Tetrahedron Letters 49 (2008) 4585–4587

Contents lists available at ScienceDirect

Tetrahedron Letters

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

2-(Trimethylsilyl)ethanesulfonyl amide as a new ammonia equivalent for palladium-catalyzed amination of aryl halides

Prakash Anjanappa[a], Dibakar Mullick[a], Kumaravel Selvakumar[a,*], Manickam Sivakumar[b,c,*]

[a] Synthetic Chemistry, Syngene International Ltd, Biocon Park, Plot 2 and 3, Jigani Link Road, Bommasandra Industrial Area, Bangalore 560 099, India
[b] Department of Pharmaceutical Engineering and Technology, Bharathidasan Institute of Technology, Bharathidasan University, Tiruchirappalli 620 024, India
[c] School of Chemical and Environmental Engineering, University of Nottingham (Malaysia campus), Semenyih 43500, Malaysia

ARTICLE INFO

Article history:
Received 26 December 2007
Revised 21 May 2008
Accepted 21 May 2008
Available online 27 May 2008

Keywords:
Palladium catalysis
Ammonia surrogates
Cross-coupling
2-(Trimethylsilyl)ethanesulfonyl amide

ABSTRACT

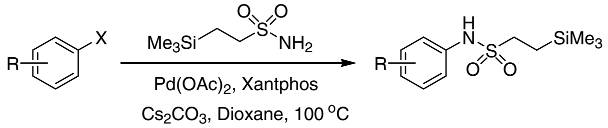
2-(Trimethylsilyl)ethanesulfonyl amide (SES-NH_2) is an ammonia equivalent for the palladium-catalyzed amination of aryl bromides and aryl chlorides. Using these amine derivatives, it has been observed that anilines and anilines with sensitive functional groups can be readily prepared.

During the past few years, great progress has been made in the development of the transition metal-catalyzed amination of aryl halides. Despite the existence of copper- and nickel-catalyzed versions of this reaction, palladium remains the metal of choice for this transformation. This is due principally to the higher efficiency of palladium complexes in aryl amination, benefiting from developments in related palladium-catalyzed cross-coupling reactions.[1–3]

As a result, a wide variety of arylamines can now be prepared efficiently using this methodology. While a variety of amines and other nitrogen nucleophiles undergo this reaction in the presence of a base, ammonia does not form exclusively primary arylamines.[4] Thus, reactions have been conducted with ammonia surrogates. Allylamine was used as an ammonia equivalent and the allyl group from the resulting aryl alkyl amine was conveniently cleaved using methanesulfonic acid and palladium on carbon.[5]

Benzophenone imine has frequently been used as an effective ammonia equivalent. The coupling reactions with this imine are high yielding and can be performed under extremely mild reaction conditions. Moreover, the resulting *N*-aryl imines can be cleaved using several orthogonal methods that are compatible with a variety of protecting groups.[6] The groups of Hartwig and Buchwald independently reported inexpensive silyl reagents such as ($LiN(SiMe_3)_2$) and Ph_3SiNH_2 as ammonia equivalents for the palladium-catalyzed amination and the resulting aryl silylamines were easily deprotected.[7] The above situation necessitates using a stable ammonia surrogate for the amination, and it is also important that the resulting aminated compound should be stable during further transformations. Toluene sulfonamides have been used as an ammonia surrogate for the palladium-catalyzed amination.[8] Unfortunately, the resulting sulfonamide requires strong acidic conditions for its cleavage. In the search for other suitable and stable ammonia surrogates we found that 2-(trimethylsilyl)ethanesulfonyl amide (SES-NH_2) is an ammonia surrogate for palladium-catalyzed amination (Scheme 1).

Weinreb developed the 2-(trimethylsilyl)ethanesulfonyl group for the protection of amines. This sulfonyl protection can be removed under mild conditions using a fluoride source. The fluoride ion attacks the silicon atom which leads to β-elimination and this releases the deprotected amine and volatile products such as fluorotrimethylsilane, ethylene, and sulfur dioxide.[9] SES-Cl can be prepared from vinyltrimethylsilane by free-radical addition of sodium bisulfite to the double bond catalyzed by *tert*-butyl perbenzoate and the resulting sulfonate can be transformed directly



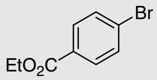
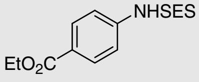
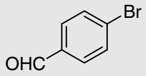
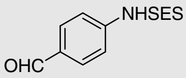
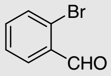
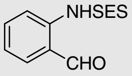
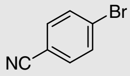
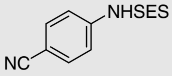
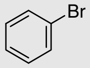
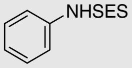
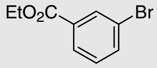
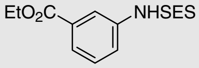
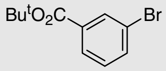
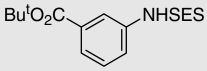
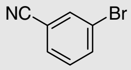
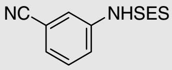
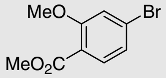
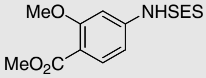
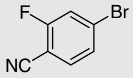
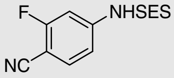
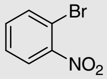
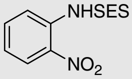
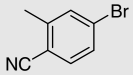
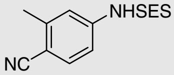
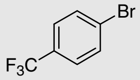
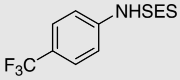
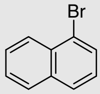
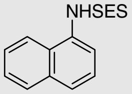
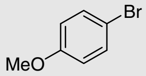
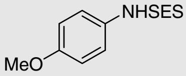
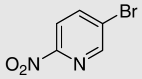
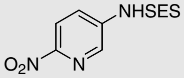
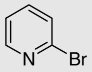
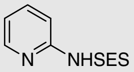
Scheme 1. Synthesis of SES-protected anilines.

---

* Corresponding authors. Tel.: +60 3 8924 8156; fax: +60 3 8924 8017 (M.S.).
E-mail addresses: selva.kumar@syngeneintl.com (K. Selvakumar), Sivakumar.Manickam@nottingham.edu.my (M. Sivakumar).

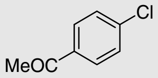
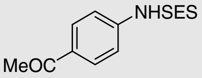
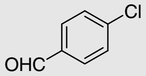
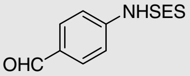
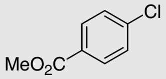
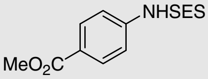
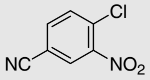
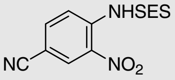
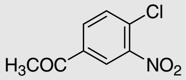
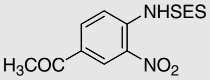
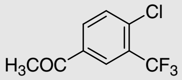
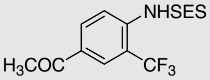
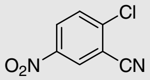
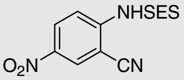
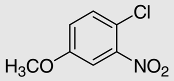
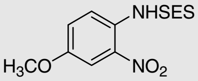
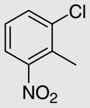
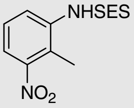
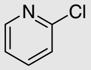
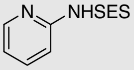
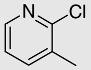
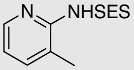
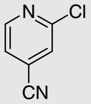
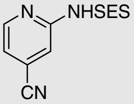
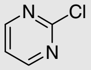
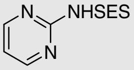
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.099

Table 1
SES-NH_2 as an ammonia surrogate in the palladium-catalyzed coupling of aryl and heterocyclic bromides

Entry	Substrate	Product	Yield[a] (%)
1			98
2			90
3			80
4			91
5			85
6			95(91)
7			92(80)
8			88
9			97
10			95
11			85(87)
12			91
13			97
14			82
15			0
16			85
17			85

[a] Isolated yield is given. Yield given in parentheses is for the deprotected product obtained from the amination product.

Table 2
SES-NH_2 as an ammonia surrogate in the palladium-catalyzed coupling of aryl and heterocyclic chlorides

Entry	Substrate	Product	Yield[a] (%)
1			92
2			88
3			90
4			88
5			89
6			84
7			75
8			74
9			73
10			67(80)
11			72
12			80
13			90

[a] Isolated yield is given. Yield given in parentheses is for the deprotected product obtained from the amination product.

into the sulfonyl chloride (SES-Cl) using thionyl chloride.[10] SES-NH_2 was prepared from SES-Cl by reaction with ammonia.[11]

In the present investigation, we have studied the potential of SES-NH_2 as a reagent for the synthesis of primary arylamines from 4-bromoethylbenzoate using a palladium source such as $Pd(OAc)_2$ or $Pd_2(dba)_3$ with *rac*-BINAP in toluene and dioxane as solvent. The maximum yield obtained using this catalyst system was only 30%.

Although the yield was low, product formation from SES-$NH_2$was apparent and thus we have screened different catalysts. Changing the ligand from BINAP to Xantphos resulted in an increase in the yield. Also, by changing the solvent, base and reaction temperature, we were able to obtain a 98% isolated yield of product from ethyl 4-bromobenzoate using a $Pd(OAc)_2$–Xantphos–Cs_2CO_3

catalyst system in dioxane at 100 °C for 15 h. Aryl bromides with various functional groups such as cyano, ester, nitro, and aldehyde groups worked well under the above optimized conditions without undergoing any other side reactions (Table 1).[12] Unfortunately, no reaction occurred when the same conditions were applied to an aryl bromide containing an electron-donating group (Table 1, entry 15).[13]

Having been successful with aryl bromides, we next extended this reaction to aryl chlorides. Aryl chloride bond activation is an industrially important field of research due to the lower cost of aryl chlorides compared with aryl bromides and aryl iodides.[14] We have used the same reaction conditions for the coupling of SES-NH_2 with aryl chlorides and the temperature was increased from 100 °C to 120 °C. The reaction worked well with aryl chlorides having different substituents such as cyano, ester, keto, nitro, and aldehyde, and the yields obtained were more than 80% in most cases. This reaction was not successful with chlorobenzene and aryl chlorides having electron-donating groups. Heterocyclic aryl chlorides also reacted with SES-NH_2 (Table 2).

The aminated aryl trimethylsilylethane sulfonamide products were very stable and could be used for further transformations without affecting the sulfonamide group. The SES group was cleaved selectively from the sulfonamide using CsF in DMF without affecting other functional groups (Table 1, entry 7).[15] We carried out the deprotection of SES with several products having acid sensitive groups, for example, the SES group was deprotected selectively from the product containing an acid sensitive *tert*-butyl ester.

In summary, we have reported the synthesis of several sulfonated aryl anilines from aryl bromides and aryl chlorides using SES-NH_2. The SES group can be cleaved selectively without affecting other functional groups and establishes SES-NH_2 as an excellent ammonia surrogate for aryl amination reactions. Further studies on N-substituted SES-NH_2 are in progress.

Acknowledgments

The authors, P.A., D.M., and K.S. thank Goutam Das, CEO, Syngene international Ltd for granting permission to carry out this work at Syngene. M.S. thanks Bharathidasan and Anna Universities for all the support.

Supplementary data

Supplementary data (the experimental and analytical data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.099.

References and notes

1. Palladium-catalyzed aryl amination: (a) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, *1*, 1051; (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (d) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560; (e) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479; (f) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746; (g) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553; (h) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470; (i) Stauffer, S. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6977; (j) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861; (k) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (l) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978; (m) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479; (n) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416; (o) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983; (p) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 9135; (q) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965; (r) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 6522; (s) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101; (t) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82; (u) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584; (v) Li, J. J.; Wang, Z.; Mitchell, L. H. *J. Org. Chem.* **2007**, *72*, 3606.
2. Nickel-catalyzed aryl amination: (a) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029; (b) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311; (c) Chen, C.; Yang, L.-M. *Org. Lett.* **2005**, *7*, 2209; (d) Kelly, R. A., III; Scott, N. M.; Dıez-Gonzalez, S.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 3442; (e) Chen, C.; Yang, L.-M. *J. Org. Chem.* **2007**, *72*, 6324.
3. Copper-catalyzed aryl amination: (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077; (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793; (c) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987; (d) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289; (e) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793; (f) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578; (g) Ran, C.; Dai, Q.; Harvey, R. G. *J. Org. Chem.* **2005**, *70*, 3724; (h) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035; (i) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107; (j) Moriwaki, K.; Satoh, K.; Takada, M.; Ishino, Y.; Ohno, T. *Tetrahedron Lett.* **2005**, *46*, 7559; (k) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903; (l) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241; (m) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120; (n) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241; (o) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435; (p) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270; (q) Barros, O. S. R.; Nogueira, C. W.; Stangherlin, E. C.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2006**, *71*, 1552; (r) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742; (s) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779; (t) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643; (u) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190.
4. Ammonia has been used recently as an amine for palladium-catalyzed aryl amination: (a) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028; (b) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354.
5. Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313.
6. (a) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367; (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827; (c) Cioffi, C. L.; Berlin, M. L.; Herr, R. J. *Synlett* **2004**, 841.
7. (a) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729; (b) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417.
8. (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101; (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043; (c) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987; (d) He, H.; Wu, Y.-Jin. Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385; (e) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295.
9. (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099; (b)2-(Trimethylsilyl)-ethanesulfonamide (SES-NH_2): *Protective Groups in Organic Synthesis*; Greene, T. W., Wuts, P. G. M., Eds., third ed.; Wiley: New York, 1999; p 612; (c) Weinreb, S. M.; Ralbovsky, J. L. (Trimethylsilyl)ethanesulfonyl Chloride. In *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. J., Eds.; Wiley: Chichester, 1999; p 425; (d) Kocienski, P. J. (Trimethylsilyl)-ethanesulfonyl (SES) Derivatives. In *Protecting Groups*; Corrected ed.; Enders, D., Noyori, R., Trost, B. M., Eds.; Thieme: Stuttgart, New York, 2000; p. 215.; (e) Chambert, S.; Desire, J.; Decout, J.-L. *Synthesis* **2002**, 2319.
10. (a) Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S. *Org. Synth.* **1998**, *75*, 161; (b) Huang, J.; Widlanski, T. S. *Tetrahedron Lett.* **1992**, *33*, 2657.
11. Parker, L. L.; Gowans, N. D.; Jones, S. W.; Robins, D. J. *Tetrahedron* **2003**, *59*, 10165.
12. *General procedure:* An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Xantphos (34.7 mg, 0.06 mmol), SES-NH_2 (217 mg, 1.2 mmol) and Cs_2CO_3 (650 mg, 2.0 mmol). The Schlenk tube was evacuated and back-filled with argon. Ethyl 4-bromobenzoate (230 mg, 1.0 mmol) and dioxane (7 ml) were added and the Schlenk tube was then sealed with a Teflon screw cap and placed in a preheated oil bath at 100 °C for 15 h for aryl bromides and 120 °C for aryl chlorides. After cooling to room temperature, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash chromatography. Yield: 324 mg, 98%.
13. We have observed that aryl bromides with electron-donating groups coupled with SES-NH_2 in the presence of a copper catalyst. This result will be published elsewhere.
14. (a) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283; (b) Beller, M.; Zapf, A. *Top. Catal.* **2002**, *19*, 101.
15. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.