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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1871–1874

$Hg(OTf)_2$-Catalyzed cycloisomerization of 2-ethynylaniline derivatives leading to indoles

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Received 4 December 2006; accepted 11 December 2006
Available online 23 December 2006

Abstract—Cycloisomerization of 2-ethynylaniline derivatives catalyzed by mercuric triflate afforded indole derivatives in excellent yield under mild reaction conditions with high catalytic turnover up to 100 times.

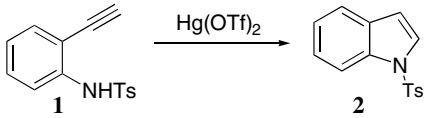
The indole derivative is distributed in a wide variety of bioactive molecules and plays a key role in the life cycle.[1] Cycloisomerization of 2-ethynylaniline derivatives is the most efficient method to construct indole skeletons, and has been achieved by using palladium complexes,[2] copper salts,[3] bases[4] and some other reagents.[5] However, these procedures are seriously compromised by poor catalytic efficiency, vigorous reaction conditions and limited general applicability. Herein we wish to disclose the first mercuric salt-catalyzed highly efficient cycloisomerization of 2-ethynylaniline derivatives furnishing indole derivatives. In 1983 we developed mercuric triflate, $Hg(OTf)_2$, as an efficient olefin cyclization agent.[6] Recently, we found the remarkable catalytic activity of $Hg(OTf)_2$ for the hydration of terminal alkynes leading to methyl ketones,[7] the hydroxylative 1,6-enyne cyclization to give exomethylene five-membered ring products,[8] cyclization of 1-alkyn-5-ones leading to 2-methylfurans,[9] arylalkyne cyclization leading to dihydronaphthalene derivatives,[10] biomimetic tandem cyclization of aryleneyne derivatives to give polycarbocycles,[11] and the reaction of propargyl acetate with water leading to vinyl ketones.[12] The key step of these reactions is the protodemercuration step of the vinylmercury intermediate[13] induced by TfOH that is generated in situ. Now we have applied $Hg(OTf)_2$ for the cyclization of 2-alkynylaniline derivatives and found a quantitative formation of indole derivatives with high catalytic turnover of up to 100 times under mild reaction conditions.

Table 1. $Hg(OTf)_2$-Catalyzed cycloisomerization of **1**

Entry	$Hg(OTf)_2$ (mol %)	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	5	CH_3CN	25	20	37
2	5	CH_3NO_2	25	3	54
3	5	$C_6H_5CH_3$	25	0.5	92
4	5	CH_2Cl_2	25	0.25	93
5	5	$(CH_2Cl)_2$	25	0.25	95
6	1	CH_2Cl_2	25	20	93
7	1	CH_2Cl_2	43	15	95
8	1	$(CH_2Cl)_2$	83	1	94
9	1	$C_6H_5CH_3$	110	0.25	99
10	0.5	$C_6H_5CH_3$	110	0.75	99
11	0.25	$C_6H_5CH_3$	110	2.5	96
12	0.1	$C_6H_5CH_3$	110	24	0

[a] Isolated yield.

We first examined the reaction of 2-ethynyl-*N*-tosylaniline (**1**) with 5 mol % of $Hg(OTf)_2$ in acetonitrile. After 20 h at 25 °C, *N*-tosylindole **2** was obtained in 37% yield after aqueous work-up and column chromatography on silica gel (Table 1, entry 1). Nitromethane was also a



Scheme 1.

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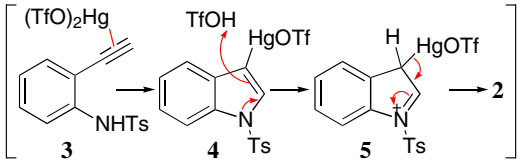
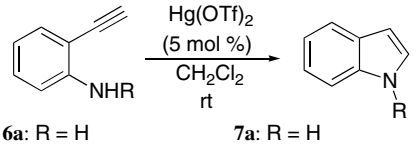
doi:10.1016/j.tetlet.2006.12.120



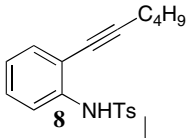
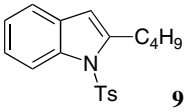
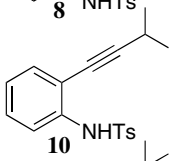
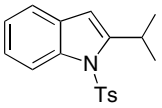
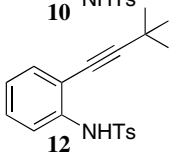
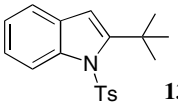
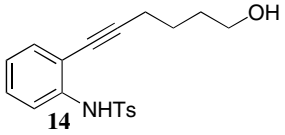
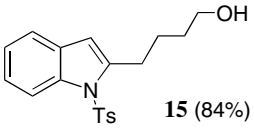
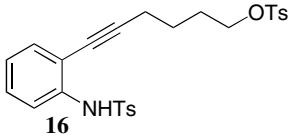
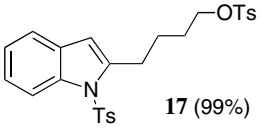
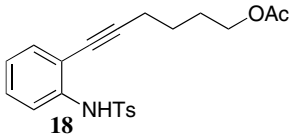
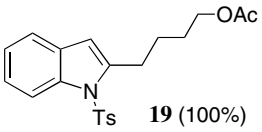
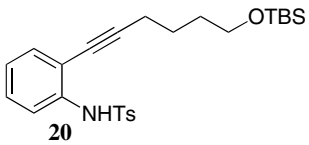
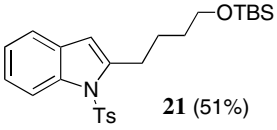
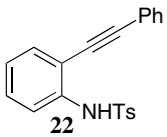
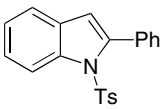
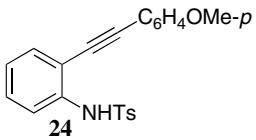
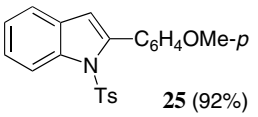
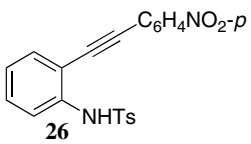
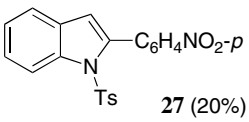
Scheme 2.



6a: R = H **7a**: R = H
6b: R = Ac **7b**: R = Ac
6c: R = $SO_2C_6H_4NO_2$-*o* **7c**: R = $SO_2C_6H_4NO_2$-*o* (78%, 24 h)
6d: R = $SO_2C_6H_4NO_2$-*p* **7d**: R = $SO_2C_6H_4NO_2$-*p* (89%, 15 min)

Scheme 3.

Table 2. $Hg(OTf)_2$ (1 mol %)-catalyzed cycloisomerization in CH_2Cl_2 at room temperature

Substrate	Time	Product (yield, %)
 **8**	15 min	 **9** (97%)
 **10**	30 min	 **11** (93%)
 **12**	40 h	 **13** (88%)
 **14**	5 min	 **15** (84%)
 **16**	30 min	 **17** (99%)
 **18**	15 min	 **19** (100%)
 **20**	15 h	 **21** (51%)
 **22**	1 h	 **23** (96%)
 **24**	5 min	 **25** (92%)
 **26**	24 h	 **27** (20%)

poor solvent and afforded **2** in 54% yield after 3 h (entry 2). However, both toluene and dichloromethane were shown to be excellent solvents giving **2** in 92% yield within 30 min (entry 3) and 93% yield within 15 min (entry 4), respectively, at 25 °C. Dichloroethane was also an excellent solvent and afforded **2** in 95% yield after 15 min at 25 °C (entry 5). Reaction using 1 mol % of $Hg(OTf)_2$ in dichloromethane required 20 h to consume the starting material and afforded **2** in 93% yield (entry 6). Reflux in dichloromethane was inadequate and required 15 h to give **2** in 95% yield (entry 7). Reflux in 1,2-dichloroethane, however, afforded **2** in 94% yield after 1 h (entry 8). Reflux in toluene using 1 mol % catalyst is more efficient to give **2** in 99% yield within 15 min (entry 9). Even 0.5 or 0.25 mol % of $Hg(OTf)_2$ is enough to complete the reactions in toluene at reflux temperature within acceptable reaction periods (entries 10 and 11). However, 0.1 mol % of catalyst did not afford any product within an acceptable reaction period (entry 12). We also examined the reaction using 1 mol % of $HgCl_2$ and $Hg(OAc)_2$ as catalysts, however, the reaction did not take place at all (Scheme 1).

The reaction is initiated by π-complexation of the alkyne with $Hg(OTf)_2$ as shown in **3** (Scheme 2). Nucleophilic attack of nitrogen leads intermediate **4** generating TfOH. Protonation of **4** with the TfOH forms nitronium ion **5**, which undergoes demercuration to produce indole **2** and regenerating the catalyst $Hg(OTf)_2$. The protonation step leading to **5** should be the rate-limiting step.

Next we examined the effect of the protecting group on nitrogen (Scheme 3). 2-Ethynylaniline **6a** afforded a complex mixture by the reaction with 5 mol % of $Hg(OTf)_2$ in CH_2Cl_2 at room temperature for 3 h, and **7a** was not detected at all. *N*-Acetyl derivative **6b** also did not afford indole **7b**, and unidentified unstable compounds were obtained. *o*-Nitrobenzenesulfonyl (*o*-Ns) protected aniline **6c** slowly reacted at room temperature and afforded **7c** in 78% yield after 24 h. While *p*-Ns protected **6d** reacted instantaneously to give **7d** in 89% yield within 15 min,[14] but still did not reach the result obtained by Ts protected **1** (Table 1, entry 4). Thus we chose Ts group as the protecting group on nitrogen.

Alkyl substituted *N*-Ts aniline derivative **8** reacted with 5 mol % of $Hg(OTf)_2$ in CH_2Cl_2 very quickly, affording 2-alkyl indole **9** in quantitative yield after 15 min (Table 2). Even 1 mol % of catalyst was enough to complete the reaction of **8**, and indole derivative **9** was obtained in 97% yield.[15] Isopropyl substituted alkynyl aniline **10** also afforded indole derivative **11** by using 5 mol % as well as 1 mol % of catalyst in 97% and 93% yield, respectively. *tert*-Butyl derivative **12** afforded **13** in 94% yield by using 5 mol % of catalyst within 1 h, however, 1 mol % catalyst required a longer reaction period (40 h) to complete the reaction and afforded **13** in 88% yield. Substrate **14** containing the free hydroxyl moiety was also applicable to the reaction with 1 mol % of $Hg(OTf)_2$ affording **15** in 84% yield after 5 min. Ditosylate **16** afforded **17** in 99% yield by using 1 mol % of catalyst within 30 min. Acetate **18** also afforded indole derivative **19** in quantitative yield by using 1 mol % of catalyst. Silicon protection used to be the course of some trouble,[16] and the case of TBS derivative **20** resulted affording in **21** as low as 51% yield after 15 h reaction using 1 mol % of catalyst. Phenyl substituted **22** as well as methoxyphenyl substituted **24** afforded indole derivatives **23** (96%) and **25** (92%), respectively, within 1 h. On the other hand, the reaction of *p*-nitro phenyl substituted **26** was very slow as expected, and afforded **27** in 20% yield even after 24 h.

Therefore, we have established a novel $Hg(OTf)_2$-catalyzed indole synthesis with broad applicability and high catalytic turnover under very mild reaction conditions.

Acknowledgements

This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government, and a MEXT.HAITEKU, 2003–2007.

Supplementary data

Spectroscopic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.120.

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15. Typical experimental procedure is as follows: To a dried suspension of $Hg(OTf)_2$ (0.003 mmol) in CH_2Cl_2 (1.5 mL), prepared from 0.01 M CH_3CN solution (0.3 mL) after solvent exchange and following sonication, was added a solution of **8** (100 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL) at room temperature, and the mixture was stirred at the same temperature for 15 min. After addition of saturated aqueous $NaHCO_3$ solution, organic material was extracted with CH_2Cl_2. Dried and concentrated extract was subjected to column chromatography on silica gel using hexane and ethyl acetate to give **9** (97 mg, 97% yield).
16. Nishizawa, M. Imagawa, H., unpublished result.