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2,4,6-Trichloro-1,3,5-triazine as an Efficient Catalyst for Synthesis of Benzopyran Derivatives Under Solvent-Free Conditions

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Abstract: An efficient and convenient procedure has been developed for the synthesis of benzopyran derivatives by one-pot condensation of substituted salicyaldehydes and substituted 1,3-hexanediones in the presence of a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) under solvent-free conditions.

Keywords: Benzopyran derivatives, 1,3-hexanedione, salicylaldehyde, solvent-free condition, 2,4,6-trichloro-1,3,5-triazine

Benzopyran and its derivatives have attracted considerable attention from organic and medicinal chemists because of their useful biological and pharmacological properties, such as anti-estrogenic activity,[1] antimicrobial activity,[2] insulin-sensitizing activities,[3] selective thrombin (THR) inhibitors,[4] hypoglycemic activity,[5] and antibacterial activity.[6] Some benzopyrans can be useful as selective estrogen receptors.[7] Thus, the synthesis of a variety of benzopyran heterocyclic molecules is desirable. Recently, benzopyran derivatives have been synthesized by the reaction of substituted salicyaldehydes with dimedone catalyzed by KF/Al_2O_3[8] or triethylbenzylammoium chloride (TEBA).[9] Considering the importance and wide range applications of the compounds, an easy

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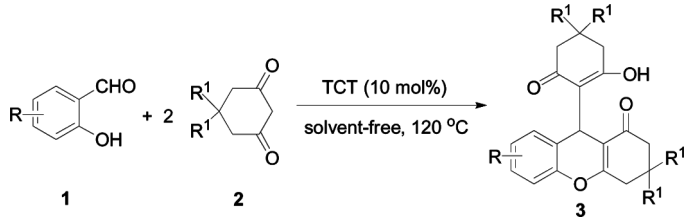

Scheme 1.

and practical method for the preparation of these compounds has still remained a challenging task.

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) has been used in organic synthesis because it is stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent.[10–13] In continuation of our work on the applications of cheap and ecofriendly materials as catalysts for development of new synthetic methodologies,[14–16] we herein report a new, convenient, and one-reaction step synthesis of benzopyran derivatives by treatment of substituted salicyaldehydes and substituted 1,3-hexanedione in the presence of catalytic amount of TCT under solvent-free conditions (Scheme 1).

To obtain some preliminary information on this synthetic reaction, initial experiments were performed with salicyaldehyde (**1a**) and 5,5-dimethyl-1,3-cyclohexanedione (**2b**, $R^1 = Me$) as model substrates. When **1a** (2 mmol) was treated with **2b** (4 mmol) in the presence of a catalytic amount of TCT (10 mol%) at 120 °C, the desired product **3a** was obtained in 93% yield. The effect of amount of catalyst on the yield and rate was also investigated. It was found that 10 mmol% of catalyst was enough for a fairly high yield. The lesser amounts gave a low yield even after a long reaction time, and more amounts could not cause the obvious increase for the yield of product. Meanwhile, we also tested the effect of reaction temperature on the catalyzed reaction. When the reaction was carried out at 120 °C, maximum yield was obtained in a short reaction period.

To explore the scope and limitation of this reaction, a variety of substrates were submitted to this reaction condition, and the results are summarized in Table 1. It is evident that electron-rich and electron-deficient salicyaldehydes as well as 2-hydroxy-naphthalene-1-carbaldehyde reacted smoothly with substituted 1,3-hexanediones to produce high yields of products. All the products were characterized by comparison of their analytical data (IR and ^{1}H NMR) and melting points with those of authentic samples.

In summary, we have report a novel, mild, and highly efficient procedure for the synthesis of benzopyran derivatives. The use of inexpensive

Table 1. Synthesis of 1-oxo-hexahydroxanthene derivatives catalyzed by cyanuric chloride

Entry	Aldehydes	R^1	Time (h)	Yield (%)[a]	Mp (°C) Found	Mp (°C) Reported
a	2–OHC_6H_4CHO	CH_3	2.5	93	210–212	206–208[9]
b	2–OH–3–$MeOC_6H_4CHO$	CH_3	2	90	229–231	230–231[17]
c	2–OH–5–MeC_6H_4CHO	CH_3	2	89	223–225	222–224[8]
d	2–OH–5–FC_6H_4CHO	CH_3	2	91	225–227	
e	2–OH–5–ClC_6H_4CHO	CH_3	3	90	236–238	238–239[9]
f	2–OH–5–BrC_6H_4CHO	CH_3	3	94	251–253	253–255[9]
g	2–OH–5–$NO_2C_6H_4CHO$	CH_3	3	94	203–205	205–207[9]
h	2–OH–3,5–$Cl_2C_6H_4CHO$	CH_3	3	91	236–237	235–237[9]
i	2–OH–3,5–$Br_2C_6H_4CHO$	CH_3	3	95	258–260	260–262[9]
J	2-Hydroxy-naphthalene-1-carbaldehyde	CH_3	2	95	240–242	245–248[9]
k	2–OHC_6H_4CHO	H	3	90	245–247	244–246[9]
l	2–OH–5–ClC_6H_4CHO	H	3	92	244–245	245–247[9]
m	2–OH–5–BrC_6H_4CHO	H	3	93	238–239	235–236[9]
n	2–OH–3,5–$Cl_2C_6H_4CHO$	H	3	94	255–256	254–256[9]
o	2–OH–3,5–$Br_2C_6H_4CHO$	H	2.5	94	258–259	255–257[9]
p	2-Hydroxy-naphthalene-1-carbaldehyde	H	2	90	217–219	216–218[9]

[a]Isolated yield.

and easily available catalyst, high yield, and relatively short reaction time are the attractive features of this method.

EXPERIMENTAL

Melting points were determined on an X-4 apparatus and are uncorrected. IR spectra were obtained using Shimadzu FTIR-8900 spectrometer. ^1H NMR spectra were recorded with a Varain Mercury Plus 400 spectrometer using TMS as internal standard. Elemental analyses were performed on Vario EL III CHNOS elemental analyzer.

Typical Procedure

A mixture of substituted salicylaldehyde (2 mmol), substituted 1,3-hexanediones (4 mmol), and TCT (0.2 mmol) were mixed and stirred for 5 min at room temperature, and then temperature was raised to 120 °C

and maintained for the specified time (Table 1). After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was diluted with water (10 mL) and stirred for 5 min at 80 °C. The resulting solid products were collected by filtration and were recrystallized from 95% ethanol.

Data

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (**3a**)

IR (KBr): $\nu = 3188, 2952, 1643, 1593, 1488, 1375, 1313, 1261, 1232, 1188, 1024, 1008, 756, 578\,cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.98 (s, 6H), 1.02 (s, 3H), 1.12 (s, 3H), 1.95–2.70 (m, 8H), 4.65 (s, 1H), 6.99–7.18 (m, 4H), 10.43 (s, 1H, OH). Anal. calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.50; H, 6.92.

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (**3b**)

IR (KBr): $\nu = 3213, 2952, 1641, 1581, 1483, 1375, 1313, 1271, 1230, 1209, 1095, 1024, 758\,cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ = δ ppm: 0.97 (s, 3H), 0,99 (s, 3H), 1.02 (s, 3H), 1.12 (s, 3H), 1.96–2.70 (m, 8H), 3.88 (s, 3H), 4.66 (s, 1H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.94 (t, $J = 8.0$ Hz, 1H), 10.44 (s, 1H, OH). Anal. calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.42; H, 7.38.

7-Fluoro-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (**3d**)

IR (KBr): $\nu = 3215, 2960, 2813, 1643, 1627, 1595,1496, 1427, 1379, 1311, 1259, 1194, 1143, 1024, 1006, 819, 748\,cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 3H), 1.01 (s, 6H), 1.12 (s, 3H), 1.97–2.60 (m, 8H), 4.62 (s, 1H), 6.70 (d, $J = 7.6$ Hz, 1H), 6.82–6.87 (m, 1H), 6.98 (dd, $J = 8.4$, 4.8 Hz, 1H), 10.50 (s, 1H, OH). Anal. calcd. for $C_{23}H_{25}FO_4$: C, 71.86; H, 6.55. Found: C, 71.68; H, 6.40.

7-Bromo-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (**3f**)

IR (KBr): $\nu = 3421, 3107, 2958, 1624, 1477, 1377, 1232, 1182, 1153, 1039, 889, 594\,cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.01 (s, 6H),

1.12 (s, 3H), 1.98–2.60 (m, 8H), 4.60 (s, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.12–7.26 (m, 2H), 10.43 (s, 1H, OH). Anal. calcd. for $C_{23}H_{25}BrO_4$: C, 62.03; H, 5.66. Found: C, 62.25; H, 5.48.

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