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Original article

Silicon-mediated highly efficient synthesis of 1,8-dioxo-octahydroxanthenes and their transformation to novel functionalized pyrano-tetrazolo [1,5-*a*] azepine derivatives

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ABSTRACT

A facile and highly efficient protocol for the synthesis of 1,8-dioxo-octahydroxanthene derivatives was achieved through cascade Knoevenagel–Michael condensations and cyclo-dehydration reaction utilizing tetrachlorosilane (TCS) as catalyst under mild conditions. Reaction of the titled compounds with TCS–NaN_3 to give novel functionalized pyrano[3,2-*c*]tetrazolo[1,5-*a*]azepine derivatives is also described.

1. Introduction

The 1,8-dioxo-octahydroxanthenes are important oxygen heterocycles which have various applications in the field of medicinal chemistry and material science. They exhibit a broad spectrum of biological activities, such as anti-inflammatory, antibacterial, antiviral activities [1], and also find applications in photodynamic therapy [2], luminescent sensors [3], fluorescent materials [4], cosmetics and pigments [5], and laser technologies [6]. Synthesis of 1,8-dioxo-octahydroxanthene is generally achieved by the condensation of 5,5-dimethyl-1,3-cyclohexadione with aromatic aldehydes using Lewis acid catalysts [7]. However, they suffer from one or more drawbacks such as longer reaction times, low yields, ease of availability of catalyst, involves cumbersome preparation of catalysts and lack of selectivity. On the other hand, tetrazoles have found numerous applications in medicinal chemistry [8]. In particular, 1,5-disubstituted tetrazoles have been described in the literature as HIV-protease inhibitors [9], glucokinase activators [10], NAD(P)H oxidase inhibitors [11], hepatitis C virus serine protease NS3 inhibitors [12], and cyclooxygenase-2 (COX-2) inhibitors [13]. In conjunction with our interest in the utility of tetrachlorosilane (TCS) [14–19] in organic synthesis, we report herein a facile and mild procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in excellent yields through the reaction of dimedone with various aromatic aldehydes in a tandem process including Knoevenagel condensation, Michael addition and cyclo-dehydration using the inexpensive and readily available tetrachlorosilane. Transformations of the prepared 1,8-dioxo-octahydroxanthene derivatives into novel functionalized pyrano-bistetrazolo[1,5-*a*]azepine derivatives were also accomplished through their reactions with $SiCl_4/NaN_3$ [20–23].

2. Experimental

Typical procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives: To a mixture of aldehyde (5 mmol) and demidone (10 mmol) in $ClCH_2CH_2Cl$ (20 mL), a catalytic amount of $SiCl_4$ (1 mmol, 0.12 mL) was added and the reaction mixture stirred at 60–70 °C. On completion (the reaction was monitored by TLC), the mixture was quenched with cold water, extracted with $CHCl_3$, dried over anhydrous $MgSO_4$, the solvent was removed under vacuum and the residue was recrystallized from EtOH to give purified **3**. The octahydroxanthenediones **3** are known compounds and all spectroscopic data were in agreement with literature.

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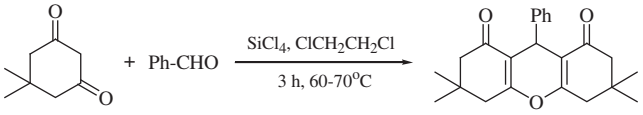
Table 1
Optimization of the amount of tetrachlorosilane.



Entry	$SiCl_4$ (mol %)	Yield (%)[a]
1	0	0
2	10	59
3	15	78
4	20	90
5	30	90

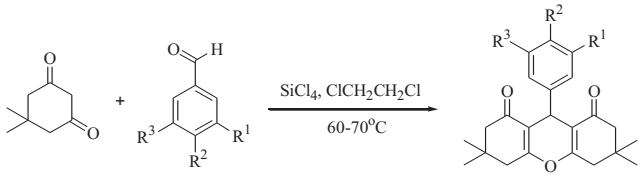
[a] Isolated yield.

Synthesis of aryl-pyrano[3,2-c]tetrazolo[1,5-a]azepine derivatives: A typical procedure for the reaction of **3** with $SiCl_4/NaN_3$ in the ratio 1:2:6, to give **4**. To a mixture of **3** and NaN_3 in CH_3CN at room temperature, $SiCl_4$ was added and the mixture warmed at 60–70 °C with stirring until TLC showed the disappearance of the starting material. The reaction was then poured into aq. $NaHCO_3$ solution and the mixture was extracted with EtOAc. The extract were dried over $MgSO_4$ and concentrated, then cooled to give pure **4**.

Data for **4b**,**d** as representative examples are showed. **4b**: Mp > 300 °C; IR (KBr, cm^{-1}): ν 2964, 2934, 2836, 1652, 1607, 1510, 1461, 1420, 1362, 1329, 1203, 1157, 837, 770, 585; ^1H NMR (300 MHz, DMSO-d_6): δ 7.34 (d, 2H, *J* = 8.5 Hz, Ar-H), 6.78 (d, 2H, *J* = 8.5 Hz, Ar-H), 5.59 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 4.44 (s, 4H, 2 × N–CH_2), 2.81 (s, 4H, 2 × CH_2), 1.03 (s, 6H, 2 × CH_3), 0.94 (s, 6H, 2 × CH_3); EI-MS: 460 (M^+); Anal. Calcd. for $C_{24}H_{28}N_8O_2$ (460.23): C 62.59, H 6.13, N 24.33. Found: C 62.42, H 6.07, N 24.19. **4d**: Mp > 300 °C; IR (KBr, cm^{-1}): ν 2964, 2934, 2874, 1652, 1514, 1485, 1402, 1329, 1177, 1116, 832, 711, 609; ^1H NMR (300 MHz, DMSO-d_6): δ 7.46 (d, 2H, *J* = 6 Hz, Ar-H), 7.31 (d, 2H, *J* = 6 Hz, Ar-H), 5.63 (s, 1H, CH), 4.46 (q, 4H, *J* = 12 Hz, 2 × N–CH_2), 2.83 (br s, 4H, 2 × CH_2), 1.04 (s, 6H, 2 × CH_3), 0.92 (s, 6H, 2 × CH_3); EI-MS: 464 (M^+); Anal. Calcd. for $C_{23}H_{25}ClN_8O$ (464.18): C 59.41, H 5.42, N 24.10. Found: C 59.30, H 5.27, N, 23.95.

3. Results and discussion

The reaction between dimedone (**1**, 2 mol) and benzaldehyde (**2a**, 1 mol) in the presence of $SiCl_4$ was studied as a model reaction. An optimization study of the reaction conditions has shown that only 20 mol% of $SiCl_4$ was sufficient to achieve the highest yields in dichloroethane as the solvent (Table 1). However, the reaction can proceed at room temperature over a long time, but it was more convenient to conduct the reaction at 60–70 °C, which shortened the reaction time to 2–3 h.



1 **2a-i** **3a-i**

2a, 3a: $R^1 = R^2 = R^3 = H$
2b, 3b: $R^1 = R^3 = H$, $R^2 = Cl$
2c, 3c: $R^1 = R^3 = H$, $R^2 = Br$
2d, 3d: $R^1 = R^3 = H$, $R^2 = Me$
2e, 3e: $R^1 = R^3 = H$, $R^2 = OMe$
2f, 3f: $R^1 = R^3 = H$, $R^2 = NO_2$
2g, 3g: $R^1 = R^2 = R^3 = OMe$
2h, 3h: $R^1 = OMe$, $R^2 = OH$, $R^3 = H$
2i, 3i: $R^1 = R^3 = H$, $R^2 = CN$

Scheme 1. Synthesis of 1,8-dioxo-octahydroxanthenes.

Table 2
TCS-catalyzed synthesis of 1,8-dioxo-octahydroxanthenes.

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	Benzaldehyde	3	**3a**	90
2	4-Chlorobenzaldehyde	2.5	**3b**	95
3	4-Bromobenzaldehyde	2	**3c**	94
4	4-Methylbenzaldehyde	3	**3d**	93
5	4-Methoxybenzaldehyde	2.5	**3e**	95
6	4-Nitrobenzaldehyde	2	**3f**	85
7	3,4,5-Trimethoxybenzadehyde	2	**3g**	92
8	4-Hydroxy-3-methoxybenzaldehyde	3	**3h**	90
9	4-Cyanobenzaldehyde	3	**3i**	91
10	*n*-Butyraldehyde	3	-	–

[a] Isolated yield

The reaction of dimedone with aryl aldehydes in the presence of $SiCl_4$ works well giving excellent yields of the respective 1,8-dioxo-octahydroxanthene (Scheme 1 and Table 2).

The general process was examined by applying the reaction conditions to various substituted aromatic aldehydes bearing either, electron-withdrawing groups (such as nitro, cyano, halide), or electron donating groups (such as methyl, hydroxyl, mono- or tri-methoxy groups). In all cases studied, the respective 1,8-dioxo-octahydroxanthenes were obtained in excellent isolated yields without chromatography. However, the reaction failed with aliphatic aldehydes. For example, the reaction with *n*-butyraldehyde gave a complex mixture with no preparative value (entry 10, Table 1). The structures of isolated 1,8-dioxo-octahydroxanthene derivatives were assigned based on their spectral analyses as well as by matching their melting points with reported analogues [7].

The mechanism of synthesis of xanthene derivatives **3** has been proposed through a $SiCl_4$-catalyzed manner, resembling the well-documented Lewis acid-catalyzed cascade Knovenagel condensation–Michael addition and cyclo-dehydration sequence [7(f) and (g)].

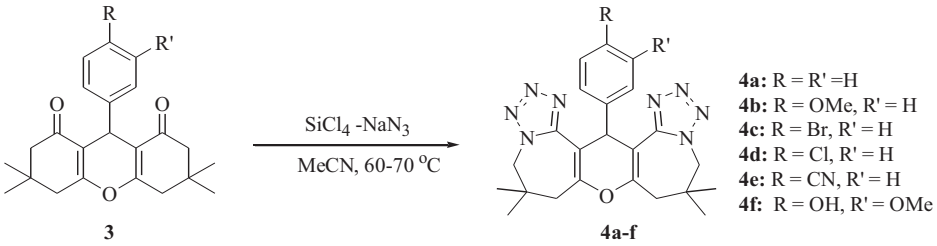
Due to the important biological activities of pyran moieties [24] as well as the existence of some potential drugs related to the terazolo[1,5-*a*]azepine core structure (*e.g.* pentetrazol) [25], we thought it may be useful to construct a chemical skeleton including both these moieties. From this point of view, and aiming at exploring the synthetic utility of the prepared 1,8-dioxo-octahydroxanthenes at the same time, we pursued studying their reaction with silyl azides (*in situ* formed by reaction of TCS and NaN_3) envisaging the formation of novel tetrazoloazepine derivatives. According to the well-documented procedure [20–23], the reaction of 1,8-dioxo-octahydroxanthenes with TCS–NaN_3 led to a smooth formation of novel functionalized pyrano-bis[3,2-*c*]tetrazolo[1,5-*a*]azepines in very good yields (Scheme 2 and Table 3).

The structural elucidation of tetrazoloazepines **4** was assigned on the basis of both elemental and spectral analyses. In the IR spectra, no absorption for the carbonyl group (C=O) was observed, rather, the products displayed the characteristic C=N stretching

Table 3
TCS–NaN_3 mediated syntheis of aryl-pyrano-bis-tetrazoloazepine derivatives.

Entry	*R*	*R′*	Time (h)	Product	Yield (%)[a]
1	H	H	3	**4a**	82
2	OMe	H	2	**4b**	85
3	Br	H	2	**4c**	87
4	Cl	H	3	**4d**	84
5	CN	H	3	**4e**	83
6	OH	OMe	3	**4f**	78

[a] Isolated yield.



Scheme 2. Synthesis of aryl-pyrano-bis-tetrazoloazepine derivatives.

band at ν_{max} 1652 cm^{-1}, supporting the formation of bis-tetrazole. The ^1H NMR spectra of bis-tetrazoloazepines were in agreement with the depicted structures. For example, the ^1H NMR spectra of **4b** showed a singlet at δ 5.59 attributed to the methine proton (CH) and two characteristic singlets corresponding to four protons each, by intergration, at δ 4.44 and 2.81. These two singlets are most likely attributed to the protons at the carbon attached to the nitrogen ($2 \times N–CH_2$) and allylic protons ($2 \times CH_2–C{=}C$), respectively. Furthermore, mass spectrum of **4b** displayed the *m/z* 460 peak corresponding in mass to its molecular ion (M^+). The simplicity, mild conditions, cheap, ease of reagent handling and toleration to diverse substrates are features of the present synthetic procedure.

4. Conclusion

In conclusion, a new, highly efficient approach to 1,8-dioxo-octahydroxanthenes catalyzed by TCS has been presented. The mild reaction conditions of the protocol, inexpensive reagents and ease of handling, the simple purification of products by recrystallization are the advantages of the present method. In addition, use of the prepared 1,8-dioxo-octahydroxanthenes in synthesis of novel aryl-pyrano-di-[3,2-*c*]tetrazolo[1,5-*a*]azepine derivatives by readily available TCS–NaN_3 was also presented. The novel, functionalized pyrano-bistetrazoloazepines described in this work may find additional importance through biological evaluation which is being currently undertaken.

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