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Cobaltpolyoxometalate-catalyzed cyclization of glucal with aryl amines: Synthesis of 2,4-disubstituted tetrahydroquinolines

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Abstract—Treatment of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with various aryl amines in the presence of dodecatungstocobaltate under mild and neutral conditions gave sugar derived tetrahydroquinoline derivates.

As appreciation for the biological importance of carbohydrates has increased, so have efforts to develop methods for the synthesis of biologically relevant oligosaccharides, glycoconjugates, and analogues thereof.[1–5] Among the more challenging synthetic targets are aminoglycosides and their derivatives. 3,4,6-Tri-*O*-acetyl-D-glucal (**1**) is an extremely useful starting material for the preparation of several biologically active compounds, especially antitumor antibiotics such as anthracyclines, aureolic acids, orthosamycins, angacyclins, and enediynes.[6–8] Significantly, as well as participating in simple addition reaction across the glycal double bond, the presence of a good leaving group at C-3 facilitates S_N2 reactions allowing for the introduction of a wide variety of nucleophiles at C-1 of the sugar nucleus with concomitant migration of the double bond.[9]

Recently, Yadav's group has reported using $CeCl_3$/NaI as an efficient catalyst for the synthesis of tetrahydroquinolines,[10] which are very important moiety in many biologically natural products.[11–17] In second report, $InBr_3$ has been used for tetrahydroquinoline synthesis from aryl amines and glucal.[18] Both require reaction times between 4 and 9 h, and achieved good to excellent yields (75–89%). The successful application of $K_5CoW_{12}O_{40}{\cdot}3H_2O$ as an electron transfer catalyst[19] in glycosidation[20] with alcohols prompted us to explore the potential of this polyoxometalate as catalyst for C-glycosidation with aryl amines to synthesize tetrahydroquinolines.

When 1 mmol of **1** was treated with 1.5 mmol of aniline, using 20 mol% of $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[†] as catalyst in acetonitrile (3 mL) for 1.5 h at ambient temperature, bicyclic adduct **12** was isolated in 82% yield (Scheme 1). A comparative study was carried out using **1** and aniline as a model system with different solvents, temperature, and different quantity of catalyst (Table 1). Acetonitrile was shown to be superior to the other solvents examined (Table 1, entries 1–4). Using 20 mol% of catalyst to **1** shows the best result for this reaction at room temperature (Table 1, entries 4–8).[21]

Encouraged by the results obtained with aniline, we turned our attention to various aryl amines. The reactions proceeded efficiently under mild conditions to give the products in high yields (Table 2). In all cases studied, the reaction was fast with $K_5CoW_{12}O_{40}{\cdot}3H_2O$ as compared to $CeCl_3$/NaI[10] and $InBr_3$,[18] two catalysts which are reported in the literature for this reaction. In cases of *m*-chloroaniline and *m*-nitroaniline, only one product was obtained from two possible regioisomers (Table 2, entries 6, 8). So this method is highly regioselective, affording sugar fused tetrahydroquinolines in a one-pot operation. 2,6-Dichloroaniline did not yield any product under these reaction conditions (Table 2, entry 11). It clearly indicated that one of the ortho positions of aniline should be free from substitution for success of the

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Keywords: Polyoxometalate; Aminoglycozidation; Glucal; Heterogeneous catalyst.

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[†] The $K_5CoW_{12}O_{40}{\cdot}3H_2O$ was prepared according to the previously reported procedure.[11]

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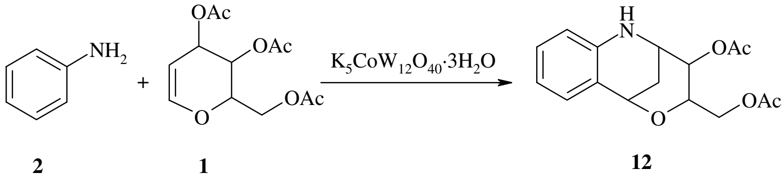


Scheme 1.

Table 1. Effect of different conditions in the reaction of **1** with aniline

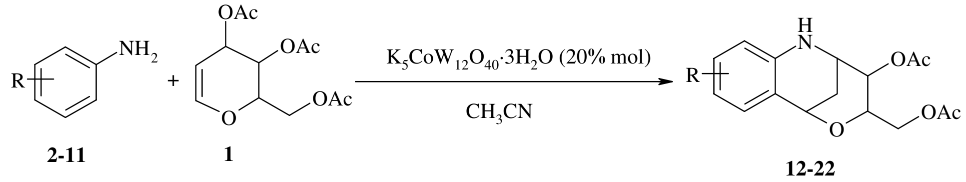
Entry	Solvent	Catalyst (mol %)	Temperature (°C)	*T* (h)	Yield[a] (%)
1	CH_2Cl_2	10	80	1.5	58
2	PhH	10	80	1.5	10
3	Et_2O	10	80	1.0	20
4	CH_3CN	10	80	1.5	67
5	CH_3CN	10	R.T.	1.5	50
6	CH_3CN	15	R.T.	1.5	68
7	CH_3CN	20	R.T.	1.5	82
8	CH_3CN	25	R.T.	1.5	84

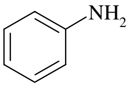
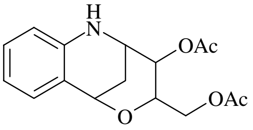
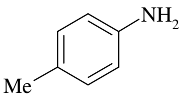
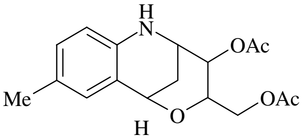
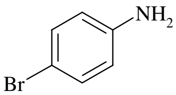
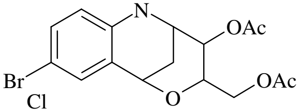
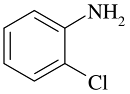
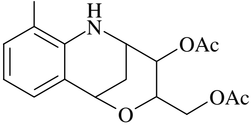
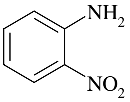
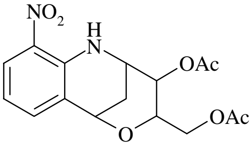
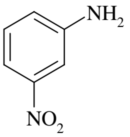
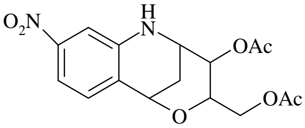
[a] Isolated yield.

reaction. In addition, we have found that $K_5CoW_{12}O_{40}·3H_2O$ can be reused several times without loss of activity by filtering the catalyst, washing with acetone, drying, and immediately reusing. The yield of **12** promoted by recovered catalyst for four times remained 80%. The authors suggest a reaction mechanism that is shown in Scheme 2.

In conclusion, the paper describes an efficient, clean, and simple method for the synthesis of tetrahydroquinoline derivatives from aryl amines and glucal, using $K_5CoW_{12}O_{40}·3H_2O$ as a reusable and non-toxic catalyst. The notable features of this procedure are mild reaction

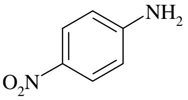
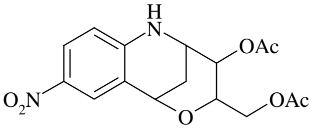
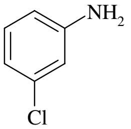
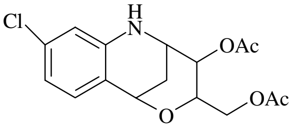
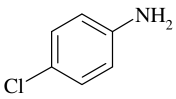
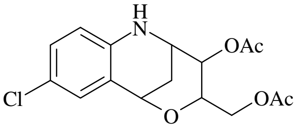
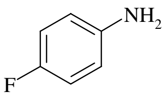
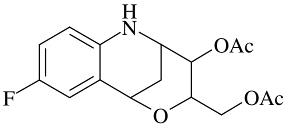
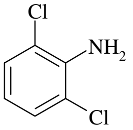
Table 2. Synthesis of fused tetrahydroquinolines from reaction of **1** with aryl amines in the presence of $K_5CoW_{12}O_{40}·3H_2O$



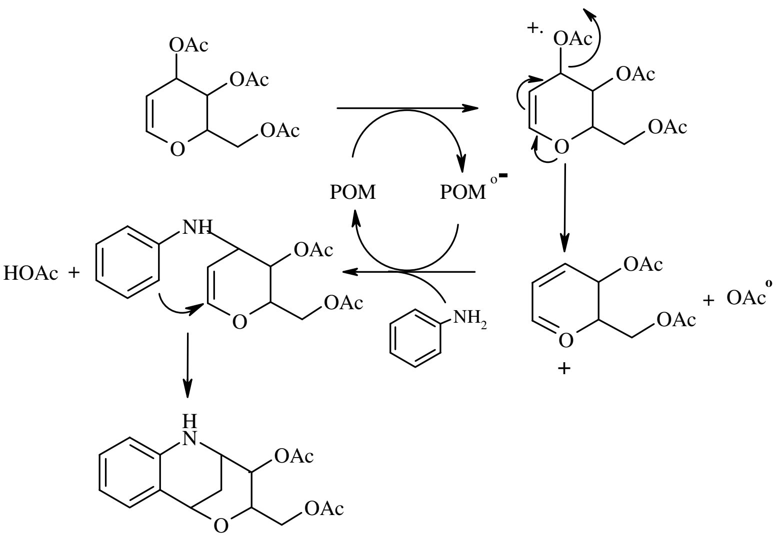
Entry	Aryl amine	Product	Time (h)	Yield[a] (%)
1		 **12**	1.5	82
2		 **13**	2.5	74
3		 **14**	2	71
4		 **15**	2.5	73
5		 **16**	2	80
6		 **17**	1.5	98

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl amine	Product	Time (h)	Yield[a] (%)
7		 **18**	1.0	98
8		 **19**	1	85
9		 **20**	1.5	84
10		 **21**	1.5	82
11		**22**	3	No reaction

[a] Isolated yield, all products were fully characterized.



Scheme 2.

conditions, high regioselectivity, high yields of products, low catalyst loading, and short reaction times.

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21. *Typical procedure*. A solution of 3,4,6-tri-*O*-acetyl-D-glucal (1 mmol), aryl amine (1.5 mmol), and acetonitrile (3 mL) in the presence of catalyst (0.2 mmol) was stirred at room temperature or 80 °C for the specified time as required to complete the reaction (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried by anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel. All products were identified by comparing their NMR values with those for authentic samples,[19] and the spectral data of new compounds are given below.

Compound **16**. Brown liquid, IR ν: 3420, 2974, 2931, 1729, 1609, 1545, 1501, 1359, 1259, 1046, 847 cm^{-1}. ^{1}HNMR (200 MHz, $CDCl_3$) δ: 7.30–7.07 (m, 2H), 6.60 (m, 1H), 4.92 (dd, J = 3.2, 10.5 Hz, 1H), 4.82 (dd, J = 1.7, 3.7 Hz, 1H), 4.51 (br s, 1H, NH), 4.23 (dd, J = 4.1, 12.0 Hz, 1H), 3.99 (dd, J = 2.1, 12.0 Hz, 1H), 3.88 (ddd, J = 2.4, 3.2, 4.5 Hz, 1H), 3.57 (ddd, J = 2.1, 4.2, 10.5 Hz, 1H), 2.29 (ddd, J = 2.4, 3.8, 13.1 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 1.97 (ddd, J = 1.7, 4.5, 13.2 Hz, 1H).

Compound **17**. Brown liquid, IR ν: 3394, 2928, 2856, 1735, 1602, 1558, 1488, 1432, 1359, 1373, 1246, 1131, 1049, 848 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.91–6.85 (m, 2H), 6.48–6.30 (m, 1H), 4.75 (dd, J = 3.2, 10.3 Hz, 1H), 4.70 (dd, J = 1.7, 3.8 Hz, 1H), 4.30 (br s, 1H, NH), 4.21 (dd, J = 4.2, 12.0 Hz, 1H), 4.02 (dd, J = 2.0, 12.0 Hz, 1H), 3.82 (ddd, J = 2.4, 3.2, 4.5 Hz, 1H), 3.57 (ddd, J = 2.0, 4.1, 10.3 Hz, 1H), 2.28 (ddd, J = 2.4, 3.7, 13.0 Hz, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.95 (ddd, J = 1.7, 4.5, 13.0 Hz, 1H).

Compound **18**. Oily brown liquid, IR ν: 3371, 2956, 1732, 1611, 1546, 1498, 1377, 1364, 1246, 1047, 872 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.91–6.80 (m, 2H), 6.49–6.42 (m, 1H), 4.81 (dd, J = 3.1, 10.5 Hz, 1H), 4.72 (dd, J = 1.8, 3.7 Hz, 1H), 4.35 (br s, 1H, NH), 4.20 (dd, J = 4.2, 12.0 Hz, 1H), 3.92 (dd, J = 2.2, 12.0 Hz, 1H), 3.81 (ddd, J = 2.4, 3.0, 4.5 Hz, 1H), 3.55 (ddd, J = 2.1, 4.2, 10.4 Hz, 1H), 2.27 (ddd, J = 2.4, 3.7, 13.0 Hz, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.94 (ddd, J = 1.7, 4.5, 13.1 Hz, 1H).