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INTRAMOLECULAR WITTIG-HORNER REACTION OF DIMETHYL 2-(*o*-ACYLBENZOYL)-1, 2-DIHYDROISOQUINOLINE-1-PHOSPHONATE : FACILE SYNTHESIS OF AN ISOQUINOLINE ALKALOID SKELETON

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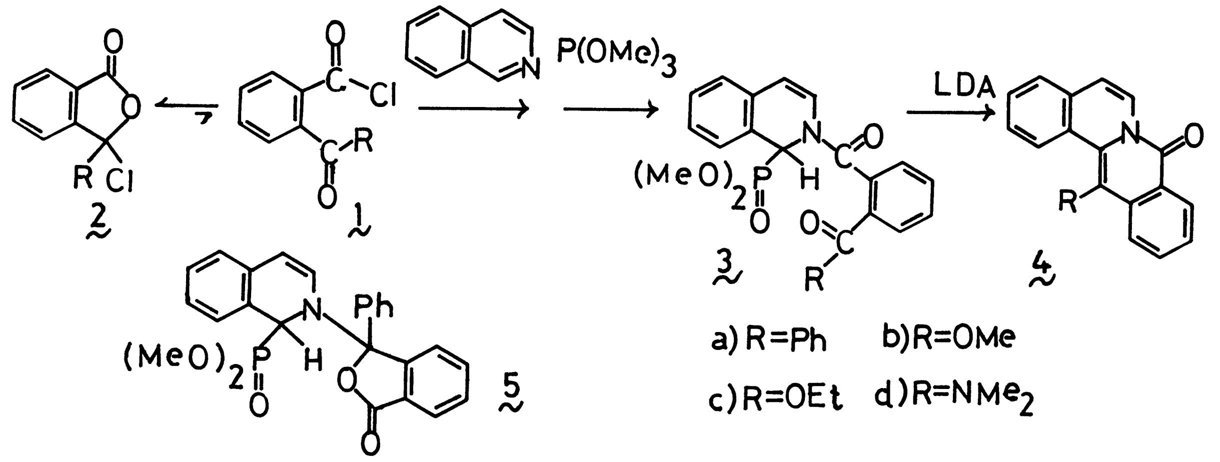
Dimethyl 2-(*o*-acylbenzoyl)-1, 2-dihydroisoquinoline-1-phosphonates (**3**) were prepared from isoquinoline, *o*-acylbenzoyl chloride, and trimethyl phosphite. Intramolecular Wittig-Horner reaction of **3** with LDA afforded good yields of 13-substituted 8H-dibenzo [a, g] quinolizin-8-ones (**4**) which bear an isoquinoline alkaloid skeleton.

In a previous paper,[2] we reported that Wittig-Horner reaction of dimethyl 2-isopropoxycarbonyl-1, 2-dihydroisoquinoline-1-phosphonate with various aldehydes afforded the corresponding 1-exo-methylene compounds, which were converted to 1-substituted isoquinolines with hydrogen chloride.

We extended the above result to use for annelation of nitrogen heterocycles by intramolecular Wittig-Horner reaction of phosphonates of Reissert analogue which were prepared by employing acylating reagents containing one more carbonyl group in a molecule.

First, we chose *o*-benzoylbenzoyl chloride (**1a**) as an acylating reagent, which is known to exist as 3-chloro-3-phenylphthalide (**2a**).[3] Therefore, **2a** (4.6 mmol) was heated in refluxing propionitrile (10 ml) to increase the proportion of **1a** and a solution of isoquinoline (4.6 mmol) in propionitrile (13 ml) was slowly added followed by addition of trimethyl phosphite (4.6 mmol) to give **3a** [mp 157.1-157.9 °C ; NMR ($CDCl_3$) : δ 6.07 (1-H, J_{PCH}=18.0 Hz)] in 62% yield, together with 19% of the phosphonate (**5**) derived directly from **2a**.[4] Deprotonation of **3a** (3.0 mmol) with lithium diisopropylamide (LDA : 3.6 mmol) in tetrahydrofuran (20 ml) at -70 °C, followed by heating at 40 °C for 0.5 h, afforded the expected 13-phenyl-8H-dibenzo [a, g] quinolizin-8-one[5] (**4a**, mp 211.1-211.7 °C) in 31% yield together with isoquinoline (41%) and 3-(N, N-diisopropylamino)-3-phenylphthalide (6% ; mp 126-128 °C) which were produced through the attack of LDA toward the benzoyl group instead of deprotonation.

Then, we tried to prepare **4** with a functional group such as alkoxy or amino group at the 13-position. Employment of chlorides of half esters (**1b**, **c**) and a half amide (**1d**) of phthalic acid as acylating reagents gave the corresponding phosphonates (**3b**-**d**) : **3b** : mp 154.1-154.6 °C; yield 83% ; IR (KBr) : 1725, 1665 cm^{-1} (ν C=O) ; NMR ($CDCl_3$) : δ 6.51 (1-H, J_{PCH}=17.4



Hz) ; **3c** : 113.9-114.4 °C ; 80% ; 1720, 1670 cm^{-1}; δ 6.49 (1-H, J_{PCH}=17.4 Hz) ; **3d** : 131.7-132.5 °C ; 78% ; 1660, 1650 cm^{-1}; δ 6.30 (1-H, J_{PCH}=16.8 Hz). Similar treatment of **3b-d** with LDA afforded **4b-d** (**4b** : mp 143.8-144.7 °C ; **4c** : 181.7-182.3 °C ; **4d** : 144.4-145.7 °C) in yields of 76, 67, and 67%, respectively.[5] Wittig-Horner reaction of the carbonyl group of esters is rather rare[6] and that of an amide here has not been described.

Starting with quinoline instead of isoquinoline, compounds corresponding to **3b** and **4b** were obtained in yields of 63 (pale yellow oil) and 54% (mp 299.5-301.2 °C), respectively. Thus versatile utility of the present method has been shown to build up isoquinoline and quinoline alkaloid skeletons.

References

1) Present address : Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima 730, Japan. 2) K. Akiba, Y. Negishi, K. Kurumaya, N. Ueyama, and N. Inamoto, Tetrahedron Lett., 1981, 4977. 3) M. S. Newman and C. Courduvelis, J. Am. Chem. Soc., 88, 781 (1966) and references cited therein. 4) A pair of diastereomers (**5**) **a** : mp 185.2-185.7 °C ; NMR ($CDCl_3$) : δ 4.65 (1-H, J_{PCH}=19.2 Hz), and **b** : mp 164.2-165.0 °C ; δ 4.82 (1-H, J_{PCH}=16.8 Hz) was obtained in a ratio of 2 : 3. All **3**, **4**, and **5** gave correct elemental analyses. 5) For 8H-dibenzo [a, g] quinolizin-8-one, see : a) D. W. Brown, S. F. Dyke, M. Sainsburry, and G. Hardy, J. Chem. Soc. (C), 1971, 3219 ; b) D. E. Ames and O. Ribeiro, J. Chem. Soc., Perkin Trans. 1, 1976, 1073. All **4** showed reasonable spectra of this skeleton. 6) M. Le Corre, Bull. Soc. Chim. France, 1974, 2005 ; V. Subramanyam, E. H. Silver, and A. H. Soloway, J. Org. Chem., 41, 1272 (1976) ; A. P. Uijttewaal, F. L. Jonkers, and A. van der Gen, ibid., 43, 3306 (1978). 7) Partial support of this work by Grant-in-Aid for Special Project Research (No. 411106) from Ministry of Education, Science, and Culture is acknowledged.

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