Table I. Spectral Features of (Dialkoxymethyl)phenyldiazenes 2[a]

Compd	Registry no.	R	^{1}H chemical shift, δ (Me_4Si) CH	OCH_3	α	β	γ	UV λ_{max} (EtOH), nm (log ε)
2b[b]	65102-03-6	$-CH_{2\alpha}CH_{3\beta}$	5.09	3.48	3.80[c]	1.19		269 (3.92), 215 (3.95)
2c[d]	65102-04-7	$-CH_{2\alpha}CH_{2\beta}CH_{3\gamma}$	5.02	3.53	3.72[c]	1.63	0.95	268 (3.96), 215 (4.01)
2d[b]	65102-05-8	$-CH_{2\alpha}CH_{\beta}{=}CH_{2\gamma}$	5.18	3.55	4.38	5.0–5.4	5.6–6.2	269 (3.92), 214 (4.02)

[a] All compounds showed NMR absorptions at δ 7.7 for *o*-Ph and at δ 7.5 for *m*- and *p*-Ph protons; IR absorptions included those at 1520 (medium, $\nu_{N=N}$), 1120 and 1060 cm^{-1} (strong, ν_{CO} acetal). [b] NMR solvent: acetone-d_6. [c] Diastereotopic splitting of the expected multiplet was observed. [d] NMR solvent: CCl_4.

The structures of **2b–d** are based on their elemental analyses and the spectral data gathered in Table I. The spectral features which distinguish the diazenes **2** from a possible (tautomeric) hydrazone structure are (1) the chemical shift of the methylidyne H, δ 4.9–5.2 (vs. δ >6.5 for the usually broad phenylhydrazone NH[4]), (2) the value of the UV extinction coefficient (ε) for the 260–280-nm absorption of phenylalkyldiazenes near 10 000[5] (vs. 18 000–20 000 for the similar absorption of phenylhydrazones[6]), and (3) the absence of NH stretch in the IR spectra of **2** (vs. ν_{NH} of 3300–3450 cm^{-1} for hydrazones[6]).

The conversion of **1** to **2**, analogous to the conversion of di(1-butyl)diazene oxide to 1-butyl-2-pentyldiazene by methyllithium,[7] joins the growing list of selective transformations which can be effected at both distal[2] and proximal[8] carbon atoms of azoxyalkanes.

Experimental Section

General. For instruments used see the Experimental Section of ref 2. VPC analyses were performed using the following aluminum tubing columns: A, 4 ft × 0.25 in. 10% SE-30 on Chromosorb W (AW and DMCS); B, 6 ft × 0.25 in. 5% silicone oil Dow 710 on Chromosorb W (AW and DMCS); C, 6 ft × 0.125 in. 5% UCW 98 on Diatoport S. Dialkyldiazene oxides are animal carcinogens. However, phenylhydroxymethyldiazene 1-oxide (**1**, R = H) produced no tumors in rats at dose levels which with dimethyldiazene oxide produced tumors with 100% frequency.[9]

(*Z*)-Phenylpropoxymethyldiazene 1-Oxide (1c). The title compound was prepared in 85% yield using the silver carbonate procedure described in ref 2. Preparative VPC (column A) provided an analytical sample: NMR ($CDCl_3$) δ 8.12 (m, 2 H, *o*-Ph), 7.4 (m, 3 H, *m*- and *p*-Ph), 5.15 (s, 2 H, distal CH_2), 3.62 (t, 2 H, OCH_2), 1.71 (m, 2 H, CCH_2), 0.97 (t. 3 H, CH_3); IR (neat) 1490, 1425, 1355, and 1325 cm^{-1}; UV λ_{max} (95% C_2H_5OH) 247 nm (ε 10 500). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27. Found: C, 61.61; H, 6.98.

(*E*)-(Methoxyethoxymethyl)phenyldiazene (2b).[10] A mixture of 0.560 g (3.1 mmol) of **1b**, 0.50 g of triethylamine, 0.50 g of magnesium sulfate, and 0.25 g of calcium sulfate in 7 mL of methanol was stirred 1 day at room temperature. After filtration and concentration in vacuo the resulting red oil was chromatographed over 30 g of silica gel. Elution with benzene gave 0.30 g (50%) of 95% pure **2b** as a red oil. Preparative VPC using column B gave an analytical sample. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.74. Found: C, 62.00; H, 7.38.

(*E*)-(Methoxypropoxymethyl)phenyldiazene (2c). This compound was prepared from **1c** and methanol in 58% yield, 98% pure, by the method described for **2b**. Preparative VPC on column A gave an analytical sample. Alternately, **2c** was prepared in similar yield from **1a** and 1-propanol using triethylamine as base and from **1a**, 1-propanol, and 0.2 mol equiv of 1 N KOH. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74. Found: C, 63.22; H, 7.57.

(*E*)-(Methoxy-2-propenoxymethyl)phenyldiazene (2d). This compound was prepared from **1d** in 49% yield by the method used to make **2b**. Preparative VPC using column B gave an analytical sample. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 63.88; H, 6.78.

Stability Studies. A solution of 0.10 g of **2c** in 0.5 mL of 0.1 N aqueous hydrochloric acid and 1.0 mL of methanol was stirred at room temperature. VPC analysis (column C) after 1 h showed no trace of **2c**.

VPC analysis (column C) of a solution of **2c** in 0.5 mL of methanolic 0.1 N KOH and 0.5 mL of water showed no loss of **2c** after 1 day at reflux and 10% loss of **2c** after 6 days at reflux.

Registry No.—**1b**, 57496-83-0; **1c**, 65102-06-9; **1d**, 57496-85-2; methanol, 67-56-1.

References and Notes

(1) (a) This work was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society; (b) For part 6, see K. G. Taylor, S. R. Isaac, and J. L. Swigert, *J. Org. Chem.*, **41**, 1146 (1976).
(2) K. G. Taylor and M. S. Clark, Jr., *J. Org. Chem.*, **41**, 1141 (1976).
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(9) Norman D. Nigro, Department of Surgery, Wayne State University School of Medicine, private communication.
(10) The assignment of compounds **2** as *E* diastereomers is based on the δ 7.7 chemical shift of the ortho protons of the phenyl rings. These protons resonate at δ 6.4 in (*Z*)-alkylphenyldiazenes.[11]
(11) S. N. Ege and R. R. Sharp, *J. Chem. Soc. B*, 2014 (1971).

An Improved Method for the Synthesis of Stabilized Primary Enamines and Imines

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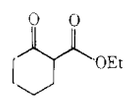
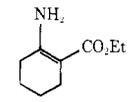
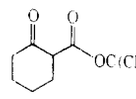
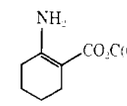
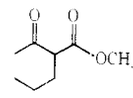
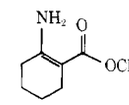
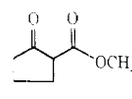
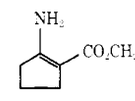
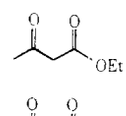
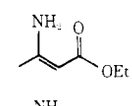
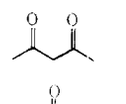
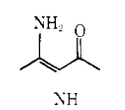
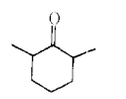
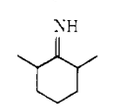
Received September 27, 1977

Primary β-enamino carbonyl compounds are interesting as potential intermediates in the synthesis of natural and synthetic compounds possessing biological activity. They are rendered especially versatile by their reactivity at both nitrogen and the α carbon, with the possibility existing of systematically directing reaction at either site.[1] Established syntheses of these compounds proceed from the corresponding β-dicarbonyl compound using ammonia[2] or a synthetic equivalent of ammonia[3] to form the enamine. Although these methods are useful, both lack generality when dealing with multifunctional compounds which are sensitive to the strongly basic and nucleophilic reagents required by each. Thus, the Dieckmann–Prelog method[2] (direct treatment with ammonia) is time consuming and apparently limited to structurally simple β-keto esters.[3] The Takaya method,[3] while more general in scope, requires in its second step the use of sodium ethoxide in refluxing ethanol, conditions which are often destructive to other moieties in a potential substrate, particularly exchangeable esters.

This note describes a new method for effecting this transformation which uses a markedly less nucleophilic reagent and proceeds under acid catalysis. *N*-Trimethylsilyliminotri-

0022-3263/78/1943-1460$01.00/0

Table I[a]

Entry	Starting material	Registry no.	Product	Registry no.	Yield,[b] %	Bp, °C (mmHg) [mp]
1		1655-07-8		1128-00-3	88	[70–72]
2		55623-56-8		65277-17-0	68	80–90 (15)
3		65277-16-9		65277-18-1	43	135 (0.05) (KR)
4		611-10-9		7149-18-0	91	[58–59]
5		141-97-9		7318-00-5	73	[33–35]
6		123-54-6		1118-66-7	68	110–115 (10)
7		2816-57-1		13652-33-0	40	65–75 (12)

[a] All compounds listed had physical and spectral properties consistent with those in the literature or satisfactory elemental analysis. [b] Yields represent isolated material and have not been maximized in all cases.

phenylphosphorane (I) (easily prepared from triphenylphosphine and azidotrimethylsilane[4]) reacts with β-dicarbonyl compounds (II) in the presence of a molar equivalent of a secondary alcohol and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding β-amino-α,β-unsaturated carbonyl compounds (III). The results are summarized in

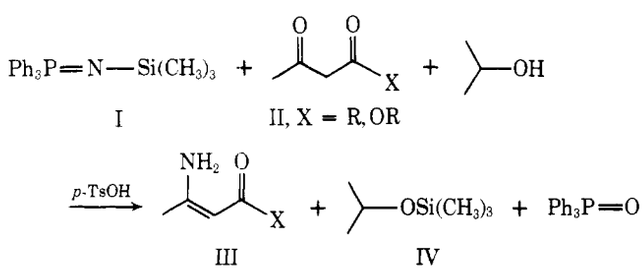


Table I. As can be seen from entry 7, the reagent also forms unconjugated imines, providing they are stable to the reaction conditions. Particularly noteworthy is the lack of ester exchange in the β-keto esters.

The observation that no reaction takes place in the absence of the alcohol suggests that the method proceeds by in situ generation of iminotriphenylphosphorane.[5] Thus the initial step is cleavage of the nitrogen–silicon bond to form the unprotected iminophosphorane and the corresponding trimethylsilyl alkoxide IV.[6] Condensation with the ketone then follows, affording the desired product III and triphenylphosphine oxide. Credence to this mechanism is lent by the report that iminotriphenylphosphorane itself undergoes a similar condensation with certain exceptionally reactive ketones.[5,7]

The principal limitation seems to be the stability of the product to the reaction conditions. Thus, when the sequence was employed with cyclohexanone, the ketone was consumed and triphenylphosphine oxide was produced, but no volatile products were found. Presumably the imine was formed and then underwent random selfcondensation.

In summary, the method described has the following advantages. It allows for the rapid, one-step conversion of appropriate ketones to their corresponding primary enamines or imines. It is the only method available for effecting this conversion without the use of strong bases and/or nucleophiles, thus allowing synthesis of a wider variety of target molecules, particularly those containing exchangeable esters. Lastly, the reagent is easily synthesized and can be readily manipulated without fear of atmospheric hydrolysis.

Experimental Section

General Procedure for the Condensation of *N*-Trimethylsilyliminotriphenylphosphorane (I) with Ketones. To a solution of 1 molar equiv each of the desired keto compound, isopropyl alcohol, and I in a convenient amount of benzene was added a catalytic amount of *p*-toluenesulfonic acid. The resulting solution was refluxed until the reaction was complete (4–8 h). The solution was cooled, concentrated on a rotary evaporator, and diluted with ether. The resulting precipitate of triphenylphosphine oxide was removed by filtration, and the filtrate was concentrated again. The resulting crude product was purified by distillation.

Registry No.—I, 13892-06-3.

References and Notes

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(4) L. Birkofer, A. Ritter, and P. Richter, *Chem. Ber.*, **96**, 2750 (1963).
(5) (a) R. Appel and A. Hauss, *Chem. Ber.*, **93**, 405 (1960); (b) *Z. Anorg. Allg. Chem.*, **311**, 290 (1961).
(6) L. Birkofer, A. Ritter, and S. M. Kim, *Chem. Ber.*, **96**, 3099 (1963).

(7) While one could picture iminotriphenylphosphorane itself effecting the transformation described here, its experimental use proves to be less than ideal. Since simple exposure to the atmosphere results in hydrolysis to ammonia and triphenylphosphine oxide, rigorously anhydrous conditions are required for its synthesis, storage, and use. Reactions of this reagent with other than the most highly reactive of ketones are thus often complicated by decomposition of the reagent. In contrast, the trimethylsilyl-protected compound employed here is stable to atmospheric moisture and requires no undue care in its manipulations.

Studies in the (+)-Morphinan Series. 4.[1] A Markedly Improved Synthesis of (+)-Morphine

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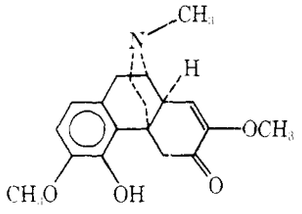
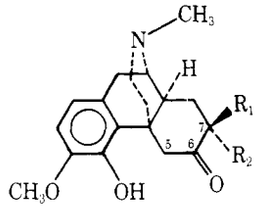
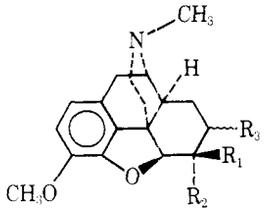
The absolute configuration of the morphinan skeleton of (−)-sinomenine (**1**)[3] is enantiomeric to natural (−)-morphine, and conversion of **1** into (+)-morphine (**10**) was reported by



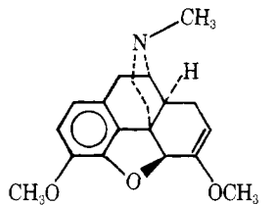
1



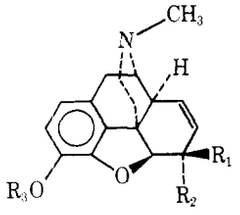
2a, R_1 = OCH_3; R_2 = H
b, R_1 = H; R_2 = OCH_3



3, R_1, R_2 = O; R_3 = H
4, R_1 = R_2 = OCH_3; R_3 = H
6, R_1 = R_2 = OCH_3; R_3 = Br



5



7, R_1 = R_2 = OCH_3; R_3 = CH_3
8, R_1, R_2 = O; R_3 = CH_3
9, R_1 = OH; R_2 = H; R_3 = CH_3
10, R_1 = OH; R_2 = R_3 = H
11, R_1 = OAc; R_2 = H; R_3 = Ac

Goto's group.[4a-c] To define morphine's interaction with opiate receptors more clearly,[5] we wanted to prepare large quantities of unnatural enantiomer **10** and several of its congeners. We now summarize our results that followed, in principal, Goto's original scheme,[4a-c] but which implemented novel reactions and the findings of others, especially those of Rapoport et al.[6] Rapoport's results in the natural (−) series became available only after we had started our project. A tenfold increase in the overall yield of (+)-morphine (**10**), previously reported by Goto, from (−)-sinomenine (**1**) was accomplished as follows.

Catalytic reduction[7] of **1** afforded a mixture of two diastereomers (**2a** and **2b**) which was separated by preparative thin-layer chromatography. The equilibrium mixture was reestablished by brief boiling of either isomer in methanol. Deuterium exchange of **2a** and **2b** allowed definitive assignment of the chemical shift of the C-5 and C-7 protons. Assuming that the preferential conformation of ring C is the chair form, the absolute configuration of **2a** and **2b** at C-7 could be determined. Major isomer **2a** and minor isomer **2b** were assigned 7*R* (axial H) and 7*S* (equatorial H) configurations, respectively, for the following reasons. The chemical shift of the C-7 equatorial proton, due to the shielding effect of the carbonyl group in the 7*S* isomer, lies upfield of the C-7 axial proton in the 7*R* isomer, in accord with previous work on α-methoxydecalones.[8] The chemical shift of the C-7 proton of the 7*S* isomer was δ 3.36 (t, J = 3.5 Hz) and that of the C-7 proton in the 7*R* isomer was δ 3.90 (center of d of d, J = 7, 12 Hz), and the coupling constants were of the magnitude expected. The equatorially oriented C-7 methoxyl group in the 7*R* isomer was deshielded by the carbonyl group (δ 3.43), as compared with the methoxy group in the 7*S* isomer (δ 3.30), again in accord with α-methoxydecalones.[8] Molecular models (Dreiding) indicate that the major product might well be the 7*R* isomer because of the less sterically hindered methoxyl group. The C-5 equatorial proton in both 7*R* and 7*S* isomers was considerably deshielded, presumably due to its proximity to the aromatic ring (see Experimental Section). A similar effect was noted in dihydrothebainone.[6]

Since the next step, the acid-catalyzed S_N2' cyclization of **2a** and **2b** to **3**, with loss of methanol, proceeds under conditions which equilibrate the two epimers, the mixture was treated directly with polyphosphoric acid at 65–70 °C. Ketone **3** is rather stable under these reaction conditions, in contrast to Goto's[9] more drastic conditions; and yields of desired ketone **3** were consistently 70–75%.

Introduction of a double bond in the 7,8 position of **3** is not easy, and attempts to introduce it by direct oxidation were unsuccessful. This could, however, be accomplished by phenylselenation and oxidative elimination, but only after the *N*-methyl group was replaced by a *N*-carbethoxy group.[10] Meanwhile, Rapoport's modification for converting (−)-dihydrocodeinone (enantiomer of **3**) into (−)-codeinone (enantiomer of **8**) became known[6] and was successfully implemented in our plan, which now took the following course: ketalization of **3** to dimethyl ketal **4** (98%); elimination of methanol with *p*-toluenesulfonic acid in chloroform to give enol methyl ether **5** (83%); addition of methyl hypobromite, leading to bromodimethyl ketal **6** (75%); elimination of HBr with potassium *tert*-butoxide in Me_2SO at room temperature instead of 60 °C[6] to give **7** (87%); and deketalization of **7** with 5% HCl instead of AcOH[6] to give (+)-codeinone (**8**; 96%).

Compounds **3** and **5–8** showed the properties previously reported by Goto et al., and **3–8** had properties identical with the corresponding compounds in the (−) series prepared as described by Rapoport,[6] except for the optical rotation. Reduction of unsaturated ketone **8** with sodium borohydride in methanol[11] afforded (+)-codeine (**9**), which was converted into (+)-morphine (**10**) by O-demethylation[12] with boron tribromide in chloroform. Unknown (+)-heroin (**11**) was obtained from **10** by treatment with acetic anhydride. Crystallization from ethyl acetate gave prisms identical with authentic (−)-heroin (enantiomer of **11**), except for the sign of optical rotation. (−)-Heroin showed specific optical rotation 10° higher than previously reported.[13]

(+)-Codeine (**9**), (+)-morphine (**10**), and (+)-heroin (**11**) showed no analgesic activity on subcutaneous injection in mice in routine screening for centrally active analgesics. Unnatural