GENERATION AND DIELS-ALDER REACTIONS OF *N*1-SUBSTITUTED PYRAZOLE-4,5-QUINODIMETHANES

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Abstract — The cycloaddition of *o*-quinodimethanes (**9-11**) generated *in situ* from the 4,5-bisbromomethylpyrazole derivatives (**6-8**), with several dienophiles leads to the formation of the cycloadducts (**12-20**). These Diels-Alder reactions are also examined on the basis of some AM1 calculations.

The first attempt for the preparation of a pyrazole-4,5-quinodimethane using the technique of flash vacuum pyrolysis on (1-phenyl-5-methylpyrazol-4-yl)methyl 4-chlorobenzoate was reported by Storr *et al.*[1] in 1990. Shortly afterwards we reported our preliminary results on pyrazole-4,5-quinodimethane, generated by dehalogenation of 1-benzoyl-3-phenyl-4,5-bisbromomethylpyrazole and trapped as its Diels-Alder cycloadducts in fair yields.[2] We also reported the pyrazole-4,5-quinodimethane cycloaddition with stable nitrile oxides.[3] Recently, Storr *et al.*[4] reported the formation of mixtures of *N*1- and *N*2-methylpyrazole- and N_1- and N_2-ben-

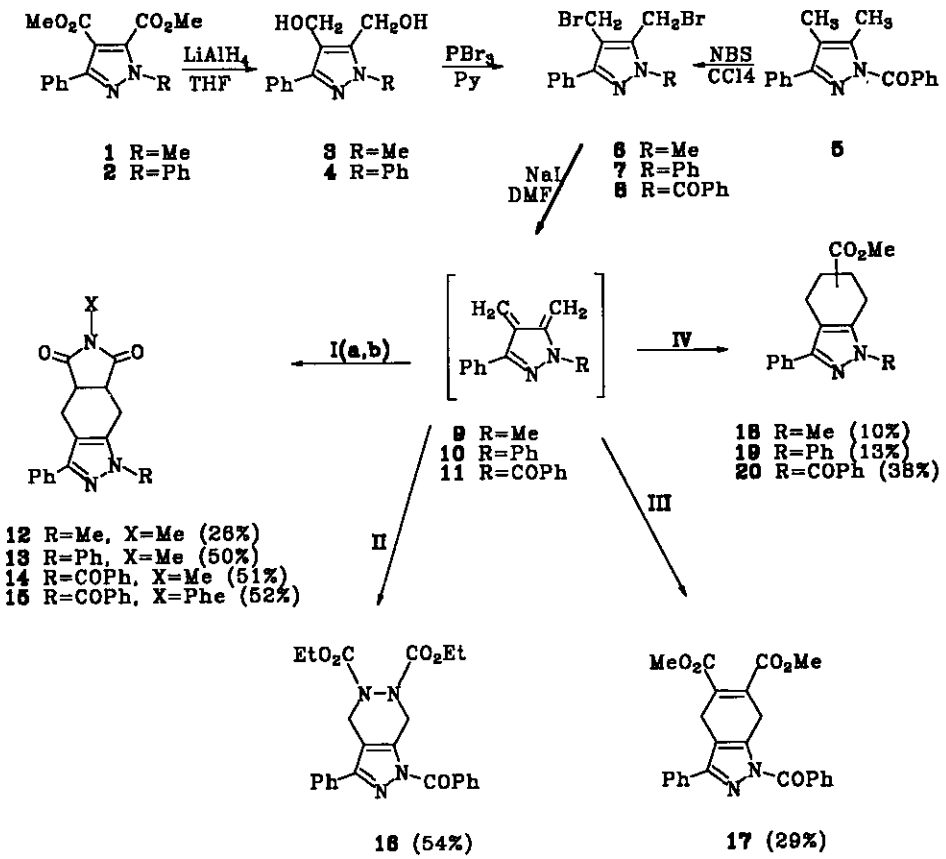
zoylpyrazole-4,5-quinodimethanes generated by thermolysis of inseparable mixtures of *N*1- and *N*2-substituted pyrazole-fused 3-sulfolenes and successfully trapped as Diels-Alder adducts with *N*-phenylmaleimide. Furthermore, Chou and Chang[5] also achieved the formation of *N*1-phenylpyra-zole-4,5-quinodimethane by thermolysis of *N*1-phenyl substituted pyrazole-fused 3-sulfolenes.

In the present paper we wish to report the preparation of *N*1-methyl-, *N*1-phenyl-, and *N*1-benzoyl-3-phenylpyrazole-4,5-quinodimethanes generated by dehalogenation of the corresponding 4,5-bisbromomethylpyrazoles and trapped as their Diels-Alder cycloadducts. We also make an attempt to evaluate the influence of the *N*1-substituent on the *o*-quinodimethane reactivity.

The *N*1-methyl-, *N*1-phenyl-, and *N*1-benzoylpyrazole-4,5-quinodimethanes (**9**), (**10**), and (**11**) were prepared in few simple steps as shown in the Scheme.

The *N*1-methyl- and *N*1-phenyl-4,5-bisbromomethylpyrazoles (**6**) and (**7**), the desired 4,5-quinodimethane precursors, were prepared from the pyrazoledicarboxylates (**1**) and (**2**) by lithium aluminum hydride reduction to the corresponding alcohols (**3**) and (**4**). Subsequent reaction of **3** and **4** with phosphorus tribromide in the presence of pyridine afforded the bisbromides (**6**) and (**7**). Treatment of **6** and **7** with sodium iodide in dimethylformamide led to *in situ* generation of the *o*-quinodimethanes (**9**) and (**10**). The *N*1-benzoyl-4,5-bisbromethylpyrazole (**8**) was prepared by bromination of the 4,5-dimethylpyrazole (**5**) with *N*-bromosuccinimide. The conversion of the *N*1-benzoyl-bisbromide (**8**) into *o*-quinodimethane (**11**) was accomplished by addition of sodium iodide in a dimethylformamide solution at 120 ^{o}C for 3 h whereupon in the presence of one or two equivalents of dienophile the Diels-Alder adducts were formed in fair yields. However, in the case of the *N*1-methyl- and *N*1-phenylbisbromides lower

Scheme



Ia. *N*–Methylmaleimide
Ib. *N*–Phenylmaleimide
II. Diethyl azodicarboxylate
III. Dimethyl acetylenedicarboxylate
IV. Methyl acrylate

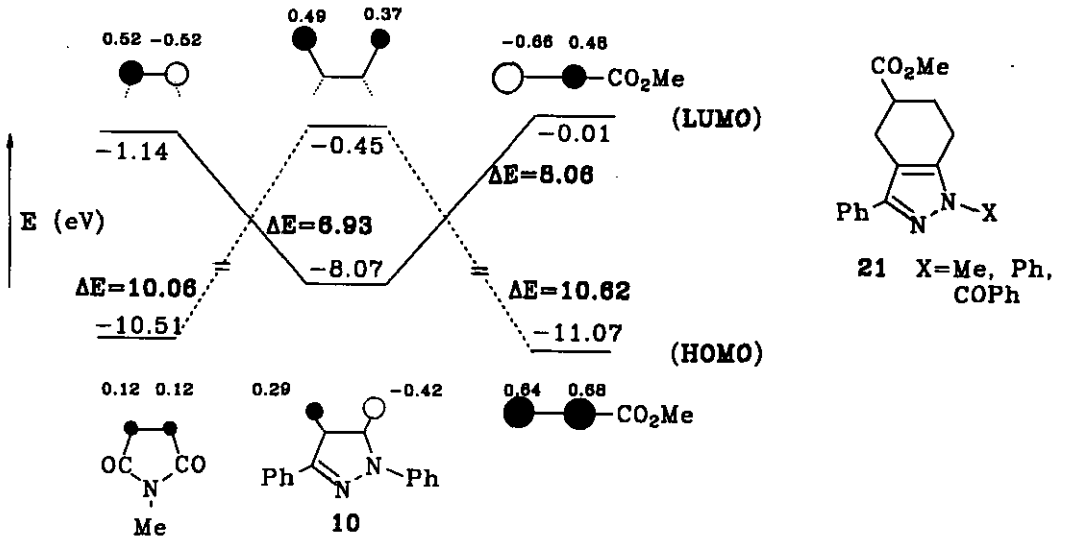


Figure. AM1 calculations for the HOMO-LUMO interactions between the *o*-quinodimethane (10) (diene) and the dienophiles, *N*-methylmaleimide and methyl acrylate, as well as the corresponding favored regioisomers (21) of the cycloaddition.

reaction temperatures (85-90 °C) and at least five equivalents of the dienophile were required to give the adduct in reasonable to low yield. The yield could be improved considerably by using a large excess (more than five equivalents) of the dienophile. In the case of reactions of 6, 7, and 8 with the unsymmetrical dienophile methyl acrylate a mixture of inseparable regioisomers was isolated and it was deduced from their ^{1}H nmr spectra (see Experimental).

Theoretical AM1 calculations performed on the addition of quinodimethanes (9-11) with *N*-methylmaleimide and methyl acrylate (Figure) show that the reaction is $HOMO_{diene}$ controlled, since this process leads to a smaller E_{LUMO}-E_{HOMO} energy difference (ΔE) in agreement with other previous calculations carried out on the cycloadditions of triazole-4,5-quinodimeth-

ane with *N*-methylmaleimide.[6] The energy differences $\Delta E = E_{LUMO}$ (dienophile) - E_{HOMO} (diene) for the quinodimethanes (9), (10), and (11) are 6.94, 6.93, and 7.46 eV, respectively. Comparing these ΔE values it is concluded that the quinodimethanes (9) and (10) should be more reactive than 11 in accordance with experiments, where the dienes (9) and (10) react with maleimide at lower temperature.

In respect to the regioselectivity of the cycloadducts (18-20), examination of the corresponding orbital coefficients of the reacting species indicates a small preference for the regioisomer (21) (Figure). It is mentioned that ^{1}H-nmr investigation of the reaction mixture of the products (18-20) showed the two regioisomers to be present in a ratio approximately 1:1.3. However, this structural problem is under further consideration.

EXPERIMENTAL

Melting points are uncorrected and were obtained with a Kofler hot stage apparatus. Ir spectra were measured on a Perkin-Elmer 297 spectrophotometer. ^{1}H Nmr spectra were recorded by a Bruker AW80 spectrometer with tetramethylsilane as internal standard, chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Mass spectra were measured with a VG TS-250 double focusing spectrometer in EI mode (70 eV). Elemental analyses were performed with a Perkin-Elmer model 240B CHN Analyser.

The theoretical calculations were carried out using version 6 of the MOPAC package on a DEC 9000 computer at the University Computer Center. The molecular geometries were fully optimised using the AM1 method[7] (with PRECISE option) by minimizing the energy with respect to all internal coordinates except the C-H bond lengths and angles of methyl and exo-methylene groups, where the SYMMETRY option was used.

4,5-Bishydroxymethyl-1-methyl-3-phenyl-1*H*-pyrazole (3).

To an ice-salt cold suspension of 190 mg (5 mmol) of lithium aluminum hydride in 20 ml of dry THF 274 mg (1 mmol) of the diester (1) were slowly added while stirring. The reaction mixture was stirred under reflux for 10 h. A standard workup procedure[8] gave the product (3) (111 mg, 51%), mp 180-182 °C; ms m/z (%) 218 (M^+, 100), 201 (32), 199 (75), 187 (14), 171 (27). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.83. Found: C, 66.13; H, 6.54; N, 13.00.

4,5-Bishydroxymethyl-1,3-diphenyl-1*H*-pyrazole (4).

To an ice-salt cold suspension of 190 mg (5 mmol) of lithium aluminum hydride in 20 ml of dry THF 336 mg (1 mmol) of the diester (2) were slowly added while stirring. The reaction mixture was stirred under reflux for 10 h. A standard workup procedure[8] gave the product (4) (154 mg, 55%) mp 160-164 °C; ir ν_{max} (nujol) 3300 cm^{-1}; ms m/z (%) 280 (M^+, 100), 263 (21), 261 (36), 249 (9), 219 (7). *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.68; H, 5.67; N, 9.81.

4,5-Bisbromomethyl-1-methyl-3-phenyl-1*H*-pyrazole (6).

A mixture of phosphorus tribromide (1.3 g, 5 mmol) and dry pyridine (0.08 ml) was added under stirring at -5 °C to a solution of 4,5-bishydroxymethylpyrazole (3) (1.1 g, 5 mmol) and dry pyridine (0.2 ml) in dry dichloromethane (40 ml). The reaction mixture was stirred at room temperature for 24 h, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in dichloromethane and the title compound (6) was crystallized by addition of petroleum ether (1.4 g, 80%) as a white solid mp 114-117 °C; ^{1}H-nmr: (δ, ppm)= 3.91 (s, 3H), 4.53 (s, 4H), 7.29-7.50 (m, 3H), 7.59-7.84 (m, 2H).

Unstable compound, therefore a satisfactory elemental analysis was not

possible.

4,5-Bisbromomethyl-1,3-diphenyl-1*H*-pyrazole (7).

A mixture of phosphorus tribromide (1.3 g, 5 mmol) and dry pyridine (0.08 ml) was added under stirring at -5 °C to a solution of 4,5-bishydroxymethylpyrazole (4) (1.4 g, 5 mmol) and dry pyridine (0.2 ml) in dry dichloromethane (40 ml). The reaction mixture was stirred at room temperature for 24 h, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in dichloromethane and the title compound (7) was crystallized by addition of petroleum ether (1.7 g, 83%), mp 52-54 °C; ^{1}H-nmr: (δ, ppm)= 4.54 (s, 2H), 4.64 (s, 2H), 7.26-7.98 (m, 10H).

General Procedure for Compounds (12) and (18).

To a mixture of 6 (344 mg, 1 mmol) and powdered sodium iodide (300 mg, 2 mmol) in dry DMF (10 ml) the dienophile (5 mmol) was added and the reaction mixture was stirred at 85-90 °C for 2 h. The solvent was subsequently evaporated under vacuum, the crude product was dissolved in dichloromethane (10 ml), treated with aqueous 10% sodium thiosulfate solution and washed with water. The organic layer was dried (Na_2SO_4), condensed under vacuum to 2 ml and purified by column chromatography (silica gel, petroleum ether/ethyl acetate 1:1 in the case of 12 and 3:1 in the case of 18).

4,5,6,7-Tetrahydro-1-methyl-3-phenyl-1*H*-indazole-5,6-dicarboxy-*N*-methylimide (12).

Prepared from 6 and *N*-methylmaleimide in 21% yield, mp 117-119 °C (from dichloromethane-ether); ir ν_{max} (nujol) 1780, 1700 cm^{-1}; ^{1}H-nmr: (δ, ppm) = 2.86 (s, 3H), 2.95-3.65 (m, 4H), 3.78 (s, 3H), 3.90-4.70 (m, 2H); ms

m/z (%) 295 (M^+, 100), 209 (22), 194 (6), 184 (93). *Anal.* Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found : C, 69.11; H, 5.84; N, 14.19. When a 10 fold excess of the dienophile was used the reaction yield was improved to 26%.

Methyl 4,5,6,7-Tetrahydro-1-methyl-3-phenyl-1*H*-indazole-5(6)-carboxylate (18).

Prepared from **6** and methyl acrylate in 2% yield, oil; ir ν_{max} (nujol) 1720 cm^{-1}; ^{1}H-nmr: (δ, ppm)= 2.09-3.16 (m, 7H), 3.68 and 3.70 (2xs, 3H), 3.73 (s, 3H), 7.12-7.47 (m, 3H), 7.55-7.79 (m, 2H); ms m/z (%) 270 (M^+, 100), 254 (53), 211 (100), 184 (90). When a 40 fold excess of the dienophile was used the reaction yield was improved to 10%.

General Procedure for Compounds (13) and (19).

To a mixture of 7 (406 mg, 1 mmol) and powdered sodium iodide (300 mg, 2 mmol) in dry DMF (10 ml) the dienophile (5 mmol) was added and the reaction mixture was stirred at 85-90 °C for 2 h. The solvent was subsequently evaporated under vacuum, the crude product was dissolved in dichloromethane (10 ml), treated with aqueous 10% sodium thiosulfate solution and washed with water. The organic layer was dried (Na_2SO_4), condensed under vacuum to 2 ml and purified by column chromatography (silica gel, petroleum ether/ethyl acetate 3:1 in the case of 13 and 15:1 in the case of 19).

4,5,6,7-Tetrahydro-1,3-diphenyl-1*H*-indazole-5,6-dicarboxy-*N*-methylimide (13).

Prepared from 7 and *N*-methylmaleimide in 50% yield, mp 170-172 °C (from dichloromethane-ether); ir ν_{max} (nujol) 1750, 1700 cm^{-1}; ^{1}H-nmr: (δ, ppm) = 2.89 (s, 3H), 3.26-3.48 (m, 4H), 3.50-3.67(m, 2H), 7.26-7.58 (m, 8H),

7.60-7.80 (m, 2H); ms m/z (%) 357 (M^+, 100), 271 (19), 246 (39), 245 (40). *Anal.* Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.20; H, 5.70; N, 11.91.

Methyl 4,5,6,7-Tetrahydro-1,3-diphenyl-1*H*-indazole-5(6)-carboxylate (19). Prepared from 6 (406 mg, 1 mmol) and methyl acrylate (430 mg, 5 mmol) in 13% yield, mp 147-150 °C (from ether-petroleum ether); ir ν_{max} (nujol) 1730 cm^{-1}; ^{1}H-nmr: (δ, ppm)= 1.78-3.29 (m, 7H), 3.68 and 3.71 (2xs, 3H), 7.27-7.66 (m, 8H), 7.70-8.05 (m, 2H); ms m/z (%) 332 (M^+, 100), 273 (56), 245 (57). *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.68; H, 6.00; N, 8.28.

General Procedure for Compounds (14-17) and (20).

To a mixture[3] of compound (8) (434 mg, 1 mmol) and powdered sodium iodide (300 mg, 2 mmol) in dry DMF (40 ml) the dienophile (1 or 2 mmol) was added and the reaction mixture was heated at 110-120 °C for 3 h. The solvent was evaporated under vacuum and the crude product was dissolved in dichloromethane and treated with aqueous 10% sodium thiosulfate solution and washed with water. The organic solution was dried (Na_2SO_4) and the product was isolated either by crystalization or by column chromatography (silica gel, petroleum ether/ethyl acetate 10:1).

1-Benzoyl-4,5,6,7-tetrahydro-3-phenyl-1*H*-indazole-5,6-dicarboxy-*N*-methylimide (14).

Prepared from 8 (434 mg, 1 mmol) and *N*-methylmaleimide (111 mg, 1 mmol) and isolated by column chromatography in 51% yield, mp 95-97 °C (from ethanol); ir ν_{max} (nujol) 1780, 1700 cm^{-1}; ^{1}H-nmr: (δ, ppm)= 2.91 (s, 3H), 3.19-3.51 (m, 4H), 3.80-4.21 (m, 2H), 7.29-7.74 (m, 8H), 8.00-8.21 (m, 2H); ms m/z (%) 385 (M^+, 44), 356 (8), 274 (24), 105 (100); *Anal.*

Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.69; H, 5.11; N, 10.81.

1-Benzoyl-4,5,6,7-tetrahydro-3-phenyl-1*H*-indazole-5,6-dicarboxy-*N*-phenylimide (15).

Prepared from **8** (434 mg, 1 mmol) and *N*-phenylmaleimide (179 mg, 1 mmol) and isolated by crystalization by addition of ether in 52% yield, mp 118-120 °C (from ethanol); ir ν_{max} (nujol) 1780, 1710 cm^{-1}; ^1H-nmr: (δ, ppm)= 3.06-3.14 (m, 1H), 3.37-3.58 (m, 4H), 4.02-4.09 (m, 1H), 7.19-7.62 (m, 11H), 7.68-7.71 (m, 2H), 8.11-8.13 (m, 2H); ms m/z (%) 447 (M^+, 17), 419 (2), 344 (2), 173 (79), 105 (100); *Anal.* Calcd for $C_{28}H_{21}N_3O_3$: C, 75.15; H, 4.73; N, 9.39. Found: C, 75.31; H, 4.88; N, 9.47.

Diethyl 5-Benzoyl-1,2,3,4-tetrahydro-7-phenyl-1*H*-pyrazole[4,5-*d*]pyridazine-2,3-dicarboxylate (16).

Prepared from **8** (434 mg, 1 mmol) and diethyl azodicarboxylate (174 mg, 1 mmol) and isolated by crystalization by addition of ether in 54% yield, mp 145-146 °C (from ethanol); ir ν_{max} (nujol) 1700 cm^{-1}; ^1H-nmr: (δ, ppm) = 1.26 (t, J=6Hz, 6H), 4.22 (q, J=6Hz, 4H), 4.52 and 5.62 (two d, J=18Hz, 2H), 4.75 and 5.21 (two d, J=18Hz, 2H), 7.25-7.77 (m, 8H), 8.12-8.33 (m, 2H); ms m/z (%) 448 (M^+, 14), 403 (1), 375 (3), 343 (12), 270 (22), 105 (100); *Anal.* Calcd for $C_{24}H_{24}N_4O_5$: C, 64.28; H, 5.39; N, 12.49. Found: C, 64.18; H, 5.50; N, 12.60.

Dimethyl 1-Benzoyl-4,7-dihydro-3-phenyl-1*H*-indazole-5,6-dicarboxylate (17).

Prepared from **8** (434 mg, 1 mmol) and dimethyl acetylene dicarboxylate (142 mg, 1 mmol) and isolated by crystalization by addition of ether in 29% yield, mp 165-167 °C (from ethanol); ir ν_{max} (nujol) 1720 cm^{-1}; ^1H-

nmr: (δ, ppm)= 3.80 (t, J=7Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.21 (t, J=7Hz, 2H), 7.38-7.62 (m, 6H), 7.73-7.76 (m, 2H), 8.12-8.15 (m, 2H); ms m/z (%) 416 (M^+, 5), 385 (2), 357 (1), 105 (100); *Anal.* Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 68.98; H, 4.96; N, 7.00.

Methyl 1-Benzoyl-4,5,6,7-tetrahydro-3-phenyl-1*H*-indazole-5(6)-carboxylate (20).

Prepared from **8** (434 mg, 1 mmol) and methyl acrylate (172 mg, 2 mmol) and isolated by column chromatography in 38% yield as oil; ir ν_{max} (nujol) 1725 cm^{-1}; ^1H-nmr: (δ, ppm)= 1.89-3.61 (m, 7H), 3.73 and 3.74 (2xs, 3H), 7.30-7.62 (m, 6H), 7.72-7.75 (m, 2H), 8.09-8.14 (m, 2H); ms m/z (%) 360 (M^+, 100), 332 (10), 329 (6), 301 (29), 355 (55), 195 (21), 105 (85); *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. **Found: C, 73.38; H, 5.39; N, 7.49.**

REFERENCES AND NOTES

1. R. M. S. Chauhan, A. P. A. Crew, G. Yenkins, R. C. Storr, S. M. Walker, and M. Yelland, *Tetrahedron Lett.*, 1990, **31**, 1487.
2. S. Mitkidou and J. Stephanidou-Stephanatou, *Tetrahedron Lett.*, 1990, **31**, 5197.
3. S. Mitkidou and J. Stephanidou-Stephanatou, *Tetrahedron*, 1992, **48**, 6059.
4. L. M. Chaloner, A. P. A. Crew, and R. C. Storr, *Tetrahedron Lett.*, 1991, **32**, 7609; L. M. Chaloner, A. P. A. Crew, P. M. Oneill, R. C. Storr, and M. Yelland, *Tetrahedron*, 1992, **48**, 8101.
5. T. Chou and R. Chang, *J. Org. Chem.*, 1993, **58**, 493.

6. G. E. Mertzanos, J. Stephanidou-Stephanatou, C. A. Tsoleridis, and N. E. Alexandrou, *Tetrahedron Lett.*, 1992, 33, 4499.

7. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, 107, 3902.

8. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley and Sons, Inc., New York, 1967, p. 584.

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