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Efficient construction of indole rings from 2-ethynylaniline derivatives catalyzed by copper(II) salts and its application to the tandem cyclization reactions

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Abstract—The efficient cyclization reactions of the *N*-methanesulfonyl or *N*-ethoxycarbonyl derivatives of 2-ethynylanilines, functionalized on the benzene ring and/or the acetylene terminal into indoles catalyzed by either $Cu(OTf)_2$ or $Cu(OAc)_2$ are accomplished. The application of this reaction to the tandem cyclization reaction is also described.

Among the many reports on indole ring synthesis, the methods using 2-ethynylaniline derivatives as the starting materials are some of the most efficient procedures, because the starting materials can be easily prepared and modified.[1–3] So far, many kinds of reagents have been reported for this type cyclization reaction,[1–5] among them the most frequently used reagents (catalysts) are the palladium complexes[1,2a,4,5a,b,c] and many applications including C3 allylation,[5a,6] alkenylation,[7] arylation[7] and carbonylation reactions[8] have also been recently established. In our laboratory, we have already published two different methods of indole ring cyclization reactions, namely, mediated by metal alkoxide[9] and tetrabutylammonium fluoride (TBAF) promoted reactions.[10] However, there are some disadvantages of these three methods, e.g. (i) metal alkoxide reactions can not be applied to the alkaline-sensitive substrates; (ii) the carbonyl or sulfonyl group has to be on the nitrogen atom for most procedures (e.g. sulfonamides, amides and carbamates are usually used);[11] and (iii) there are no reports of these procedures being applied to the substrates which have an electron-withdrawing group on the acetylene terminal. Herein, we now report the mild, applicable and versatile method for indole cyclization catalyzed by Cu(II) salts and its application to the tandem cyclization reaction.

Our basic idea is shown in Fig. 1. To realize the cyclization reaction, the triple bond has to be first activated by some metal species, but not make a complex with the nitrogen atom. When the bond between the nitrogen and carbon atom is established, the proton on the nitrogen atom will be transferred to the C3 position (indole number) and the metal will be regenerated. Therefore, the key feature to realize this reaction is finding some compound(s) that can selectively activate the triple bond. For this purpose, we first started testing various Lewis acids with **1a** as the substrate

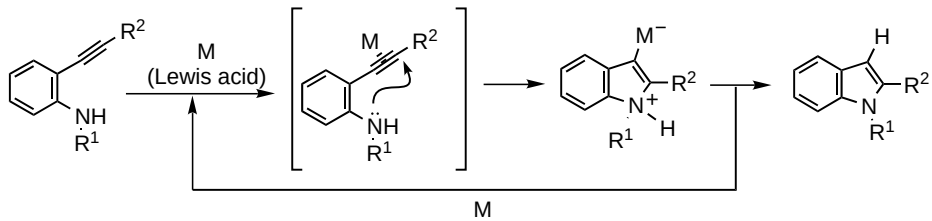

Figure 1.

Keywords: indole; cyclization reaction; copper(II) trifluoromethanesulfonate; copper(II) acetate; 2-ethynylaniline.
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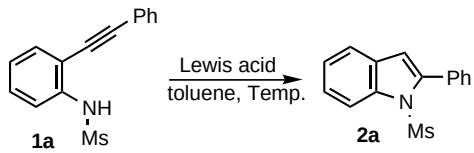
(Table 1). Among the tested Lewis acids, $Cu(OTf)_2$ showed the effective promotion of the cyclization reaction (entry 8) while the recovery of the starting material or decomposition are observed when using the other Lewis acids (entries 1–7).

Next, we investigated the effects of the counter anions and these results are summarized in Table 2. It was elucidated from the results that (i) halide anions did not show catalytic activities (entries 2 and 3); (ii) the copper salts which have crystal water could also not be used as catalysts (entries 4, 5 and 6) except for $Cu(OCOCF_3)_2{\cdot}xH_2O$ (entry 9); and (iii) the salts which have either a triflate or carboxylate (acetate and benzoate) as the counter anion are good catalysts. In 1995, Saulnier et al. reported the $Cu(OAc)_2$-promoted cyclization reaction of 2-ethynyltrifluoroacetanilide.[12] To our knowledge, this is the only report for the indole cyclization promoted by copper(II) salts. However, as their purpose was a coupling reaction between two molecules of 2-ethynyltrifluoroacetanilide by $Cu(OAc)_2$, only one example had been reported and no further studies have been published.

The application of this cyclization reaction on various substrates is shown in Table 3. When the methanesufonyl amides were used as the substrates and $Cu(OAc)_2$ was used as the catalyst, the cyclized indoles were obtained irrespective of the nature of the substituted group on the acetylene terminal [entry 1; R^3=Ph (**1a**→**2a**), entry 4; R^3=Bu (**3a**→**4a**), entry 7; R^3=H (**5a**→**6a**)]. However, the compounds, which have bulky substituents on the acetylene terminal, are hard to cyclize presumably due to steric hindrance [entry 12; R^3=*t*-Bu (**9**→**10**), entry 13; R^3=TMS (**11**→**12**)]. It is noteworthy that even if R^3 is an electron-withdrawing group (-CO_2Me), the cyclization reaction proceeded smoothly to afford methyl indole-2-carboxylate in 79% yield [entry 18 (**21**→**22**)]. This is the first example of synthesizing methyl indole-2-carboxylate from 2-ethynylaniline derivatives to our knowledge. Another remarkable feature of the Cu(II)-catalyzed reaction is

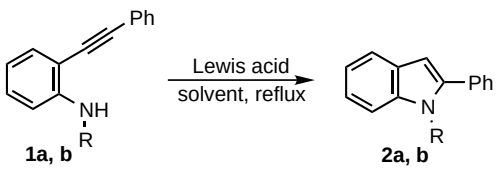
Table 1. Reaction with various Lewis acids



Entry	Lewis acid (equiv.)	Temp.	Time (h)	Yield **2a** (%)	Recovered **1a** (%)
1	$BF_3{\cdot}OEt_2$ (1.5)	100°C	17	13	87
2	$TiCl_4$ (3)	100°C	22	14	69
3	$TiCl_2(O^iPr)_2$ (3)	Reflux	24	~0	N.D.[a]
4	$Ti(O^iPr)_4$ (3)	Reflux	24	8	92
5	$AlCl_3$ (3)	60°C	2.5	Decomp.	–
6	$ZnCl_2$ (3)	Reflux	72	12	86
7	$Sn(OTf)_2$ (3)	Reflux	24	28	13
8	$Cu(OTf)_2$ (3)	Reflux	10	89	0

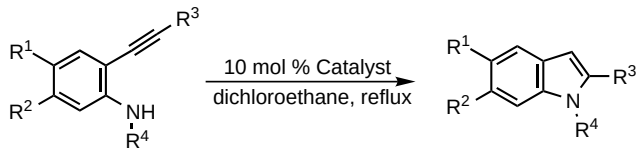
[a] Not determined.

Table 2. Reaction with Cu(II) salts



Entry	R	Lewis acid (mol%)	Solvent	Time (h)	Yield **2a**,**b** (%)	Recovered **1a**,**b** (%)
1	Ms (**1a**)	$Cu(OTf)_2$ (10)	Dichloroethane	72	89	0
2	Ms (**1a**)	CuF_2 (10)	Dichloroethane	72	7	93
3	Ms (**1a**)	$CuBr_2$ (10)	Dichloroethane	43	Trace	~100
4	Ts (**1b**)	$Cu(BF_4)_2{\cdot}xH_2O$ (120)	Toluene	48	Trace	95
5	Ts (**1b**)	$Cu(NO_3)_2{\cdot}3H_2O$ (20)	Toluene	43	2	79
6	Ts (**1b**)	$Cu(ClO_4)_2{\cdot}6H_2O$ (20)	Toluene	20	15	84
7	Ms (**1a**)	$Cu(OAc)_2$ (10)	Dichloroethane	18	94	0
8	Ts (**1b**)	$Cu(OCOPh)_2$ (20)	Toluene	9	88	0
9	Ts (**1b**)	$Cu(OCOCF_3)_2{\cdot}xH_2O$ (10)	Toluene	18	94	0

Table 3. Reaction with various Lewis acids



1a, 1c, 3a, 3b, 5a, 5b, 7, 9, 11, 13, 15, 17, 19, 21 → **2a, 2c, 4a, 4b, 6a, 6b, 8, 10, 12, 14, 16, 18, 20, 22**

Entry	R^1	R^2	R^3	R^4	Catalyst	Time	Product	Yield (%)	Recovered (%)
1 (**1a**)	H	H	Ph	Ms	$Cu(OAc)_2$	18 h	**2a**	94	0
2 (**1c**)	H	H	Ph	CO_2Et	$Cu(OAc)_2$	3 days	**2c**	20	65
3 (**1c**)	H	H	Ph	CO_2Et	$Cu(OTf)_2$	28 h	**2c**	88	0
4 (**3a**)	H	H	Bu	Ms	$Cu(OAc)_2$	20 h	**4a**	92	0
5 (**3b**)	H	H	Bu	CO_2Et	$Cu(OAc)_2$	3 days	**4b**	55	32
6 (**3b**)	H	H	Bu	CO_2Et	$Cu(OTf)_2$	2 days	**4b**	81	0
7 (**5a**)	H	H	H	Ms	$Cu(OAc)_2$	1.5 h	**6a**	87	0
8 (**5b**)	H	H	H	CO_2Et	$Cu(OAc)_2$	3 days	**6b**	87	5
9 (**5b**)	H	H	H	CO_2Et	$Cu(OTf)_2$	2 days	**6b**	35	4
10[a] (**7**)	H	H	Ph	H	$Cu(OAc)_2$	3 days	**8**	28	56
11[a] (**7**)	H	H	Ph	H	$Cu(OTf)_2$	1.5 h	**8**	68	0
12 (**9**)	H	H	*t*-Bu	Ms	$Cu(OAc)_2$	72 h	**10**	22	74
13 (**11**)	H	H	TMS	Ms	$Cu(OAc)_2$	72 h	**12**	9	64
14 (**13**)	Br	H	Ph	Ms	$Cu(OAc)_2$	7 h	**14**	76	0
15 (**15**)	H	OMe	Ph	Ms	$Cu(OAc)_2$	38 h	**16**	95	0
16 (**17**)	CN	H	Ph	Ms	$Cu(OAc)_2$	50 h	**18**	74	0
17 (**19**)	Me	H	Ph	Ms	$Cu(OAc)_2$	6 h	**20**	95	0
18 (**21**)	H	H	CO_2Me	Ms	$Cu(OAc)_2$	24 h	**22**	79	0

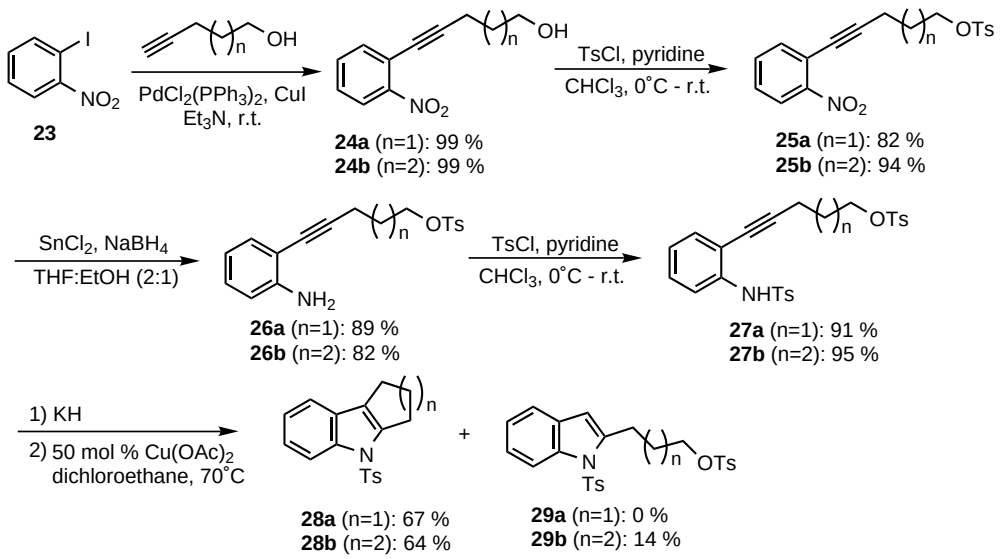
[a] Toluene was used as solvent.

that an unsubstituted aniline derivative can be cyclized to obtain an unsubstituted indole in good yield. In this case, $Cu(OTf)_2$ is a much better catalyst than $Cu(OAc)_2$ [entries 10 and 11 (**7**→**8**)]. On the other hand, the effects of the functional group on the aromatic ring toward the cyclization reaction are negligible. The compounds which have a bromo (**13**), methoxy (**15**), cyano (**17**), and methyl group (**19**) on the aromatic ring moiety gave the indoles (**14**, **16**, **18** and **20**) in good yields (entries 14–17). The reaction of carbamates are not as straightforward as with the methanesulfonamides. When R^3 = Ph and Bu, $Cu(OTf)_2$ is a better catalyst than $Cu(OAc)_2$ [entry 2 (20%) versus entry 3 (88%), entry 5 (55%) versus entry 6 (81%)]. However, in the case of R^3 = H, the yield was higher when $Cu(OAc)_2$ was used as the catalyst [entry 8 (87%) versus entry 9 (35%)]. The compatibility between the substrate and the catalyst is not clarified yet. Further studies using the other substrates and catalysts are now in progress.

In general, the reaction rates of the carbamates were much slower than that of the methanesulfonamides [entry 1 (18 h) versus entry 3 (3 days), entry 4 (20 h) versus entry 6 (2 days), entry 7 (1.5 h) versus entry 8 (3 days)]. These results suggested that the p*K*a values of the nitrogen-attached proton were closely related to the efficiency of the reaction.

At this point, we were interested in the further applications of this cyclization reaction which have never been reported by the other reagents (palladium complexes, copper(I) salts, etc.). Thus far, C3 palladium species (indole number) that come from palladium-catalyzed cyclization reactions of 2-ethynylaniline derivatives can be trapped by only unsaturated and/or activated molecules (e.g. allyl group, double bond, aromatic group and carbon monoxide).[5a,6–8] However, by copper(II)-mediated reaction, it seems likely that C3 organocopper species can be trapped by sp^3 carbon having appreciated leaving group in the same molecule, if proton does not exist in the reaction mixture. Therefore, we next tried to extend this particular reaction for the tandem cyclization reaction. The substrates (**27a**, **b**) were synthesized from 2-iodonitorobenzene (**23**) via Sonogashira coupling reacition according to Scheme 1. When the ditosylates (**27a**, **b**) were first treated with KH to remove the amide proton, followed by being warmed at 70°C in the presence of 50 mol% $Cu(OAc)_2$ in dichloroethane, tandem cyclization reaction proceeded smoothly as we expected to give tricyclic compounds (**28a**, **b**) in 67 and 64% yield, respectively [14% of monocyclized compound (**29b**) were isolated when **27b** (n = 2) was used as the starting material].[13]

From the results, especially from that of tandem cyclization reactions, we postulate that the mechanism of the Cu(II) salt-catalyzed cyclization reaction may be shown in Fig. 1. However, the other mechanisms, which include the radical species or both the nitrogen lone pair and alkyne ligated intermediate, cannot be ruled out. Further studies to clarify the mechanism and applications toward the total synthesis of biologically active



Scheme 1.

compounds using this cyclization reaction are currently under study in our laboratory.

References

1. (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p. 207; (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
2. (a) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866; (b) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804–5812 and references cited therein.
3. (a) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741–2746; (b) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507–6511.
4. (a) Yu, M. S.; Leon, L. L.; McGguire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347–9350; (b) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305–1308.
5. (a) Iritani, K.; Matsubara, S.; Uchimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802; (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584; (c) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289–296; (d) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687–7690; (e) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *29*, 2488–2490.
6. Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011.
7. (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363–1366; (b) Yasuhara, A.; Kaneko, M.; Sakamoto, T. *Heterocycles* **1998**, *48*, 1793–1799.
8. (a) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437–452; (b) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812; (c) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620–622.
9. (a) Sakamoto, T.; Konodo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31–32; (b) Sakamoto, T.; Konodo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845–1847; (c) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823–1828.
10. Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534.
11. Only limited number of the examples for unsubstituted aniline cyclization reaction have been reported. See Refs. 4a and 5.
12. Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841–7844.
13. Procedure for the tandem cyclization: A solution of 2-ethynylaniline derivatives (**27a** or **b**) in dry dichloroethane was added to a suspension of KH in dry dichloroethane at 0°C and the mixture was stirred at the same temperature for 1 h then at room temperature for 1 h. The mixture was added to a mixture of $Cu(OAc)_2$ in dry dichloroethane and was stirred at 70°C for 48 h. Aq. NH_4Cl solution was added and extracted with AcOEt. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford the tricyclic compound (**28a** or **b**). **28a**: ^{1}HNMR (300 MHz, $CDCl_3$/TMS) δ (ppm): 2.31 (3H, s), 2.50 (2H, quint, $J=7.1$ Hz), 2.73 (2H, t, $J=7.1$ Hz), 3.14 (2H, t, $J=7.1$ Hz), 7.18–7.27 (4H, m), 7.32 (1H, dd, $J=7.1$ Hz, $J=2.1$ Hz), 7.72 (2H, d, $J=8.5$ Hz), 8.02 (1H, dd, $J=7.1$ Hz, $J=2.1$ Hz).; m/z (EI) 311 (M^+). HRMS: calcd for $C_{18}H_{17}NO_2S$: 311.3991. Found: 311.0936. **28b**: ^{1}HNMR (300 MHz, $CDCl_3$/TMS) δ (ppm): 1.70–1.95 (4H, m), 2.30 (3H, s), 2.57 (2H, t, $J=6.0$ Hz), 3.00 (2H, t, $J=6.0$ Hz), 7.12–7.29 (4H, m), 7.32 (1H, d, $J=7.7$ Hz), 7.64 (2H, d, $J=8.5$ Hz), 8.15 (1H, d, $J=7.7$ Hz).; m/z (EI) 325 (M^+). HRMS: calcd for $C_{19}H_{19}NO_2S$: 325.4257. Found: 325.1140.