

## Perchloric Acid – Silica ( $\text{HClO}_4 \cdot \text{SiO}_2$ )-Catalyzed Synthesis of 14-Alkyl- or 14-Aryl-14*H*-dibenzo[*a,j*]xanthenes and *N*-[(2-Hydroxynaphthalen-1-yl)methyl]amides<sup>1)</sup>

by Biswanath Das\*, D. Nandan Kumar, Keetha Laxminarayana, and B. Ravikanth

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India  
(phone: + 91-40-7193434; fax: + 91-40-7160512; e-mail: biswanathdas@yahoo.com)

The synthesis of 14-aryl- or 14-alkyl-14*H*-dibenzo[*a,j*]xanthenes **3** involving the treatment of naphthalen-2-ol (**1**) with arenecarboxaldehydes or alkanals **2** in the presence of  $\text{HClO}_4 \cdot \text{SiO}_2$  as a heterogeneous catalyst was achieved (*Table 1*), and this reaction was extended to the preparation of *N*-[(2-hydroxynaphthalen-1-yl)methyl]amides **5** by a three-component reaction with urea (**4a**) or an amide **4b–d** as a third reactant (*Table 2*).

**Introduction.** – The synthesis of xanthene derivatives, particularly of benzo-fused xanthenes, has attracted considerable attention by chemists because of their biological and pharmaceutical properties. These compounds possess anti-inflammatory [1], antiviral [2], and antibacterial [3] activity. Furthermore, xanthene derivatives can be utilized in photodynamic therapy [4] and as antagonism for the paralyzing action of zoxazolamine [5]. The other useful applications of these compounds are as dyes [6], fluorescent materials for visualization of biomolecules [7], and in laser technologies [8]. It is also noteworthy that several polycyclic compounds containing the xanthene skeleton have been reported from natural sources [9]. Thus, the synthesis of xanthene derivatives is currently of great interest.

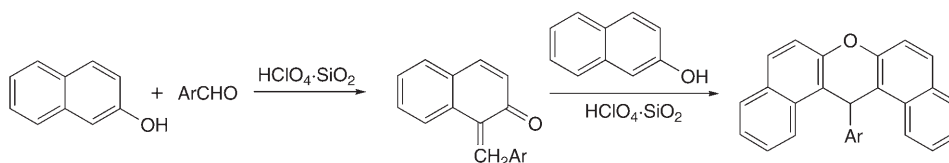
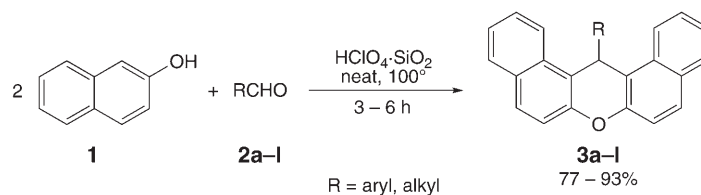
Various methods have been developed for the synthesis of xanthenes such as the reactions of naphthalen-2-ol (**1**) with formamide [10], 2-hydroxynaphthalene-1-methanol [11] and carbon monoxide [12], aryne cycloaddition to phenols [13], cyclodehydration [14], and intramolecular coupling of aldehydes and ketones [15]. However, several of these methods suffer from harsh reaction conditions, long reaction times, and poor yields. Consequently, there is a need for the development of a clean, facile, and efficient process for the synthesis of xanthene derivatives.

**Results and Discussion.** – Heterogeneous catalysts have gained much importance in recent years due to economic and environmental benefits [16]. These catalysts make synthetic processes clean, safe, high yielding, and inexpensive. A tremendous interest has sparked in various chemical transformations promoted by catalysts under heterogeneous conditions. Recently  $\text{HClO}_4 \cdot \text{SiO}_2$  has been found to be an efficient heterogeneous catalyst in various useful chemical transformations [17]. In continuation

<sup>1)</sup> Part 143 in the series, 'Studies on Novel Synthetic Methodologies'.

of our work on the application of heterogeneous catalysts to the development of simplified synthetic methodologies [18], we observed that  $\text{HClO}_4 \cdot \text{SiO}_2$  [19] can act as an efficient catalyst for the synthesis of 14-aryl- or 14-alkyl-14*H*-dibenzo[*a,j*]xanthenes **3** by the condensation of naphthalen-2-ol (**1**) with aldehydes **2** (Table 1). Initially, we carried out the reaction of **1** with 4-chlorobenzaldehyde (**2b**) in the presence of the catalyst  $\text{HClO}_4 \cdot \text{SiO}_2$  by stirring the mixture for 3 h at 100° in the absence of solvent. We observed the formation of the desired xanthene derivative **3b** (Table 1) in 91% yield (isolated material). The same method applied to the conversion of **1** with other aldehydes **2** proceeded within 3–6 h to form the products **3** in high yields (77–93%) (Table 1). The reaction was equally effective with both aromatic and aliphatic aldehydes. The aromatic aldehydes containing electron-donating as well as electron-withdrawing groups underwent the conversion smoothly. We believe that in the present transformations the xanthenes could be generated by ‘*in situ*’ formation of ‘*o*-quinomethane’ intermediates [20] (Scheme).

Scheme

Table 1. Preparation of 14-Aryl- or 14-Alkyl-14*H*-dibenzo[*a,j*]xanthenes **3**<sup>a)</sup>

| Aldehyde  | R                                                | Product   | Time [h] | Yield [%] <sup>b)</sup> |
|-----------|--------------------------------------------------|-----------|----------|-------------------------|
| <b>2a</b> | Ph                                               | <b>3a</b> | 3.5      | 92                      |
| <b>2b</b> | 4-Cl–C <sub>6</sub> H <sub>4</sub>               | <b>3b</b> | 3.0      | 91                      |
| <b>2c</b> | 4-F–C <sub>6</sub> H <sub>4</sub>                | <b>3c</b> | 3.75     | 90                      |
| <b>2d</b> | 3-CF <sub>3</sub> –C <sub>6</sub> H <sub>4</sub> | <b>3d</b> | 4.0      | 93                      |
| <b>2e</b> | 3-NO <sub>2</sub> –C <sub>6</sub> H <sub>4</sub> | <b>3e</b> | 3.75     | 88                      |
| <b>2f</b> | 4-Me–C <sub>6</sub> H <sub>4</sub>               | <b>3f</b> | 4.25     | 81                      |
| <b>2g</b> | 4-Et–C <sub>6</sub> H <sub>4</sub>               | <b>3g</b> | 4.0      | 89                      |
| <b>2h</b> | 4-OH–C <sub>6</sub> H <sub>4</sub>               | <b>3h</b> | 4.5      | 92                      |
| <b>2i</b> | 4-MeO–C <sub>6</sub> H <sub>4</sub>              | <b>3i</b> | 4.0      | 84                      |
| <b>2j</b> | 3-MeO,4-OH–C <sub>6</sub> H <sub>3</sub>         | <b>3j</b> | 4.75     | 89                      |
| <b>2k</b> | Et                                               | <b>3k</b> | 6.0      | 77                      |
| <b>2l</b> | <sup>i</sup> Pr                                  | <b>3l</b> | 5.5      | 82                      |

<sup>a)</sup> All the products were characterized by <sup>1</sup>H-NMR and MS data. <sup>b)</sup> Yield of isolated material.

Encouraged by the above results, we extended this protocol to a three-component coupling reaction involving urea (**4a**) or an amide (**4b–d**) as a third reactant to obtain the corresponding *N*-(2-hydroxynaphthalen-1-yl)methyl]amides **5** (Table 2). Here the ‘*o*-quinomethane’ intermediates are trapped by urea or amides. The reaction was conducted under neat conditions by heating the corresponding mixture at 125°. This conversion proceeded within 5–9 h to form the products in good to high yields (68–93%). The aromatic aldehydes containing both electron-donating and electron-withdrawing groups (see **2b–f**) afforded the products in high yields. When the reaction was conducted with aliphatic aldehydes, the products were formed in lower yields. The reaction proceeded equally with urea (**4a**) or amides such as acetamide (**4b**), benzamide (**4c**), and acrylamide (= prop-2-enamide; **4d**). The structures of the products were established by their <sup>1</sup>H-NMR and MS data.

Table 2. Preparation of *N*-(2-Hydroxynaphthalen-1-yl)methyl]amides **5**<sup>a)</sup>

| Aldehyde  | R                                                  | Urea or Amide | R'                  | Product    | Time [h] | Yield [%] <sup>b)</sup> |
|-----------|----------------------------------------------------|---------------|---------------------|------------|----------|-------------------------|
| <b>2a</b> | Ph                                                 | <b>4a</b>     | NH <sub>2</sub>     | <b>5aa</b> | 5        | 90                      |
| <b>2b</b> | 4-Cl–C <sub>6</sub> H <sub>4</sub>                 | <b>4a</b>     | NH <sub>2</sub>     | <b>5ba</b> | 5.5      | 83                      |
| <b>2m</b> | 2,4-Cl <sub>2</sub> –C <sub>6</sub> H <sub>3</sub> | <b>4a</b>     | NH <sub>2</sub>     | <b>5ma</b> | 3        | 81                      |
| <b>2e</b> | 3-NO <sub>2</sub> –C <sub>6</sub> H <sub>4</sub>   | <b>4a</b>     | NH <sub>2</sub>     | <b>5ea</b> | 5.75     | 93                      |
| <b>2n</b> | 2-Br–C <sub>6</sub> H <sub>4</sub>                 | <b>4a</b>     | NH <sub>2</sub>     | <b>5na</b> | 6.0      | 87                      |
| <b>2f</b> | 4-Me–C <sub>6</sub> H <sub>4</sub>                 | <b>4a</b>     | NH <sub>2</sub>     | <b>5fa</b> | 5.25     | 86                      |
| <b>2o</b> | Naphth-1-yl                                        | <b>4a</b>     | NH <sub>2</sub>     | <b>5oa</b> | 7        | 71                      |
| <b>2a</b> | Ph                                                 | <b>4b</b>     | Me                  | <b>5ab</b> | 6.5      | 82                      |
| <b>2h</b> | 4-OH–C <sub>6</sub> H <sub>4</sub>                 | <b>4b</b>     | Me                  | <b>5hb</b> | 5.5      | 78                      |
| <b>2f</b> | 4-Me–C <sub>6</sub> H <sub>4</sub>                 | <b>4c</b>     | Ph                  | <b>5fc</b> | 7.75     | 75                      |
| <b>2b</b> | 4-Cl–C <sub>6</sub> H <sub>4</sub>                 | <b>4c</b>     | Ph                  | <b>5bc</b> | 9        | 68                      |
| <b>2o</b> | Naphth-1-yl                                        | <b>4c</b>     | Ph                  | <b>5oc</b> | 8.5      | 73                      |
| <b>2f</b> | 4-Me–C <sub>6</sub> H <sub>4</sub>                 | <b>4d</b>     | CH <sub>2</sub> =CH | <b>5fd</b> | 8.75     | 77                      |
| <b>2b</b> | 4-Cl–C <sub>6</sub> H <sub>4</sub>                 | <b>4d</b>     | CH <sub>2</sub> =CH | <b>5bd</b> | 7.5      | 76                      |

<sup>a)</sup> All the products were characterized by <sup>1</sup>H-NMR and MS data. <sup>b)</sup> Yield of isolated material.

In conclusion, we have developed a clean and simple method for the synthesis of 14*H*-dibenzo[*a,j*]xanthenes **3** and *N*-(2-hydroxynaphthalen-1-yl)methyl]amides **5** under solvent-free conditions using HClO<sub>4</sub>·SiO<sub>2</sub> as a heterogeneous catalyst. The mild reaction conditions, short reaction times, simplicity of the reaction, and high yields are notable advantages of this protocol.

The authors thank CSIR, New Delhi, for financial assistance.

## Experimental Part

**14-Aryl- or 14-Alkyl-14H-dibenzo[a,j]xanthenes 3:** *General Procedure:* A mixture of naphthalen-2-ol (**1**; 1 mmol), aldehyde **2** (0.5 mmol), and  $\text{HClO}_4 \cdot \text{SiO}_2$  (100 mg; prepared as reported [19]) was heated at 100°. After completion of the reaction (TLC monitoring) the mixture was filtered, the filtrate concentrated, and the residue purified by column chromatography CC (silica gel, hexane): pure 14-aryl- or 14-alkyl-14H-dibenzo[a,j]xanthene **3**.

**N-[(2-Hydroxynaphthalen-1-yl)methyl]amides 5:** *General Procedure:* A mixture of naphthalen-2-ol (**1**; 1 mmol), aldehyde **2** (1 mmol), urea (**4a**) or an amide **4b–d** (1.4 mmol), and  $\text{HClO}_4 \cdot \text{SiO}_2$  (100 mg) was heated at 125°. After completion of the reaction (TLC monitoring), the mixture was filtered, the filtrate concentrated, and the residue purified by CC (silica gel, 30% AcOEt/hexane): pure N-[(2-hydroxynaphthalen-1-yl)methyl]amide **5**.

The  $^1\text{H-NMR}$  ( $\delta$  in ppm,  $J$  in Hz) and MS (in  $m/z$ ) data of some representative products are given below.

**14-(3-Nitrophenyl)-14H-dibenzo[a,j]xanthene (3e):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.40 (s, 1 H); 8.25 (d,  $J = 8.0$ , 2 H); 7.90–7.70 (m, 6 H); 7.63–7.21 (m, 7 H); 6.50 (s, 1 H). FAB-MS: 404 ( $[M + \text{H}]^+$ ).

**14-(4-Methoxyphenyl)-14H-dibenzo[a,j]xanthene (3f):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.31 (d,  $J = 8.0$ , 2 H); 7.85–7.71 (m, 3 H); 7.60–7.30 (m, 9 H); 6.90 (d,  $J = 8.0$ , 2 H); 6.35 (s, 1 H); 2.10 (s, 3 H). FAB-MS: 373 ( $[M + \text{H}]^+$ ).

**14-(4-Methoxyphenyl)-14H-dibenzo[a,j]xanthene (3i):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.30 (d,  $J = 8.0$ , 2 H); 7.90–7.70 (m, 4 H); 7.60–7.30 (m, 8 H); 6.62 (d,  $J = 8.0$ , 2 H); 6.35 (s, 1 H); 3.60 (s, 3 H). FAB-MS: 389 ( $[M + \text{H}]^+$ ).

**14-Isopropyl-14H-dibenzo[a,j]xanthene (3l):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.26 (d,  $J = 8.0$ , 2 H); 7.90–7.70 (m, 4 H); 7.61–7.40 (m, 2 H); 7.43–7.32 (m, 4 H); 5.42 (d,  $J = 7.0$ , 1 H); 2.28 (m, 1 H); 0.81 (d,  $J = 7.0$ , 6 H). FAB-MS: 325 ( $[M + \text{H}]^+$ ).

**N-[(2-Bromophenyl)(2-hydroxynaphthalen-1-yl)methyl]urea (5na):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3/(\text{D}_6)\text{DMSO}$ , 200 MHz): 9.28 (br. s, 1 H); 8.04 (d,  $J = 8.0$ , 1 H); 7.74–6.78 (m, 13 H); 5.22 (br. s, 2 H). FAB-MS: 371, 373 ( $[M + \text{H}]^+$ ).

**N-[(2-Hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methyl]acetamide (5hb):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3/(\text{D}_6)\text{DMSO}$ , 200 MHz): 9.64 (br. s, 1 H); 8.72 (br. s, 1 H); 8.14 (d,  $J = 8.0$ , 1 H); 8.01 (d,  $J = 8.0$ , 1 H); 7.42–6.98 (m, 8 H); 6.62 (d,  $J = 8.0$ , 2 H); 2.04 (s, 3 H). FAB-MS: 296 ( $[M + \text{H}]^+$ ).

**N-[(2-Hydroxynaphthalen-1-yl)naphthalen-1-ylmethyl]benzamide (5oc):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3/(\text{D}_6)\text{DMSO}$ , 200 MHz): 10.01 (br. s, 1 H); 8.97 (d,  $J = 8.0$ , 1 H); 8.24 (d,  $J = 8.0$ , 1 H); 7.98–7.16 (m, 18 H). FAB-MS: 404 ( $[M + \text{H}]^+$ ).

**N-[(2-Hydroxynaphthalen-1-yl)(4-methylphenyl)methyl]prop-2-enamide (5fd):**  $^1\text{H-NMR}$  ( $\text{CDCl}_3/(\text{D}_6)\text{DMSO}$ , 200 MHz): 9.62 (br. s, 1 H); 8.25 (d,  $J = 8.0$ , 1 H); 8.00 (d,  $J = 8.0$ , 1 H); 7.78–7.62 (m, 2 H); 7.39 (t,  $J = 8.0$ , 1 H); 7.28–6.90 (m, 10 H); 6.36–6.22 (m, 2 H); 5.61 (m, 1 H); 2.12 (s, 3 H). FAB-MS: 318 ( $[M + \text{H}]^+$ ).

## REFERENCES

- [1] J. P. Poupelin, G. Saint-Ruft, O. Foussard-Blanpin, G. Narcisse, G. Uchida-Ernouf, R. Lacroix, *Eur. J. Med. Chem.* **1978**, *13*, 67.
- [2] R. W. Lambert, J. A. Martin, J. H. Merrett, K. E. B. Parkes, G. J. Thomas, PCT Int. Appl. WO 9706178, 1997 (*Chem. Abstr.* **1997**, *126*, 212377y).
- [3] T. Hideo, Jpn. Tokkyo koho JP 56005480, 1981 (*Chem. Abstr.* **1981**, *95*, 80922b).
- [4] R. M. Ion, D. Frackowiak, A. Planner, K. Wiktorowicz, *Acta Biochim. Pol.* **1998**, *45*, 833.
- [5] G. Saint-Ruf, A. De, H. T. Hieu, *Bull. Chim. Ther.* **1972**, *7*, 83; G. Saint-Ruf, H. T. Hieu, J. P. Poupelin, *Naturwissenschaften* **1975**, *62*, 584.
- [6] A. Banerjee, A. K. Mukherjee, *Stain Technol.* **1981**, *56*, 83; S. M. Menchen, S. C. Benson, J. Y. L. Lam, W. Zhen, D. Sun, B. B. Rosenblum, S. Khan, M. Taing, U.S. Pat. 6,583,168, 2003 (*Chem. Abstr.* **2003**, *139*, 54287f).
- [7] C. G. Knight, T. Stephens, *Biochem. J.* **1989**, *258*, 683.

- [8] O. Sirkecioglu, N. Talinli, A. Akar, *J. Chem. Res., Synop.* **1995**, 502.
- [9] B. Ravindranath, T. R. Seshadri, *Phytochemistry* **1973**, *12*, 2781.
- [10] P. Papini, R. Cimmarusti, *Gazz. Chim. Ital.* **1947**, 142.
- [11] R. N. Sen, N. Sarkar, *J. Am. Chem. Soc.* **1925**, *47*, 1079.
- [12] K. Ota, T. Kito, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1167.
- [13] D. W. Knight, P. B. Little, *J. Chem. Soc., Perkin Trans. 1* **2001**, *14*, 1771.
- [14] A. Bekaert, J. Andrieux, M. Plat, *Tetrahedron Lett.* **1992**, *33*, 2805.
- [15] C. W. Kuo, J.-M. Fang, *Synth. Commun.* **2001**, *31*, 877.
- [16] C. Ramesh, N. Ravindranath, B. Das, *J. Org. Chem.* **2003**, *68*, 7101; C. Ramesh, G. Mahender, N. Ravindranath, B. Das, *Tetrahedron Lett.* **2003**, *44*, 1465; B. Das, J. Banerjee, N. Ravindranath, *Tetrahedron* **2004**, *60*, 8357.
- [17] P. K. Mandal, A. K. Misra, *Lett. Org. Chem.* **2006**, *3*, 848; B. Das, A. Majhi, J. Banerjee, *Tetrahedron Lett.* **2006**, *47*, 7619; A. T. Khan, T. Parvin, L. H. Choudhury, *Synthesis* **2006**, 2497; A. K. Misra, P. Tiwari, G. Agnihotri, *Synthesis* **2005**, 260.
- [18] B. Das, K. Ravinder Reddy, P. Thirupathi, *Tetrahedron Lett.* **2006**, *47*, 5855; B. Das, K. Venkateswarlu, M. Krishnaiah, H. Holla, *Tetrahedron Lett.* **2006**, *47*, 7551.
- [19] A. K. Chakrabarti, R. Gulhane, *Chem. Commun.* **2003**, 1896.
- [20] A. Wolff, V. Boechmer, W. Vogt, F. Ugozzoli, G. D. Andreotti, *J. Org. Chem.* **1990**, *55*, 5665; K.-W. No, J. E. Kim, K. M. Kwon, *Tetrahedron Lett.* **1995**, *36*, 8453; S. H. Mashraqui, M. B. Patil, H. D. Mistry, S. Ghadigaonkar, A. Meetsma, *Chem. Lett.* **2004**, *33*, 1058.

Received March 16, 2007