

단 신

Synthesis of *N*-Diethoxyphosphinyl-1,2,3,4-tetrahydroisoquinoline 유도체의 합성

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Synthesis of *N*-Diethoxyphosphinyl-1,2,3,4-Tetrahydroisoquinolines

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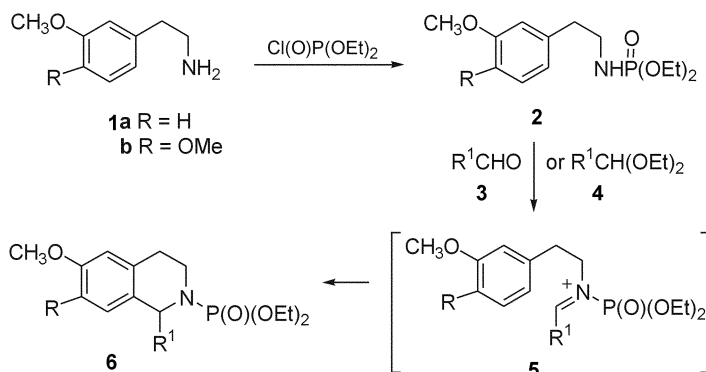
1,2,3,4-tetrahydroisoquinoline(THIQ) 알칼로이드는 자연의 동식물에 넓게 분포되어 있으며 다양한 생물학적 성질 때문에 합성법과 약리작용에 관하여 많은 주목을 받고 있다.¹ Pictet-Spengler 및 Bishler-Napieralski 반응은 THIQ 화합물의 합성에서 기본적으로 응용되는 합성 수단이며, 2-arylethylamine **1**이 출발물질이고 반응 중간체 iminium 이온에 의하여 진행되는 분자간 고리화 반응이다.² 최근, 본 연구실에서는 아미노기에 전자를 당기는 치환기가 치환된 *N*-위치에 전자를 당기는 작용기를 가진 2-arylethylamine 유도체 **2**를 출발물질로 사용하여 sulfamidoalkylation,³ ureidoalkylation,⁴ α -hydroxysulfonamidoalkylation⁵ 반응에 의한 THIQ 유도체의 합성법을 연구하여 보고하였다. 전자를 당기는 치환기를 가진 *N*-dialkoxyposphinyl-2-arylethylamine **2**로부터 *N*-dialkoxyposphinyl-1,2,3,4-tetrahydroisoquinoline 유도체의 합성은 세 가지 방법이 보고되었다. 첫 번째는 acetic acid 및 toluene에서 적당한 산을 촉매로 사용하여 화합물 **2**와 paraformaldehyde의 반응,⁶ 두 번째는 *N*-methylidene-2-arylethylamine과 diethyl chlorophosphate의 반응,⁷ 그리고 마지막으로 1-benzyl-3,4-dihydro-1,2,3,4-tetrahydroisoquinoline과 diisopropyl chlorophosphate의 반응에 이

은 NaBH₄의 환원으로 합성하는 반응이다.⁸ 그러나 첫 번째와 두 번째는 모두 단 하나의 화합물 **6b**만을 합성하였 뿐이고 마지막 방법도 단 하나의 반응 예만 보고하였을 뿐이다.

본 논문에서는 용매 dichloromethane에서 methanesulfonic acid 촉매로서 화합물 **2**와 aldehyde **3**(또는 acetal **4**)의 반응으로 *N*-diethoxyphosphinyl-THIQ **6** 유도체의 일반적인 합성법(Scheme 1) 및 선택적인 분광학적 성질과 이 계열의 대표적 화합물인 **6f**의 X-선구조결정 자료를 함께 보고한다.

실 험

시약은 Aldrich제를 정제하지 않고 사용하였고, 용매는 Aldrich 및 덕산시약 EP급을 사용하였으며 필요에 따라 알려진 방법으로 정제하여 사용하였다. 합성된 물질의 확인을 위한 IR 스펙트럼은 JASCO FT/IR-5300 spectrophotometer, 그리고 ¹H 및 ¹³C NMR 스펙트럼은 JEOL FT/NMR spectrophotometer(500 MHz)를 사용하였으며 내부표준물질은 tetramethylsilane(TMS)을 사용하였다. 질량분석 스펙트럼은 원광대학교의 Quatro AC



Scheme 1.

분광기를 사용하여 얻었다.

Diethoxyphosphinyl-1,2,3,4-tetrahydroisoquinolines 6의 일반적인 합성법

화합물 **2** (1.0 mmol), aldehyde **3** 또는 acetal **4** (1.0 mmol), 그리고 $\text{CH}_3\text{SO}_3\text{H}$ (0.3 mL)을 녹인 dichloromethane (10 mL) 용액을 24 h 동안 실온에서 교반한다. 반응용액을 물 (50 mL \times 3)로 씻고, 무수 MgSO_4 로 건조시키고, 그리고 감압하에서 농축시킨다. 나머지를 flash column chromatography (chloroform: Ethylacetate=1:8)로 정제하면 THIQ **6**이 얻어진다.

2-Diethoxyphosphinyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6a). 수득률: 75% (0.22 g); IR (KBr) 1257, 1030 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.24 (t, $J=7.1$ Hz, 6H), 2.76 (t, $J=5.7$ Hz, 2H), 3.36 (td, $J=5.7$ Hz, $^3J_{\text{H,P}}=9.2$ Hz, 2H), 3.72 (s, 3H), 3.93 (qdd, $^3J_{\text{H,P}}=6.7$ Hz, $J=6.7$ and 10.2 Hz, 2H), 4.01 (qdd, $^3J_{\text{H,P}}=6.7$ Hz, $J=6.7$ and 10.2 Hz, 2H), 4.19 (d, $^3J_{\text{H,P}}=5.9$ Hz, 2H), 6.59 (d, $J=2.4$ Hz, 1H), 6.69 (dd, $J=8.6$ and 2.4 Hz, 1H), 6.91 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 16.1, 16.2, 29.3 (d, $^3J_{\text{C,P}}=15.2$ Hz), 42.1 (d, $^2J_{\text{C,P}}=11.4$ Hz), 45.7 (d, $^2J_{\text{C,P}}=15.2$ Hz), 55.1, 55.2, 62.2, 62.3, 112.4, 113.8, 125.8 (d, $^3J_{\text{C,P}}=26.7$ Hz), 127.0, 135.3, 158.0 ppm; LR FBA MS: calcd for $[\text{M}-1]^+$ 300.1, found 299.5

2-Diethoxyphosphinyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6b).⁷ 수득률: 80% (0.26 g); mp 68–70 $^\circ\text{C}$; IR (KBr) 1248, 1020 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27 (t, $J=7.1$ Hz, 6H), 2.74 (t, $J=5.7$ Hz, 2H), 3.40 (td, $J=5.7$ Hz, $^4J_{\text{H,P}}=9.0$ Hz, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 3.96 (qdd, $^3J_{\text{H,P}}=7.1$ Hz, $J=7.1$ and 10.2 Hz, 2H),

4.04 (qdd, $^3J_{\text{H,P}}=7.1$ Hz, $J=7.1$ and 10.2 Hz, 2H), 4.21 (d, $^3J_{\text{H,P}}=5.9$ Hz, 2H), 6.51 (s, 1H), 6.58 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.2, 16.3, 28.5 (d, $^3J_{\text{C,P}}=15.2$ Hz), 42.3 (d, $^2J_{\text{C,P}}=11.4$ Hz), 45.9 (d, $^2J_{\text{C,P}}=15.3$ Hz), 55.9, 56.0, 62.2, 62.3, 108.9, 111.9, 125.6 (d, $^3J_{\text{C,P}}=26.7$ Hz), 126.0, 147.5, 147.6 ppm; LR FBA MS: calcd for $[\text{M}-1]^+$ 330.1, found 330.6.

2-Diethoxyphosphinyl-1-cyanomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6c). 수득률: 64% (0.23 g); mp 102–104 $^\circ\text{C}$; IR (KBr) 1228, 1024 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.28 (t, $J=7.1$ Hz, 3H), 12.9 (t, $J=7.1$ Hz, 3H), 2.59–2.64 (m, 1H), 2.85 (d, $J=6.3$ Hz, 2H), 2.88 (ddd, $J=16.6$, 11.3, and 5.8 Hz, 1H), 3.29 (dddd, $^3J_{\text{H,P}}=13.9$ Hz, $J=13.9$, 11.3, and 3.9 Hz, 1H), 3.60 (dddd, $J=13.9$, 8.0, and 5.8 Hz, $^3J_{\text{H,P}}=1.9$ Hz 1H), 3.85 (s, 6H), 3.98 (qdd, $^3J_{\text{H,P}}=7.6$ Hz, $J=7.6$ and 10.2 Hz, 1H), 4.04 (qdd, $^3J_{\text{H,P}}=7.6$ Hz, $J=7.6$ and 10.2 Hz, 2H), 4.10 (qdd, $^3J_{\text{H,P}}=7.6$ Hz, $J=7.6$ and 10.2 Hz, 1H), 4.91 (td, $J=6.3$ Hz, $^3J_{\text{H,P}}=8.6$ Hz, 1H), 6.59 (s, 1H), 6.65 (s, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{C,P}}=30.5$ Hz), 16.2 (d, $^3J_{\text{C,P}}=34.3$ Hz), 26.0, 27.7, 37.7, 50.9 (d, $^2J_{\text{C,P}}=22.9$ Hz), 55.3, 56.1, 62.7 (d, $^2J_{\text{C,P}}=22.9$ Hz), 62.8 (d, $^2J_{\text{C,P}}=22.9$ Hz), 109.6, 111.9, 118.0, 125.9 (d, $^3J_{\text{C,P}}=19.1$ Hz), 126.2, 147.7, 148.6 ppm; LR FBA MS: calcd for $[\text{M}-1]^+$ 369.1, found 369.7

2-Diethoxyphosphinyl-1-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6d). 수득률: 50% (0.18 g); mp 70–72 $^\circ\text{C}$; IR (KBr) 1249, 1016 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.15 (td, $J=7.1$ Hz, $^4J_{\text{H,P}}=0.9$ Hz, 3H), 1.25 (td, $J=7.1$

Hz, $^4J_{\text{HP}}=0.9$ Hz, 3H), 2.65-2.69 (m, 1H), 3.00 (ddd, $J=12.1$, 12.7, and 6.3 Hz, 1H), 3.07 (dddd, $^3J_{\text{HP}}=13.3$ Hz, $J=12.9$, 12.7, and 3.8 Hz, 1H), 3.42 (ddd, $J=12.9$, 6.2, and 6.3 Hz, 1H), 3.70 (qdd, $^3J_{\text{HP}}=7.3$ Hz, $J=7.3$ and 10.0 Hz, 1H), 3.79 (s, 1H), 3.86 (qdd, $^3J_{\text{HP}}=7.3$ Hz, $J=7.3$ and 10.0 Hz, 1H), 3.92 (qdd, $^3J_{\text{HP}}=7.3$ Hz, $J=7.3$ and 10.0 Hz, 1H), 4.00 (qdd, $^3J_{\text{HP}}=7.3$ Hz, $J=7.3$ and 10.0 Hz, 1H), 5.82 (d, $^3J_{\text{HP}}=8.2$ Hz, 1H) 6.66-6.71 (m, 2H), 6.86-6.88 (m, 1H), 7.18-7.28 (m, 5H) ppm; ^{13}C NMR (CDCl_3) δ 16.0 (d, $^3J_{\text{CP}}=30.5$ Hz), 16.2 (d, $^3J_{\text{CP}}=30.5$ Hz), 28.7, 36.8, 55.2, 57.3 (d, $^2J_{\text{CP}}=19.1$ Hz), 61.9 (d, $^2J_{\text{CP}}=22.9$ Hz), 62.2 (d, $^2J_{\text{CP}}=22.9$ Hz), 112.4, 113.5, 127.2, 127.8, 128.0, 129.0, 129.6, 135.9, 143.6, 158.2 ppm; LR FBA MS: calcd for $[\text{M}-1]^+$ 376.1, found 376.4.

2-Diethoxyphosphinyl-1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6e). 수득률: 56%(0.23 g): mp 88-90 °C; IR (KBr) 1230, 1026 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.16 (t, $J=7.1$ Hz, 3H), 1.27 (t, $J=6.9$ Hz, 3H), 2.60-2.63 (m, 1H), 2.93-3.07 (m, 2H), 3.39 (ddd, $J=13.3$, 5.9, and 5.9 Hz, 1H), 3.72 (s, 3H), 3.86 (s, 3H), 3.96-4.04 (m, 4H), 5.81 (d, $^3J_{\text{HP}}=8.2$ Hz, 1H), 6.41 (s, 1H), 6.65 (s, 1H), 7.24-7.27 (m, 6H) ppm; ^{13}C NMR (CDCl_3) δ 16.0 (d, $^3J_{\text{CP}}=30.5$ Hz), 16.2 (d, $^3J_{\text{CP}}=30.5$ Hz), 27.8, 36.8, 55.8, 55.9, 57.4 (d, $^2J_{\text{CP}}=19.0$ Hz), 61.9 (d, $^2J_{\text{CP}}=22.9$ Hz), 62.2 (d, $^2J_{\text{CP}}=22.8$ Hz), 111.0, 111.4, 126.8, 127.3, 128.0, 129.1, 143.3, 147.3, 148.0 ppm; LR FBA MS: calcd for $[\text{M}-1]^+$ 406.1, found 406.4

2-Diethoxyphosphinyl-1-[3-methoxy-4-hydroxyphenyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6f); 수득률: 53%(0.22 g): mp 67-69 °C; IR (KBr) 1246, 1032 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.16 (t, $J=7.1$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 2.64-2.69 (m, 1H), 2.98 (ddd, $J=14.2$, 13.6, and 6.5 Hz, 1H), 3.05 (dddd, $^3J_{\text{HP}}=13.0$ Hz, $J=13.3$, 13.6, and 3.0 Hz, 1H), 3.39 (ddd, $J=13.3$, 6.7, and 6.5 Hz, 1H), 3.72 (qdd, $^3J_{\text{HP}}=6.9$ Hz, $J=6.9$ and 10.0 Hz, 1H), 3.79 (s, 3H), 3.83 (s, 3H), 3.89 (qdd, $^3J_{\text{HP}}=6.9$ Hz, $J=6.9$ and 10.0 Hz, 1H), 3.92 (qdd, $^3J_{\text{HP}}=6.9$ Hz, $J=6.9$ and 10.0 Hz, 1H), 4.01 (qdd, $^3J_{\text{HP}}=6.9$ Hz, $J=6.9$ and 10.0 Hz, 1H), 3.69-4.04 (m, 4H), 5.77 (d, $^3J_{\text{HP}}=8.2$ Hz, 1H), 6.48 (dd, $J=8.2$ and 1.9 Hz, 1H), 6.68-6.70 (m, 2H), 6.75 (d, $J=8.2$ Hz, 1H), 6.88 (d, $J=8.2$ Hz, 1H), 6.99 (d, $J=1.9$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{CP}}=26.7$

Hz), 16.2 (d, $^3J_{\text{CP}}=26.7$ Hz), 28.7, 36.6, 55.2, 55.9, 57.0, 61.8 (d, $^2J_{\text{CP}}=19.1$ Hz), 62.3 (d, $^2J_{\text{CP}}=19.1$ Hz), 111.8, 112.3, 113.4, 113.5, 121.9, 128.1, 129.6, 135.9, 144.8, 146.3, 158.2 ppm; LR FBA MS: calcd for $[\text{M}-1]^-$ 420.1, found 420.7.

2-Diethoxyphosphinyl-1-[3-methoxy-4-hydroxyphenyl]-6,7-methoxy-1,2,3,4-tetrahydroisoquinoline (6g); 수득률: 56%(0.25 g): mp 118-120 °C; IR (KBr) 1228, 1032 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.17 (td, $J=6.9$ Hz, $^4J_{\text{HP}}=0.9$ Hz, 3H), 1.26 (td, $J=6.9$ Hz, $^4J_{\text{HP}}=0.9$ Hz, 3H), 2.58-2.62 (m, 1H), 2.93 (ddd, $J=15.8$, 15.0, and 6.4 Hz, 1H), 3.03 (dddd, $^3J_{\text{HP}}=14.2$ Hz, $J=13.9$, 15.0, and 4.1 Hz, 1H), 3.37 (ddd, $J=13.9$, 6.4, and 6.7 Hz, 1H), 3.73 (s, 3H), 3.69-3.77 (m, 1H) 3.83 (s, 3H), 3.89 (s, 3H), 3.85-3.95 (m, 2H), 4.01 (qdd, $^3J_{\text{HP}}=7.0$ Hz, $J=7.0$ and 10.1 Hz, 1H), 5.60 (bs, 1H), 5.76 (d, $^3J_{\text{HP}}=8.2$ Hz, 1H), 6.43 (s, 1H), 6.52 (dd, $J=8.0$ and 1.8 Hz, 1H), 6.63 (s, 1H), 6.76 (d, $J=8.0$ Hz, 1H), 7.00 (d, $J=1.8$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{CP}}=30.5$ Hz), 16.3 (d, $^3J_{\text{CP}}=30.5$ Hz), 27.9, 36.7, 55.8, 55.9, 56.0, 57.2 (d, $^2J_{\text{CP}}=19.1$ Hz), 61.8 (d, $^2J_{\text{CP}}=19.1$ Hz), 62.3 (d, $^2J_{\text{CP}}=22.9$ Hz), 111.0, 111.3, 111.8, 113.4, 122.0, 126.7, 127.4, 135.5, 144.9, 146.3, 147.2, 147.9 ppm; LR FBA MS: calcd for $[\text{M}-1]^-$ 450.1, found 450.7.

2-Diethoxyphosphinyl-1-[2-furyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6h); 수득률: (0.19 g): mp 90-91 °C; IR (KBr) 1251, 1022 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.20 (t, $J=7.1$ Hz, 3H), 1.27 (t, $J=7.1$ Hz, 3H), 2.63-2.67 (m, 1H), 2.97 (ddd, $J=16.7$, 12.2, and 6.4 Hz, 1H), 3.19 (dddd, $^3J_{\text{HP}}=12.9$ Hz, $J=13.3$, 12.2, and 4.0 Hz, 1H), 3.53 (ddd, $J=13.3$, 7.1, and 6.4 Hz, 1H), 3.78 (s, 3H), 3.86 (qdd, $^3J_{\text{HP}}=7.1$ Hz, $J=7.1$ and 10.1 Hz, 1H), 3.92 (qdd, $^3J_{\text{HP}}=7.1$ Hz, $J=7.1$ and 10.1 Hz, 1H), 4.00 (qdd, $^3J_{\text{HP}}=7.1$ Hz, $J=7.1$ and 10.1 Hz, 1H), 4.04 (qdd, $^3J_{\text{HP}}=7.1$ Hz, $J=7.1$ and 10.1 Hz, 1H), 5.74 (d, $^3J_{\text{HP}}=8.2$ Hz, 1H), 5.92 (d, $J=3.0$ Hz, 1H), 6.24 (dd, $J=3.0$ and 1.8 Hz, 1H), 6.66 (d, $J=2.5$ Hz, 1H), 6.71 (dd, $J=8.2$ and 2.5 Hz, 1H), 7.00 (d, $J=8.2$ Hz, 1H), 7.34 (d, $J=1.8$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.0 (d, $^3J_{\text{CP}}=30.5$ Hz), 16.1 (d, $^3J_{\text{CP}}=30.5$ Hz), 28.7, 37.9, 51.9 (d, $^2J_{\text{CP}}=22.9$ Hz), 55.2, 62.1 (d, $^2J_{\text{CP}}=19.0$ Hz), 62.3 (d, $^2J_{\text{CP}}=19.0$ Hz), 108.8, 109.9, 112.4, 113.6, 125.9, 129.2, 135.8, 142.2,

156.0, 158.4 ppm; LR FBA MS: calcd for $[M-1]^+$ 366.1, found 366.5.

2-Diethoxyphosphinyl-1-[2-furyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6i). 수득률: 59%(0.23 g); IR (KBr) 1248, 1024 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.19 (td, $J=7.1$ Hz, $^4J_{\text{H,P}}=0.9$ Hz, 3H), 1.27 (td, $J=7.1$ Hz, $^4J_{\text{H,P}}=0.9$ Hz, 3H), 2.56-2.60 (m, 1H), 2.91 (ddd, $J=16.7$, 12.3, and 6.3 Hz, 1H), 3.16 (dddd, $^3J_{\text{H,P}}=13.0$ Hz, $J=13.4$, 12.3, and 4.1 Hz, 1H), 3.51 (ddd, $J=13.4$, 6.9, and 6.3 Hz, 1H), 3.76 (s, 3H), 3.85 (s, 3H), 3.82-3.88 (m, 1H), 3.92 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.1 Hz, 1H), 3.99 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.1 Hz, 1H), 4.03 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.1 Hz, 1H), 5.71 (d, $^3J_{\text{H,P}}=7.3$ Hz, 1H), 5.93 (dd, $J=3.2$ and 0.9 Hz, 1H), 6.24 (dd, $J=3.2$ and 1.8 Hz, 1H), 6.54 (s, 1H), 6.60 (s, 1H), 7.34 (dd, $J=1.8$ and 0.9 Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{C,P}}=30.5$ Hz), 16.2 (d, $^3J_{\text{C,P}}=30.5$ Hz), 27.9, 37.9 (d, $^2J_{\text{C,P}}=7.6$ Hz), 52.0 (d, $^2J_{\text{C,P}}=22.9$ Hz), 55.8, 56.0, 62.1 (d, $^2J_{\text{C,P}}=19.0$ Hz), 62.3 (d, $^2J_{\text{C,P}}=19.0$ Hz), 108.9, 109.9, 110.7, 111.5, 125.5 (d, $^3J_{\text{C,P}}=15.2$ Hz), 126.6, 142.2, 147.2, 148.2, 155.8 (d, $^3J_{\text{C,P}}=11.4$ Hz) ppm; LR FBA MS: calcd for $[M-1]^+$ 396.1, found 396.7.

2-Diethoxyphosphinyl-1-[2-thiophenyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6j). 수득률: 54%(0.20 g); mp 92-94 $^{\circ}\text{C}$; IR (KBr) 1247, 1020 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.19 (t, $J=7.1$ Hz, 3H), 1.27 (t, $J=7.1$ Hz, 3H), 2.63-2.67 (m, 1H), 2.98 (ddd, $J=17.0$, 12.6, and 6.4 Hz, 1H), 3.21 (dddd, $^3J_{\text{H,P}}=13.5$ Hz, $J=13.8$, 12.6, and 4.1 Hz, 1H), 3.51 (ddd, $J=13.8$, 7.1, and 6.4 Hz, 1H), 3.79 (s, 3H), 3.83 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.0 Hz, 1H), 3.91 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.0 Hz, 1H), 3.98 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.0 Hz, 1H), 4.03 (qdd, $^3J_{\text{H,P}}=6.8$ Hz, $J=6.8$ and 10.0 Hz, 1H), 5.98 (d, $^3J_{\text{H,P}}=8.2$ Hz, 1H), 6.67 (d, $J=2.6$ Hz, 1H), 6.71 (dd, $J=8.3$ and 2.6 Hz, 1H), 6.77 (dd, $J=3.6$ and 1.1 Hz, 1H), 6.87 (dd, $J=5.1$ and 3.6 Hz, 1H), 7.02 (d, $J=8.3$ Hz, 1H), 7.20 (dd, $J=5.1$ and 1.1 Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{C,P}}=30.5$ Hz), 16.2 (d, $^3J_{\text{C,P}}=30.5$ Hz), 28.6, 37.3, 53.4 (d, $^2J_{\text{C,P}}=22.9$ Hz), 55.2, 62.1 (d, $^2J_{\text{C,P}}=22.8$ Hz), 62.4 (d, $^2J_{\text{C,P}}=22.8$ Hz), 112.3, 113.6, 125.3, 126.2, 126.9, 127.9, 129.5, 135.4, 148.1, 158.4 ppm; LR FBA MS: calcd for $[M-1]^+$ 382.1, found 382.4.

2-Diethoxyphosphinyl-1-[2-thiophenyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6k). 수득률: 58% (0.249 g); IR (KBr) 1228, 1030 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.19 (t, $J=6.9$ Hz, 3H), 1.27 (t, $J=7.1$ Hz, 3H), 2.58-2.61 (m, 1H), 2.94 (ddd, $J=16.9$, 12.6, and 6.5 Hz, 1H), 3.19-3.21 (dddd, $^3J_{\text{H,P}}=13.6$ Hz, $J=13.9$, 12.6, and 3.9 Hz, 1H), 3.49 (ddd, $J=13.9$, 7.1, and 6.5 Hz, 1H), 3.77 (s, 3H), 3.92 (qdd, $^3J_{\text{H,P}}=7.2$ Hz, $J=7.2$ and 10.2 Hz, 1H), 3.87 (s, 3H), 3.92 (qdd, $^3J_{\text{H,P}}=7.2$ Hz, $J=7.2$ and 10.2 Hz, 1H), 4.01 (qdd, $^3J_{\text{H,P}}=7.2$ Hz, $J=7.2$ and 10.2 Hz, 1H), 4.02 (qdd, $^3J_{\text{H,P}}=7.2$ Hz, $J=7.2$ and 10.2 Hz, 1H), 5.95 (d, $^3J_{\text{H,P}}=8.2$ Hz, 1H), 6.57 (s, 1H), 6.61 (s, 1H), 6.79 (d, $J=3.4$ Hz, 1H), 6.88 (dd, $J=5.0$ and 3.4 Hz, 1H), 7.21 (d, $J=5.0$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.0 (d, $^3J_{\text{C,P}}=26.7$ Hz), 16.1 (d, $^3J_{\text{C,P}}=22.9$ Hz), 27.7, 37.3, 53.5 (d, $^2J_{\text{C,P}}=26.7$ Hz), 55.8, 56.0, 62.1 (d, $^2J_{\text{C,P}}=22.9$ Hz), 62.4 (d, $^2J_{\text{C,P}}=22.9$ Hz), 111.0, 111.4, 125.3, 126.2, 126.3, 127.0, 127.5 (d, $^3J_{\text{C,P}}=15.2$ Hz), 147.2, 147.7 (d, $^3J_{\text{C,P}}=15.3$ Hz), 148.2 ppm; LR FBA MS: calcd for $[M-1]^+$ 412.1, found 412.6.

2-Diethoxyphosphinyl-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6l). 수득률: 61%(0.25 g); mp 99-101 $^{\circ}\text{C}$; IR (KBr) 1244, 1028 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.11 (t, $J=7.1$ Hz, 3H), 1.19 (t, $J=7.1$ Hz, 3H), 2.54-2.58 (m, 1H), 2.91 (ddd, $J=16.7$, 11.4, and 5.9 Hz, 1H), 3.01 (dd, $J=7.8$ and 13.5 Hz, 1H), 3.13 (dd, $J=7.8$ and 13.5 Hz, 1H), 3.28 (dddd, $^3J_{\text{H,P}}=14.8$ Hz, $J=14.8$, 11.4, and 4.1 Hz, 1H), 3.52-3.57 (m, 2H), 3.58 (s, 3H), 3.69 (qdd, $^3J_{\text{H,P}}=7.1$, $J=7.1$ and 10.2 Hz, 1H), 3.72 (qdd, $^3J_{\text{H,P}}=7.1$, $J=7.1$ and 10.2 Hz, 1H), 3.83 (s, 3H), 3.90 (qdd, $^3J_{\text{H,P}}=7.1$, $J=7.1$ and 10.2 Hz, 1H), 4.77 (ddd, $J=7.8$ and 7.8 Hz, $^3J_{\text{H,P}}=7.9$ Hz, 1H), 69.1 (s, 1H), 6.55 (s, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H), 7.28 (s, 1H) ppm; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{C,P}}=30.5$ Hz), 16.2 (d, $^3J_{\text{C,P}}=30.5$ Hz), 27.7, 37.3, 43.5 (d, $^2J_{\text{C,P}}=11.4$ Hz), 55.6, 55.8, 61.8 (d, $^2J_{\text{C,P}}=22.9$ Hz), 62.1 (d, $^2J_{\text{C,P}}=22.9$ Hz), 110.3, 111.5, 125.4, 126.3, 128.3, 129.1 (d, $^3J_{\text{C,P}}=15.2$ Hz), 130.0, 138.7, 146.5, 147.6 ppm; LR FBA MS: calcd for $[M-1]^+$ 420.1, found 420.7.

6i의 X선 결정학적 실험. X선 결정학적 연구에 적당한 6i의 단결정은 methanol-chloroform 포화용액으로부터

Table 1. Reaction condition, mp, and yield of THIQs **6**

	No.	R ¹	R ²	Reaction conditions		Mp(°C) ^a	Yield(%) ^b
				Temp.(°C)	Time (h)		
1	9a	H	H	0-5	3	.	75
2	9b	OMe	H	0-5	3	68-70 ⁷	80
3	9c	OMe	CH ₂ CN	rt	8	102-104	64
4	9d	H	Phenyl	0-5	24	70-73	50
5	9e	OMe	Phenyl	0-5	24	88-90	56
6	9f	H	3-methoxy-4-hydroxyphenyl	0-5	6	65-72	53
7	9g	OMe	3-methoxy-4-hydroxyphenyl	0-5	6	118-121	56
8	9h	H	2-furyl	0-5	3	90-91	54
9	9i	OMe	2-furyl	0-5	2	.	59
10	9j	H	2-thiophenyl	0-5	4	92-95	54
11	9k	OMe	2-thiophenyl	0-5	3	.	58
12	9l	OMe	Benzyl	rt	12	99-101	61

^aMelting points are uncorrected. ^bIsolated yieldsTable 2. Crystal data and structure refinement for **6l**

Empirical formula	C ₂₂ H ₃₀ NO ₃ P
Formula weight	419.44
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	$a = 26.1190(11)$ Å $b = 11.9826(5)$ Å, $\beta = 111.5270(10)^\circ$ $c = 15.2042(7)$ Å
Volume	4426.6(3) Å ³
Z, D _{calcd}	8, 1.259 g/cm ³
μ	0.156 mm ⁻¹
$F(000)$	1792
Crystal size	0.5 × 0.4 × 0.35 mm
θ range for data collection	1.68 to 28.34°
hkl collected	-34 ≤ h ≤ 28, -12 ≤ k ≤ 15, -19 ≤ l ≤ 20
Reflections collected / unique	15981 / 5502 [R(int) = 0.0407]
Completeness to $\theta = 28.34$	99.6%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5502 / 0 / 262
Goodness-of-fit on F^2	0.999
Final R indices [$I > 2\sigma(I)$]	^a $R_1 = 0.0654$, ^b $wR_2 = 0.1865$
R indices (all data)	^a $R_1 = 0.1450$, ^b $wR_2 = 0.2445$
Largest diff. peak and hole	0.545 and -0.307 e. Å ⁻³

^a $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ (based on reflections with $F_o^2 > 2\sigma F^2$)^b $wR_2 = [\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]]^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (0.095P)^2]$; $P = [\max(F_o^2, 0) + 2F_c^2] / 3$ (also with $F_o^2 > 2\sigma F^2$)

터 느린 증발법으로 만들었으며, 적절한 단결정을 선택하여 무작위 배향의 유리봉에 부착하였다. 회절반점의 세기는 Enraf-Nonius CAD-4 회절기로 얻었으며, Mo-K α radiation($\lambda=0.71073\text{\AA}$)을 사용하였다. 분자구조는

SHELX-86의 직접법으로 풀었으며,⁹ 자료의 정밀화에는 SHELX-97 최소자승법을 이용하여 해석하였다.¹⁰ 회절자료 수집 및 정밀화 단계에서 사용한 정보와 최종 단위 세포상수 값 등은 Table 2와 같다.

결과 및 고찰

N-diethoxyphosphinyl-2-arylethylamine **2**는 이미 잘 알려진 방법에 따라, 2-arylethylamines **1**과 diethyl chlorophosphate/triethylamine의 반응으로 제조하였다.¹¹ 출발물질 **2**와 aldehyde **3**(또는 **4**)의 반응은 dichloromethane에서 methanesulfonic acid를 촉매로 사용하였고, 실온에서 24시간의 반응으로 적당한 수득율로 THIQ **6**이 생성되었으며, 반응은 iminium ion **5**에 의하여 분자내 고리화 반응이 진행되는 것으로 예측된다.

THIQ **6**의 수득율, 녹는점, 그리고 반응조건은 Table 1과 같다.

THIQ **6**의 구조는 IR 흡수스펙트럼, NMR 스펙트럼 및 질량 분광스펙트럼, 그리고 **6**의 X선 구조결정 연구로 확인하였다. IR 스펙트럼에서 P=O기는 1226-126 cm⁻¹에서 특징적 흡수띠가 나타났다.¹² Aldehyde **3** 또는 acetal **4**에 의하여 주어진 THIQ **6**의 methine기의 양성자는 ¹H NMR 스펙트럼에서 δ 4.19-5.98에서, 그리고 ¹³C NMR 스펙트럼에서 탄소는 δ 45.7-57.4 ppm에서 나타났다. THIQ **6**의 고리의 두 methylene기의 양성자는 ¹H NMR 스펙트럼에서 δ 3.01-3.32, 3.13-3.60 및 2.55-2.69, 2.91-3.007 ppm에서 다중선으로 각각 나타났다으며, 두 methylene기의 탄소는 ¹³C NMR 스펙트럼에서 δ 36.3-42.3과 27.4-29.3 ppm에서 각각 나타났다. **6**의 대표적 화합물 **6**의 X선 결정학 구조 연구에 의한

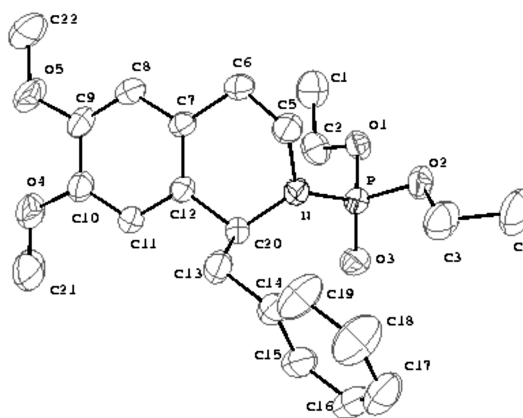


Fig. 1. ORTEP view of **6l**, with atom labeling scheme.

입체구조는 Fig. 1과 같으며 선별된 결합길이와 결합각은 Table 3에 나타내었다. **6**의 입체구조에서 두 개의 tetrahydroisoquinoline 고리의 평면에 대하여 고리 외부의 벤질기는 서로 거의 수직을 이루어 입체장해를 최소화하고 있음을 보여준다.

결론

N-diethoxyphosphinyl-(2-arylethyl)amine과 aldehyde (또는 acetal)의 반응으로 *N*-diethoxyphosphinyl-1,2,3,4-tetrahydroisoquinoline의 일반적인 합성법을 개발하였으

Table 3. Selected bond lengths [Å] and angles [deg] for **6l**

Bond lengths			
P-O(3)	1.460(3)	C(12)-C(20)	1.524(4)
P-O(2)	1.572(2)	C(13)-C(14)	1.488(4)
P-O(1)	1.574(2)	C(13)-C(20)	1.540(5)
P-N	1.634(3)	N-C(5)	1.479(4)
O(1)-C(2)	1.453(4)	C(1)-C(2)	1.496(6)
O(2)-C(3)	1.438(5)	C(3)-C(4)	1.475(6)
N-C(20)	1.475(4)	C(5)-C(6)	1.506(5)
Bond angles			
O(3)-P-O(2)	116.69(15)	C(14)-C(13)-C(20)	115.5(3)
O(3)-P-O(1)	114.73(15)	N-C(20)-C(12)	110.0(3)
O(2)-P-O(1)	96.33(13)	N-C(20)-C(13)	111.7(3)
O(3)-P-N	111.84(14)	O(1)-C(2)-C(1)	108.8(3)
O(2)-P-N	106.27(14)	O(2)-C(3)-C(4)	108.2(4)
O(1)-P-N	109.73(13)	C(20)-N-C(5)	114.5(2)
C(2)-O(1)-P	117.0(2)	C(20)-N-P	122.0(2)
C(3)-O(2)-P	119.2(3)	C(5)-N-P	120.2(2)
C(21)-O(4)-C(10)	118.7(4)	N-C(5)-C(6)	111.4(3)
C(9)-O(5)-C(22)	118.1(4)	C(5)-C(6)-C(7)	112.8(3)

며, X-선 구조결정법으로 화학구조를 확인하였다.

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