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Yttrium triflate-catalyzed efficient chemoselective S-benzylation of indoline-2-thiones using benzyl alcohols

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ABSTRACT

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Indole derivatives possess a diverse array of biological and pharmacological activities.¹ Owing to their high biological importance, development of the efficient syntheses of indole derivative continues to attract significant attention of synthetic chemists.² Among various indole derivatives, indole-based sulfides and sulfoxides are of particular interest because of their medicinal properties and potential application in synthetic chemistry as intermediates.^{3–11} Biological activities such as antiviral,³ HIV-1 reverse transcriptase inhibitors,⁴ protein tyrosine kinase inhibitor,⁵ antitumor,⁶ antihyperlipidemic,⁷ and antiulcer⁸ have been reported from indole-conjugated sulfides and sulfoxides (Fig. 1). On the other hand, sulfides can be used as alkylating⁹ and sulfenylating¹⁰ agents whereas optically active sulfoxides can be used as chirality inducing agents^{9,11} and, therefore, may find applications in synthetic chemistry.

The benzylation reaction is frequently used in synthetic chemistry as a tool for the protection of heteroatoms (N, O and S). The ease with which the benzyl group can be introduced and removed makes this strategy quite valuable for synthetic chemists.¹² Benzyl halides, which are toxic, carcinogenic, and lachrymose,¹³ are most commonly used as benzyl donors for the benzyl protection reactions. Several other reagents, which use activated benzyl alcohols, have been developed for the benzylation of heteroatoms. For example, 2-benzyloxy-1-methylpyridinium triflate efficiently alkylates alcohols under mild conditions,¹⁴ oligomeric sulfonate es-

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0040-4039/\$ - see front matter © 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2010.11.163 ters,¹⁵ and oligomeric benzyl phosphates¹⁶ have been shown to benzylate amines, benzylation of aromatic amines using benzyl alcohols is efficiently catalyzed by magnetite¹⁷ and benzyldimethylsulfonium salts have been used for the benzylation of alcohols and thiols.¹⁸

A highly efficient yttrium triflate-catalyzed chemoselective S-benzylation of indolin-2-thiones using var-

iously substituted benzyl alcohols has been developed for the synthesis of indole-based sulfides. This pro-

cedure presents a greener approach for the synthesis of S-alkylated indoles. The reaction condition is

amenable to primary, secondary, and tertiary benzylic alcohols as the benzyl group donors.

Recently, we have reported the first example of the S-benzylation reaction using benzyl alcohols as an electrophile source in the presence of BF_3 etherate.¹⁹ In this finding, treatment of indoline-2-thiones with aromatic substituted primary benzyl alcohols in the presence BF_3 etherate in aprotic solvents, resulted in the chemoselective formation of 2-(benzylthio)-1*H*-indoles in







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excellent yields. The indoline-2-thione (1) moiety has three potential nucleophilic sites, namely the 1-N, the S of thione group in the thiol form and the 3-C. Among them, S is the most nucleophilic and results in exclusive formation of S-benzylated products in the reaction. To systematically conclude our study on S-benzylation of indoline-2-thiones, we have screened a series of rare earth metal triflates as potential catalysts for the S-benzylation of indoline-2-thiones. We wish to now disclose that rare earth metal triflates can also efficiently catalyze the chemoselective S-benzylation of indoline-2-thione using benzylic alcohols. After logical and systematic screening, we have identified yttrium triflate (Y(OTf)₃) as a highly efficient and environmentally friendly catalyst to catalyze this transformation. The substrate scope is expanded by using benzyl alcohols with a higher degree of substitution on the benzylic carbon to synthesize new S-benzylated analogs and to further obtain support for the proposed reaction mechanism.

The Lewis acid complex BF₃ etherate is an effective catalyst widely used for a variety of organic transformations, among them the most common being C-alkylation.²⁰ Indoline-2-thione (1), which can be readily obtained from indolin-2-one,²¹ is a useful precursor for the synthesis of indole based heterocycles. We are actively involved in exploring the chemistry around the indole nucleus to develop useful synthetic methodologies to access indole-based novel molecular structures.^{19,22} In our preliminary report,¹⁹ we noted that the reaction of indoline-2-thiones (1-3) with arylmethanols in the presence of BF₃ etherate in aprotic solvents resulted in the chemoselective formation of S-benzylated indoles. The reactions progressed quite efficiently in the case of electron rich benzyl alcohols. 4-Nitrobenzyl alcohol was found to be inert toward the benzylation reaction under similar conditions. Our results support the involvement of benzyl carbocations in this protocol. Benzyl alcohols upon reaction with the Lewis acid BF₃ etherate lead to the formation of resonance-stabilized benzyl carbocation intermediates.²³ Subsequently, a nucleophilic attack of the thiol tautomers of the indoline-2-thiones results in the formation of the S-benzvlated products. This is further substantiated by the observation that benzyl alcohols capable of forming resonance stabilized carbocations give faster and efficient reactions while those with lacking stabilizing groups give slower reactions or do not react at all. Further, these resonance stabilized soft electrophiles (carbocations) react chemoselectively with soft nucleophile -SH,²⁴ in the presence of other nucleophilic centers such as N-1 and C-3 of the indole nucleus. The treatment of indolin-2-one (as opposed to indoline-2-thione) with benzyl alcohol under similar conditions did not yield any product; this

Table 1

Screening of potential catalysts for the S-benzylation of indoline-2-thiones

highlights the unique nucleophilicity of *S* in indoline-2-thiones versus the O at C-2 in indolin-2-one. All these observations further accentuate the involvement of resonance-stabilized carbocation intermediates in this highly selective benzylation in electron rich species.

Although a versatile catalyst,²⁰ BF₃ etherate is not a reagent of choice owing to its corrosive and fuming nature. In the previous report,¹⁹ 2 equiv of BF₃ etherate was used without optimization to carry out the synthesis of indole sulfides. It should be noted that a molecule of water is formed as a by-product in the reaction. Also, most main group and d-block Lewis acid halides are water sensitive and produce catalytically less effective hydroxides.²⁵ We first decided to optimize the best catalytic condition for the reaction under investigation. For the optimization experiments, benzhvdrol and *N*-methvlindoline-2-thione (**3**) were chosen as the model reactants. Molecular sieve (4 Å) was introduced in the reaction to absorb the liberated water. Using lower molar ratios than originally employed, we have now established that 20 mol % of BF₃ etherate is as effective as using 200 mol % (Table 1, entries 1-3). We had also disclosed previously¹⁹ that BF₃ etherate can be substituted with 5–20 mol % of *p*-toluenesulfonic acid (p-TSA) to perform the same reactions but the rate of the reaction and the product yield was found to be considerably lower. Use of 20 mol % of *p*-TSA under optimization conditions yielded only 58% of the product (Table 1, entry 4). Further increase in the concentration of *p*-TSA was not appealing for a catalytic transformation. Rare earth metal triflates are known to be effective, mild, and relatively less toxic Lewis acids with considerably higher water stability.²⁶ This prompted us to screen a series of rare earth metal triflates as Lewis acid catalysts capable of effectively catalyzing the reaction under investigation with low catalyst loading. The results are presented in Table 1. As it can be clearly seen, three of the four rare earth metal triflates $(Sc(OTf)_3, Eu(OTf)_3 \text{ and } Y(OTf)_3)$, used were as effective as BF₃ etherate in catalyzing the reaction under question. Y(OTf)₃ was found to be most effective at 20 mol %;²⁷ however, use of a lower concentration led to lower vields even after longer reaction time (Table 1).

Having identified an efficient catalyst and an optimal reaction condition, we set out to further study the substrate scope where we employed a variety of benzyl alcohols with varying bulk (primary, secondary, and tertiary) on the benzylic carbon. The results are presented in Table 2. The isolated yields of the desired products ranged from 76% to 93%. It is noteworthy that the reaction condition is not only amenable to alcohols having higher degree of substitutions but also to heteroaromatic 2-furanyl methanol (Table 2,

Ph

	N 3	+ HO Ph Moleculars Ph 100	$\frac{Ph}{PC} \xrightarrow{Ph} S$	
Entry	Catalyst	Catalyst (mol %)	Reaction time (h)	Isolated yield (%)
1	BF ₃ etherate	100	1	88
2	BF ₃ etherate	50	1	81
3	BF ₃ etherate	20	1.5	84
4	p-TSA	20	2	58
5	La(OTf) ₃	20	2	55
6	$Sc(OTf)_3$	20	1	88
7	$Eu(OTf)_3$	20	1	79
8	Y(OTf) ₃	20	1	91
9	Y(OTf) ₃	10	3	71
10	Y(OTf) ₃	5	3	68

Catalvst

Table 2

Yttrium triflate-catalyzed chemoselective S-benzylation of indoline-2-thiones

	R	$ = S + HO \overset{R^4}{\underset{R^2}{\leftarrow} R^3} = MO$	D mol% Y(OTf) ₃ Dioxane ecular sieves (4Å) 100 °C, 1h R R R R R R R	3 R ²
	1 R, R ¹ = 2 R = Cl, 3 R = H, I	H R ¹ = H R ¹ = CH ₃	4-14	
Entry	Substrate	Benzyl alcohol	Product	Isolated yield (%)
1	1	OH	S N H S	76
2	3	OH		89
3	1	Ph	N S Ph	90
4	2	Ph		78
5	1	OH		93
6	2	OH		88
7	3	OH		92
8	1	OH Ph Ph	$ \begin{array}{c} $	85
9	2	OH Ph Ph	CI N 12	81
10	3	OH Ph Ph	$ \begin{array}{c} $	91
11	3	OH PhPh Ph	Ph Ph Ph Ph Ph Ph Ph Ph Ph Ph Ph Ph Ph Ph P	87

entries 1 and 2). It has been suggested that rare earth metal triflate-catalyzed alkylation using benzylic alcohols proceeds via

benzylic carbocations.^{28,29} In agreement with these observations and our previous results,¹⁹ formation of products in Table 2 further

support the involvement of stabilized carbocations as reaction intermediates.

In conclusion, we have devised a general chemoselective S-benzylation reaction of indoline-2-thiones using benzyl alcohols catalyzed by Lewis acids under mild conditions. The optimization of reaction conditions led to the discovery of commercially available solid Y(OTf)₃ as an efficient, inexpensive, and environmentally benign catalyst over previously reported BF₃ etherate for this transformation. The reaction condition required relatively low catalyst loading (20 mol %) compared to BF₃ etherate in the previous report. Furthermore, benzyl alcohols with varying degree of substitutions at benzylic position reacted quite effectively with indolin-2thiones under optimized reaction conditions, thus expanding the reaction scope substantially. Mechanistically, the exclusive formation of S-benzylated products in all the cases supports the involvement of resonance stabilized benzylic carbocation as the reaction intermediate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.163.

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