Synthesis of Additional unreported 4- and 5-Aryl Substituted 1,3 (3H) Oxazine-2,6-Diones.; 4-(4-bromophenyl)-1,3(3H) Oxazine-2,6-Dione and related 4 and 5-aryl substituted -1,3(3H) Oxazine-2,6-Diones

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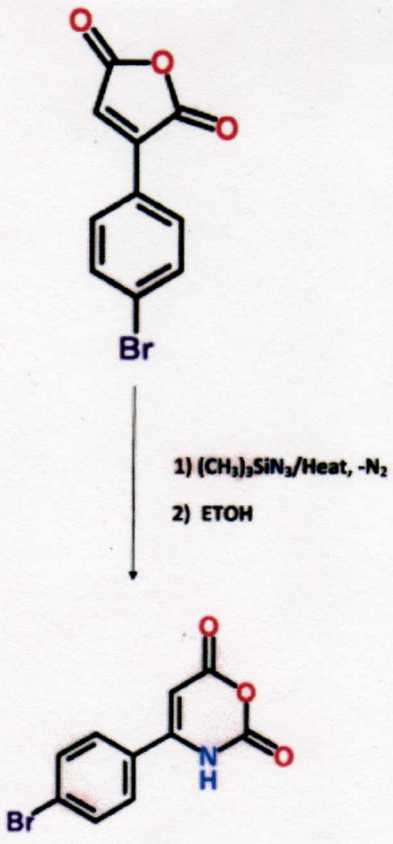

Chemicals Used

4-bromophenyl maleic anhydride and additional aryl substituted maleic anhydrides
Trimethylsilyl Azide

Dimethyl sulfate
Diethyl sulfate

Procedure

Preparation of 4-(4-bromophenyl)-1,3(3H) Oxazine-2,6-Dione

A 50 ml 3 neck round bottom flask, equipped with condenser, heating mantle, dropping funnel, nitrogen inlet, magnetic stirrer, and calcium chloride drying tube, was charged with 4.75g (0.019 mole) 4-bromophenyl maleic anhydride, 12ml (~ 0.09 mole) trimethylsilyl azide, and 3 ml dry dioxane. The mixture was refluxed 3 hrs after which nitrogen gas evolution ceased. TLC (silica gel, ethyl acetate eluent) showed primarily the 4- isomer with traces of the 5-isomer. The solution was cooled in ice to 0 ^{o} and 40 ml benzene was added with stirring. Addition of 1 ml ethanol gave a copious white precipitate which TLC showed to be pure 4-isomer. The precipitate was suction filtered and mother liquor concentrated further, giving 2.9g (58%), 4-(4-bromophenyl)-1,3(3H) Oxazine-2,6-Dione in three crops. Recrystallization of a small sample from ethyl acetate gave white crystals,

m.p. 207-9^{o} (dec).

Ir, (mull), 3220(w), 3160(w), 3100 (w), 1790(s), 1800(s),1710(s), 1630(s), 1595(m), 1500(m), 1400(w), 1305(w), 1270(w), 1220(w) 1110(m), 1085(m), 1070(m), 1005(w),980(m), 840(m), 805(m), 750 (m) cm^{-1}.

Pmr (DMSO-d_6, 60mz), δ 7.7(broad singlet, 4H, aromatics), 6.0 (s, 1H, N-H), 5.66 (s, 1H, C5-H).

Anal. Calc. For $C_{10}H_6BrNO_3$:

C, 44.80, H, 2.26, N, 5.23, Br, 29.81.

Found: C, 44.74, H, 2.17, N, 5.18, Br, 29.79. Satisfactory

Additional unreported aryl substituted 1,3(3H) Oxazine-2,6-Diones were synthesized by essentially the procedure above in similar yields, and converted to their N-alkylated derivatives by refluxing the corresponding aryl substituted oxauracil with a di-alkyl sulfate/sodium bicarbonate slurry in acetone, as described in J.H. MacMillan and S.S. Washburne, J. Heterocyclic Chemistry, Vol. 12, p 1215, (1975).

Author's Comments

The following unreported additional 4-and 5-Aryl Substituted 1,3(3H) oxazine-2,6-diones (oxauracils) were synthesized for anti malarial screening by the reaction of the corresponding aryl maleic anhydride with trimethylsilyl azide, by the procedure described in J. Heterocyclic Chemistry, Vol. 12, p 1215, (1975). The N-Alkylated derivatives were prepared by refluxing the corresponding aryl substituted oxauracil with a di alkyl sulfate/sodium bicarbonate slurry in acetone, as described in the above paper.

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Data

4-(3-chloro-4-methylphenyl)-1,3(3H) Oxazine-2,6-Dione, 1

m.p. 184-6° (dec), Ir, ($CDCl_3$), 3400(w), 1795(s), 1740(s), 1720(s), 1640(m), 1560(w), 1160(w), 1090 (m), 1050(w), 980(m), 805(m), cm^{-1}.

Pmr (acetone-d_6, 60mz), δ 10.0 (broad, 1H, seen only in integration, N-H), 7.7 (m, 3H, aromatics), 5.95 (s, 1H, C5-H), 2.40(s, 3H, CH_3).

Anal. Calc. For $C_{11}H_8ClNO_3$:

C, 55.59, H, 3.39, N, 5.89, Cl, 14.92.

Found: C, 55.47, H, 3.40, N, 5.73, Cl, 14.85. Satisfactory

N-Methyl-4-(3-chloro-4-methylphenyl)-1,3(3H) Oxazine-2,6-Dione, 1a.

m.p. 179-82° (dec), Ir, ($CDCl_3$), 1790(s), 1730(s), 1640(s), 1605(m), 1500(w), 1420(m), 1380(s), 1330 (s), 1220(w) 1160(w), 1080(m), 1045(w), 1030(w), 980(m), 820(m), cm^{-1}.

Pmr (acetone-d_6, 60mz), δ 8.1(s, 1H, C4-H), 7.7(d, 1H, J=1.5Hz, H ortho), 7.55(d of d, 1H, H ortho, J ortho-meta = 8Hz, J ortho-ortho =1.5 Hz), 7.30 (distorted doublet, 1H, H meta, J ortho-meta = 8Hz), 3.55 (s, 3, N-CH_3), 2.40 (s, 3H, phenyl-CH_3).

Anal. Calc. For $C_{12}H_{10}ClNO_3$:

C, 57.27, H, 4.01, N, 5.57, Cl, 14.09.

Found: C, 57.32, H, 4.00, N, 5.40, Cl, 14.06. Satisfactory

4-(p-bromophenyl)-1,3(3H) Oxazine-2,6-Dione, 2.

m.p. 207-9° (dec), Ir, (mull), 3220(w), 3160(w), 3100 (w), 1790(s), 1800(s),1710(s), 1630(s), 1595(m), 1500(m), 1400(w), 1305(w), 1270(w), 1220(w) 1110(m), 1085(m), 1070(m), 1005(w),980(m), 840(m), 805(m), 750 (m) cm^{-1}.

Pmr (DMSO-d_6, 60mz), δ 7.7(broad singlet, 4H, aromatics), 6.0 (s, 1H, N-H), 5.66 (s, 1H, C5-H).

Anal. Calc. For $C_{10}H_6BrNO_3$:

C, 44.80, H, 2.26, N, 5.23, Br, 29.81.

Found: C, 44.74, H, 2.17, N, 5.18, Br, 29.79. Satisfactory

N-Methyl-4-(p-bromophenyl)-1,3(3H) Oxazine-2,6-Dione, 2a.

m.p. 173-5° (dec), Ir, ($CDCl_3$), 3110(w), 1790(s), 1730(s), 1660(s), 1590(w), 1490(s), 1440(s), 1395(s), 1340(s), 1220(m) 1180(m), 1090(m), 1045(w), 1070(m), 1015(m), 1005(s), 980(m), 820(m), cm^{-1}.

4-(p-tolyl)-1,3(3H) Oxazine-2,6-Dione, 3.

m.p. 200-2° (dec), Ir, (mull), 3240(m), 3160(m), 3110 (m), 1810(s), 1710(s), 1625(s), 1510(m), 1280 (w), 1260(w), 1185(m), 1110(m), 1080(m), 1030(m), 980(m), 840(m), 800(m), 740 (s) cm^{-1}.

Pmr (DMSO-d_6, 60mz), δ 7.5 (AB Pattern, 4H, aromatics), 5.90 (s, 1H, C5-H), 2.4 (s, 3H, phenyl-CH_3).

N-Methyl-4-(p-tolyl)-1,3(3H) Oxazine-2,6-Dione, 3a.

m.p. 99-100°, IR ($CDCl_3$), 3120(w), 2960 (m), 1780(vs), 1720(vs), 1620(s), 1510(m), 1470(s), 1430(s), 1390(m), 1320(m), 1240(m), 1200(m), 1180(m), 1080(m), 1060(m), 1010(m), 1005(m), 960(m), 840(s), 800(m), cm^{-1}.

Pmr ($CDCl_3$, 60mz), δ 7.3 (AB Pattern, 4H, aromatics), 5.50 (s, 1H, C5-H), 3.2 (s, 3H, N-CH_3) 2.4 (s, 3H, phenyl-CH_3).

^{13}C NMR (DMSO-d_6), δ 162.0, 159.2 (carbonyls), 151.2 (C-4 of oxauracil), 142.0, 130.1, 130, 128.5 (aromatics). 96.5 (C-5 of oxauracil), 34.8, (N-CH_3), 20.8 (phenyl-CH_3).

Anal. Calc. For $C_{12}H_{11}NO_3$:

C, 66.35, H, 5.10, N, 6.45.

Found: C, 66.41, H, 5.20, N, 6.33. Satisfactory

N-Ethyl-5-(3,4-dichlorophenyl)-1,3(3H) Oxazine-2,6-Dione, 4.

m.p. 149-50° IR ($CDCl_3$), 1790(s), 1730(s), 1640(s), 1430(m), 1340(m), 1290(m), 1260(m),1220(m), 1150(m), 1130(m), 1080(m), 1090(m), 1025(m), 980(m), 820(m), cm^{-1}.

Pmr ($CDCl_3$, 60mz), δ 7.3 (m, 4H, aromatics, C4-H), 3.8 (quartet, 2H, N-CH_2) 1.4 (triplet, 3H, CH_3).

Anal. Calc. For $C_{12}H_9Cl_2NO_3$:

C, 50.37, H, 3.17, N, 4.90, Cl, 24.78.

Found: C, 50.42, H, 3.20, N, 4.82, Cl, 24.72. Satisfactory

Lead Reference

John H. MacMillan and Stephen S. Washburne, J. Heterocyclic Chemistry, Vol. 12, p 1215, (1975).

Other References

James D. Warren, John H. MacMillan and Stephen S. Washburne, J. Org. Chem., Vol 40, p 375 (1975).