A Novel Synthesis of 2-(1-Imidazolyl)benzophenones

Yasutaka KAYAMA, Takeshi HARA,* and Tamiko SUNAMI
Teijin Institute for Bio-medical Research, Asahigaoka, Hino, Tokyo 191
(Received July 5, 1979)

Synopsis. 2-(1-Imidazolyl)benzophenones were prepared from 3-(2,2-dialkoxyethyl)-3,4-dihydro-4-hydroxy-4-phenylquinazolines and a corresponding 4-alkoxy derivative by heating in formic acid or in sulfuric acid–ethanol.

2-(1-Imidazolyl)benzophenones with appropriate substituents are themselves pharmacologically active compounds[1,2] or important intermediates for the synthesis of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines[3] or 6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepines.[4] This type of compounds have so far been prepared by nucleophilic reaction of imidazolide anions with 2-halobenzophenones,[2] oxidation of 1-(2-benzylphenyl)-1*H*-imidazoles[5] or seven-membered ring cleavage of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines.[1,4,6] We now wish to report a novel synthesis of 2-(1-imidazolyl)benzophenones.

When 3-(2,2-dialkoxyethyl)-3,4-dihydro-4-hydroxy-4-phenylquinazolines **3a, c** prepared by the reaction[7] of aminoacetaldehyde dialkyl acetals (**2**) with 2-(1-alkoxyethylideneamino)benzophenones (**1**) were heated with formic acid, ring opening and recyclization occured to afford the 2-(1-imidazolyl)benzophenones **5a, b** in good yields (Table 1).

The conversion of **3c** to **5b** could also be carried out with sulfuric acid, but in a decreased yield. As we previously reported,[7] the 4-hydroxydihydroquinazolines **3** formed by refluxing an ethanolic solution of **1** and **2** are converted to the corresponding 4-ethoxy derivatives **4** under the reaction conditions, and the latters can be isolated as such avoiding acidic treatment such as silica gel chromatography; the chromatography converted **4** to **3**. So, next we examined the conversion of **4** to **5**. Treatment of **4b** with formic acid also afforded **5b** in 81% yield. The 2-(1-imidazolyl)benzophenones **5a, b** thus obtained gave satisfactory elemental analysis and IR and NMR spectral properties. Ring opening and recyclization of dihydroquinazolines to yield 2-(4*H*-1,2,4-triazol-4-yl)benzophenones, a reaction similar to the one reported herein, was previously reported.[8]

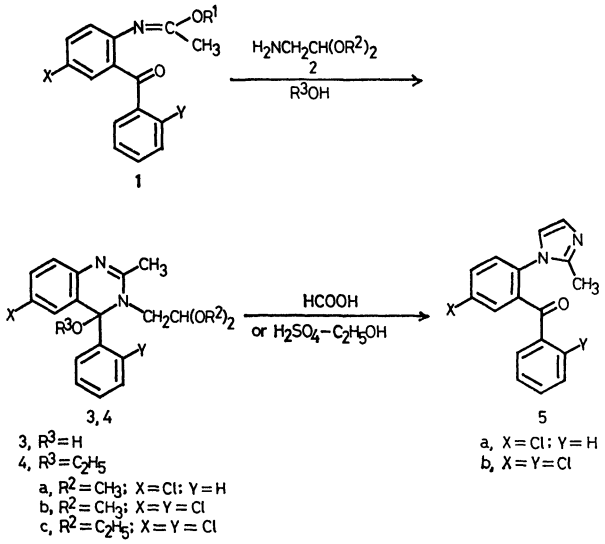

TABLE 1. CONVERSION OF QUINAZOLINES (**3, 4**) TO IMIDAZOLYLBENZOPHENONES (**5**)

Run	Starting material	Catalyst-solvent	Refluxing period/h	Product	Yield/%
1	**3a**	80% HCO_2H[a]	3	**5a**	83
2	**3c**	99% HCO_2H[a]	1	**5b**	85
3	**3c**	H_2SO_4–C_2H_5OH	3	**5b**	55
4	**4b**	85% HCO_2H[a]	3	**5b**	81

a) Formic acid was employed as solvent as well as catalyst.

Experimental

Melting points were taken with a Yanagimoto hot-stage apparatus and are uncorrected. Combustion analyses were carried out by the Analytical Chemistry Laboratory of Central Research Institute, Teijin Limited. IR spectra were measured on a Hitachi EPI-S2 spectrophotometer. NMR spectra were obtained on a JEOL JNM-MH-100 spectrometer, and chemical shifts are expressed in parts per million (δ) relative to TMS as an internal standard.

*5-Chloro-2-(2-methyl-1-imidazolyl)benzophenone (**5a**).*

A solution of 6-chloro-4-hydroxy-3-(2,2-dimethoxyethyl)-2-methyl-4-phenyl-3,4-dihydroquinazoline (**3a**) (2.03 g, 5.62 mmol) in 80% formic acid (10 ml) was refluxed for 3 h. The formic acid was evaporated. Ice–water (10 g) was added to the residue, and the mixture was made alkaline with 4 M (1M=1 mol dm^{-3}) NaOH and extracted with dichloromethane (40 ml). The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was crystallized with ether and triturated after addition of a small amount of hexane. The crystals were collected on a filter, washed with ether–hexane, and dried to give 1.40 g (83%) of **5a** as colorless crystals. Recrystallization from ether–hexane gave colorless plates: mp 115.5—117.0 °C; IR (KBr) 1656, 1596, 1485, 1414, 1303, 1284, 1242, 827, 737, 711; NMR ($CDCl_3$) δ 2.18 (s, 3H), 6.73 (s, 2H), 7.24—7.67 (m, 8H).

Found: C, 68.51; H, 4.24; N, 9.60%. Calcd for $C_{17}H_{13}N_2OCl$: C, 68.80, H, 4.42; N, 9.44%.

*2',5-Dichloro-2-(2-methyl-1-imidazolyl)benzophenone (**5b**).*

a) Compound **5b** isolated by silica gel column chromatography [eluent; dichloromethane–ethyl acetate (2:1)] of the product mixture in Run 2 of Table 1 was recrystallized from dichloromethane–hexane to give colorless prisms: mp 112—113.5 °C; IR (KBr) 1665, 1591, 1482, 1415, 1298, 1258, 1238, 837, 747; NMR ($CDCl_3$) δ 2.12 (s, 3H), 6.69 (m, 2H), 7.20—7.34 (m, 5H), 7.61 (dd, J=8.0 and 2.5 Hz, 1H), 7.71 (d, J=2.5 Hz, 1H).

Found: C, 61.65; H, 3.48; N, 8.43%. Calcd for $C_{17}H_{12}N_2OCl_2$: C, 61.65; H, 3.65; N, 8.46%.

b) A mixture of 6-chloro-4-(2-chlorophenyl)-3-(2,2-diethoxyethyl)-3,4-dihydro-4-hydroxy-3-methylquinazoline (**4b**) (1.00 g, 2.36 mmol), ethanol (5 ml), and 9 M H_2SO_4 (5 ml) was refluxed for 3 h. To the reaction mixture, after evapora-

tion of ethanol, was added ice–water (10 g) and dichloromethane (30 ml), and the resulting mixture was made alkaline with 4 M NaOH. The layers were separated, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with benzene–ethyl acetate (2:1 to 0:1) as eluent to give 0.427 g (55%) of **5b** as yellowish crystals. Recrystallization from dichloromethane–hexane gave colorless prisms of mp 112.5—113 °C, showing identical IR and NMR spectra with those of **5b** prepared in Run 2 of Table 1.

The authors wish to thank Miss A. Mineo for NMR spectral measurement. Particular appreciation is expressed to Dr. T. Noguchi for his encouragement during the course of this work.

References

1) M. Gall, J. B. Nester, Jr., A. D. Rudzik, and R. A Lahti, *J. Med. Chem.*, **19**, 1057 (1976).

2) a) M. Nakanishi, T. Yokobe, T. Arai, and M. Abe (to Yoshitomi Pharm. Ind. Ltd.), Japanese Patent Kokai 74-117 466 (1974); *Chem. Abstr.*, **84**, 44045g (1976); b) M. Nakanishi, T. Yokobe, T. Arai, and M. Abe, Japanese Patent Kokai 75-41 860 (1975); *Chem. Abstr.*, **83**, 193312y (1975).

3) M. Gall (to Upjohn Co.), U.S. Patent 3 941 803 (1976); *Chem. Abstr.*, **85**, 21368w (1976).

4) M. Gall (to Upjohn Co.), U. S. Patent 4 005 099 (1977); *Chem. Abstr.*, **86**, 190029n (1977).

5) a) T. Yokobe, T. Arai, and M. Abe (to Yoshitomi Pharm. Ind. Ltd.), Japanese Patent Kokai 75-95 264 (1975); *Chem. Abstr.*, **84**, 105590e (1976); b) M. Gall (to Upjohn Co.), U. S. Patent 3 941 802 (1976); *Chem. Abstr.*, **85**, 63067c (1976).

6) J. P. Maffrand, G. Ferrand, and F. Eloy, *Tetrahedron Lett.*, **1973**, 3449.

7) T. Hara, Y. Kayama, and T. Sunami, *J. Org. Chem.*, **43**, 4865 (1978).

8) a) M. E. Derieg, R. Ian Fryer, and S. S. Hillery, *J. Heterocycl. Chem.*, **8**, 181 (1971); b) Y. Kuwada, K. Meguro, and H. Tawada (to Takeda Chem. Ind. Ltd.), Japanese Patent Kokai 73-5 796 (1973); *Chem. Abstr.*, **78**, 97730j (1973).