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A Mild and Efficient Synthesis of Intermediates for the Pomeranz-Fritsch Reaction

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ABSTRACT

Reaction of 1-chloro-2,2-dimethoxyethane with sodium azide affords 1-azido-2,2-dimethoxyethane which, upon treatment with triphenylphosphine followed by aromatic aldehydes, alkyl bromides, or isocyanates, gives the corresponding dimethyl α-arylimino-, α-alkylamino-, and α-carbodiimido-acetals, respectively, in good to excellent yields.

INTRODUCTION

The Pomeranz–Fritsch reaction has been an important tool for the construction of the isoquinoline nucleus, which appears ubiquitously in the structures of various alkaloids and other physiologically active compounds [1–3]. The preparation of the so-called Pomeranz–Fritsch intermediates **4** has uniformly relied on the condensation of 2-amino-1,1-dialkoxyethane with the corresponding aromatic aldehydes [3,4]. Cyclizations of *N*-(β,β-dialkoxyethyl)benzalimines **4** are well documented [4,5].

In the course of our investigation of iminophosphorus reagents in organic synthesis [6–9], we have developed a mild and efficient alternative procedure for the preparation of compounds of types **4**, **6**, and **8**, based on an adaptation of the Staudinger transformation [10], in which *N*-triphenylphosphoridenyl-2,2-dimethoxyethylamine (**5**) is reacted with the appropriate electrophiles.

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RESULTS AND DISCUSSION

Treatment of 1-chloro-2,2-dimethoxyethane (**3**) with sodium azide and catalytic amounts of potassium iodide in DMSO afforded the azido derivative **2** in nearly quantitative yield. The catalytic function of iodide ion was vital, as no reaction was observed in its absence even at elevated temperatures. The reaction of **2** with triphenylphosphine in tetrahydrofuran proceeded smoothly at room temperature and provided the iminophosphorane **5** after 5 hours (Scheme 1). As expected, **5** is highly sensitive and attempts to purify it result in its rapid decomposition. In the present procedure, **5** was treated directly with electrophiles in situ. For example, treatment of **5** with aromatic aldehydes afforded the corresponding dimethyl α-aryliminoacetals **4** in excellent yields (Table 1). A variety of aldehydes, including 2-furanal, 1-pyrenecarboxaldehyde, and benzene-1,4-dicarboxaldehyde, were employed and each reaction was complete within 12 hours at room temperature. After evaporation of the solvent, the only by-product, triphenylphosphine oxide ($Ph_3P{=}O$), was easily removed by trituration of the reaction residue with diethyl ether, followed by filtration. The products were then purified by either distillation or recrystallization (Table 1). Reaction of **5** with alkyl bromides yielded initially the corresponding triphenylphosphonium bromides which were directly subjected to basic hydrolysis to afford the corresponding dimethyl α-alkylaminoacetals **8** in good to excellent yields. In addition to cyclizing to the tetrahydroisoquinolines (for **8a,b**), as mentioned previously, **8** are also easily hydrolyzable protected equivalents of the corresponding α-aminoaldehydes [11,12]. To further assess its reactivity, iminophosphorane **5** was

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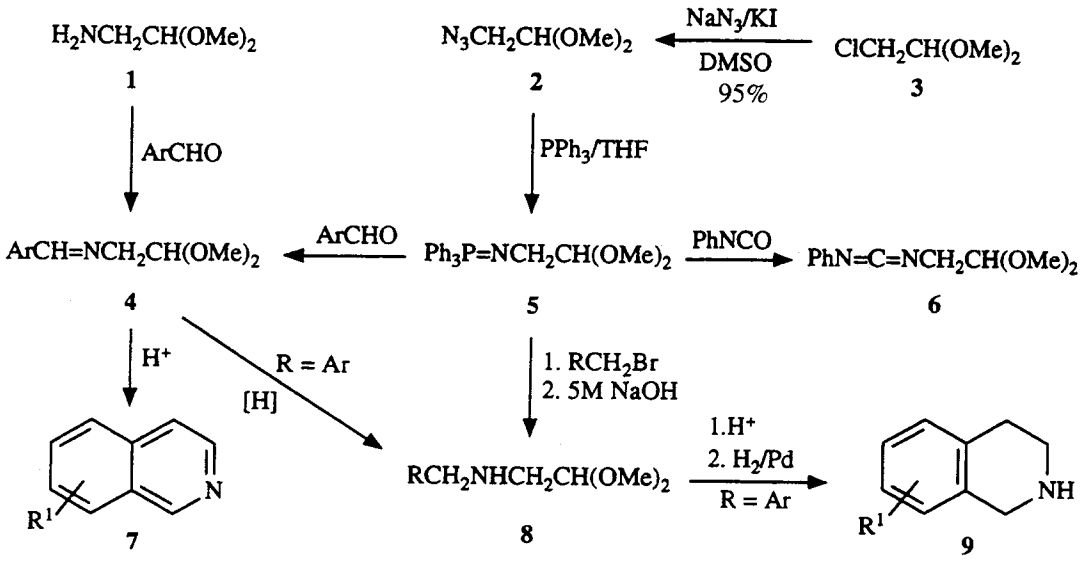
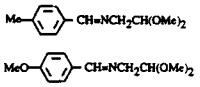
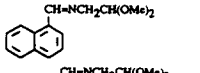
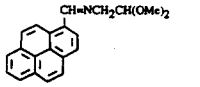
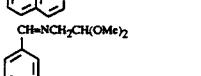
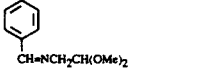
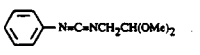
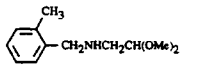


SCHEME 1

TABLE 1 Preparation of Dimethyl Arylimino-, Alkylamino-, and Carbodimido-Acetals

Entry	Product	Yield (%)	Mp (°C) or Bp (°C/mmHg)	Molecular Formula	Found (Required) C	H	N
4a		86	95–97/0.2	$C_{12}H_{17}NO_2$	69.51 (69.52	8.36 8.27	6.67 6.76)
4b		91	89–91/0.1	$C_{12}H_{17}NO_3$	64.70 (64.55	7.58 7.67	6.48 6.27)
4c		92	76–78/0.1	$C_9H_{13}NO_3$	58.93 (59.00	7.27 7.15	7.58 7.65)
4d		89	145–148/0.1	$C_{15}H_{17}NO_2$	73.72 (74.05	6.95 7.04	5.89 5.76)
4e		87	71–73[a]	$C_{21}H_{19}NO_2$	79.47 (79.47	6.03 6.02	4.41 4.26)
4f		84	57–59[b]	$C_{16}H_{24}N_2O_4$	62.69 (62.32	7.79 7.84	8.73 9.08)
6		92	89–90/0.1	$C_{11}H_{14}N_2O_2$	64.10 (64.06	6.45 6.84	13.30 13.58)
8a		94	82–83/0.1	$C_{11}H_{17}NO_2$	67.63 (67.66	8.90 8.78	7.22 7.17)
8b		79	86–87/0.1	$C_{12}H_{19}NO_2$	68.83 (68.87	9.18 9.15	6.63 6.69)
8c		55	89–91/0.7	$C_{12}H_{27}NO_2$	66.12 (66.31	12.69 12.52	6.35 6.44)

[a]Recyrstallized from hexane/ethyl acetate (10:1).
[b]Recrystallized from hexane/ethyl acetate (6:1).

also treated with phenyl isocyanate under similar conditions, and the phenylcarbodiimido derivative **6** was obtained in a yield of 92%. Attempts to extend this procedure to aromatic ketones and to thiobenzophenone resulted in only recovery of the starting material even at elevated temperatures.

In conclusion, the preparation of dimethyl α-arylimino-, α-alkylamino-, and α-phenylcarbodimido-acetals has been accomplished by the Staudinger reaction of triphenylphosphoridenyl-2,2-dimethoxyethylamine with the corresponding aromatic aldehydes, alkyl bromides, and phenyl isocyanate. The high yields, mild conditions, and the generality demonstrated herein make this

TABLE 2 ^{1}H NMR Data of Compounds **4a–f**, **6**, and **8a–c**.

Compound	*CH = N*	*NCH$_2$*	*CH(OMe)$_2$*	*(OMe)$_2$*	*Other Signals*
4a	8.25 (s, br, 1H)	3.76 (dd, 2H, J_1 = 5.3 and J_2 = 1.3 Hz)	4.67 (t, 1H, J = 5.3 Hz)	3.42 (s, 6H)	7.63 (d, 2H, J = 8.2 Hz), 7.21 (d, 2H, J = 8.2 Hz), 2.37 (s, 3H)
4b	8.21 (s, br, 1H)	3.73 (dd, 2H, J_1 = 5.3 and J_2 = 1.3 Hz)	4.66 (t, 1H, J = 5.3 Hz)	3.41 (s, 6H)	7.68 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 3.81 (s, 3H)
4c	8.09 (s, br, 1H)	3.74 (dd, 2H, J_1 = 5.3 and J_2 = 1.2 Hz)	4.71 (t, 1H, J = 5.3 Hz)	3.41 (s, 6H)	7.52 (s, 1H), 6.77 (d, 1H, J = 3.4 Hz), 6.47 (dd, 1H, J_1 = 3.4 Hz and J_2 = 1.8 Hz)
4d	8.93 (s, br, 1H)	3.90 (dd, 2H, J_1 = 5.3 and J_2 = 1.2 Hz)	4.78 (t, 1H, J = 5.3 Hz)	3.45 (s, 6H)	8.86 (d, 1H, J = 8.3 Hz), 7.91–7.87 (m, 3H), 7.60–7.48 (m, 3H)
4e	9.17 (s, br, 1H)	3.96 (dd, 2H, J_1 = 5.2 and J_2 = 1.1 Hz)	4.82 (t, 1H, J = 5.3)	3.48 (s, 6H)	8.73 (d, 1H, J = 9.4 Hz), 8.44 (d, 1H, J = 8.0 Hz), 8.10–7.90 (m, 7H)
4f	8.30 (s, br, 2H)	3.79 (dd, 4H, J_1 5.3 and J_2 = 1.3 Hz)	4.69 (t, 2H, J = 5.3 Hz)	3.42 (s, 12H)	7.79 (s, 4H)
6	—	3.46 (d, 2H, J = 5.4 Hz)	4.56 (t, 1H, J = 5.4 Hz)	3.40 (s, 6H)	7.32–7.26 (m, 2H), 7.19–7.10 (m, 3H)
8a	3.79[a] (s, 2H)	2.74 (d, 2H, J = 5.5 Hz)	4.48 (t, 1H, J = 5.5 Hz)	3.35 (s, 6H)	7.32–7.21 (m, 5H), 1.50 (s, br, 1H)
8b	3.78[a] (s, 2H)	2.78 (d, 2H, J = 5.5 Hz)	4.49 (t, 1H, J = 5.5 Hz)	3.36 (s, 6H)	7.30–7.14 (m, 4H), 2.34 (s, 3H), 1.35 (s, br, 1H)
8c	2.61[a] (t, 2H, J = 7.1 Hz)	2.73 (d, 2H, J = 5.5 Hz)	4.47 (t, 1H, J = 5.5 Hz)	3.39 (s, 6H)	1.53–1.44 (m, 2H), 1.35–1.25 (m, 10H) 1.10 (s, br, 1H), 0.88 (t, 3H, J = 6.5 Hz)

[a]Signals for RCH$_2$NH-.

TABLE 3 ^{13}C NMR Data of Compounds **4a–f**, **6**, and **8a–c**

Compound	*CH = N*	*NCH$_2$*	*CH(OMe)$_2$*	*OMe*	*Other Signals*						
4a	163.8	64.0	104.4	54.6	141.4	133.9	129.6	128.6	21.9		
4b	162.6	63.4	103.9	54.0	161.6	129.7	128.9	113.8	55.2		
4c	151.7	63.4	103.6	54.1	151.2	144.7	114.4	111.4			
4d	163.0	64.4	103.9	54.2	133.7	131.5	131.2	131.0	128.7	128.5	
					127.1	125.9	125.1	124.2			
4e	162.0	64.5	104.1	54.2	132.7	131.0	130.4	129.7	128.4	128.35	
					128.31	127.2	126.2	125.9	125.7	125.4	
					124.7	124.6	124.4	122.3			
4f	162.7	63.5	103.6	54.0	137.9	128.2					
6	129.4[a]	47.5	102.6	53.8	129.2	125.5	124.5	123.7			
8a	53.7[b]	50.3	103.7	53.7	140.0	128.2	127.9	126.8			
8b	51.5[b]	50.8	103.8	53.8	138.0	136.2	130.2	128.3	126.9	125.8	18.8
8c	51.2[b]	50.0	103.9	53.9	31.8	30.1	29.4	29.2	27.2	22.6	14.0

[a]Chemical shifts for N = C = N.
[b]Chemical shifts for RCH$_2$NH-.

method a useful complement to the existing procedures. Previously, few examples of the preparation of the imines derived from polynuclear aromatic aldehydes, dialdehydes, or heteroaromatic aldehydes have been reported. Despite the good yield (80%) of (**4f**) obtained when 2-amino-1,1-dimethoxyethane (**1**) was condensed with benzene-1,4-dicarboxaldehyde, the modest improvement in the yield realized by the present procedure, together with the generality demonstrated by the aldehydes herein, underlines the value of this method. Additionally, for the preparation of **8**, our method obviates the reduction step employed in the classical procedure (**4** → **8**). This is important if the substrate contains other reducible functional groups. Also, reaction of a primary amine such as **1** with alkyl bromides generally gives complex mixtures. Finally, no previous method was available for the preparation of compounds of type **6**.

EXPERIMENTAL

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using the solvent peak ($CDCl_3$, δ = 77.0 ppm; DMSO-d_6, δ = 39.50 ppm) as reference. Microanalyses were carried out using a Carlo Erba 1106 elemental analyzer.

2-Azido-1,1-dimethoxyethane (**2**)

A mixture of 2-chloro-1,1-dimethoxyethane (12.7 g, 100 mmol), sodium azide (7.8 g, 120 mmol), potassium iodide (1.2 g, 7.2 mmol), and DMSO (80 mL) was heated to 90°C and maintained at this temperature for 4 days. The mixture was poured into ice-water (150 mL) and extracted with diethyl ether (3 × 100 mL). The organic layer was washed with water (5 × 50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to afford the almost pure product as a colorless liquid, yield 95%. ^{1}H NMR ($CDCl_3$): δ 4.48 (t, 1H, J = 5.3 Hz), 3.42 (s, 6H), and 3.26 (d, 2H, J = 5.3 Hz).^{13}C NMR ($CDCl_3$): 102.9, 54.1, and 51.5.

Preparation of Arylimino- (**4a–f**) *and Phenylcarbodiimido-dimethyl* (**6**) *Acetals*

General Procedure. Triphenylphosphine (10.5 g, 40 mmol) was added to a solution of 2-azido-1,1-dimethoxyethane (5.24 g, 40 mmol) in dry tetrahydrofuran (70 mL), and the mixture was stirred at room temperature for 5 hours. Aldehydes (for **4a–e**, 40 mmol; for **4f**, 20 mmol) or phenylisocyanate (for **6**, 40 mmol) were added, and the mixture was allowed to stand at room temperature for 12 hours. Evaporation of the solvent under reduced pressure gave a residue to which dry diethyl ether was added. The insoluble white solid (Ph_3P=O) was filtered off, and the solvent was evaporated to afford the crude product which was then purified as described in Table 1.

Preparation of Alkylamino Dimethyl Acetals **8a–c**

General Procedure. Triphenylphosphine (10.5 g, 40 mmol) was added to a solution of 2-azido-1,1-dimethoxyethane (5.24 g, 40 mmol) in dry tetrahydrofuran (70 mL), and the mixture was stirred at room temperature for 5 hours. Alkyl bromides (40 mmol) were added, and the mixture was stirred at room temperature for 12 hours. The white solid precipitated was collected by filtration, washed with diethyl ether (1 × 50 mL), and dried.

The white solid obtained was added to aqueous sodium hydroxide (200 mL, 5 M), and the mixture was refluxed overnight. The mixture was extracted with diethyl ether (3 × 40 mL), and the ether extracts were washed with water (2 × 40 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Diethyl ether (50 mL) was added to the residue, and the insoluble white solid (Ph_3P=O) was filtered off. Evaporation of the solvent gave the crude product which was then purified as described in Table 1.

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