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One-Pot Synthesis of 9-Arylxanthenediones and 9-Pyrazoloxanthenediones Using [DBU]OAc[1]

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Abstract—The synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-dione derivatives starting from benzaldehydes or synthesized pyrazolcarbaldehydes and dimedone in the presence of 2,3,4,5,7,8,9,10-octahydropyrido[1,2-*a*]-[1,3]diazepin-1-ium acetate in high yields is reported. The synthesis provides several advantages, including short reaction time, simple work-up, and environmental friendliness.

Keywords: xanthene, one- pot reaction, ionic liquid, solvent free

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The synthesis of xanthene derivatives has been of considerable interest to chemists, because such compounds are widely used in medicine and pharmaceutics as antiviral [1] and antibacterial agents [2], as well as photosensitizers for photodynamic theraphy and antagonists of zoxazolamine [2, 3], and anti-inflammatory drugs [4]. Furthermore, the use of xanthenes as staining dyes [5, 6], fluorescent probes [7], and laser dyes [8] has been reported.

Many synthetic approaches to xanthene derivatives have been developed, including trapping of benzynes by phenols [9], cyclodehydration [10], and cyclocondensation between 2-tetralone and *o*-hydroxybenzaldehydes [11], as well as condensation of aromatic aldehydes and dimedone in the presence of $InCl_3.4H_2O$ [12], $NaHSO_4{\cdot}SiO_2$ [13], silica sulfuric acid [14], TiO_2/SO_4^{2-} [15], $ZrOCl_2{\cdot}8H_2O$ [16], $FeCl_3{\cdot}6H_2O$ [17], Dowex-50W [18], Fe^{3+}-montmorillonite [19], amberlyst-15 [20] and alumina sulfuric acid [21] as solid acid catalysts. In addition, the synthesis of other xanthenedione derivatives, catalyzed by a Preyssler-type heteropoly acid [22], HPA/SiO_2 [23], and HPWA/MCM-41 [24] has been recently reported.

Ionic liquids are being more and more widely used in modern synthetic chemistry because of their interesting properties [25, 26]. Ionic liquids offer an attractive alternative to conventional organic liquids for clean synthesis, since they are easy to recycle, lack flammability, and possess almost no effective vapor pressure. Compared with classical molecular solvents, ionic liquids are environmentally benign reaction media [27].

In continuation of our ongoing studies on the synthesis of heterocyclic and pharmaceutical compounds by mild and practical protocols [28–31], in the present work we developed a synthesis of xanthene derivatives using various benzaldehydes **1** or synthesized pyrazolcarbaldehyde **4** [28] (2 mmol) and dimedone **2** (4 mmol) in the presence of the ionic liquid [DBU]OAc (2,3,4,5,7,8,9,10-octahydropyrido-[1,2-*a*][1,3]diazepin-1-ium acetate) (Scheme 1, Table 1).

To check the efficiency of catalyst, the model reaction between benzaldehydes **1** and dimedone **2** in the presence of different catalysts was carried out. All the reactions were carried out with catalytic amounts of catalysts. As shown in Table 1, the results gained with 0.1 mmol of [DBU]OAc (Table 1) were to a great extent satisfactory.

Table 1 showed other interesting points in that the ability and efficiency of catalyst NaY Zeolite, nano-Fe_3O_4 and K10 montmorillonite are somehow similar, while ionic liquid [DBU]OAc was more efficient for the synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-diones. The [DBU]OAc, rather than other catalysts, can accelerate the reaction time.

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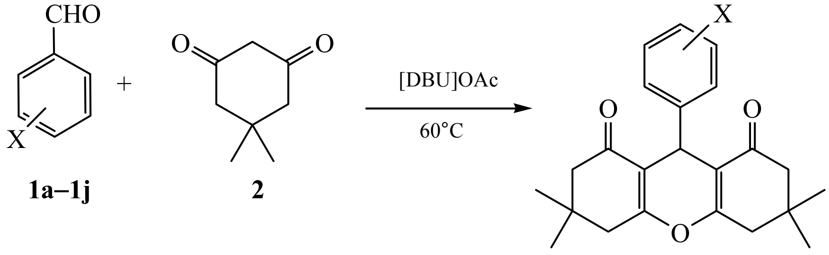
[1] The text was submitted by the authors in English.

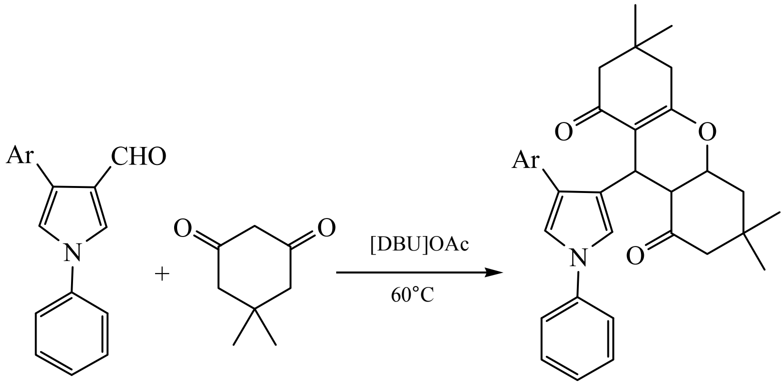
Scheme 1. Synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-diones **3a–3j** using [DBU]OAc.



1a–1j **2** **3a–3j**

3: X= H (**a**); 4-NO_2 (**b**); 3-NO_2 (**c**); 4-Cl (**d**); 3-Cl (**e**); 2-Cl (**f**); 4-Br (**g**); 3-Br (**h**); 4-CH_3O (**i**); 3-CH_3O (**j**).

Scheme 2. Synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-diones **5a–5d** using [DBU]OAc.



4a–4d **2** **5a–5d**

5: Ar = 3-$NO_2C_6H_4$ (**a**); 4-ClC_6H_4 (**b**); 3-HOC_6H_4 (**c**); 3-$CH_3OC_6H_4$ (**d**).

All of compounds **5** are new. Structure of products **5a–5d** were characterized by IR, NMR and Elemental analyses. For example, singlet peaks about 7.78–8.02 ppm in ^{1}H NMR spectra are related to pyrazolic protons. So, saturated protons in pyran's rings were shown in about 5.19–5.26 ppm as singlet peaks.

With the best catalyst in hand, we moved to study the effects of the catalyst amount on the model reaction (Table 1, compounds **3b** and **3i**). It was found that 0.1 mmol of [DBU]OAc was enough to bring the reaction to completion, while 0.05 mmol of the catalyst was not enough. With a higher amount of the catalyst, no significant change in the reaction yields was observed.

The washed [DBU]OAc was dried for reuse in subsequent reactions. It was shown that after six runs [DBU]OAc was as active as the fresh catalyst (Table 2).

Several aldehydes could be converted to the corresponding products in good to high yield using [DBU]OAc. Aldehydes containing electron-acceptor (NO_2 or Hal) and electron-donor groups (OH and AlkO) were employed and reacted well to give the corresponding xanthenes **3a–3j** in yields ranging from 82 to 97% (Table 1).

Thus, we developed an efficient and convenient procedure for the mild synthesis of 9-aryl-1*H*-xanthenediones and 9-pyrazoloxanthenediones by a one-step reaction of aldehydes and dimedone, catalyzed by [DBU]OAc as a reusable catalyst. The remarkable advantages offered by this method include: nontoxic, easily handled, and reusable catalyst; simple work-up procedure; short reaction time; high yields of products of a better purity; and environmental safety (non-toxic catalyst and no hazardous solvents are used). To the best of our knowledge, this is the first report on the synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-diones using [DBU]OAc.

EXPERIMENTAL

Chemicals were purchased from Merck and Fluka and used as received. The melting points were measured on an Electrothermal 9100 apparatus and

Table 1. Synthesis of 9-aryl-1*H*-xanthene-1,8(2*H*)-diones **3a–3j** and **5a–5d** in the presence of [DBU]OAc

Comp. no.	X or Ar	Time, min	Yield, %[a]	mp, °C (published mp °C)
3a	H	60 (180)[b] (420)[e]	87 (75)[b] (65)[e]	206–208 (205 [32])
3b	4-NO_2	30 (180)[b] (90)[f]	97 (72)[b] (75)[f]	226–228 (222–224 [32])
3c	3-NO_2	45 (180)[c]	88 (72)[c]	165–167 (165–166 [32])
3d	4-Cl	45 (240)[d]	89 (68)[d]	232–234 (231–233 [33])
3e	3-Cl	60 (240)[d]	82 (68)[d]	183–185 (183–185 [33])
3f	2-Cl	60 (120)[b]	95 (82)[b]	224–226 (226–227 [32])
3g	4-Br	30	95	241–243 (240–242 [32])
3h	3-Br	60	95	189–191 (190–192 [32])
3i	4-CH_3O	90 (150)[f]	82 (70)[f]	241–243 (242–243 [32])
3j	3-CH_3O	45 (240)[d]	86 (68)[d]	259–261 (261–263 [32])
5a	3-$NO_2C_6H_4$	60 (180)[b] (420)[e]	94 (75)[b] (65)[e]	263–265
5b	4-ClC_6H_4	60 (180)[c]	85 (72)[c]	281–283
5c	3-HOC_6H_4	90 (240)[d]	82 (68)[d]	271–273
5d	4-$CH_3OC_6H_4$	90 (120)[b]	90 (82)[b]	270–272

[a] Yield based upon the starting aldehyde. [b] In the presence of 0.1 g of NaY Zeolite. [c] In the presence of 0.1 g of nano-Fe_3O_4. [d] In the presence of 0.1 g of K10 montmorillonite. [e] In the thermal condition without catalyst. [f] In the presence of 0.05 mmol of [DBU]OAc.

reported uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. The ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX 500 Avance spectrometer in $CDCl_3$ and DMSO-d_6 internal standard TMS. Elemental analysis was performed on a Carlo-Erba EA1110CNNO-S analyzer. Reaction progress was monitored by TLC on silica gel (60 GF_{254} Merck) in ethyl acetate–*n*-hexane (1 : 2).

Synthesis of compounds 3 and 5 *(general procedure)*. Benzaldehyde **1** (2 mmol) or pyrazolaldehyde **4** (2 mmol), dimedone **2** (4 mmol), and [DBU]OAc (0.1 mmol) were heated at 60°C for 30–120 min. After the reaction had been complete, the reaction mixture was allowed cool down to room temperature, poured into crashed ice, and stirred for 5 min. The precipitate that formed was filtered off, recrystallized from ethanol, and dried to obtain compound **3** or **5**, respectively, as a powder. The identity and purity of the products were confirmed by IR, ^1H NMR, ^{13}C NMR, and elemental analysis. Physicochemical characteristics and spectra of product **3a–3j** correspond to published data [34–37].

Table 2. Evaluation of reusability of [DBU]OAc in the synthesis of compound **3a**

Run no.	1	2	3	4	5	6
Time, min	60	60	60	60	60	60
Yield, %	87	88	87	86	87	86

3,3,6,6-Tetramethyl-9-[3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (5a). Yield 94%, white solid; mp 263–265°C. IR spectrum (KBr), ν, cm^{-1}: 3380, 3051, 2954, 1643, 1496, 1414. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.93 s (6H, CH_3), 1.02 s (6H, CH_3), 1.98–2.28 m (8H, CH_2), 5.22 s (1H, CH), 7.27 t (J = 8.0 Hz, 1H), 7.43 t (J = 7.6 Hz, 2H), 7.66 d (J = 8.0 Hz, 1H), 7.70 d (J = 8.0 Hz, 1H), 7.89 (s, 1H), 8.24 dd (J = 8.2, 1.6 Hz, 1H), 8.57 d (J = 8.0 Hz, 1H), 9.0 s (1H). Found, %: C 71.51; H 5.78; N 7.84. $C_{32}H_{31}N_3O_5$. Calculated, %: C 71.49; H 5.81; N 7.82.

9-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (5b). Yield 85%, white solid; mp 281–283°C. IR spectrum (KBr), ν, cm^{-1}: 3446, 3068, 2958, 1647, 1502, 1614, 1022. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.94 s (6H, CH_3), 1.00 s (6H, CH_3), 2.08–2.22 m (8H, CH_2), 5.19 s (1H, CH), 7.25 t (J = 7.2 Hz, 1H), 7.39–7.48 m (5H), 7.65 d (J = 8.2 Hz, 2H), 7.78 s (1H), 8.08 d (J = 8.2 Hz, 2H). Found, %: C

72.89; H 5.91; N 5.29. $C_{32}H_{31}ClN_2O_3$. Calculated, %: C 72.92; H 5.93; N 5.32.

9-[3-(3-Hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (5c). Yield 82%, white solid; mp 271-273°C. IR spectrum (KBr), ν, cm^{-1}: 3409, 3066, 2954, 1649, 1463, 1506, 1220. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.93 s (6H, CH_3), 1.00 s (6H, CH_3), 2.00–2.20 m (8H, CH_2), 5.26 s (1H, CH), 6.83 d (*J* = 7.2 Hz, 1H), 7.21-7.25 m (3H), 7.37 t (*J* = 7.6 Hz, 3H),7.65 d (*J* = 8.0 Hz, 2H), 8.02 s (1H). Found, %: C 75.54; H 6.31; N 5.49. $C_{32}H_{32}N_2O_4$. Calculated, %: C 75.57; H 6.34; N 5.51.

9-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (5d). Yield 90%, white solid; mp 270–272°C. IR spectrum (KBr), ν, cm^{-1}: 2954, 1645, 1471, 1502, 1608. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.89 s (6H, CH_3), 0.95 s (6H, CH_3), 1.95–2.18 m (8H, CH_2), 3.78 s (3H, OCH_3), 5.21 s (1H, CH), 6.98 d (*J* = 8.8 Hz, 2H), 7.22 t (*J* = 7.8 Hz, 1H), 7.40 t (*J* = 8.0 Hz, 2H), 7.65 d (*J* = 8.0 Hz, 2H), 7.78 s (1H), 8.02 d (*J* = 7.8 Hz, 2H). Found, %: C 75.88; H 6.54; N 5.38. $C_{33}H_{34}N_2O_4$. Calculated, %: C 75.84; H 6.56; N 5.36.

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