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Synthesis of *N*-(3, 4, 4a, 10a-tetrahydro-2H, 5H-pyrano [2,3-b]chromen-5-yl)amines derivatives as antitumor compounds

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Abstract: A Considering the importance of aromatic amines derivatives due to their biological activities, a new synthesis of 1-aminoanthraquinone and 4-nitroaniline through a one-pot three-component reaction with salicylaldehyde and 3,4-dihydro-2*H*-pyran under mild conditions is reported.

Keywords: Anthraquinone; Salicylaldehyd; Aniline; Antitumor; Multicomponent reaction.

Introduction

Secondary and Tertiary amino group is often engraved as a structural motif in various biologically active compounds [1-3] and also, are important and crucial intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals [4]. Aminoanthraquinones have drawn considerable attention from both synthetic and medicinal chemists due to their biological activities covering a wide range of applications. In recent years, the problem of multidrug resistance (MDR) towards multitudinous antitumor compounds has also become important and seminal and much effort has been directed towards incorporation of a five- or six-membered heterocyclic ring in the anthracenedione moiety [5]. Numerous aminoanthraquinone derivatives were identified as DNA intercalating agents [6] and the antitumor antibiotics, daunomycin and adriamycin [7] are examples of derivatives.

Anthraquinone derivatives have been utilized for the activation of human telomerase reverse transcriptase expression [8, 9]. Annulated arene heterocycles and carbocycles such as chromanones, chromans, quinolines and tetrahydroquinolines [10, 14] are present as important and vital core structures in many biologically active natural products and pharmaceuticals. 2*H*-1-Benzopyrans (chromenes) and 3, 4-dihydro-2*H*-1-benzopyrans (chromens) are important and paramount classes of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally betiding representatives [15-17]. Numerous 4-aminobenzopyrans and their derivatives have attracted considerable attention in the last decade as the modulators of potassium channels influencing cardiac activity of the heart and blood pressure [18]. The appropriate choice of aldehyde and amine in these reactions provides a facile entry to bis-heterocyclic systems, which is an essential moiety in many active pharmaceuticals.

A number of Lewis acids such as lanthanide triflates, $Yb(OTf)_3$, $Sc(OTf)_3$, $BF_3.Et_2o$ and $GdCl_3$ were found to catalyze this kind of reactions. Triphenylphosphonium perchlorate (TPPP) is mild and does not require anhydrous conditions [19]. The use of a convergent three-component reaction between aldehydes, aminoanthraquinone, and alkenes in which the heterocycle is assembled in one-pot is of a particular note and especially valuable for its potential application in combinatorial synthesis.

In this work, we now report a new and highly efficient protocol for the stereoselective and cytotoxicity of *cis*-fused pyrano chromenylaminoanthraquinone or *cis*-fused pyrano chromenylamino-N-4-nitrophenyl.

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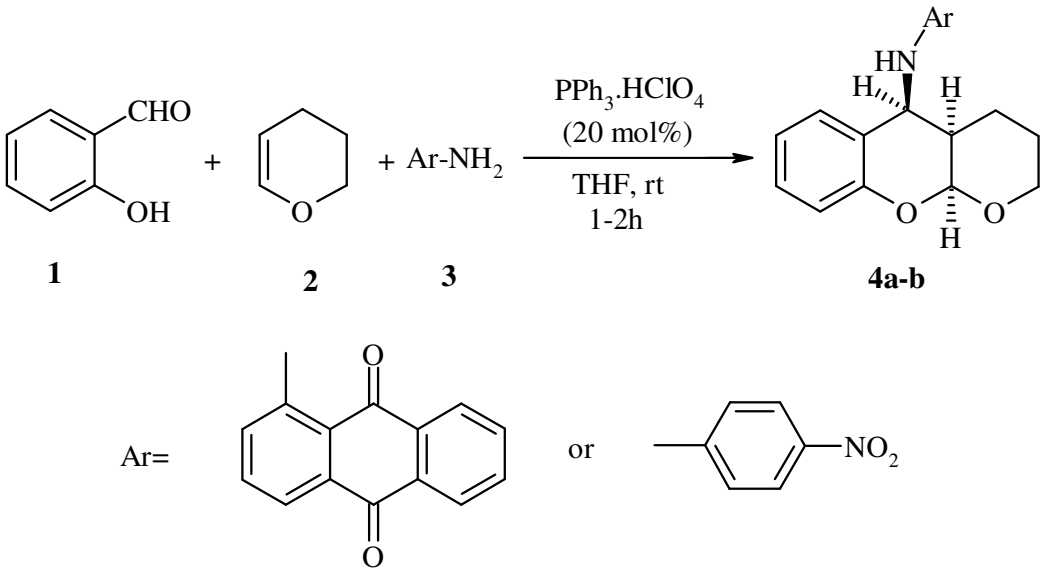
The reaction of an imine, generated from salicylaldehyde and 1-aminoanthraquinone or 4-nitroanilin cycloaddition with 3,4-dihydro-2*H*-pyran, catalyzed by TPPP gave *cis*-chromenylaminoanthraquinone or *cis*-chromenylamino-N-4-nitrophenyl in good yields (Scheme 1).

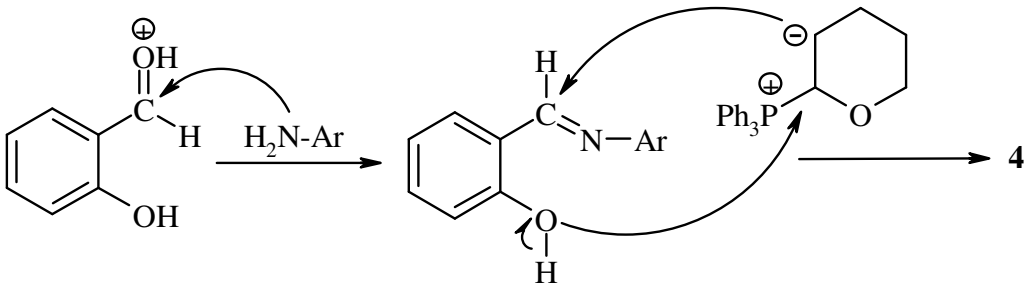


Scheme 1.

Results and Discussion

The reaction between 1-aminoanthraquinone **(3a)** or 4-nitroanilin **(3b)**, with salicylaldehyde **(1)** and 3,4-dihydro-2*H*-pyran **(2)** catalyzed by TPPP at room temperature leads to highly functionalized 1-(3, 4, 4a, 10a-tetrahydro-2*H*, 5*H*-pyrano[2,3-b]chromen-5-ylamino)anthra-9, 10-quinone or N-(3, 4, 4a, 10a-tetrahydro-2*H*, 5*H*-pyrano[2, 3-b]chromen-5-yl)-N-(4-nitrophenyl)amine **4a-b** in a **71** or **80%** yield (Scheme 1, Table 1). The stereochemistry of compounds **4a** and **4b** were assigned based on the coupling constant values. The ^{1}H NMR spectrum of compounds **4a-b** exhibited, the six-membered tetrahydropyran rings *cis*-fused. $J_{3\text{-}4}$ = 2.5 Hz between H_3 (δ = 5.29) and H_4 (δ = 2.56). Also, $J_{4\text{-}5}$ = 5.9 Hz, (H_5, δ = 5.28).

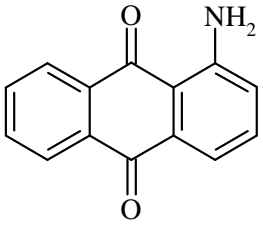
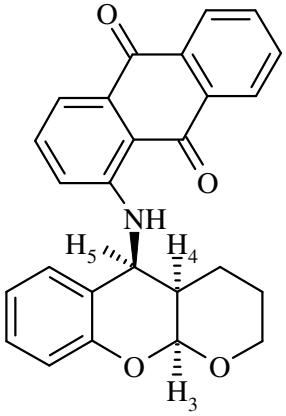
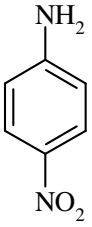
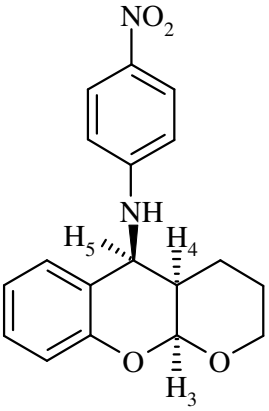
The cytotoxicity of **4a** is **IC_{50} = 50** that show a good value as a screen synthesis. Mechanistically, the reaction starts with the formation of an imine, generated from salicylaldehyde and 1-aminoanthraquinone or 4-nitroanilin cycloaddition with 3, 4-dihydro-2*H*-pyran, catalyzed by TPPP gave *cis*-chromenylaminoanthraquinone or *cis*-chromenylamino-N-4-nitrophenyl in good yields (Scheme 2).



Scheme 2

In conclusion, we have described a novel and practical method for the synthesis *cis*-fused pyrano chromenylaminoanthraquinone or *cis*-fused pyranochromenylamino-N-4-nitrophenyl from The reaction between 1-aminoanthraquinone or 4-nitroanilin with salicylaldehyde and 3,4-dihydro-2*H*-pyran catalyzed by TPPP at room temperature. The cytotoxicity of **4a** is **IC_{50} = 50** that show a good value as a screen synthesis.

Table 1.

Entry	3	4	Yield (%)
a			71
b			80

Experimental

All compounds in these reactions were obtained from Merck co. and were used without further purification. Mp: Thomas- Hoover capillary. FT-IR spectra: Bruker VERTEX-70. ^{1}H and ^{13}CNMR spectra: Bruker DRX-500Avance instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in part per million, J in hertz.

General experimental procedure:
To a stirred solution of 1-aminoanthraquinone **3** (2.5 mmol), salicylaldehyde **1** (2.5 ml), 3, 4-dihydro-2*H*-pyran **2** (2 ml) and 1-aminoanthraquinone **3** (2.5 mmol) or *P*-nitroaniline in THF, was added TPPP (20 mol %) and the reaction stirred at room temperature for about 1 hour. After completion of the reaction, as indication by the TLC, excess THF was distilled off and the residue was poured into water (50 mL). The organic layer was dried over Na_2SO_4 and distilled under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh size) fused chromentlaminoanthraquinone **4a** and **4b** as a red or yellow solid.

1-(3, 4, 4a, 10a-tetrahydro-2H, 5 H-pyrano[2,3-b]chromen-5-ylamino)anthra-9,10-quinone **(4a)**
Red crystal, (0.17g, 71%), IR (KBr) (ν_{max}/cm^{-1}): 3451 (NH), 3063 (CH,aromatic) 2945-2885 (CH, aliphatic), 1720 (C=O), 1666 (C=C), cm^{-1}.^{1}H NMR (500.1 MHz, TMS, $CDCl_3$): δ= 10.13 (1 H, *d*, *J* = 8.6 Hz, NH), 8.25–8.27 (2 H, *m*, ArCH), 7.71–7.76 (2 H, *m*, ArCH), 7.56–7.60 (2 H, *m*, ArCH), 7.42 (1 H, *d*, *J* = 10 Hz,

ArCH), 7.29–7.31 (2 H, *m*, ArCH), 6.95–6.98 (2 H, *m*, ArCH), 5.29 (1 H, *d*, *J* = 2.4 Hz, OCHO), 5.28 (1 H, *t*, *J* = 6.4 Hz, NH–CH), 3.79–4.05 (2 H, *m*, OCH_2), 2.59 (1 H, *q*, *J* = 5.9 Hz), 1.94–1.99 (3 H, *m*), 1.56–1.64 (1 H, *m*) ppm. ^{13}C NMR (125.7 MHz, TMS, $CDCl_3$): δ = 185.2 (C=O), 183.5 (C=O), 152.1 (Ar*C*–O), 151.7 (ArC), 135.5, 135.0, 134.9, 133.9, 133.1, 133.0, 128.9, 126.8, 126.7, 126.5, 123.8, 121.4, 118.0, 117.0, 116.0, 113.3 (aromatic C); 99.6, 49.1, 45.1, 38.9, 29.6, 23.0(aliphatic C).

N-(3, 4, 4a, 10a-tetrahydro-2H, 5H-pyrano [2, 3-b] chromen-5-yl)-N-(4-nitrophenyl) amine **(4b)**
Yellow crystal, (0.19 g, 80%), IR (KBr) (ν_{max}/cm^{-1}): 3419 (NH), 2900, 2885 (CH, aromatic) 1666 (C=C), 1528,1348 (NO_2), cm^{-1}. ^1H NMR (500.1 MHz, TMS, $CDCl_3$): δ= 11.34 (1 H, NH), 8.16–8.14 (2 H, *m*, ArCH), 7.31–7.30 (1 H, *d*, *J* = 5.1 Hz, ArCH), 7.26–7.22 (1 H, *m*, ArCH), 6.98–7.97 (1 H, *d*, *J* = 5.1 Hz ArCH), 6.70–6.68 (1 H, *m*, ArCH), 6.58–6.57 (2 H, *m*, ArCH), 5.59 (1 H, *d*, *J* = 5.1 Hz, OCHO), 5.43 (1 H, *d*, *J* = 2.25 Hz, CH), 5.12–5.11 (1 H, *m*), 4.43–4.42 (2 H, *m*,OCH_2), 3.08–3.05 (1 H, *m*), 2.53–2.49 (2 H, *m*), 2.35–2.28 (2 H, *m*) ppm. ^{13}C NMR (125.7 MHz, TMS, $CDCl_3$): δ 153.0 (Ar*C*–O), 151.2 (Ar*C*–NH), 138.7 (Ar*C*–NO_2), 129.6, 129.2, 126.6, 121.5, 118.9, 117.4, 111.3 (aromatic C), 94.4, 62.0, 52.9, 24.8, 22.6, (aliphatic C).

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