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REGIOSELECTIVE SYNTHESIS OF 4-ALKYLQUINOLINES FROM QUINOLINE VIA 1-ETHOXYCARBONYL-1, 2-DIHYDROQUINOLINE-2-PHOSPHONATES

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Abstract : 1-Ethoxycarbonyl-1, 2-dihydroquinoline-2-phosphonates (3) were treated with n-butyllithium followed by alkyl halides to afford the corresponding 4-alkylated phosphonates (7) with complete regioselectivity in 67-97% yields. The phosphonates (7) were converted to 4-alkylquinolines (8) in ca. 50% yields by treatment with sodium iodide in HMPA or by alkaline hydrolysis in aqueous ethanol.

Considerable efforts have been paid to introduce substituents directly to 4-position of pyridine and quinoline, it is only quite recent that successful and easily applicable methods were reported on pyridine by us and by Katritzky's group, i.e., i) synthesis of diisopropyl 1-ethoxycarbonyl-1, 4-dihydropyridine-4-phosphonate and its alkylation, [1] ii) reaction of N-ethoxycarbonylpyridinium chloride and $RCu \cdot BF_3$, [2] iii) synthesis of pyridiniopyridone and its alkylation.[3] However, there is no successful report on regioselective introduction of substituents to 4-position of quinoline, starting from quinoline or its N-oxide.[4] Here we report the first example of such an approach starting from quinoline itself.

First, we tried to prepare 1, 4-dihydroquinoline-4-phosphonate (2) selectively by using trialkyl phosphites with bulky groups analogously to the case of pyridine.[1, 5] However, the reaction of the quinolinium salt (1) with trialkyl phosphites gave only 1-ethoxycarbonyl-1, 2-dihydroquinoline-2-phosphonates (3) in high yields irrespective of bulkiness of the alkyl group and the presence of 2 was not detected by ^1H NMR and TLC.[6] The results are shown in Table 1.

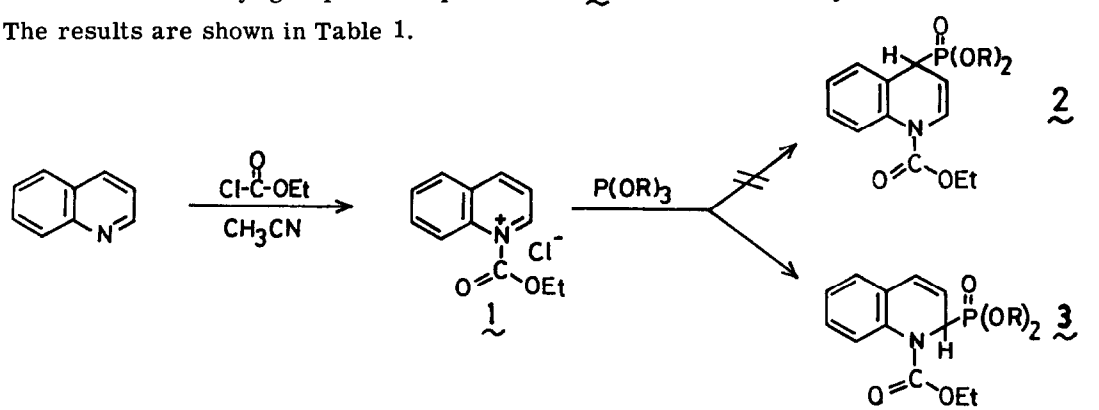

Table 1 Yields of 1-ethoxycarbonyl-1, 2-dihydroquinoline-2-phosphonates (3)

Compound 3[a]	R	Yield (%)[b]	bp (°C / mmHg)
3a	CH_3-	85	180 / 0.25
3b	C_2H_5-	97	190 / 0.25
3c	$(CH_3)_2CH$-	98	220 / 0.50

a) Satisfactory IR, ^{1}H NMR, and MS data were obtained for these compounds.[6a] b) Isolated yields by Kugel-Rohr distillation. c) 3c gave correct elemental analyses, but 3a and 3b gave correct results only when ca. 0.25 mole of water is assumed to be contained since these compounds are hygroscopic.

When 3 was treated with an equimolar amount of n-butyllithium in tetrahydrofuran at -78 °C under nitrogen and quenched with deuteroxide, the corresponding 2-deuterated phosphonate was recovered quantitatively.[6b] However, to our great surprise, when alkylation of the anion (4b) thus generated was tried with benzyl bromide at -20 °C and quenched with water at the same temperature, the expected 2-benzylated phosphonate (5b-y : R=Et, R'=CH_2Ph) was not obtained at all, but 4-benzylated phosphonate (6b-y : R=Et, R'=CH_2Ph) was obtained exclusively in a 94% yield.[6c] On the other hand, a mixture of 6b-y and 7b-y (R=Et, R'=CH_2Ph) was obtained when the reaction mixture was stirred at 0 °C for 15 min and then quenched with water. Fortunately, 7b-y was the sole product in a 93% yield when the reaction mixture was stirred at room temperature for one hour[6d] and this was confirmed repeatedly by using 0.90, 1.10, and 1.20 molar amounts of n-butyllithium under otherwise the same conditions.

In order to test steric effect of the alkyl group of the phosphonates (3) on regioselectivity of the alkylation, all 3 were alkylated in a similar manner to afford 4-alkylated phosphonates (7) with complete selectivity and reaction scheme and the results are shown in the next page.

The final stage of the synthesis of 4-alkylquinolines is elimination of the ethoxycarbonyl and the phosphonyl groups. This was carried out on 7b by the following two procedure : i) Method A, 7b was heated with 1.2 equivalents of sodium iodide in HMPA at 160-180 °C for 15-60 min to give 4-alkylquinolines (8) in ca. 50% yields ; ii) Method B, 7b was heated with sodium hydroxide in aqueous ethanol at 80 °C for 60 min to afford 4-alkylquinolines (8) also in ca. 50% yields. Some of the results are summarized in Table 3.

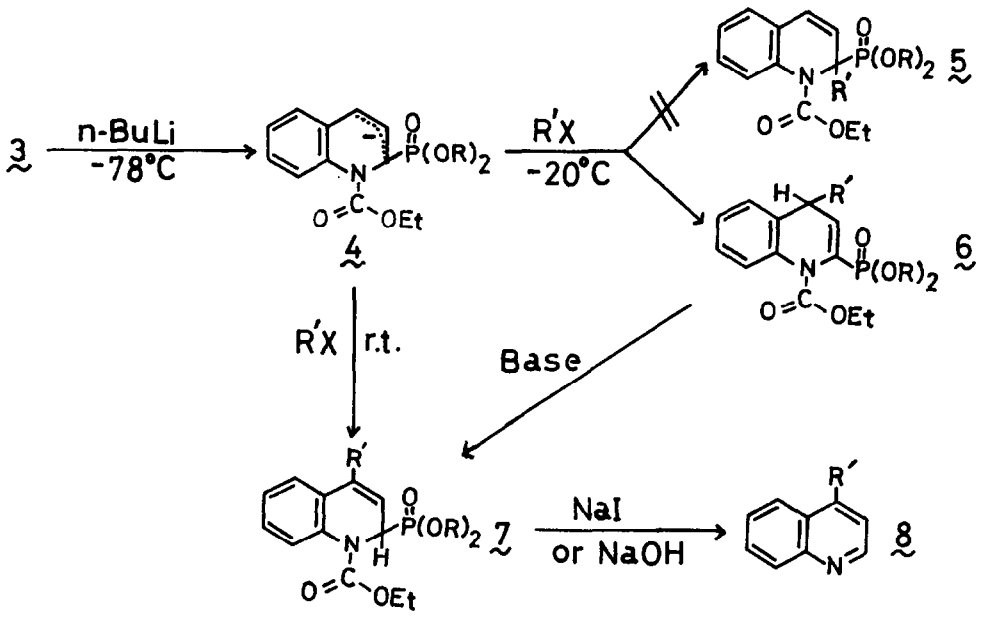

Table 2 Yields of 4-Alkyl-1-ethoxycarbonyl-1, 2-dihydroquinoline-2-phosphonates (7)

R	R'X	Yield (%)[a]	bp (°C / mmHg)[b]
a) CH_3-	i) $PhCH_2Br$	97	
b) C_2H_5-	i) CH_3I	87	200 / 0.65
	ii) C_2H_5I	92	
	iii) $(CH_3)_2CHI$	67	
	iv) $CH_2=CH-CH_2Br$	92	
	v) $PhCH_2Br$	93[c]	235 / 0.1
c) $(CH_3)_2CH$-	i) CH_3I	93	205 / 0.5
	ii) C_2H_5I	77	
	iii) $CH_3CH_2CH_2CH_2Br$	92	

a) The extract from the reaction mixture was pure by ^1H NMR without purification. b) Kugel-Rohr distillation. c) This compound has been fully characterized by IR, ^1H NMR, MS and elemental analyses data.

Table 3 Yields of 4-Alkylquinolines (8)[a]

R'	Yield (%)[b] Method A	Method B
i) CH_3-	48	53
ii) C_2H_5-	56	52
iv) CH_2=CH-CH_2-	47[c]	60[c]
v) $PhCH_2$-	57	53

a) These compounds were identified by IR, ^{1}H NMR and MS, or comparison with authentic samples. b) The extract from the reaction mixture was pure by ^{1}H NMR without purification. c)  was obtained via isomerization.

In summary, we have presented a novel and unexpected method for regioselective synthesis of 4-alkylquinolines from quinoline itself, and that the lithium salt (4) is protonated at 2-position and is alkylated at 4-position with complete selectivity and it is also noteworthy here that 4 reacts with aldehydes at 2-position during Wittig-Horner reaction.[7]

References and Notes

1) K. Akiba, H. Matsuoka, and M. Wada, Tetrahedron Lett., 22, 4093 (1981) and references cited therein. 2) K. Akiba, Y. Iseki, and M. Wada, ibid., in press. 3) A. R. Katritzky, H. Beltrami, J. G. Keay, D. N. Rogers, M. P. Sammes, C. W. G. Leung, and C. M. Lee, Angew. Chem. Intern. Ed., 18, 792 (1979) ; A. R. Katritzky, J. G. Keay, and M. P. Sammes, J. C. S. Perkin I, 1981, 668. 4) Regioselective introduction of substituents to 2-position of quinoline has been studied extensively : i) via Reissert compounds, F. D. Popp in " Advances in Heterocyclic Chemistry " ed. by A. R. Katritzky and J. A. Boulton, Academic Press, New York, 1968, Vol. 9, p 1. ii) via N-oxide, M. M. Yousif, S. Saeki, and M. Hamana, J. Heterocyclic Chem., 17, 102, 305 (1980) and references cited therein. 5) K. Akiba, Y. Negishi, and N. Inamoto, Synthesis, 1979, 55. 6) Structures of 3, 6, and 7 were fully confirmed by comparison of the following data and also by a series of reactions leading to the formation of 4-alkylquinolines. (a) ^{1}H NMR of 3b (CCl_4): δ 0.99 (t, 3H, J=7 Hz), 1.17 (t, 3H, J=7 Hz), 1.33 (t, 3H, J=8 Hz), 3.50-4.15 (m, 4H), 4.25 (q, 2H, J=7 Hz), 5.47 (dd, 1H, J_{PCH}=20 Hz, J=6 Hz, 2-H), 6.00 (ddd, 1H, J=9.4, 6, 4 Hz, 3-H), 6.50 (dd, 1H, J=9.4, 6 Hz, 4-H), 6.88-7.67 (m, 4H). (b) The NMR signal at 5.47 ppm (dd) disappeared completely. (c) Selected NMR signals of 6b-v : δ 3.35-3.60 (m, 1H, 4-H), 6.35 (dd, 1H, J=12, 6.4 Hz, 3-H). Satisfactory IR, MS, and elemental analyses data were obtained for 6b-v. (d) Selected NMR signals of 7b-v : δ 5.45 (dd, 1H, J_{PCH}=20 Hz, J=6 Hz, 2-H), 5.62-5.97 (m, 1H, 3-H). 7) K. Akiba, Y. Negishi, K. Kurumaya, N. Ueyama, and N. Inamoto, Tetrahedron Lett., 22, 4977 (1981). 8) Grant-in-Aid for Scientific Research (No. 554139) and Special Project Research (No. 56109002) are acknowledged.
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