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Cyanuric chloride-catalyzed synthesis of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones

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Abstract

An environmentally friendly procedure for the preparation of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones under thermal solvent-free conditions in the presence of cyanuric chloride as heterogeneous catalyst was developed.

Keywords: Benzo[1,3]dioxoles; 3,4-Methylenedioxyphenol; 1,3-Dimethylbarbituric acid; Cyanuric chloride; Solvent-free

Benzo[1,3]dioxoles have been attractive to synthetic organic chemists and biochemists over the last two decades since, these compounds have shown interesting biological properties such as antitumor [1], antimicrobial [1a], antiproliferative [2], antioxidant [3], anti-inflammatory [3], anti-HIV [4], antineoplastic and antiviral activities [5]. The methylenedioxy unit, present in these compounds, can be identified in the clinical antitumor agents etoposide and teniposide [6] and lignan lactone podophylotoxin [7]. Therefore, much attention has been focused on the efficient synthesis of benzo[1,3]dioxole derivatives [8].

Cyanuric chloride (TCT), an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions [9]. In the present research, we wish to describe a simple and efficient protocol for the rapid preparation of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*]-[1,3]dioxole-7,9-diones using a catalytic amount of TCT under solvent-free conditions (Scheme 1). To the best of our knowledge, there are no reports on three-component coupling of aldehyde, 3,4-methylenedioxyphenol and 1,3-dimethylbarbituric acid to produce a new class of 3,4-methylenedioxyphenol derivatives.

To optimize reaction conditions, the reaction of 3,4-methylenedioxyphenol (1 mmol), benzaldehyde (1 mmol), and 1,3-dimethylbarbituric acid (1 mmol) was selected as a model reaction to provide the desired 10-phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-dione. At first, the reaction was examined using various amounts of TCT at different temperatures. The results are displayed in Table 1. As Table 1 indicates, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 0.05 mol catalyst at 120 °C.

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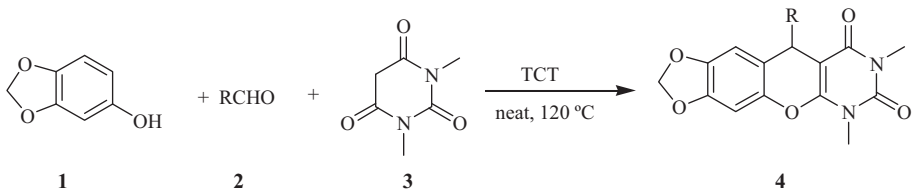


Scheme 1.

Table 1
Synthesis of 10-phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-dione under various conditions.

Entry	TCT (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	0	120	6	<5
2	1	120	4	49
3	4	120	1.5	81
4	5	110	1.5	82
5	5	140	1	87
6	6	120	1.5	85

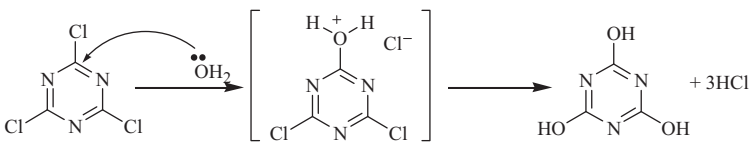
When reactions were carried out in the absence of catalyst for long period of time (4–6 h), the yield of product was low (<5%). Thus, we applied these optimal conditions for all other reactions.

With these results in hand, we turned our attention to the scope of the aromatic aldehydes in the reaction. The results were summarized in Table 2. Aromatic aldehydes containing electron-donating as well as electron-withdrawing groups smoothly underwent the conversion. The reaction proceeded at 120 °C within 2.5 h in excellent yields after the addition of the catalyst TCT (5 mol%) (Table 2). The structures of the products were established from their spectral properties (^{1}H NMR, ^{13}C NMR, MS and elemental analysis).

The plausible mechanism of the reaction is as shown Scheme 2. The adventitious moisture reacts with TCT to release 3 mol of HCl, and cyanuric acid (removable by water washing) as by-product [9]. The *in situ* generated HCl acts as a protic acid to activate the carbonyl oxygen to form the 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones. In order to verify the role of HCl which is probably generated upon

Table 2
Preparation of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones.

Entry	R	Time (min)	Product	Yield (%)
1	C_6H_5	1.5	**4a**	89
2	4-Cl-C_6H_4	1.5	**4b**	91
3	4-F-C_6H_4	1	**4c**	94
4	4-Me-C_6H_4	2.5	**4d**	85
5	4-NO_2-C_6H_4	1	**4e**	96
6	3-NO_2-C_6H_4	2	**4f**	88
7	2,4-Cl_2-C_6H_3	2	**4g**	89
8	2-Cl-C_6H_4	2	**4h**	86
9	2,4-MeO_2-C_6H_3	2.5	**4i**	82



Scheme 2.

moisturizing the TCT with water, we conducted the reaction under the similar conditions by directly using HCl in the absence of TCT. A test reaction was performed between 3,4-methylenedioxyphenol (1 mmol), benzaldehyde (1 mmol), and 1,3-dimethylbarbituric acid (1 mmol) in the presence of HCl (one drop) at 120 °C without solvent. It was found that the generation of 10-phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-dione occurred in 56% after 3 h.

In conclusion, we developed a simple one-step method for the preparation of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones from the corresponding commercially available aldehyde, 3,4-methylenedioxyphenol and 1,3-dimethylbarbituric acid. The method offers several advantages including high yield of products, short reaction times, and ease of work-up procedure.

1. Experimental

NMR spectra were recorded on Bruker AV-400 spectrometer at room temperature using TMS as an internal standard, coupling constants (*J*) were measured in Hz; mass spectra were taken on a macro mass spectrometer (waters) by electro-spray method (ES); elemental analysis were performed by a Vario-III elemental analyzer; melting points were determined on a XT-4 binocular microscope and were uncorrected.

General procedure for the preparation of **4**: A mixture of 3,4-methylenedioxyphenol (1 mmol), aldehyde (1 mmol), and 1,3-dimethylbarbituric acid (1 mmol) and TCT (0.05 mmol) was stirred at 120 °C for the appropriate time (Table 2). Completion of the reaction was monitored by TLC. The material was cooled to 25 °C, after addition of 20 mL water; the mixture was stirred for 5 min. The solid so obtained was filtered off and recrystallized from ethanol.

The spectral data of **4a**–**4b** are given below, spectral data for **4c**–**4i** can be found in Supporting information.

10-Phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3]dioxole-7,9-dione (**4a**): White powder, mp 245–246 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.16 (m, 5H), 6.68 (s, 1H), 6.52 (s, 1H), 5.95 (d, 1H, J = 0.8 Hz), 5.91 (d, 1H, J = 0.8 Hz), 5.03 (s, 1H), 3.55 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 152.6, 150.7, 147.2, 145.6, 145.1, 143.1, 128.6, 127.8, 127.7, 126.9, 116.8, 108.2, 101.8, 98.0, 90.0, 39.2, 29.0, 28.1; MS (ESI): *m/z* 365 $[M+H]^+$; Anal. Calcd. for $C_{20}H_{16}N_2O_5$: C 65.93, H 4.43, N 7.69; found: C 65.90, H 4.48, N 7.74.

10-(4-Chlorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3]dioxole-7,9-dione (**4b**): White powder, mp 254–255 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, 2H, J = 6.4 Hz), 7.18 (d, 2H, J = 6.8 Hz), 6.67 (s, 1H), 6.47 (s, 1H), 5.97 (d, 1H, J = 0.8 Hz), 5.92 (d, 1H, J = 0.8 Hz), 5.00 (s, 1H), 3.54 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8, 152.6, 150.6, 147.4, 145.7, 143.6, 143.0, 132.7, 129.3, 128.8, 128.7, 116.1, 108.0, 101.9, 98.1, 89.6, 38.6, 29.0, 28.1; MS (ESI): *m/z* 399 $[M+H]^+$; Anal. Calcd. for $C_{20}H_{15}ClN_2O_5$: C 60.23, H 3.79, N 8.89; found: C 60.19, H 3.85, N 8.95.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2011.01.020.

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