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Environmentally friendly organic synthesis using bismuth compounds. Bismuth(III) bromide catalyzed synthesis of substituted tetrahydroquinoline derivatives

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The bismuth bromide catalyzed synthesis of a range of substituted tetrahydroquinoline derivatives via a three component coupling reaction between substituted anilines and enol ethers is reported. Bismuth compounds are attractive for use as catalysts because of their remarkably low toxicity. Bismuth bromide is relatively inexpensive and easy to handle, and hence preferable to other corrosive catalysts previously used for synthesis of tetrahydroquinoline derivatives.

Substituted tetrahydroquinoline derivatives are of considerable interest due to the range of their biological activities and presence in a variety of natural products [1]. The tetrahydroquinoline skeleton is also found in many compounds that have been tested as potential drugs [2]. In addition to the interest generated due to their biological properties, tetrahydroquinolines also have applications as pesticides [3], and antioxidants [4], and are found in several dyes as well [5]. Their use as photosensitizers in photography has also been reported [6]. Hence, considerable efforts have been directed towards methods for their efficient synthesis [7]. One approach to their synthesis involves the Lewis acid catalyzed cycloaddition reaction between an imine and an aldehyde. Often, the imine is generated *in situ* from an aldehyde and an amine. Povarov and coworkers have described a synthesis of tetrahydroquinolines in which the imine, formed *in situ* from a substituted aniline and an enol ether, undergoes the Diels–Alder reaction with a second equivalent of the enol ether [8]. Several reagents have been utilized to catalyze such reactions. These include $Yb(OTf)_3$ [9], $Ln(OTf)_3$ [10], $Sc(OTf)_3$ [10], $Dy(OTf)_3$ [11], $InCl_3$ [12], $AlCl_3$ [13], $FeCl_3$-NaI [14], I_2 [15], ceric ammonium nitrate [16] and TMSCl-NaI [17]. Many of these catalysts are corrosive ($AlCl_3$, I_2), toxic ($InCl_3$) or very expensive (for example, 5.0 g of scandium triflate costs $169, and 5.0 g of dysprosium triflate costs $60). An uncatalyzed synthesis of tetrahydroquinolines in hexafluoroisopropanol has also been reported [18]. However, the use of a toxic and corrosive solvent (hexafluoroisopropanol) detracts from this procedure. Our continued interest in bismuth compounds, due largely to their remarkably low toxicity [19–21], low costs (25.0 g of $BiBr_3$ costs $34) and ease of handling prompted us to investigate a bismuth(III) bromide catalyzed synthesis of tetrahydroquinoline derivatives. Herein we report the bismuth bromide, $BiBr_3$ (5.0–20.0 mol%) catalyzed synthesis of trisubstituted tetrahydroquinolines via a coupling reaction between substituted anilines and dihydrofuran or dihydropyran (Table 1) [22]. The best results were obtained with the use of 20 mol% $BiBr_3$ for most entries. No reaction was observed between aniline and the enol ether in the absence of $BiBr_3$.

As can be seen from Table 1, the reaction works with a range of substituted anilines. Although the reaction was attempted in several solvents (CH_2Cl_2, THF, toluene and CH_3CN), the best results were obtained in CH_3CN. In all cases the product was obtained as a mixture of the *cis* and *trans* isomers, with a slight preference for the *cis* isomer. The stereochemistry of the isomers was established by NOE experiments (see Fig. 1) on 3b/4b.

In summary, the synthesis of a range of substituted tetrahydroquinolines has been accomplished using bismuth bromide as a catalyst. The use of a relatively nontoxic, non-corrosive and inexpensive catalyst is the attractive feature of this methodology.

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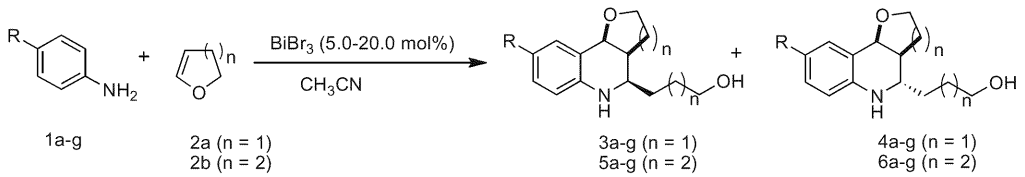
Table 1
Reaction of anilines with enol ethers catalyzed by bismuth(III) bromide [23].



1a-g

2a (n = 1)
2b (n = 2)

3a-g (n = 1)
5a-g (n = 2)

4a-g (n = 1)
6a-g (n = 2)

Entry	R=	Enol ether	mol% $BiBr_3$	T (°C)[a]	t (h)[b]	Ratio[c] 3:4 (n = 1) 5:6 (n = 2)	Yield[d]
1a	H	2a	5	rt	4	63:38	64
		2b	20	rt	26	57:43	41
1b	Cl	2a	20	65	1	53:47	67
		2b	20	rt	18	71:29	49
1c	Br	2a	20	rt	30.5	60:40	57
		2b	20	50	2	70:30	56
1d	I	2a	20	rt	23	60:40	66
1e	OMe	2a	20	rt	22.5	66:34	53
		2b	20	50	44	50:50	59
1f	CN	2a	20	65	19.5	60:40	78
		2b	20	rt	52	60:40	52
1g	COOMe	2a	20	rt	6	50:50	80

[a] Reactions were held at the indicated temperature using an oil bath.
[b] Reaction progress was followed by ^{1}H NMR or TLC.
[c] The ratio of *cis* and *trans* isomers in the crude product was determined by ^{1}H NMR as described in Ref. [14]. Although the *cis* and *trans* isomers were not completely separable by column chromatography, some separation did occur on the column.
[d] Refers to yield of purified, isolated product. All products have been reported previously in the literature (see Ref. [12a] for entries 1a–c and 1e–f; see Ref. [11] for entry 1d and 1g).

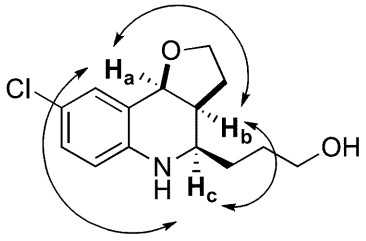


Fig. 1. NOE observed between H_a, H_b and H_c.

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[23] Representative Procedure: A solution of *p*-bromoaniline (0.5012 g, 2.914 mmol) in anhydrous acetonitrile (10.0 mL) was stirred under nitrogen in an oil bath at 50 °C as 3,4-dihydro-2H-pyran (0.52 mL, 0.4776 g, 5.678 mmol, 1.95 equivalents) and $BiBr_3$ (0.2614 g, 0.5825 mmol, 20.0 mol%) were added. After 2 h, the reaction mixture was suction filtered and the filtrate was diluted with diethyl ether (20 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.9879 g of a mixture of 5c:6c (60:40, respectively) as a yellow oil. The crude product was purified via flash chromatography on silica gel (75 g) (1:3:6 v/v/v MeOH/EtOAc/hexanes) to give 0.55 g (56%) of a mixture of 5c:6c (75:25) as a light, yellow oil. The change in ratio of 5c:6c in crude product mixture and after chromatography was a consequence of some separation that occurs during chromatography.