strongly basic conditions.[7] Undoubtedly, some of **5** decomposed to *N*-benzylideneaniline, which then proceeded to react to give the condensation product. Since the benzoin condensation of Schiff bases was not known at the time, the significance of the reaction was not recognized.

The formation of **3** thus appears to occur via a benzoin-type condensation. The isolation of **6** is peculiar to reaction with Schiff bases. For example, the benzoin condensation of benzaldehyde was studied with a phase-transfer agent in a H_2O–organic system, and a high yield of benzoin was observed with no mention of isolation of any other compounds.[8] The greater basicity of the Schiff base intermediate evidently allows it to be trapped in the presence of a proton donor, whereas aldehyde intermediates more readily decompose.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were obtained from a Perkin-Elmer Model 137 spectrophotometer, and ultraviolet spectra were run on a Hitachi Perkin-Elmer Model 139 UV–visible spectrophotometer. NMR spectra were recorded on a Varian Associates Model A-60 instrument. Elemental analyses were performed by Integral Microanalytical Laboratories, Raleigh, NC, and the mass spectrum was run by Gollob Analytical Services, Berkeley Heights, NJ.

Reactions of *N*-Benzylideneaniline with NaCN and Tetrabutylammonium Chloride (TBACl). The following represent typical results. (a) A mixture of 0.50 g (0.010 mol) of NaCN and 0.28 g (0.0010 mol) of TBACl was dried under reduced pressure at 100 °C for 1 h and then finely ground. The solids were added to a solution of 1.81 g (0.010 mol) of *N*-benzylideneaniline[9] dissolved in 5.0 mL of toluene (dried over Na), and the resulting mixture was stirred vigorously at room temperature under an atmosphere of dry N_2. Within 1 to 2 h, a fluorescent yellow solid began to precipitate from solution. After 4.5 h, the reaction was stopped, and the yellow solid filtered and washed with water to give 0.63 g (35%) of crude **3**, mp 175–190 °C (lit.[2c] mp 205–210 °C). Recrystallization improved the melting point only slightly, but an IR spectrum was identical with that of **3** prepared by the method of Becker.[2c]

The filtrate from isolation of **3** was evaporated to dryness under reduced pressure, and the oily residue was allowed to stand open to air overnight.[10] The oil was then chromatographed on 20 g of Florisil.[11] Elution with hexane gave 0.35 g (19%) of crude **4**, which was recrystallized from 95% ethanol to yield bright yellow crystals with mp 140–144 °C (lit.[2c] 146–148 °C) whose IR spectrum was identical with that of authentic **4**.

Continued elution with 10% acetone–hexane resulted in the isolation of 0.11 g of benzanilide, a reported decomposition product of **3**.[2b] A significant amount of more polar material was isolated from the column, but none of this material could be crystallized or easily purified.[12]

(b) To a mixture of 0.50 g (0.010 mol) of NaCN, 0.28 g (0.0010 mol) of TBACl, and 1.81 g (0.010 mol) of *N*-benzylideneaniline were added 5.0 mL of toluene and 2.0 mL of H_2O. Vigorous stirring was continued for 5 h, after which time a thick, white precipitate had collected. The weight of crude material was 1.90 g (98%), which, after washing thoroughly with 95% ethanol and crystallization from toluene, gave 1.42 g of **6**, mp 199–202 °C. This material was sufficiently pure for most purposes, but it held onto toluene tenaciously, so purer samples were obtained by recrystallization from benzene. One additional recrystallization from benzene gave material melting from 207 to 209 °C (lit.[7] mp 210–211 °C): IR (Nujol) 3300 (NH), 1595 (aromatic) cm^{-1}; UV λ_{max} (isooctane) 240 nm (ϵ 32 000) 283 (3900); MS, *m/e* (relative intensity) 389 (0.07), 362 (51), 347 (5), 285 (7), 270 (6), 182 (26), 181 (32), 180 (100), 152 (3), 104 (8), 77 (39), 51 (11), 27 (5); NMR ($CDCl_3$) δ 4.82 (br s, 1 H), 5.80 (br, 2 H), 6.6–7.3 (m, 20 H). The broad absorption at δ 5.80 disappeared when D_2O was added.

Anal. Calcd for $C_{27}H_{23}N_3$: C, 83.26; H, 5.95; N, 10.79. Found: C, 83.46; H, 6.18; N, 10.38.

Brief heating of a mixture of **6** and alcoholic NaOH resulted in rapid decomposition. After dilution with water, the solution gave a heavy Prussian blue precipitate when tested in the usual way for cyanide ion.

When the above reaction with NaCN and TBACl was performed with a methylene chloride–H_2O medium rather than a toluene–H_2O medium, the results were considerably different. Compound **6** was obtained as described above, but its yield was variable in different runs—on the order of 0.2–0.4 g (10–20%) of crude material.

The organic layer of the filtrate from the isolation of crude **6** was separated and washed with water. After drying over $CaCl_2$, the solvent was removed under reduced pressure, and the residue was taken up in a small amount of hot methanol. The solution was filtered to remove a small amount of **6**. The methanol was then allowed to evaporate slowly in air overnight to give an oil, which was chromatographed on 15 g of Florisil. Elution with 1% acetone–hexane, followed by recrystallization of the eluted solid from ethanol, gave 0.15 g (8%) of **4**, mp 140–142 °C. Continued elution with 10% acetone–hexane gave, after crystallization from petroleum ether (bp 60–90 °C), 0.10 g (15%) of **5** melting at 80–82 °C (lit.[4b] mp 85 °C): IR (Nujol) 3320 (NH), 2220 (C≡N), 1595 (aromatic) cm^{-1}. The IR spectrum of a sample prepared by the method of von Walther[4b] was identical with that of **5**, and the NMR spectrum of **5** was identical in all respects with that reported for **5** by McEwen.[4c]

Reaction of Compounds 5 and 6 with NaCl and TBACl. When **6** was treated with NaCN in a methylene chloride–H_2O medium in the same manner as *N*-benzylideneaniline (except for a longer reaction period of 7 h), only about 1% of starting material was recovered. Use of the same workup procedure and chromatography described above resulted in the isolation of a very small amount of **4** (2%) and a 25% yield of **5**. A great deal of uncharacterized, highly polar material was formed.

Reaction of **6** with NaCN in a methylene chloride–1 M NaOH medium gave a higher yield of **4** (10%), and the amount of **5** stayed about the same.

Compound **5** was unreactive when stirred with NaCN in methylene chloride–H_2O in the presence of TBACl. There was a nearly complete recovery of starting material. Use of 1 M NaOH in place of the water resulted in the formation of a small amount of **4** (1%) and **6** (25%), as well as substantial recovery of starting material (25%).

Registry No. **3** (Ar = Ph), 24099-48-7; **5**, 4553-59-7; **6**, 86712-42-7; *N*-benzylideneaniline, 538-51-2.

(7) Clarke, R. W. L.; Lapworth, A. *J. Chem. Soc.* **1907**, *91*, 694.
(8) Solodar, J. *Tetrahedron Lett.* **1971**, 287.
(9) Bigelow, L.; Batough, H. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. I, p 80.
(10) Since **3** is difficult (if not impossible) to isolate from solution in a pure state, this procedure ensures that any **3** in solution is converted to **4**. A similar procedure is used in subsequent reactions.
(11) The adsorbent was 60–200 mesh supplied by Matheson, Coleman and Bell.
(12) For the structure of compounds that could be formed under these reaction conditions, see: El-Gawad, I.; Harhash, A; El-Zahab, M. *Z. Naturforsch., Anorg. Chem., Org. Chem.* **1980**, *35B*, 712.

An Efficient Synthesis of Substituted Isoquinolines

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There are a number of synthetic methods for preparing isoquinolines,[1] but all require two or more isolation steps and most suffer from harsh conditions, less than ideal

(1) A quick review of isoquinoline synthesis methods is given by Boger et al.: Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron* **1981**, *37*, 3977.

0022-3263/83/1948-3344$01.50/0

Table I. Isoquinolines (4) Prepared

no.	X	Y	Z	yield, %	mp, °C (lit.)
1	OCH_3	H	H	75	36 223 (225)[4,a]
2	H	H	OCH_3	65	182 (184)[5,a]
3	OCH_3	OCH_3	H	57	89 (90)[6]
4	CH_3	H	H	71	88 (89)[7]
5	OCH_3	OH	H	30	179 (183)[3]
6	OCH_3	OH	Br	25	203 (dec) 235 (dec)[a]
7	OCH_2O		H	36	122 (120)[6]
8	H	OMe	H	36	198 (198)[a]

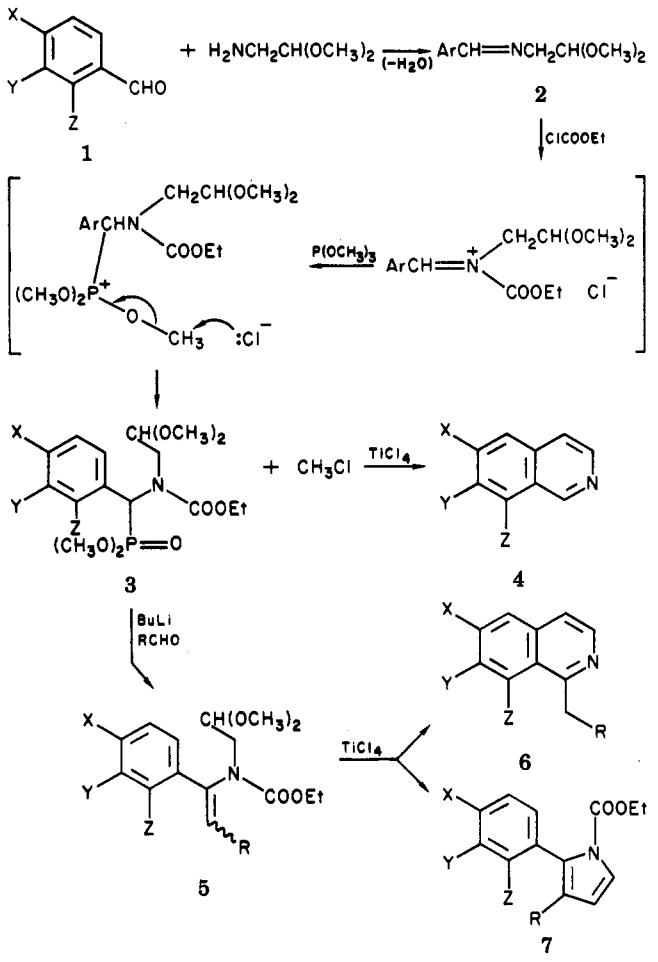
[a] Noncrystalline isoquinoline; picrate melting point.

starting materials, and reaction conditions incompatible with various common substituent functionalities. We offer here a new method that yields the isoquinolines directly without intermediate isolations and is relatively mild and specific in reaction conditions. Among the possible starting materials the aromatic aldehydes are the most commonly available, and, as in the traditional Pomeranz–Fritsch synthesis, the remaining carbons of the heterocyclic ring are linked as the aldimine from amino acetal.

We find that these imines react readily with ethyl chloroformate followed by trimethyl phosphite to form the intermediate carbamate phosphonate **3**, which is presumably created by addition of phosphite to the acyl-activated imine followed by a slower Arbuzov rearrangement, as shown in Scheme I. The intermediate carbamate phosphonates **3** were isolated as oils and characterized by TLC and NMR spectra; all showed the proton adjacent to phosphorus as a doublet of $J = 23$ Hz at $\delta \simeq 5.5$ (6.1 for no. 2 and 6 in Table I). Treatment of intermediates **3** with titanium tetrachloride in refluxing methylene chloride effects cyclization to the isoquinolines with loss of the appended phosphonate and carbamate groups. Several isoquinolines were prepared in this way without isolation of intermediates as shown in Table I and detailed in the Experimental Section.[2]

It should be noted that protection of phenolic hydroxyl groups is not necessary in this procedure.[8] Also noteworthy is the fact that the yields in cases 1, 2, and 4 with no para activation are unusually good for this kind of cyclization. Our attempts to cyclize without aromatization, i.e., retaining carbamate and phosphonate, were uniformly unsuccessful. Acting on a referee's suggestion that the three successive solvents used in our procedure (below) made it unwieldy, we examined several common solvents for all steps and chloroform was found satisfactory. When the aldehyde and amino acetal are first mixed (exothermic) and then dissolved in chloroform and half the solvent boiled off, then the solvent is dry and the imine fully formed. Chloroformate and phosphite are added at 0 °C, and the mixture is allowed to stand at room temperature for 15 h followed by direct addition of the titanium tetrachloride and refluxing for 24 h. This mixture worked up as below affords a 65% yield of 6-methoxyisoquinoline in a much simpler protocol.

Scheme I. Isoquinoline Synthesis



We sought to take advantage of the intermediate phosphonate to provide 1-substituted isoquinolines **6** via a Wittig–Horner reaction with other aldehydes prior to cyclization. The Wittig reaction was successful with several aromatic aldehydes, but the subsequent cyclization in the cases tried (no. 1, 3, 7; Table I) all gave unpromising mixtures from which only minor amounts of benzylisoquinoline **6** were produced, as well as some of the pyrrole derivative **7**. However, the conversion of the two aldehydes to **5** does offer the possibility of a new acyl anion equivalent, which we are currently investigating as a general synthetic method.

Experimental Section

General Procedure. A benzene solution (50 mL) of equimolar amounts of aromatic aldehyde (10 g, 0.07 mol) and aminoacetaldehyde dimethyl acetal (7.8 g, 0.07 mol) is refluxed overnight into a Dean–Stark trap. The solution is evaporated in vacuo and then twice evaporated again with added benzene and the viscous oil dissolved in dry THF.[8] This solution is cooled to −10 °C and 1 equiv (7.1 mL, 0.07 mol) of ethyl chloroformate[8] is added with rapid stirring and the mixture stirred 5 more min. The cooling bath is removed and 1.2 equiv (10.5 mL, 0.09 mol) of trimethyl phosphite added with stirring. The solution is allowed to stir at room temperature for 15 h and then evaporated to an oil. The oil is then reevaporated twice with added toluene to remove traces of trimethyl phosphite. The oil is dissolved in dry CH_2Cl_2, 6 equiv (50.0 mL, 0.45 mol) of titanium tetrachloride is added, and the solution is refluxed for 36 h under a drying tube. The cooled solution is shaken with 1 equiv of aqueous NaOH to neutrality, whereupon TiO_2 precipitates as a white solid. The filtrate is extracted with 3 N HCl, and the extract is washed with CH_2Cl_2,

(2) The isoquinolines were characterized by NMR and mass spectra and by comparison of melting points with those in the literature as shown in Table I. Example 6 is a new compound with satisfactory analysis as well. Cyclization catalysts other than $TiCl_4$ were generally not effective.

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(7) Miller, R. B.; Frincke, J. M. *J. Org. Chem.* **1980**, *45*, 5312.

(8) The phenolic aldehydes proceeded in better yield in CH_3CN as solvent; 1 equiv of chloroformate is still adequate in the phenolic cases.

basified strongly with aqueous alkali, and extracted with CH_2Cl_2. Drying (with Na_2SO_4) and evaporation of the organic phase affords the isoquinoline, characterized as in Table I.

Wittig Reaction to 5 and Cyclization to 6 and 7. To a solution of isolated phosphonate **3** (X = Y = OMe; Z = H; 2.05 g, 4.7 mmol) in 40 mL of dry tetrahydrofuran was added 2 mL of *n*-butyllithium (2.6 M in hexane) under nitrogen at −78 °C and stirred 15 min. To this was slowly added (−78 °C) a solution of 784 mg (4.6 mmol) of veratraldehyde in 10 mL of dry tetrahydrofuran. After half an hour at −78 °C the solution was allowed to come to room temperature and stirred for 3 h. Quenched with aqueous ammonium chloride and extracted with chloroform, the organic phase was washed with brine, dried over magnesium sulfate, filtered through Celite, and concentrated to an oil (2.07 g), which showed one spot on TLC and spectra consistent with **5**.

The oil (524 mg) was dissolved in 14 mL of dry methylene chloride and 0.75 mL of titanium tetrachloride was added at −78 °C under nitrogen. The solution was stirred at −78 °C for 15 min and warmed to room temperature and then stirred for 3 h and worked up as above to provide 64 mg of papaverine (**6**, X = Y = OCH_3; Z = H; R = 3,4-dimethoxyphenyl), identical with an authentic sample. Preparative TLC of the complex neutral fraction yielded 80 mg of the corresponding pyrrole **7** as an oil: NMR ($CDCl_3$) δ 1.15 (3 H, t), 3.55, 3.75, 3.80, 3.90 (12 H as four OCH_3 singlets), 4.15 (2 H, q), 6.4 (1 H, d, J = 4.0 Hz), 6.6–6.8 (6 H, m), 7.4 (1 H, d, J = 4.0 Hz).

Acknowledgment. We acknowledge with thanks partial support of this work by a grant from the National Institute of Drug Abuse (DA-02735).

Registry No. 1 (X = OMe; Y = Z = H), 123-11-5; 1 (X = Y = H; Z = OMe), 135-02-4; 1 (X = Y = OMe; Z = H), 120-14-9; 1 (X = Me; Y = Z = H), 104-87-0; 1 (X = OMe; Y = OH; Z = H), 621-59-0; 1 (X = OMe; Y = OH; Z = Br), 2973-58-2; 1 (X = Y = OCH_2O; Z = H), 120-57-0; 1 (X = Z = H; Y = OMe), 591-31-1; **3** (X = Y = OMe; Z = H), 86727-46-0; **4** (X = OMe; Y = Z = H) picrate, 86712-43-8; **4** (X = Y = H; Z = OMe) picrate, 1723-71-3; **4** (X = Y = OMe; Z = H), 15248-39-2; **4** (X = Me; Y = Z = H), 42398-73-2; **4** (X = OMe; Y = OH; Z = H), 1810-58-8; **4** (X = OMe; Y = OH; Z = Br), 86712-44-9; **4** (X = OMe; Y = OH; Z = Br) picrate, 86712-46-1; **4** (X = Y = OCH_2O; Z = H), 269-44-3; **4** (X = Z = H; Y = OMe) picrate, 86712-47-2; **5** (X = Y = OMe; Z = H; R = 3,4-dimethoxyphenyl), 86712-48-3; **6** (X = Y = OMe; Z = H; R = 3,4-dimethoxyphenyl), 58-74-2; **7** (X = Y = OMe; Z = H; R = 3,4-dimethoxyphenyl), 86712-49-4; $H_2NCH_2CH(OCH_3)_2$, 22483-09-6; ClCOOEt, 541-41-3; $P(OCH_3)_3$, 121-45-9; $TiCl_4$, 7550-45-0.

Synthesis of 4-Methylene-1,3-dioxolan-2-one, a Bifunctional Cyclic Carbonate

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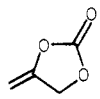
In the course of a study directed toward the development of conjunctive reagents, it was of interest to synthesize 4-methylene-1,3-dioxolan-2-one (**1**) to investigate



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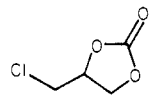
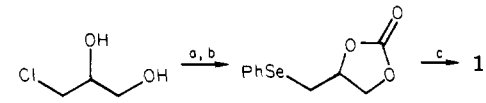


2

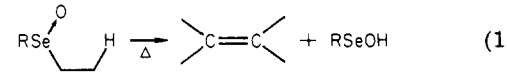
the interaction of such a bifunctional substrate with palladium(0) complexes in the hope of generating oxatrimethylenemethane intermediates. Our initial attempt involved dehydrochlorination of the known chloromethyl carbonate **2**.[2] However, treatment of **2** with DBU (1,5-diazabicyclo[5.4.0]undec-5-ene), potassium *tert*-butoxide, or basic alumina led only to destruction of starting material. The failure of this approach was not unexpected because of the predicted sensitivity of **1** toward basic conditions. The facile thermal elimination of selenenic acid from a selenoxide to produce an olefin[3,4] (eq 1) seemed an

Scheme I[a]



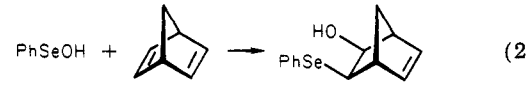
3 4

[a] (a) PhSeNa, MeOH, reflux, 99% yield; (b) $(CH_3O)_2C{=}O$, catalyst $NaHCO_3$, reflux, 92% yield, (c) O_3, CH_2Cl_2, −78 °C and then norbornadiene, $ClCH_2CH_2Cl$, and reflux, 57% yield.



(1)

attractive solution. We now report the first synthesis of **1** as depicted in Scheme I based on such a methodology. The starting material was the commercially available 3-chloro-1,2-propanediol (**3**). Reaction of the chloro diol with sodium phenylselenide[5] (generated in situ from diphenyl diselenide and sodium borohydride) followed by treatment with dimethyl carbonate gave the phenylselenenyl carbonate **4** in 91% yield. Oxidation of **4** with ozone at −78 °C produced the corresponding selenoxide.[3] The same product can also be prepared by reacting **4** with MCPBA. However, the yield was lower due to the high water solubility of the selenoxide during the aqueous workup. Thermolysis of the crude ozone-oxidation product at 100 °C under vacuum gave a low yield of the desired product **1** and a substantial amount of selenide **4**. Apparently, benzeneselenenic acid, the byproduct of the pyrolysis, effected the reduction of the starting material. Despite the success in the literature,[3] the use of amines such as diethylamine, piperidine, or diisopropylamine for the removal of PhSeOH proved unsatisfactory. To circumvent this problem, we were able to employ an activated olefin, e.g., norbornadiene, as a neutral trap. Presumably, the benzeneselenenic acid was removed as the innocuous and nonvolatile adduct **5** (eq 2). Thus, when the selenoxide



(2)

5

of **4** was added slowly to a refluxing solution of dichloroethane and 25 equiv of norbornadiene, the desired vinyl carbonate **1** was isolated in 57% yield after distillation of the crude reaction mixture.

The title compound was therefore obtained in 52% overall yield from **3** in a simple three-step operation. The

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