Nitrogen insertion reaction of maleic anhydrides; 2-H-1,3-oxazine-2,6(3H)dione

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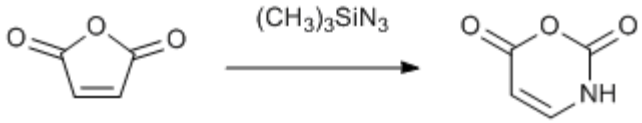

Chemicals Used

Trimethysilylazide (Sigma Aldrich),15,507-1, 95%
Maleic Anhydride, lump, (Sigma Aldrich), M18-8, freshly opened bottle. freshly ground briquettes
Ethanol, Absolute, absolute, 200 proof, (Sigma Aldrich) 45,984-4
Chloroform (Sigma Aldrich), 36,692-7, 99.9%, A.C.S. grade
Ethyl acetate (Sigma Aldrich), 31,990-2, 99.5%, A.C.S. reagent
Diethyl ether (Sigma Aldrich),17,926-4, 99%, A.C.S. reagent

Procedure

A 50 ml 3 neck round bottom flask, equipped with water condenser, water bath, stirring hot plate,dropping funnel, nitrogen inlet, magnetic stirrer, and calcium chloride drying tube, was charged under nitrogen with 4.90g (0.059 mole) maleic anhydride and 14ml (~ 0.1 mole) trimethylsilyl azide. A rubber tube exiting the water condenser lead to a one liter water filled inverted graduate cylinder in a water trough, allowing for easy monitoring of nitrogen evolution. Stirring was commenced and the solution was warmed to ~ 40^{o}C with the water bath, upon which the maleic anhydride dissolved. The reaction was gently exothermic at this point with gas evolution into the inverted graduate cylinder. External heating was discontinued. Gas evolution became moderate at ~ 55-60^{o}C. The mixture was alternatively heated and cooled with the water bath to maintain a temperature range of ~ 55-60^{o}C. After 3 h nitrogen gas evolution had ceased. The solution was cooled to room temperature in ice water and 30 ml chloroform was added with stirring. Addition of 2.5 ml absolute ethanol (0.054 mole) and cooling in an icebath to ~ 0^{o}C gave a copious white precipitate which TLC (silica gel, ethyl acetate eluent) showed to be essentially pure "oxauracil". The precipitate was suction filtered, and washed with diethyl ether, yielding 3.2 g (57%), of material. Mother liquor concentration gave a second crop, 1.2g (total 78%). The product is sufficiently pure for most purposes but may be recrystallized from ethyl acetate. Yields are typically in the 60-80% range.

Author's Comments

- Trimethlsilylazide is toxic and must always be handled in a fume hood. Never allow azide wastes to contact heavy metal, as explosive azide salts may result.
- I have found that unsubstituted parent "oxauracil" is especially sensitive to decomposition under basic conditions and to impurities in common reaction solvents. Therefore it is very important that glassware should be washed ,soaked in a mild acid bath, and oven dried prior to use. Glassware cleaned under basic conditions, such as with potassium hydroxide in ethanol, gave much lower yields.
- Maleic anhydride briquettes should always be ground from a freshly opened bottle. Anhydride can contain substantial maleic acid after prolonged storage, resulting in much lower yields. Maleic anhydride may be quickly purified by stirring the powder in methylene chloride. Maleic acid impurity will not dissolve. Filtration and evaporation of the solution on a rotory evaporator gives anhydride of sufficient purity for this synthesis.
- This solvent free procedure should also be applicable to syntheses with substituted maleic anhydrides (see other refereces).
- As this reaction is mildly exothermic with nitrogen evolution at point of full solution homogeneity, scaleup should be attempted in small increments, to determine the proper heating and cooling sequences. In our hands doubling the scale gave no problems with runaway gas evolution.

Data

m.p. 158-162^{o}C. The infrared and pmr spectra were in accord with the literature values (see other reference 2).

Lead Reference

John H. MacMillan, "Improved Procedure for the Preparation of "Oxauracil", 2H-1,3(3H)-Oxazine-2,6-Dione", Organic Preparations and Procedures Int. Vol 9, p 87, (1977).

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Other References

1) James D. Warren, John H. MacMillan and Stephen S. Washburne, "Synthesis of Substituted 2H-1,3-Oxazine-2,6-Diones by Reaction of Trimethylsilyl Azide with Maleic Anhydrides",

J.Org.Chem., Vol. 40, p 743, (1975).

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2)Stephen S. Washburne, W.R. Peterson and Dennis A Bermann, " Reaction of trimethylsilyl azide with anhydrides and imides. Uracil synthesis via nitrogen insertion"

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