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# CYCLOADDITIONS OF NON-STABILIZED AZOMETHINE YLIDES AND QUINONES

## SYNTHESIS OF THE *RENIERA* ISOINDOLE

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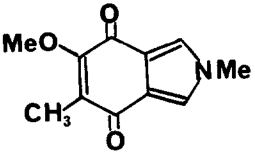
Azomethine ylides, generated from cyanomethylamino silanes and excess silver fluoride, undergo cycloaddition with quinones to give, after oxidation *in situ*, quinonoid isoindoles. This reaction provides the key step for a short, high yield synthesis of the *Reniera* isoindole **1a**.

Among the antimicrobial compounds isolated from the bright blue Mexican sponge, *Reniera* sp., Frincke and Faulkner found the first naturally occurring isoindole, 2,5-dimethyl-6-methoxy-4,7-dihydroisoindole-4,7-dione (**1a**).[1] Isoindole **1a** is active against *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio anguilarium*, and B-392, a marine psudomonal.



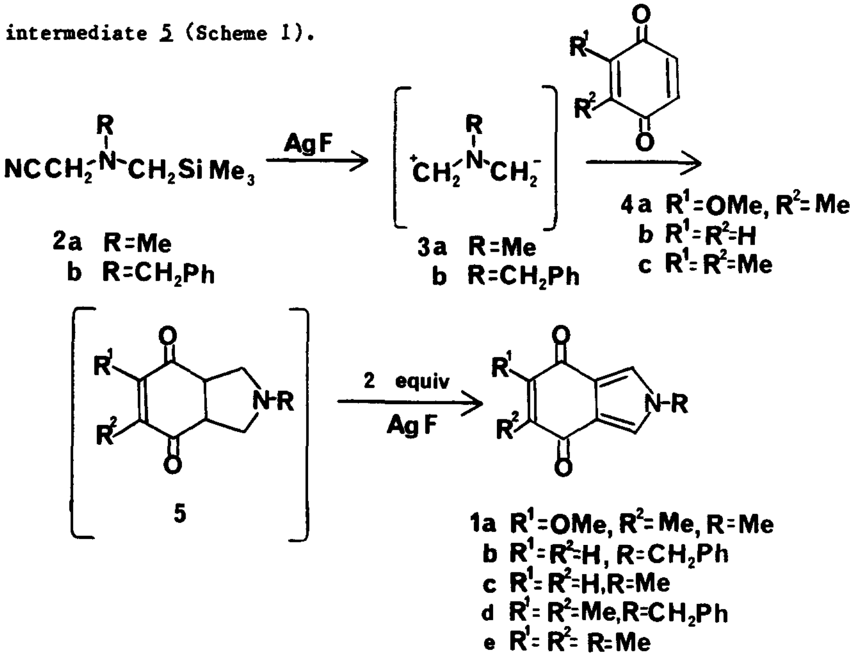
1a

The structure **1a** was assigned on the basis of a combination of ir, $^1$H NMR, and mass spectroscopy and confirmed by a 4-step synthesis (approx. 3% yield) from 3,4-dicarbomethoxy-1-methylpyrrole. We are now pleased to report the efficient synthesis of the *Reniera* isoindole **1a** by a short sequence based on a new conversion, the cycloaddition of a non-stabilized azomethine ylide and a quinone.

Substituted tetra-and dihydro pyrroles have been prepared by the addition of arylidene imines of $\alpha$-amino acid esters to electon-deficient olefins; this reaction is believed to proceed by way of stabilized methine ylides which undergo cycloaddition with dipolarophiles.[2] The synthesis of

1a by a strategy based on the cycloaddition of an azomethine ylide to a quinone[3], requires ylide 3a; however, until recently, non-stabilized ylides have been unavailable.

In 1983, Padwa and Chen[4] showed that non-stabilized azomethine ylides 3 could be generated from the reaction of cyanomethylamino silanes with silver fluoride. The investigation of the reaction of ylides 3 with quinones was initiated with the study of the reaction of the 2b[4] with 5 equivalents of silver fluoride in the presence of benzoquinone. A 60% yield of the quinonoid isoindole 1b was obtained directly. The reaction presumably proceeds *via* cycloaddition followed by oxidation of intermediate 5 (Scheme 1).



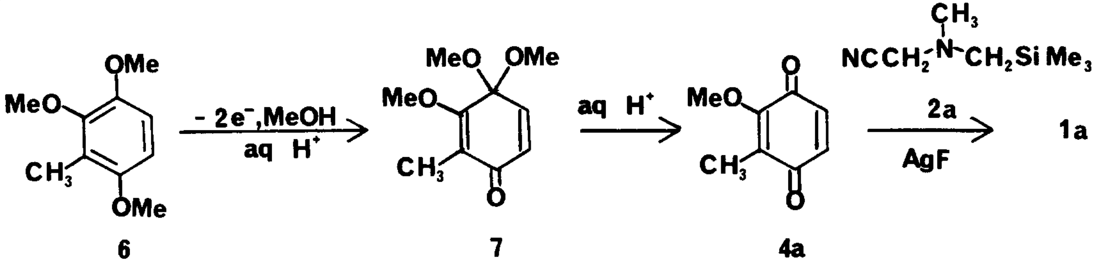
Scheme 1

Additional examples of quinonoid isoindoles prepared by this method are shown in Table I.

Table I-Conditions for Scheme 1[5] and Yields[6]

| Quinone | Ylide Precursor | AgF/$CH_3CN$ | Yield (mp) |
|---|---|---|---|
| 4b, (94 mg) | 2b (200 mg) | 550 mg/5 mL | 1b, 60% (170-171°) |
| 4b, (138 mg) | 2a (200 mg) | 800 mg/6 mL | 1c, 64% (161-162°) |
| 4c, (130 mg) | 2b(220 mg) | 600 mg/6 mL | 1d, 75% (159-160°) |
| 4c, (175 mg) | 2a (200 mg) | 800 mg/6 mL | 1e, 72% (161-162°) |
| 4a, (38 mg) | 2a (40 mg) | 160 mg/4 mL | 1a, 68% (160°, lit[1] 153-154°) |

For the last entry, the synthesis of the *Reniera* isoindole (see Scheme 2), we required N-methyl $\alpha$-cyanoamino silane 2a and quinone 4a. The azomethine ylide precursor 2a was prepared by alkylation of methyl amine with chloromethyltrimethylsilane followed by condensation with formaldehyde and potassium cyanide.[4] Quinone 4a was prepared by hydrolysis[7] of quinone monoacetal 7[8], readily available by application of Swenton's electrochemical oxidation sequence[9] to 1,2,4-trimethoxy-3-methylbenzene (6).[10] When aminosilane 2a was treated with 5 equivalents of silver fluoride in the presence of quinone 4a, the *Reniera* isoindole 1a was obtained in 68% yield [5,6] (see Table I).



Scheme 2

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3. The reaction of an arylidene imine of an $\alpha$-amino ester with naphthoquinone is referred to (but not described) by Grigg, (ref. 2a). Benzonitrile benzylide has been reported to add to quinones to give, after air oxidation, a variety of quinonoid diphenyl isoindoles: see Gilgen, P., Jackson, B., Hansen, H. J., Heimgartner, H.,and Schmid, H., *Helv. Chim. Acta.*, *1974*, *57*, 2634.

   For related annelations, see Myers, J. A., Moore, L. D., Whitter, W. L., Council, S. L., Waldo, R. M., Lanier, J. L., and Omoji, B. U., *J. Org. Chem.*, *1980*, *45*, 1202 and Parker, K. A., Cohen, I. D., and Babine, R. E., *Tetrahedron Lett.*, in press.

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5. After stirring in the dark at 25° for 10 hours, the reaction mixtures were filtered and concentrated. All products, purified by chromatography on silica gel with 20-40% ethyl acetate/hexane as eluent, were isolated as yellow solids.

6. Isoindole products 1b - 1e had satisfactory elemental analyses (C, H, N).

Spectroscopic data: IR ($cm^{-1}$, KBr), NMR ($\delta$, $CDCl_3$), uv (nm, MeOH)

1a: IR 1650; NMR (360MHz) 7.16 (d, J=2.0 Hz, 1H), 7.14 (d, J=2.0 Hz, 1H), 4.03 (s, 3H), 3.73 (s, 3H), 1.99 (s, 3H); uv 361 ( $\varepsilon$ 3,000), 273 (11,000), 232 (12,000).

1b: IR 1650; NMR (90MHz) 7.10-7.14 (m, 7H), 6.60 (s, 2H), 5.10 (s, 2H); uv 373 ( $\varepsilon$ 4,000), 242 (15,000), 226 (20,000).

1c: IR 1650; NMR (90MHz) 7.18 (s, 2H), 6.60 (s, 2H), 3.77 (s, 3H); uv 366 ( $\varepsilon$ 2,000), 262 (10,000), 225 (10,000).

1d: IR 1650; NMR (90MHz) 7.10-7.15 (m, 7H), 5.10 (s, 2H), 2.07 (s, 6H); uv 366 ($\varepsilon$ 2,900), 264 (11,000), 226 (19,000).

1e:IR 1650; NMR (90MHz) 7.19 (s, 2H), 3.77 (s, 3H), 2.07 (s, 6H); uv 366 ($\varepsilon$ 2000), 265, (10,500), 223 (10,000).

7. 2-Methyl-3,4,4-trimethoxycyclohexa-2,5-dienone (7)[8] (745 mg, 376 mmol) was stirred in a solution of oxalic acid (63 mg of dihydrate, 0.5 mmol) in 5mL of water and 15mL of THF for 15 hr. Extraction with ether, washing with aq $NaHCO_3$ and brine, drying, concentrating, and flash chromatography gave 517mg (90%) of an orange oil. IR (film) 2970, 1668, 1648, 1590 $cm^{-1}$, NMR 1.97 (s,3H), 4.07 (s,3H) 6.66 (d, J=11 Hz, 1H), 6.74 (d, J=11 Hz, 1H), $M^+$ 152.0468 (calc. for $C_8H_8O_3$: 152.0473).

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