Niobium Pentachloride Catalyzed Multicomponent Povarov Reaction

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Abstract: A single-step method for the synthesis of furan- and pyranoquinoline derivatives through multicomponent Povarov reactions between aniline derivatives, benzaldehyde and two different enol ethers (2,3-dihydrofuran and 3,4-dihydropyran) using niobium pentachloride as catalyst under mild conditions, providing good yields and high diastereoselectivity, is described.

Key words: niobium pentachloride, multicomponent Povarov reaction, furanoquinolines, pyranoquinolines, Lewis acid

The tetrahydroquinoline derivatives, compounds that have the basic structure of quinolines, are an important class of natural products and have several important biological activities,[1] such as psychotropic,[2] antiallergic,[3] anti-inflammatory[4] and estrogenic activity.[5] Pyranoquinoline and furanoquinoline derivatives have pharmacological potential.[6] Among these compounds we can mention the simulenoline (**1**) and the huajiaosimuline[7] (**2** ; Figure 1), extracted from the *Zanthoxylum simulans*, a bush found in China and Taiwan, compounds that act as strong platelet inhibitors.

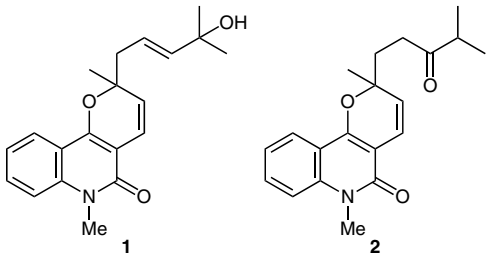

Figure 1 Structures of the simulenoline (**1**) and the huajiaosimuline (**2**)

In addition to this good applicability observed for the simulenoline and the huajiaosimuline, some recent studies found in the literature[8] show other possible applications for tetrahydroquinoline derivatives. Among them, their application as an anticancer drug, acting as mitotic kinesin inhibitors (enzyme responsible for cell division) and also for Alzheimer's disease treatment, inhibiting the acetylcholinesterase enzyme (an enzyme necessary for the transmission of nerve impulses and also responsible for acetylcholine degradation, an important neurotransmitter).

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The tetrahydroquinoline derivatives can be easily synthesized through Povarov multicomponent reactions (MCRs) using several catalysts[9] (Lewis acids), such as, $InCl_3$, $LiBF_4$, $BF_3{\cdot}OEt_2$ and others, in which, usually, a pair of diastereoisomers with *cis* and *trans* stereochemistry (Figure 2) is formed between the hydrogens H-1 and H-2, providing different ratios between these isomers, depending on the conditions used.

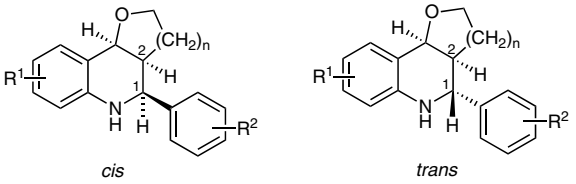


Figure 2 Stereochemistry of the tetrahydroquinoline derivatives

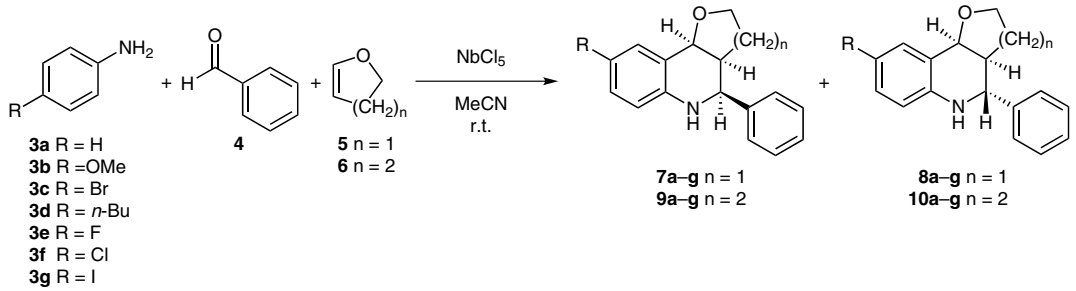
Some of the Lewis acids are not easily available or are expensive. In addition, they require longer reaction times and form the products with poor yields. Therefore, developing simple and efficient synthetic methods for preparing this type of compound becomes increasingly important.

Niobium pentachloride, which is a low-cost and commercially available reagent, has been used by our group and other researchers as an effective catalyst in synthetic methodologies in a variety of reactions.[10,11]

In the present report, we describe a highly efficient one-pot method for the synthesis of furano- and pyranoquinolines using $NbCl_5$ as catalyst. We reacted aniline derivatives **3a**–**g**, benzaldehyde (**4**) and different dienophile types [2,3-dihydrofuran (**5**) and 3,4-dihydropyran (**6**)], in the presence of $NbCl_5$ as catalyst (Scheme 1), producing the tetrahydroquinoline derivatives **7**–**9** and **10a**–**g**, in a typical Povarov multicomponent reaction.

The Povarov multicomponent reactions were carried out under an inert atmosphere of N_2, at room temperature and using anhydrous MeCN as solvent. $NbCl_5$ was used as catalyst, at the proportions of 10 mol% and 25 mol% for each aniline derivative used. The products obtained were purified by column chromatography on silica gel and characterized by spectroscopic methods,[12] whenever possible. The results obtained are described in Tables 1 and 2.

Through the analysis of Tables 1 and 2, it is possible to observe the high efficiency of niobium pentachloride as a catalyst in the reactions between aniline derivatives, benzaldehyde and enol ethers for the tetrahydroquinoline derivatives synthesis, presenting short reaction times and



Scheme 1 Povarov multicomponent reaction catalyzed by $NbCl_5$

good yields in both cases. Also, a high diastereoselectivity can be verified when using 3,4-dihydropyran (**6**) as dienophile. The diastereoselectivity of the products formed was determined by comparing the integrals of the vicinal hydrogens to nitrogen atom, for both products, in the ^{1}H NMR spectrum of crude product.

It was also possible to observe that, even when we changed the aniline substituent, the reactions took place rapidly and presented good yield when compared with other catalysts largely used in organic syntheses.[9] It was also observed in Tables 3 and 4 that high diastereoselectivity was obtained when low concentrations of the catalyst were used.

In Tables 3 and 4, the results obtained in this work are compared with other studies described in the literature.

When compared with other Lewis acids,[9] niobium pentachloride is more effective, requiring shorter reaction times, providing competitive yields and high diastereoselectivity in some of the cases, especially with lower molar concentrations of $NbCl_5$. These notable features make this procedure a useful and attractive process for the synthesis of furano- and pyranoquinolines, compounds with high biological interest, evidenced in a recent research.[8]

Recent reports[13] in the literature suggest that multicomponent Povarov reaction occur by formal aza-Diels–Alder cycloaddition with inverse electron demand by a nonconcerted process, and a possible explanation to the high diastereoisomeric difference found, is that in the moment of the Schiff base formation, the Lewis acid bonds with the nitrogen causing an steric impediment in the reaction, making the formation of the *cis* adduct difficult. On the formation of the *trans* adduct this impediment has no influence, favoring then the formation of this adduct in a larger proportion (Scheme 2).

This affirmation can be confirmed by NMR analyses used to determine the relative stereochemistry of the products.

Table 1 Multicomponent Povarov Reaction Catalyzed by Niobium Pentachloride for the Synthesis of Furanoquinolines **7a**–**g** and **8a**–**g**

Aniline	$NbCl_5$ (mol%)	Time (min)	Yield (%)	Ratio[a] **7/8**
3a	10	30	70	11:89
	25	15	71	25:75
3b	10	60	69	30:70
	25	20	70	20:80
3c	10	50	77	30:70
	25	30	77	35:65
3d	10	70	77	08:92
	25	40	70	15:85
3e	10	50	65	10:90
	25	20	60	12:88
3f	10	50	75	18:82
	25	10	83	27:73
3g	10	90	67	30:70
	25	30	70	34:66

[a] The products ratios were determined by ^{1}H NMR analysis of the crude product.

Table 2 Multicomponent Povarov Reaction Catalyzed by Niobium Pentachloride for the Synthesis of Piranoquinolines **9a**–**g** and **10a**–**g**

Aniline	$NbCl_5$ (mol%)	Time (min)	Yield (%)	Ratio[a] **9/10**
3a	10	30	85	5:95
	25	20	80	15:85
3b	10	60	69	2:98
	25	20	75	5:95
3c	10	120	88	3:97
	25	60	83	7:93
3d	10	60	68	2:98
	25	30	65	5:95
3e	10	40	70	3:97
	25	10	75	6:94
3f	10	50	61	5:95
	25	10	70	8:92
3g	10	80	83	10:90
	25	30	90	11:89

[a] The products ratios were determined by ^{1}H NMR analysis of the crude product.

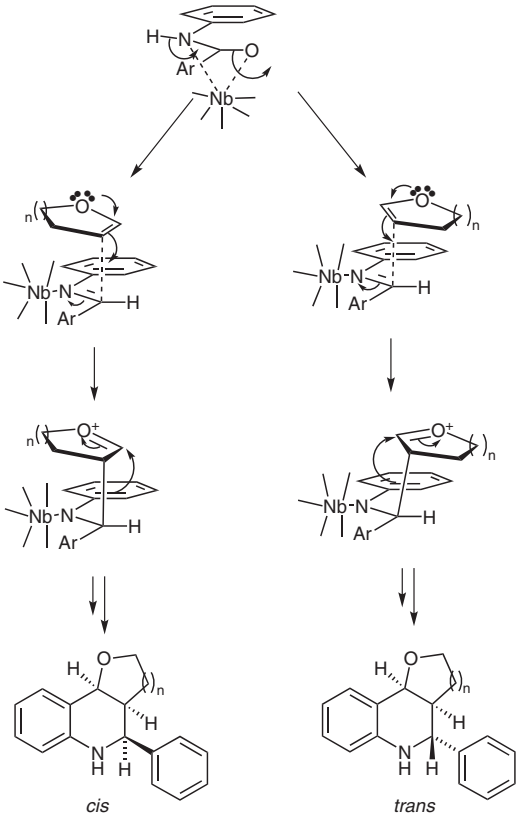
Small values of ^1H–^1H scalar coupling constant between the hydrogens H-3a and H-9b ($J_{3a,9b}$), in the adducts obtained in the reaction with 2,3-dihydrofuran (**5**), and between hydrogens H-4a and H-10b ($J_{4a,10b}$), in the adducts obtained through reaction with 3,4-dihydropyran (**6**), are characteristic of *cis* conformation between these hydrogens, confirming the mechanism proposed. The product with *trans* orientation between these hydrogens was not isolated (Figure 3).

Table 3 Comparison of this Work with Literature Results; Furanoquinoline Derivatives

Aniline	Lewis acid	mol%	Time (min)	Yield (%)	Ratio **7**/**8**
3a	**$NbCl_5$**	**25**	**15**	**71**	**25:75**
	$GdCl_3$[9e]	25	180	96	24:76
	VCl_3[9q]	20	120	88	15:85
	$CuBr_2$[9r]	50	150	68	47:53
3b	**$NbCl_5$**	**10**	**60**	**69**	**30:70**
	$CuBr_2$[9r]	50	288	53	38:62

Table 4 Comparison of this Work with Literature Results; Pyranoquinoline Derivatives

Aniline	Lewis acid	mol%	Time (min)	Yield (%)	Ratio **9**/**10**
3a	**$NbCl_5$**	**25**	**20**	**80**	**15:85**
	SmI_2[9m]	20	600	88	27:73
	$GdCl_3$[9e]	25	720	84	61:39
	VCl_3[9q]	20	150	90	20:80
	$CuBr_2$[9r]	50	120	76	21:79
3b	**$NbCl_5$**	**25**	**20**	**75**	**02:98**
	SmI_2[9m]	20	300	95	02:98
	$GdCl_3$[9e]	25	2160	62	03:97
	$CuBr_2$[9r]	50	135	46	37:63
3c	**$NbCl_5$**	**25**	**60**	**83**	**07:93**
	$GdCl_3$[9e]	25	1800	82	18:82
	VCl_3[9q]	20	180	82	25:75
	$CuBr_2$[9r]	50	270	57	26:74
3e	**$NbCl_5$**	**25**	**10**	**75**	**06:94**
	SmI_2[9m]	20	300	76	11:89
	$GdCl_3$[9e]	25	2160	70	18:82
3f	**$NbCl_5$**	**25**	**10**	**70**	**08:92**
	SmI_2[9m]	20	300	74	09:91
	$GdCl_3$[9e]	25	1800	82	20:80



Scheme 2 Mechanistic proposal for Povarov multicomponent reaction catalyzed by $NbCl_5$

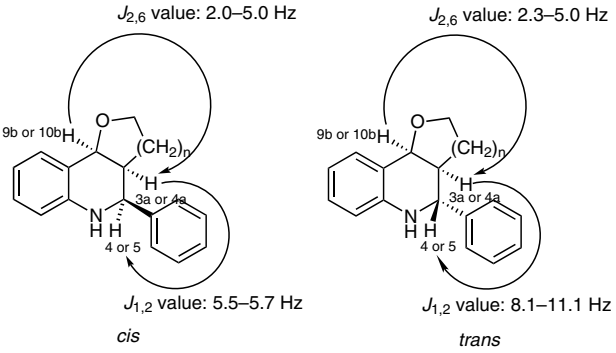


Figure 3 Coupling constant values used for determining stereochemistry

Another important information obtained through NMR analyses to determine the relative stereochemistry is that on the position of furan or pyran ring. The *cis* adducts, show smaller coupling constants $J_{4/3a}$ or $J_{5/4a}$ (5.5–5.7 Hz), typical for a *gauche* conformation. This is consistent with an orientation where the furan or pyran ring and the phenyl group are on the same side (Figure 3). In *trans* adducts, the coupling constants are significantly higher, $J_{4/3a}$ or $J_{5/4a}$ between 8.1 and 11.1 Hz, indicative of the *anti* orientation of H-4/H-3a and H-5/H-4a, which is only possible when the furan or pyran ring and the phenyl group are on opposite sides of the quinoline ring.

In summary, we have developed an efficient, rapid and good-yielding procedure to synthesize tetrahydroquinolines derivatives. Notable features of this protocol are mild reaction conditions, good selectivity, cleaner reaction profiles, short reaction times, and operational simplicity.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure for the Multicomponent Povarov Reaction of Benzaldehyde, Aniline Derivatives and Enol**

Ether with $NbCl_5$: To a solution of niobium pentachloride (10 mol% or 25 mol%) in anhyd MeCN (2.0 mL), maintained at r.t. under a nitrogen atmosphere, was added a solution of the benzaldehyde (1.0 mmol), 2,3-dihydrofuran or 3,4-dihydropyran (1.0 mmol) and the respective aniline (**3a–g**; 1.0 mmol) in anhyd MeCN (3.0 mL). After completion of the addition, stirring was continued at r.t. The reaction mixture was quenched with H_2O addition (3.0 mL). The mixture was extracted with EtOAc (10.0 mL). The organic layer was separated and washed with sat. $NaHCO_3$ solution (3 × 10.0 mL), sat. brine (2 × 10.0 mL), and then dried over anhyd $MgSO_4$. The solvent was removed under vacuum and the products were purified by column chromatography through silica gel using mainly a mixture of hexane and EtOAc (9.0:1.0) as eluent.

(3a*S*,4*S*,9b*S*)-4-Phenyl-2,3,3a,4,5,9b-hexahydrofuran-[3,2-*c*]quinoline (7a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, 1 H, J_1 = 7.6 Hz), 7.40–7.43 (m, 5 H), 7.10 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 7.0 Hz), 6.82 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 7.0 Hz), 6.61 (d, 1 H, J = 8.0 Hz), 5.29 (d, 1 H, J = 7.9 Hz), 4.71 (d, 1 H, J = 2.4 Hz), 3.70–3.88 (m, 2 H), 2.80 (m, 1 H), 2.21 (m, 1 H), 1.55 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9 (C), 141.2 (C), 129.1 (CH), 127.6 (2 × CH), 127.3 (CH), 126.6 (CH), 125.5 (2 × CH), 121.7 (C), 118.2 (CH), 113.9 (CH), 74.9 (CH), 65.8 (CH_2), 56.5 (CH), 44.8 (CH), 23.7 (CH_2). IR (film): 3348, 2975, 2855, 1615, 1480, 1039 cm^{-1}. MS: *m*/*z* = 251 $[M]^+$, 220, 206, 174, 130, 115, 91, 77.

(3a*S*,4*R*,9b*S*)-4-Phenyl-2,3,3a,4,5,9b-hexahydrofuran-[3,2-*c*]quinoline (8a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, 1 H, J = 7.0 Hz), 7.27–7.35 (m, 5 H), 7.06 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 7.0 Hz), 6.73 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 7.7 Hz), 6.56 (d, 1 H, J = 7.7 Hz), 4.54 (d, 1 H, J = 4.9 Hz), 3.96 (m, 1 H), 3.77 (m, 1 H), 3.74 (d, 1 H, J = 11.2 Hz), 2.40 (m, 1 H), 1.95 (m, 1 H), 1.65 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.8 (C), 142.1 (C), 131.6 (CH), 129.6 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 120.5 (CH), 118.8 (C), 115.1 (CH), 76.63 (CH), 65.6 (CH_2), 58.2 (CH), 43.8 (CH), 29.3 (CH_2). IR (film): 3348, 2975, 2855, 1615, 1480, 1039 cm^{-1}. MS: *m*/*z* = 251 $[M]^+$, 220, 206, 174, 130, 115, 91, 77.

(4a*S*,5*S*,10b*S*)-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyran[3,2-*c*]quinoline (9a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.44 (m, 5 H), 7.30 (m, 1 H), 7.09 (dt, 1 H, J_1 = 7.7 Hz, J_2 = 0.8 Hz), 6.79 (dt, 1 H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 6.60 (dd, 1 H, J_1 = 7.7 Hz, J_2 = 0.8 Hz), 5.33 (d, 1 H, J = 5.6 Hz), 4.69 (d, 1 H, J = 2.3 Hz), 3.85 (NH, 1 H), 3.58 (m, 1 H), 3.43 (dt, 1 H, J_1 = 11.6 Hz, J_2 = 2.5 Hz), 2.16 (m, 1 H), 1.47–1.58 (m, 2 H), 1.43 (m, 1 H), 1.31 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6 (C), 141.5 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.2 (CH), 120.3 (C), 118.7 (CH), 114.8 (CH), 73.2 (CH), 61.0 (CH_2), 59.7 (CH), 39.3 (CH), 25.8 (CH_2), 18.4 (CH_2). IR (film): 3312, 2941, 2865, 1608, 1486, 1317, 1265, 1069, 737 cm^{-1}. MS: *m*/*z* = 265 $[M]^+$, 234, 220, 194, 129, 117, 91, 77.

(4a*S*,5*R*,10b*S*)-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyran[3,2-*c*]quinoline (10a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.44 (m, 5 H), 7.22 (dd, 1 H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.09 (dt, 1 H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 6.71 (dt, 1 H, J_1 = 7.3 Hz, J_2 = 0.7 Hz), 6.53 (dd, 1 H, J_1 = 7.7 Hz, J_2 = 0.7 Hz), 4.72 (d, 1 H, J = 10.9 Hz), 4.39 (d, 1 H, J = 2.8 Hz), 4.10 (dt, 1 H, J_1 = 11.4 Hz, J_2 = 2.3 Hz), 3.72 (dt, 1 H, J_1 = 11.4 Hz, J_2 = 2.5 Hz), 2.11 (m, 1 H), 1.84 (tdt, 1 H, J_1 = 13.4 Hz, J_2 = 12.4 Hz, J_3 = 4.5 Hz), 1.65 (tt, 1 H, J_1 = 13.4 Hz, J_2 = 4.5 Hz), 1.47 (m, 1 H), 1.33 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (C), 142.7 (C), 131.3 (CH), 129.8 (CH), 129.0 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 121.0 (C), 117.9 (CH), 114.5 (CH), 74.9 (CH), 69.0 (CH_2), 55.2 (CH), 39.3 (CH), 24.5 (CH_2), 22.4 (CH_2). IR (film): 3360, 2940, 2865, 1610, 1488, 1315, 1265, 1070, 737 cm^{-1}. MS: *m*/*z* = 265 $[M]^+$, 234, 220, 194, 129, 117, 91, 77.

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