Tetrahedron Letters 53 (2012) 416–418

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transfer hydrogenation of imines with carboxyl-tailed benzothiazoline as readily removable hydrogen donor

Chen Zhu, Takahiko Akiyama *

Department of Chemistry, Gakushuin University, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

ARTICLE INFO

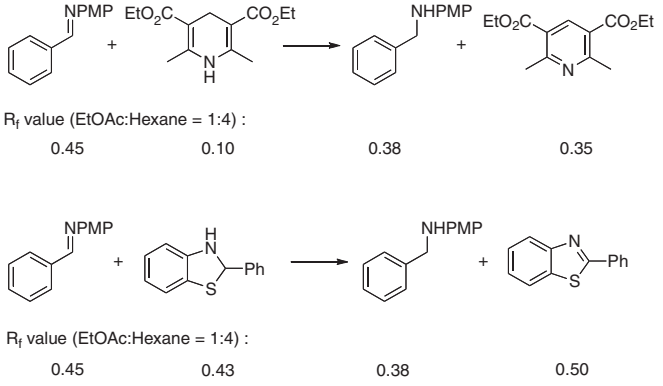
Article history:
Received 13 October 2011
Revised 7 November 2011
Accepted 11 November 2011
Available online 18 November 2011

Keywords:
Transfer hydrogenation
Reduction
Imine
Benzothiazoline
Reductive amination

ABSTRACT

A benzothiazoline bearing 4-carboxyphenyl group at 2-position was developed as an efficient hydrogen donor for the transfer hydrogenation reaction. Introduction of the carboxyl group significantly facilitated the removal of the residual benzothiazoline and benzothiazole by washing with aqueous basic solution. The present approach provides a convenient and straightforward access to various amines with broad substrate scope and in good yields.

The reduction of imines, including the direct hydrogenation and transfer hydrogenation pathways, is an important reaction for the preparation of amines.[1] In addition to several known methods that employ metal catalysts,[2] a biomimetic approach that relies on the utilization of Hantzsch esters as the hydrogen source has been established in the fields of asymmetric synthesis,[3] inspired by naturally occurring hydrogenation processes. As the most prevalent mimic of NADH, Hantzsch esters are efficiently applied in the reduction of C=N and C=C bonds.[4–6] We have recently reported the first example of the use of benzothiazoline[7] as the hydrogen source in the transfer hydrogenation of ketimines and α-imino esters, which furnished a variety of chiral amines and α-amino esters with excellent enantioselectivities, respectively.[8,9] Enders et al. successfully used benzothiazoline in the reductive amination of ketones to construct tetrahydroisoquinolines.[10] The process of transfer hydrogenation involving Hantzsch esters or benzothiazolines, however, is accompanied by difficulties in the purification as the amine product is mixed with the byproducts because of their similar R_f values. This inconvenience in the purification procedure clearly limits the application of the hydrogen source in both industry and academia. Thus, the development of a readily removable hydrogen source is strongly desired from a practical point of view. We wish to report herein an environment-friendly approach to the transfer hydrogenation of imines with carboxyl-tailed benzothiazoline **1** as the hydrogen source, which can be easily removed by washing with an aqueous basic solution, allowing us to simplify the purification process significantly.



Scheme 1. R_f values of the components in the transfer hydrogenation of aldimine.

Fueled by our continued interests in the transfer hydrogenation reaction,[8] we examined the reduction of imines with a range of reducing agents, including Hantzsch esters and benzothiazoline. The measured R_f values of all the components in the reaction are shown in Scheme 1. Separation of the generated amine from the reaction mixture by column chromatography is not a trivial issue due to the similar R_f values. Nevertheless, the ease of tuning of the reactivity and chemical properties by changing the 2-substituent on the backbone of benzothiazoline is a significant advantage.

* Corresponding author. Tel.: +81 3 3986 0221; fax: +81 3 5992 1029.
E-mail address: takahiko.akiyama@gakushuin.ac.jp (T. Akiyama).

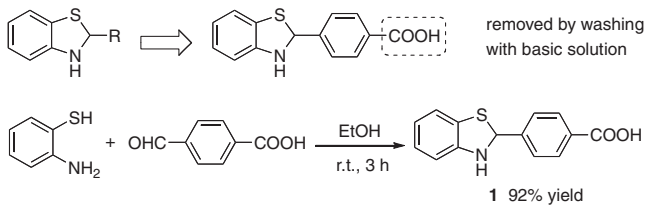
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.061

Thus, we designed a benzothiazoline with a carboxyl moiety, which was envisaged to be readily removable from the reaction mixture by washing with an aqueous basic solution (Scheme 2).

A mixture of *o*-aminothiophenol with *p*-formylbenzoic acid in ethanol was stirred for a few hours to give benzothiazoline **1** as a white precipitate in excellent chemical yield. Benzothiazoline **1** is sufficiently stable to allow storage in a refrigerator for several months without decomposition. An initial screening of the solvent effect on the transfer hydrogenation reaction of aldimine **2a**, derived from benzaldehyde and *p*-anisidine, with benzothiazoline **1** in the presence of TFA revealed that polar solvents were more efficient than nonpolar solvents, and acetonitrile gave the best result (Table 1). It is noted that the use of 20 mol % TFA as an acid and acetonitrile as the solvent gave the highest yield, whereas an increase in the loading of TFA to 50 mol % diminished the chemical yield because of the decomposition of imine.

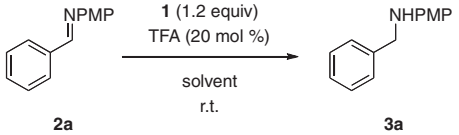
With the optimized reaction conditions in hand, we set out to define the substrate scope of the transfer hydrogenation reaction (Table 2). Both R^1 and R^2 functional groups were well tolerated. Aldimines bearing a variety of substituents with different steric and electronic effects on the aromatic ring underwent the transfer hydrogenation smoothly to give **3** in high chemical yields (entries 1–6). Aldimines derived from heteroaromatic aldehyde, cinnamaldehyde, and aliphatic aldehyde also gave the corresponding amines in good yields (entries 7–9). Not only *N*-PMP imine but also other *N*-aryl imines proved to be suitable substrates (entries 10 and 11).

Remarkably, the work-up procedures became easy due to the ease of removal of the reducing agent. After the completion of the transfer hydrogenation, both the excess of benzothiazoline and the corresponding benzothiazole were eliminated by simply washing with 10% aqueous NaOH.



Scheme 2. Synthesis of 2-(4′-carboxyl)phenyl benzothiazoline.

Table 1
Examination of various solvents

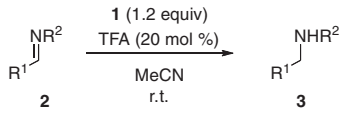


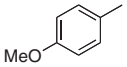
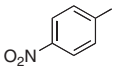
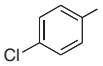
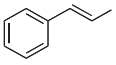
2a 3a

Entry	Solvent	Time (h)	Yield[a] (%)
1	THF	24	33
2	Toluene	25	47
3	MeOH	24	53
4	EtOAc	24	68
5	DMF	24	19
6	CH_2Cl_2	24	85
7	MeCN	22	87
8[b]	MeCN	12	55

[a] Isolated yield.
[b] 50 mol % TFA.

Table 2
The scope of substrates in the transfer hydrogenation of imines[a]



Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)
1		PMP	**3a**	22	87
2		PMP	**3b**	25	90
3		PMP	**3c**	21	92
4		PMP	**3d**	23	95
5		PMP	**3e**	23	94
6		PMP	**3f**	22	96
7		PMP	**3g**	80	79
8		PMP	**3h**	26	75
9		PMP	**3i**	40	60
10		Ph	**3j**	22	93
11		*p*-Cl-Ph	**3k**	23	92

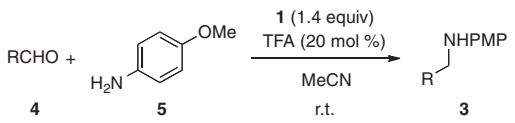
[a] Reactions were performed with imine **2** and benzothiazoline **1** (1.2 equiv) at 0.1 M concentration.
[b] Isolated yield.

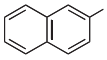
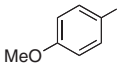
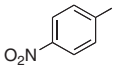
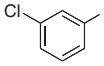
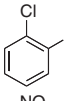
Encouraged by the above results, we further studied the reductive amination with benzothiazoline **1** as the hydrogen source (Table 3). In the presence of benzothiazoline **1**, the one-pot mixture of aldehydes **4** and *p*-anisidine (**5**) afforded amines **3** in good chemical yields. A range of aromatic substrates bearing electron-rich and electron-deficient substituents proved to be compatible with the reductive amination conditions.

Furthermore, the transfer hydrogenation of α-imino esters was also investigated (Scheme 3). Using the previous optimized reaction conditions, we found that raising the temperature to 50 °C enhanced the reaction rate. The reduction of imino ester **6a** furnished the corresponding α-amino ester **7a** in an 84% yield in 26 h. Replacing R^1 with a naphthyl group, changing R^2 from PMP to phenyl or replacing methyl ester with ethyl ester did not lead to any loss of reactivity.

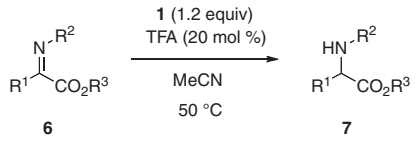
In summary, we have developed a novel hydrogen donor for the acid-catalyzed transfer hydrogenation of imines. Benzothiazoline bearing a carboxylic acid moiety proved to be practically useful because the corresponding benzothiazole as well as the recovered benzothiazoline were readily removable by simple phase separation. Undoubtedly, this environment-friendly approach reduces the volume of organic solvents used for the purification process and offers a convenient and straightforward access to various amines with a broad substrate scope and in high chemical yields. Studies of other applications of the asymmetric transfer hydrogenation are ongoing.

Table 3
Reductive amination[a]



Entry	R	Product	Time (h)	Yield[b] (%)
1		**3a**	22	82
2		**3l**	23	87
3		**3b**	26	80
4		**3c**	22	80
5		**3m**	22	78
6		**3e**	22	79
7		**3f**	22	91

[a] Reactions were performed with aldehyde **4** (1.0 equiv), $PMPNH_2$ (1.2 equiv), and benzothiazoline **1** (1.4 equiv) at 0.1 M concentration.
[b] Isolated yield.



6a: R^1= Ph, R^2= PMP, R^3= Me — 26 h, **7a**: 84%
6b: R^1= 2-Naphthyl, R^2= PMP, R^3= Me — 28 h, **7b**: 87%
6c: R^1= Ph, R^2= Ph, R^3= Me — 23 h, **7c**: 80%
6d: R^1= Ph, R^2= PMP, R^3= Et — 27 h, **7d**: 94%

Scheme 3. Transfer hydrogenation of α-imino esters.

Acknowledgment

This work was partially supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.061.

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