# Diethyl 2,4-Dioxoimidazolidine-5-phosphonates: Horner–Wadsworth–Emmons Reagents for the Mild and Efficient Preparation of C-5 Unsaturated Hydantoin Derivatives

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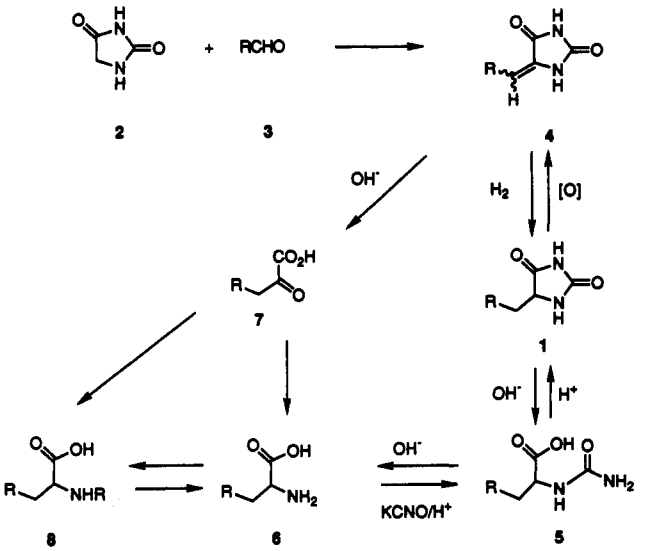
The phosphonates **19** and **20** were prepared from hydantoin and 1-methylhydantoin, respectively, by way of bromination at C-5 and a subsequent Michaelis–Arbuzov reaction with triethyl phosphite. The Horner–Wadsworth–Emmons-type reagents **19** and **20** were found to react readily with aromatic and aliphatic aldehydes, in the presence of a base, to produce C-5 unsaturated hydantoin derivatives **22** and **26**, generally in high yield. The products **22** and **26** were frequently isolated as mixtures of *E* and *Z* isomers depending upon the identity of the aldehyde and phosphonate. The isomeric configuration of the products was determined from an analysis of NMR spectral data. Long-range $^{13}C$–$^{1}H$ coupling constants between the C-4 carbonyl of the hydantoin ring and the olefinic proton were found to be diagnostic of isomer geometry. Conditions were also developed that allowed coupling of **19** and **20** with cyclic and acyclic ketones and α-dicarbonyl compounds to afford the corresponding olefinic products. C-5 unsaturated hydantoin derivatives are of synthetic utility as precursors to α-amino acid derivatives, pyruvates, and the imidazo[4,5-*b*]quinolin-2-one heterocyclic ring system, a class of potent inhibitors of low Km cAMP phosphodiesterase and the chromophore present in the siderophore azotobactin.

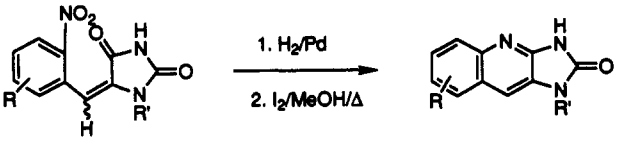
Hydantoins substituted at C-5 are associated with a wide range of biological properties, including anticonvulsant,[1] antidepressant,[2] antiviral,[3] and platelet inhibitory activities,[4] and are a conspicuous structural feature of several inhibitors of aldose reductase.[5] Moreover, C-5 substituted hydantoin derivatives, **1**, are of synthetic utility[6-8] as precursors to α-amino acid derivatives **6** after hydrolytic degradation, which proceeds through the intermediacy of a ureido acid **5**, as depicted in Scheme I. This transformation can be accomplished chemically by heating with aqueous alkali ($Ba(OH)_2/H_2O$[9] or $NaOH/H_2O$/160 °C[10]) or enzymatically, the latter process offering the advantage of mild conditions that can deliver optically pure material of either absolute configuration.[11] An attractive synthetic approach to **1** comprises hydrogenation of C-5 unsaturated derivatives **4** which are, in turn, available from hydantoin (**2**) and an aldehyde **3** by condensation.[6-8] Hydantoins **4** can be hydrolyzed to pyruvic acid derivatives **7**,[12] which are useful precursors to amino acids **6** and **8** either by reductive[13] or enzymatic[14] amination.

The imidazo[4,5-*b*]quinolin-2-one heterocycle **10**, Scheme II, forms the chromophoric element of the iron-chelating siderophore, azotobactin,[15] which has recently attracted attention as a synthetic target.[16] We have demonstrated that derivatives of **10** are potent inhibitors of blood platelet low Km cAMP phosphodiesterase and induced aggregation and exhibit antithrombotic activity in animal models.[17] As part of our effort to study struc-

**Scheme I. Synthesis and Reactions of C-5 Unsaturated Hydantoin Derivatives**




**Scheme II. Synthesis of Imidazo[4,5-*b*]quinolin-2-ones**




(1) Mehta, N.; Risinger Dinguid, C. A.; Soroko, F. E. *J. Med. Chem.* **1981**, *24*, 465.
(2) Wessels, F. L.; Schwan, T. J.; Pong, S. F. *J. Pharm. Sci.* **1980**, *69*, 1102.
(3) Bharucha, K. R.; Pavilinis, V.; Ajdukovic, D.; Shrenk, H. M. Ger. Offen. 2,329,745, 1974; *Chem. Abstr.* **1974**, *80*, 95948d.
(4) Caldwell, A. G.; Harris, C. J.; Stepney, R.; Wittaker, N. *J. Chem. Soc., Perkin Trans. 1.* **1980**, 495.
(5) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841.
(6) Ware, E. *Chem. Rev.* **1950**, *46*, 403.
(7) Bateman, J. H. *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley-Interscience: New York, 1978; Vol. 12, p 692.
(8) Lopez, C. A.; Trigo, G. G. *Adv. Het. Chem.* **1985**, *38*, 177.
(9) Johnson, T. B.; Bengis, R. *J. Am. Chem. Soc.* **1913**, *35*, 7606.
(10) White, H. C. U.S. Patent 2,557,920, 1951; 2,642,459, 1953.
(11) (a) Yokozeki, K.; Nakamori, S.; Yamanaka, S.; Eguchi, C.; Mitsugi, K.; Yoshinaga, F. *Agric. Biol. Chem.* **1987**, *51*, 715. (b) Yokozeki, K.; Kubota, K. *Agric. Biol. Chem.* **1987**, *51*, 721. (c) Yokozeki, K.; Hirose, Y.; Kubota, K. *Agric. Biol. Chem.* **1987**, *51*, 737.
(12) (a) Billek, G. *Monatsh. Chem.* **1961**, *92*, 335. (b) Billek, G. *Monatsh. Chem.* **1961**, *92*, 343. (c) Billek, G. *Org. Synth.*; Wiley: New York, 1973; Collect. Vol. V, p 627.
(13) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(14) Asano, Y.; Tamada, A.; Kato Y.; Yamaguchi, K.; Hibino, Y.; Hirai, K.; Kondo, K. *J. Org. Chem.* **1990**, *55*, 5567.
(15) (a) Corbin, J. L.; Karle, I. L.; Karle, J. *Chem. Commun.* **1970**, 186. (b) Karle, I. L.; Karle, J. *Acta Crystallogr.* **1971**, *B27*, 1891. (c) Fukasawa, K.; Goto, M.; Sasaki, K.; Hirata, Y.; Sato, S. *Tetrahedron* **1972**, *28*, 5359. (d) Demange, P.; Bateman, A.; Dell, A.; Abdallah, M. A. *Biochemistry* **1988**, *27*, 2745.
(16) Miller, M. J.; Kolasa, T. *J. Org. Chem.* **1990**, *55*, 4246.
(17) (a) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright J. J. 193rd ACS Meeting, Denver, CO, April 5–10, 1987; MEDI, 16. (b) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright J. J. *J. Med. Chem.* **1991**, *34*, 2906.

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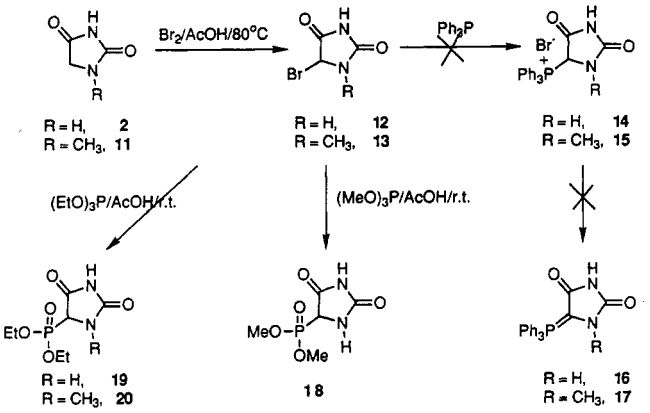
**Scheme III**




ture–activity relationships for **10**, we required a reliable and efficient method of coupling hydantoin (**2**) and its derivatives with aromatic aldehydes substituted at the ortho position with a protected or latent primary amine moiety. These compounds, typified by the nitro benzene **9**, can be efficiently converted to **10** as depicted in Scheme II. Poor yields and purification difficulties encountered with previously described procedures[6,7] (e.g., NaOAc/$Ac_2O$/AcOH/Δ, piperidine/EtOH/Δ) prompted us to explore application of the classical Wittig[18] and Horner–Wadsworth–Emmons[18,19] olefin-forming reactions to the preparation of C-5 unsaturated hydantoin derivatives **4**.

## Results and Discussion

**(i) Preparation of Reagents.** Initial efforts were directed toward the preparation of the Wittig-type reagent, salt **14** and its ylide **16**. Bromination of **1** at C-5 in hot acetic acid[20] followed by exposure of **12** to triphenylphosphine ($Ph_3P$), under a variety of conditions, failed to provide either **14** or **16** after exposure of the crude material to aqueous alkali. Since elimination of $Ph_3P$ from **14**, with concomitant formation of HBr, constituted a possible alternative reaction pathway, the sequence of reactions was repeated starting with **11**. Again, salt **15** and ylid **17** proved to be elusive.

As a consequence, attention was focused upon preparation of the Horner–Wadsworth–Emmons-type reagents by way of a Michaelis–Arbuzov[21] reaction.[22] Exposure of crude bromide **12** to an excess of trimethyl phosphite in acetic acid at room temperature resulted in an exothermic reaction. Removal of the volatile material left a white crystalline solid which exhibited spectral data in accord with the designated structure **18**.[23] However, this material proved to be extremely hygroscopic, to the extent that deliquescence occurred within seconds of exposure to the atmosphere. This property precluded convenient manipulation of **18** but preliminary experiments revealed that **18** reacted with *o*-nitrobenzaldehyde to provide the expected adduct. In contrast, the diethyl ester **19**,[24] prepared analogously in 60–70% overall yield from **1**, proved to be a stable, nonhygroscopic, white crystalline solid, freely soluble in water and warm ethanol. This preparative procedure is amenable to large scale (we routinely perform the reaction on a 2-mol scale) and applicable to the synthesis of the 1-methyl homologue **20**.

**Scheme IV. Reaction of Phosphonates 19 and 20 with Carbonyl Derivatives**

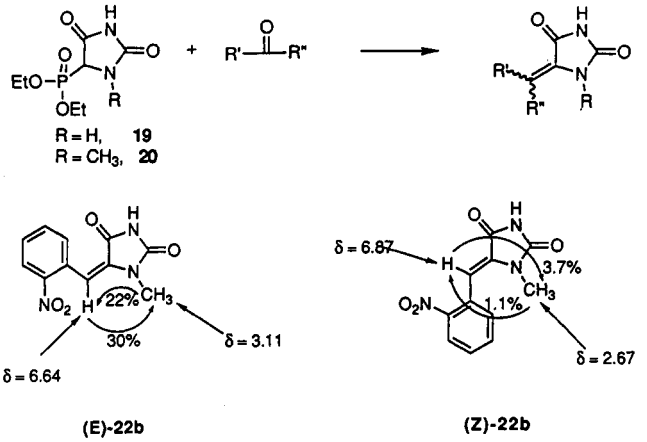



**Figure 1.**

**(ii) Reaction of Phosphonates with Carbonyl Compounds.** The reaction of phosphonates **19** and **20** with a variety of carbonyl-containing compounds was investigated as summarized in Scheme IV.

**(a) Reaction with Aromatic Aldehydes.** Addition of aromatic aldehydes **21** to a slight excess of phosphonates **19** and **20** and sodium ethoxide in ethanol at room temperature generally resulted in the rapid separation of the corresponding 5-benzylidene hydantoin derivatives **22** in excellent yield, Scheme IV. The results with a variety of aldehydic substrates are presented in Table I. The experimental procedure is characterized by operational simplicity. Since the starting phosphonates **19** and **20** and the diethyl phosphate side product are soluble in water, isolation of the products **22** entailed simply diluting the reaction mixture with water and/or 2 N HCl solution followed by filtration of the crystalline products. In some cases, prior removal of the solvent facilitated this process. The crude products isolated in this fashion were generally of high purity as judged by NMR spectral data and elemental analysis, although mixtures of geometrical isomers were often obtained (vide infra). From the results summarized in Table I, it is apparent that high yields of adducts **22** are generally obtained from a variety of aromatic aldehydes. However, hindered and/or electron-rich aldehydes react at a slower rate, and mesitaldehyde gave a relatively poor yield of product, **22v** (entry 22).

The geometry of the products **22** was determined from a consideration of NMR spectral data. Hydantoins **22** were generally isolated as mixtures of *E* and *Z* isomers, although in some cases a single product was obtained (Table I, entries 15, 21, and 22) while in others, purification led to the recovery of a single product (Table I, entries 11 and 12).

(18) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*, Cadogan, J. I. G., Ed.; Academic Press: London, 1979; Chapter 2.

(19) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Wadsworth, W. S., Jr. *Org. React.* **1978**, *25*, 73.

(20) Ben-Ishai, D.; Ber-Et, G.; Warshawsky, A. *J. Heterocycl. Chem.* **1970**, *7*, 1289.

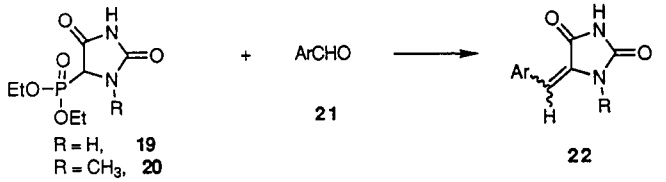
(21) Arbusov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

(22) 5-Halohydantoins are known to participate in the Arbuzov reaction; see: Willson, M.; Bouisson, T.; Mathis, F. *C. R. Hebd. Seances Acad. Sci.* **1982**, *295*, 567.

(23) $^1H$ NMR: δ (DMSO-$d_6$/$CDCl_3$) 3.79 (6 H, d, $J$ = 11 Hz), 4.66 (1 H, d, $J$ = 14 Hz), 7.67 (1 H, bs), 8.37 (1 H, bs); IR (KBr) 1710 (C=O), 1250 (P=O), 1030 (P—$OCH_3$) $cm^{-1}$; MS $m/z$ 208 ($M^+$).

(24) Khokhlov, P. S.; Kashemirov, B. A.; Mikityuk, A. D.; Chimishkyan, A.; Strepikheev, Yu. A. *Zh. Obshch. Khim.* **1984**, *54*, 2237. These authors describe an alternative but less direct preparation of **19** and report a melting point of 83–84 °C, after recrystallization from $CHCl_3$. The preparative procedure described in the Experimental Section gave a product **19**, mp 161–163 °C, after recrystallization from EtOH. The melting point did not significantly change after recrystallization from $CHCl_3$. The reason for the discrepancy in melting points is not understood. Spectral data for material prepared by both routes are comparable.

**Table I. Coupling of Hydantoins 19 and 20 with Aromatic Aldehydes**




| entry no. | phosphonate | Ar | R | product | % yield | isomer ratio *Z*:*E* | mp, °C |
|---|---|---|---|---|---|---|---|
| 1 | **19** | 2-$NO_2C_6H_4$ | H | **22a** | 94 | 2:1 | 300–305 |
| 2 | **20** | 2-$NO_2C_6H_4$ | $CH_3$ | **22b** | 96 | 7.3:1 | 255–263 |
| 3 | **19** | 3-$NO_2C_6H_4$ | H | **22c** | 100 | 3.2:1 | 269–272 dec |
| 4 | **19** | 4-$NO_2C_6H_4$ | H | **22d** | 100 | 2.6:1 | 340–344 dec |
| 5 | **19** | 2,3-$(CH_3)_2$, 6-$NO_2C_6H_2$ | H | **22e** | 98 | *Z* 86% 1st crop | 293–295 |
| | | | | | | 1:1 12% 2nd crop | 267–270 |
| 6 | **20** | 2,3-$(CH_3)_2$, 6-$NO_2C_6H_2$ | $CH_3$ | **22f** | 88 | 1:1 | 195–198 |
| 7 | **19** | 2-$CH_3$, 6-$NO_2C_6H_3$ | H | **22g** | 81 | 84:1 | 238–239 dec |
| 8 | **20** | 2-$CH_3$, 6-$NO_2C_6H_3$ | $CH_3$ | **22h** | 80 | 11:9 | 194–197 |
| 9 | **20** | 3-$CH_3$, 6-$NO_2C_6H_3$ | $CH_3$ | **22i** | 66 | 1:6 | 261–262 |
| 10 | **20** | 3-$CH_3O$, 6-$NO_2C_6H_3$ | $CH_3$ | **22j** | 93 | 1:3 | 258–260 |
| 11 | **19** | 2,3,4-$(CH_3O)_3$, 6-$NO_2C_6H$ | H | **22k** | 91 | *Z* (5:1 crude) | 206–208 |
| 12 | **19** | 2-$AcNHC_6H_4$ | H | **22l** | 86 | *Z* | 295–298 dec |
| 13 | **19** | 2,3-$(CH_3O)_2$, 6-$^tBuO_2CNHC_6H_2$[a] | H | **22m** | 89 | *Z* (3:1 crude) | 227–229 |
| 14 | **20** | 2,3-$(CH_3O)_2$, 6-$^tBuO_2CNHC_6H_2$[a] | $CH_3$ | **22n** | 83 | 12:1 (3:1 crude) | 206–216 |
| 15 | **19** | 2-$HOC_6H_4$ | H | **22o** | 86 | *Z* | 280–282 |
| 16 | **19** | 3-$HOC_6H_4$ | H | **22p** | 88 | 3.9:1 | 287–290 |
| 17 | **19** | $C_6H_5$ | H | **22q** | 97 | 5:1 | 206–209 |
| 18 | **20** | $C_6H_5$ | $CH_3$ | **22r** | 87 | 4:1 | 115–122 |
| 19 | **19** | 4-$(CH_3)_2NC_6H_4$ | H | **22s** | 77 | 85:15 | 272–277 |
| 20 | **19** | 2,6-$Cl_2C_6H_3$ | H | **22t** | 89 | 24:1 1st crop 83%, | 257–259 |
| | | | | | | 1:1 2nd crop 6% | 232–236 |
| 21 | **19** | 2,4,6-$(CH_3O)_3C_6H_2$ | H | **22u** | 88 | single isomer[b] | 258–260 |
| 22 | **19** | 2,4,6-$(CH_3)_3C_6H_2$ | H | **22v** | 20[c] | single isomer[b] | 242–244 |
| 23 | **19** | 3-thienyl | H | **22w** | 96 | 7:1 | 264–266 dec |
| 24 | **19** | 2-pyridyl | H | **22x** | 86 | 2:1 | 220–223 |
| 25 | **19** | 3-pyridyl | H | **22y** | 91 | 4:1 (2.8:1 crude) | 311–313 dec |

[a] Aldehyde prepared according to; Conley, R. A.; Barton, D. L.; Lame, M. M.; Stefanick, S. M.; Fabian, A. C.; Levine, S. D. 10th International Congress of Heterocyclic Chemistry, Aug 11–16, 1985, Abstract S3-19. [b] Geometrical identity of the product not definitively determined. [c] Preparative procedure employed LiOH/EtOH/$H_2O$.

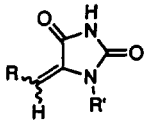
The isomer in which the olefinic proton resonated at lower field in the $^1H$ NMR spectrum usually predominated, suggesting this to be the *Z* isomer based upon application of substituent shielding constants.[25] Confirmation was obtained from NOE experiments that involved irradiation of the N-1 $CH_3$ and olefinic protons of the two separated isomers of **22b**, and the results are summarized in Figure 1. Only the isomer in which the olefinic proton resonated upfield exhibited a significant NOE enhancement, indicating that the protons are spatially proximate and allowing firm identification as the *E* isomer of **22b**. The shift to higher field of the N-1 $CH_3$ of the *Z* isomer of **22b**, relative to the *E* isomer, is presumably due to the fact that these protons lie within the shielding region produced by the aromatic ring current.[26]

This procedure was not applicable where a single geometric isomer was produced and alternative means of structural assignment were sought. Measurement of the long-range $^{13}C$–$^1H$ coupling constant between the olefinic proton and the C-4 carbonyl carbon of the hydantoin ring in the fully coupled $^{13}C$ NMR spectra proved to be diagnostic. This coupling is known to be dependent upon geometry, with the trans arrangement (*E* in this case) giving rise to the greater *J* value.[27-29] The results of several experiments are summarized in Table II. The structural assignments are consistent with conclusions subsequently reached using a similar approach[30] and a combination of other spectroscopic methods.[26]

From an examination of the results presented in Table I, it is apparent that the geometrical outcome of the reaction is dependent upon both the identity of the aldehyde substrate **21** and the phosphonate, **19** or **20**, employed as a reaction partner. In general, the N–H phosphonate **19** provides a preponderance of the *Z* isomer with unhindered aldehydes (entries 3, 4, 16, 17, and 23–25) that seems to be reinforced by ortho substitution of the aryl ring (entries 5, 7, 12, and 20). In contrast, the N-1 methylated phosphonate **20** exhibits reduced selectivity (compare entries 5 with 6 and entries 7 with 8) with the *E* isomer sometimes predominating (entries 9 and 10). These observations may be understood by considering the stereochemical demands of the *pro-Z* and *pro-E* intermediate oxyanions, **23**-(*Z*) and **23**-(*E*) respectively, Scheme V. The steric interactions in **23**-(*Z*) and **23**-(*E*) should reflect demands in the transition state of the rate-determining[19b] elimination of diethylphosphate from the transient four-centered intermediates **24**-(*Z*) and **24**-(*E*) leading to **22**-(*Z*) and **22**-(*E*). In the *pro-Z* intermediate **23**-(*Z*), the hydantoin N-1 substituent and the aryl ring are spatially proximate while in **23**-(*E*) it is the hydantoin C-4 carbonyl moiety and aryl ring that occupy this arrangement. For phosphonate **19**, where the N-1 substituent is a proton, **23**-(*Z*) would be

(25) Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691.
(26) Tan, S.-F.; Ang, K.-P.; Fong, Y.-F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1941.
(27) Marshall, J. L.; Seiwell, R. *J. Magn. Res.* **1974**, *15*, 150.
(28) Vogeli, U.; Von Philipsborn, W. *Org. Magn. Res.* **1975**, *7*, 617.
(29) Prokof'ev, E. P.; Karpeiskaya, E. I. *Tetrahedron Lett.* **1979**, 737.
(30) Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 773.

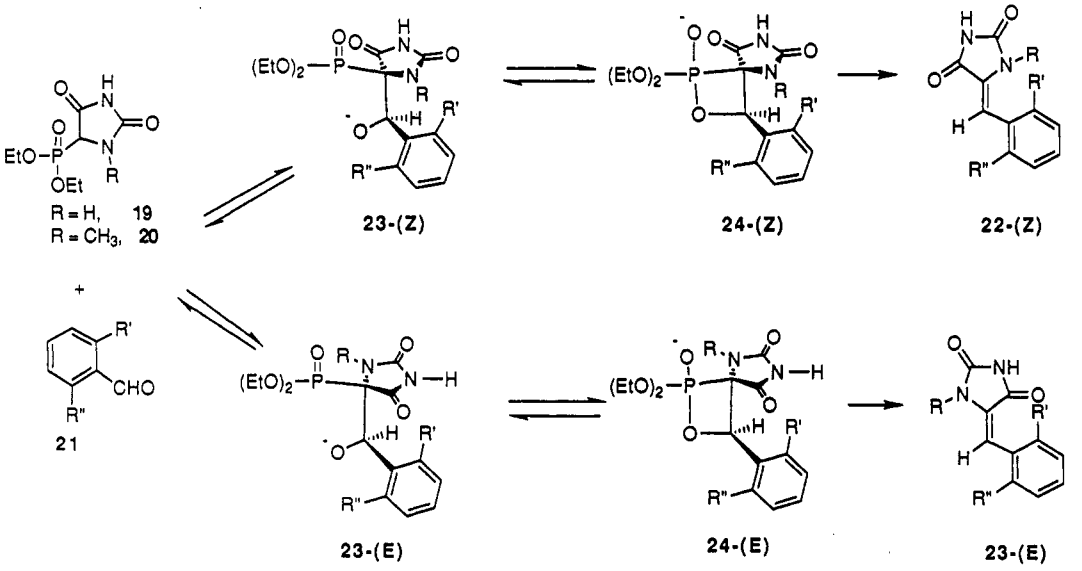
**Table II. NMR Data for C-5 Unsaturated Hydantoin Derivatives[a]**



| compd no. | R | $R^1$ | δ olefinic proton | other | δ C* | $J$ $^{13}C^*-^1H^*$, Hz | isomer assignment | comments |
|---|---|---|---|---|---|---|---|---|
| **22b** | 2-$NO_2C_6H_4$ | $CH_3$ | 6.87 | $NCH_3$: δ 2.67 | 163.8 | 5 | *Z* | NMR experiments performed on a 85:15 *Z*:*E* mixture, mp 210–213 °C |
| | | $CH_3$ | 6.64 | $NCH_3$: δ 3.11 | 162.4 | 10 | *E* | pure isomer, mp 273–275 °C |
| **22a** | 2-$NO_2C_6H_4$ | H | 6.68 | | 164.9 | 6 | *Z* | NMR experiments performed on a 2:1 mixture of *Z*:*E* isomers |
| | | | 6.62 | | 163.3 | 9 | *E* | |
| **22e** | 2,3-$(CH_3)_2$, 6-$NO_2C_6H_2$ | H | 6.66 | | 164.3 | 5 | *Z* | NMR experiments performed on a 1:1 mixture of *Z*:*E* isomers |
| | | | 6.45 | | 163.4 | 10 | *E* | |
| **22f** | 2,3-$(CH_3)_2$, 6-$NO_2C_6H_2$ | $CH_3$ | 6.78 | $NCH_3$: δ 2.45 | 163.3 | 6 | *Z* | NMR experiments performed on a 1:1 mixture of *Z*:*E* isomers |
| | | | 6.51 | $NCH_3$: δ 3.14 | 162.2 | 11 | *E* | |
| **22l** | 2-$AcNHC_6H_4$ | H | 6.45 | $COCH_3$: δ 2.07 | 164.6 | 5 | *Z* | pure isomer |
| **22t** | 2,6-$Cl_2C_6H_3$ | H | 6.11 | | 164.4 | 4 | *Z* | DMSO/$D_2O$ solvent sytem. Sample a >24:1 mixture of isomers |
| | | H | 6.28 | | 162.8 | | *E* | Sample a 1:1 mixture of *Z*:*E*. Fully coupled $^{13}C$ not recorded |
| **30c** | PhC(O) | H | 6.85 | | 165.0 | 6 | *Z* | pure isomer |
| **30d** | PhC(O) | $CH_3$ | 6.74 | $NCH_3$: δ 3.12 | 164.2 | 6 | *Z* | minor product |
| | | | 6.38 | $NCH_3$: δ 3.09 | 161.8 | 11 | *E* | Major product. NMR experiments performed on a 6:1 mixture of *E*:*Z* isomers |

[a] All NMR spectra were recorded in DMSO-$d_6$ except where stated.

**Scheme V**




expected to be more stable than **23**-(*E*), leading to predominantly the *Z*-configured product **22**-(*Z*). Ortho substitution of the aromatic ring would be expected to reinforce this bias. However, with phosphonate **20**, in which the N-1 substituent is a bulkier methyl group, intermediate **23**-(*Z*) would be destabilized with respect to **23**-(*E*), where the smaller carbonyl moiety is adjacent to the large aromatic ring, leading to increased amounts of the *E* isomer of **22**.

The anhydrous conditions employed to provide the majority of the products listed in Table I are not crucial to the success of the reaction. Solutions of hydroxides in aqueous ethanol were found to be very effective when the aldehyde did not incorporate sensitive functionality. Thus, benzaldehyde reacted with **19** in the presence of LiOH, NaOH, or KOH to provide the adduct **22q** in 90, 93, and 88% yield respectively as summarized in Table III. Under these conditions, the geometrical outcome of the reaction showed some dependence on the identity of the counter ion although the differences are not large. $Li^+$ was the least selective, providing 1.7:1 mixture of *Z* and *E* isomeric adducts while $Na^+$ and $K^+$ gave 2.5:1 and 2.2:1 *Z*:*E* ratios of **22q**, respectively. A two-phase system comprising $CH_2Cl_2$ and aqueous NaOH, with or without[31] a phase-transfer catalyst, also furnished adducts in high yield (Table III, entries 6 and 7). In order to complete a study of structure–activity relationships associated with imidazo[4,5-*b*]quinolin-2-ones, **10**, milder conditions for effecting this transformation were sought that would allow preservation of sensitive functionality in the aldehyde. The use of organic bases in the presence of metal halides has been

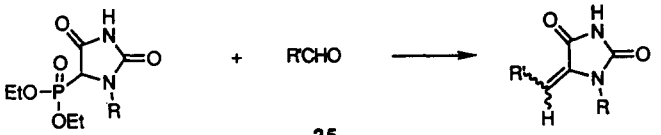
(31) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 397.

**Table III. Reaction of Phosphonate 19 with Aromatic Aldehydes under Various Conditions**

| entry no. | aldehyde | conditions | product | % yield | isomer ratio Z:E |
|---|---|---|---|---|---|
| 1 | PhCHO | 1 ≡ 5 N LiOH/EtOH/rt/5 h | **22q** | 90 | 1.7:1 |
| 2 | PhCHO | 1 ≡ 5 NaOH/EtOH/rt/5 h | **22q** | 93 | 2.5:1 |
| 3 | PhCHO | 1 ≡ 5 N KOH/EtOH/rt/5 h | **22q** | 88 | 2.2:1 |
| 4 | PhCHO | dilute NaOH/$CH_2Cl_2$/rt/cat. $Bu_4NHSO_4$ | **22q** | 82 | ND[a] |
| 5 | PhCHO | dilute NaOH/$CH_2Cl_2$/rt | **22q** | 84 | ND[a] |
| 6 | PhCHO | $Et_3N$/LiBr/$CH_3CN$/rt/18 h | **22q** | 90 | 2.5:1 |
| 7 | PhCHO | $Et_3N$/$CH_3CN$/rt/18 h | **22q** | 91 | 2.6:1 |
| 8 | 2-$NO_2C_6H_4CHO$ | $Et_3N$/$CH_3CN$/rt/45 min | **22a** | 90 | 4:1 |
| 9 | 2-$NO_2C_6H_4CHO$ | $C_5H_5N$/LiBr/$CH_3CN$/rt/18 h | **22a** | 79 | 2.5:1 |

[a] ND = not determined.

**Table IV. 5-Alkylidene Hydantoin Derivatives**




| entry no. | aldehyde | phosphonate | product R[1] | product R | product no. | conditions | % yield | isomer ratio Z:E | mp, °C |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3CHO$ | 19 | $CH_3$ | H | **26a** | $Et_3N$/LiBr/$CH_3CN$ or NaOEt/EtOH | 47[a] | single product Z | 274–276 |
| 2 | $^nC_3H_7CHO$ | 19 | $^nC_3H_7$ | H | **26b** | NaOEt/EtOH | 70 | 2.5:1 | 125–130 |
| 3 | $^nC_8H_{17}CHO$ | 19 | $^nC_8H_{17}$ | H | **26c** | LiOH/EtOH | 46 | 1.4:1 | 135–144 |
| 4 | PhCH=CHCHO | 19 | PhCH=CH | H | **26d** | NaOEt/EtOH | 95 | 2.8:1 | 256–274 |
| 5 | $PhCH_2CHO$ | 19 | $PhCH_2$ | H | **26e** | NaOEt/EtOH | 90 | 2:1 | 180–186 |
| 6 | $PhCH_2CHO$ | 20 | $PhCH_2$ | $CH_3$ | **26f** | NaOEt/EtOH | 86 | 1:1 | indistinct |
| 7 | $cC_6H_{11}CHO$ | 19 | $cC_6H_{11}$ | H | **26g** | LiOH/EtOH/$H_2O$ | 91 | 1.85:1 | 200–235 |

[a] Based on phosphonate 19. Excess acetaldehyde used.

described[18a,32,33] and proved applicable to the case at hand. Benzaldehyde reacted with **19** in acetonitrile in the presence of triethylamine and LiBr[32] to provide the adduct **22q** in 90% yield as 2.5:1 mixture of *Z*:*E* isomers (Table IV, entry 6). Remarkably, LiBr proved to be an unnecessary additive since triethylamine alone in acetonitrile was to found to very effectively mediate the reaction and **22q** was isolated in 91% yield as a 2.6:1 mixture of *Z*:*E* isomers after stirring for 18 h at room temperature (Table III, entry 7). The more electrophilic 2-nitrobenzaldehyde reacted with **19** in the presence of triethylamine to furnish adduct **22a** in 90% yield after only 45 min at room temperature (Table III, entry 8). Pyridine was also an effective base in this reaction, providing that LiBr was added, although the reaction was markedly slower (Table III, entry 9).

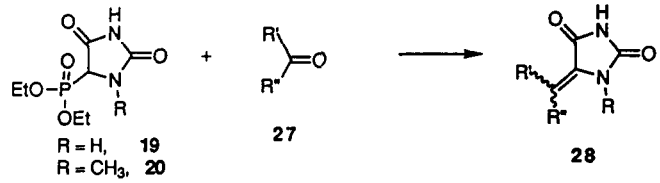
One final aspect that deserves comment concerns isomerization of the adduct **22a** under alkaline conditions. Dissolution of a 2:1 *E*:*Z* mixture of **22a**, a yellow solid, in excess aqueous NaOH in methanol gave a deep red solution. Quenching with excess 2 N HCl solution resulted in a 95% recovery of a white solid which by $^1H$ NMR was identified as the pure *Z* isomer of **22a**. In contrast, exposure of a 1:1 mixture of the N-1 methyl derivatives **22b** to the same conditions had no effect on the isomer ratio, demonstrating the importance of the N-1 H of the hydantoin ring in this process. The presence of the *o*-nitro substituent on the aromatic ring was also essential since a 1.7:1 *Z*:*E* mixture of adducts **22q** was not significantly altered under these conditions. The N-1 H of C-5 benzylidene hydantoins is known to be more acidic than that in saturated derivatives and the acidity is enhanced by electron-withdrawing groups on the aryl ring.[34] In the case of **22a**, the N-1 H is evidently sufficiently acidic to allow formation of an anion which is stabilized by delocalization into the aromatic ring. Subsequent protonation provided geometrically pure product of the *Z* configuration.

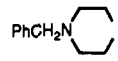
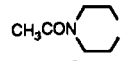
**(b) Reaction with Aliphatic Aldehydes.** Aliphatic aldehydes were found to react with phosphonates **19** and **20** to furnish 5-alkylidene hydantoin derivatives **26** in modest to excellent yields, Scheme IV. The results are summarized in Table IV. Phosphonate **19** reacted with an excess of aceteldehyde to afford olefin **26a** in 47% yield whether NaOEt in ethanol or $Et_3N$/LiBr in acetonitrile was used as the base (Table IV, entry 1). Particularly noteworthy is the fact that freshly distilled phenylacetaldehyde coupled exothermically with **19** and **20** to produce the corresponding adducts **26e** and **26f** in high yield in less than 20 min using NaOEt in EtOH as the base (Table IV, entries 5 and 6). Direct condensation of *p*-methoxy phenylacetaldehyde with hydantoin (**2**) was reported to fail under a variety of conditions.[35] The geometrical outcome of the reaction between **19** and **20** and aliphatic aldehydes was quite similar to that observed when aromatic aldehydes were employed as the substrate.

**(c) Reaction with Ketones.** Phosphonates **19** and **20** reacted with ketones **27** to provide tetrasubstituted alkene adducts **28**, generally in good to excellent yield, Scheme IV. The results are compiled in Table V. Cyclopentanone and acetophenone, which are known to be reluctant partners in the Horner–Wadsworth–Emmons reaction as a result of facile proton transfer leading to ketone enolate formation,[18,19] are exceptions. Acetophenone failed to yield detectable adduct but 2,2,2-trifluoroacetophenone did react with **19** to afford **28a** in 60% yield as a single geometrical

(32) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.
(33) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(34) Tan, S.-F.; Ang, K.-P.; Fong, Y.-F.; Jayachandran, H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 473.
(35) Evans, W. C.; Walker, N. *J. Chem. Soc.* **1947**, 1571.

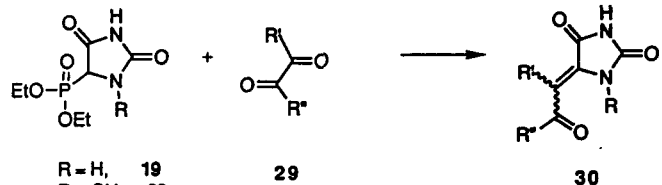
**Table V. 5-Cycloalkylidene Hydantoin Derivatives**




| entry no. | ketone | phosphonate | product R′, R″ | product R | product no. | % yield | mp, °C |
|---|---|---|---|---|---|---|---|
| 1 | $PhCOCF_3$ | 19 | Ph, $CF_3$ | H | 28a | 60[a] | 170–180 |
| 2 | cyclopentanone | 19 | $-(CH_2)_4-$ | H | 28b | 20 | 279–282 |
| 3 | cyclohexanone | 19 | $-(CH_2)_5-$ | H | 28c | 81 | 253–255 |
| 4 | 1-benzyl-4-piperidone | 19 |  | H | 28d | 81 | 243–245 dec |
| 5 | 1-acetyl-4-piperidone | 19 |  | H | 28e | 81 | 296–300 dec |
| 6 | $CH_3COCH_3$[b] | 19 | $CH_3$, $CH_3$ | H | 28f | 87 | 277–279 dec |
| 7 | $CH_3COCH_3$[b] | 20 | $CH_3$, $CH_3$ | $CH_3$ | 28g | 69 | 196–199 |

[a] Single isomer of undetermined configuration. [b] Acetone used as the solvent.

**Table VI. 5-(2-Oxoethylidene)hydantoin Derivatives**




| entry no. | substrate | phosphonate | product | conditions | % yield | isomer ratio | mp, °C |
|---|---|---|---|---|---|---|---|
| 1 | **29a**, $PhCOCO_2Et$ | 19 | 30a | NaOEt/EtOH/0.5 h | 99 | 88:12[a] | 140–150 |
| 2 | **29b**, $CH_3COCO_2Et$ | 19 | 30b | NaOEt/EtOH/0.5 h | 57 | 6:1[a] | 143–150 |
| 3 | **29c**, PhCOCHO | 19 | 30c | NaOEt/EtOH/0.5 h | 100 | single isomer *Z* | 264–266 dec |
| 4 | **29d**, PhCOCHO | 20 | 30d | NaOEt/EtOH/2 h | 89 | 1:6 *Z*:*E* | 164–169 |
| 5 | **29e**, 1,2-cyclohexanedione | 19 | 30e | NaOEt/EtOH/1 h | 83 | single isomer[a] | 223–226 |
| 6 | **29f**, isatin | 19 | 30f | $Et_3N$/LiBr/$CH_3CN$/18 h | 80 | single isomer *Z* | >360 |
| 7 | **29g**, isatin | 20 | 30g | $Et_3N$/LiBr/$CH_3CN$/18 h | 78 | single isomer *Z* | 317–319 dec |
| 8 | **29h**, 1-methylisatin | 19 | 30h | NaOEt/EtOH | 88 | single isomer *Z* | 308–310 |
| 9 | **29i**, 5-methoxyisatin | 19 | 30i | $Et_3N$/LiBr/$CH_3CN$/18 h | 52 | single isomer *Z* | 362–364 dec |
| 10 | **29j**, 5-methoxyisatin | 20 | 30j | $Et_3N$/LiBr/$CH_3CN$/18 h | 59 | single isomer *Z* | 329–331 dec |

[a] Identity of geometrical isomers not established.

isomer of undetermined configuration. Cyclopentanone coupled with **19** to give olefin **28b** in only 20% yield (Table V, entry 2) but cyclohexanone and 4-piperidones reacted with **19** much more efficiently to furnish the corresponding adducts in 81% yield (Table V, entries 3–5). Acetone, employed as the solvent, provided adducts with both **19** and **20**, although in somewhat lower yield with the latter phosphonate. The presence of lithium as a counterion was found to be absolutely essential for successful coupling of **19** and **20** with ketones. Sodium-derived bases were ineffective, even over extended reaction periods. Lithium is known to form stable chelates with β-keto phosphonates,[36] and although this provides a less reactive nucleophile, it may facilatate the desired transformation by reducing the propensity for proton transfer, either from the ketone substrate or the N-3 hydrogen atom of phosphonates **19** and **20**.

**(d) Reaction with α-Dicarbonyl Compounds.** The reaction of phosphonates **19** and **20** with several α-dicarbonyl compounds, both cyclic and acyclic, was investigated, (Scheme IV) and the results are presented in Table VI. Ethyl benzoylformate reacted with **19** to provide adduct **30a** in almost quantitative yield as an 88:12 mixture of isomers of unknown configuration (Table VI, entry 1). Ethyl pyruvate gave **30b** in 57% yield when exposed to phosphonate **19** in the presence of NaOEt in EtOH. Phenylglyoxal monohydrate reacted exothermically with **19** and **20**, rapidly affording the corresponding olefins in excellent yield (Table VI, entries 3 and 4). The configuration of the single product **30c** was determined to be *Z* using the NMR techniques described earlier and reported in Table II. Phosphonate **20** reacted with phenylglyoxal monohydrate to provide a preponderance of the *E* isomer of **30d**, the identity of which was determined from long-range coupling constants also summarized in Table II. The stereochemical results of the reaction of **19** and **20** with acyclic α-dicarbonyl compounds appears to be similar to that observed with aromatic and aliphatic aldehydes. However, with cyclic α-dicarbonyl derivatives a single geometrical isomer was produced in all cases examined, regardless of the identity of the substrate or phosphonate (Table VI, entries 5–10). The identity of the adducts **30f–j** was inferred from $^1H$ NMR spectral data. For **30f–h**, one of the aromatic protons invariably resonated as a doublet, $J$ = 7.5 Hz, at δ 8.47–8.50, which is over 1 ppm downfield of the remainder of the aromatic hydrogen atoms. This is consistent with the *Z* configuration, in which $H_a$ resides

(36) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simmonin, M.-P. *J. Org. Chem.* **1980**, *45*, 1270.

Scheme VI

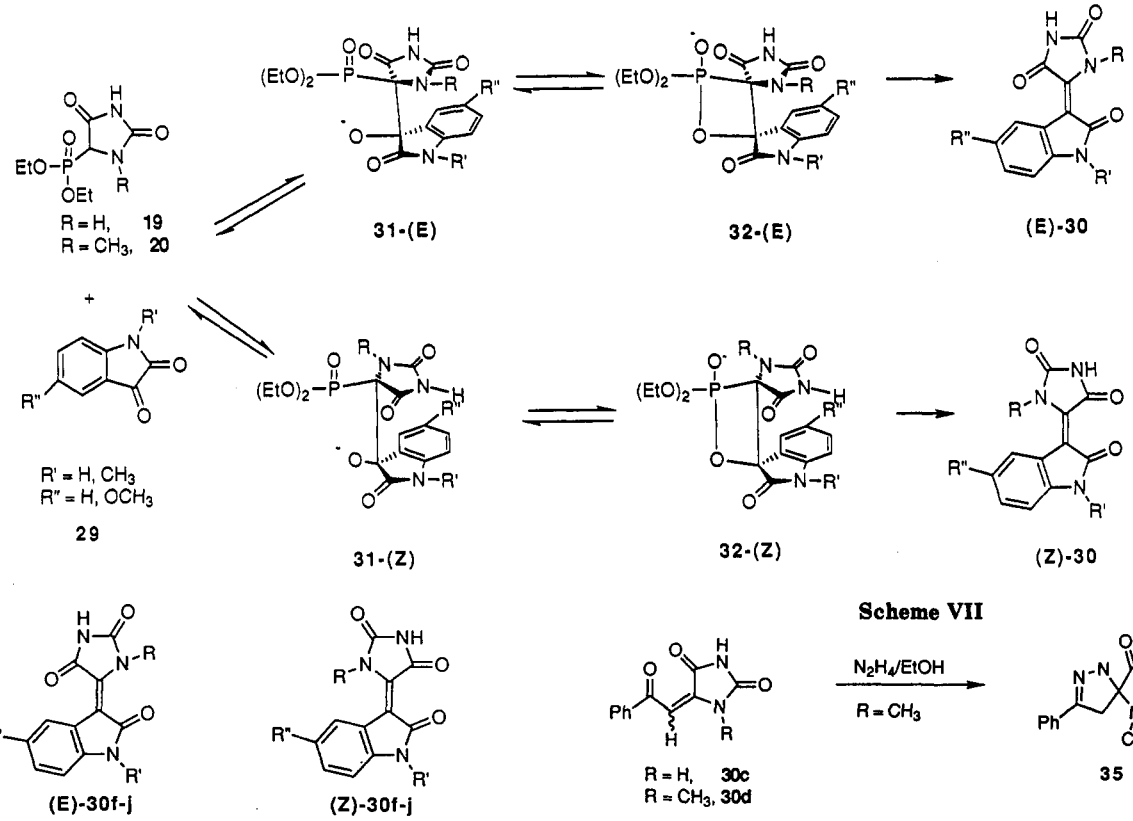



**Figure 2.**

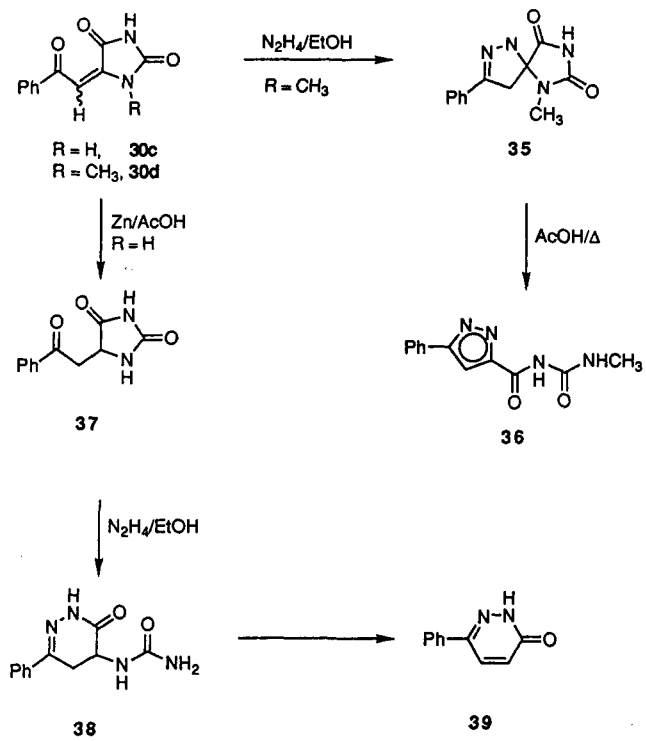
in the deshielding region of the anisotropic C-4 carbonyl moiety of the hydantoin ring as decipted in Figure 2. For adducts **30i** and **30j**, the downfield aromatic signals resonated as a doublets, $J$ = 2.5 Hz, at $\delta$ 8.11 and 8.05, respectively, also in accord with the $Z$ configuration. The exclusive formation of the $Z$ olefin from phosphonates **19** and **20** and isatins may be a consequence of unfavorable dipole–dipole interactions that develop in the intermediates ($E$)-**31** and ($E$)-**32** precursors to the $E$ isomer, as depicted in Scheme VI. With acyclic $\alpha$-dicarbonyl compounds **30a-d**, this circumstance can be relieved as a consequence of free rotation around the C–C bond linking the two electrophilic carbon atoms.

Some aspects of the chemistry associated with adducts **30c** and **30d** were explored in an attempt to synthesize bicyclic analogues **33** of 6-phenylpyridazin-3-ones **34**, po-

**33** **34**

tent inhibitors of low Km cAMP PDE that display myocardial stimulant, hypotensive, and blood platelet inhibitory properties.[37] Treatment of **30d** with hydrazine in EtOH resulted in the production of a white solid identified as the spiro substituted pyrazoline **35**, Scheme VII. Heating **35** in acetic acid led to aromatization of the pyrazoline ring providing pyrazole **36**. In order to circumvent pyrazoline ring formation, the olefin of **30c** was reduced, using zinc in acetic acid, to give **37** in good yield. Exposure

Scheme VII




of **37** to an excess of hydrazine in ethanol produced the pyridazinone **38**. Attempts to cyclize **38** to **33**, R = H, were unsuccessful, leading only to the isolation of the pyridazinone **39**.

## Conclusion

In summary, we have described an effective and generally efficient procedure for the synthesis of C-5 unsaturated hydantoin derivatives that takes advantage of the Horner–Wadsworth–Emmons protocol. Aromatic and aliphatic aldehydes, cyclic and acyclic ketones, and cyclic and acyclic $\alpha$-dicarbonyl compounds participate as reaction partners, providing the corresponding olefinic adducts under mild reaction conditions that tolerate a wide range of functionality. The procedure allows production of C-5 unsaturated hydantoins not readily accessible by other synthetic approaches. Isolation of the products is straightforward, involving precipitation by the addition

(37) (a) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537. (b) Meanwell, N. A.; Seiler, S. M. *Drugs Future* **1990**, *15*, 369.

of water and/or dilute mineral acid and the products isolated in this fashion are frequently analytically pure. C-5 unsaturated hydantoin derivatives are synthetically useful as precursors to α-amino acid and pyruvic acid derivatives and the imidazo[4,5-*b*]quinolin-2-one heterocyclic ring system.

## Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker AM 300 or Varian Gemini 300 FT spectrometers operating at 300 MHz for $^1H$ and 75 MHz for $^{13}C$, or on a Perkin-Elmer R32 (90 MHz for $^1H$) continuous wave instrument. Infrared spectra were determined on a Nicolet MX-1 FT spectrometer scanning from 4000 to 400 $cm^{-1}$ and calibrated to the 1601 $cm^{-1}$ absorption of a polystyrene film. Mass spectral data were obtained employing a Finnigan 4500 spectrometer using either chemical or electrical ionization procedures. Combustion analyses were provided by the Bristol-Myers Squibb Analytical Research Group or Oneida Research Services, Whitesboro, NY. Analytical samples were heated in vacuo at 78 °C or over $P_2O_5$ in vacuo at room temperature for at least 18 h prior to C, H, N determination.

**Diethyl 2,4-Dioxoimidazolidine-5-phosphonate (19).** A mixture of imidazolidine-2,4-dione, **2** (hydantoin) (200 g, 2 mol), and acetic acid (800 mL) was heated to 85 °C in an oil bath. An addition funnel was charged with bromine (352 g, 112.8 mL, 2.2 mole) and a small amount of bromine (≈5 mL) introduced into the reaction mixture with vigorous stirring. Once the orange color had dissipated, the remainder of the bromine was added rapidly dropwise over approximately 7 min to afford a clear solution. After being stirred at 85 °C for 30 min, the reaction mixture was cooled to 30 °C in an ice bath and triethyl phosphite (465 g, 479 mL, 2.8 mole) introduced at such a rate that the internal temperature was maintained at 40–45 °C. After the addition was completed, the mixture was stirred at ambient temperature for 90 min. The solvent was removed in vacuo and the residue diluted with diethyl ether (800 mL) with stirring to induce precipitation of a white solid. The mixture was poured onto diethyl ether (2 L) with vigorous stirring. After 30 min, filtration afforded **19** (337.0 g, 71%), which was used without further purification. An analytical sample was prepared by recrystallization from ethanol and had mp 161–163 °C: IR (KBr) 1775, 1720 (C=O), 1250 (P=O), 1035 (P—OEt) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.25 (6 H, t, $J$ = 7 Hz, $OCH_2CH_3$), 4.10 (4 H, m, $OCH_2CH_3$), 4.76 (1 H, d, $J$ = 15 Hz, P(O)C*H*CO), 8.42 (1 H, bs, N*H*), 10.92 (1 H, bs, N*H*); MS $m/z$ 237 ($MH^+$). Anal. Calcd for $C_7H_{13}N_2O_5P$: C, 35.61; H, 5.55; N, 11.87. Found: C, 35.21; H, 5.60; N, 12.04.

**Diethyl 1-Methyl-2,4-dioxoimidazolidine-5-phosphonate (20).** A mixture of 1-methylimidazolidine-2,4-dione, **11** (202.5 g, 1.8 mol), and acetic acid (1 L) was heated to 90 °C in an oil bath. An addition funnel was charged with bromine (311.5 g, 100 mL, 1.95 mole) and a small amount of bromine introduced into the reaction mixture. After dissipation of the organge color, the remainder of the bromine was introduced dropwise at such a rate that instant decolorization occurred. After the addition was complete, the mixture was stirred at 90 °C for 60 min and overnight at room temperature. The acetic acid was decanted from a white precipitate and removed in vacuo. The residue was combined with the precipitate and suspended in diethyl ether (2 L). Triethyl phosphite (295 g, 320 mL, 1.8 mol) was added portionwise with stirring and cooling. A solution resulted which, on continued stirring, yielded a white precipate. After 60 min, the mixture was diluted with diethyl ether (4 L), allowed to stand overnight, and filtered to give **20** (331.7 g, 75%), mp 95–96 °C. An analytical sample was recrystallized from MeOH/diethyl ether and had mp 95–96 °C: IR (KBr) 1775 (C=O), 1725 (C=O), 1275, 1250 (P=O), 1050, 1025 (PO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.26 (6 H, m, $OCH_2CH_3$), 2.90 (3 H, s, $NCH_3$), 4.12 (4 H, m, $OCH_2CH_3$), 4.72 (1 H, d, $J$ = 14 Hz, P(O)C*H*CO), 11.06 (1 H, bs, N*H*); MS $m/z$ 251 ($M^+$). Anal. Calcd for $C_8H_{15}N_2O_5P$: C, 38,41; H, 6.04; N, 11.20. Found: C, 38.22; H, 6.07; N, 11.04.

**General Experimental Procedure for Coupling Phosphonates 19 and 20 with Carbonyl Compounds.** The carbonyl compound was added to a stirred mixture of phosphonate **19** or **20** and base, both taken to between 10 and 20% excess, at room temperature. After consumption of the carbonyl-containing substrate as judged by TLC analysis, the reaction mixture was diluted with water and/or 2 N HCl solution and the product isolated by filtration. When precipitation of the product from the reaction mixture did not occur, the solvent was removed in vacuo before adding water and/or 2 N HCl solution. The products isolated in this fashion were generally of high purity.

**6-Methyl-3-phenyl-1,2,6,8-tetraazaspiro[4.4]nonane-7,9-dione (35).** Anhydrous hydrazine (1.11 g, 1.12 mL, 34 mmol) was added to a suspension of **30d** (4.00 g, 17 mmol) in EtOH (35 mL). The mixture was stirred at room temperature for 66 h before filtering off **35** (3.40 g, 80%), mp 218–220 °C dec: IR (KBr) 3330, 1780, 1725, 1475, 1440, 1400, 1350, 760, 690 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.65 (3 H, s, $NCH_3$), 3.42 (2 H, q, $J$ = 14 Hz, $CH_2$), 7.40 (3 H, m, aromatic *H*), 7.66 (2 H, m, aromatic *H*), 8.14 (1 H, s, N*H*); $^{13}C$ NMR 23.50, 38.69, 82.93, 125.32, 128.22, 131.61, 146.41, 153.77, 173.52; MS $m/z$ 245 ($MH^+$). Anal. Calcd for $C_{12}H_{12}N_4O_2$: C, 59.02; H, 4.96; N, 22.94. Found: C, 59.07; H, 4.90; N, 22.89.

***N*-[(Methylamino)carbonyl]-3-phenyl-1*H*-pyrazole-5-carboxamide (36).** A mixture of **35** (3.00 g, 12 mmol) in AcOH (50 mL) was stirred at reflux for 4.5 h. The mixture was cooled, diluted with water, and filtered to give **36** (2.32 g, 77%), mp 270–273 °C: IR (KBr) 3285, 1695, 1560, 1510, 1250, 750 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.80 (3 H, d, $J$ = 4.5 Hz, $NCH_3$), 7.30 to 7.60 (4 H, m, aromatic *H* + pyrazole *H*), 7.82 (2 H, d, $J$ = 7.5 Hz, aromatic *H*), 8.33 (1 H, d, $J$ = 4.5 Hz, N*H*$CH_3$), 9.65 (1 H, bs, N*H*); MS $m/z$ 244 ($MH^+$). Anal. Calcd for $C_{12}H_{12}N_4O$: C, 59.02; H, 4.96; N, 22.94. Found: C, 59.02; H, 4.80; N, 22.86.

**5-(2-Oxo-2-phenylethyl)-2,4-imidazolidinedione (37).** Zinc dust (8.40 g, 129 mg atom) was added to a suspension of **30c** (7.00 g, 32 mmol) in AcOH (90 mL) with stirring at 105 °C. After 75 minutes, the mixture was cooled, filtered and concentrated in vacuo to leave a white solid, **37** (7.00 g, 99%). A 1.00-g sample was recrystallized from EtOH to give 0.65 g of analytically pure material, mp 198–200 °C: IR (KBr) 3350, 3180, 1750, 1725, 1680, 1665 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 3.52 (2 H, d, overlapping ABq's, $J$ = 14 Hz, $CH_2CO$), 4.45 (1 H, bs, C*H*CO), 7.55 (2 H, t, $J$ = 7.5 Hz, aromatic *H* meta to CO), 7.67 (1 H, t, $J$ = 7.5 Hz, aromatic *H* para to CO), 7.85 (1 H, s, N*H*), 7.98 (2 H, d, $J$ = 7.5 Hz, aromatic *H* ortho to CO); $^{13}C$ NMR δ 39.52, 53.85, 127.92, 128.64, 133.42, 135.98, 157.65, 175.90, 196.31; MS $m/z$ 219 ($MH^+$). Anal. Calcd for $C_{11}H_{10}N_2O_3 \cdot 0.05\ H_2O$: C, 60.03; H, 4.65; N, 12.79; $H_2O$, 0.41. Found: C, 60.11; H, 4.65; N, 12.61; $H_2O$, 0.19.

**4-[(Aminocarbonyl)amino]-4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone (38).** A mixture of **37** (5.00 g, 23 mmol), anhydrous hydrazine (1.10 g, 1.10 mL, 34 mmol), and EtOH (100 mL) was stirred at reflux. After 2 h, the mixture was cooled and filtered to give **38** (3.75 g, 70%), mp 222–224 °C: IR (KBr) 3450, 3350, 1785, 1650, 1600, 1550, 1350 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.78 (1 H, t, $J$ = 15 Hz, $CH_2$), 3.38 (1 H, dd, $J$ = 15 Hz, $J'$ = 7 Hz, $CH_2$), 4.29 (1 H, quintet, $J$ = 7 Hz, C*H*CO), 5.83 (2 H, s, $NH_2$), 6.40 (1 H, d, $J$ = 7 Hz, N*H*CH), 7.42 (2 H, bs, aromatic *H*), 7.73 (3 H, bs, aromatic *H*); $^{13}C$ NMR δ 29.66, 45.10, 125.46, 128.40, 129.32, 135.63, 150.24, 158.18, 167.11; MS $m/z$ 232 ($MH^+$), 172 ($M^+ - NH_2CO \cdot NH_2$). Anal. Calcd for $C_{11}H_{12}N_4O_2 \cdot 0.2H_2O$: C, 56.03; H, 5.31; N, 23.76. Found: C, 55.74; H, 5.19; N, 23.48.

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**Supplementary Material Available:** Experimental details and $^1H$ and $^{13}C$ NMR data for compounds listed in Tables I, IV, V, and VI (18 pages). Ordering information is given on any current masthead page.