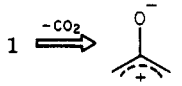
cyclic carbonate was thermally stable and showed no particular tendency toward olefin isomerization on silica gel. It can serve as a potential precursor for the oxyallyl synthon 6.



6 (3)

Experimental Section

Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were determined in chloroform-*d* on a Bruker WH-270 (270 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane, which was used as the internal standard. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are reported in hertz (Hz). Carbon (^{13}C) NMR spectra were determined on a JEOLCO FX-60 (15.4 MHz) spectrometer in chloroform-*d*. Infrared spectra (IR) were determined on a Perkin-Elmer 267 instrument and are reported in reciprocal centimeters. Mass spectra were obtained on an AEI-902 instrument.

4-[(Phenylselenenyl)methyl]-1,3-dioxolan-2-one (4). To a solution of diphenyl diselenide (20.0 g, 64 mmol) in 300 mL of absolute ethanol was added sodium borohydride (7.5 g, 197 mmol) in small portions (to prevent excessive evolution of hydrogen). The sodium phenylselenide solution was then added to 3-chloro-1,2-propanediol (13.6 g, 123 mmol) in a 500-mL flask. The resulting yellowish orange solution was refluxed for 50 h. The excess selenide anion was quenched with 0.8 mL of dichloroacetic acid, and the reaction mixture was filtered to remove sodium chloride. The bulk of the ethanol was removed by rotatory evaporation, and the residue was partitioned between ethyl acetate (500 mL) and saturated sodium bicarbonate solution (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic layers were washed with saturated aqueous bicarbonate (2 × 100 mL) followed by brine (100 mL) and then dried over anhydrous potassium carbonate. After removal of the solvent, 28.2 g (99%) of 3-(phenylselenyl)-1,2-propanediol was obtained as a yellow solid. This was not purified but carried on to the next step.

A mixture of the crude diol (13.1 g, 57 mmol), dimethyl carbonate (35 mL, 415 mmol), and sodium bicarbonate (0.3 g, 3.5 mmol) was refluxed for 2 h. The reaction mixture was then heated to 120 °C to distill the volatile components. The pot residue was dissolved in ether (300 mL), washed successively with water (2 × 50 mL) and brine (50 mL), and then dried over anhydrous magnesium sulfate. After removal of solvent in vacuo, 13.5 g (92%) of the title compound was obtained as an orange oil. An analytical sample was obtained by flash chromatography[6] (25% ethyl acetate in hexane): ^1H NMR δ 7.54 (m, 2 H), 7.30 (m, 3 H), 4.78 (d of d of d of d, J = 8.8, 8.1, 6.6, 4.6 Hz, 1 H), 4.50 (d of d, J = 8.6, 8.1 Hz, 1 H), 4.14 (d of d, J = 8.6, 6.6 Hz, 1 H), 3.28 (d of d, J = 13.2, 4.6 Hz, 1 H), 3.00 (d of d, J = 13.2, 8.8 Hz, 1 H); IR (neat) 3070, 3000, 1801, 1582, 1480, 1440, 1392, 1162, 1062, 772, 740, 690 cm^{-1}. Mass spectrum, m/e (relative intensity) M^+ – 258 (2), 171 (3), 91 (3), 87 (10), 77 (3), 57 (100), 56 (5), 55 (3), 45 – (16), 44 (6), 43 (14), 41 (23), 40 (3), 39 (4); calcd for $C_{10}H_{10}O_3Se$ m/e 257.9792, found m/e 257.9794.

4-Methylene-1,3-dioxolan-2-one (1). Ozone was bubbled into a solution of 4-[(phenylselenenyl)methyl]-1,3-dioxolan-2-one (4; 3.0 g, 11.6 mmol) in 36 mL methylene chloride at −78 °C until a blue color persisted. After being purged with nitrogen, the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo to give 3.0 g of the crude selenoxide as a white solid which was dissolved in 18 mL of 1,2-dichloroethane and added dropwise at a rate of 15 mL/h (via a syringe pump) to a refluxing solution (pot temperature 110–115 °C) of 25 mL of 1,2-dichloroethane and 2,5-norbornadiene (30 mL, 300 mmol). After the addition, refluxing was continued for 10 min, and the volatile components were removed by distillation. The orange residue (4.0 g) was then Kugelrohr distilled (50 °C, 0.25 mmHg) to give 650 mg (57%) of the methylene carbonate 1 as a low-melting waxy solid: mp 28–29.5 °C; ^1H NMR δ 5.04 (d of d, J = 2.6, 2.2 Hz, 2 H), 4.91 (d of t, J = 4.0, 2.6 Hz, 1 H), 4.47 (d of t, J = 4.0, 2.2 Hz, 1 H); ^{13}C NMR 152.8, 149.1, 87.1, 67.8; IR ($CDCl_3$) 1838, 1698, 1353, 1283, 1137, 1079, 972, 845 cm^{-1}; mass spectrum, m/e (relative intensity M^+ – 100 (12), 69 (1), 56 (4), 44 (16), 42 (1), 40 (10), 32 (100), 30 (1); calcd for $C_4H_4O_3$ m/e 100.0159, found m/e 100.0163.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial assistance.

Registry No. 1, 4362-24-7; 3, 96-24-2; 4, 86728-47-4; 5, 86728-48-5; 3-(phenylselenyl)-1,2-proipoanediol, 65349-59-9; diphenyl diselenide, 1666-13-3.

Silica Gel Assisted Reductive Cyclization of Alkoxy-2,β-dinitrostyrenes to Alkoxyindoles[1]

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The biochemical and pharmacological importance of numerous indole derivatives[2,3] have served to maintain a continuing interest in the development of new and improved methods for the synthesis of the indole nucleus.[2,4,5] We became interested in this area in connection with our synthesis of analogues of pharmacologically important serotonin neurotoxins 5,6- and 5,7-dihydroxytryptamines.[3,6] For the synthesis of these analogues we needed access to 5,6- and 5,7-dihydroxyindoles as their methyl and benzyl ethers with various other substituents on the indole ring. The most suitable method for the synthesis of these indoles appeared to be the reductive cyclization of appropriate 2,β-dinitrostyrenes using Fe in HOAc. This method is widely used[4] and is the most convenient one for the synthesis of N-unsubstituted alkoxyindoles. Although this method of constructing the indole nucleus is of broad

(1) Presented in part at the 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 12–17, 1982, Abstract ORGN 208.

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(5) (a) Norlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778–782 and references 4a–r cited therein for a list of representative recent references. (b) Somei, M.; Shoda, T. *Heterocycles* **1982**, *17*, 417–423.

(6) Sinhababu, A. K.; Borchardt, R. T., manuscripts in preparation. For example, synthesis of 4-methyl-, 7-methyl-, and 4,7-dimethyl-5,6-dihydroxytryptamines and 4-methyl-, 6-methyl-, and 4,6-dimethyl-5,7-dihydroxytryptamines.

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scope, it suffers from poor yields,[4] usually 35–50%, and cumbersome purification procedures. Many examples are known, including our target methoxy- and especially (benzyloxy)indoles,[7] where the yields are much lower. The only modification[8] of this important method that has been developed so far is the catalytic hydrogenation using Pd/C in the presence of a suitable acid. Although this modification allows isolation of indoles often in good yields, it is not applicable to the synthesis of (benzyloxy)indoles.

Consideration of the possible mechanisms[9,10] of reductive cyclization of 2,β-dinitrostyrenes to the corresponding indoles by Fe/HOAc suggests that poor yields in this reaction, in general, may be due to intermolecular reactions involving basic (neutral or negatively charged) intermediates and the starting material, giving rise to dimeric and/or intractable polymeric byproducts.[11] As silica gel binds polar materials strongly, we thought that by conducting the Fe/HOAc-induced reductive cyclization in the presence of silica gel in a nonpolar solvent, it should be possible to maintain the relatively nonpolar but reactive starting material in the solvent phase and the polar intermediates on the silica gel surface, thereby minimizing interactions between the polar and the nonpolar species and also between polar intermediates themselves. In this paper we describe a modification of the Fe/HOAc method based on the above-mentioned considerations which allows conversion of a variety of 2,β-dinitrostyrenes to the corresponding indoles in high yields.

Results and Discussion

We found that when a mixture of the alkoxydinitrostyrene, Fe, and HOAc is refluxed in a nonpolar solvent system (benzene-cyclohexane or toluene) in the presence of silica gel (column chromatography grade, 70–270 mesh) the reaction is complete in less than 1 h, and the corresponding alkoxyindole is produced in a high state of purity with dramatic improvements in yields over the Fe/HOAc method. Isolated yields for a variety of indoles containing methoxy, methylenedioxy, or benzyloxy groups were generally in the neighborhood of 90% (Table I). Significantly, the reductive cyclization of **1a** proceeded in 93% yield, and no dimer was formed, in contrast to the formation of a dimeric byproduct in 14% yield by the Fe/HOAc method.[12]

The amounts of silica gel reported in Table I are the minimum amounts that were necessary for optimum yields. It was desirable to find reaction conditions that require a minimum of silica gel, especially for relatively large-scale operations, for two reasons: first, to minimize the volume

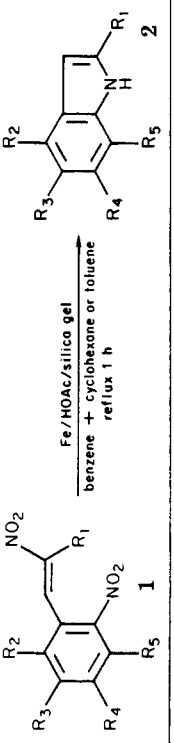

Table I. Silica Gel Assisted Reductive Cyclization of 2,β-Dinitrostyrenes to Indoles

entry	R_1	R_2	R_3	R_4	R_5	dinitrostyrene 1 mp, °C[a]	conditions[b]: nonpolar solvent system[c]	conditions[b]: silica gel[j]	indole: % yields: this method[d]	indole: % yields: lit. method[e]	indole: mp, °C: this study	indole: mp, °C: lit.	ref[f]
A	Me	H	OMe	OMe	H	130–132	A	1	93[g]	63[h]	90–91	91	12
B	H	H	OMe	OMe	H	169–173	A	1	95	60[i]	152–154	152–153	8
C	H	Me	OMe	OMe	H	112–114	A	1	96	37	115–117	112–114	13
D	H	H	OMe	OMe	Me	166–168	A	1	95	32	78–80	76–80	13
E	H	H	OCH_2O		H	120–122	A	1	91	33	109–110	108–110	14
F	H	H	OMe	OCH_2Ph	H	170–173	B	1.5	91	55	148–150	148–150	15
G	H	H	OCH_2Ph	OMe	H	205–208	B	1.5	89	50	95–96	95–96	15
H	H	H	OCH_2Ph	OCH_2Ph	H	162–163	B	1.5	94	50	114–115	113–115	15, 16
I	H	H	OMe	H	OMe	182–184	A	1	88	57	83–84	83–84	17
J	H	H	OCH_2Ph	H	OCH_2Ph	167–169	C	2.5	75	53	87–88	85–87	18

[a] As observed in the present study, these values are in good agreement with those reported in the literature. For references see reference column. [b] For other details see the Experimental Section. [c] A, 1:3 benzene–cyclohexane; B, 3:1 benzene–cyclohexane; C, toluene. [d] Isolated yields of pure indoles. [e] Unless otherwise mentioned, reference is made to the Fe/HOAc method. [f] Reference cited describes the preparation of the indole as well as the precursor dinitrostyrene. [g] No dimeric product was detected. [h] A dimeric product was also formed in 14% yield.[12] [i] By the Pd/C-catalyzed reduction method. [j] In g/mmol of 1.

(7) For example, 4-methyl-, 7-methyl-, and 4,7-dimethyl-5,6-bis(benzyloxy)indoles and 4-methyl-, 6-methyl-, and 4,6-dimethyl-5,7-bis(benzyloxy)indoles.

(8) Heubner, C. F.; Troxell, H. A.; Schroeder, D. C. *J. Am. Chem. Soc.* **1953**, *75*, 5887–5890.

(9) (a) Reference 4a, pp 182–183. (b) Brown, R. K. In ref 2a pp 479–484.

(10) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 1125–1126.

(11) The only experimental support for this assumption is found in Harley-Mason's observation that in the conversion of **1A** to **2A** (Table I) using Fe/HOAc, a highly insoluble dimeric indole is also formed as a byproduct in 14% yield.[12]

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of the reaction mixture and second, to increase the ease of recovery of the product indole during workup from the mixture of silica gel and iron-derived solid byproducts. The amount of silica gel required for the optimum yields of the indoles depended upon the polarity of the nonpolar solvent system. For example, use of benzene alone in place of 1:3 benzene–cyclohexane required larger amounts of silica gel. The type of nonpolar solvent system required, in turn, was dictated by the nature of the dinitrostyrene. Thus the use of cyclohexane alone as the nonpolar solvent system was quite effective for the synthesis of the methoxy and (methylenedioxy)indoles but not for the (benzyloxy)indoles.

It is surprising that application of the reaction conditions, which furnished 5,6-bis(benzyloxy)indole (**2H**) in 94% yield, gave 5,7-bis(benzyloxy)indole (**2J**) in only 40–45% yield. With toluene as the nonpolar solvent and at reflux temperature, the yield of **2J** could be increased to 75% (Table I). Interestingly, synthesis of 4-methyl-, 6-methyl-, and 4,6-dimethyl-5,7-bis(benzyloxy)indoles also required toluene under reflux; however, the yields were 92%, 78%, and 90%, respectively.[19] It is possible that the presence of a methyl group ortho to the nitrovinyl moiety minimizes, through steric hindrance, by product-formation arising from Michael addition at the carbon β to the nitro group.

The above results, including the observation that no dimer was formed in the conversion of **1A** to **2A**, lend support to our original premise for using silica gel.[20] The efficacy of silica gel, when used together with a nonpolar solvent system, in preventing byproduct formation is undoubtedly due to its ability to bind polar (neutral or charged) intermediates, which minimizes intermolecular reactions involving these intermediates.[21]

Experimental Section

General Methods. Iron powder (reduced, N.F. IX electrolytic) was purchased from Mallinckrodt. Silica gel used for the reactions as well as for chromatography was 70–270 mesh (silica gel 60, Brinkmann). The 2,β-dinitrostyrenes were synthesized by the literature methods (see Table I). Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected.

General Procedure for the Silica Gel Assisted Reductive Cyclization. A mixture of the 2,β-dinitrostyrene 1 (2 mmol), silica gel (see Table I for amounts), reduced iron powder (1.7 g for **1A–I**, 2.1 g for **1J**), glacial HOAc (12 mL), and 20 mL of the nonpolar solvent system (see Table I) were refluxed under N_2 for 1 h with efficient mechanical stirring. In each case a vigorous exothermic reaction ensued within 5 min of reflux, and the mixture turned dark (color varied). (The dark color disappeared after 15–20 min, indicating essential completion of reaction.) The mixture was then cooled to 25 °C, diluted with CH_2Cl_2, and filtered. The filter cake was washed thoroughly with 10% Et_2O in CH_2Cl_2 (for **2A–E,I**) or with CH_2Cl_2 (for **2F–H,J**). The combined filtrates were washed with sodium metabisulfite solution, $NaHCO_3$ solution (until aqueous layer was basic), and brine, dried (Na_2SO_4), and then evaporated in vacuo to dryness. Indoles **2A–E** were quite pure at this stage except for traces of colored impurities whereas indoles **2F–J** were less pure. The crude indoles were chromatographed on a column of silica gel (3–6 g/mmol of 1 cyclized) with CH_2Cl_2 (for **2A–E,I**) or CH_2Cl_2–hexane (for **2F–H,J**) to give solid product, pure by TLC (silica gel, Analtech; solvent CH_2Cl_2). The yields and melting points of the indoles are reported in Table I.

Acknowledgment. The support of this work through a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NS-15692) and a postdoctoral fellowship to A.K.S. from the American Heart Association Kansas Affiliate are gratefully acknowledged.

Registry No. **1A**, 86712-40-5; **1B**, 16551-84-1; **1C**, 80547-82-6; **1D**, 80547-83-7; **1E**, 15794-43-1; **1F**, 2426-89-3; **1G**, 4775-68-2; **1H**, 4790-17-4; **1I**, 86712-41-6; **1J**, 50545-13-6; **2A**, 57330-45-7; **2B**, 14430-23-0; **2C**, 80547-84-8; **2D**, 80547-85-9; **2E**, 267-48-1; **2F**, 2426-59-7; **2G**, 4790-04-9; **2H**, 4790-19-6; **2I**, 27508-85-6; **2J**, 50545-14-7; iron, 7439-89-6; HOAc, 64-19-7.

Supplementary Material Available: Full ^1H NMR spectral data for indoles **2A–J** (1 page). Ordering information is given on any current masthead page.

(19) Sinhababu, A. K.; Borchardt, R. T., unpublished observations.
(20) In recent years many applications of silica gel as a support for reagents have been made. For an excellent review on this and related topics see: McKillop, A.; Young, D. W. *Synthesis* **1979**, 401–422, 481–500. The manner in which silica gel has been used in the present study does not, however, qualify silica gel as a support for a reagent, but there are certain similarities.
(21) Cf.: (a) Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227–230. (b) Sinhababu, A. K.; Borchardt, R. T. *J. Labelled Compd. Radiopharm.*, in press.

On the Aprotic Robinson Annelation of Dihydrocarvone and 2-Methylcyclohexanone with Methyl and Ethyl Vinyl Ketone

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The Robinson annelation reaction is a time-tested method for ring construction. It is generally conceded that the reaction of cyclohexanone enolates and simple alkyl vinyl ketones in an aprotic medium cause polymerization.[1] McQuillin was able to achieve annelation of dihydrocarvone (33%) using sodamide/ether and the "slow" ethyl vinyl ketone releasing reagent diethylmethyl(3-oxopentyl)ammonium iodide.[2] Marshall and Fanta sought to obviate this difficulty by employing base catalysis in protic medium with subsequent isolation of the resultant ketol prior to dehydration. Application of this technique to dihydrocarvone and ethyl vinyl ketone provided a 49% yield of ketols **1a**/**1b** (7/3) (Chart I) derived from the thermodynamic enolate.[3] Stork and Ganem have demonstrated that α-trialkylsilyl vinyl ketones permit the first step of the Robinson sequence, namely, the Michael addition, to be accomplished in both protic and aprotic media.[4] When applicable, the Robinson annelation sequence can be conducted in acid medium.[5]

Because we had a need for an efficient preparation of (+)-6-epi-α-cyperone, we chose to reinvestigate the aprotic annelation sequence of the thermodynamic enolates of 2-methylcyclohexanones with simple alkyl vinyl ketones.

Reduction of (+)-carvone with lithium bronze[7] provided (−)-dihydrocarvone, which was converted into its thermodynamic enolate by exposure to 0.9 equiv of lithium diisopropylamide (LDA) in THF at 20 °C for 24 h. Treatment of the enolate with ethyl vinyl ketone (EVK) at −78 °C followed by warming to ambient temperature provided, after chromatography, the known crystalline ketol **1a** in

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