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Syntheses, addition–eliminations, and addition–displacements of 5-(bromomethylene)hydantoins

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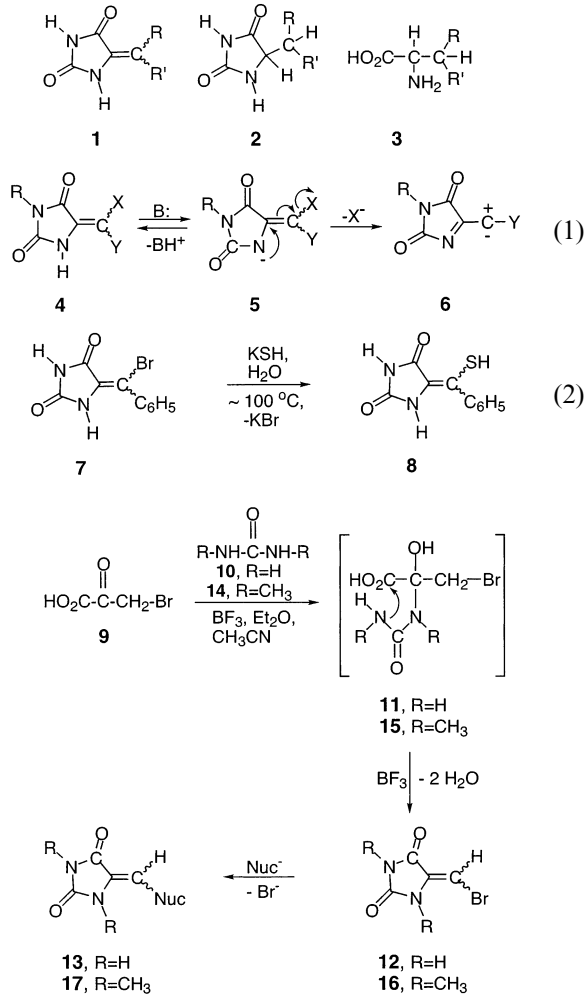
Abstract—5-(Bromomethylene)hydantoins, prepared from bromopyruvic acid and ureas in the presence of BF_3, react with various nitrogen, phosphorus, sulfur, and carbon nucleophiles by addition–elimination to give the corresponding 5-(substituted-methylene)hydantoins. The 5-(bromomethylene)hydantoins also undergo acid-catalyzed reactions with nucleophiles by addition–displacement and addition–elimination processes.

C-5 unsaturated hydantoins (**1**) are important as biological and pharmaceutical intermediates and as precursors to C-5-substituted hydantoins (**2**) and their subsequent α-amino acids (**3**).[1,2] Classic methods for preparing **1** are (1) base- or acid-catalyzed condensations of 5-unsubstituted hydantoins with aldehydes and unhindered or activated ketones[1] and (2) reactions of aldehydes, certain ketones, and α-dicarbonyl compounds in the presence of bases with diethyl hydantoinyl-5-phosphonate as obtained from 5-bromohydantoin, triethyl phosphite, and acetic acid.[2] Synthesis of C-5 functionally-substituted, unsaturated hydantoins (**1**, R and/or R′ = functional groups) however has been limited.[2,3] Of interest with respect to present programs for (1) preparing **1** in which R and/or R′ are functional groups and (2) eliminative-conversions of 5-(halomethylene)hydantoins (**4**, Eq. (1)) to 5-hydantoenylcarbenes (**6**)[4] by strong bases is that 5-(α-bromobenzal)hydantoin (**7**) reacts with hot aqueous KSH (Eq. (2)) to give 5-(α-mercaptobenzal)hydantoin (**8**).[3,5] Now reported are (1) novel syntheses (Scheme 1) of 5-(bromomethylene)hydantoin (**12**) and (*Z*)-5-(bromomethylene)-1,3-dimethylhydantoin (**16**) from bromopyruvic acid (**9**) and ureas (**10** and **14**) and (2) nucleophilic addition–elimination reactions (Scheme 1) of **12** and **16** to give varied C-5 unsaturated hydantoins (**13** and **17**) of interest. Of further importance as will be illustrated, **12** and **16** also undergo efficient addition–displacement reactions with nucleophiles in acidic environments to yield novel C-5-substituted hydantoins (**2**).



Scheme 1.

Keywords: addition–eliminations; 5-(bromomethylene)hydantoins; 5-(substituted-methylene)hydantoins.

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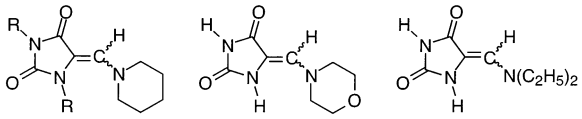
5-(Bromomethylene)hydantoin (**12**, 47%) is now preparable (Scheme 1) by condensation of equivalent quantities of bromopyruvic acid[6a–c] [**9**; generated in situ from pyruvic acid, Br_2, (1.0 equiv.) and H_2SO_4 (trace amounts)], with urea (**10**) in CH_3CN at ~40°C as catalyzed by $BF_3{\cdot}Et_2O$.[7,8] Synthesis of **12** is practical, safe, and inexpensive. (*Z*)-(Bromomethylene)dimethylhydantoin **16** (40%, Scheme 1) is obtained similarly by refluxing solutions of **9**, *N*,*N*′-dimethylurea (**14**), $BF_3{\cdot}Et_2O$ (1.0 equiv.), and CH_2Cl_2.[7] Condensation–elimination to give **16** as in Scheme 1 also occurs with $POCl_3$, $SnCl_4$, or HCl as catalysts.[7] Use of $AlCl_3$ (1.0 equiv.) yields (*Z*)- and (*E*)-**16** in a 1:2 ratio.[7] The stereochemical assignment of (*Z*)-**16** is based on its ^{13}C NMR vicinal C,H spin coupling ($^3J_{C,H}$) of 4.0 Hz for its exocyclic olefinic proton with the C-4 carbonyl carbon.[9]

(Bromomethylene)hydantoins **12** and **16** react readily with various nitrogen and phosphorus nucleophiles. The secondary amine, piperidine (excess), and **12** undergo reaction in 1-propanol at 20–25°C by addition, elimination of Br^-, and deprotonation to give 5-(*N*-piperidinomethylene)hydantoin (**18**, 78%). Similarly, **12** is converted by morpholine (excess) at 20–25°C to 5-(*N*-morpholinomethylene)hydantoin (**20**, 91%) and by diethylamine (excess) in ethanol at 60°C to 5-(*N*-diethylaminomethylene)hydantoin (**21**, >52%). Piperidine (excess) and **16** in warm $CHCl_3$ give 1,3-dimethyl-5-(*N*-piperidinomethylene)hydantoin (**19**, ≫30%).[9,10] 5-(Azidomethylene)hydantoin (**22**) is formed (94%) from **12** and aqueous sodium azide at 20–25°C. Further, pyridine (excess) upon reflux effects addition–eliminations of **12** and **16** to yield [5-(*N*-pyridiniummethylene)hydantoin bromides **23** (90%) and **24** (96%), respectively.[11,12] Of note is that reactions of **12** and **16** with triphenylphosphine [$(C_6H_5)_3P$] in refluxing CH_3CN give 5-(triphenylphosphoniummethylene)hydantoin bromides **25** (89%) and **26** (48%), respectively. The ^{13}C NMR vicinal spin coupling values ($^3J_{C,H}$) of the exocyclic olefinic protons with the C-4 carbonyl carbons of **24** and **26** are 4.3 and 10.0 Hz, respectively, and lead to the tentative stereochemical assignments as **24** (*Z*) and **26** (*E*).[9,12] 5-(Hydantoenylmethylene)triphenylphosphorane (**27**, 91%) is formed from phosphonium bromide **25** and triethylamine (excess) in CH_2Cl_2 at 20–25°C. The utilities of **27** (and its 3-substituted analogs) as a Wittig reagent and as a carbene source[7] are being evaluated.

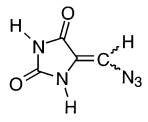
As expected, **12** and **16** react readily with sulfur nucleophiles by addition–elimination. Thiophenol and (1) **12** and triethylamine (1.7 equiv.) in $CHCl_3$ at 50–55°C and (2) **16** and tetramethylguanidine (2.0 equiv.) in THF at 25°C give 5-[(phenylthio)methylene]hydantoins **28** (84%) and **29** (85%),[13] respectively. Heating **16** with aqueous sodium *p*-toluenesulfinate yields 1,3-dimethyl-5-[*p*-toluenesulfonylmethylene]hydantoin (**30**, 52%). Addition–elimination products **29** and **30** have values of 5.2 and 6.16 Hz, respectively, for the vicinal C,H spin couplings (^{13}C NMR, $^3J_{C,H}$) of their exocyclic olefinic hydrogens with their C-4 carbonyl carbons and are assigned (*Z*)-stereochemistries.[9]



18, R = H
19, R = CH_3

20

21



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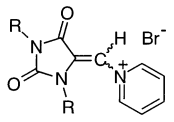
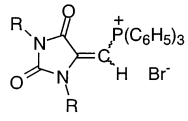
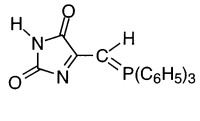


23, R = H
24, R = CH_3



25, R = H
26, R = CH_3



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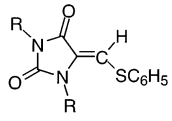
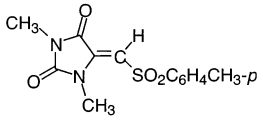


28, R = H
29, R = CH_3



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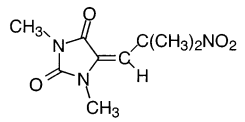
Carbon nucleophiles also effect addition–elimination reactions in (*Z*)-(bromomethylene)hydantoin **16**. Warming an initial mixture of **16**, 2-nitropropane (1.5 equiv.), and tetramethylguanidine (1.6 equiv.) results in Michael addition of the 2-propanenitronate ion [$(CH_3)_2C{=}NO_2^-$] to **16** and elimination of Br^- to yield (*E*)-1,3-dimethyl-5-(2-methyl-2-nitropropylidene)hydantoin (**31**, >36%).[9] Similarly, lithium diethyl malonate reacts rapidly with **16** in THF at 20–25°C to give, upon neutralization (HCl), an equilibrium mixture (54% yield) of (*E*)-5-(diethyl malonylmethylene)-1,3-dimethylhydantoin (**32**, major)[9] and its enol **33**. Further, 1-phenylsulfonyl-2-trimethylsilylethane[14] with *n*-BuLi in THF at −78°C and then **16** in THF/HMPA (−78 to 25°C) yield (*E*)-1,3-dimethyl-5 - [2 - (phenylsulfonyl) - 3 - (trimethylsilyl)propylidene]-hydantoin (**34**, 47%).[9] The stereochemistries of **31**, **32**, and **34** are assigned as (*E*) on the basis that the ^{13}C NMR spin coupling values ($^3J_{C,H}$) for their H on methylene carbon and their C-4 carbonyl carbon are 10.0, 9.1, and 9.0 Hz, respectively.[9]



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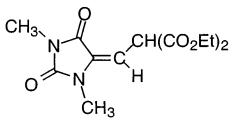

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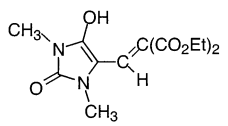

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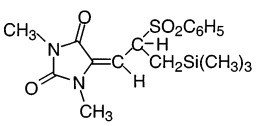

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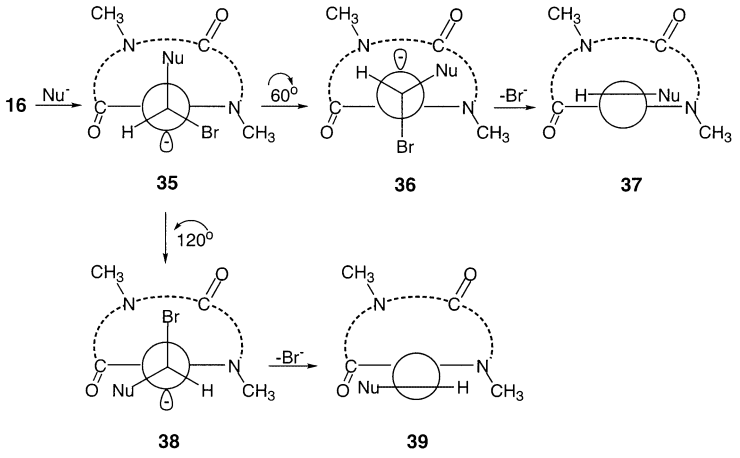
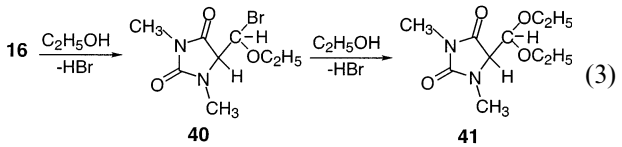


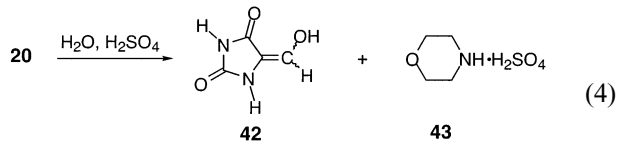
Scheme 2.

The mechanisms of the above nucleophilic addition–elimination reactions merit discussion. (*Z*)-1,3-Dimethylhydantoin **16** is converted by C_5H_5N (pyridine), $C_6H_5S^-$, and p-$CH_3C_6H_4SO_2^-$ to (*Z*)-products **24**, **29**, and **30**, respectively; the bulky carbon nucleophiles $(CH_3)_2C{=}NO_2^-$, $^-CH(CO_2C_2H_5)_2$, and $C_6H_5SO_2^-CHCH_2Si(CH_3)_3$ along with $(C_6H_5)_3P$ yield the (*E*)-products **31**, **32**, **34**, and **26**, respectively.[9] Stepwise sequences in reactions of **16** leading to (*Z*)-**37** and to (*E*)-**39** are illustrated in Scheme 2. (*Z*)-**37** products may be formed upon early elimination of **36** in which there is kinetic electronic and steric control and in which there has been small structural change (60° rotation) in adducts **35**. (*E*)-**39** products are less strained than their (*Z*)-**37** isomers and can arise upon reorganization (120° rotation) of **35** to **38** which then eliminate in late transition states which are primarily thermodynamically sterically controlled. In late transition states originating from **38** to give **39**, steric interactions involving the bonded nucleophile will be less with the C-4 oxygen than with the methyl group at N-1.

Of further significance are that **16** reacts with warm ethanol to give 5-(diethoxymethyl)-1,3-dimethylhydantoin (**41**, Eq. (3); >40%) and **20** is converted by dilute sulfuric acid to 5-(hydroxymethylene)hydantoin (**42**, Eq. (4), 89%).[4d] These results reveal that 5-(halomethylene)hydantoins (**1**) and related 5-(substituted-methylene)hydantoins undergo (acid-catalyzed) addition–displacements readily and indicate that such reactions will be of value for synthesis.



(3)



(4)

Studies of (1) the scope,[15] synthesis products, stereochemistries, kinetic and thermodynamic effects, and further mechanistic details in the addition–elimination and the (acid-catalyzed) addition–displacement reactions of various nucleophiles and electrophiles with **12**, **16**–**21**, **23**, **24**, 5-(bromomethylene)-3-methylhydantoin, 5-(dibromomethylene)hydantoin, their analogs, and their derivatives, (2) reactions of alkoxide, amide, and stronger bases with **4** (Eq. (1)) to give usable carbenes (**6**),[4] and (3) chiral conversions of **1**, **13**, and their derivatives to optically-active α-amino acids (**3**)[16] and other products are being made.

Acknowledgements

This research has been supported by the National Institutes of Health, the National Science Foundation, The Ohio State University, and private funds.

References

1. For summaries, discussions, and additional references with respect to such preparative methodologies, see: (a) Avendano, C.; Menendez, J. C. *Kirk-Othmer 'Encyclopedia of Chemical Technology'*; Wiley-Interscience: New York, 1995; Vol. 13, p. 512; (b) Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 773; (c) Lopez, C. A.; Trigo, G. G. *Adv. Heterocyclic Chem.* **1985**, *38*, 177; (d) Bateman, J. H. *Kirk-Othmer 'Encyclopedia of Chemical Technology'*; Wiley-Interscience: New York, 1978; Vol. 12, p. 762; (e) Ware, E. *Chem. Rev.* **1950**, *46*, 403.
2. (a) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897; (b) Base-catalyzed condensation–eliminations of diethyl hydantoinyl-5-phosphonates with ethyl benzoylformate, ethyl pyruvate, phenylglyoxal monohydrate, 1,2-cyclohexanedione, and various isatins have been reported in Ref. 2a. The C-5 functionally-substituted, unsaturated hydantoins (**1**, R and/or R′ = functional groups) from this methodology[2a] are very different from those of the present communication.
3. Wheeler, H. L.; Hoffman, C.; Johnson, T. B. *J. Biol. Chem.* **1911**, *45*, 147.

4. (a) Mathur, N. C.; Shechter, H. *J. Org. Chem.* **1990**, *55*, 3001; (b) Mathur, N. C.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 6965; (c) Mathur, N. C.; Shechter, H. *Tetrahedron Lett.* **1991**, *32*, 3799; (d) 5-(Hydroxymethylene)hydantoins **42** have been previously prepared by decomposition of 5-diazo-6-hydroxydihydrouracil with rhodium(II) acetate at 105°C.[4c]
5. (a) Hydantoin **7** (stereochemistry unknown) was prepared from 5-benzalhydantoin and Br_2 in acetic acid.[3] Synthesis of no other 5-(α-haloalkylidene)hydantoins has been reported; (b) The products from reactions of **7** with other nucleophiles were not identified;[3,5c] (c) See Ref. 14 for further studies of addition–eliminations of **7**.
6. (a) Sprinson, D. B.; Chargaff, E. *J. Biol. Chem.* **1946**, *164*, 417; (b) Stubbe, J. A.; Kenyon, G. L. *Biochemistry* **1971**, *10*, 2669; (c) Hirschbein, B. L.; Mazenod, F. P.; Whitesides, G. M. *J. Org. Chem.* **1982**, *47*, 3765.
7. (a) Conversions of **9** by **10** and **14** (Scheme 1) to **12** and **16**, respectively, apparently involve acid-catalyzed (1) ring-closures of **11** and **15** to their corresponding 5-bromomethyl-5-hydroxyhydantoins and then dehydrations or/and (2) eliminations of H_2O from **11** or **15** and then heterocyclizations of the (*E*)- and (*Z*)-3-bromo-2-ureidoacrylic acids generated. It is emphasized that products from (1) intramolecular displacements of Br^- in **11** or **15** and/or (2) formation and intramolecular additions in 3-bromo-2-ureidoacrylic acids and eliminations of Br^- were not obtained. The mechanisms of conversions of **9** by **10** and **14** to **12** and **16**, respectively, will be discussed further in a future publication; (b) 5-Methylenehydantoin (24%) has been prepared from pyruvic acid, urea (**10**), hydrochloric acid, and acetic acid and (2) 5-hydroxy-5-methylhydantoin (69%) is obtained from pyruvic acid and aqueous urea (**10**) at 20–25°C for 14 days;[7c,d] (c) Of note in the above preparations of 5-methylenehydantoin and **12** is that such methylenehydantoins are more stable than their respective (endocyclic) 5-methyl- and 5-(bromomethyl)hydantoene isomers; (d) Murahashi, S.; Yuki, H.; Kosai, K.; Doura, F. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1559.
8. The experimental procedure for preparing **12** is described as follows. Bromine (6.7 ml, 20.8 g, 0.13 mol) was added to a solution of pyruvic acid (9.6 ml, 20.8 g, 0.13 mol), conc H_2SO_4 (one drop), and CH_2Cl_2 (10 mL). The solvent and HBr in the reaction mixture were removed in vacuo. Upon dissolving the residue, crude bromopyruvic acid (**9**), in anhydrous CH_3CN (250 mL), boron trifluoride etherate (7 mL, 8.09 g, 0.05 mol), and then urea (**10**, 7.8 g, 0.13 mol, 15 min) were added. The mixture was refluxed for 9 h and then cooled to room temperature. The dark precipitate formed was suction-filtered. Additional product was obtained upon concentrating the filtrate. The combined solids were washed with water, dissolved in ethanol, treated with charcoal, and crystallized from ethanol to give **12** (11.6 g, 47%) as a white solid; mp 247–249°C; ^{1}H NMR (DMSO-d_6): δ 11.3 (1H, bs), 10.6 (1H, bs), 6.54 (1H, s); MS: 192 (M+2, 98), 190 (M, 100), 149 (27), 121 (89), 119 (89). Anal. calcd for $C_4H_3BrN_2O_2$: C, 25.16; H, 1.58; N, 14.67; Found: C, 25.21; H, 1.61; N, 14.60.
9. (a) The stereochemical assignments of **16**, **24**, **26**, **29**–**32**, and **34** are made by ^{13}C NMR from the long-range ^{13}C–^{1}H coupling constants between their exocyclic olefinic protons and their C-4 carbonyl carbons.[2a] The present 5-methylenehydantoins that have $^3J_{C,H}$ values of 9.0 Hz and higher (a range of 9–11) are assigned as *trans* (*E*)-isomers; the 5-methylenehydantoin isomers with $^3J_{C,H}$ values ranging from 4 to 6 Hz are assigned as *cis* (*Z*)-isomers.[9b] The stereochemistries of further products of the present study are to be investigated by NMR and crystallographic methods; (b) The ^{13}C NMR assignment methods are based on that of Ref. 2a and references cited therein.
10. The $^3J_{C,H}$ spin coupling value between the exocyclic olefin proton and the C-4 carbonyl carbon in **19** is 8.0 Hz. Assignment of the stereochemistry of **19** has not yet been made.
11. Reactions of 5-(*N*-pyridiniummethylene)hydantoin bromides (**23**)[12] and 3-alkyl-[5-(*N*-pyridiniummethylene)-hydantoin bromides, respectively, with strong bases are of interest with respect to advantageous generation of 5-hydantoenylcarbenes **6**[4] as in Eq. (1).
12. Pyridinium bromide **24** was obtained as follows. A solution of bromide **16** (96.1 mg, 0.439 mol) in pyridine (10 mL) was refluxed for 2 h, stirred at room temperature for 2 days, cooled, and then filtered. The precipitate, on rinsing with Et_2O, gave **24** (125 mg, 96%) as a brown solid; mp 191–193°C; ^{1}H NMR (DMSO-d_6): δ 9.15 (2H, d, J=4.85 Hz), 8.79 (1H, t, J=7.45 Hz), 8.30 (2H, t, J=7.50 Hz), 7.60 (1H, s), 3.05 (3H, s), 2.70 (3H, s); ^{13}C NMR (DMSO-d_6): δ 162.1, 154.7, 147.5, 146.2, 130.3, 127.8, 110.4, 28.3, 25.2; exact mass calcd for $C_{11}H_{12}BrN_3O_2$ (M^+–C_5H_5NBr) m/e 139.0507, found m/e 39.0508. Anal. calcd for $C_{11}H_{12}BrN_3O_2$: C, 44.32; H, 4.06. Found C, 44.44; H, 4.03.
13. [(Phenylthio)methylene]hydantoin **29** was prepared by adding tetramethylguanidine (237 mg, 2.05 mmol, 1.5 equiv.) dropwise to a solution of **16** (300 mg, 1.3 equiv.) and thiophenol (196 mg, 1.78 mmol, 1.3 equiv.) in THF (3 mL) at 25°C. The mixture formed a yellow precipitate which was stirred for 24 h. Filtration and then concentration of the filtrate at reduced pressure followed by column chromatography (1:3 ethyl acetate/petroleum ether) gave **29** as a yellow solid (290.0 mg, 85%). An analytical sample of **29** was obtained by recrystallization from ethanol: mp 89–91°C; ^{1}H NMR ($CDCl_3$): δ 3.09 (s, 3H), 3.51 (s, 3H), 6.75 (s, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 25.02, 28.98, 112.17, 127.21, 128.23, 129.58, 130.86, 133.51, 154.69, 161.27; exact mass calcd for $C_{12}H_{12}N_2O_2S$ m/e 248.0619, found m/e 248.0618. Anal. calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.88. Found: C, 58.03; H, 4.91.
14. (a) Kocienski, P. J. *Tetrahedron Lett.* **1979**, *20*, 2649; (b) Hsiao, C.-N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688 and references cited therein.
15. S. Negi of this laboratory has found that (1) **12** and **7** are converted by aqueous sodium *p*-toluenesulfinate at 95°C to 5-(*p*-toluenesulfonylmethylene)hydantoin (71%) and 5-(α-*p*-toluenesulfonylbenzal)hydantoin (85%), respectively, and (2) **7** reacts with piperidine and morpholine in dioxane at 105–120°C to give 5-(α-*N*-piperidinobenzal)hydantoin (68%) and 5-(α-*N*-morpholinobenzal)hydantoin (55%), respectively. The stereochemistries of these products have not yet been determined.
16. For recent developments in catalytic asymmetric hydrogenations of functionally-substituted olefins, see: Rajan-Babu, T. V.; Casalnuovo, A. L.; Ayers, T. A.; Nomura, N.; Jin, J.; Park, H.; Nandi, M. *Curr. Org. Chem.* **2003**, *7*, 1 and references cited therein.