Seiko Nan'ya*, Hirofumi Ishida and Yasuo Butsugan

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, 466 Nagoya, Japan Received May 9, 1994

o-Dibromoacetylbenzophenone, 2 or o-bromoacetylbenzophenone 3 reacted with aqueous ammonia to produce 3-phenylisoindolin-1-one 5. The reaction of 3 with methylamine afforded 3-hydroxy-2-methyl-3-phenylisoindolin-1-one 4 and 2-methyl-3-phenylisoindolin-1-one 5. Whereas from 2 with methylamine only 5 was obtained.

J. Heterocyclic Chem., 31, 1725 (1994).

o-Acetylbenzophenone 1 reacted with several primary amines to produce red, deep blue and yellow pigments including isoindole moieties [1-2]. To modify the reactivity of 1, the bromination of acetyl group of 1 with some brominating reagents were carried out [3-4]. In previous study [4], the bromination of 1 with bromine in tetrachloromethane under ultraviolet irradiation afforded dibromoacetylbenzophenone 2. Now 1 was treated in dry ether with 5,5dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (dibromo Meldrum acid) to produce monobromoacetylbenzophenone 3 instead of 2. In this paper, the reactions of 2 and 3 with aqueous ammonia as well as methylamine are reported.

The reaction of 2 with aniline in ethanol produced 2phenylimino-3-ethoxy-3-phenylindan-1-one [4]. Whereas the product isolated in the reaction of 2 and aqueous ammonia in methanol was 3-phenylisoindolin-1-one (5a). Furthermore, in the case of 2 with methylamine in methanol only decomposition products were obtained even in an icebath, instead in benzene 2-methyl-3-phenylisoindolin-1one (5b) was isolated.

3

On the other hand, monobromoacetylbenzophenone 3 reacted with aqueous ammonia in methanol afforded 5a in lower yield than the case of 2. When 3 was allowed to react with methylamine in benzene 3-hydroxy-2-methyl-3-phenylisoindolin-1-one (4b) and 5b were obtained. Treating a methanol solution of 4b with methylamine, some of 5b was prepared. Products 4b and 5a,b were identified with mass, ir and nmr spectra as well as some data in the literature for these compounds prepared by different methods. One possible mechanism of 2 or 3 with amine may be through formation of 1-bromomethyl-1,3-dihydroxy-3phenylisoindoline intermediate as shown as Scheme 1.

EXPERIMENTAL

Melting points were determined on Yanaco micro-melting point apparatus and are uncorrected. The ¹H and ¹³C nmr spectra were measured on a Varian Gemini-200 or Hitachi R-90 spectrometers, using tetramethylsilane as the internal standard. Mass spectra were obtained with Hitachi M-2000 spectrometer. The infrared spectra were recorded with JASCO A-102 spec-

trometer using potassium bromide pellets. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh ASTM) was used. Elemental analyses were performed at Elemental Analysis Center in Kyoto University.

o-Bromoacetylbenzophenone (3).

A mixture of o-acetylbenzophenone 1 (1 mmole) in dry ether and 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (dibromo-Meldrum Acid) [5] (0.5 mmole) was heated under reflux for 4 days. After neutralization of the mixture with sodium bicarbonate solution, the products was extracted with ether or chloroform and washed with water. The extract was chromatographed on a silica gel column using tetrachloromethane-chloroform (9:1) as the eluent. From the first fraction 56% of 3 was obtained and from the next fraction 43% of 1 was recovered. By use of excess dibromo Meldrum acid (1 mmole), the product 3 was contaminated with the by-products which were difficult to separate from 3.

Compound 3 had mp 50° dec; ir: 1680 and 1660 cm⁻¹ (ν CO); ¹H nmr (deuteriochloroform): δ 7.86-7.41 (m, 8H), 7.36 (m, 1H), 4.31 (s, 2H, CH₂Br); ms: m/z 304/302 (M*), 303/301 (M-1)*, 223 (M-Br)*, 209 (base peak, M-CH₂Br)*).

Anal. Calcd. for C₁₅H₁₁BrO₂ (303.15): C, 59.43; H, 3.63; Br, 26.36. Found: C, 59.02; H, 3.71; Br, 26.81.

3-Phenylisoindolin-1-one (5a).

A. From 2 and Aqueous Ammonia.

To a methanol solution (5 ml) of 2 (0.3 mmole) 3 ml of 28% aqueous ammonia was added and the mixture was stirred at room temperature for three days. After concentrating the mixture, the residue was chromatographed on a silica gel column using chloroform-methanol (9:1) as the eluent to give colorless 5a in 61% yield. When the reaction was carried out in benzene under the above conditions, 5a was obtained in 24% yield.

B. From 3 and Aqueous Ammonia.

The mixture of 3 and aqueous ammonia in methanol was treated in a similar manner as for A to give 5a in 11% yield. When the reaction was followed in benzene, only decomposition products were obtained.

Compound **5a** had mp 215.1-216.5° (ethyl acetate) (lit [6] mp 214-216°); ir: 3210 (ν NH) and 1690 (ν CO) cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.88 (m, 1H), 7.48 (m, 3H), 7.35-7.15 (m, 5H), 6.71 (br, 1H, NH), 5.61 (s, 1H, 3-H); (lit [6] ¹H nmr (DMSO-d₆): δ 7.86 (m, 1H, 7-H), 5.61 (s, 1H, 3-H); ¹³C nmr (deuteriochloroform): δ 171.1 (CO), 148.0, 132.3, 130.5, 129.6, 129.1, 128.6, 128.4, 128.1, 126.8, 123.8, 123.3, 60.9 (CHN =); ms: m/z 209 (M⁺, base peak), 180 (M-COH)⁺.

Anal. Calcd. for C₁₄H₁₁NO (209.25): C, 80.36; H, 5.30; N, 6.69; O, 7.65. Found: C, 79.95; H, 5.52; N, 6.68; O, 7.60.

2-Methyl-3-phenylisoindolin-1-one (5b) and 3-Hydroxy-2-methyl-3-phenylisoindolin-1-one (4b).

To a benzene solution of **3** (0.5 mmole) 0.2 ml of aqueous methylamine solution (40%) was added under stirring in an ice-bath and the mixture was stirred for 3 hours. After neutralization of the mixture with hydrochloric acid, the benzene layer was washed with water and concentrated. The residue was chromatographed on a silica gel column using tetrachloromethane-chloroform (3:1) as the eluent. From the first pale yellow fraction **5b** was obtained in the yield of 7% and the second pale green fraction 21% of **4b** was yielded. The reaction was carried out at room temperature to afford **5b** in 11% and **4b** in 17% yield respectively. Treating **3** with aqueous ammonia in methanol instead of benzene **5b** in 3% and **4b** in 2.5% were isolated. When a methanol solution of **4b** with methylamine was stirred formation of **5b** was observed.

Compound 4b had mp 185-187° (lit [7] mp 187-188°); ir: (cm⁻¹) 3250 (ν OH), 1675 (ν CO), 1050 (ν COH); ¹H nmr (deuteriochloroform): δ 7.59 (m, 1H), 7.51-7.29 (m, 8H), 4.21 (br, 1H, OH), 2.66 (s, 3H, NCH₃); ¹H nmr (DMSO-d₆): δ 7.71 (m, 1H), 7.51 (m, 2H), 7.38-7.25 (m, 6H), 7.02 (s, 1H, OH), 2.68 (s, 3H, NCH₃); (lit [7] 7.37 (s, 5H) 7.9-7.3 (m, 4H), 7.02 (s, 1H, OH), 2.70 (s, 3H, NCH₃); ms: m/z 239 (M*), 222 (M-OH)*, 210 (M-CO-1)*, 162 (base peak, M-Ph)*) ([7] 239, 222, 210, 162 (100%)).

Compound **5b** had mp 103-105° (carbon tetrachloride) (lit [6] 102-104°); ir: 1680 cm⁻¹ (ν CO); ¹H nmr (deuteriochloroform): δ 7.89 (m, 1H), 7.49-7.33 (m, 5H), 7.20-7.12 (m, 3H), 5.34 (s, 1H), 2.98 (s, 3H, NCH₃); (lit [6] ¹H nmr (DMSO-d₆): δ 7.90 (m, 1H, 7-H), 5.33 (s, 1H), 2.97 (s, 3H); ms: m/z 223 (base peak, M*), 194 (M-CO-1), 146 (M-Ph)*.

Reaction of 2 and Methylamine.

The mixture of 2 and aqueous methylamine in benzene was stirred at room temperature for 3 hours. After the usual workup as above only 5b isolated in 19% yield. The reaction in methanol even in an ice-bath none of the 4b and 5b were obtained.

REFERENCES AND NOTES

- S. Nan'ya and E. Maekawa, Nippon Kagaku Kaishi, 1953 (1974),
 1535 (1975), 1747 (1977).
- [2] S. Nan'ya, T. Fujii and Y. Butsugan, J. Heterocyclic Chem., 27, 1407 (1990).
- [3] S. Nan'ya, T. Kitahara, K. Fujii, A. C. Bajji and Y. Butsugan, J. Heterocyclic Chem., 29, 1525 (1992).
- [4] S. Nan'ya, A. C. Bajji, H. Ishida, E. J. Moiji and Y. Butsugan, J. Heterocyclic Chem., 31, 401 (1994).
 - [5] H. Synder and C. W. Kruse, J. Am. Chem. Soc., 80, 1942, (1958).
- [6] I. Tikk, G. Déak and J. Tamás, Acta. Chim. Hung., 125, 289 (1988)
- [7] W. L. F. Armarego and S. C. Sharma, J. Chem. Soc. (C), 1600 (1970).