

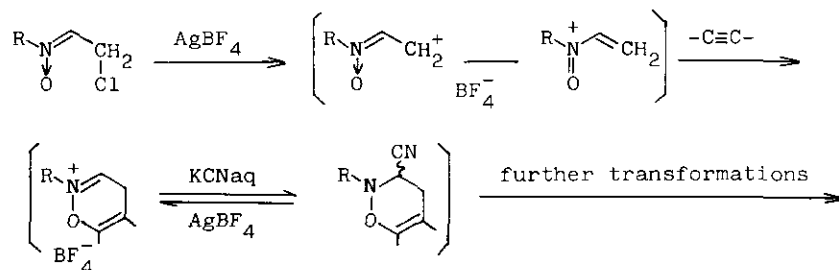
OXIDATIVE 1,4-DIPOLAR CYCLOADDITION OF QUINALDINE N-OXIDE
WITH DIMETHYL ACETYLENEDICARBOXYLATE¹

Kazuko Wada, Kazuhisa Funakoshi, Seitaro Saeki,
and Masatomo Hamana^{*2}

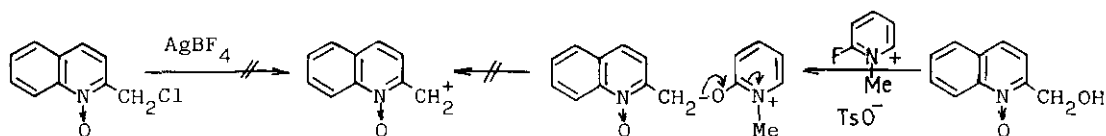
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

Abstract—Quinaldine N-Oxide undergoes oxidative 1,4-dipolar cycloaddition with dimethyl acetylenedicarboxylate upon treatment with $\text{Ti}(\text{OAc})_3$ in acetonitrile or with DDQ in benzene, giving dimethyl quino[1,2-b][1,2]oxazine-2,3-dicarboxylate.

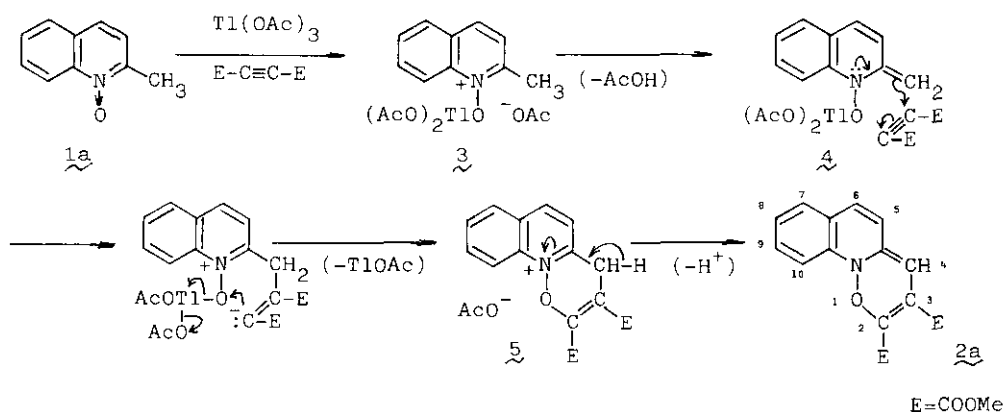
Eschenmoser and coworkers have reported on the extensive studies of the Ag^+ -induced 1,4-dipolar cycloaddition of α -chloroaldonitrone with olefinic and acetylenic compounds and the diverse transformations of cycloadducts thus formed as illustrated below by the reaction with acetylenes.^{3,4}



Since 2-chloromethylquinoline N-oxide⁵ can be regarded as an aromatic analogue of α -chloroaldonitrone, the reaction with dimethyl acetylenedicarboxylate (DMAD) in the presence of AgBF_4 was examined under several conditions, but even precipitation of AgCl was not noticed at all and the N-oxide was recovered. The reaction of 2-hydroxymethylquinoline N-oxide⁵ with DMAD in the presence of 2-fluoro-1-methylpyridinium tosylate,⁶ a powerful dehydrating agent, was also tried, but no definite product was obtained in this case, either.



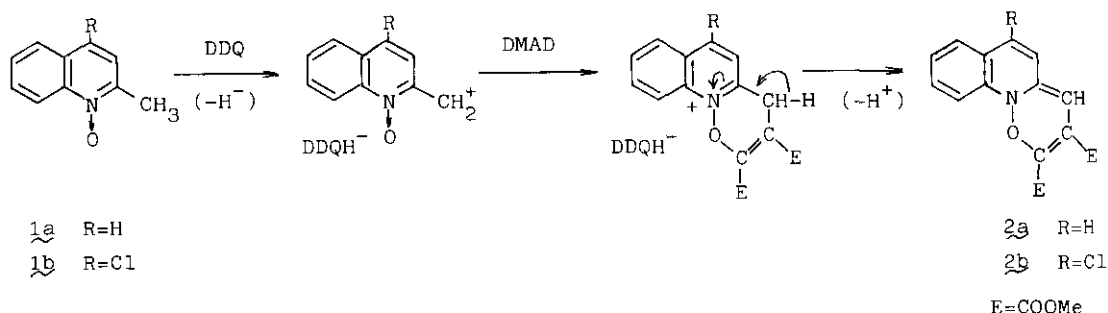
However, during the course of an investigation of electrophilic reaction of an anhydro base⁷ derived from quinaldine N-oxide (1a) and thallium triacetate $\text{Tl}(\text{OAc})_3$, we happened to find that treatment of 1a with DMAD in the presence of $\text{Tl}(\text{OAc})_3$ afforded a cycloaddition product (2a). Thus, one equivalent of $\text{Tl}(\text{OAc})_3$ was added to a solution of 1a in acetonitrile and the mixture was exposed to ultrasonic waves for 40 min in order to divide insoluble $\text{Tl}(\text{OAc})_3$ in fine powder.⁸ Then, a solution of DMAD (1 equiv.) in acetonitrile was added dropwise, and the reactants were stirred at room temperature for 16 h to give dimethyl quino[1,2-b][1,2]oxazine-2,3-dicarboxylate (2a), colorless prisms, mp 141–142°C(dec.), in 20.5% yield. Heating of the reactants or a prolonged reaction time was unfavorable because of causing decomposition of DMAD. Apparently, the reaction was accompanied by the one-stage oxidation and may be visualized by the following course, although the details of the mechanism are not yet clear.



Thallium triacetate adds first to 1a to give an adduct (3), which is then converted to an anhydro base (4).⁷ The C-C bond formation between 4 and DMAD is brought about by the enamine-like polarization of 4, and the consecutive or the concerted C-O bond formation with liberation of TlOAc leads to a cycloadduct (5), which loses a proton to give the product 2a.

Subsequently, reactions using dichlorodicyano-p-benzoquinone (DDQ) as an oxidant were investigated. When a solution of 1a, DMAD (1 equiv.) and DDQ (1.2 equiv.)

in benzene was stirred at room temperature for 16 h, **2a** was obtained in 19.3% yield. A similar reaction of 4-chloroquinaldine N-oxide (**1b**) also gave the cycloaddition product (**2b**) in a lower yield of 7.9%. These reactions should be considered to follow an alternate process, and appear to be initiated by abstraction of a hydride anion from the 2-methyl group by DDQ.



Further studies are in progress to optimize the reaction conditions and extend the scope of this novel type reaction.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a JASCO A-202 spectrophotometer. ^1H -NMR spectra were measured with a JEOL JNM-PS-100 spectrometer at 100 MHz using TMS as an internal reference. Mass spectra were obtained on a JMS-01SG spectrometer. Ultrasonic treatment was made by Ultrasonic Cleaner CA-3380. Thin layer chromatography was performed on plates of silica gel (Kiesel-gel 60 PF₂₅₄, Merck).

Reaction of Quinaldine N-Oxide (**1a**) with Dimethyl Acetylenedicarboxylate (DMAD)

1) $\text{Ti}(\text{OAc})_3$ (1.2 g) was added to a solution of **1a** (518 mg) in MeCN (4 ml) and the mixture was exposed to ultrasonic waves for 40 min. A solution of DMAD (475 mg) in MeCN (2 ml) was added, and the reactants were stirred at room temperature for 16 h. A precipitate was filtered, the filtrate was concentrated under reduced pressure and the residue was subjected to preparative TLC with hexane-AcOEt (3:1) to give 200 mg (20.5%) of dimethyl quino[1,2-*b*][1,2]oxazine-2,3-dicarboxylate (**2a**), colorless prisms, mp 141-142°C (dec.) (acetone-hexane). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.22; H, 4.40; N, 4.51. MS m/z : 299 (M^+). $\text{IR}_{\text{max}}^{\text{Nujol}} \text{cm}^{-1}$: 1760, 1730, 1715 (C=O), 1635 (C=C), 1220, 1250, 1275 (-O-). ^1H -NMR(CDCl_3) δ : 3.82 (3H, s, CH_3), 3.86 (3H, s, CH_3), 7.48 (1H, d, $J_{5,6}=8$ Hz, H_5),

7.6-8.0 (4H, m, H₇₋₁₀), 7.91 (1H, s, H₄), 8.17 (1H, d, J_{5,6}=8 Hz, H₆).

2) A solution of 1a (535 mg), DMAD (570 mg) and DDQ (800 mg) in benzene (20 ml) was stirred at room temperature for 16 h. A precipitate was filtered, the filtrate was concentrated under reduced pressure and the residue was subjected to preparative TLC with benzene-acetone (4:1) to give 194 mg (19.3%) of 2a.

Reaction of 4-Chloroquinoline N-Oxide (1b) with DMAD — A solution of 1b (485 mg), DMAD (360 mg) and DDQ (680 mg) in benzene (30 ml) was stirred at room temperature for 16 h. The reaction mixture was worked up in the same way to give 66 mg (7.9%) of dimethyl 6-chloroquino[1,2-b][1,2]oxazine-2,3-dicarboxylate (2b), colorless prisms, mp 158.5-161°C (dec.) (EtOH). Anal. Calcd for C₁₆H₁₂ClNO₅: C, 57.58; H, 3.62; N, 4.20. Found: C, 57.52; H, 3.68; N, 4.09. MS m/z: 333 (M⁺). IR_{max}^{Nujol} cm⁻¹: 1760, 1730, 1715 (C=O), 1630 (C=C), 1220, 1240 (-O-). ¹H-NMR(CDCl₃) δ: 3.82 (3H, s, CH₃), 3.87 (3H, s, CH₃), 7.60 (1H, s, H₅), 7.6-8.2 (4H, m, H₇₋₁₀), 7.84 (1H, s, H₄).

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8. Omitting of this procedure resulted in the recovery of 1a.

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