

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

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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]benzodiazepines³⁾ 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 imidazolidine anions with 2-halobenzophenones,²⁾ oxidation of 1-(2-benzylphenyl)-1*H*-imidazoles⁵⁾ 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 reaction⁷⁾ of aminoacetaldehyde dialkyl acetals (**2**) with 2-(1-alkoxyethylideneamino)benzophenones (**1**) were heated with formic acid, ring opening and recyclization occurred 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 latter 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⁾

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 (Na₂SO₄), 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 (CDCl₃) 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 C₁₇H₁₃N₂OCl: 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 (CDCl₃) 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 C₁₇H₁₂N₂OCl₂: 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 H₂SO₄ (5 ml) was refluxed for 3 h. To the reaction mixture, after evapora-

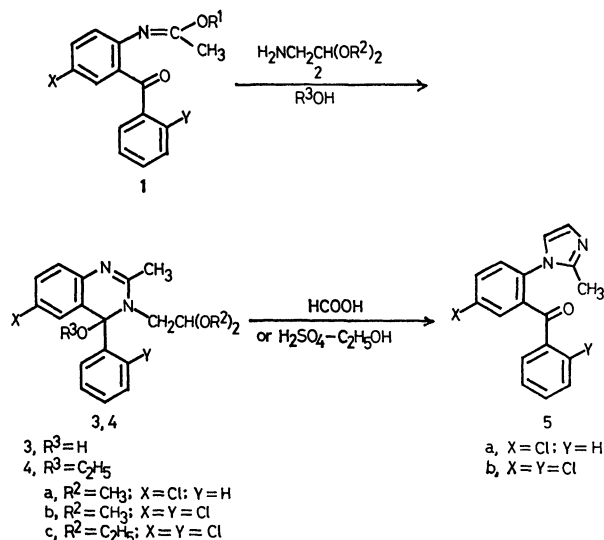


TABLE 1. CONVERSION OF QUINAZOLINES (**3, 4**) TO IMIDAZOLYLBENZOPHENONES (**5**)

Run	Starting material	Catalyst-solvent	Refluxing period/h	Product	Yield/%
1	3a	80% HCO ₂ H ^{a)}	3	5a	83
2	3c	99% HCO ₂ H ^{a)}	1	5b	85
3	3c	H ₂ SO ₄ -C ₂ H ₅ OH	3	5b	55
4	4b	85% HCO ₂ H ^{a)}	3	5b	81

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

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.

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