SIMPLE SYNTHETIC METHOD OF DIALKYL 1,2-DIHYDRO(ISO)QUINOLINE (1 or 2)-PHOSPHONATES

Michiharu Sugiura, Koosuke Asai, * and Yoshiki Hamada

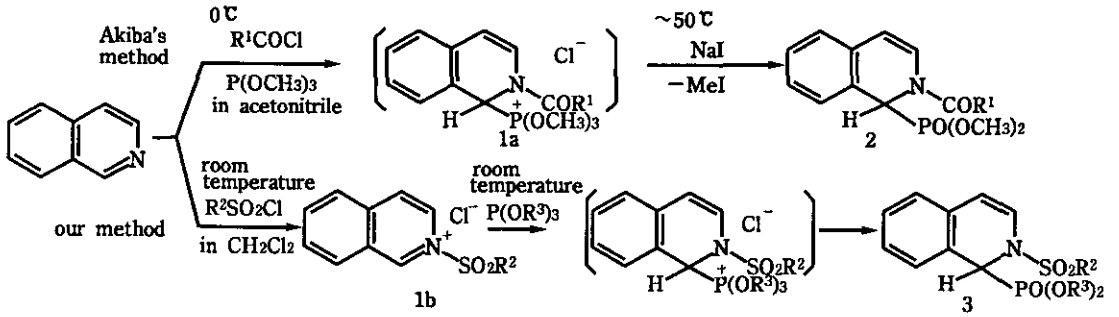
Faculty of Pharamacy, Meijo University, Yagotoyama, Tempaku-cho, Tempaku-ku, Nagoya 468, Japan

Abstract-1,2-Dihydro(iso)quinoline-2 (or 1)-phosphonates were synthesized from (iso)quinoline, sulfonyl chloride and trialkyl phosphite in CH_2Cl_2 at room temperture for 1 day in high yields.

This paper presents a new and easy method for preparing dialkyl 1,2-dihydroisoquinoline-1-phosphonates and dialkyl 1,2-dihydroquinoline-2-phosphonates from isoquinoline and quinoline. Pseudo-base type compounds were previously used to obtain nitrogen-containing heterocyclic compounds. [1] In Reissert compounds, differences in reactivity of *N*-sulfonyl and *N*-acyl derivatives have been reported by F. D. Popp *et al.* [2] The title compounds were prepared for a comparison of their hydrolysis reaction products with those of *N*-sulfonyl and *N*-acyl derivatives of dialkyl 1,2-dihydroisoquinoline-1-phosphonates.

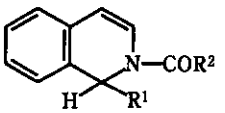
The synthetic method of *N*-acyl derivatives such as dimethyl 2-acyl-1,2-dihydroisoquinoline-1-phosphonate (2a) was previously reported by Akiba *et al*, using isoquinoline, acyl chloride, sodium iodide and trimethyl phosphite in acetonitrile in good yields (Akiba's method). [3] (Scheme 1) This method was applied to the preparation of dimetyl 2-methanesulfonyl-1,2-dihydroisoquinoline-1-phosphonate (3a), but 3a was not obtained at all and much I_2 from NaI was observed in purification of the product. By Akiba's method, it was considered that NaI would to accelerate the formation of 2 from intermediate (1a) in acetonitrile as a polar solvent, but in the preparation of 3a, NaI in acetonitrile prevented the formation of 3a. The reaction was thus conducted in CH_2Cl_2, a non-polar solvent, instead of acetonitrile without NaI at room temperature for 1 day. 3a was obtained in 95% yield. This method was also used to prepare various dialkyl 2-sulfonyl-1,2-dihydroisoquinoline-1-phosphonates, as summarized in Table I. (Scheme 1)

On using benzenesulfonyl instead of acyl group, *N*-benzenesulfonylisoquinolinium salts (1b), the

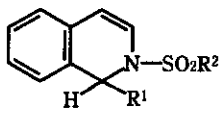


Scheme 1

Table I Yield of compounds (2a ~ l and 3a ~ g) from isoquinoline.



2a – l



3a – g

Entry	R¹	R²	Yield(%)
2a	P(=O)(OCH3)2	CH3	85 [a]
2b		C6H5	82 [b]
2c		OC2H5	90 [c]
2d		N(CH3)2	80 [d]
2e	P(=O)(OC2H5)2	CH3	87
2f		C6H5	82
2g		OC2H5	88
2h		N(CH3)2	80
2i	P(=O)(OiC3H7)2	CH3	86
2j		C6H5	84
2k		OC2H5	88
2l		N(CH3)2	85

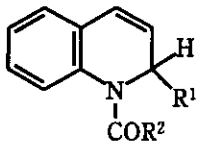
Entry	R¹	R²	Yield(%)
3a	P(=O)(OCH3)2	CH3	95 [e]
3b		C6H5	65 [e]
3c		*p*–CH3C6H5	90 [f]
3d	P(=O)(OC2H5)2	CH3	65
3e		C6H5	55
3f	P(=O)(OiC3H7)2	CH3	65
3g		C6H5	35

a) Yield:85% in the ref. 3. b) Yield:75% in the ref. 3. c) Yield:77% in the ref. 3. d) Yield:22% in the ref. 3. e) This compound was not obtained by the method from the ref. 3. f) Yield:70% in the ref. 3.

intermediate to dimethyl 2-benzenesulfonyl-1,2-dihydroisoquinoline-1-phosphonate (3b) was obtained in several hours. Even in CH_2Cl_2 at room temperature, 3b was obtained in 1 day. This method was used to obtain other compounds which are listed in Tables I and II.

Isoquinolines (2a ~ d) and quinolines (4a ~ c) have been reported by Akiba *et al.* But the title compounds were obtained milder conditions and our method generally provides better yields. NaI is not really necessary in the preparations of dialkyl 2-acyl (or sulfonyl)-1,2-dihydroisoquinoline-1-phosphonates.

Table II Yield of compounds (4a ~ c) from quinoline.



4a–c

Entry	R^1	R^2	Yield(%)
4a	P(=O)(OCH_3)$_2$	CH_3	50 [a]
4b		C_6H_5	82 [b]
4c		OC_2H_5	81 [c]

a) yield:36% in the ref. 3. b) yield:65% in the ref. 3. c) yield:91% in the ref. 3.

EXPERIMENTAL

General comments

Melting points were measured on a Yanagimoto Micromelting Point Apparatus and are uncorrected. The ^{1}H-Nmr and ^{13}C-Nmr spectras were recorded on a JEOL JNM A-400(400 MHz) with tetramethylsilane as an internal standard. Chemical shifts are given in ppm(δ), and signals are described as d (doublet), m (multiplet), and br (broad). Mass spectra (ms) were taken with JEOL HX-110 and Hitachi M-80B-GC-MS spectrometers. Aluminum oxide used for column chromatography was Merck Aluminium oxide 90 active, neutral (70-230 mesh).

Dimethyl 2-methanesulfonyl-1,2-dihydroisoquinoline-1-phosphonate (2a ~ l, 3a ~ g, 4a ~ d)

To a stirred solution of isoquinoline (12.9 g, 0.1 mol) in CH_2Cl_2 (500 ml) were added slowly methanesulfonyl chloride (12.6 g, 0.11 mol) and trimethyl phosphite (13.7 g, 0.11 mol) at room temperature and the whole was kept at room temperature for 1 day. The reaction mixture was poured into ice water and extracted with CH_2Cl_2 and the CH_2Cl_2 solution was washed with 6N HCl and next 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and concentrated. The crystalline residue was recrystallized from benzene–hexane (1 : 1) to give 3a (30.1g, 95%). The other compounds (2a ~ l, 3a ~ g, 4a ~ d) were obtained by the same way. Oily compounds were purified by column chromatography (neutral alumina) with CH_2Cl_2 as an eluent. Physical properties of compounds (2a ~ l, 3a ~ g, 4a ~ c) were shown in Tables III-VII. The compounds (2a ~ d, 3c, 4a ~ c) were identified by ir spectrum [3].

Table III Physical properties (mp, ms, ir) of compounds (2a ~ l, 3a ~ g, 4a ~ c)

Entry	mp ℃	Ms M/Z (FAB MH^+)	Ir ν cm^{-1}
2a [a]	80–81	282	1255(P=O)
2b [a]	98–99	344	1255(P=O)
2c [a]	oil	312	1250(P=O)
2d	83–84	311	1250(P=O)
2e	oil	310	1670(C=O) 1249(P=O)
2f	oil	372	1660(C=O) 1252(P=O)
2g	oil	340	1720(C=O) 1250(P=O)
2h	oil	339	1658(C=O) 1250(P=O)
2i	oil	338	1671(C=O) 1248(P=O)
2j	oil	400	1661(C=O) 1250(P=O)
2k	oil	368	1713(C=O) 1251(P=O)
2l	oil	367	1660(C=O) 1250(P=O)
3a	126–128	318	1331,1155(SO_2) 1259(P=O)
3b [a]	127–130	380	1353,1173(SO_2) 1250(P=O)
3c	116–117	394	1255(P=O)
3d	53–54	346	1347,1159(SO_2) 1250(P=O)
3e	108–110	408	1171(SO_2) 1252(P=O)
3f	63–64	374	1347,1160(SO_2) 1236(P=O)
3g [a]	99–100	436	1180(SO_2) 1251(P=O)
4a [a]	118–119	282	1245(P=O)
4b [a]	82–83	344	1260(P=O)
4c	oil	312	1260(P=O)

a) ref. 3.

Table IV Physical properties(^{1}H–nmr in $CDCl_3$) of compounds (2a ~ l, 3a ~ g)

Entry	1–H	3–H	4–H
2a	6.30(d,J=18.0 Hz)	6.69(d,J=8.0 Hz)	5.98(d,J=8.0 Hz)
2b [a]	6.38(d,J=17.6 Hz)	6.56(d,J=7.6 Hz)	5.57(d,J=7.6 Hz)
2c [a]	5.81(d,J=15.6 Hz)	6.88(br)	5.97(d,J=6.8 Hz)
2d	5.69(d,J=15.6 Hz)	6.56(d,J=7.2 Hz)	5.87(d,J=7.2 Hz)
2e	6.28(d,J=18.0 Hz)	6.68(d,J=7.6 Hz)	5.96(d,J=7.6 Hz)
2f [b]	6.37(d,J=18.0 Hz)	6.56(d,J=7.8 Hz)	5.84(d,J=7.8 Hz)
2g [b]	5.75(d,J=16.4 Hz)	6.87(br)	5.94(d,J=6.8 Hz)
2h	5.69(d,J=15.6 Hz)	6.56(d,J=7.8 Hz)	5.81(d,J=7.8 Hz)
2i	6.24(d,J=18.3 Hz)	6.69(d,J=8.0 Hz)	5.94(d,J=8.0 Hz)
2j [c]	6.34(d,J=18.4 Hz)	6.56(d,J=8.0 Hz)	5.83(d,J=8.0 Hz)
2k [c]	5.70(d,J=15.6 Hz)	6.85(br)	5.92(br)
2l	5.67(d,J=15.6 Hz)	6.55(d,J=7.8 Hz)	5.77(d,J=7.8 Hz)
3a	5.62(d,J=20.0 Hz)	6.59(d,J=7.6 Hz)	6.23(d,J=7.6 Hz)
3b	5.63(d,J=21.6 Hz)	6.64(d,J=7.8 Hz)	6.14(d,J=7.8 Hz)
3c	5.63(d,J=21.6 Hz)	6.63(d,J=7.2 Hz)	6.12(d,J=7.2 Hz)
3d	5.58(d,J=19.8 Hz)	6.57(d,J=7.2 Hz)	6.20(d,J=7.2 Hz)
3e	5.62(d,J=22.0 Hz)	6.86(d,J=7.6 Hz)	6.63(d,J=7.6 Hz)
3f	5.51(d,J=20.4 Hz)	6.56(d,J=7.2 Hz)	6.20(d,J=7.2 Hz)
3g	5.53(d,J=22.2 Hz)	6.61(d,J=7.2 Hz)	6.13(d,J=7.2 Hz)

a), b), c) 10% solution in DMSO-d_6 at 65 ℃ .

Table V Physical properties(^{13}C-nmr in $CDCl_3$) of compounds (2a ~ l, 3a ~ g)

Entry	1-C	3-C	4-C	C=O
2a	50.14, 51.61	125.15	111.22	167.97
2b [a]	51.40, 52.89	126.73	110.30	168.41
2c	54.43, 53.38	125.24	109.06	151.85
2d	55.50, 54.52	128.45	107.51	159.54
2e	52.08, 50.58	125.20	111.32	167.91
2f [b]	53.08, 52.09	126.86	110.43	168.44
2g	53.79, 52.30	124.68	109.13	151.92
2h	55.73, 54.73	128.25	107.15	159.66
2i	52.82, 51.29	125.19	111.53	167.77
2j [c]	54.08, 52.57	126.95	110.66	168.31
2k	55.30, 54.35	124.28	109.25	151.75
2l	56.62, 55.61	128.37	107.25	160.00
3a	55.57, 53.97	124.70	114.76	
3b	55.60, 54.53	124.76	116.43	
3c	55.62, 54.55	124.90	116.03	
3d	55.69, 54.62	124.77	114.78	
3e	56.22, 54.61	124.83	116.75	
3f	55.96, 54.89	124.60	114.99	
3g	56.38, 55.30	124.74	117.51	

a), b), c) 10 % solution in DMSO-d6 at 65 ℃

Table VI Physical properties(^{1}H-nmr in $CDCl_3$) of compounds (4a ~ c)

Entry	2-H	3-H	4-H
4a	6.12 (d, J=24.0 Hz)	6.14 (br)	6.63 (m)
4b	5.91 (d, J=21.3 Hz)	6.21 (m)	6.73 (m)
4c	5.68 (d, J=16.8 Hz)	6.59 (m)	6.60 (m)

Table VII Physical properties(^{13}C-nmr in $CDCl_3$) of compounds (4a ~ c)

Entry	1-C	3-C	4-C	C=O
4a	48.90,47.89	124.79	127.65	169.85
4b	50.80,49.78	123.75	127.70	169.26
4c	51.39,50.38	122.30	127.93	162.24

N-Benzenesulfonylisoquinolinium salt (1b)

To a stirred solution of isoquinoline (12.9 g, 0.1 mol) in CH_2Cl_2 (500 ml) were added slowly benzenesulfonyl chloride (19.4 g, 0.11 mol) and trimethyl phosphite (13.7 g, 0.11 mol) at room temperature and the whole was kept at room temperature for 1 day. The precipitated substance was filtered. Yield 28 % (7.6 g), mp 38 ~ 39 ℃ .

1b: ^{1}H-Nmr ($CDCl_3$) δ 9.91 (1H, s), 8.66 (3H, d, J=6.8 Hz), 8.23 (4H, d, J=6.4 Hz).

^{13}C-Nmr(CDCl$_3$) δ :125.1, 125.9, 127.2, 127.3, 128.1, 129.9, 130.6, 130.8, 131.6, 136.4, 138.5, 144.9, 146.9. Ms m/z: 270 (M^+).

REFERENCE

1. M. Sugiura, Y. Sakurai, and Y. Hamada, *Heterocycles*, 1992, 34, 561. ; M. Sugiura, K. Hatano, K.Hirao, K. Mogi, Y. Kurono, T. Yashiro, T. Usami, and Y. Hamada, *Chem. Pharm. Bull.*, 1992 , 40, 2262.
2. J. M. Wefer, A. Catala, and F .D. Popp, *J. Org. Chem.*, 1965, 30, 3075. ; H. W. Gibson and F. D. Popp, *J. Chem. Soc. (C)*, 1966, 1860.
3. K. Akiba, Y. Negishi, and N. Inamoto, *Synthesis*, 1979, 55.

Received, 11th October, 1995