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Note

SnCl$_2$ mediated efficient *N,N*-dialkylation of azides to *tertiary*-amine via potential stannaimine intermediate

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Abstract

A base free one-pot conversion of azides to *N,N*-dialkylamine is described. A two-step reaction pathway has been postulated invoking the intermediacy of stannaimine. This new carbon–nitrogen bond formation strategy adds to the repertoire of tin(II) chemistry.
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Keywords: Stannaimine; Sn–N; Tin(II); Tin(IV); Azides; Amine

1. Introduction

Prodrugs (6-AAP) for antiviral nucleosides ara-A are designed in such a way that it utilizes azide reduction biotransformation pathway [1]. On the other hand, tertiary amino group is often embedded as a structural motif in various biologically active compounds and natural products [2,3]. Intramolecular *N*-alkylation strategies are often used for the synthesis of fused polycyclic heterocycles [4]. RCM of diallylamines is also an efficient approach to pyrrolidine derivatives [5]. In our laboratory to study the metathesis catalysts, we required a method for the facile construction of *N,N*-diallyl amino compounds under base-free condition. Note that primary amines can be easily allylated in the presence of a base or basic additive; however, such a method may lead to complicacy in case of base-sensitive functionalities. Thus, we became interested to look into an one-pot conversion of azide, immediate precursor of amine, to the corresponding *N,N*-diallyl amine in a neutral medium. In this short communication, we wish to report our preliminary result on SnCl$_2$ mediated *N,N*-dialkylation of azides (Scheme 1). The reaction has been suc-

cessfully tested with aliphatic and aromatic azides **1–6**, and alkyl, benzyl, allyl, propargyl halides **7–12**. As detailed later, the effect of catalytic additives had also been tested, and in case of allyl halides Pd(0) catalyst was found to be promising in further enhancing the product yield.

2. Results and discussion

In our laboratory, we have been exploring a bimetallic strategy to generate allyl, allenyl, and propargyl organometallic reagents for new carbon–carbon bond formation [6]. Recent reports on the successful utilization of allylstannane for the preparation of *N*-allylsulfonamide from sulfonyl azides [7], and also of allylzinc for the preparation of *N*-allylamines from azides [8] prompted us to devise an approach towards the *N,N*-bisallylation of azides via in situ generated allyltin. Surprisingly control experiment with allyltrihalostannane did not lead to expected allylation [9].

Upon addition of anhydrous SnCl$_2$ to a solution of azidobenzene in DMSO led to a strong nitrogen evolution at room temperature. The rate of nitrogen evolution is solvent dependent, and decreases in the order DMSO > DMF ≫ DCM, THF. Transition metal catalyst has little effect on this decomposition. Furthermore, decomposition rate is found to be in the order aryl azide > aliphatic

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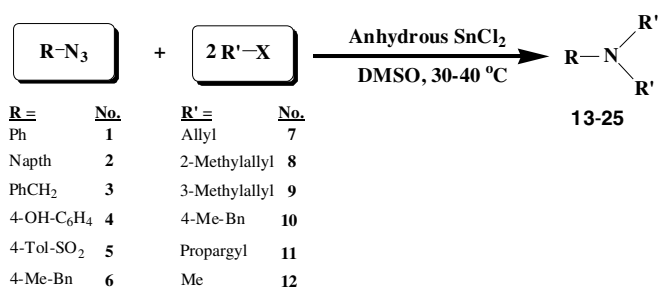
Scheme 1. SnCl$_2$ mediated *N,N*-dialkylation of azide.

azide > benzyl azides. We propose the formation of a reactive stannaimine intermediate **A** for this transformation (Scheme 2). A similar suggestion is forwarded by Bartra et al. for the reaction of azide with tin(II)trithiolate in presence of Et$_3$N wherein intermediate **B** is postulated (Scheme 3) [10]. Also noteworthy is the isolation of a stannaimine [(TMS)$_2$N]$_2$Sn=NR (where $R = 2,6$-^{i}Pr$_2$C$_6$H$_3$) by Ossig et al. from the reaction of tin(II)amide with arylazide [11]. However, preliminary attempts by us to isolate the postulated intermediate **A** by employing coordinated complexes of SnCl$_2$ proved to be futile.

Stannaimines are known to be highly reactive and have been trapped in a variety of reactions. For example their reaction with stannylene yields azadistanniridine in a [2+1] cycloaddition [12] and with azides [2+3] stannatetrazoles are formed via cycloadditions [12,11]. In absence of suitable coupling partner dimerization products of stannaimines are formed [12,13]. The reactivity of N–Sn(IV) is also exploited in a number of synthetically useful N–C bond forming reactions by coupling with various electrophiles [14].

We made initial attempts to couple the postulated stannaimine intermediate **A** with allyl halide, and the results from various control experiments have been accrued in Table 1. Thus, the model reaction of azidobenzene **1** (1 mmol) with anhydrous SnCl$_2$ (1.2 mmol) and allyl bromide **7** (3 mmol) in freshly dry and distilled DMSO at

Table 1
Anhydrous SnCl$_2$ promoted *N,N*-diallylation of phenyl azide: control studies[a]

Entry	X	Catalyst (mol%)[b]	Solvent	Yield (%)
1	Br	Nil	DMSO	63
2	Br	Pd$_2$(dba)$_3$ (1)	DMSO	92
3	Cl	Pd$_2$(dba)$_3$ (1)	DMSO	64
4	Br	Pd$_2$(dba)$_3$ (1)	DMF	82
5	Br	Pd$_2$(dba)$_3$ (1)	H$_2$O	Nil
6	Br	Pd$_2$(dba)$_3$ (1)	DCM	Trace
7	Br	Pd$_2$(dba)$_3$ (1)	THF	Trace
8	Br	CuCl$_2$, 2H$_2$O (30)	DMSO	79
9	Br	CuCl (20)	DMSO	71

[a] Condition: azide (1 mmol), SnCl$_2$ (1.2 mmol), allyl halide (3 mmol).
[b] mol% with respect to azide; dba = dibenzylideneacetone.

room temperature for 3 h gave rise to *N,N*-diallyl aniline **13** in 63% yield (Table 1, entry 1). Under identical condition but in presence of catalytic Pd$_2$(dba)$_3$ (0.01 mmol) a smooth reaction was observed giving rise to **13** in 92% yield (entry 2). Among other catalysts, CuCl$_2$ · 2H$_2$O and CuCl were found satisfactory (entries 8 and 9). The effect of transition metal catalyst in enhancing the yield of allylated product could well be due to the simultaneous activation of allyl halide leading to well known π-allyl metal complex, the latter being a better electrophile compared to allyl bromide itself. Screening of solvents showed that DMSO is better compared to others (entries 2 and 4–7). Furthermore, allyl bromide was found to be better than allyl chloride (entries 2 and 3).

This new *N*-allylation strategy has been further extended to a number of allyl halides and aryl or benzyl azides giving rise to good to excellent yields of the corresponding *N,N*-diallylated products (Table 2, entries 1–6). Note that in case of azide **4**, selective *N*-allylation takes place over *O*-allylation (entry 6). However, sulfonylazide remain unreactive towards allylation (entry 7).
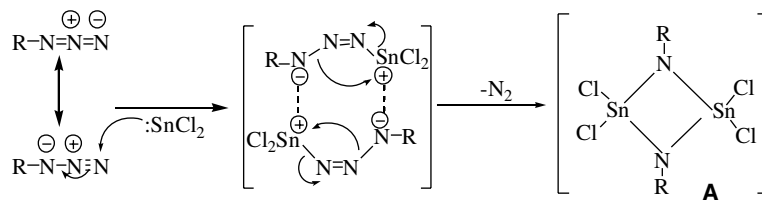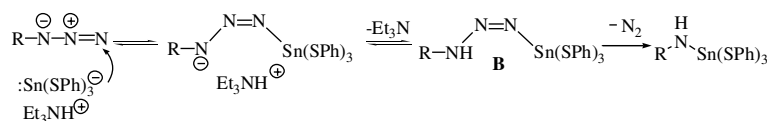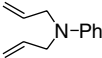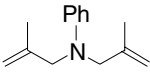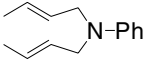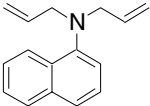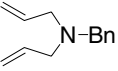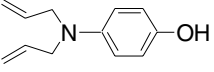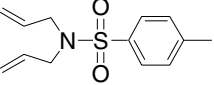

Scheme 2. Proposed stannaimine intermediate **A** from SnCl$_2$ and azide.

Scheme 3. Proposed Sn^{IV}–N intermediate from azide and tin(II)trithiolate [10].

Table 2
Anhydrous $SnCl_2$ promoted *N,N*-diallylation of aryl and benzyl azide R–N_3 with allyl bromide R^1CH=$C(R^2)CH_2Br$ using $Pd_2(dba)_3$ as catalyst in DMSO[a]

Entry	Azide R (No.)	Bromide R^1/R^2 (No.)	Product	Pdt. No.	Time (h)	Yield (%)
1	Ph (**1**)	H/H (**7**)		**13**	3	92
2	Ph (**1**)	H/Me (**8**)		**14**	3	90
3	Ph (**1**)	Me/H (**9**)		**15**	3	91
4	Napth (**2**)	H/H (**7**)		**16**	4	87
5	$PhCH_2$ (**3**)	H/H (**7**)		**17**	5	72
6	4-OH–C_6H_4 (**4**)	H/H (**7**)		**18**	7	81
7	4-Tol-SO_2- (**5**)	H/H (**7**)		**19**	7	Nil

[a] Condition: azide (1 mmol), $SnCl_2$ (1.2 mmol), allyl halide (3 mmol), Pd (0.01 mmol).

The generality of the coupling reaction was tested further with benzyl halides and propargyl bromides as electrophiles (Table 3). Curiously, these coupling reactions proceed smoothly even in absence of a transition metal catalyst leading to high yields of products (entries 1–5). Alkyl halides are even more reactive, and in case of methyl iodide reaction proceeds even at 0 °C (entry 6).

While mechanistic delineation warrants further studies, a proposal is presented which involves the key stannaimine intermediate **A** discussed earlier (chiefly Scheme 2). According to this proposal (Scheme 4), intermediate **A** is involved for the direct electrophilic activation of a halide (path b), or of a π-allylmetal (path a). Note that for *N*-monomethylation using methyl iodide and alkyl azides in presence of trialkylphosphine, Kato et al. suggested a similar electrophilic attack on iminophosphorane intermediate [15].
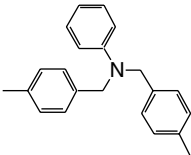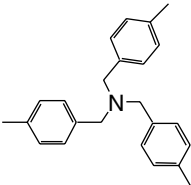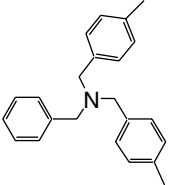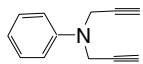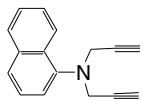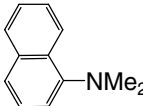
In conclusion, we demonstrated here a base-free procedure for the direct one-pot conversion of azides to *N,N*-dialkylated amine. We are currently attempting to isolate the key stannaimine intermediate, and explore its reactivity with other electrophiles.

3. Experimental

Table 3
Anhydrous SnCl$_2$ promoted alkylation of azide R–N$_3$ with halide in DMSO[a]

Entry	Azide R (No.)	Halide (No.)	Product	Pdt. No.	Time (h)	Yield (%)
1	Ph (**1**)	4-MeC$_6$H$_4$CH$_2$I (**10**)		**20**	4	77
2	4-MeC$_6$H$_4$CH$_2$ (**6**)	4-MeC$_6$H$_4$CH$_2$I (**10**)		**21**	5	71
3	PhCH$_2$ (**3**)	4-MeC$_6$H$_4$CH$_2$I (**10**)		**22**	5	80
4	Ph (**1**)	HCCCH$_2$Br (**11**)		**23**	5	91
5	Napth (**2**)	HCCCH$_2$Br (**11**)		**24**	5	92
6[b]	Napth (**2**)	Me–I (**12**)		**25**	6	51

[a] Condition: azide (1 mmol), SnCl$_2$ (1.2 mmol), halide (3 mmol).
[b] At 0 °C, MeI (30 mmol).

argon atmosphere in flame dried glassware using Schlenk techniques. Chromatographic purifications were done with either 60–120 or 100–200 mesh silica gel (SRL). For reaction monitoring, precoated silica gel 60F$_{254}$ TLC sheets (Merck) were used. Petroleum ether refers to the fraction boiling in the range 60–80 °C.

3.1. General procedure

The typical procedures given below were followed in all cases (please see Supporting information for details). All products showed satisfactory spectral and analytical data, and also were compared with authentic compounds wherever possible.

N,N-diallylation of azidobenzene: Azido-benzene **1** (119 mg, 1 mmol) was added to a mixture of anhydrous SnCl$_2$ (228 mg, 1.2 mmol) in dry DMSO (3 ml) under argon atmosphere at room temperature and was allowed to stir (10 min). 3-Bromo-propene **7** (363 mg, 0.26 ml, 3 mmol) and Pd$_2$(dba)$_3$ (10 mg, 0.01 mmol) were added to it. The solution is stirred for 3 h. Upon completion (TLC monitoring: silica gel, eluent: _n_-hexane–EtOAc 9:1), the reaction was quenched by starring with water and NH$_4$F. The reaction mixture was extracted into ethyl acetate (3 × 20 ml). The combined ethyl acetate layer was washed with distilled water (3 × 50 ml.), brine, and dried over anhydrous magnesium sulfate. Solvent removal under reduced pressure followed by column chromatogra-
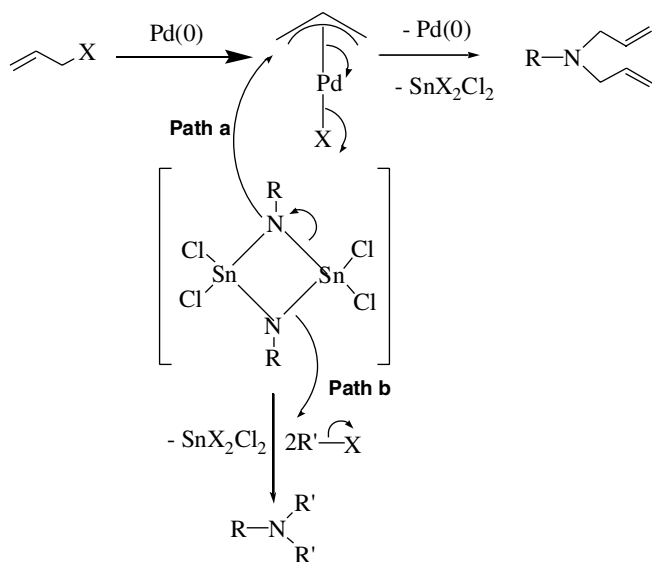
Scheme 4. Proposed electrophilic activation of halide from reactive Sn^{IV}–N intermediate.

phy over silica gel 60–120 (gradient elution with EtOAc–hexane 0–1%) afforded diallyl phenyl amine **13**, colourless liquid (159 mg, 92% with respect to azide). ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.92–3.94 (d, 4H, $J = 4.9$ Hz), 5.14–5.24 (m, 4H), 5.81–5.89 (m, 2H), 6.70–6.74 (m, 3H), 7.17–7.26 (m, 2H). ^{13}C NMR (50.3 MHz, CDCl$_3$): δ 52.74, 112.38, 115.97, 116.32, 129.03, 134.03, 148.67. ESI-MS for C$_{12}$H$_{15}$N [M], [M + H]$^+$ = 174.13. Anal. Calcd. for C$_{12}$H$_{15}$N: C, 83.19; H, 8.73. Found: C, 83.27; H, 8.65%.

N,N-dipropargylation of azidobenzene: Following identical method as above using the reagents azido-benzene **1** (119 mg, 1 mmol), anhydrous SnCl$_2$ (228 mg, 1.2 mmol), DMSO (3 ml), 3-bromo-propyne **11** (0.27 ml, 357 mg, 3 mmol) afforded phenyl-di-prop-2-ynyl-amine **23**, colourless viscous liquid (154 mg, 91% with respect to azide). ^{1}H NMR (200 MHz, CDCl$_3$): δ 2.26 (t, 2H, $J = 2.3$ Hz), 4.13–4.14 (d, 4H, $J = 2.3$ Hz), 6.87–7.01 (m, 3H), 7.26–7.35 (m, 2H). ^{13}C NMR (50.3 MHz, CDCl$_3$): δ 40.54, 72.85, 79.38, 115.89, 119.95, 129.26, 147.86. ESI-MS for C$_{12}$H$_{11}$N [M], [M + H]$^+$ = 170.1. Anal. Calcd. for C$_{12}$H$_{11}$N: C, 85.17; H, 6.55. Found: C, 85.31; H, 6.59%.

N,N-bis-4-methylbenzylation of benzyl azide: Following identical method as above using the reagents benzyl azide **3** (133 mg, 1 mmol), anhydrous SnCl$_2$ (228 mg, 1.2 mmol), DMSO (3 ml), 4-methylbenzyl iodide **10** (696 mg, 3 mmol) afforded benzyl-bis-(4-methyl-benzyl)-amine **22** (252 mg, 80% with respect to azide). ^{1}H NMR (200 MHz, CDCl$_3$): δ 2.36 (s, 6H), 3.56 (s, 6H), 7.14–7.47 (m, 13H). ^{13}C NMR (50.3 MHz, CDCl$_3$): δ 21.1, 57.45, 57.51 126.8, 128.22, 128.82, 128.93, 136.36, 139.72. ESI-MS for C$_{23}$H$_{25}$N [M], [M + H]$^+$ = 316.22. Anal. Calcd. for C$_{23}$H$_{25}$N: C, 87.57; H, 7.99. Found: C, 87.53; H, 7.82%.

Appendix A. Supplementary data

General procedure, spectral and analytical data of products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.12.017.

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