Synthesis of 2,4-Diphenyl-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazines

Mataka, Shuntaro
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Kitagawa, Hirohisa
Department of Energy Conversion Engineering, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University: Hisamitsu Pharmaceutical Co., Inc.

Tashiro, Masashi
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Tsukinoki, Takehito
Institute of Advanced Material Study, Kyushu University

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Synthesis of 2,4-Diphenyl-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazines

Shuntaro MATAKA*, Hirohisa KITAGAWA**, Masashi TASHIRO*
Takehito TSUKINOKI*** and Kichinosuke KAMATA****

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Reaction of 4-benzoyl-3-methyl-2-phenyl-N-methylpyrrole with hydrazine dihydrochloride in the presence of either arylaldehyde or paraformaldehyde gave 7-aryl-2,4-diphenyl-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazines or the 7-unsubstituted derivative via the corresponding 6,7-dihydro compounds.

Introduction

Recently it was reported that a novel ring-transformation reaction of 3,4-diaroyl-N-alkylypyrrolidines leads to 3-aryl-4-aroyl-2-methyl-N-alkylpyrroles. These pyrroles are synthetically of interest since they have two reactive sites, the electron-poor carbon atom of the benzoyl group on the β-position of the pyrrole-ring and the unsubstituted electron-rich α-carbon atom of the pyrrole-ring, in a favorable arrangement for the construction of 5- or 6-membered rings.

Earlier, several pyrrolo[2,3-d]pyridazines (5,6-diazaindoles) have been prepared as potential antineoplastic agents. In this report, we describe pyridazine ring construction on 4-benzoyl-3-methyl-2-phenyl-N-methylpyrrole (1) by the reaction with hydrazine and aldehyde, giving 1H-pyrrolo[2,3-d]pyridazines.

Results and Discussion

It was found that when 1 was heated with a large excess of hydrazine dihydrochloride in acetic acid under reflux for 96h, 2,4,7-triphenyl-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazine (2a) was given in 14% yield, together with unchanged 1 in 25% yield (Scheme 1). In order to build up the molecular structure of 2a, 1 had to take up a C7H5 unit, in addition to the two nitrogen atoms from hydrazine molecule. This C7H5 unit was supposed to be a benzoylmethine unit and might be derived from either benzoic acid or benzaldehyde hydrazone, which might be produced from 1 under the reaction conditions.

An addition of benzoic acid scarcely influenced the yield of 2. Interestingly, when the reaction of 1 with hydrazine dihydrochloride was carried out in the presence of benzaldehyde for 24h in acetic acid under reflux, 2a and the N-acetylated dihydro derivative 3 were obtained in 13% and 22% yields, respectively. The formation of 3 suggests the intermediacy of dihydro derivative 4 in the formation pathway of 2. Indeed, the reaction

*Department of Molecular Science and Technology
**Graduate Student of Molecular Science and Technology (At present; Hisamitsu Pharmaceutical Co. Ltd.)
***Institute of Advanced Material Study, Kyushu University
****Kurume National College of Technology, Komorino 1232, Kurume 830
carried out in butanol for 1.5h gave air-sensitive 4\(^{39}\) in 4\% yield, accompanied by 2a in 22\% yield. As expected, 4 was gradually oxidized during work-up or on standing at room temperature in air, giving 2a. Thus, 7-aryl derivatives 2a-c were obtained in 50-60\% yield by the following procedure: the reaction of 1, arylaldehyde, and hydrazine dihydrochloride was carried out in butanol under reflux for a short period and after removing an excess of hydrazine, the reaction mixture was dissolved in dichloromethane and oxygen was bubbled through the solution at room temperature, giving 2a-c.

The reaction in the presence of paraformaldehyde gave the 7-unsubstituted 2d in 27\% yield in acetic acid under reflux, but the corresponding N-acetyl derivative was not obtained.

Finally, a tentative formation pathway of 2 is presented in Scheme 1. As mentioned above, the reaction of 1 with hydrazine proceeded very slowly in the absence of aldehyde and unchanged 1 was recovered in 25\% yield. Thus, the initial step of the formation
pathway is assumed to be the addition of 1 to the aldehyde hydrazone, giving intermediate A which cyclizes to 4. Compound 4 is oxidized to afford 2. In acetic acid under reflux, 4 is acetylated, giving 3.

**Experimental**

**General.** All of the melting points were determined on a Mitamuraiken MELT THERMO and are uncorrected. The IR spectra were measured as KBr pellets on a Nippon Bunko IR-700. The NMR spectra were recorded at 270 MHz with a JEOL GSX-270 using TMS as an internal standard. The mass spectra were obtained on a JEOL JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

**Reaction of 1 with Hydrazine Dihydrochloride.** A mixture of pyrrole 1 (100 mg, 0.36 mmol), hydrazine dihydrochloride (381 mg, 3.63 mmol), and benzaldehyde (38 mg, 0.36 mmol) in acetic acid (5 ml) was heated under reflux for 24h under Ar atmosphere. It was cooled, poured into water, neutralized with sodium hydrogen carbonate, and extracted with dichloromethane. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo, leaving the residue. Chromatography of the residue gave 1 (a trace amount) (dichloromethane), acyl derivative 3 (33 mg, 22%) (hexane/ethyl acetate = 3/2), and 2a (17 mg, 13%) (hexane/ethyl acetate = 1/3).

**6-Acetyl-2,4,7-Triphenyl-1,3-dimethyl-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine (3):** Colorless prisms (hexane-dichloromethane); mp 212-214°C; IR 1661 cm⁻¹; 'HNMR δ = 1.71 (3H, s), 2.41 (3H, s), 3.34 (3H, s), 7.19 (1H, s), 7.21-7.48 (13H, m), and 7.70-7.78 (2H, m); ¹³CNMR δ = 11.89, 21.85, 31.47, 50.59, 110, 32, 112.51, 127.82, 127.96, 128.12, 128.23, 128.45, 128.55, 128.72, 129.16, 130.73, 131.12, 131.38, 133.46, 136.80, 138.65, 151.19, and 172.15; MS m/z 419 (M⁺). Found: C: 80.48; H, 6.09; N, 9.66%. Caled for C₂₅H₂₅N₃O: C, 80.16; H, 6.01; N, 10.02%.

**Reaction of 1 with Hydrazine Dihydrochloride in the Presence of Benzaldehydes.** A mixture of pyrrole 1 (100 mg, 0.36 mmol), hydrazine dihydrochloride (381 mg, 3.63 mmol) and benzaldehyde (38 mg, 0.36 mmol) in degassed butanol (5 ml) was heated under reflux for 45 min under Ar atmosphere. It was cooled and evaporated in vacuo, leaving the residue, to which water was added. It was extracted with dichloromethane, dried over magnesium sulfate, and evaporated in vacuo, leaving a residue. The residue was dissolved into dichloromethane (5 ml) and oxygen was bubbled gently through the mixture for 24h at room temperature. The solvent was evaporated in vacuo, leaving the residue. Chromatography (ethyl acetate) of the residue gave 2a (82 mg, 60%).

**2,4-Diphenyl-7-(p-methylphenyl)-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazine (2b):** A mixture of pyrrole 1 (100 mg, 0.36 mmol), hydrazine dihydrochloride (381 mg, 3.63 mmol) and benzaldehyde (38 mg, 0.36 mmol) in acetic acid (5 ml) was heated under reflux for 24h under Ar atmosphere. It was cooled, poured into water, neutralized with sodium hydrogen carbonate, and extracted with dichloromethane. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo, leaving the residue. Chromatography of the residue gave 1 (a trace amount), acyl derivative 3 (33 mg, 22%) (hexane/ethyl acetate = 3/2), and 2a (17 mg, 13%) (hexane/ethyl acetate = 1/3).
mmol) and \(p\)-methylbenzaldehyde (44 mg, 0.36 mmol) in degassed butanol (5 ml) was heated under reflux for 75 min under Ar atmosphere. It was cooled and evaporated in vacuo, leaving a residue, to which water was added. It was extracted with dichloromethane, dried over magnesium sulfate, and evaporated in vacuo, leaving a residue. The residue was dissolved into dichloromethane (5 ml) and oxygen was bubbled gently through the mixture for 24h at room temperature. The solvent was evaporated in vacuo, leaving the residue. Chromatography (ethyl acetate) of the residue gave 2b (84 mg, 60%) as colorless prisms (hexane-dichloromethane); mp 172.174°C; \(^1\)HNMR \(\delta = 1.85\) (3H, s), 2.45 (3H, s), 3.23 (3H, s), 7.26-7.36 (4H, m), 7.47-7.54 (6H, m), 7.59 (2H, d, J=8.3Hz), and 7.69-7.72 (2H, m); MS m/z 389 (M').

2,4-Diphenyl-7-(p-chlorophenyl)-1,3-dimethyl-IH-pyrrolo[2,3-d]pyridazine (2c): A mixture of pyrrole 1 (100 mg, 0.36 mmol), hydrazine dihydrochloride (381 mg, 3.63 mmol) and \(p\)-chlorobenzaldehyde (51 mg, 0.36 mmol) in degassed butanol (5 ml) was heated under reflux for 30 min under Ar atmosphere. It was cooled and evaporated in vacuo, leaving the residue, to which water was added. It was extracted with dichloromethane, dried over magnesium sulfate, and evaporated in vacuo, leaving a residue. The residue was dissolved in dichloromethane (5 ml) and oxygen was bubbled gently through the mixture for 24h at room temperature. The solvent was evaporated in vacuo, leaving the residue. Chromatography (ethyl acetate) of the residue gave 2c (79 mg, 53%) as colorless prisms (hexane-dichloromethane); mp 223-224°C; \(^1\)HNMR \(\delta = 1.85\) (3H, s), 3.25 (3H, s), 7.33-7.37 (2H, m), 7.45-7.55 (8H, m), and 7.63-7.72 (4H, m); MS m/z 411 (M') and 409 (M'). Found: C, 75.68; H, 5.17; 10.16%. Calcd for C\(_{26}\)H\(_{20}\)N\(_3\)Cl: C, 76.18; H, 4.92; N, 10.25%.

2,4-Diphenyl-1,3-dimethyl-1H-pyrrolo[2,3-d]pyridazine (2d). A mixture of pyrrole 1 (100 mg, 0.36 mmol), hydrazine dihydrochloride (381 mg, 3.63 mmol) and paraformaldehyde (55 mg, 1.82 mmol) in acetic acid (5 ml) was heated under reflux for 30h under Ar atmosphere. It was cooled, poured into water, neutralized with sodium hydrogen carbonate, and extracted with dichloromethane. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo, leaving a residue. Chromatography (ethyl acetate) of the residue gave 2d (29 mg, 27%) as pale yellow needles (hexane-dichloromethane); mp 187-188°C; \(^1\)HNMR \(\delta = 1.88\) (3H, s), 3.75 (3H, s), 7.36-7.39 (2H, m), 7.46-7.56 (6H, m), 7.67-7.70 (2H, m), and 9.28 (1H, s); MS m/z 299 (M'). Found: C, 79.50; H, 5.81; N, 13.80%. Calcd for C\(_{20}\)H\(_{17}\)N\(_3\): C, 80.24; H, 5.72; N, 14.04%.

References

5) Compound 4 was obtained by column chromatography with hexane-ethyl acetate (3:1) in 4% yield as a 9:1 mixture with 2a; pale yellow powder; \(^1\)HNMR (CDCl\(_3\)) \(\delta = 1.71\) (3H, s), 3.22 (3H, s), 5.54 (1H, s), 6.1-6.4 (1H, br s), 7.25-7.44 (13H, m), and 7.62-7.66 (2H, m).