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Direct CH/CH functionalization of 1,3-dihydroxy-9*H*-xanthen-9-one and 1,3-dimethoxy-9*H*-xanthen-9-one with 1,2,4-triazines and quinazoline

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Abstract. An electron-deficient series of 1,2,4-triazines and quinazoline have been used for cross-dehydrogenative coupling with 1,3-dihydroxy and 1,3-dimethoxyxanthones to give stable nucleophilic addition products. The adducts and their subsequent oxidation products were obtained in good yields and the structures of the compounds were confirmed by ^{1}H NMR spectroscopy. These results expand the scope of the methodology of nucleophilic substitution of hydrogen with the participation of xanthones with azines. Moreover, this methodology makes it possible to obtain new organic materials based on xanthones, which have a wide spectrum of biological activity.

Keywords: cross-dehydrogenative coupling reactions; 1,2,4-triazines; quinazolines; xanthones

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Introduction

Mangiferin is a representative of xanthones. It is present in significant quantities in higher plants and in particular in fruits, stems, leaves, bark and kernels of mangoes. It is a promising antioxidant with many health-related properties such as antiviral, antineoplastic, antidiabetic, antioxidant, immunomodulatory, hepatoprotective, and analgesic (Fig. 1) [1].

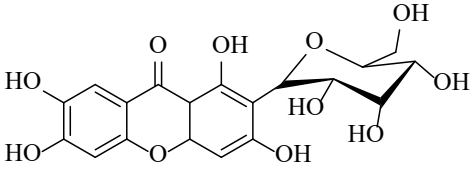
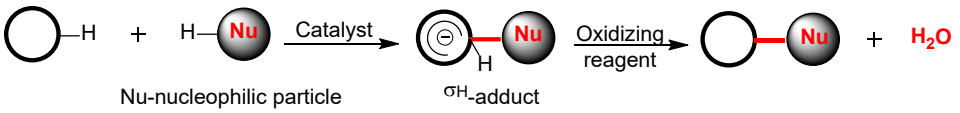


Fig. 1. Mangiferin as a biologically active representative of xanthones

The transformation of xanthones with azaheterocyclic compounds may be promising not only for obtaining new biological properties, but also for developing the methodology of nucleophilic substitution of hydrogen in chemistry of natural compounds.

Reactions of nucleophilic substitution of hydrogen (S_N^H) in a series of π-deficient heterocycles are one of the types of cross-dehydrogenation coupling (CDC) and proceed as the addition of a nucleophile to an electrophile with the formation of the so-called σ^H-adduct, which can subsequently be oxidized to a product with a completely aromatic structure (Scheme 1).



Scheme 1. General scheme of reaction of nucleophilic substitution of hydrogen

This direction makes it possible to abandon the preliminary functionalization of the initial reagents and to reduce the amount of side reagents-waste [2].

Thus, the present work is devoted to the study of the reactivity of naturally occurring nucleophilic systems such as xanthones containing two active sites with 1,2,4-triazines and quinazoline.

Results and discussion

1,3-Dihydroxyxanthones contain two different nucleophilic centers in the *m*-dihydroxybenzene ring (carbon atoms C2 and C4) and in reactions with electrophiles are capable of producing two isomeric products. We found that when 1,3-dihydroxyxanthone **1** interacts with 1,2,4-triazines **a** or **b** and quinazoline **c** in trifluoroacetic acid a mixture of two σ^H-adducts **2** and **3** is formed. These are products of nucleophilic attack at the C4 and C2 positions with a ratio of 85:15, respectively, with total yields of 68–72% (Scheme 2).

The reaction of fully methylated 1,3-dihydroxyxanthone **4** with azines **a**, **b** and quinazoline **c** in the presence of $MeSO_3H$ in acetic acid at room temperature proceeds regioselective with the formation of C4 σ^H-adduct **5a-c**. The adducts are subsequently oxidized under the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to nucleophilic substitution of hydrogen products **6a-c** in 60–71% yields (Scheme 3).

Thus, using calculations in the "Gaussian Interface program", in the case of 1,3-dihydroxanthone, carbon C2 has a more negative charge than carbon atom C4. It can be assumed in connection with the data obtained that in the case of xanthone **1** there is a competition between orbital and charge control, which leads to the formation of a mixture of products.

Experimental

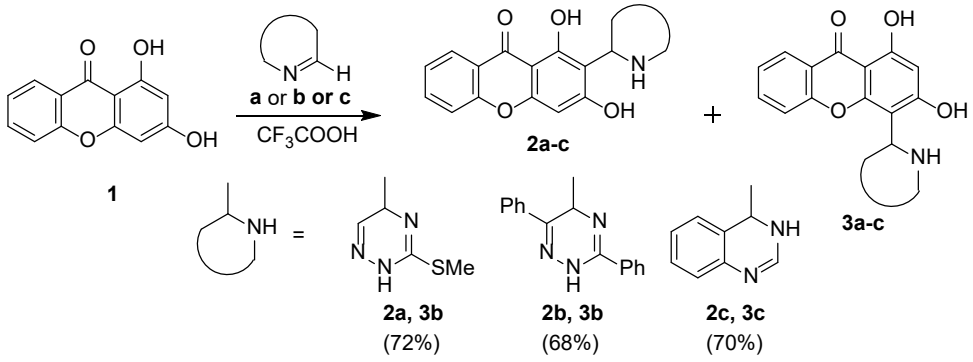
Unless otherwise noted, all commercially available compounds were used without further purification.

^{1}H NMR spectra was recorded at ambient temperature on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 as a solvent.

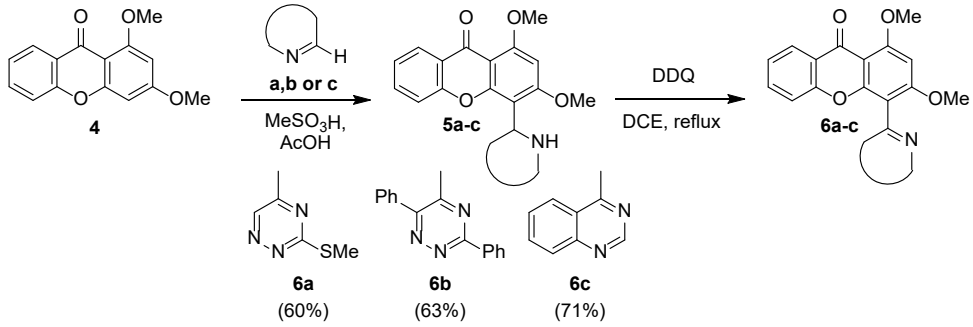
1,3-Dihydroxyxanthone 1 and **1,3-dimethoxyxantone 4** were prepared according to known procedures [3,4].

Typical procedure for synthesis 2a-c and 3a-c. Xanthone **1** (1 mmol) and azines **a, b** or **c** (1 mmol) were dissolved in TFA (10 mL). The mixture was allowed to stand for 72 h. The mixture was diluted with $NaHCO_3$ (5 mL), the precipitate formed was collected by filtration, and recrystallized from benzene.

4-(3-(Methylthio)-4,5-dihydro-1,2,4-triazin-5-yl)-1,3-dihydroxy-9H-xanthen-9-one **2a**. ^{1}H NMR (DMSO-d_6): δ = 10.98 (s, 1H, 3-OH), 9.74 (s, 1H, 1-OH), 9.70 (s, 1H, NH), 7.84 (s, 1H, H'5), 7.67–7.77 (m, 4H, benzene), 6,51 (s, 1H, C2H), 5,30 (s, 1H, sp^3-CH), 2.49 (s, 1H, CH_3).



Scheme 2. Interaction of 1,3-dihydroxyxanthone with 1,2,4-triazines and quinazoline



Scheme 3. Interaction of 1,3-dimetoxyxanthone with 1,2,4-triazines and quinazoline

4-(3,6-Diphenyl-4,5-dihydro-1,2,4-triazin-5-yl)-1,3-dihydroxy-9H-xanthen-9-one **2b**. ^{1}H NMR (DMSO-d_6): δ = 11.15 (s, 1H, 3-OH), 9.68 (s, 1H, 1-OH), 7.45–7.65 (m, 4H, Ph), 7.43 (2m, 10H, Ph) 6,12 (s, 1H, C2H), 3,52 (s, 1H, sp^3-CH).

4-(3,4-Dihydroquinazolin-4-yl)-1,3-dihydroxy-9H-xanthen-9-one **2c**. ^{1}H NMR (DMSO-d_6): δ = 11.15 (s, 1H, 3-OH), 9.68 (s, 1H, 1-OH), 7.84–7.95 (m, 4H, Quin), 7.67–7.77 (m, 4H, Ph), 6,12 (s, 1H, C2H), 5,52 (s, 1H, sp^3-CH).

Typical procedure for synthesis of 5a-c. Xanthone **4** (1 mmol) and azines **a,b** or **c** (1 mmol) were dissolved in AcOH (10 mL) and was added $MeSO_3H$ (3 equiv). The mixture was allowed to stand for 72 h. The mixture was diluted with $NaHCO_3$ (5 mL), the precipitate formed was collected by filtration, and recrystallized from benzene.

4-(3-(Methylthio)–4,5-dihydro-1,2,4-triazin-5-yl)-1,3-dimetoxy-9H-xanthen-9-one **5a**. ^{1}H NMR (DMSO-d_6): δ = 9.75 (s, 1H, NH), 7.84 (s, 1H, H'5), 7.67–7.77 (m, 4H, Ph), 6,51 (s, 1H, C2H), 4,35 (s, 1H, sp^3-CH), 2.62 (s, 3H, CH_3), 2.49 (s, 3H, CH_3).

4-(3,6-Diphenyl-4,5-dihydro-1,2,4-triazin-5-yl)-1,3-dimetoxy-9H-xanthen-9-one **5b**. ^{1}H NMR (DMSO-d_6): δ = 7.45–7.65 (2m, 10H, Ph), 6,12 (s, 1H, C2H), 3,52 (s, 1H, sp^3-CH), 2.74 (s, 3H, CH_3), 2.67 (s, 3H, CH_3).

4-(3,4-Dihydroquinazolin-4-yl)-1,3-dimetoxy-9H-xanthen-9-one **5c**. ^{1}H NMR (DMSO-d_6): δ = 7.84–7.95 (m, 4H, Quin), 7.67–7.77 (m, 4H, benzene),

6,12 (s, 1H, C2H), 4,53 (s, 1H, sp^3-CH), 2.76 (s, H, CH_3), 2.45 (s, H, CH_3).

Typical procedure for oxidation of 5a-c. To a solution of **5a-c** (1 mmol) in DCE (4 mL) was added DDQ (3 equiv). The reaction mixture was heated at 65 °C for 6 h and diluted with DCM (5 mL). The solution was passed through an alumina pad and evaporated yielding pure **6a-c**.

4-(3-Methylthio-1,2,4-triazin-5-yl)-1,3-dimetoxy-9H-xanthen-9-one **6a**. ^{1}H NMR (DMSO-d_6): δ = 9.75 (s, 1H, NH), 7.84 (s, 1H, H'5), 7.67–7.77 (m, J = 2.44, 4H, benzene), 6,51 (s, 1H, C2), 2.62 (s, 6H, $2CH_3$), 2.49 (s, 3H, CH_3).

4-(3,6-Diphenyl-1,2,4-triazin-5-yl)-1,3-dimetoxy-9H-xanthen-9-one **6b**. ^{1}H NMR (DMSO-d_6): δ = 9.75 (s, 1H, NH), 7.84 (s, 1H, H'5), 7.67–7.77 (m, 4H, Ph), 6,51 (s, 1H, C2H), 2.62 (s, 3H, $2CH_3$), 2.44 (s, 3H, CH_3).

4-(3,4-Quinazolin-4-yl)-1,3-dimetoxy-9H-xanthen-9-one **6c**. ^{1}H NMR (DMSO-d_6): δ = 9.75 (s, 1H, NH), 7.84 (s, 1H, H'5), 7.67–7.77 (m, 4H, Ph), 6,51 (s, 1H, C2H), 2.62 (s, 3H, CH_3), 2.44 (s, 3H, CH_3).

Conclusions

In summary, we have developed a convenient method introduction of 1,3-dihydroxy and 1,3-dimetoxyxanthones into 1,2,4-triazines and quinazoline based on nucleophilic substitution of hydrogen S_N^H in these nitrogen-containing heterocycles. The direct reaction CH/CH-functionalization was performed using MsOH or TFA as catalyst for the addition step, DDQ as oxidant. High yields of the coupling products, short reaction times, and mild conditions appear to be the main advantages of this promising synthetic approach.

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