol with Na₂[PdCl₄] (10⁻⁴ mol L⁻¹). Such crystals **1** were hydrogenated with excess H₂ at 1 bar and 30 °C for 6 days and yielded 48% of **2**.

References: G. Kaupp, D. Matthies, *Mol. Cryst. Liq. Cryst.*, **161**, 119 (1988).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: epoxide, disodium *trans*-epoxysuccinate, palladium catalyst, disodium malate, alkene



Experimental procedures:

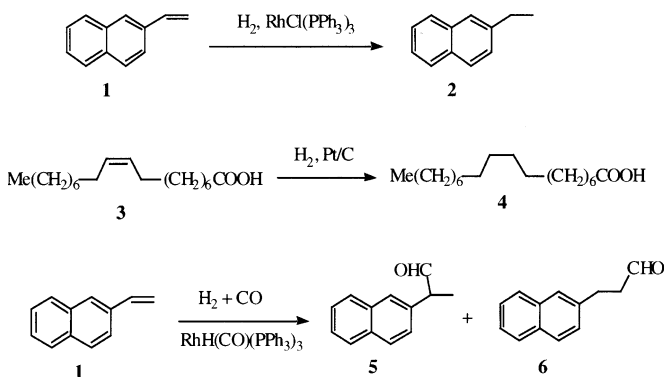
A supported palladium catalyst (0.50 g) was prepared with hydrogen gas at 200 °C for 30 min. The catalyst was mixed with disodium *trans*-epoxysuccinate (0.10 g), and the mixture was ground well with a mortar and pestle at room temperature. The mixture was placed in an autoclave and then shaken in the presence of hydrogen gas (9.0 MPa) at 100 °C for 14 h.

References: T. Kitamura, T. Harada, *J. Mol. Catal.*, **148**, 197 (1999).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: 2-vinylnaphthalene, hydrogenation, hydroformylation, subcritical CO₂

**Experimental procedures:**

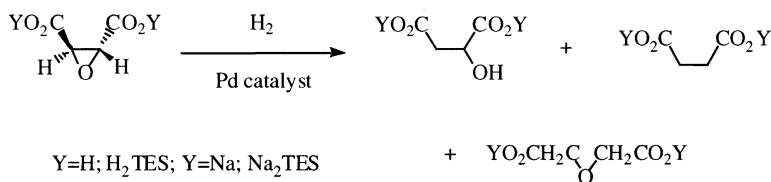
The hydrogenation of vinylnaphthalene **1** was performed by mixing solid chloro-tris(triphenylphosphine)rhodium catalyst (7.0 mg, 7.6 μmol) with solid 2-vinylnaphthalene (350 mg, 2.27 mmol, substrate:Rh=300:1), both fine powders. The mixture was placed, with a stirring bar, into a 22 mm diameter flat-bottomed glass liner in a 160-mL high-pressure vessel, which was then sealed and warmed to 33 °C in a water bath. The vessel was flushed and pressurized with H₂ to 10 bar. This was considered the start of the reaction. Carbon dioxide was then added to a total pressure of 67 bar. After 30 min, the vessel was removed from the water bath and vented. The product mixture was dissolved in CDCl₃ and characterized by ¹H NMR spectroscopy.

References: P. Jessop, D.C. Wynne, S. DeHaai, D. Nakawatase, *Chem. Commun.*, 693 (2000).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: epoxide, *trans*-epoxysuccinic acid, hydrogenation, hydrogenolysis, alcohol



Experimental procedures:

A supported Pd catalyst (0.1 g) was pretreated at 200 °C for 30 min with a H₂ stream. The resulting catalyst was mixed with H₂TES or Na₂TES (0.1 g), and the mixture was ground to a fine powder using a mortar and pestle. The mixture was placed in a Schlenk tube, and then the air in the tube was replaced by hydrogen gas. The reaction vessel was allowed to stand at 30 °C in the pressure of hydrogen (0.1 MPa) for 2 days.

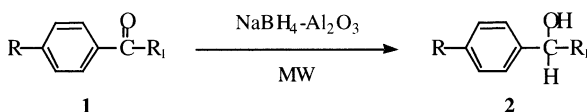
References: T. Kitamura, T. Harada, *Green Chem.*, **3**, 252 (2001).

1.2 Solvent-Free Reduction under Microwave Irradiation

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, aldehyde, NaBH₄, alumina, microwave irradiation, alcohol



- a: R=Me ; R₁=H
 b: R=Cl; R₁=H
 c: R=NO₂; R₁=H
 d: R=H; R₁=Me
 e: R=R₂=Me
 f: R=H; R₁=Ph
 g: R=H; R₁=CH(OH)Ph
 h: R=OCH₃; R₁=CH(OH)C₆H₄-OCH₃-*p*

Experimental procedures:

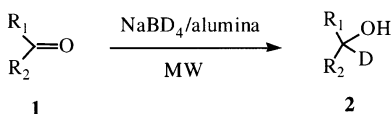
Freshly prepared NaBH₄-alumina (1.13 g, 3.0 mmol of NaBH₄) is thoroughly mixed with neat acetophenone **1d** (0.36 g, 3.0 mmol) in a test tube and placed in an alumina bath inside the microwave oven and irradiated (30 s). Upon completion of the reaction, monitored on TLC (hexane-EtOAc, 8:2, v/v), the product is extracted into ethylene chloride (2×15 mL). Removal of solvent under reduced pressure essentially provides pure *sec*-phenethyl alcohol **2d** in 87% yield. No side product formation is observed in any of the reactions investigated and no reaction takes place in the absence of alumina.

References: R. S. Varma, R.K. Saini, *Tetrahedron Lett.*, **38**, 4337 (1997).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, aldehyde, deuteration, alumina, sodium borodeuteride, microwave irradiation, alcohol



- a: R₁=Ph, R₂=H
- b: R₁=PhCH=CH, R₂=H
- c: R₁=4-NO₂C₆H₄, R₂=H
- d: R₁=2,4,6-(MeO)₃C₆H₂, R₂=H
- e: R₁=PhCH₂, R₂=H
- f: R₁=1-naphthyl, R₂=H
- g: R₁=2-naphthyl, R₂=H
- h: R₁=Ph, R₂=Me
- i: R₁=4-NO₂C₆H₄, R₂=Me
- j: R₁=3-ClC₆H₄, R₂=Me

Experimental procedures:

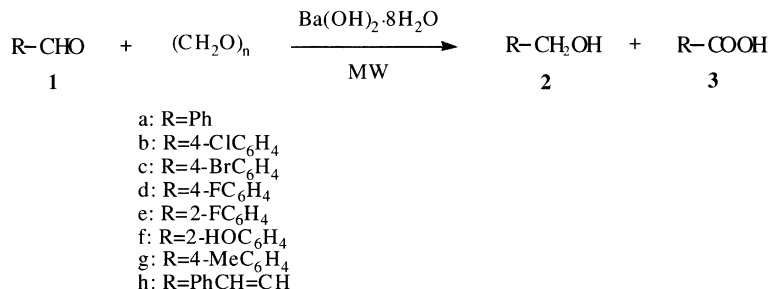
For solid carbonyl compounds, the substrate e.g. *p*-nitroacetophenone **1i** (50 mg, 0.3 mmol) was thoroughly mixed with alumina doped NaBD₄ (0.126 g, 0.3 mmol of NaBD₄) using a pestle and mortar. The mixture was transferred to a loosely capped glass vial and irradiated in the microwave oven for 1 min at full power (750 W). The sample was allowed to cool to room temperature. The product was extracted using CHCl₃ (2 mL). The solvent was removed by rotary evaporation before being re-dissolved in CHCl₃ or CDCl₃ prior to NMR analysis. For liquid carbonyl compounds, thoroughly mixing was achieved by shaking the substrate with alumina doped NaBD₄ in the glass vial.

References: W. T. Erb, J. R. Jones, S. Lu, *J. Chem. Res. (S)*, 728 (1999).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: aldehyde, Cannizzaro reaction, barium hydroxide, microwave irradiation, alcohol, carboxylic acid



Experimental procedures:

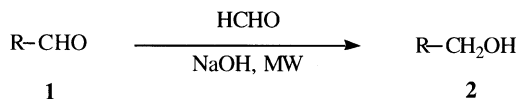
In a typical experiment, benzaldehyde (106 mg, 1 mmol) was added to the finely powdered paraformaldehyde (60 mg, 2 mmol). To this mixture, powdered barium hydroxide octahydrate (631 mg, 2 mmol) was added in a glass test tube and the reaction mixture was placed in an alumina bath (neutral alumina: 125 g, mesh ~ 150, Aldrich; bath: 5.7 cm diameter) inside a household microwave oven and irradiated for the specified time at its full power of 900 W intermittently or heated in an oil bath at 100–110 °C. On completion of the reaction, as indicated by TLC (hexane-EtOAc, 4:1, v/v), the reaction mixture was neutralized with dilute HCl and the product extracted into ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The pure benzyl alcohol (99 mg, 91%), however, is obtained by extracting the reaction mixture with ethyl acetate prior to neutralization and subsequent removal of the solvent under reduced pressure.

References: R.S. Varma, K.P. Naicker, P.J. Liesen, *Tetrahedron Lett.*, **39**, 8437 (1998).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: aldehyde, cross-Cannizzaro reaction, microwave irradiation, alcohol



- | | |
|---|--|
| a: R=Ph | g: R=3-O ₂ NC ₆ H ₄ |
| b: R=4-ClC ₆ H ₄ | h: R=2-O ₂ NC ₆ H ₄ |
| c: R=4-MeOC ₆ H ₄ | i: R=PhCH=CH |
| d: R=4-Me ₂ NC ₆ H ₄ | j: R=2-furyl |
| e: R=4-MeC ₆ H ₄ | k: R=2-thienyl |
| f: R=4-O ₂ NC ₆ H ₄ | |

Experimental procedures:

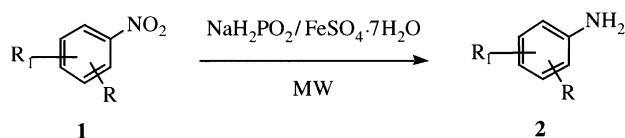
A mixture of benzaldehyde **1a** (0.53 g, 5 mmol), paraformaldehyde (1 g, 30 mmol) and solid sodium hydroxide (0.16 g, 4 mmol) were taken in an Erlenmeyer flask and placed in a commercial microwave oven operating at 2450 MHz frequency. After irradiation of the mixture for 25 s (monitored by TLC), it was cooled to room temperature, extracted with chloroform and dried over anhydrous sodium sulfate. Then the solvent was evaporated to give the corresponding benzylalcohol **2a** in 90% yield exclusively without the formation of any side products. Preparative column chromatography with silica gel was used for further purification of the alcohols, eluting with petroleum ether (60/80)-CHCl₃ (1:1).

References: J. A. Thakuria, M. Baruah, J. S. Sandhu, *Chem. Lett.*, 995 (1999).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: aromatic nitro compound, sodium hypophosphite, microwave irradiation, aromatic amine



R, R₁ = H, Me, OH, CONH₂, Ph, COOH, CN, NH₂

Experimental procedures:

Nitrobenzene (1 mmol) dissolved in minimum amount of dichloromethane, adsorbed over the neutral alumina (substrate:alumina=1:2, w/w), dried and mixed with ferrous sulfate (1.2 mmol) and sodium hydrogen phosphite (5 mmol). It was transferred into a test tube and subjected to microwave irradiation (BPL make, BMO 700T, 650 W, power 80%). Reaction was monitored by TLC (hexane-ethyl acetate, 70:30). After completion of the reaction (50 s), it was leached with di-

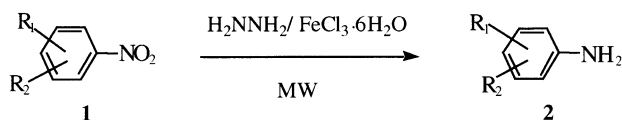
chloromethane (3×20 mL). Evaporation of the solvent under reduced pressure gave the amino product in good yield (78%). The product was further purified by passing through a column of silica gel (60–120 mesh) using hexane-ethyl acetate (8:2) as eluent.

References: H.M. Meshram, Y.S.S. Ganesh, K.C. Sekhar, J.S. Yadav, *Synlett*, 993 (2000).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: aromatic nitro compound, hydrazine hydrate, alumina, microwave irradiation, aromatic amine



- a: R₁=R₂=H
- b: R₁=4-OMe; R₂=H
- c: R₁=4-Me; R₂=H
- d: R₁=4-Cl; R₂=H
- e: R₁=4-I; R₂=H
- f: R₁=3-OH; R₂=H
- g: R₁=2-OH; R₂=H
- h: R₁=2-NH₂; R₂=H
- i: R₁=4-NH₂; R₂=H
- j: R₁=2-NH₂; R₂=5-Me
- k: R₁=2-NH₂; R₂=5-CF₃

Experimental procedures:

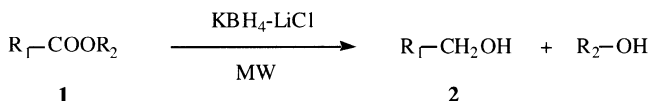
Aromatic nitro compound (10 mmol) was mixed with inorganic solid support or alumina (10 g) and the mixture was added to hydrazine hydrate (30 mmol) and FeCl₃·6H₂O (0.5 mmol). The solid homogenized mixture was placed in a modified reaction tube which was connected to a removable cold finger and sample collector to trap excess hydrazine hydrate. The reaction tube was placed in a Maxidigest MX 350 (Prolabo) microwave reactor fitted with a rotational mixing system. After irradiation for a specified period, the contents were cooled to room temperature and the product extracted into ethyl acetate (2×20 mL). The solid inorganic material was filtered and the solvent was removed under reduced pressure to afford the product that was further purified by crystallization.

References: A. Vass, J. Dudas, J. Toth, R.S. Varma, *Tetrahedron Lett.*, **42**, 5347 (2001).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ester, potassium borohydride-lithium chloride, microwave irradiation, alcohol



a: R₁=Ph; R₂=Et

b: R₁=*p*-ClC₆H₄; R₂=Et

c: R₁=*p*-BrC₆H₄; R₂=Et

d: R₁=*p*-MeC₆H₄; R₂=Et

e: R₁=*o*-ClC₆H₄; R₂=Et

f: R₁=*o*-NO₂C₆H₄; R₂=Et

g: R₁=*m*-MeC₆H₄; R₂=Et

h: R₁=PhCH₂; R₂=Et

i: R₁=PhCH₂; R₂=Me

j: R₁=4-pyridyl; R₂=Et

k: R₁=3,4-(PhCH₂O)₂C₆H₃; R₂=Et

l: R₁=*p*-EtOCOC₆H₄; R₂=Et

Experimental procedures:

Potassium borohydride (1.0 g, 20 mmol), anhydrous lithium chloride (0.8 g, 20 mmol) were thoroughly mixed in a mortar and transferred to a flask (100 mL) connected with reflux equipment, then dry THF (10 mL) was added and the mixture was heated to reflux for 1 h. After cooling, the ester (10 mmol) was added and stirred for 0.5 h at room temperature, then the THF was removed under reduced pressure. After the mixture was irradiated by microwave for 2–8 min, the mixture was cooled to room temperature, water (20 mL) was added, extracted with ether (3×15 mL), dried with magnesium sulfate, and evaporated to give the crude product, which was purified by crystallization, distillation or column chromatography.

References: J.-C. Feng, B. Liu, L. Dai, X.-L. Yang, S.-J. Tu, *Synth. Commun.*, **31**, 1875 (2001).

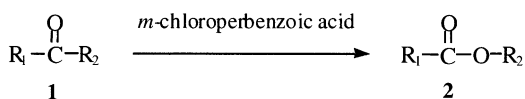
2 Oxidation

2.1 Solvent-Free Oxidation

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: ketone, Baeyer-Villiger reaction, *m*-chloroperbenzoic acid, ester



a: $\text{R}_1=4\text{-BrC}_6\text{H}_4$; $\text{R}_2=\text{Me}$

b: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{CH}_2\text{Ph}$

c: $\text{R}_1=\text{R}_2=\text{Ph}$

d: $\text{R}_1=\text{Ph}$; $\text{R}_2=4\text{-MeC}_6\text{H}_4$

e: $\text{R}_1=\text{Ph}$; $\text{R}_2=2\text{-MeC}_6\text{H}_4$

Experimental procedures:

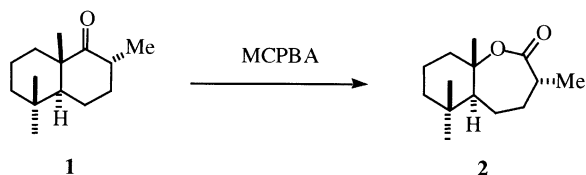
The oxidations were carried out at room temperature with a mixture of powdered ketone and 2 mol equiv. of powdered *m*-chloroperbenzoic acid. When the reaction time was longer than 1 day, the reaction mixture was ground once a day with agate pestle and mortar. The excess of peroxy acid was decomposed with aqueous 20% NaHSO_4 , and evaporated. The crude product was chromatographed on silica gel (benzene- CHCl_3).

References: F. Toda, M. Yagi, K. Kiyoshige, *Chem. Commun.*, 958 (1988).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: decalone, Baeyer-Villiger oxidation, norsesquiterpenoid, lactone



Experimental procedures:

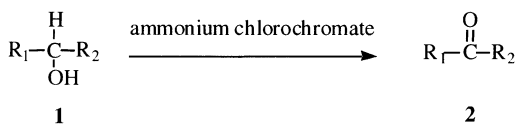
A mixture of the decalone **1** (40.8 mg, 196 μmol) and MCPBA (127 mg, 80%, 589 μmol) was left to stand at room temperature for 8 h and at 60 °C for 12 h. The resulting mixture was diluted with EtOAc and the organic layer was washed with sat. NaHCO_3 (2 \times), water and brine. Evaporation of the solvent followed by MPLC purification of the residue (EtOAc-*n*-hexane, 1:10) gave lactone **2** (31.5 mg, 72%) as a colorless oil.

References: H. Hagiwara, H. Nagatome, S. Kazayama, H. Sakai, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc., Perkin Trans. 1*, 457 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: alcohol, ammonium chlorochromate, montmorillonite K-10, ketone



- a: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{H}$
- b: $\text{R}_1=4\text{-MeC}_6\text{H}_4$; $\text{R}_2=\text{H}$
- c: $\text{R}_1=5\text{-Me-2-NO}_2\text{C}_6\text{H}_3$; $\text{R}_2=\text{H}$
- d: $\text{R}_1=4\text{-NO}_2\text{C}_6\text{H}_4$; $\text{R}_2=\text{H}$
- e: $\text{R}_1=2\text{-HOC}_6\text{H}_4$; $\text{R}_2=\text{H}$
- f: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{Me}$
- g: $\text{R}_1=\text{R}_2=\text{Ph}$
- h: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{COPh}$
- i: $\text{R}_1, \text{R}_2=(\text{CH}_2)_5-$

Experimental procedures:

Preparation of Ammonium Chlorochromate/Montmorillonite K-10. To a solution of chromium trioxide (40 g, 0.4 mol) in water (100 mL) was added ammonium chloride (21.4 g, 0.4 mol) within 15 min at 40 °C. The mixture was cooled until a yellow-orange solid formed. Reheating to 40 °C gave a solution. Montmorillonite K-10 (200 g) was then added with stirring at 40 °C. After evaporation in a rotary evaporator, the orange solid was dried in vacuo for 2 h at 70 °C. It can be kept for several months in air at room temperature without losing its activity.

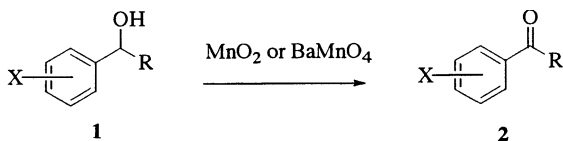
Oxidation of Alcohols in the Solventless System. The above reagent (1.7 g, 2.6 mmol) was added to an appropriate neat alcohol (1.3 mmol). This mixture was thoroughly mixed using a pestle and mortar. An exothermic reaction ensued with darkening of the orange reagent and was complete almost immediately as confirmed by TLC (hexane-AcOEt, 8:2). The product was extracted into CH_2Cl_2 and passed through a small bed of silica gel (1 cm) to afford the corresponding pure carbonyl compounds.

References: M.M. Heravi, R. Kiakojoori, K.T. Hydar, *J. Chem. Res. (S)*, 656 (1998).

Type of reaction: oxidation

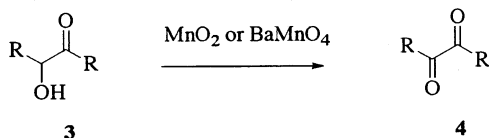
Reaction condition: solvent-free

Keywords: allylic alcohol, manganese dioxide, barium manganate, aldehyde, ketone



- a: X=R=H
 b: X=4-MeO; R=H
 c: X=4-Me; R=H
 d: X=3-Me; R=H
 e: X=3-Cl; R=H

- f: X=3,4-OCH₂O-; R=H
 g: X=H; R=Me
 h: X=4-Br; R=Me
 i: X=H; R=Et
 j: X=H; R=Ph



- a: R=Ph
 b: R=4-MeOC₆H₄
 c: R=furyl

Experimental procedures:

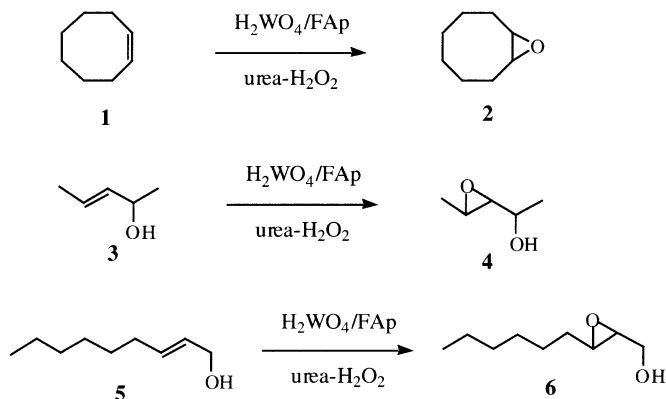
Oxidation of Benzoin to Benzil by MnO₂ as a Typical Procedure for the Oxidation of Biaryl Acyloins. A mixture of benzoin **3a** (0.212 g, 1 mmol) and MnO₂ (0.174 g, 2 mmol) was prepared and magnetically agitated in an oil bath at 90 °C for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was applied on a silica gel pad (3 g) and washed with Et₂O (20 mL) to afford pure benzil **4a** quantitatively (mp 94 °C). The same reaction with BaMnO₄ proceeded to completion after 2 h using 1.5 mmol of the oxidant.

References: H. Firouzabani, B. Karimi, M. Abbasi, *J. Chem. Res. (S)*, 236 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: olefin, allylic alcohol, epoxidation, tungstic acid, fluoroapatite, urea-H₂O₂, epoxide

**Experimental procedures:**

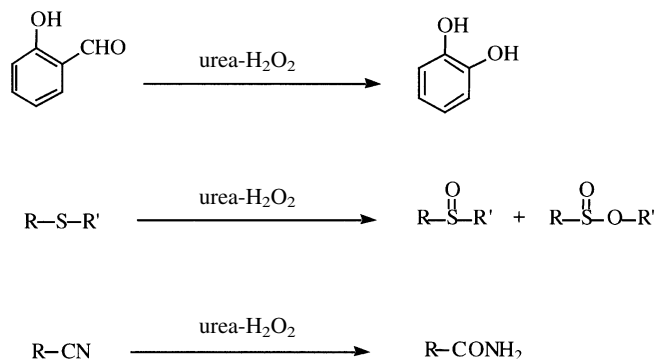
To a solid mixture of FAP powder (0.50 g) with urea-H₂O₂ powder (0.235 g, 2.5 mmol) was added tungstic acid powder (0.025 g, 0.10 mmol) in a test tube with a screw-cap, and mixed sufficiently. The solid mixture was permeated by a cyclooctene liquid **1** (0.110 g, 1.0 mmol), and the mixture was left without stirring at room temperature. After 48 h the reaction smoothly proceeded to afford epoxyoctane **2** in 90% yield.

References: J. Ichihara, *Tetrahedron Lett.*, **42**, 695 (2001).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: 2-hydroxybenzaldehyde, sulfide, nitrile, pyridine, urea-hydrogen peroxide complex, catechol, sulfoxide, sulfinic ester, amide, pyridine-*N*-oxide



Experimental procedures:

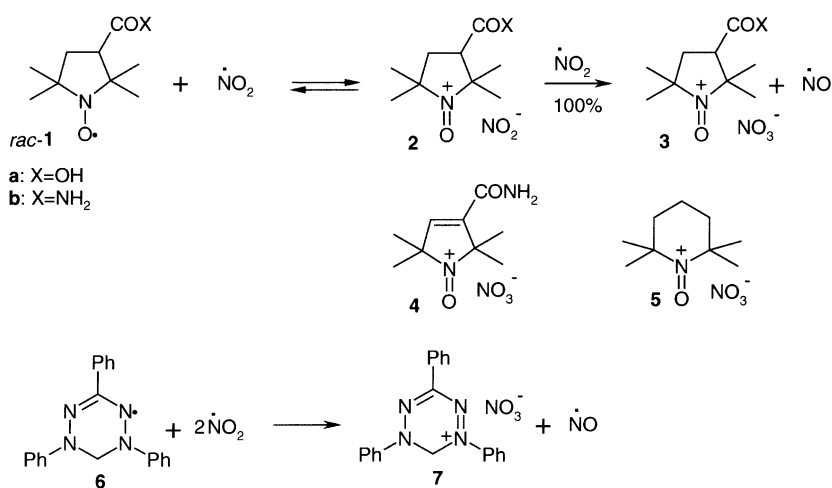
The starting material (2 mmol) was added to the finely powdered urea-hydrogen peroxide adduct (376 mg, 4 mmol) in a glass test tube, and the reaction mixture was placed in an oil bath at 85 °C. After completion of the reaction, monitored by TLC, the reaction mixture was extracted into ethyl acetate and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography to deliver pure product, as confirmed by the spectral analysis.

References: R. S. Varma, K. P. Naicker, *Org. Lett.*, **1**, 189 (1999).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: nitroxyl, verdazyl, nitrogen dioxide, bromine, xenon difluoride, gas-solid reaction

**Experimental procedures:**

An evacuated 100-mL flask was filled with N₂O₄/NO₂ to a pressure of 650 mbar (296 mg, 6.4 mmol NO₂). The sampling flask was connected to an evacuated 1-L flask which was then connected to an evacuated 10-mL flask that was cooled to 5 °C and contained the nitroxyl **1a**, or **1b**, or the nitroxyl precursor to **4** (500 mg, 2.70 mmol). After 1 h, the cooling bath was removed and excess NO₂ and NO were condensed to a cold trap at -196 °C for further use. The yield was 665 mg (100%) of pure **3a**, or **3b**, or **4**. (Ref. 1)

Similarly, 2 g quantities of tetramethylpiperidine-*N*-oxyl (TEMPO) were reacted at -10°C (initial pressure of NO_2 0.03 bar) in 12 h with a quantitative yield of pure **5**. (Ref. 1)

Similarly, triphenylverdazyl **6** (200 mg, 0.64 mmol) was oxidized with NO_2 (3.2 mmol) at an initial pressure of 0.2 bar at 0°C with a quantitative yield of pure **7**. (Ref. 1)

Similarly, the corresponding bromides of **3**, **4**, **5**, **7** were quantitatively obtained if the free radical precursors were oxidized with bromine vapor in evacuated flasks. (Ref. 2)

Similarly, the corresponding fluorides of **3**, **4**, **5**, **7** were quantitatively obtained by oxidation with gaseous XeF_2 . (Ref. 3)

References: (1) G. Kaupp, J. Schmeyers, *J. Org. Chem.*, **60**, 5494 (1995).

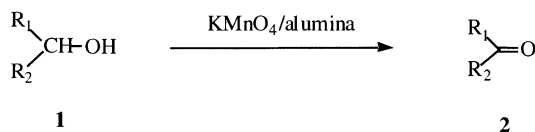
(2) S. Nakatsuji, A. Takai, M. Mizumoto, H. Anzai, K. Nishikawa, Y. Morimoto, N. Yasuoka, J. Boy, G. Kaupp, *Mol. Cryst. Liq. Cryst.*, **334**, 177 (1999).

(3) G. Kaupp, *Comprehensive Supramolecular Chemistry*, Vol. 8, 381 (Ed. J.E.D. Davies), Elsevier, Oxford (1996).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: alcohol, alumina-supported permanganate, ketone, aldehyde



a: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{H}$

b: $\text{R}_1=4\text{-NO}_2\text{C}_6\text{H}_4$; $\text{R}_2=\text{H}$

c: $\text{R}_1=3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$; $\text{R}_2=\text{H}$

d: $\text{R}_1=4\text{-PhC}_6\text{H}_4$; $\text{R}_2=\text{Me}$

e: $\text{R}_1=2\text{-pyridyl}$; $\text{R}_2=\text{Ph}$

f: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{Me}$

g: $\text{R}_1=4\text{-MeOC}_6\text{H}_4$; $\text{R}_2=\text{H}$

h: $\text{R}_1=2\text{-MeOC}_6\text{H}_4$; $\text{R}_2=\text{H}$

i: $\text{R}_1=\text{R}_2=\text{Ph}$

j: $\text{R}_1=3\text{-MeOC}_6\text{H}_4$; $\text{R}_2=\text{H}$

k: $\text{R}_1=4\text{-ClC}_6\text{H}_4$; $\text{R}_2=\text{H}$

l: $\text{R}_1=2\text{-ClC}_6\text{H}_4$; $\text{R}_2=\text{H}$

m: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{PhCH}_2$

n: $\text{R}_1=4\text{-BrC}_6\text{H}_4$; $\text{R}_2=\text{Me}$

o: $\text{R}_1=4\text{-ClC}_6\text{H}_4$; $\text{R}_2=\text{Me}$

p: $\text{R}_1=\text{Ph}$; $\text{R}_2=\text{PhCO}$

q: $\text{R}_1=2,3\text{-(MeO)}_2\text{C}_6\text{H}_3$; $\text{R}_2=\text{H}$

r: $\text{R}_1=\text{PhCH}=\text{CH}$; $\text{R}_2=\text{Ph}$

s: $\text{R}_1=\text{PhCH}=\text{CH}$; $\text{R}_2=\text{Me}$

t: $\text{R}_1=4\text{-NO}_2\text{C}_6\text{H}_3\text{CH}=\text{CH}$; $\text{R}_2=\text{H}$

u: $\text{R}_1=\text{PhCH}=\text{CH}$; $\text{R}_2=\text{H}$

Experimental procedures:

The alumina supported permanganate is prepared by combining KMnO_4 (4 g, 25.3 mmol) and alumina (neutral, 5 g) in a mortar and grinding with a pestle until a fine, homogeneous, purple powder is obtained. Benzoin (0.42 g, 2 mmol) is added to $\text{KMnO}_4/\text{Al}_2\text{O}_3$ (1 g, 2.8 mmol), the mixture was grinded with a pestle in a mortar until TLC showed complete disappearance of starting material, which