Perchloric Acid–Silica ($HClO_4 \cdot SiO_2$)-Catalyzed Synthesis of 14-Alkyl- or 14-Aryl-14*H*-dibenzo[*a*,*j*]xanthenes and *N*-[(2-Hydroxynaphthalen-1-yl)methyl]amides[1])

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 $HClO_4 \cdot SiO_2$ 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 $HClO_4 \cdot SiO_2$ has been found to be an efficient heterogeneous catalyst in various useful chemical transformations [17]. In continuation

[1]) 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 $HClO_4 \cdot SiO_2$ [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 $HClO_4 \cdot SiO_2$ 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

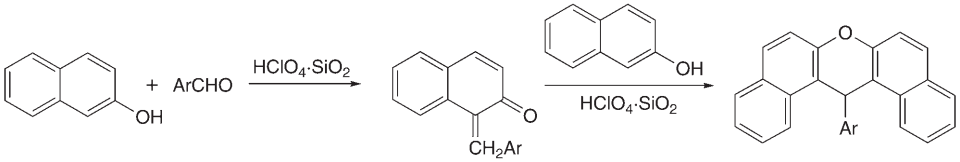
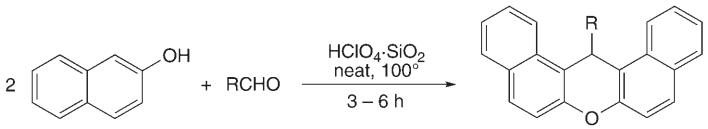


Table 1. *Preparation of 14-Aryl- or 14-Alkyl-14*H*-dibenzo[*a,j*]xanthenes* **3**[a])

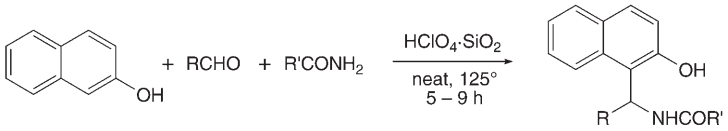


Aldehyde	R	Product	Time [h]	Yield [%][b])
2a	Ph	**3a**	3.5	92
2b	4-Cl–C_6H_4	**3b**	3.0	91
2c	4-F–C_6H_4	**3c**	3.75	90
2d	3-CF_3–C_6H_4	**3d**	4.0	93
2e	3-NO_2–C_6H_4	**3e**	3.75	88
2f	4-Me–C_6H_4	**3f**	4.25	81
2g	4-Et–C_6H_4	**3g**	4.0	89
2h	4-OH–C_6H_4	**3h**	4.5	92
2i	4-MeO–C_6H_4	**3i**	4.0	84
2j	3-MeO,4-OH–C_6H_3	**3j**	4.75	89
2k	Et	**3k**	6.0	77
2l	^{i}Pr	**3l**	5.5	82

[a]) All the products were characterized by ^{1}H-NMR and MS data. [b]) 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 ^{1}H-NMR and MS data.

Table 2. *Preparation of* N-*[(2-Hydroxynaphthalen-1-yl)methyl]amides* **5**[a])



1 **2** **4a–d** **5**
68 – 93%

Aldehyde	R	Urea or Amide	R′	Product	Time [h]	Yield [%][b])
2a	Ph	**4a**	NH_2	**5aa**	5	90
2b	4-Cl–C_6H_4	**4a**	NH_2	**5ba**	5.5	83
2m	2,4-Cl_2–C_6H_3	**4a**	NH_2	**5ma**	3	81
2e	3-NO_2–C_6H_4	**4a**	NH_2	**5ea**	5.75	93
2n	2-Br–C_6H_4	**4a**	NH_2	**5na**	6.0	87
2f	4-Me–C_6H_4	**4a**	NH_2	**5fa**	5.25	86
2o	Naphth-1-yl	**4a**	NH_2	**5oa**	7	71
2a	Ph	**4b**	Me	**5ab**	6.5	82
2h	4-OH–C_6H_4	**4b**	Me	**5hb**	5.5	78
2f	4-Me–C_6H_4	**4c**	Ph	**5fc**	7.75	75
2b	4-Cl–C_6H_4	**4c**	Ph	**5bc**	9	68
2o	Naphth-1-yl	**4c**	Ph	**5oc**	8.5	73
2f	4-Me–C_6H_4	**4d**	CH_2=CH	**5fd**	8.75	77
2b	4-Cl–C_6H_4	**4d**	CH_2=CH	**5bd**	7.5	76

[a]) All the products were characterized by ^{1}H-NMR and MS data. [b]) 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 $HClO_4 \cdot SiO_2$ 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-14*H*-dibenzo[*a,j*]xanthenes* **3**: *General Procedure*: A mixture of naphthalen-2-ol (**1**; 1 mmol), aldehyde **2** (0.5 mmol), and $HClO_4 \cdot SiO_2$ (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-14*H*-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 $HClO_4 \cdot SiO_2$ (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}H-NMR (δ in ppm, J in Hz) and MS (in m/z) data of some representative products are given below.

*14-(3-Nitrophenyl)-14*H*-dibenzo[*a,j*]xanthene* (**3e**): ^{1}H-NMR ($CDCl_3$, 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 ($[M+H]^+$).

*14-(4-Methylphenyl)-14*H*-dibenzo[*a,j*]xanthene* (**3f**): ^{1}H-NMR ($CDCl_3$, 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 ($[M+H]^+$).

*14-(4-Methoxyphenyl)-14*H*-dibenzo[*a,j*]xanthene* (**3i**): ^{1}H-NMR ($CDCl_3$, 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 ($[M+H]^+$).

*14-Isopropyl-14*H*-dibenzo[*a,j*]xanthene* (**3l**): ^{1}H-NMR ($CDCl_3$, 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 ($[M+H]^+$).

N-*[(2-Bromophenyl)(2-hydroxynaphthalen-1-yl)methyl]urea* (**5na**): ^{1}H-NMR ($CDCl_3$/(D_6)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 ($[M+H]^+$).

N-*[(2-Hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methyl]acetamide* (**5hb**): ^{1}H-NMR ($CDCl_3$/(D_6)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 ($[M+H]^+$).

N-*[(2-Hydroxynaphthalen-1-yl)naphthalen-1-ylmethyl]benzamide* (**5oc**): ^{1}H-NMR ($CDCl_3$/(D_6)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 ($[M+H]^+$).

N-*[(2-Hydroxynaphthalen-1-yl)(4-methylphenyl)methyl]prop-2-enamide* (**5fd**): ^{1}H-NMR ($CDCl_3$/(D_6)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 ($[M+H]^+$).

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. Andreetti, *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