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An Unexpected Reaction of 3-Ethoxycyclohex-2-enone with 3-Oxo-1,2-pyrazolidinium ylides: Preparation of 9-aryl-xanthenediones

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ABSTRACT

An unexpected result from the reaction of 3-ethoxycyclohex-2-enone with 3-oxo-1,2-pyrazolidinium ylide is described. This transformation catalyzed by TFA/H_2O in the presence of DMSO, leading to 9-aryl-xanthenediones in good yields (75-94%). The structures of the prepared compounds were characterized thoroughly by IR, elemental analysis, MS, NMR together with X-ray crystallographic analysis. A possible mechanism of this unusual reaction process is proposed.

Keywords: 3-Ethoxycyclohex-2-enone, 3-Oxo-1,2-pyrazolidinium ylides, 9-Aryl-xanthenediones, X-ray structure determination.

INTRODUCTION

Xanthene and, in particular, benzoxanthene derivatives are an important class of organic compounds because of their biological activities [1-6]. One of the most widely used methods for the synthesis of these compounds is via condensation of appropriate active methylene carbonyl compounds with aldehydes catalyzed mainly by organic and mineral acids [7-13]. In this work, we report the reactivity of 3-ethoxy-2-cyclohexenone **1** with various 4-methyl-3-oxo-1,2-pyrazolidinium ylides **2a-e**. For an ongoing program within our research group we needed to synthesize cycloadduct of the type **3**. We reasoned that **3** could be easily prepared by 1,3-dipolar cycloaddition reaction between the double bond C=C of compound **1** and azomethines **2a-e**. These reaction conditions, however, led to an unexpected 9-aryl-xanthenediones **4a-e** (Scheme 1).

MATERIALS AND METHODS

Melting points were determined using a Büchi-Tottoli apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (^{1}H) or 75MHz (^{13}C) instruments. Chemical shifts are given in d parts per million (ppm) downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light. Commercial reagents were used without further purification unless stated.

General procedure for the synthesis of 9-aryl-xanthenediones 4a-e. The 3-methoxy-cyclohex-2-enone (0.2 mmol) was added to a mixture of 2-arylidene-4-methyl-5-oxo-1,2-pyrazolidinium ylides (0.2 mmol), TFA catalyst (0.01 mmol) and H_2O (6µl) in DMSO (1.0 mL) at 20 °C. The reaction was maintained at this temperature and monitored by TLC. Then the solution was diluted in cold water with stirring for 10 minutes and allowed to precipitate. The precipitate was filtered, washed with petroleum ether, then dissolved in the minimum of dichloromethane and purified by column chromatography on silica gel using EtOAc/hexane (9/1) to afford the desired product in good yield.

9-Phenyl-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (4a): Yield 75 %; mp: 203-205°C (lit. [20] 201-203°C); IR (KBr, □cm^{-1}): 698, 800, 1022, 1095, 1176, 1261, 1359, 1402, 1658, 2962 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.79-1.84 (m, 4H, 2CH$_2$-), 2.18-2.23 (m, 4H, 2CH$_2$-), 2.50-2.61 (m, 4H, 2CH$_2$-), 4.51 (s, 1H, -CH-), 6.96-7.05 (m, 5H, H-Ar); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 20.3 (2CH$_2$), 26.9 (2CH$_2$), 30.8 (CH), 36.9 (2CH$_2$), 104.3 (CH), 116.1 (2C), 128.3 (2CH), 129.0 (2CH), 142.1 (C), 165.2 (2C), 196.8 (2CO); EI-MS (m/z) = 295 [M+1]$^+$, Anal. Calcd for $C_{19}H_{18}O_3$; C, 77.53; H, 6.16. Found: C, 77.45; H, 6.24.

9-p-Tolyl-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (4b): Yield 94 %; mp: 258-260°C; IR (KBr, □cm^{-1}): 835, 1134, 1178, 1465, 1620, 1662, 2965, 3040; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.79-1.95 (m, 4H, 2CH$_2$-), 2.18 (s, 3H, CH$_3$), 2.18-2.24 (m, 4H, 2CH$_2$-), 2.54-2.66 (m, 4H, 2CH$_2$-), 4.51 (s, 1H, -CH-), 6.97 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 20.3 (2CH$_2$), 21.0 (CH$_3$), 26.9 (2CH$_2$), 30.8 (CH), 36.9 (2CH$_2$), 116.1 (2C), 128.3 (2CH), 129.0 (2CH), 135.6 (C), 142.1 (C), 165.2 (2C), 196.8 (2CO); EI-MS (m/z) = 309 [M+1]$^+$, Anal. Calcd for $C_{20}H_{20}O_3$; C, 77.90; H, 6.54. Found: C, 77.78; H, 6.64.

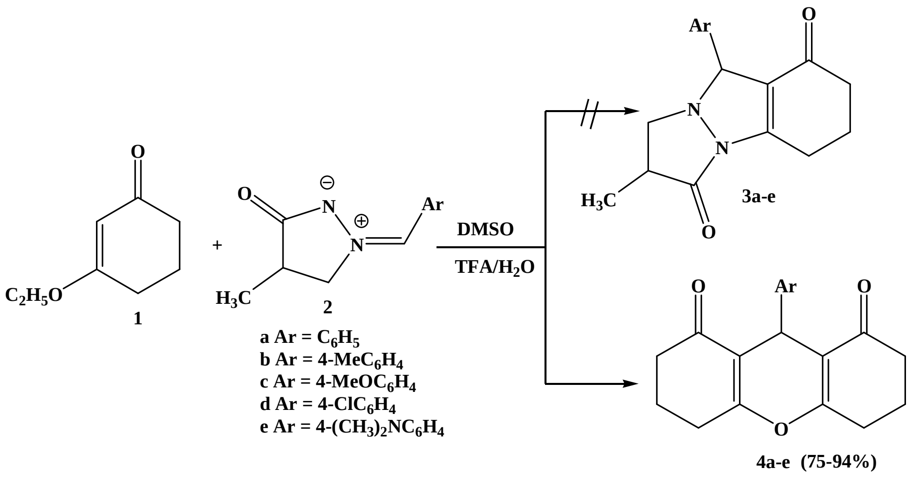
9-(4-Methoxyphenyl)-3,4,5,6,9-hexahydro-2H-xanthene-1,8-dione (4c): Yield 88%; mp: 244-246°C; IR (KBr, □cm^{-1}): 684, 842, 1033, 1138, 1193, 1301, 1358, 1462, 1510, 1625, 1666, 2877, 3003, 3311 cm^{-1}; ^{1}H NMR(300 MHz, DMSO-d$_6$): δ 1.91-2.10 (m, 4H, 2CH$_2$-), 2.21-2.48 (m, 4H, 2CH$_2$-), 2.54-2.69 (m, 4H, 2CH$_2$-), 3.77 (s, 3H, CH$_3$O), 4.78 (s, 1H, -CH-), 6.75 (d, 2H, J = 9.0 Hz), 7.22 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 20.5 (2CH$_2$), 27.4 (2CH$_2$), 31.8 (CH), 37.2 (2CH$_2$), 55.4 (CH$_3$O), 121.2 (2C), 114.8 (2CH), 129.2 (2CH), 146.1 (C), 159.4 (C), 164.4 (2C), 196.8 (2CO); EI-MS (m/z) = 325 [M+1]$^+$, Anal. Calcd for $C_{20}H_{20}O_4$; C, 74.06; H, 6.21. Found: C, 74.16; H, 6.28.

9-(4-Chlorophenyl)-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (4d): Yield 82%; mp: 234-236°C (lit. [20] 231-233°C); IR (KBr, □cm^{-1}): 1166, 1380, 1595, 1664, 1719, 2253, 2929, 2960, 3064, 3392; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.84-1.93 (m, 4H, 2CH$_2$-), 2.22-2.27 (m, 4H, 2CH$_2$-), 2.49-2.62 (m, 4H, 2CH$_2$-), 4.53 (s, 1H, -CH-), 7.17 (d, 2H, J = 9.0 Hz), 7.23 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 20.3 (2CH$_2$), 26.9 (2CH$_2$), 31.1 (CH), 36.8 (2CH$_2$), 115.5 (2C), 128.3 (2CH), 130.4 (2CH), 131.2 (C), 143.9 (C), 165.5 (2C), 196.9 (2CO); EI-MS (m/z) = 329 (^{35}Cl) [M+1]$^+$, 331 (^{37}Cl) [M+3]$^+$, Anal. Calcd for $C_{19}H_{17}ClO_3$; C, 69.41; H, 5.21. Found: C, 69.35; H, 5.30.

9-(4-Dimethylaminophenyl)-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (4e): Yield 79%; mp: 202-204°C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.98-2.04 (m, 4H, 2CH$_2$-), 2.30-2.36 (m, 4H, 2CH$_2$-), 2.55-2.74 (m, 4H, 2CH$_2$-), 2.96 (s, 6H, -N(CH$_3$)$_2$), 4.75 (s, 1H, -CH-), 7.23 (d, 2H, J = 9.0 Hz), 7.27 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.3 (2CH$_2$), 21.0 (CH$_3$), 27.1 (2CH$_2$), 31.0 (CH), 36.9 (2CH$_2$), 116.7 (2C), 128.0 (C), 129.7 (4CH), 135.6 (C), 163.9 (2C), 196.6 (2CO); EI-MS (m/z) = 338 [M+1]$^+$, Anal. Calcd for $C_{21}H_{23}NO_3$; C, 74.75; H, 6.87. Found: C, 74.86; H, 6.78.

RESULTS AND DISCUSSION

The cyclic azomethine imine, 3-oxo-1,2-diazetidinium ylide, was recognized as a 1,3-dipole, it was successfully employed in the reactions with dipolarophiles, such as alkynes [14] and alkenes (including unsaturated aldehydes [15], unsaturated ketones and esters [16] and others [17]). In this context, we decided to investigate the reactivity of 3-ethoxy-2-cyclohexenone **1** with various 4-methyl-3-oxo-1,2-pyrazolidinium ylides **2a-e**, in the presence of dimethyl sulfoxide (DMSO) and catalytic amounts of TFA/H_2O at room temperature. These reaction conditions, lead unexpectedly to the formation of 9-aryl-xanthenediones **4a-e** in good to excellent yields (75-94 %, Scheme 1). No cycloadduct resulting from the addition of the dipole **2** on the double bond C=C was detected under the identical conditions. Azomethine imines **2a-e** used in this study were prepared more recently by our group [19] according to literature procedures [14h,18].



Scheme 1 : Synthesis of 9-aryl-xanthenediones 4a-e

All compounds have been identified on the basis of their spectral (NMR, IR, MS) data and elemental analysis. In addition, the structure of compound **4d** was confirmed by means of X-ray crystallographic analysis (Figure 1).

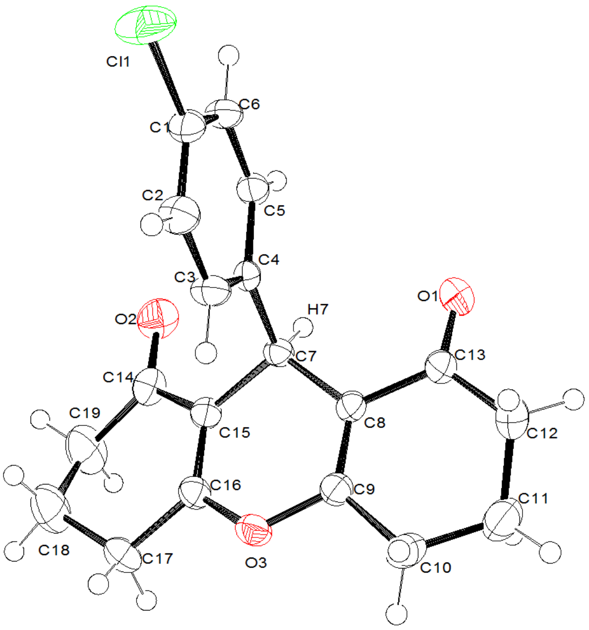


Figure 1: ORTEP diagram of 9-(4-chlorophenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8-dione 4d

X-Ray analysis of 4d. Crystallographic data were collected on Bruker D8 VENTURE diffractometer using Mo K_α radiation (λ = 0.71073 Å) at 193(2) K with CCD detector. A suitable crystal was mounted on a glass fiber or nylon loop and shock-cooled on the goniometer head. Semi-empirical absorption corrections were employed. The structures were solved by direct methods (SHELXS-97), and refined using the least-squares method on F^2 (see Table 1).

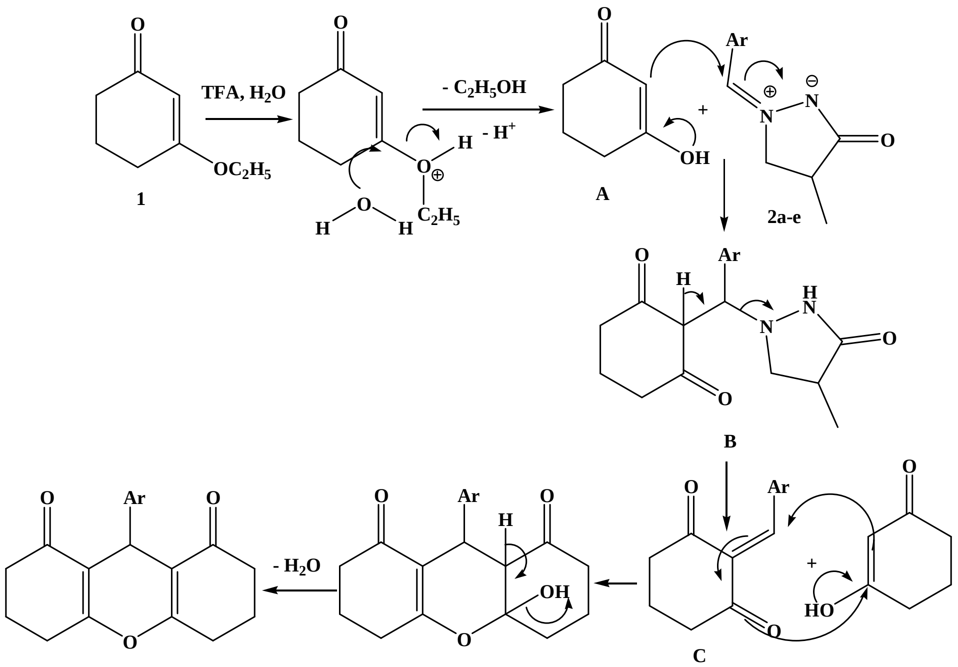
Table 1. Crystal data, data collection, and structure refinement for 4d

Crystal data	
formula	$C_{19}H_{17}ClO_3$
M_r	328.77
crystal system	monoclinic
space group	P 21/n
a (Å)	8.857(5)
b (Å)	10.565(6)
c (Å)	16.963(9)
α (°)	90
β (°)	97.949(19)
γ (°)	90
V (Å^3)	1572.0(15)
Z	4
ρ_{calc} (g cm^{-3})	1.389
μ(mm^{-1})	0.256
F(000)	688
crystal size (mm^3)	0.25 x 0.1 x 0.1
Data collection and Refinement	
T/K	193(2)
measdreflns	18744
Unique reflns (Rint)	49209 (0.0301)
reflns used for refinement	3184
refined parameters	208
GOF on F^2	1.015
R_1[a][I>2σ (I)]	0.0486
wR_2[b][I>2σ (I)]	0.1304
R_1[a]all data	0.0593
wR_2[b] all data	0.1453
$\Delta\rho_{max/min}$/ e.Å^{-3}	0.436/0.709

[a] $R1 = \Sigma||Fo| \Sigma |Fc||/ \Sigma |Fo|$.

[b] $wR2 = [[\Sigma w(Fo^2 \Sigma Fc^2)^2]/[\Sigma w(Fo^2)^2]]^{1/2}$

For A possible mechanism is depicted in Scheme 2. The 3-ethoxy-2-cyclohexenone **1** in the presence of DMSO and TFA/H_2O offered the corresponding 3-hydroxy-2-cyclohexenone intermediates **A** in the first step. Then, the intermediate **A** can react with 1,3-dipôles **2a-e** to afford the corresponding intermediate **B**, followed by elimination of pyrazolidinone thus leading to the formation of the corresponding intermediate **C**. Similarly, the intermediate **C** can react with 3-hydroxy-2-cyclohexenone **A** to afford compound **D** under the same conditions.



Scheme 2. Proposed mechanism for the formation of 9-aryl-xanthenediones 4a-e

CONCLUSION

In summary, we have developed a facile, efficient, and potentially general method for the synthesis of 9-(aryl)-xanthenedione by the reactions of 3-ethoxycyclohex-2-enone with 3-oxo-1,2-pyrazolidinium ylides under very mild conditions. Therefore, we believe that our present results would enrich the chemistry of benzoxanthenedione derivatives.

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