An Efficient Synthesis of [(Tosylamino)alkyl]naphthalenols by Nucleophilic Addition of Naphthalen-2-ol with *N*-Tosyl Imines Using Boron Trifluoride Etherate as Catalyst[1])

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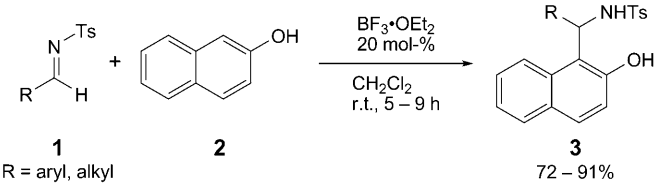
[(Tosylamino)alkyl]naphthalenols have efficiently been synthesized by nucleophilic addition of naphthalen-2-ol with *N*-tosyl imines (derived from both aromatic and aliphatic aldehydes) in the presence of $BF_3 \cdot OEt_2$ as a catalyst at room temperature. The products are formed within 5–9 h in high yields (72–91%).

Introduction. – Compounds possessing 1,3-amino oxygenated functional groups are found in different bioactive natural products and important drugs such as HIV protease inhibitors and nucleoside antibiotics [1]. They also exhibit biological properties including bradycardiac and hypotensive activities [2]. In addition, they have been applied as chelating agents and as catalysts [3]. Here, we report a simple method for the synthesis of 1-[(tosylamino)alkyl]naphthalen-2-ols, which contains 1,3-amino oxygenated function.

Results and Discussion. – In continuation of our work [4] on the development of useful synthetic methodologies, we have discovered that 1-[(tosylamino)alkyl]naphthalen-2-ols can be synthesized efficiently within 6–9 h by treatment of *N*-tosyl aldimines with naphthalen-2-ol in the presence of $BF_3 \cdot OEt_2$ as catalyst at room temperature (*Scheme 1*). Recently, one method for the synthesis of these compounds (in chiral form) has been reported, the synthesis involved a dinuclear zinc complex as a catalyst, and the reaction time was 48 h [5].

Scheme 1



1 R = aryl, alkyl **2** **3** 72 – 91%

[1]) 'Studies on Novel Synthetic Methodologies', Part 207.

Initially, *N*-tosylbenzaldimine (**1a**; R = Ph) was treated with naphthalen-2-ol for 8 h using various catalysts at room temperature (*Table 1*). Considering the yield of the products, $BF_3 \cdot OEt_2$ was found to be most effective to catalyze the reaction. Even within 6 h, a similar yield of the product was obtained in the presence of this catalyst. Consequently, this catalyst was used to prepare a series of 1-[(tosylamino)alkyl]naphthalen-2-ols from various *N*-tosyl aldimines and naphthalen-2-ol (*Table 2*). The conversion was complete within 6–9 h, and the products were formed in high yields (72–91%). *N*-Tosyl aldimines were derived from both aromatic and aliphatic aldehydes. The aromatic aldehydes containing electron-donating as well as electron-withdrawing groups were used. A sterically hindered *N*-tosyl aldimine prepared from naphthalene-2-carbaldehyde also underwent the conversion smoothly. Different functional groups such as ether, halogen, nitrogen, and nitrile remained unchanged.

Table 1. *Evaluation of the Activity of Different Catalysts for the Preparation of 1-[(Tosylamino)alkyl]-naphthalen-2-ols*[a])

Entry	Catalyst	Yield [%][b])
1	$BF_3 \cdot Et_2O$	91
2	$Sc(OTf)_3$	81
3	$Cu(OTf)_2$	79
4	$InCl_3$	77
5	$ZnCl_2$	69
6	$ZrCl_4$	67
7	$FeCl_3$	64
8	$NaHSO_4 \cdot SiO_2$	62
9	I_2	43
10	$Ba(NO_3)_2$[c])	Trace

[a]) Reaction conditions: *N*-tosylbenzaldimine (1 mmol), naphthalen-2-ol (1 mmol), and catalyst (20 mol-%) were stirred at r.t. for 8 h. [b]) Yield of the isolated product. [c]) The mixture was stirred for 24 h.

Table 2. *Synthesis of [(*N*-Tosylamino)alkyl]naphthalen-2-ols*[a])

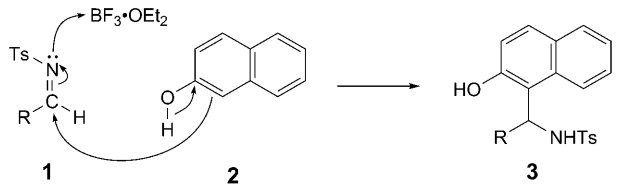
Entry	R	Time [h]	Product[b])	M.p. [°] (solvent of crystallization)	Yield [%][c])
1	4-Cl–C_6H_4	7	**3a**	168–170 (hexane/AcOEt 85 : 15)	91
2	3,4,5-$(MeO)_3$–C_6H_2	9	**3b**	195–197 (hexane/AcOEt 80 : 20)	87
3	4-NC–C_6H_4	8	**3c**	181–183 (hexane/AcOEt 85 : 15)	84
4	4-Me–C_6H_4	5	**3d**	156–158 (hexane/AcOEt 90 : 10)	89
5	3-F–C_6H_4	7	**3e**	155–157 (hexane/AcOEt 85 : 15)	90
6	Naphthalen-2-yl	6	**3f**	174–176 (hexane/AcOEt 90 : 10)	86
7	Ph	6	**3g**	171–173 (hexane/AcOEt 90 : 10)	91
8	2,3-$(MeO)_2$–C_6H_3	8	**3h**	207–209 (hexane/AcOEt 80 : 20)	89
9	3-NO_2–C_6H_4	9	**3i**	182–185 (hexane/AcOEt 80 : 20)	88
10	4-NO_2–C_6H_4	9	**3j**	184–186 (hexane/AcOEt 80 : 20)	88
11	Pr	9	**3k**	177–179 (hexane/AcOEt 85 : 15)	72

[a]) Reaction conditions: *N*-tosyl aldimine (1 mmol), naphthalen-2-ol (1 mmol) and $BF_3 \cdot OEt_2$ (20 mol-%) were used. [b]) The structures of the products were determined by their spectral analysis (IR, ^{1}H- and ^{13}C-NMR, and ESI- and HR-ESI-MS). [c]) Yield of isolated product.

The structures of the products were deduced from their spectral data (IR, ^{1}H- and ^{13}C-NMR, and ESI-, and HR-ESI-MS).

The catalyst, $BF_3 \cdot OEt_2$ polarizes the –CH=N– bond of the *N*-tosyl aldimines to facilitate the nucleophilic addition of naphthalen-2-ol (*Scheme 2*).

Scheme 2



The *N*-Ts group of the products can easily be removed [6] to afford the corresponding (aminoalkyl)naphthalenols, which can be utilized to prepare their various derivatives.

In conclusion, we have demonstrated a facile method for the synthesis of 1-[(tosylamino)alkyl]naphthalen-2-ols from *N*-tosyl aldimines and naphthalen-2-ol using $BF_3 \cdot OEt_2$ as catalyst. The mild reaction conditions, shorter reaction times, operational simplicity, and application of an inexpensive catalyst are the notable advantages of the present method.

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Experimental Part

General Procedure. To a soln. of *N*-tosyl aldimine (1.0 mmol) in CH_2Cl_2 (5 ml), naphthalen-2-ol (1 mmol) was added under N_2, followed by the addition of $BF_3 \cdot OEt_2$ (0.2 mmol). The mixture was stirred at r.t., and the reaction was monitored by TLC. After completion, the mixture was concentrated, and H_2O and AcOEt (10 ml each) were added. The org. layer was separated and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/AcOEt) to obtain pure 1-[(tosylamino)alkyl]naphthalen-2-ol.

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