Facile N-Methylation Reaction of Amide Functional Heterocycles with Dimethyl Sulfate; N-Methyl 4-(4-methylphenyl)-1,3(3H) oxazine-2,6-dione

SyntheticPage 529
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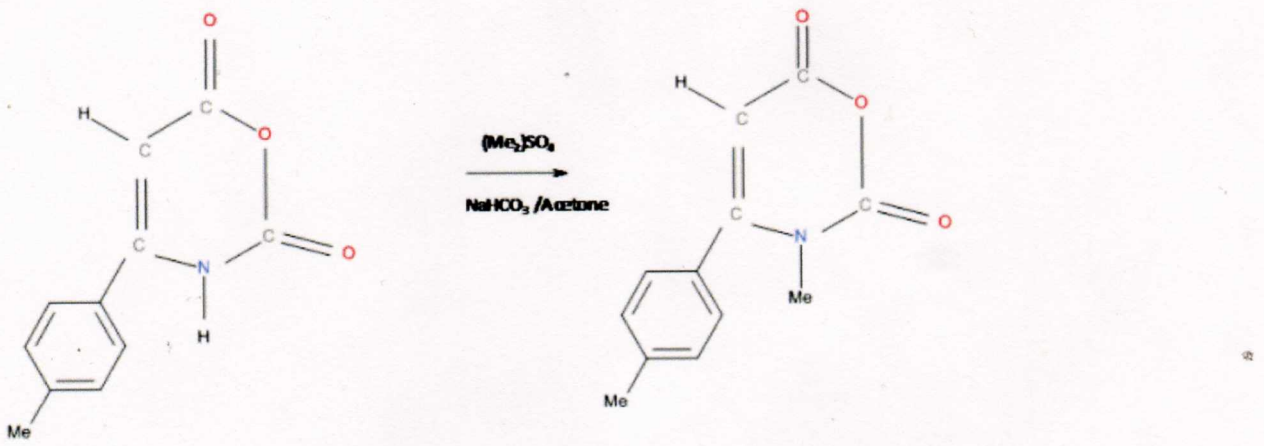
John MacMillan (john.macmillan@temple.edu)



Chemicals Used

4-(4-Methylphenyl)-1,3(3H) oxazine-2,6-dione, prepared from the reaction of p-methylphenyl maleic anhydride with trimethylsilyl azide,see James D. Warren, John H. MacMillan and Stephen S. Washburne, J. Org. Chem., Vol 40, p 375 (1975).
DOI: 10.1021/jo00894a016
Dimethyl sulfate,(99%, Sigma Aldrich)
Sodium bicarbonate (99.7%), A.C.S. Reagent, Sigma Aldrich)
Acetone (99.5%, A.C.S. Reagent, Sigma Aldrich)
Ethyl acetate (99.5%, A.C.S Spectrophtometric grade, Sigma Aldrich)
Hexane (99%, Sigma Aldrich)

Procedure

A 100 ml 3neck round bottom flask equipped with heating mantel, nitrogen inlet,water cooled dropping funnel, magntic stirrer and calcium chloride drying tube was charged with 2.4 g)(0012 mole) 4-(-Methylphenyl)-1,3(3H) oxazine-2,6-dione, 3.0 g (0.024 mole) dimethyl sulfate, 2.5 g sodium bicarbonate and 50 ml acetone. The mixture was heated to reflux under nitrogen and monitored by thin layer chromatography (silica gel, ethyl acetate eluent). After 20 hours reflux the spot corresponding to the starting material had disappeared and a single new spot with higher Rf value was prominent. The mixture was cooled to room temperature and the sodium carbonate fitered off under water aspirator pressure. The acetone was removed from the fitrate on a rotovap with water bath at 80° C and the residue taken up in 10 ml ethyl acetate. Hexane was added dropwise to the solution in an icebath to permanent turbidity. Suction filtration gave 1.38g, white crystals, mp 99-100° C. The filtrate was concentrated to half volume and the above procedure repeated, giving a second crop, mp 99-100° C. Total yield 1.72 g (66%).

Anal: Calc for $C_{12}H_{11}NO_3$ C 66.35 H 5.10 N 5.65

Found: C 66.41 H 5.20 N 6.33

Author's Comments

Caution! Dimethyl sulfate is toxic and carcinogenic. Weigh and manipulate in a fume hood. Wear latex gloves. Other runs of this N-alkylation reaction with p-methylphenyl maleic anhydride, and with other alkyl, halo and aryl substituted1,3(3H) oxazine-2,6-diones gave yields routinely in the 60-70% range. See lead refrerence and other references below.
Also see http://furlip.solidwebhost.com/Additional-unreportd-N-alkylated-oxauracils.htm
This reaction also N-ethylates 1,3(3H) oxazine-2,6-diones (oxauracils) with diethyl sulfate by the same synthetic procedure in yields of 50-70%. Uracils should readily mono and dialkylate in an analogous fashion.

Data

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}.

^1H NMR ($CDCl_3$, 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).

Lead Reference

James D. Warren, John H. MacMillan and Stephen S. Washburne, J. Org. Chem., Vol 40, p 375 (1975).
DOI: 10.1021/jo00894a016

Other References

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

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Supplementary Information

e.g. Actual NMR spectra (as images or jdx files for interactive spectra), photographs of apparatus, TLC's or crystals or videos. Please contact the ChemSpider team (ChemSpider-at-rsc.org) for help with this.
Additional unreportd N-Methyl-Oxauracils.doc
Keywords: aromatics/arenes, heterocyclic compounds, Methylation Alkylation, nucleosides, substitution