# Studies Related to Alkylations of Enolate Anions of 1,4-Benzodiazepinones‡



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Treatment of 1,4-benzodiazepinone derivatives with a Wittig-Horner reagent, led to the desired carbon-carbon bond formation at the amide carbonyl carbon atom in reasonable yield. An examination of this reaction has shown that only secondary amides can be used, indicating that this process requires the amide proton. This observation would exclude the accepted mechanism for Wittig-Horner type reactions (four membered spiro ring intermediate), and an alternate mechanism, that involves cleavage of the anion prior to addition of the reagent to substrate is proposed.

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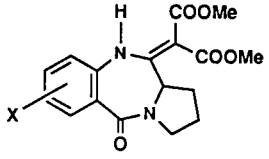
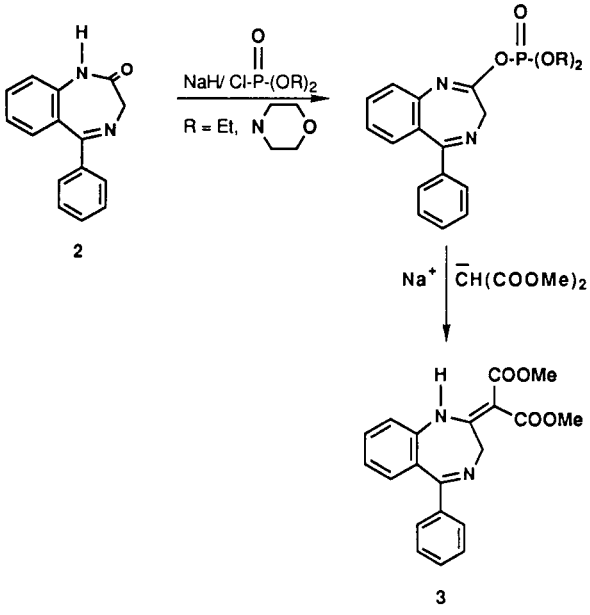
In connection with research related to the chemistry of 1,4-benzodiazepines, a reasonably large quantity of a benzodiazepine synthon of type **1**, was required for use in the preparation of 1,3-disubstituted imidazobenzodiazepines.



**1**

The approach previously used for the synthesis of a related 1,4-benzodiazepine derivatives [1,2], involved, as the first step, treatment of the ambient anion of a 5-phenyl-1,4-benzodiazepin-2-one **2** with either diethyl or dimorpholinylphosphonic chloride (Scheme 1). In the latter case,

Scheme 1



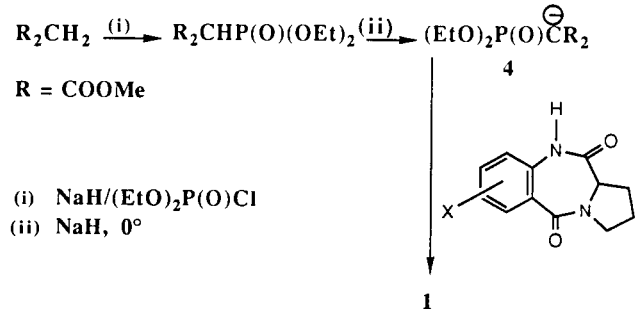

**2** **3**

Ning and coworkers [1] were able to isolate the corresponding dimorpholinylphosphinyloxy imines. These intermediates are quite susceptible to nucleophilic attack and subsequent reaction of the phosphonate with the anion of dimethyl malonate gave compounds of type **3** with the desired C=C bond.

These procedures were applied for the synthesis of **1** but, in general, the overall yield of isolated product was low. In an attempt to improve this, an approach similar to the Wittig-Horner [3] type of reaction was used and resulted in the synthesis of the desired synthon in somewhat higher yield.

This one pot procedure involved the formation of the phosphoryl stabilized anion **4** at 0° under an atmosphere of nitrogen (Scheme 2), followed by subsequent addition of the appropriate 1,4-benzodiazepine-2,6-dione.

Scheme 2



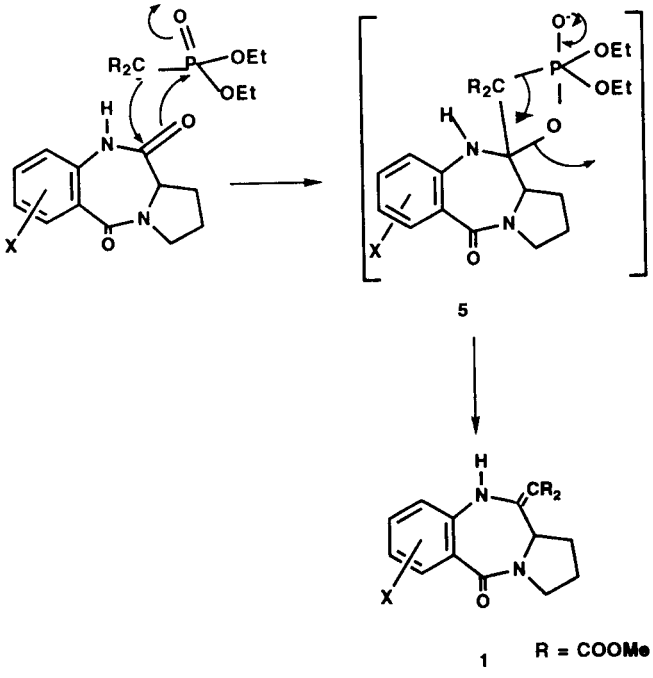

**1**

The accepted mechanism for the formation of olefins by Wittig reactions proceeds *via* a four membered intermediate, generated by attack of the ylide anion on the carbon atom of the carbonyl group and stabilization of the carbon-oxygen anion by a corresponding phosphorus-oxygen anion [3]. This would lead to the spiro intermediate **5** (Scheme 3). Collapse of **5** would then lead to product **1**.

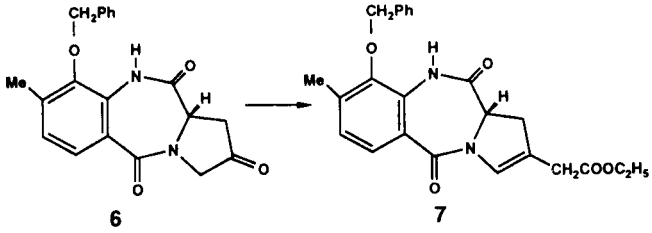
Information in the chemical literature concerning this type of reaction, *i.e.* that of ylides with amides, is rather

scanty, but the successful reaction of ylides with both secondary and tertiary amides including β-lactams has been reported [4,5].

Scheme 3



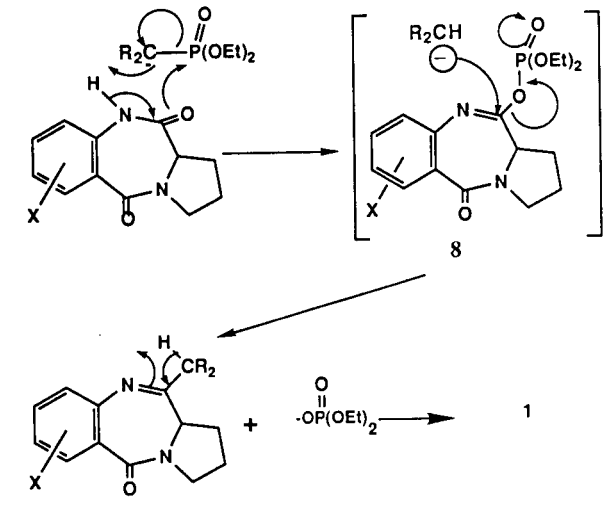
A somewhat related reaction, in which the sodium salt of triethyl phosphonoacetate was treated with **6**, a ketopyrrolo analog of **1**, was reported to give the corresponding β,γ-unsaturated carbethoxy derivative **7** as the only product isolated (normal Wittig-Horner product). No reaction was observed at either amide carbonyl [6]. The lack of relative reactivity of secondary and this tertiary amide carbonyl functions was believed to be due to the stoichiometry used, (unspecified) and to the enhanced reactivity of the keto group.



It was noted that unlike the tertiary amide carbonyl groups of ring strained β-lactams, the tertiary amide of compound **1** (Scheme 3) was unreactive upon treatment with the Wittig-Horner reagent.

It was further noted that no reports of a Wittig-Horner type of alkylation of 5-, 6-, or 7-membered cyclic amides appear in the literature. The reactivity of the β-lactam carbonyl oxygen may be a special case in which the $sp^2$ oxygen acts more like a ketone (ir C=O stretch 1715 $cm^{-1}$) than a typical cyclic secondary or tertiary amide $sp^2$ oxygen (ir C=O stretch 1650 $cm^{-1}$) [7]. A mechanism for the supposed ylide reaction (Scheme 4) can be drawn in which the malonate can act as a leaving group. This would generate the enol phosphate **8** as before. Such a mechanism would require the loss of the acidic proton on the secondary nitrogen atom and is supported by the fact that no reaction was ever observed at the tertiary amide carbonyl

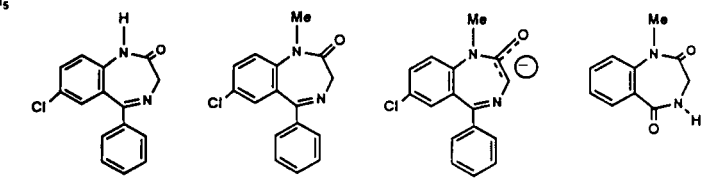
Scheme 4



carbon atom of **1**. Since the Wittig-Horner mechanism (Scheme 3) does not involve acidic protons, it was felt that an unambiguous proof was required in order to establish whether or not this reaction proceeds *via* a Wittig-Horner mechanism.

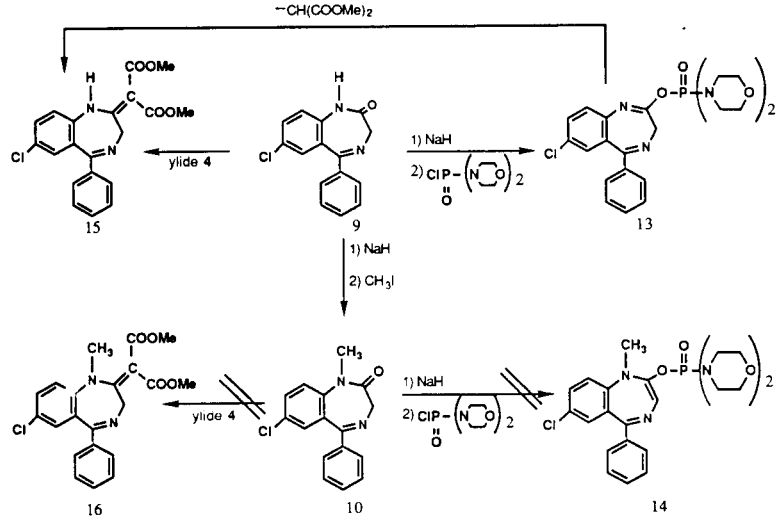
The slight (10%) but consistently higher yield of product that was obtained by the anion reactions would seem difficult to explain if the reaction was simply an enolate addition.

It was felt that this problem could be resolved by an examination of the reaction products obtained by treatment of the secondary and tertiary amides **9**, **10** and **12** with the anion **4**. Thus compound **9** was reacted with the phosphoryl stabilized anion **4** in a one pot reaction to give compound **15** in 50% yield (Scheme 5).



The same conditions were used in an attempt to react **10** but only starting material was recovered. It was interesting to note that although the enolate anion **11** (bright

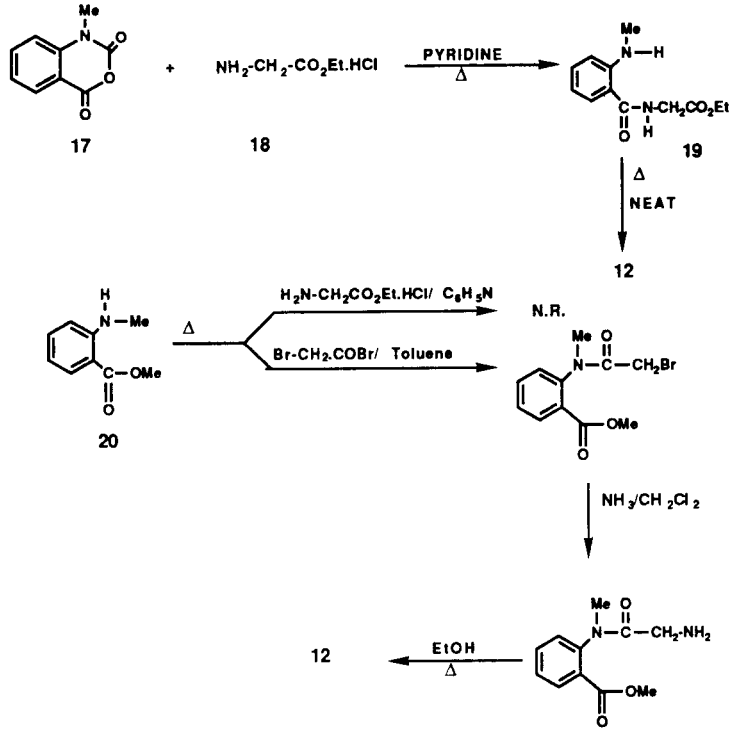
Scheme 5




red solution) was formed by using various bases and in various solvents no evidence for the reaction of **11** with the anion **4** was observed under any of the various conditions used (Table 1, Experimental).

The general sequence of addition for the preparation of analogs of **1**, *e.g.* compound **15**, from compound **9** was to prepare a solution of the ylide anion **4** and treat this by the portionwise addition of the solid 1,4-benzodiazepine (Table 1, Method A). Since this same sequence did not prove to be successful for substrate **10**, a two step synthesis was attempted (**10** → **14** → **16**). In this case, a solution of the anion of **10** was generated and was treated with a solution of the phosphorylating agent. This was done in the hope of forming intermediate **14**, which could then be reacted *in situ* with the anion of dimethyl malonate to yield **16**. However, unlike the corresponding reactions with **9** (**9** → **13** → **15**) neither **14** or **16** were formed and only starting materials were recovered. Variation of the stoichemetry of the base used in these reactions had little, if any, effect on the outcome, even when a four fold excess

Scheme 6



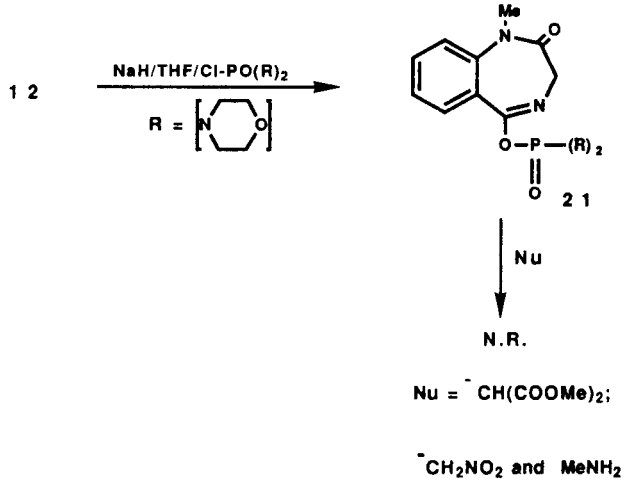
of the stoichemetric amount was present in the reaction mixture.

The study of the secondary amide lactam carbonyl functionality was extended to a third benzodiazepine (compound **12**) which has both a secondary and a tertiary amide carbonyl group. Based on the results of the study discussed above, it was anticipated that the secondary amide carbonyl would form the C=C bond even though tertiary amide carbonyls of this type remain unreactive.

Compound **12** was synthesized by reaction of *N*-methylisatoic anhydride **17** and glycine ethyl ester hydrochloride, **18** in refluxing pyridine (Scheme 6) [8]. The open ring intermediate, **19**, was cyclized by direct heating (neat) with a flame to form compound **12**. A low yield synthesis of compound **12** [9] (Scheme 6) had been previously carried out from methyl *N*-methylanthranilate **20** by treatment with bromoacetyl bromide in toluene, followed by the addition of ammonia to the bromoacetanilide intermediate and cyclization in refluxing ethanol.

The anion of compound **12** was phosphorylated with dimorpholinophosphonic chloride as described above for compound **10**, (Table 1, Method B) and the resulting enolate **21** (Scheme 7) was isolated. Attempts to further react this enolate with a number of nucleophiles in order to form new C=C bonds were unsuccessful. The enolate only formed, as expected, at the secondary amide carbonyl carbon and no reaction was observed at the tertiary amide. Once again this indicates that the proton of the secondary amide is involved in this mechanism.

Scheme 7




While the phosphinyloxy imine **21** was readily formed, attempted displacement by nucleophiles was not successful. Thus, treatment of **21** with methylamine or with the anion of either dimethyl malonate or of nitromethane was unsuccessful, only starting material being recovered. The enol phosphate **21**, may be a less reactive, more hindered position for further reaction with a nucleophile. However, even though there was no evidence for nucleophilic attack, the fact that there was a reaction at the secondary amide carbonyl and not at the tertiary amide carbonyl is consistent with the results of the study of compounds **9** and **10** discussed above.

What seems to be a reasonable mechanism is shown in Scheme 4. The proton from the secondary amide protonates the anion which then cleaves as shown to give malonate anion and the imino phosphate intermediate **8**. Intermediate **8** can now react with malonate anion as shown to give *via* a proton shift, product **1**. The higher yield of **1** obtained in this reaction by use of the Wittig ylide may be rationalized as being due to the formation of malonate anion proximate to the site of the phosphate leaving group.

This alternate mechanism seems to be more viable in terms of understanding the non-reactivity of the tertiary cyclic lactams. Thus, it is felt that treatment of 1,4-benzodiazepinones (*e.g.* **1**) with a Wittig-Horner reagent proceeds through a mechanism involving initial cleavage of the reagent and not through a mechanism involving a spiro intermediate. While it was anticipated that the secondary amide carbonyl carbon of compound **12** should give C=C bond formation, it appears that the enol phosphate of the benzoic acid amide must be either a poor leaving group and/or steric hinderance at the 6-position prohibits nucleophilic attack.

## EXPERIMENTAL

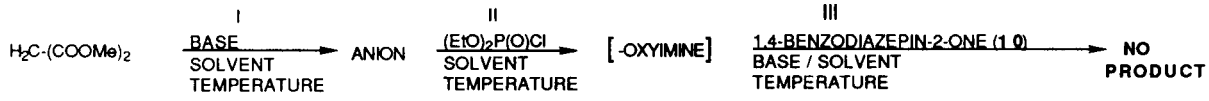
General.

All starting materials, except where noted, were purchased from the Aldrich, Fisher or Janssen Companies and were used as purchased. Most solvents were used as purchased (Fisher). Anhydrous tetrahydrofuran where required, was either purchased in sure seal cap bottles (Aldrich) or was distilled over lithium metal. A standard workup of most reactions, except where noted, included washing of the organic phase with an equal volume of water followed by washings with equal volumes of saturated sodium chloride (x3), dried (magnesium or sodium sulfate), filtered (gravity) and then solvents were concentrated, except where noted, under reduced pressure (water aspirator) on a rotary evaporator. Analytical samples were prepared by recrystallization until a constant melting point was obtained (±2°) in the indicated solvents. Reported yields were not optimized, although for repetitive experiments, the procedure reported represents the most successful procedure carried out.

Melting points were determined in a capillary tube with a "Mel-Temp" apparatus and are not corrected. The $^1$H nmr spectra were determined at 200 or 400 MHz, using the following spectrometers; Bruker Model WP 200, IBM Model WP-200sy, Bruker Model AM 400, and Varian Model VXR-400S. Spectra were recorded in deuteriochloroform or DMSO-$d_6$ and chemical shifts are expressed in parts per million (ppm) on the $\delta$ scale relative to TMS as the internal standard. Infrared spectra were determined by using a Nicolet Model 2DX infrared spectrophotom-

**TABLE 1. EXPERIMENTAL CONDITIONS USED FOR ATTEMPTED ALKYLATIONS OF THE TERTIARY AMIDE CARBONYL CARBON ATOM OF A 1,4-BENZODIAZEPINE**

METHOD A




| | I | | II | | III | | |
|---|---|---|---|---|---|---|---|
| BASE | SOLVENT | TEMPERATURE | SOLVENT | TEMPERATURE | BASE | SOLVENT | TEMPERATURE |
| Sodium hydride | THF [c] | 0-10 | THF [c] | 0-10 | ------ | THF [c] | 0 |
| Sodium hydride | THF [c] | 0-10 | THF [c] | 0-10 | ------ | DMF [d] | -78 |
| Sodium hydride | DMF [d] | -20 | DMF [d] | -20 | Sodium hydride | DMF [d] | -78 |
| Li-TMSA [a] | EGDE [b] | 0 | EGDE [b] | -20 | -------- | EGDE [b] | 0 |

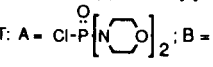
[a] Li-TMSA = Lithium-bis-(trimethylsilyl) amide. [b] EGDE = ethylene glycoldimethyl ether. [c] THF = tetrahydrofuran.
[d] DMF = dimethylformamide.

**TABLE 1.** (continued)

METHOD B


| | I | | | II | | III | | |
|---|---|---|---|---|---|---|---|---|
| BASE | SOLVENT | TEMPERATURE | PHOSPHATE REAGENT | SOLVENT | TEMPERATURE | BASE | SOLVENT | TEMPERATURE |
| Sodium hydride | THF | ambient | A | THF | 10-65 | ------ | ------- | ------- |
| Sodium hydride | EGDE | 10-25 | A | EGDE [b] | 10-25 | sodium hydride | EDGE [b] | -10-25 |
| Li-TMSA [a] | EGDE [b] | 25 | A | EGDE [b] | 10-25 | ----- -- | ---------- | ------- |
| Li-TMSA [a] | EGDE [b] | 25 | A | EGDE [b] | 10-20 | Li-TMSA [a] | EGDE [b[ | 0 |
| Li-TMSA [a] | EGDE [b] | 0 | B | EGDE [b] | 0 | Li-TMSA [a] | EGDE [b] | 0 |

[a] Li-TMSA = lithium-bis-(trimethylsilyl) amide. [b] EGDE = ethylene glycol dimethyl ether.

PHOSPHATE REAGENT: A =  ; B = $(EtO)_2P(O)Cl$.

eter. Mass spectra were recorded on a Hewlett Packard HP5890 gas chromatography-Finnigan Mat Incos 50 mass spectrometer (70 eV).

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**10**).

Compound **10** was prepared from 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**9**, 12.9 g, 500 mmoles) [11] as described in the literature [10], as pale yellow needles, mp 124-126° (lit mp 124-125°); $^1$H nmr (200 MHz, deuteriochloroform): δ 7.3-7.6 (8 H, m), 4.8 (1 H, d, J = 7.0 Hz), 3.8 (1 H, d, J = 7.0 Hz), 3.3 (3 H, s).

Attempted Alkylation of 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**10**). General Procedure.

Method A.

A solution of dimethyl malonate (1.3 g, 12 mmoles) in 10 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of sodium hydride (0.33 g, 14 mmoles, 80% dispersion in mineral oil), in 40 ml of anhydrous tetrahydrofuran, kept at 0° and under nitrogen. The reaction mixture was stirred for 1 hour when a solution of diethyl chlorophosphate (1.9 g, 12 mmoles) in 10 ml of anhydrous tetrahydrofuran was slowly added at 0°. The mixture was stirred for an additional 2 hours at room temperature at which time 2.8 g (10 mmoles) of compound **10** was added in one portion. (An experiment in which the order of addition was reversed, *i.e.*, malonate anion to a solution of the anion of the benzodiazepine, showed no difference in yield of the final product). After stirring overnight (14 hours) at room temperature, 10 ml of methanol was added to destroy any excess hydride and the solution was concentrated to dryness. Methylene chloride (20 ml) was added to the residue. The solution was washed successively with water, and saturated sodium chloride solution then dried, filtered and concentrated. The residue was determined to be unchanged starting material by thin layer chromatography and/or $^1$H nmr and/or recrystallization from ether followed by melting point and mixture melting point determination with an authentic sample.

Method B.

A solution of 1.0 g (3.5 mmoles) of **10** in 25 ml of ethylene glycol dimethyl ether (EGDE) was treated with lithium-bis(trimethyl silyl) amide (Li-HMSA) (7 ml, 7 mmoles) at 0°. The reaction was stirred at room temperature for 30 minutes by which time hydrogen evolution had ceased. Diethylchlorophosphate (0.72 g, 4.2 mmoles) in EGDE (10 ml) was added dropwise to the mixture. The reaction mixture was stirred for 2 hours, after which time, the anion of dimethyl malonate, [generated in a separate flask by treatment of 0.5 g (4.2 mmoles) of dimethyl malonate with Li-HMSA (3.5 ml, 3.5 mmoles) in tetrahydrofuran (10 ml)], was added *via* syringe. The mixture was stirred overnight (16 hours), then concentrated on a rotary evaporator. The residue was found to be unchanged starting material, as determined by thin layer chromatography and/or $^1$H nmr and/or recrystallization from ether followed by melting point and mixture melting point with an authentic sample.

7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (**15**).

Method A.

A solution of dimethyl malonate (7.9 g, 60 mmoles) in 10 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of sodium hydride (2.1 g, 87.5 mmoles, 80% dispersion in mineral oil), in 60 ml of anhydrous tetrahydrofuran, kept at 0° under nitrogen. The reaction mixture was stirred for 1 hour at room temperature then cooled to 0°. A solution of diethyl chlorophosphate (10.5 g, 60 mmoles) in 10 ml of anhydrous tetrahydrofuran was slowly added keeping the temperature at 0°. The mixture was stirred for an additional 2 hours at room temperature at which time 5.4 g (20 mmoles) of **9** was added in one portion. After stirring overnight (14 hours) at room temperature, 10 ml of methanol was added to destroy excess hydride and the solution was concentrated to dryness. Methylene chloride (30 ml) was added to the residue. The solution was washed with water, with saturated sodium chloride solution, dried, filtered and evaporated. The product was crystallized from ether and recrystallized from a mixture of methylene chloride and isopropanol to yield 3.8 g (50%) of **15** as white needle, mp 162-165° (lit mp 165-166°) [1]; $^1$H nmr (200 MHz, deuteriochloroform): δ 11.4 (1 H, s), 7.0-7.5 (8 H, m), 3.8 (3 H, s), 3.7 (3 H, s); ir (potassium bromide): 3200, 3000, 1720, 1630, 1450, 1200, 1000 cm$^{-1}$.

Method B.

A solution of 1.0 g (3.7 mmoles) of **9** in 25 ml of anhydrous tetrahydrofuran was treated with sodium hydride (0.33 g, 13.9 mmoles, 80% dispersion in mineral oil) at 0°. The reaction was stirred at room temperature for 30 minutes by which time hydrogen evolution had ceased. Dimorpholinophosphonic chloride (2.2 g, 11 mmoles) was added to the mixture in one portion followed by an additional 10 ml of tetrahydrofuran. The reaction stirred for 2 hours and a solution of the anion of dimethyl malonate (1.1 g, 11 mmoles) in tetrahydrofuran (10 ml) was added *via* syringe at 0°. The mixture stirred overnight (16 hours) at room temperature. Methanol (10 ml) was added to destroy excess hydride and the solution was concentrated to dryness. Methylene chloride (30 ml) was added to the residue. The solution was washed with water, with saturated sodium chloride solution, dried and filtered. Solvent was removed and the product was crystallized from ether and recrystallized from a mixture of methylene chloride and isopropanol to yield 0.6 g (42%) of **15** as white needles, mp 163-165° (lit mp 165-166°) [1].

2-(Methylamino)hippuric Acid Ethyl Ester (**19**).

This ester was made on a 15 mmoles scale according to the literature procedure reported by Kim [8]. The compound was isolated in 62% yield (22 g), mp 51-55° (lit mp 55-59°) [8]; $^1$H nmr (200 MHz, deuteriochloroform): δ 7.4 (1 H, d, J = 5.8 Hz), 7.2-7.3 (2 H, m), 6.4-6.7 (3 H, m), 4.2 (2 H, q, J = 7.0 Hz), 4.1 (2 H, d, J = 5.8 Hz), 2.8 (3 H, s), 1.3 (3 H, t, J = 7.0 Hz).

3*H*-1-Methyl-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**12**).

Method A.

The open ring compound **19** (25 g, 11 mmoles) was fused in an Ehrlenmeyer flask directly over a bunsen burner until evolution of water had ceased (30 minutes). The cyclized product was crystallized from methylene chloride and ether to yield 12.6 g (63%), mp 183-186° (lit mp 184-186°) [8].

Method B.

The same product was also synthesized by refluxing methyl *N*-methylaminoacetylanthranilate (46 g, 21 mmoles) in ethanol overnight. The mixture was concentrated on a rotary evaporator and

10 ml of methylene chloride was added to the residue. The mixture was heated with a spatulaful each of charcoal (*ca.* 250 mg) and of Celite (*ca.* 500 mg) and then was filtered over silica gel (10 g, on a 6.5 cm x 5.5 cm medium frit sintered glass funnel). The Celite/silica mixture was washed with methylene chloride and the combined filtrates were evaporated on a rotary evaporator. The product was crystallized from a mixture of methylene chloride and ether to yield 6.0 g (15%) of **12**, mp 184-188°; mixed mp with a sample prepared as in method A, above, 183-187°; $^1$H nmr (200 MHz, deuteriochloroform): δ 7.9 (1 H, dd, J = 6.1 Hz), 7.2-7.6 (4 H, m), 3.8 (2 H, dd, J = 6.1 Hz), 3.4 (3 H, s); ir (methylene chloride): 3180, 3068, 1672, 1629, 1460 cm$^{-1}$; ms: m/z (relative intensity) 190 ($M^+$, 87), 161 (60), 133 (35), 119 (4), 104 (100), 92 (15), 77 (48), 63 (17), 51 (36), 39 (13).

5-(Di-4-morpholinyl)phophinyloxy-3*H*-1-methyl-1,4-benzodiazepin-2-one (**21**).

A solution of 1.9 g (10 mmoles) of **12** in 25 ml of anhydrous tetrahydrofuran was treated with the portionwise addition of 0.45 g (18 mmoles) of sodium hydride, (80% dispersion in mineral oil), at 0°. The reaction was stirred at room temperature for 45 minutes by which time hydrogen evolution had ceased. Dimorpholinophosphinic chloride (3.81 g, 15 mmoles) was added to the mixture in one portion followed by an additional 25 ml of tetrahydrofuran (10°). The reaction mixture was stirred for 1 hour. The mixture was then filtered over a pad of Celite (4 g on a 6.5 cm x 5.5 cm medium frit sintered glass funnel) and concentrated. The product was crystallized from ethyl acetate and recrystallized from methylene chloride and ethyl acetate to yield 0.85 g (21%) of **21** as white prisms, mp 137-140°; $^1$H nmr (400 MHz, DMSO-$d_6$): δ 7.3-7.6 (4 H, m), 3.7-4.1 (2 H, br s), 3.5 (8 H, s), 3.3 (3 H, s), 3.1 (8 H, s); ir (potassium bromide): 3600, 3000, 1674, 1660, 1255 cm$^{-1}$.

*Anal.* Calcd. for $C_{18}H_{25}N_4O_5P$: C, 52.94; H, 6.17; N, 13.65. Found: C, 52.71; H, 6.27; N, 13.26.

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* To whom correspondence should be addressed.

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