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$GaCl_3$-Catalyzed *ortho*-ethynylation reaction of *N*-benzylanilines

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Abstract—Lithiated *N*-benzylanilines were ethynylated at the *ortho*-position with silylchloroethyne at 120 °C in the presence of a catalytic amount of $GaCl_3$. Trimethylsilylated *N*-methylaniline could also be used for this transformation.

ortho-Ethynylanilines are versatile intermediates for the synthesis of indoles, and a variety of methods have been investigated for the cyclization.[1] Introduction of an ethynyl group to the aniline nuclei therefore is an important transformation in organic synthesis. The most common method to prepare the ethynylanilines is the Sonogashira coupling reaction of *ortho*-haloanilines with terminal alkynes.[2] The Stille coupling using stannylated alkynes was also reported.[3] These methods, however, require multi-step preparation of the halogenated substrates particularly in case of substituted anilines. Taylor reported the coupling reaction of *ortho*-thallated anilines with alkynyl copper reagents.[4] The reaction also required the preparation of the *ortho*-thallated anilines using stoichiometric amount of toxic thallium reagent. Yamamoto developed the ethynylation reaction of *N*-benzyl-*N*-phenyl-*O*-(trimethylsilyl)-hydroxyamine prepared from aniline with excess trialkynylaluminum.[5] This reaction gave mixtures of the *ortho*- and *para*-isomers. Direct and catalytic introduction of ethynyl group to aniline nuclei apparently is the most convenient and straightforward. Previously, we developed *ortho*-ethenylation reaction of anilines with acetylene using stoichiometric amounts of $SnCl_4$–Bu_3N reagent.[6] We also reported the catalytic *ortho*-ethynylation reaction of phenols with chlorosilylethyne using $GaCl_3$.[7] The latter reaction proceeded via carbometalation (carbogallation) between phenoxygallium and chlorosilylethyne, which was followed by the β-elimination of $GaCl_3$.[8] It was considered that the addition–elimination methodology could be applied to the catalytic *ortho*-ethynylation of anilines. Following problems, however, were conceivable: Aniline itself did not react with chlorosilylethyne in the presence of $GaCl_3$, which was probably due to the lower acidity of the amine proton; $GaCl_3$ could readily be deactivated by the basic amino group of anilines. Use of *N*-metalated anilines, therefore, was examined to overcome such problems.

N-Trimethylsilyl-*N*-methylaniline **1**[9] prepared from *N*-methylaniline **4** was initially selected as the substrate to examine the $GaCl_3$-catalyzed ethynylation. A solution of **1** in *o*-dichlorobenzene was treated with a stoichiometric amount of $GaCl_3$ (1 equiv) at room temperature for 10 min, to which chlorotriethylsilylethyne **2** (1 equiv) in *o*-dichlorobenzene was added. The mixture was heated at 90 °C for 1 h, and workup with 2 M NaOH gave *N*-methyl-2-(triethylsilylethynyl)aniline **3** in 52% yield with the recovered *N*-methylaniline **4** in 11% yield (Table 1, entry 1). This result indicated that the transmetalation of **1** with $GaCl_3$ and the carbogallation of the resulted organogallium intermediate with **2** did occur. The material balance could be improved by treating the reaction mixture with excess ethylenediamine at 100 °C for 30 min giving **3** in 60% yield with the recovered **4** in 23% yield (entry 2). The reaction mixture of **1**, **2**, and $GaCl_3$ (1 equiv) treated at 90 °C for 1 h showed a single N–Me peak at δ 3.36 by ^{1}H NMR. It disappeared after the treatment with ethylenediamine, and the peaks of **3** (δ 2.90) and **4** (δ 2.89) were observed. The results showed that $GaCl_3$ formed strong complex with **3** and **4**, which could be liberated by ethylenediamine.

The next examination was directed to the development of the catalytic reaction by liberating **3** from the complex with $GaCl_3$ during the reaction. A plausible mechanism is as follows: $GaCl_3$ reacts with silylated **5**

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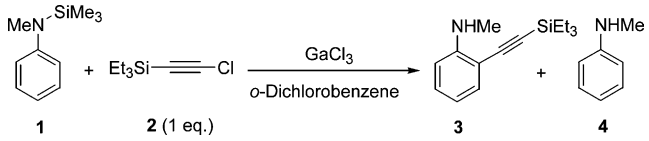
Table 1. *ortho*-Ethynylation reaction *N*-trimethylsilyl-*N*-methylaniline

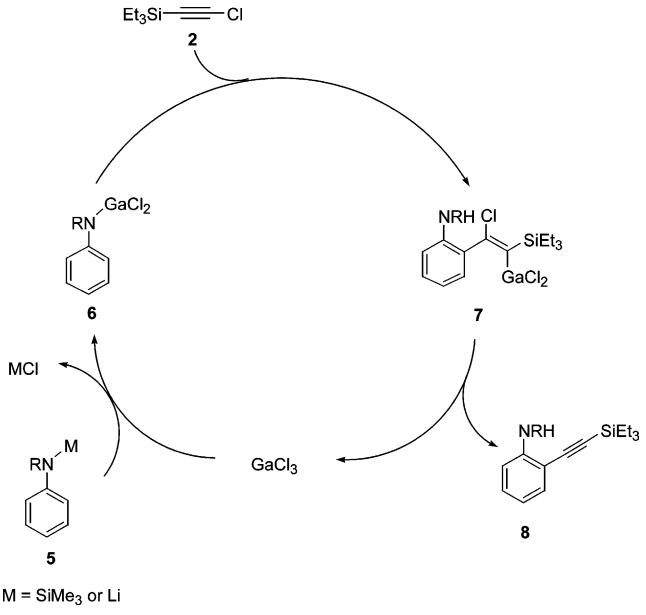


Entry	$GaCl_3$/mol%	Temp/°C	Time/h	Workup method[a]	Yield/%	
					3	**4**
1	100	90	1	A	52	11
2	100	90	1	B	60	23
3	20	90	1	A	20	55
4	20	120	3	A	38	26
5	20	120	3	B	43	53

[a] Method A: Treated with 2 M NaOH–THF at room temperature. Method B: Treated with ethylenediamine at 100 °C for 30 min, and then with 2 M NaOH–THF.

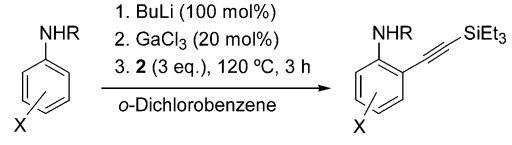
($R = SiMe_3$) to generate gallated aniline **6**, and carbometalation of **6** and **2** provides vinylgallium **7**. The β-elimination of **7** leads to the *o*-ethynylated aniline **8** regenerating $GaCl_3$ (Scheme 1). When **1** was treated with a catalytic amount of $GaCl_3$ (20 mol%) and **2** (1 equiv) in *o*-dichlorobenzene at 90 °C for 1 h, **3** was obtained in 20% yield (Table 1, entry 3). The yield increased to 38% by reacting at 120 °C for 3 h (entry 4). The same procedures followed by the workup with ethylenediamine gave **3** with the turn over number (TON) 2.2 (entry 5).

We next conducted the direct *ortho*-ethynylation of *N*-alkylanilines without forming the silylated derivative **5** ($M = SiMe_3$). *N*-Benzylaniline itself did not react in the absence of base under the same conditions, and was recovered quantitatively. Several metalated derivatives, therefore, were examined, and it turned out that lithiated **5** ($M = Li$) gave favorable results. Butyllithium (1 equiv) was added to a solution of *N*-benzylaniline **9** in *o*-dichlorobenzene at 0 °C, which was followed by $GaCl_3$ (1 equiv) and **2** (3 equiv). The reaction mixture was heated at 90 °C for 1 h, and *N*-benzyl-2-(triethylsilylethynyl)aniline **10** was obtained in 65% yield (Table 2, entry 1).[10] The amount of $GaCl_3$ could be reduced to 20 mol%, when the reaction was conducted at 120 °C for 3 h giving **10** in 58% yield (TON 2.9) (entry 2).[11] *N*-Methylaniline **4** was ethynylated in low yield under the catalytic conditions, and required a stoichiometric amount of $GaCl_3$ for the modest yield of **3** (entries 3 and 4). *N*-Butylaniline gave the product in 52% yield under the catalytic conditions (entry 5). The substituents at the benzyl group were not influential (entries 6 and 7). The substituent effect on the nitrogen atom is considered to be related to the solubility of the lithiated **5** ($M = Li$) or organogallium intermediate **6**. Aniline lacking the *N*-substituent did not give the ethynylated product.



Scheme 1. Catalytic *ortho*-ethynylation reaction of *N*-alkylanilines.

Table 2. *ortho*-Ethynylation reaction of *N*-alkylanilines



Entry	R	X	Yield/%
1[a]	$PhCH_2$ **9**	H	65 **10**
2	$PhCH_2$ **9**	H	58 **10**
3[a]	Me **4**	H	55 **3**
4	Me **4**	H	19 **3**
5	n-C_4H_9	H	52
6	p-$MeOC_6H_4CH_2$	H	60
7	p-$FC_6H_4CH_2$	H	59
8	$PhCH_2$	3,4,5-MeO	85
9	$PhCH_2$	4-MeO	75
10	$PhCH_2$	4-Me	74
11	$PhCH_2$	3,5-MeO	59
12	$PhCH_2$	3,5-Me	60
13	$PhCH_2$	4-F	47
14	$PhCH_2$	4-Cl	38
15	$PhCH_2$	3-Me	70 (41 + 29)[b]

[a] Reaction was conducted at 90 °C for 1 h with 100 mol% of $GaCl_3$.
[b] Yields of 1,2,5-substituted and 1,2,3-substituted anilines.

This catalytic reaction could be applied to substituted *N*-benzylanilines. Substrates possessing electron-donating substituent at the aniline nuclei gave the *ortho*-ethynylanilines in higher yields and TON (entries 8–12). The yields decreased when halogen groups were attached at the *para*-position (entries 13 and 14). Two regioisomers were obtained in equal amounts in the case of *meta*-methylaniline (entry 15). No reaction occurred with *ortho*-methoxyaniline or α-naphtylamine possessing the *ortho*-substituents.

In summary, *N*-benzylanilines are ethynylated at the *ortho*-position with chlorotriethylsilylethyne in the presence of a catalytic amount of $GaCl_3$. The addition–elimination process of organogallium compound to chlorosilylethyne is successfully employed in the introduction of ethynyl group to aniline nuclei.

Acknowledgement

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10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (6H, q, $J = 7.6$ Hz), 0.97 (9H, t, $J = 8.0$ Hz), 4.37 (2H, d, $J = 5.2$ Hz), 5.04 (1H, s, br), 6.55 (1H, d, $J = 8.0$ Hz), 6.60 (1H, t, $J = 7.6$ Hz), 7.14 (1H, t, $J = 8.0$ Hz), 7.26 (1H, d, $J = 6.8$ Hz), 7.30–7.37 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.6, 7.7, 47.9, 97.7, 103.3, 107.6, 109.5, 116.2, 127.1, 127.2, 128.5, 129.9, 131.9, 138.7, 149.1. IR (neat) 3398, 2954, 2142, 1602, 1575 cm^{-1}. MS (EI) m/z 321 (M^+, 100%). HRMS Calcd for $C_{21}H_{27}NSi$: 321.1913. Found: 321.1890.
11. Typical procedures for the catalytic *ortho*-ethynylation of *N*-benzylaniline (**9**): Under an argon atmosphere, 1.6 M butyllithium in hexane (0.3 mL, 0.5 mmol) was added to a solution of **9** (92 mg, 0.5 mmol) in *o*-dichlorobenzene (1 mL) at 0 °C, and the mixture was stirred at the temperature for 5 min. 1.0 M $GaCl_3$ (20 mol%) in methylcyclohexane (0.1 mL) was added, and the mixture was stirred at 0 °C for 5 min and at room temperature for 5 min. Compound **2** (261 mg, 1.5 mmol) in *o*-dichlorobenzene (1 mL) was added, and the mixture was heated at 120 °C for 3 h. Ethylenediamine (1.65 mL, 10 mmol) was added, and the solution was heated at 100 °C for 30 min. After the mixture was cooled to room temperature, 2 M NaOH (4 mL) and THF (4 mL) were added. The organic materials were extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexane/ethyl acetate = 100/3) to give **10** (94 mg, 58%).