

REACTION OF N-ALKYLHETEROAROMATIC CATION WITH PHOSPHITE

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Abstract — Treatment of N-methylquinolinium iodide (1) with trimethyl phosphite afforded dimethyl N-methyl-1,4-dihydroquinoline-4-phosphonate (3), whereas when 1 was treated with dimethyl sodiophosphonate, dimethyl N-methyl-1,2-dihydroquinoline-2-phosphonate (2) was obtained.

The 2-phosphonate (2) underwent thermal rearrangement to the more stable 4-phosphonate (3). Similar results were obtained with some analogous heteroaromatics.

Redmore reported that dialkyl phosphonate anions add to N-alkyl quaternary salts of heteroaromatics, giving dialkyl α - or γ -phosphonate of the corresponding dihydroheteroaromatics.¹ Similar results were also obtained from reactions of N-acyl salts of heteroaromatics with trialkyl phosphites.² In recent years Akiba and his co-workers have developed a general synthesis of these types of phosphonate by treatment of N-acyl salts of heteroaromatics with trialkyl phosphites and sodium iodide in acetonitrile (MeCN).³ We investigated reactions of various N-acylbenzo-[f]quinolinium chlorides with trimethyl phosphite under these conditions, which gave rise to a mixture of the α - and γ -phosphonates in each case.⁴

As an extension of this work, we carried out the phosphonylation of N-methylquinolinium iodide and some analogues, and found that the α - or γ -phosphonates are selectively obtainable upon the reaction conditions and α -phosphonates undergo thermal rearrangement to γ -isomers.

Reactions of N-methylquinolinium iodide (1) with trimethyl phosphite and sodium iodide in MeCN (Conditions A) at 30° or 40°C gave the corresponding γ -phosphonate (3) as the sole product (Table I, entry 1, 2 and 4) or accompanied with a very small amount of the α -phosphonate (2) (Table I, entry 3). From the reaction at 40°C for 30 min, 3 was obtained in 52% yield (Table I, entry 4). On the other hand, when 1 was treated with dimethyl sodiophosphonate at 30°C for 15 min in a mixture of MeCN and benzene (10:1) (Conditions B), only the α -phosphonate (2) was

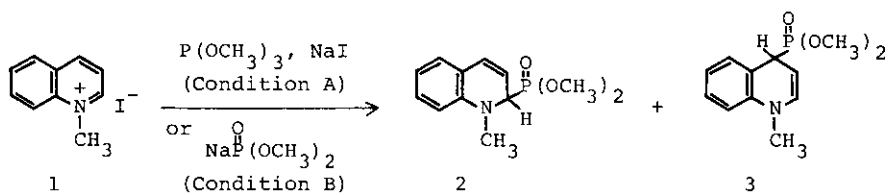


Table I. The Reaction of N-Methylquinolinium Iodide (1) with Phosphite

Entry	Condition	Solvent	Temp (°C)	Time	Yield (%)	
					(<u>2</u>)	(<u>3</u>)
1	A	CH ₃ CN	30	5 min	—	4.7
2	A	CH ₃ CN	40	5 min	—	11.8
3	A	CH ₃ CN	40	10 min	0.8	15.7
4	A	CH ₃ CN	40	30 min	—	52
5	B	CH ₃ CN-C ₆ H ₆ (10:1)	30	15 min	57	—
6	B	CH ₃ CN-C ₆ H ₆ (10:1)	75	2 h	24.4	36.6
7	B	CH ₃ CN-C ₆ H ₆ (10:1)	75	15 h	—	47
8	B	DMF	75	1 h	—	24
9	B	C ₆ H ₆	75	2 h	44	15

Table II. The Reaction of N-Methylheteroaromatic Cations with Phosphite

Entry	Methiodide	Condition	Solvent	Temp (°C)	Time	Yield (%)	
						α-Phos- phonate	γ-Phos- phonate
	Benzo[<i>f</i>]quinoline Methiodide (<u>4</u>)					(<u>5</u>)	(<u>6</u>)
10		A	CH ₃ CN	50	30 h	—	15
11		B	CH ₃ CN-C ₆ H ₆ (10:1)	5	10 min	66.5	5.5
12		B	CH ₃ CN-C ₆ H ₆ (10:1)	75	30 min	—	79
	Benzo[<i>h</i>]quinoline Methiodide (<u>7</u>)					(<u>8</u>)	(<u>9</u>)
13		A	CH ₃ CN	50	1 h	—	30
14		B	CH ₃ CN-C ₆ H ₆ (10:1)	5	10 min	79	—
15		B	CH ₃ CN-C ₆ H ₆ (10:1)	75	2 h	69	trace
	1,7-Phenanthroline 7-Methiodide (<u>10</u>)					(<u>11</u>)	(<u>12</u>)
16		A	CH ₃ CN	50	20 h	—	77
17		B	CH ₃ CN-C ₆ H ₆ (10:1)	10	10 min	89	—
18		B	CH ₃ CN-C ₆ H ₆ (10:1)	75	1 h	—	72
	1,5-Naphthyridine 1-Methiodide (<u>13</u>)					(<u>14</u>)	(<u>15</u>)
19		A	CH ₃ CN	50	1 h	—	21
20		B	C ₆ H ₆	75	2 h	30	—
	1,8-Naphthyridine 1-Methiodide (<u>16</u>)					(<u>17</u>)	(<u>18</u>)
21		A	CH ₃ CN	50	1 h	—	65
22		B	C ₆ H ₆	75	2 h	43	—

afforded in 57% yield, the γ -isomer (3) being not detected (Table I, entry 5). However interestingly, it was disclosed that, when the reaction was conducted at 75°C, the γ -phosphonate (3) was preferentially formed; the reaction for 2 h gave 2 and 3 in 24.4 and 36.6% yields, respectively, and only 3 was obtained in 47% yield from the reaction for 15 h (Table I, entry 6 and 7). Further the reaction at 75°C in DMF or benzene was explored (Table I, entry 8 and 9). These observations suggest the possibility of a thermal rearrangement of 2 to the more stable 3. This was confirmed by the fact that 2 was converted into 3 in 45% yield upon warming at 75°C for 2 h in MeCN. Apparently such rearrangement is affected by polarity of solvents, and the ease of the rearrangement follows the order: DMF > MeCN > benzene (Table I, entry 6, 8 and 9). Comparable rearrangements were already documented for the reaction of *N*-methyl-3-cyanopyridinium iodide or *N*-methylquinolinium iodide with methoxide⁵ and cyanide ions⁶. However, this type of rearrangement of phosphonyl group seems to have no precedent.

Subsequently we explored the reactions of methiodide of benzo[*f*]quinoline (4), benzo[*h*]quinoline (7), 1,7-phenanthroline (7-methiodide, 10), 1,5- (13) and 1,8-naphthyridine (16) under similar conditions and obtained results summarized in Table II. Yields were fairly varied, but the correlation of regioselectivity with the reaction conditions held for all systems; γ -phosphonate (6, 9, 12, 15 and 18) or α -phosphonates (5, 8, 11, 14 and 17) were selectively obtained under the conditions A or B, respectively. The thermal rearrangement of the α -phosphonate to the γ -isomer occurred also in the derivatives of 4, 7 and 10, though we did not explore the possibility in the naphthyridine systems (13 and 16). The ease of rearrangement for the heteroaromatics studied was benzo[*f*]quinoline (4) > 1,7-phenanthroline (10) > quinoline (1) > benzo[*h*]quinoline (7); the γ -phosphonate (6) was formed, though as a minor product, even in the reaction of 4 at 5°C for 10 min under the conditions B (Table II, entry 11), whereas the reaction of 7 at 75°C for 2 h under the same conditions gave the α -phosphonate (8) as the main product (69%) accompanied with only a trace of the γ -isomer (9) (Table II, entry 15).

The structures of products were confirmed by spectral examinations. Particularly the values of coupling constants, J_{PCH} , in ¹H-NMR spectra are very informative for differentiation between α - and γ -phosphonates; the former constants are apprecia-

billy smaller (ca. 15-21 Hz) as compared with the latter ones (ca. 24-30 Hz).^{3,4,7} Thus, for example, 2 and 3 were assigned by the J_{PCH} values, 10.0 and 24.8 Hz, respectively.⁸

A typical procedure of the reaction as follows:

Condition A — *N*-Methylquinolinium iodide (0.01 mol) was added to dry CH_3CN (30 ml) at 0°C, the mixture was stirred for 10 min, and trimethyl phosphite (0.011 mol) and NaI (0.014 mol) were added successively at 0°C. The mixture was stirred at 40°C for 30 min. After cooling, water (60 ml) was added and the aqueous solution was extracted with benzene (2 X 30 ml). The extract was evaporated to afford an unstable colorless oil 3⁹ (52%).

Condition B — *N*-Methylquinolinium iodide (0.01 mol) was added to a solution of dimethyl sodiophosphonate [derived from dimethyl phosphite (0.015 mol) and 60% NaH (0.014 mol)] in benzene (4 ml), and CH_3CN (40 ml). The mixture was stirred at 30°C for 15 min. After cooling, water (80 ml) was added and the aqueous solution was extracted with benzene (2 X 40 ml). The extract was evaporated. The crude product was washed with petroleum ether to afford an unstable colorless oil 2¹⁰ (57%).

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8. The J_{PCH} values in the *N*-alkyl α -phosphonates are smaller than the *N*-acyl α -phosphonates.
9. 3: ¹H-NMR (CDCl_3) δ : 4.10 (1H, dd, $J=24.0$ Hz, PCH, 5.6 Hz), 4.50 (1H, m, PCCH), 6.07 (1H, dd, $J=8.0, 6.8$ Hz, PCCCH), 3.58, 3.65 (6H, d, $J=10.8$ Hz, P(OMe)_2), 6.59-7.28 (4H, aromatic protons), 3.03 (3H, d, $J=2.0$ Hz, N-Me). MS m/e : 253 (M^+), 144 (M^+-109).
10. 2: ¹H-NMR (CDCl_3) δ : 4.44 (1H, dd, $J=10.0$ Hz, PCH, 6.0 Hz), 5.65 (1H, m, PCCH), 6.46 (1H, dd, $J=(\text{overlapped})$, PCCCH), 3.55, 3.63 (6H, d, $J=10.4$ Hz, P(OMe)_2), 6.44-7.22 (4H, aromatic protons), 2.92 (3H, d, $J=2.0$ Hz, N-Me). MS m/e : 253 (M^+), 144 (M^+-109).

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