Reaction of Benzyne with 2-Hydroxy- and 2-Aminophenyl Ketones: Synthesis of Xanthenes and Acridines

Kentaro OKUMA[1)], Nahoko MATSUNAGA[1)], and Saori OZAKI[1)]

(Received November 30, 2010)

Abstract

Reaction of benzyne with 2-hydroxybenzophenone afforded 9-phenyl-9-hydroxyxanthene, whereas reaction with 2-hydroxyacetophenone yielded 9-methylenexanthene. 9-Methyl-9-hydroxyxanthene, initial cycloadduct, further dehydrated to give exo-methylene xanthene. Reaction of benzyne with 2-aminophenyl ketones gave acridines in good yields.

Introduction

Arynes are highly reactive intermediates that have found numerous applications in organic synthesis.[1,2] Our ongoing interest in the exploration of reactive benzyne with thio- and selenocarbonyl compounds for the synthesis of functionalized *S*- and *Se*-heterocycles has led to our investigation of the synthesis of benzothietes, benzothianes, and benzoselenates.[3] Xanthenes and acridines are of biochemical and pharmaceutical importance.[4] Recently, xanthene derivatives were referred to photocatalysis in metal-free hydrogenation and ligands in transition metal catalysis.[5] Acridine moieties usually have seen in many useful dyes which could bond to RNA.[6] Acridines are potential drugs due to their trypanocidal activities.[7] It is noteworthy that although substituents at the 9-positions of xanthenes and acridines are essential linkers to attach biomolecules, the linking modes were rather limited. This is probably because of the fact that the existing strategies to afford 9-functionalized xanthenes or acridines are rare, most of which often include Friedel-Crafts cyclization reactions.[8] Although reactions of aldehydes with benzyne to give C=O bond insertion products (ca. 30%) were reported in the early seventies,[9] Yoshida et al. reported the formation of 9-arylxanthenes by a novel insertion reaction of benzyne derived from 2-trimethylsilylphenyl triflate (**1**)[10] with aromatic aldehydes (22-70%).[11] Larock and Zhao have reported the reaction of arynes with benzoates, which afforded xanthones and thioxanthones, and acridones (35-81%).[12] Recently, our group reported the reaction of benzyne with salicylaldehydes, which afforded xanthenes and xanthones in good overall yields under very mild conditions.[13] These interesting observations raise the question whether 2-hydroxyphenyl ketones or 2-aminophenyl ketones will react with benzyne to give any 9-substituted 9-hydroxyxanthenes or 9-substituted acridines. In this paper, we would like to show the annulation reaction of benzyne by 2-hydroxyphenyl or 2-aminophenyl ketones.

Results and Discussion

Synthesis of xanthenes

We frist tried the reaction of benzyne with 2-hydroxyphenyl ketone derivatives in the hope that

1) Department of Chemistry, Faculty of Science, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan

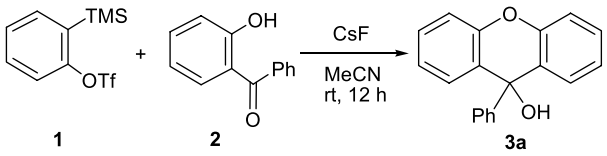
9-substituted 9-hydroxylxantenes would be obtained. When a solution of 2-hydroxybenzophenone (**2**) and triflate **1** was treated with CsF in acetonitrile at rt for 12 h, 9-hydroxy-9-phenylxanthene (**3a**) was obtained in 82% yield (Scheme 1).

On the other hand, when 2-hydroxyacetophenone (**4a**) was used as a substrate, 9-methylenexanthene (**5a**) was obtained in 64% yield. Initially formed 9-hydroxy-9-methylxanthene (**3b**) would be dehydrated to give **5a** (Scheme 2). Other reactions also proceeded in a similar manner (Table 1).

Synthesis of 9-substituted acridines

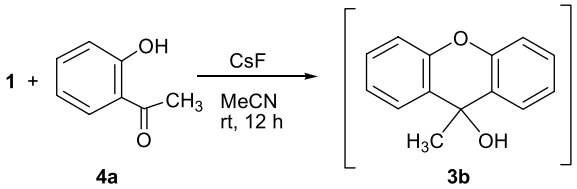
Reaction of 2-aminoacetophenone (**6a**) with halogeno-substituted benzynes to afford acridines **7** was already reported by Yoon et al.[14] However, starting benzyne precursor, 5-(3-halogeno-4-methoxyphenyl)thianthrenium perchlorates must be required both methoxy and halogeno groups, otherwise benzyne could not be formed even under strong basic conditions. Recently, Larock et al. also reported that the reaction of 2-aminoacetophenone **6a** with **1** as a benzyne precursor gave 9-methylacridine (**7a**).[15] However, there is no report on the reaction of benzyne with other alkyl 2-aminophenyl ketones such as 1-(2-aminophenyl)-2-phenylethanone (**6b**) and 1-(2-aminophenyl)hexan-1-one (**6c**). Phenyl ketones **6b** and **6c** were very difficult to synthesize by conventional methods. Recently, we have reported the synthesis of 2-aminophenyl ketones **6** by the reaction of 2-alkynylnitrobenzenes **8** with Sn/HCl (Scheme 3).[16] This method provides a general synthesis of long chained 2-aminophenyl ketones **6**. These results prompted us to investigate the reaction with benzyne with ketones **6**.

Treatment of triflate **1** with phenylethanone **6b** followed by the addition of CsF at rt for 12 h resulted in the formation of 9-methylacridine (**7b**) in 91% yield (Table 2. Entry 1). Interestingly, 1-(2-aminophenyl)-4-hydroxybutanone (**6d**) reacted

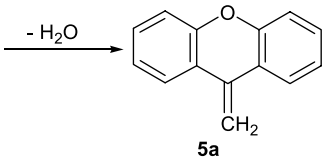


1 **2** **3a**

Scheme 1.

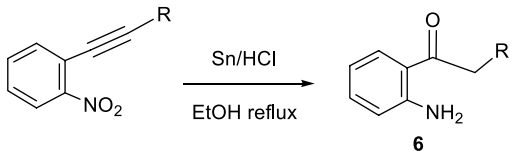


4a **3b**



5a

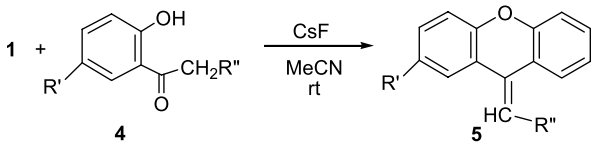
Scheme 2.



6

Scheme 3.

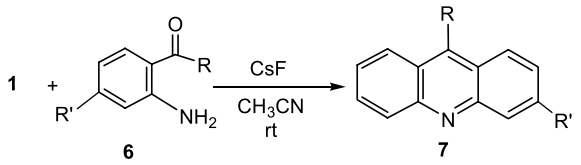
Table 1. Reaction of 1 with 2-hydroxyphenyl ketones 4



4 **5**

Hydroxyphenyl ketone **4**	Time (h)	**5**	Yield/ %
4a R' = H, R"= H	12	**5a**	64
4b R' = Br, R"= H	13	**5b**	68
4c R' = H, R"= CH_3	15	**5c**	82

Table 2. Reaction of triflate 1 with 2-aminophenyl ketones 6.



Entry	2-Aminophenyl ketone	R	R'	Time (h)	7	Yield/ %
1	**6b**	$PhCH_2$	H	12	**7b**	91
2	**6c**	*n*-pentyl	H	12	**7c**	84
3	**6d**	$HOCH_2CH_2CH_2$-	H	16	**7d**	85
4	**6e**	neopentyl	H	18	**7e**	81
5	**6f**	$PhCH_2$	Cl	12	**7f**	72
6	**6g**	$PhCH_2$	OCH_3	13	**7g**	73

with triflate **1** to give 9-(3-hydroxypropyl)acridine (**7d**) in 85% yield, indicating that amino substituent is more reactive than hydroxy substituent (Entry 3). Other acridines were synthesized in good yields (Entries 4-6). Thus, general and chemoselective synthesis of 9-substituted acridines **7** was achieved.

In summary, reaction of 2-aminophenyl ketones **6** with benzyne gave acridines **7** in high yields. The present method provides a novel approach to the synthesis of 9-hydroxyxanthenes and 9-methylenexanthenes by reaction of benzyne with 2-hydroxyphenyl ketones.

Experimental

General

All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra (^1H at 400 MHz; ^{13}C at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS for ^1H- and ^{13}C-NMR. Melting points were uncorrected.

Materials: 9-Phenyl-9-hydroxyxanthene **3a** was purchased from Aldrich. Triflate **1** was synthesized by the method in the literature.[10]

Reaction of Triflate 1a with 2-Hydroxybenzophenone 2 in the Presence of CsF

To a mixture of CsF (0.334 g, 2.2 mmol), 2-hydroxybenzophenone **2** (0.198 g, 1.0 mmol), and K_2CO_3 (0.414 g, 3.0 mmol) in acetonitrile (7 mL) was added triflate **1** (0.327 g, 1.1 mmol) in one portion. After stirring for 12 h, 5% aq Na_2CO_3 (10 mL) was added to the reaction mixture and the mixture was extracted with ether (5 mL x 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow oily crystals, which were chromatographed over alumina by elution with hexane-ethyl acetate (10:1) to afford 9-phenyl-9-hydroxyxanthene (**3a**) (0.225 g, 0.82 mmol). Colorless crystals mp 159-160 °C. ^1H NMR spectral data and mp were identical with the authentic sample (mp 160-161 °C).

^1H NMR ($CDCl_3$) δ = 2.64 (s, OH), 7.05 (dd, 2H, J = 7.2 and 7.6 Hz, Ar), 7.24 (d, 2H, J = 7.2 Hz, Ar), 7.28-7.45 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$) δ = 70.66, 116.64, 123.80, 126.45, 126.98, 127.39, 128.20, 129.25, 129.32, 148.17, 149.89.

Reaction of Triflate 1 with 2-Hydroxyacetophenone 4a in the Presence of CsF

To a solution of CsF (0.456 g, 3.0 mmol), 2-hydroxyacetophenone **4a** (0.136 mg, 1.0 mmol),

and K_2CO_3 (0.414 g, 3.0 mmol) in acetonitrile (5 mL) was added triflate **1** (0.447 g, 1.5 mmol) in one portion. After stirring for 12 h, 5% aq Na_2CO_3 (10 mL) was added to the reaction mixture and the mixture was extracted with ether (5 mL x 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give a pale yellow oil, which was chromatographed over alumina by elution with hexane-ethyl acetate (5:1) to afford 9-methylenexanthene (**5a**) (0.132 g, 0.68 mmol). colorless crystals: mp 110-111 ℃ (lit.[17] mp 112 ℃). ^{1}H NMR ($CDCl_3$) δ = 5.51 (s, 2H, CH_2), 7.10-7.13 (m, 4H, Ar), 7.30 (dd, 2H, J = 7.6 and 8.0 Hz, Ar), 7.73 (d, 2H, J = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 77.45, 101.28, 117.47, 121.46, 123.56, 124.06, 129.74, 150.81. MS: Calcd for C_{10} $H_{10}O$: 194.07. Found: 194.01 (M^+).

Other reactions were carried out in a similar manner. 2-Bromo-9-methylenexanthene **5b**: colorless crystals. mp 152-156 ℃. ^{1}H NMR ($CDCl_3$) δ = 5.46 (s, 1H, =CH), 5.52 (s, 1H, =CH), 6.89 (d, 1H, J = 8.8 Hz, Ar), 7.06-7.15 (m, 2H, Ar), 7.30 (dd, 1H, J = 7.2 and 8.4 Hz, Ar), 7.37 (d, 1H, J = 8.4 Hz, Ar), 7.68 (d, 1H, J = 8.0 Hz, Ar), 7.81 (br s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ = 102.37 (=CH), 116.17, 117.48, 119.29, 120.90, 123.38, 123.88, 123.88, 124.05, 126.84, 129.69, 131.70, 132.49, 149.82, 150.47. MS: Calcd for $C_{14}H_9BrO$: 271.98 and 273.98. Found: 273.96 and 275.89.
9-Ethylidenexanthene **5c**: colorless crystals, mp 149-153 ℃ (lit.[18] mp was not shown); ^{1}H NMR ($CDCl_3$) δ = 2.12 (d, 3H, J = 7.2 Hz, CH3), 6.04 (q, 1H, J = 7.2 Hz, =CH), 7.05-7.30 (m, 6H, Ar), 7.51 (d, 1H, J = 8.4 Hz, Ar), 7.59 (d, 1H, J = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 16.00 (CH_3), 116.66, 116.86, 120.65, 122.74, 122.96, 123.59, 123.89, 126.13, 127.37, 128.18, 128.19, 128.57, 151.45, 153.11.

Reaction of triflate 1 with ethanone 6b: To a solution of triflate **1** (0.108 g, 0.36 mmol) and dried CsF (0.182 g, 1.2 mmol) in acetonitrile (5 mL) was added 1-(2-aminophenyl)-2-phenylethanone **6b** (0.040 g, 0.30 mmol) in one portion. After being stirred for 12 h, the reaction mixture was poured into sat. aq NaCl, and extracted with ethyl acetate, which was dried over $MgSO_4$, filtered, and evaporated to give yellow crystals. The mixture was chromatographed over silica gel by elution with hexane-ethyl acetate (1:1) to give 9-benzylacridine **7b** (0.049 g, 0.27 mmol). 9-benzylacridine **7b**: mp 171-172 ℃. (lit.[19] mp 173-174 ℃)

Other reactions were carried out in a similar manner. 9-pentylacridine **7c**: yellow crystals, mp 67-69 ℃ (lit.[20] mp 69 ℃) : ^{1}H NMR ($CDCl_3$) δ = 0.931 (t, 3H, J = 7.2 Hz, CH_3), 1.44 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 3.59 (t, 2H, J = 7.6 Hz, CH_2), 7.54 (dd, 2H, J = 6.8 and 7.6 Hz, Ar), 7.75 (dd, 2H, J = 6.8 and 7.6 Hz, Ar), 8.22 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.20 (CH_3), 22.60 (CH_2), 27.95 (CH_2), 31.20 (CH_2), 32.35 (CH_2), 124.35, 125.05, 125.81, 130.05, 130.65, 147.75, 149.20 (Ar).
9-(3-hydroxypropyl)acridine **7d**: yellow crystals; mp 225-226 ℃. ^{1}H NMR (CD_3OD) δ = 2.04 (m, 2H, CH_2), 3.78 (t, 2H, J = 6.0 Hz, CH_2), 3.90 (dd, 2H, J = 6.0 and 8.0 Hz, OCH_2), 7.77 (dd, 2H, J = 7.7 and 8.8 Hz, Ar), 8.02 (dd, 2H, J = 7.7 and 8.8 Hz, Ar), 8.20 (d, 2H, J = 8.8 Hz, Ar), 8.60 (d, 2H, J = 8.8 Hz, Ar). ^{13}C NMR (CD_3OD) δ = 26.72 (CH_2), 35.64 (CH_2), 61.90 OCH_2), 121.62 (Ar), 126.11 (Ar), 127.42 (Ar), 128.98 (Ar), 137.98 (Ar), 140.97 (Ar), 164.25 (Ar). HRMS: Calc for $C_{16}H_{15}NO$; 237.1154. Found 237.1151 (M^+).
9-neopentyl-acridine **7e**: yellow crystals, mp 114-115 ℃; ^{1}H NMR ($CDCl_3$) δ = 0.98 (s, 9H, tert-Bu), 3.68 (s, 2H, CH_2), 7.53 (dd, 2H, J = 7.6 and 7.6 Hz, Ar), 7.77 (dd, 2H, J = 7.6 and 7.6 Hz, Ar), 8.22 (d, (2H, J = 7.6 Hz, Ar), 8.36 (d, 2H, J = 7.6 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 31.50 (*tert*-Bu), 35.40 (*tert*-Bu), 39.60 (CH_2), 125.50, 125.85, 126.10, 129.30, 130.05, 145.10, 149.10 (Ar). HRMS: Calcd for $C_{18}H_{19}N$; 249.1517. Found; 249.1511 (M^+).
9-benzyl-3-chloroacridine **7f**: yellow crystals; mp 144-145 ℃; ^{1}H NMR ($CDCl_3$) δ = 4.93 (s, 2H, CH_2), 7.04 (d, 2H, J = 7.2 Hz, Ar), 7.15-7.24 (m, 3H, Ar), 7.38 (d, 1H, J = 9.2 Hz, Ar), 7.48 (dd, 1H, J = 7.2 and 7.6 Hz, Ar), 7.73 (dd, 1H, J = 7.2 and 7.6 Hz, Ar), 8.09 (d, 1H, J = 9.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 33.42 (CH_2), 124.21, 125.01, 125.86, 126.51, 126.63, 126.85, 127.55, 128.28, 128.93, 129.03,. 130.51, 130.68, 136.16, 139.22, 144.21, 149.09, 149.68 (Ar). HRMS: Calcd for $C_{20}H_{12}ClN$; 303.0815. Found; 303.0824 (M^+).
9-Benzyl-3-methoxyacridine **7g**: mp 117-118 ℃, ^{1}H NMR ($CDCl_3$) δ = 4.01 (s, 3H, OMe), 4.96 (s, 2H, CH_2), 7.08 (d, 2H, J = 7.2 Hz, Ar), 7.16-7.23 (m, 4H, Ar), 7.44 (d, 1H, J = 7.2 Hz, Ar), 7.48 (s, 1H, Ar), 7.73 (dd, 1H, J = 7.4 and 7.8 Hz, Ar), 8.09 (d, 1H, J = 9.6 Hz, Ar), 8.17 (d, 1H, J = 8.8 Hz, Ar). ^{13}C NMR

($CDCl_3$) δ = 33.37 (CH_2), 55.84 (OMe), 105.98, 121.62, 122.08, 124.84, 125.04, 125.29, 126.28, 126.67, 128.29, 128.93, 129.74, 130.12, 139.52, 143.67, 149.22, 150.87, 161.23 (Ar). HRMS: Calcd for $C_{21}H_{15}NO$; 299.1310. Found; 299.1312 (M^+).

References

1 For reviews, see: a) R. W. Hoffmann, Dehydrobenzene and cycloalkynes; Academic Press, New York, 1967. b) H. Hart, In The Chemistry of Triple-Bonded Functional Groups, Supplement C2, S. Patai, Ed, Wiley, Chichister, UK, 1994, Chapter 18.

2 Recent examples, see: J. B. Feltenberger, R. Hayashi, Y. Tang, E. S. C. Babiash, R. P. Hsung, *Org. Lett.* **2009**, *11*, 3666. Z. Qiu, Z. Xie, *Angew. Chem. Int.* Ed. **2009**, *48*, 5729. A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem. Int. Ed.* **2009**, *48*, 5199. H. Ankati, E. Biehl, *Tetrahedron Lett.* **2009**, *50*, 4677. Y. –L. Liu, Y. Liang, S. –F. Pi, J. –H. Li, *J. Org. Chem.* **2009**, *74*, 5691. D. C. Rogness, R. C. Larock, *Tetrahedron Lett.* **2009**, *50*, 4003. F. Zhang, J. E. Moses, *Org. Lett.* **2009**, *11*, 1587. H. Ding, Y. Zhang, W. Yao, D. Xu, C. Ma, *Chem. Commun.* **2008**, 5797. K. Okuma, H. Hino, A. Sou, N. Nagahora, K. Shioji, *Chem. Lett.* **2009**, *38*, 1030.

3 K. Okuma, T. Shirokawa, T. Yamamoto, T. Kitamura, Y. Fujiwara, *Tetrahedron Lett.* **1996**, *37*, 8883. K. Okuma, K. Shiki, K. Shioji, *Chem. Lett.* **1998**, *79*. K. Okuma, S. Sonoda, Y. Koga, K. Shioji, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2997. K. Okuma, K. Shiki, S. Sonoda, Y. Koga, K. Shioji, T. Kitamura, Y. Fujiwara, Y. Yokomori, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 155. K. Okuma, T. Shigetomi, Y. Nibu, K. Shioji, M. Yoshida, Y. Yokomori, *J. Am. Chem. Soc.* **2004**, *126*, 9508. K. Okuma, T. Tsubone, T. Shigetomi, K. Shioji, Y. Yokomori, *Heterocycles* **2005**, *65*, 1553. T. Shigetomi, H. Soejima, Y. Nibu, K. Shioji, K. Okuma, Y. Yokomori, *Chem. Eur. J.* **2006**, *12*, 7742.

4 "Burger's Medicinal Chemistry", 4th ed.; M. E. Wolff, ed, John Wiley & Sons, Inc.: New York, 1981, Part III, pp397-407. M. P. Okoh, J. L. Hunter, J. E. T. Corrie, M. R. Webb, *Biochemistry* **2006**, *45*, 14764. M. S. T. Goncalves, *Chem. Rev.* **2009**, *109*, 190.

5 T. Lazarides, T. Mcormick, P. Du, G. Luo, B. Lindley, R. Eisenberg, *J. Am. Chem. Soc.* **2009**, *131*, 9192. J. Yin, S. L. Buchbald, *Org. Lett.* **2000**, *2*, 1101.

6 A. Kuzuya, R. Mzoguchi, T. Sasayama, J. -M. Zhou, M. Komiyama, *J. Am. Chem. Soc. 126*, 1430.

7 O. Inhoff, J. M. Richards, J. W. Briet, G. Lowe, R. L. Krauth-Siegel, *J. Med. Chem.* **2002**, *45*, 4524. S. Bonse, C. Santelli-Rouvier, J. Barbe, R. L. Krauth-Siegel, *J. Med. Chem.* **1999**, *42*, 5448.

8 H. Isibashi, K. Takagaki, N. Imada, M. Ikeda, *Tetrahedron*, **1994**, *50*, 10215.

9 H. Heaney, C. T. McCarty, *Chem. Commun.* **1970**, 123. J. Nakayama, M. Yoshida, O. Simamura, *Chem. Lett.* **1973**, 451.

10 Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

11 H. Yoshida, M. Watanabe, J. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2004**, *6*, 4049.

12 J. Zhao, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 583.

13 K. Okuma, A. Nojima, N. Matsunaga, K. Shioji, *Org. Lett.* **2009**, *11*, 169.

14 K. Yoon, S. M. Ha, K. Kim, *J. Org. Chem.* **2005**, *70*, 5741.

15 D. C. Rogness, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 2289.

16 K. Okuma, S. Ozaki, J. Seto, N. Nagahora, K. Shioji, *Heterocycles* **2010**, 81, 935.

17 A. A. Goldberg, A. H. Wragg, *J. Chem. Soc.* **1957**, 4823. A. Schoenberg, E. Frese, *Chem. Ber.* **1963**, *96*, 2420.

18 S. R. Abrams, *J. Labelled Com. and Radiopharm.* **1987**, *24*, 941.

19 H. Nozaki, M. Yamabe, R. Noyori, R. *Tetrahedron* 1965, *21*, **1657**.

20 N. Buu-Hoi, *J. Chem. Soc.* **1950**, 1146.