Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

2-(Phenylseleno)ethanesulfon-amide as a novel protecting group for aniline that can be deprotected by a radical reaction

Nobuhiro Kihara *, Yuji Mitsuhashi, Makoto Sato, Shun-ichi Hirose, Erika Goudo, Yoshinori Uzawa, Natsumi Shirai, Sari Hamamoto, Ryo Iwasaki, Akane Fujioka

Department of Chemistry, Faculty of Science, Kanagawa University, 2946 Tsuchiya, Hiratsuka 259-1293, Japan

ARTICLE INFO

Article history:
Received 21 March 2016
Revised 23 April 2016
Accepted 2 May 2016
Available online xxxx

Keywords:
2-(Phenylseleno)ethanesulfonamide
Tributyltin hydride
Radical deprotection
Chemoselectivity
Slow addition

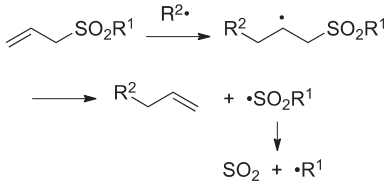
ABSTRACT

Anilines were protected as 2-(phenylseleno)ethanesulfonanilide (SeES anilide) via sulfonylation by 2-chlorosulfonyl chloride followed by the conjugate addition of benzeneselenol. The SeES anilide was deprotected by radical reduction using tributyltin hydride in the presence of AIBN. The corresponding anilines were obtained in high yields when the hydride and AIBN were added to the system slowly. Since the radical reaction proceeds under neutral conditions, chemoselective deprotection of the SeES group was accomplished. The SeES anilide was stable under various conditions, including some severe conditions.

Introduction

The protecting group of an amine is one of the most important tools in organic synthesis. The sulfonamide group has been considered as one of the most stable protecting groups of amines as it strongly resists both nucleophiles and electrophiles.[1] Because of the stability of the sulfonamide group, severe reaction conditions are necessary for their deprotection; therefore, their use has been limited in organic synthesis. Recently, novel sulfonamides that can be selectively deprotected under mild reaction conditions have been reported.[2] However, more efficient deprotection strategies are desired.

Radical reactions proceed under neutral conditions with high chemoselectivity. If sulfonamide could be deprotected by a radical reaction, it can be a potentially useful protecting group for an amine.[3] Zard et al. reported that the 2-(alkylsulfonyl)ethyl radical produced from allylsulfone decomposes with the release of olefin and sulfur dioxide to form an alkyl radical (Scheme 1).[4] Further, Moutrille and Zard reported the formation of amidyl radical from allylsulfonamide in the same manner.[5] These reactions prompted us to develop a novel sulfonamide that can be deprotected by radical reduction. The β-radical of alkylsulfonamide produced from the abstraction of the phenylseleno group can be expected to decompose to afford an aminyl radical that can be reduced to an amine.



Scheme 1.

Results and discussion

N-Methylaniline **1a** was used as a precursor for the novel sulfonamide. Thus, **1a** was treated with 2-chloroethanesulfonyl chloride **2**, a cheap sulfonylation agent, in the presence of triethylamine to afford the vinylsulfonamide **3a**. The conjugate addition of benzeneselenol to **3a** afforded the 2-(phenylseleno)ethanesulfonamide (SeES amide) **4a** (Scheme 2). Both the reactions proceeded in high yield. The crude product of **3a** was analytically pure and could be used in the second step without further purification.

The radical deprotection of the SeES group was investigated. The reduction of **4a** was carried out using tributyltin hydride as the reducing agent to optimize the deprotection conditions. The addition of tributyltin hydride to the reaction system all at once

* Corresponding author. Tel.: +81 463 59 4111; fax: +81 463 58 9684.
E-mail address: kihara@kanagawa-u.ac.jp (N. Kihara).

http://dx.doi.org/10.1016/j.tetlet.2016.05.002
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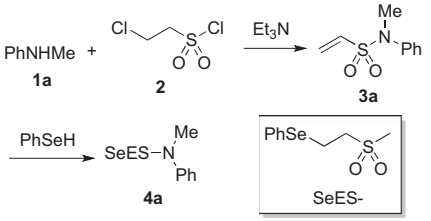


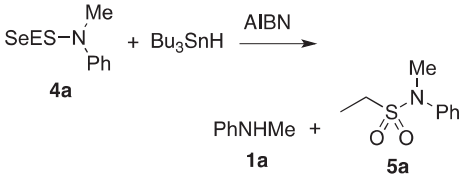
Scheme 2.

afforded ethanesulfonamide **5a** as the sole product. The primary radical produced by the abstraction of the phenylseleno group was trapped by tributyltin hydride before releasing ethylene. Therefore, it was deduced that the slow addition of tributyltin hydride was necessary to minimize the simple reduction. The solution of tin hydride and the initiator was added simultaneously to the reaction system over a period of 20 h. First, the reaction was attempted using 0.2 equiv of AIBN as the initiator. However, the result obtained under this condition was not very reproducible. The reproducibility improved with increasing amounts of AIBN. At least, 1 equiv of AIBN was necessary to obtain reproducible results. The yield of the reaction was maximum when 2 equiv of AIBN was used; the use of 3 equiv of AIBN decreased the yield. Therefore, 2 equiv of AIBN was used in further investigations.

The results are summarized in Table 1. The yield of **1a** significantly improved with increasing amounts of tributyltin hydride. At least 4 equiv of tributyltin hydride was necessary to afford **1a** in good yield. When the reaction was carried out at 60 °C, a significant amount of **5a** was produced. However, the yield decreased when the reaction was carried out at 100 °C, and the highest yield of **1a** was obtained when the reaction was carried out at 80 °C.

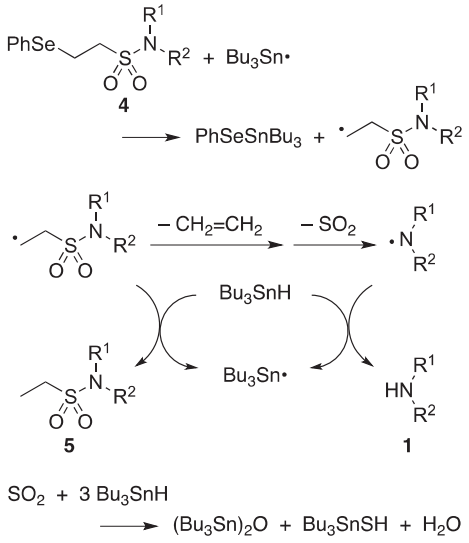
The possible reaction mechanism is shown in Scheme 3. The tributyltin radical abstracts the phenylseleno group to form the β-sulfonyl radical. When the concentration of tributyltin hydride was high, the β-sulfonyl radical was directly reduced by tributyltin hydride to afford **5**. When the concentration of tin hydride was kept to a minimum by slow addition, the reaction proceeded in an intramolecular fashion with the sequential release of ethylene and sulfur dioxide. High reaction temperatures are necessary because of the higher activation energy required for releasing ethylene from the primary radical. However, higher reaction temperatures decreased the efficiency of the radical initiator. The resulting

Table 1
Optimization of the reaction conditions for the deprotection of the SeES group[a]



Bu_3SnH (equiv)	Temperature (°C)	Yield (%)	
		1a	**5a**
1.0	80	6	7
2.0	80	49	6
3.0	80	81	2
4.0	80	92	4
3.0	60	29	35
3.0	100	72	4
3.0	Reflux	55	4

[a] Reactions were carried out in toluene. Bu_3SnH and AIBN were added dropwise over the period of 20 h.



Scheme 3.

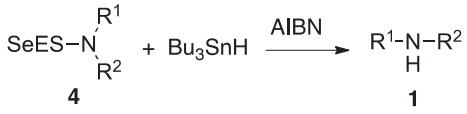
aminyl radical abstracts hydrogen from tributyltin hydride to afford amine **1**, and regenerates the tributyltin radical, thus completing the cycle. It was deduced that 1 equiv of tributyltin hydride was used for the reduction of the SeES group, whereas 3 equiv of tributyltin hydride was used for the reduction of the released SO_2. Because the resulting thiol (or tin sulfide) inhibited the radical reaction, an excess amount of AIBN was necessary to consume the radical scavengers.

One can suppose that benzeneselenol produced by the hydrolysis of $PhSeSnBu_3$ strongly inhibited the radical reaction. Thus, the radical reduction of *N*-methyl-2-(phenylthio)ethanesulfonanilide, sulfur analogue of SeES amide **4a**, was examined. Because of less reactivity of the phenylthio group toward radical, higher temperature (160 °C) was necessary. However, excess initiator (6 equiv of di-*tert*-butyl peroxide) and excess Bu_3SnH (4 equiv) were also necessary to obtain **1a** in good yield (72%). These results indicate that SO_2 is the main source of radical scavenger although we cannot exclude the possibility that benzeneselenol inhibited the radical reaction in the case of **4a**.

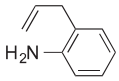
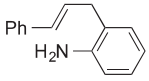
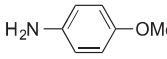
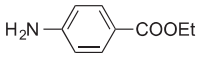
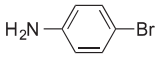
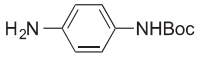
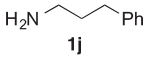
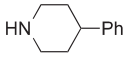
To avoid using excess tin hydride, we examined other hydride sources such as triarylmethane, silanes, cyclohexadiene, benzothiazoline, and benzoxazoline. Triarylmethanes acted as the hydride sources. However, the best yield of **1a** was less than 10% when 4-methoxytriphenylmethane was used under xylene reflux condition. When tris(trimethylsilyl)silane[6] (TMS_3SiH) was used, 65% of **1a** was obtained with 1 equiv of TMS_3SiH. Excess TMS_3SiH was unnecessary because TMS_3SiH did not reduce SO_2 although the efficiency and the reproducibility were lower than those of Bu_3SnH. Other hydride sources did not afford **1a** at all.

The radical deprotection of some SeES-protected amines **4** was investigated. The results are summarized in Table 2. The SeES group bound to the amino group of aniline derivatives was smoothly deprotected under the standard conditions. When the allyl group was introduced at the *ortho*-position (**4d** and **4e**), no radical cyclization product was observed although the system became complex, and the yields of the starting amines were lower. The SeES group could be selectively deprotected from **4g** even in the presence of the ester group because of the high chemoselectivity of the radical reaction under neutral conditions. Since aryl bromide and 1,4-phenylenediamine interfered with the radical reaction, the radical reduction of **4h** and **4i** was incomplete. In the case of **4h**, **1h** was obtained in lower yield while over-reduction product **1b** was observed only in the yield of 1%. When **4j** was

Table 2
Radical deprotection of SeES-protected amine **4**[a]



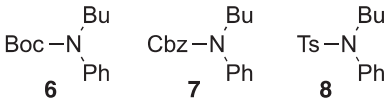
4 **1**

Amine	Preparation of **4**[b] (%)	Solvent	Temp. (°C)	Yield of **1** (%)
MeNH–Ph **1a**	66	Toluene	80	92[c]
H_2N–Ph **1b**	37	Toluene	80	79[d]
BuNH–Ph **1c**	42	Toluene	80	75[c]
 **1d**	36	Toluene	80	21[d]
 **1e**	43	Toluene	80	28[d]
 **1f**	51	Toluene	80	79[d]
 **1g**	32	Toluene	80	87[e]
 **1h**	61	Toluene	80	32[d,f]
 **1i**	40	Toluene	80	54[e,g]
 **1j**	72	Xylene	120	35[d]
 **1k**	40	Xylene[h]	Reflux	34[c]

[a] Bu_3SnH (4 equiv) and AIBN (100 mol%) were added dropwise over the period of 20 h.
[b] Yield from **1** to **4** (two steps). Yields were not optimized.
[c] GC yield.
[d] Isolated after acetylation of the reaction mixture.
[e] Isolated yield.
[f] 18% of SeES amide was recovered.
[g] 49% of SeES amide was recovered.
[h] 1,1′-azobis(cyclohexane-1-carbonitrile) was used as the initiator.

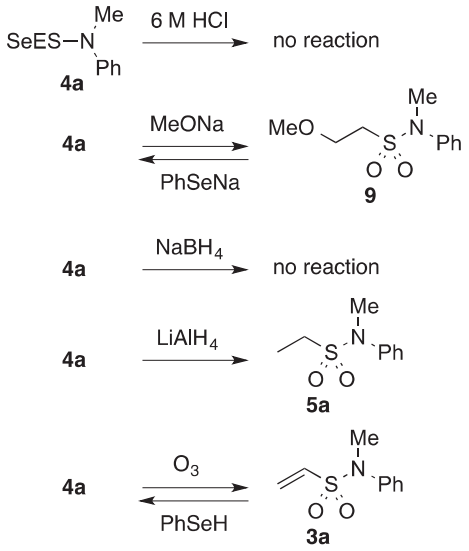
treated under the standard deprotection conditions, only trace amounts of **1j** were observed, although neither **4j** nor **5j** was recovered and $PhSeSnBu_3$ was obtained. Therefore, the release of SO_2 is slow in the case of **4j**. The lower efficiency for the SO_2-release can be explained by the absence of an aromatic or related conjugate substituent that stabilizes the aminyl radical intermediate.[5,7] To enhance the SO_2-release, the reaction of **4j** was carried out at higher temperatures, and the maximum yield of 35% was obtained when the reaction was carried out at 120 °C. Similarly, the deprotection of **4k** gave **1k** in 34% yield when the reaction was carried out under xylene-reflux condition.

The chemoselective deprotection of SeES group was demonstrated. The radical reduction of **4a** in the presence of Boc-, Cbz-, and Ts-protected *N*-butylanilines **6**, **7**, and **8** was carried out (Chart 1). The deprotection proceeded without the loss of the yield of **1a**. No *N*-butylaniline was observed, and **6**, **7**, and **8** were quantitatively recovered, respectively. The stability of Ts group under the deprotection condition indicates the importance of the phenylseleno group for the deprotection reaction.



6 **7** **8**

Chart 1.



Scheme 4.

The stability of the SeES protecting group under various reaction conditions was studied as shown in Scheme 4. Sulfonamide **4a** was stable even under strongly acidic conditions. When **4a** was treated with sodium methoxide, **4a** was slowly converted into the ether **9**. However, **9** could be reverted to **4a** by treating with PhSeNa. Although **4a** was inert to sodium borohydride, it reacted with lithium aluminum hydride to afford the ethanesulfonamide **5a**. Although reversion of sulfonamide **5a** to **4a** was not attained, the former was so stable under lithium aluminum hydride condition that no deprotection of **5a** to afford **1a** was observed either. As expected, **4a** reacted rapidly with ozone to afford **3a**, which easily reverted to **4a**, as shown in Scheme 2.

Conclusion

We have developed a novel sulfonamide, 2-(phenylseleno) ethanesulfonamide (SeES amide), as an effective protecting group for aniline derivatives. SeES anilide was stable under various reaction conditions; however, it could be readily deprotected in good yield by a radical reaction. High chemoselectivity was achieved because the radical reaction proceeded under neutral conditions. Tin-free deprotection and application of the intermediary aminyl radical are in progress.

Supplementary data

Supplementary data (experimental details and spectroscopic and analytical data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.002.

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Please cite this article in press as: Kihara, N.; et al. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2016.05.002