THE REACTION OF 3-BROMO-4-METHOXYQUINOLINE 1-OXIDE WITH DIMETHYL ACETYLENEDICARBOXYLATE

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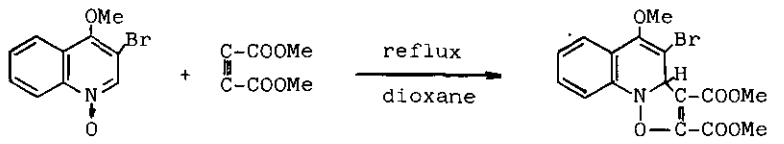
Abstract —— 3-Bromo-4-methoxyquinoline 1-oxide (1) reacts with dimethyl acetylenedicarboxylate (DMAD) at room temperature in dioxane, CH_2Cl_2, MeCN or DMF to give α-[N-(3-bromo-4-methoxyquinolinium)]-α,β-bismethoxycarbonyl-β-oxo-ethylide (2) and methyl 2-(3-bromo-4-methoxyquinoline)-acetate (4). On the other hand, heating 1 with DMAD in dioxane or DMF affords dimethyl α-[N-(3-bromo-4-oxo-1,4-dihydroquinolyl)]-β-methoxyfumalate (3) as the predominant product, which is proved to be formed by thermal rearrangement of 2.

Previously, we isolated colorless prisms of mp 188-192°C from the reaction of 3-bromo-4-methoxyquinoline 1-oxide (1) with dimethyl acetylenedicarboxylate (DMAD) in boiling dioxane, and assigned a 1,2-dihydroquinoline structure (A) principally based on the elemental analyses and the MS and PMR spectroscopies.[2,3] However, it



1 DMAD A

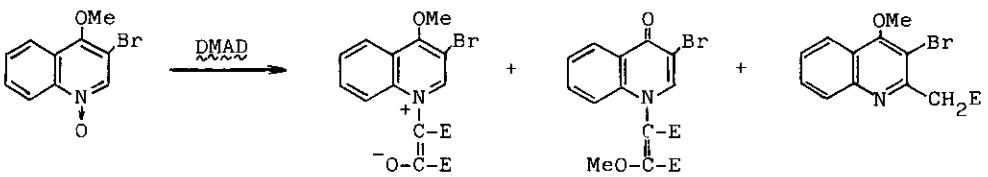
was recently found that its ^{13}C NMR spectrum does not show any signals due to methine-carbon. This finding prompted us to re-examine the reaction in some detail, and it was disclosed that the reaction of 1 with DMAD affords three products,

that is, α-[N-(3-bromo-4-methoxyquinolinium)]-α,β-bismethoxycarbonyl-β-oxo-ethylide (2: orange needles), dimethyl α-[N-(3-bromo-4-oxo-1,4-dihydroquinolyl)]-β-methoxy-fumalate (3: colorless prisms, mp 191-191.5°C) and methyl 2-(3-bromo-4-methoxy-quinoline)acetate [4: colorless prisms, mp 276-278°C (decomp.)], and that the previously reported product is not the 1,2-dihydroquinoline A, i.e., the primary cycloadduct, but a novel rearrangement product 3.

According to the procedure reported previously, 1 was first treated with DMAD (1.2 equiv.) for 1 h in boiling dioxane, and the mixture of products was carefully chromatographed on silica gel to give 2, 3 and 4 in 19.3, 44.8 and 18.2% yields, respectively.

Subsequently, various conditions were examined and the results listed in Table were obtained.

Table. The Reaction of 3-Bromo-4-methoxyquinoline 1-Oxide (1) with Dimethyl Acetylenedicarboxylate (DMAD)



1 2 3 4

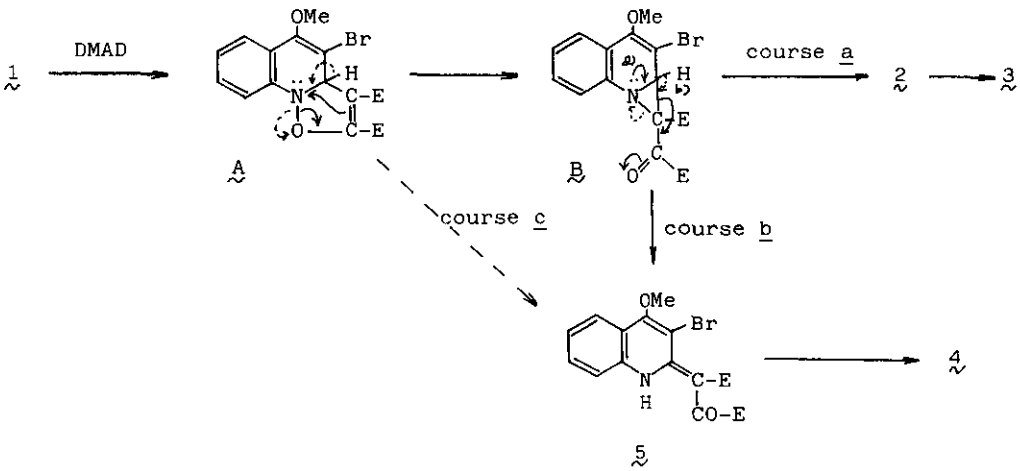
Solvent	Reaction		Product, Yield (%)		
	temp.	time (h)	2	3	4
dioxane	r.t.	12	59.0	---	11.7
dioxane	101°	1	19.3	44.8	18.2
CH_2Cl_2	r.t.	12	51.3	---	8.2
MeCN	r.t.	12	71.8	---	13.1
MeCN	80°	1	46.2	---	16.4
DMF	r.t.	12	46.2	---	24.6
DMF	100°	1	---	50.0	16.4

Product 4 was formed as a minor one under all the conditions employed. In reactions conducted below 100°C, the main product was always 2, no formation of 3 being noticed at all. On the other hand, yield of 2 substantially decreased and 3 was predominantly yielded when the reaction temperature was raised to ca. 100°C;

nevertheless, 3 was curiously not formed at all in the reaction at 80°C in MeCN. Product 2 was rather unstable and could not be recrystallized from the usual solvent because of partial conversion to 3. Furthermore, 2 was quantitatively transformed into 3 upon direct melting or heating at 100°C in DMF. These observations evidently demonstrate that 3 is produced by thermal rearrangement of 2.

The structure assignments of the products were based on elemental analyses, and the IR and PMR spectroscopies.[4-6] Further, the structure of 3 was unambiguously established by an X-ray diffraction study.[7] Apparently, the product previously reported as A should be corrected as 3.

An acceptable mechanistic interpretation of the reaction is formulated below. The primary cycloadduct A initially formed is not stable enough to be isolated and readily converts to an aziridine intermediate (B)[8,9] which isomerizes to 2, and 2 undergoes thermal rearrangement to give 3 (course a). The concerted loss of the α-proton with a C-N bond fission in B (course b) produces a 2-substituted quinoline (5) which loses a methoxalyl group to give 4, although the details of the elimination process of methoxalyl group is not clear.



According to the recent observations on the 1,3-dipolar cycloaddition of aromatic N-oxides of pyridine series[9,10], the direct transformation of the primary cycloadduct A to 5 (course c) appears unlikely. Taking account of the fact that N-substituted products, 2 or/and 3, were produced predominantly in all the reactions, it seems most probable that the intermediate B is the common and key species in the above reactions.

Details of this work and further studies on the reaction of other 3,4-disubstituted quinoline 1-oxides will be published shortly.

ACKNOWLEDGEMENT

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4. 2, orange needles. IR (Nujol) cm^{-1} : 1670, 1740 (C=O). PMR ($CDCl_3$) δ : 3.63 (3H, s, $COOCH_3$), 3.93 (3H, s, $COOCH_3$), 4.52 (3H, s, 4-OCH_3), 7.68-8.38 (4H, m, Ar-H), 8.90 (1H, s, C_2-H).
5. 3, colorless prisms, mp 191-191.5°C. IR (Nujol) cm^{-1} : 1710, 1750 (C=O). PMR ($CDCl_3$) δ : 3.68 (3H, s, $COOCH_3$), 3.82 (3H, s, $COOCH_3$), 4.06 (3H, s, 4-OCH_3), 7.04-7.72 (3H, m, Ar-H), 7.80 (1H, s, C_2-H), 8.45 (1H, dd, $J_{5,6}$=8 Hz, $J_{5,7}$=2 Hz, C_5-H).
6. 4, colorless needles, mp 106-107°C (decomp.). IR (Nujol) cm^{-1} : 1735 (C=O). PMR ($CDCl_3$) δ : 3.74 (3H, s, $COOCH_3$), 4.08 (3H, s, 4-OCH_3), 4.24 (2H, s, CH_2), 7.40-8.12 (4H, m, Ar-H).
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