One-pot synthesis of 14*H*-dibenzo[*a,j*]xanthene and its 14-substituted derivatives

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Preparation methods of the titled compounds are mentioned and an easy, environment friendly, common and one-pot synthesis of these compounds is described.

Keywords: 2-naphthalenol, aldehydes, microwave-assisted reaction, dibenzoxanthenes

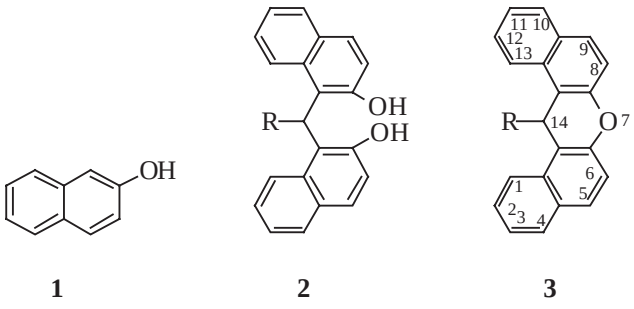
Dibenzoxanthene derivatives have been the subject of many research works because of their importance in organic synthesis and as candidates in PDT (photodynamic therapy).[1] [PDT uses non-thermal lasers to activate light sensitive drugs (photosensitisers) in order to treat cancer and other diseases in a non-surgical, minimally invasive way. PDT photosensitisers are injected directly into malignant tissue and, when activated by a light source, generate highly reactive oxygen radicals that react with crucial cell biochemicals, such as proteins and DNA, damaging them beyond repair and killing the tumor cells].

As concerning the parent compound **3**, Scheme 1 R=H (abbreviated as dibenzoxanthene) many authors have attempted its synthesis. For example, Wolf has dehydrated bis(2-hydroxy-1-naphthyl)methane **2**, R=H (which we abbreviate here as bisnaphthol) by $POCl_3$.[2] Rosenbush has proposed another way to dibenzoxanthene by boiling acetic acid diester of compound **2**.[3] Casiraghi and coworkers have prepared **3**, R=H and its 2,12-dibromo- derivatives by refluxing magnesium salts of the corresponding 2-naphthalenols in ethyl orthoformate.[4] Dimerisation of 2-naphthalenol under CO–CO_2 flow has also been attempted by Ohta and others to prepare dibenzoxanthene in 35% yield.[5] In the other method of preparing dibenzoxanthene, use has been made of a two-step addition of HCO_2NH_4 to **1** at 190–200 °C.[6]

Recently we reported that 14-alkyl-14*H*-dibenzo[*a,j*]xanthenes **3**, R= Alkyl (abbreviated here as alkyldibenzxanthenes) may be prepared without further purification by condensation of 2-naphthalenol **1** and unhindered aliphatic aldehydes in acetic acid (as solvent) and a catalytic amount of concentrated HCl or H_3PO_4 at 0–5 °C.[7] There is also a recent report in which 14-ethyl substituted dibenzoxanthene was prepared in 31% yield by condensing **1** and propanal at high pressure.[8] Benzyldibenzoxanthene (**3**, R= $C_6H_5CH_2$) has been prepared by passing gaseous HCl through concentrated acetic acid for 2 h.[9] In another report, propyldibenzoxanthene (**3**, R= $CH_3CH_2CH_2$) has been obtained by boiling a mixture of **1** and butanal in HCl/acetic acid.[10]

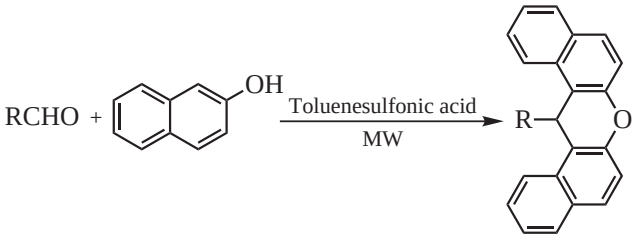
The case of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes **3**, R= Aryl (abbreviated here as aryldibenzoxanthenes) is similar to that of alkyldibenzoxanthenes. They have been prepared through dehydration of their corresponding bisnaphthols **2**,[11-15] or by boiling a mixture of aromatic aldehydes and 2-naphthalenol in HCl/acetic acid.[16-18] There is also a report on room temperature preparation of such compounds from the starting materials in acetic acid by adding concentrated HCl.[19]

As is evident, nearly all these methods make use of acetic acid and suffer from harsh reaction conditions and long reaction times. This is the case where the general trend in organic synthesis is conducting reactions in milder and "greener conditions", gaining higher yields of products and, decreasing the required reaction times. Having all these points in mind, and after carrying out several reactions, we decided to use microwave radiation in order to achieve such a goal.



1 **2** **3**

Scheme 1



4 **1** **3**

a, R= H
b, R= CH_3CH_2
c, R= $CH_3CH_2CH_2$
d, R= $(CH_3)_2CH$
e, R= C_6H_5
f, R= 4-$CH_3OC_6H_4$
g, R= 4-ClC_6H_4
h, R= 2-$CH_3C_6H_4$
i, R= 3-$CH_3C_6H_4$
j, R= 4-$CH_3C_6H_4$
k, R= 4-BrC_6H_4

Scheme 2

Results and discussion

Inspection of Table 1, which shows the results for the reaction of 2-naphthalenol and 11 aldehydes, reveals that product yields for volatile aldehydes are lower than those of non-volatile ones; albeit similar to those obtained by conventional methods. In addition, the reaction time for entries 4, 7 and 11 is much longer than the reaction time for the other entries. For entry 4 [product **3d**, R= $(CH_3)_2CH$], this may be attributed to the steric hindrance. (This is confirmed by the results of our previous experiments that in contrast to the unhindered aldehydes such as acetaldehyde, propionaldehyde and butyraldehyde, the reaction of isobutyraldehyde with 2-naphthalenol, does not proceed at 0–5 °C.[7]) In the case of products **3g** and **3k**, the long reaction time is necessary for the mixture to liquefy.

The ^{1}H NMR spectra of all products have a similar pattern for aromatic hydrogens 6 and 8 (see Scheme 1 for numbering system): These two hydrogens appear as a doublet (coupled to number 5 and 9 hydrogens) at lowest field because of inductive

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Table 1 Reaction times, yields and melting points for product **3**

Entry	**4**, RCHO	Product, yield/%	Reaction time/s	M.p. /°C	
				Found	Reported
1	**4a**[a] (paraformaldehyde)	**3a**, 53.0	70	205–206	202[6]
2	**4b**	**3b**, 35.0	80	151–153	151–152[20]
3	**4c**	**3c**, 57.0	80	151–153	150–151[20]
4	**4d**	**3d**, 49.0	150	153–154	151–152[20]
5	**4e**	**3e**, 94.0	80	191–192	189[21],191[12]
6	**4f**	**3f**, 78.9	80	205–206	208[19]
7	**4g**	**3g**, 98.9	120	292–293	292[22]
8	**4h**	**3h**, 88.0	80	199–200	–
9	**4i**	**3i**, 84.0	70	197–198	–
10	**4j**	**3j**, 93.0	60	230–231	231[19]
11	**4k**	**3k**, 96.6	140	299–301	–

Paraformaldehyde was taken as the source of formaldehyde.

effect of oxygen. The chemical shift of hydrogen number 14, which appears at the right part of aromatic hydrogens, was deduced both by integration and comparing all ^{1}H NMR spectra. The absence of exchangeable hydrogen of the starting 2-naphthalenol was confirmed both with the aid of IR spectra and by adding D_2O (1─2 drops) to the NMR tube.

Conclusion

In short, the advantages of this procedure are: good to excellent yields, short reaction times, easy work up and "greener conditions".

Experimental

Melting points were determined by electrothermal melting point apparatus without further correction. IR and NMR spectra were run using Perkin-Elmer FT─IR and Jeol 90MHz FT NMR spectrometers respectively. The source of microwave radiation was the LG domestic microwave oven (model MG-583MC).

For all ^{1}H NMR spectra with $DMSO_{d6}$ as solvent, the residual non-deuterated DMSO was chosen as internal standard and its chemical shift set at δ2.600. In the case of ^{13}C NMR spectra with $DMSO_{d6}$ as solvent, the chemical shift of $DMSO_{d6}$ was set at δ39.500. For other spectra with $CDCl_3$ as solvent, TMS was the internal standard. In the following, the ^{1}H NMR data and selected ^{13}C NMR and/or IR data are given. The mass spectrum for **3j** is given as an example to confirm the molecular mass of such a compound.

In all our experiments, a mixture of 2-naphthalenol (0.02 mole), aldehyde (0.01 mole), and toluenesulfonic acid (0.288g) was subjected to the radiation (100% power) of the microwave oven for a certain period of time. It should be noted that for solid aldehydes the best result was obtained when the mixture of starting materials was ground to a fine powder. After the required time, 5 ml of ethanol was added to the cold reaction mixture, the precipitate was separated and then recrystallised from propanol.

14H-dibenzo[a,j]*xanthene* (**3a**); ^{1}H NMR ($DMSO_{d6}$): δ4.75 (s, 2H), δ7.43─8.11 (10H, aromatic), δ8.37 (d, 2H, number 6 and 8, *J*=7.83Hz).

14-ethyl-14H-dibenzo[a,j]*xanthene* (**3b**); ^{1}H NMR ($DMSO_{d6}$); δ0.66 (d, 6H, CH_3, *J*=7.40Hz), δ2.11 (m, 2H, CH_2, *J*=7.40Hz and *J*=4.30Hz), δ5.57 (t, 1H, CH, *J*=4.30Hz), δ7.23-7.90 (10H, aromatic), δ8.24 (d, 2H, number 6 and 8, *J*=8.46Hz).

IR ($\bar{\nu}$ cm^{-1}): 3065, 2931, 1621, 1590, 1514, 1456, 1433, 1399, 1240, 1076, 960, 869, 809, 750, 705, 584, 503, 567.

14-propyl-14H-dibenzo[a,j]*xanthene* (**3c**); ^{1}H NMR ($DMSO_{d6}$): δ0.59 (t, CH3, *J*=7.6Hz), δ1.00 (m, 2H, CH_2, *J*= 7.60Hz and *J*=12.4Hz), δ2.00 (m, 2H, CH_2, *J*=12.4Hz and *J*=4.40Hz), δ5.56 (t, CH, *J*=4.40Hz), δ7.24─7.88 (10H, aromatic), δ8.25 (d, 2H, number 6 and 8, *J*=9.20Hz).

14-isopropyl-14H-dibenzo[a,j]*xanthene* (**3d**); ^{1}H NMR ($DMSO_{d6}$): δ0.81 (d, 3H, CH_3, *J*=6.93Hz), δ2.19 (m, 1H, CH, *J*=6.93Hz and *J*=3.96Hz), δ5.70 (d, 1H, CH, *J*=3.93Hz), δ7.62─8.09 (10H, aromatic), δ8.69 (d, 2H, hydrogen number 6 and 8, *J*=8.73Hz).

IR ($\bar{\nu}$ cm^{-1}): 3053, 2961, 2859, 1621, 1589, 1514, 1456, 1423, 1397, 1237, 956, 815, 739, 700, 657, 614, 509, 472.

14-phenyl-14H-dibenzo[a,j]*xanthene* (**3e**); ^{1}H NMR ($CDCl_3$), δ6.39 (s, 1H, CH), δ6.89─79 (15H, aromatic), δ8.31 (d, 2H, hydrogen number 6 and 8, *J*= 7.83Hz)

^{13}C NMR ($CDCl_3$): δ117.4, δ118.0, δ122.7, δ124.2, δ126.4, δ126.745, δ128.3, δ128.5, δ128.8, δ131.1, δ131.5, δ145.1, δ148.7.

14-(4-methoxyphenyl)-14H-dibenzo[a,j]*xanthene* (**3f**); ^{1}H NMR ($DMSO_{d6}$): δ3.58 (s, 3H, CH_3), δ6.75 (s, 1H, CH), δ6.80─8.03 (14H, aromatic), δ8.77 (d, 2H, hydrogen number 6 and 8, *J*=8.10Hz).

^{13}C NMR ($DMSO_{d6}$): δ54.8, δ113.8, δ117.7, δ123.5, δ124.5, δ126.9, δ128.6, δ128.9, δ129.0, δ130.7, δ131.0, δ137.8, δ148.0, δ157.6.

IR ($\bar{\nu}$ cm^{-1}): 3071, 2834, 1621, 1592, 1510, 1458, 1432, 1399, 1249, 1179, 1110, 1080, 1030, 961, 830, 810, 781, 743, 609, 514.

14-(4-chlorophenyl)-14H-dibenzo[a,j]*xanthene* (**3g**); ^{1}H NMR ($DMSO_{d6}$): δ6.84 (s, 1H, CH), δ7.23─8.07 (14H, aromatic), δ8.75 (d,2H, hydrogen number 6 and 8, *J*=8.46Hz).

IR ($\bar{\nu}$ cm^{-1}): 3067, 1622, 1592, 1514, 1485, 1458, 1431, 1401, 1239, 1141, 1083, 1012, 959, 831, 807, 778, 741, 711, 608, 518, 447.

14-(2-methylphenyl)-14H-dibenzo[a,j]*xanthene* (**3h**); ^{1}H NMR ($DMSO_{d6}$): δ2.41(s, 3H, CH_3), δ6.708 (s, 1H, CH), δ6.87─8.34 (14H, aromatic), δ8.75 (d, 2H, hydrogen number 6 and 8, *J*=9.01Hz).

IR ($\bar{\nu}$ cm^{-1}): 3050, 2863, 1621, 1593, 1514, 1459, 1429, 1401, 1250, 1070, 965, 807, 765, 742, 507.

Mass spectrum: *m/z*=372 (6.5%, molecular ion), *m/z*=281 (100%, xanthylium ion resulting from expulsion of *2-methylphenyl* fragment; nearly the same fragmentation pattern as that of compounds **3i** and **3j**).

Elemental analysis: C, 89.8%; H, 5.4%. (Calculated 90% and 5.4% respectively)

14-(3-methylphenyl)-14H-dibenzo[a,j]*xanthene* (**3i**); ^{1}H NMR ($DMSO_{d6}$): δ2.16 (s, 3H, CH_3), δ6.77 (s, 1H, CH), δ6.90─8.06 (14H, aromatic), δ8,77 (d, 2H, hydrogen number 6 and 8, *J*=9.01Hz).

^{13}C NMR ($DMSO_{d6}$): δ20.7, δ117.3, δ117.6, δ123.3, δ124.3, δ125.1, δ126.8, δ126.9, δ128.0, δ128.2, δ128.4, δ128.6, δ128.8, δ130.5, δ130.8, δ137.5, δ145.4, δ148.0.

IR ($\bar{\nu}$ cm^{-1}): 3063, 3019, 2919, 1620, 1592, 1514, 1458, 1430, 1401, 1251, 964, 809, 772, 746, 702, 508.

Mass spectrum: *m/z*=372 (5%, molecular ion), *m/z*=281 (100%, xanthylium ion resulting from expulsion of *3-methylphenyl* fragment).

Elemental analysis: C, 89.8%; H, 5.3%. (Calculated 90% and 5.4% respectively)

14-(4-methylphenyl)-14H-dibenzo[a,j]*xanthene* (**3j**); ^{1}H NMR ($DMSO_{d6}$) δ2.13 (s, 3H, CH_3), δ6.75 (s, 1H, CH), δ6.96─8.06 (14H, aromatic), δ8.74 (d, 2H, hydrogen number 6 and 8, *J*=8.37Hz),

^{13}CNMR ($DMSO_{d6}$): δ20.2, δ117.4, δ117.4, δ117.5, δ123.3, δ124.3, δ126.7, δ127.7, δ128.4, δ128.8, δ130.8, δ135.9, δ142.5, δ147.9, δ147.9.

Mass spectrum: *m/z*=372 (molecular ion), *m/z*=281 (100%, xanthylium ion resulting from expulsion of 4-methylphenyl fragment).

IR ($\bar{\nu}$ cm^{-1}): 3067, 3021, 2897, 1620, 1591, 1510, 1458, 1432, 1399, 1246, 961, 810, 740, 608, 517, 488.

14-(4-bromophenyl)-14H-dibenzo[a,j]*xanthene* (**3k**); ^{1}H NMR ($DMSO_{d6}$): δ6.83 (s, 1H, CH), δ7.38─8.09 (14H, aromatic), δ8.75 (d, 2H, hydrogen number 6 and 8, *J*=8.46Hz).

^{13}C NMR ($DMSO_{d6}$): δ116.7, δ117.5, δ117.5, δ123.1, δ124.4, δ126.9, δ128.5, δ128.5, δ129.0, δ129.9, δ130.5, δ130.6, δ131.1, δ147.9.

IR ($\bar{\nu}$ cm^{-1}): 3070, 1621, 1591, 1514, 1481, 1457, 1430, 1400, 1239, 1073, 1009, 962, 829, 807, 740, 704, 508, 517, 429.

Mass spectrum: *m/z*=436 and 438 (equal intensity corresponding to the molecular ion), *m/z*=281 (100%, xanthylium ion resulting from losing *4-bromophenyl* fragment).

Elemental analysis: C, 73.9%; H, 3.8%; Br, 3.8%. (Calculated 74.1%, 3.9% and 3.7% respectively)

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