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Chemoenzymatic synthesis of novel 1,4-disubstituted 1,2,3-triazole derivatives from 2-heteroaryl substituted homopropargyl alcohols

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ABSTRACT

The one-pot synthesis of novel 1,4-disubstituted 1,2,3-triazoles from homopropargyl alcohol backbones is described. The key intermediates 2-benzothiophenyl **1a** and 2-benzofuranyl **1b** substituted homopropargyl alcohols were synthesized starting from their corresponding carboxyaldehyde derivatives. The racemic heteroaryl-substituted homopropargyl alcohol derivatives are successfully resolved to give the corresponding enantiopure acetates and the alcohols with 84–99% ee by applying chemoenzymatic methods using various lipases. Enantiomerically enriched homopropargyl alcohol derivatives were reacted with various aromatic and aliphatic halides and sodium azide via a one-pot synthesis method and novel chiral benzothiophenyltriazoles **3a**–**9a** and benzofuranyltriazoles **3b**–**9b** were constructed without the isolation of potentially unstable organic azide intermediates.

1. Introduction

Since the advent of asymmetric synthesis and the discovery of novel biological activities, there has been a growing demand for the development of simple and efficient methods for the production of chiral compounds as single enantiomers. Catalytic enantioselective synthesis is highly preferred for the preparation of enantiopure compounds. Due to their homochirality, biocatalysts have become predominantly suitable tools for the synthesis of enantiopure stereoisomers.[1–3] Hydrolases, especially lipases, are important biocatalysts for synthetic biotransformations.[4–6] Remarkable enantioselectivity towards a broad range of substrates and the low cost of many lipases make them useful catalysts for the kinetic resolution of secondary alcohols including heteroaromatic groups.[7–11]

The benzothiophene unit is recognized as a pharmacophore having the advantages of chemical and pharmacological stability, low intrinsic toxicity[12] and a rich chemistry to explore molecular diversity. The benzothiophene-based structures show diverse pharmacological activities such as nervous system depression,[13] analgesic,[14] muscle relaxant[15] and herbicidal[16] activities.

Benzofuran derivatives are another important class of heterocyclic compounds which not only act as key structural subunits in naturally occurring compounds but also they exhibit remarkable biological activities. Substituted benzofurans have applications as fluorescent sensors,[17] oxidants,[18] antioxidants, a variety of drugs[19–22] and agricultural compounds.[23]

Benzothiophene and benzofuran derivatives incorporating thiazole, triazole and oxadiazole moieties have attracted widespread attention due to their versatile pharmacological properties such as antimicrobial, anti-inflammatory, anti-tumour and analgesic activities.[24–27]

Triazole containing compounds show various biological activities including antimicrobial,[28] antidepressant,[29] anti-inflammatory,[30] anticonvulsant[31] and antifungal[32] activities. The Huisgen 1,3-dipolar cycloadditions of azides and alkynes are regioselective, and yield 1,4-disubstituted 1,2,3-triazoles.[33] The one-pot multicomponent synthesis of 1,4-disubstituted 1,2,3-triazoles has received much attention because it not only minimizes the time and the cost of the synthesis, and also avoids the isolation of potentially toxic and explosive organic azides formed in situ.[34,35]

It has been shown that when one biodynamic heterocyclic system is coupled with another, a molecule with a pronounced biological activity may be produced. Prompted by these observations, we decided to develop new biologically active heterocycles containing heteroaryl and triazole moieties. We planned to synthesize various 1,4-disubstituted benzothiophenyltriazoles and benzofuranyltriazoles from enantiomerically enriched heteroaryl homopropargyl alcohols via a one-pot triazole synthesis.

2. Results and discussion

The parent benzothiophenyl **1a** and benzofuranyl **1b** homopropargylic alcohols were used as templates for the construction

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of triazole scaffolds, and were synthesized by the addition of propargyl bromide to commercially available benzo[*b*]thiophene-2-carbaldehyde and benzofuran-2-carbaldehyde (Scheme 1).

2.1. Enzymatic resolution of racemic homopropargylic alcohols

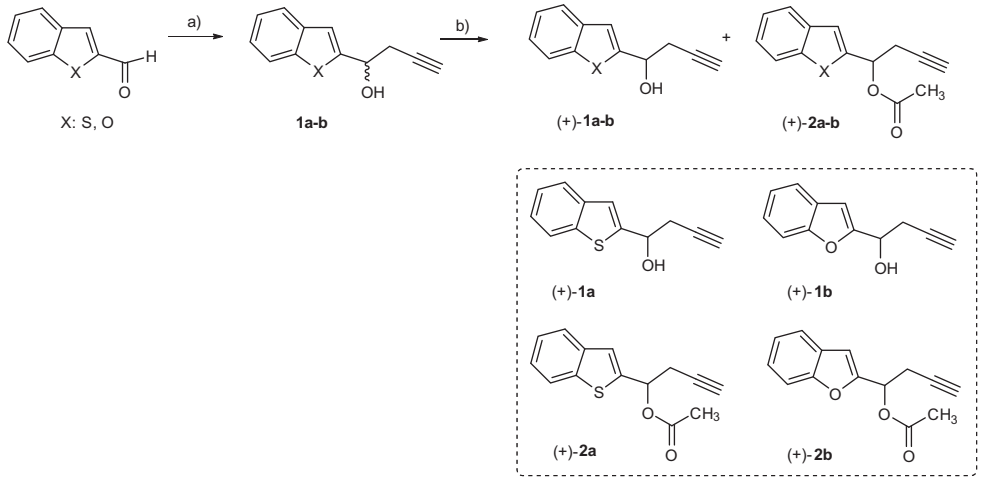
The most important step is the enantiomeric resolution of racemic secondary alcohol substrates *rac*-**1a**–**b** with enzymes to produce the enantiomerically enriched homopropargylic alcohols, which are good candidates for the preparation of substituted triazoles. All resolution reactions were performed using various lipases; *Lipozyme*, *Novozyme 435* and *AA1* with a substrate:enzyme ratio (w/w) 1:1 and 1:0.5 at a screening temperature 30 °C and 40 °C in vinyl acetate as the acyl donor. Lipozyme gave the most promising results among the lipases screened in terms of reaction time and enantioselectivity. The effect of the co-solvent was tested by THF and the best results are summarized in Table 1.

AA1 showed no activity towards the homopropargyl alcohols. *Novozyme* 435 exhibited moderate enantioselectivities towards the racemic 1-heteroaryl homopropargyl alcohols *rac*-**1a**–**b**. The resolution of benzothiophenyl homopropargyl alcohol substrate *rac*-**1a** (entry 6) by *Lipozyme* IM gave (+)-1-benzo[*b*]thiophen-2-yl)but-3-yn-1-ol (+)-**1a** and (+)-1-(benzo[*b*]thiophen-2-yl)but-3-ynyl acetate (+)-**2a** in 84% and 99% ee, respectively, at 40 °C after 72 h of shaking. Additionally, *rac*-**1b** (entry 13) resulted in (+)-1-(benzofuran-2-yl)but-3-yn-1-ol, (+)-**1b** and (+)-1-(benzofuran-2-yl)but-3-ynyl acetate (+)-**2b** both with 99% ee at 40 °C after shaking for 72 h.

2.2. One-pot triazole synthesis

The terminal acetylene units on homopropargylic alcohol derivatives **1a**–**b** make them valuable candidates for the one-pot synthesis of the target triazole structures. Aliphatic and aromatic azides from the corresponding halides can be easily generated as intermediates via a one-pot synthesis method and converted into the desired triazole derivatives without isolation. The operational simplicity of this method makes it attractive for a wide variety of applications. Initially, enantiomerically enriched (+)-1-(benzo[*b*]thiophen-2-yl)but-3-yn-1-ol **1a** was employed in one-pot, two-step procedure by reaction with sodium azide and a halide (Scheme 2). Various aromatic and allylic halides were screened under the optimized conditions and finally, novel chiral 1,4-disubstituted 1,2,3-triazole derivatives **3a**–**9a** were obtained in moderate to good yields (60–88%) (Table 2).

The successful synthesis of benzothiophenyl substituted triazole derivatives **3a**–**9a** prompted us to investigate the construction of benzofuranyl substituted triazole compounds from enantiomerically enriched (+)-1-(benzofuran-2-yl)but-3-yn-1-ol (+)-**1b**. One-pot triazole reactions afforded chiral benzofuranyl triazole derivatives **3b**–**9b** in moderate to good yields (48–82%) (Table 2).



Scheme 1. Reagents and conditions: (a) propargyl bromide, Zn, NH_4Cl, THF, (b) enzyme, vinyl acetate.

Table 1
Results for the enzymatic resolution of homopropargylic alcohols *rac*-**1a** and *rac*-**1b**

Entry	Substrate	Enzyme	Temperature (°C)	Co-solvent	Time (h)	Ester ee_p[a] (%)	Alcohol ee_s[a] (%)	c[b] (%)	E[c]
1	*rac*-**1a**	*Novozyme* 435	30	—	96	99	42	30	150
2	*rac*-**1a**	*Novozyme* 435	30	THF	96	>99	21	18	55
3	*rac*-**1a**	*Novozyme* 435	40	—	96	99	77	44	>200
4	*rac*-**1a**	*Lipozyme* IM	30	—	72	99	81	45	>200
5	*rac*-**1a**	*Lipozyme* IM	30	THF	72	>99	80	45	>200
6	*rac*-**1a**	*Lipozyme* IM	40	—	72	>99	84	46	>200
7	*rac*-**1a**	*AA1*	30	—	96	—	—	—	—
8	*rac*-**1b**	*Novozyme* 435	30	—	96	85	45	35	17
9	*rac*-**1b**	*Novozyme* 435	30	THF	96	87	26	23	19
10	*rac*-**1b**	*Novozyme* 435	40	—	96	82	71	46	23
11	*rac*-**1b**	*Lipozyme* IM	30	—	72	99	95	49	⩾200
12	*rac*-**1b**	*Lipozyme* IM	30	THF	72	>99	84	46	>200
13	*rac*-**1b**	*Lipozyme* IM	40	—	72	>99	99	50	⩾200
14	*rac*-**1b**	*AA1*	30	—	96	—	—	—	—

[a] Enantiomeric excesses were determined by HPLC analysis with Daicel Chiralcel OJ-H.
[b] $c = ee_s/(ee_s + ee_p)$.
[c] $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$.