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Zinc-Catalyzed Reactions of Ethenetricarboxylates with 2-(Trimethylsilylethynyl)anilines Leading to Bridged Quinoline Derivatives

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ABSTRACT

Zinc Lewis acid-catalyzed cyclization of ethenetricarboxylate derivatives 1 with 2-ethynylanilines has been examined. Reaction of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate 1b with 2-(trimethylsilylethynyl)aniline substrates in the presence of Zn(OTf)$_2$ gave bridged quinoline derivatives in 43−85% yield. The reaction of 1b with 2′-aminoacetophenone also gave the bridged quinoline derivative in 41% yield. Thermal reaction of bridged quinolines (180−190 °C) afforded indole derivatives in moderate to good yields.

Benzo-annulated six- and five-membered nitrogen-containing heterocyclic systems such as quinolines and indoles are an important class of compounds.[1,2] They are present in many biologically active compounds. Many efforts have been devoted to the development of new synthetic methods to construct quinolines and indoles in recent years.[3,4]

We have recently reported zinc and indium-promoted formal [3 + 2] cycloadditions of ethenetricarboxylates **1** with propargylamines to afford methylenepyrrolidines (Scheme

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(1) For quinolines, see: (a) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 245. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873, and references cited therein.

(2) For indoles, see: (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 207. (b) Brossi, A.; Holmes, H. L.; Manske, R. H. F. *The Alkaloids: Chemistry and Pharmacology*; Academic Press: New York, 2001. (c) *The Chemistry of Heterocyclic Compounds, Part 4*; Vol. 25, Indoles: The Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed.; Wiley: New York, 1983. (d) *Monoterpenoid Indole Alkaloids: Supplement to Part 4*; Saxton, J. E., Ed.; Wiley: Chichester, 1994.

(3) For recent examples of synthesis of quinolines, see: (a) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116. (b) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141. (c) Yan, M.-C.; Tu, Z.; Lin, C.; Ko, S.; Hsu, J.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 1565. (d) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653. (e) Arcadi, A.; Aschi, M.; Marinelli, F.; Verdecchia, M. *Tetrahedron* **2008**, *64*, 5354. (f) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 2755. (g) Mierde, H. V.; Voort, P. V. D.; Verpoort, F. *Tetrahedron Lett.* **2009**, *50*, 201. (h) Qi, C.; Zheng, Q.; Hua, R. *Tetrahedron* **2009**, *65*, 1316. (i) Likhar, P. R.; Subhas, M. S.; Roy, S.; Kantam, M. L.; Sridhar, B.; Seth, R. K.; Biswas, S. *Org. Biomol. Chem.* **2009**, *7*, 85. (j) Sandelier, M. J.; DeShong, P. *Org. Lett.* **2007**, *9*, 3209. (k) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875. (l) Tanaka, S.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800. (m) Jia, C.-S.; Zhang, Z.; Tu, S.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2006**, *4*, 104.

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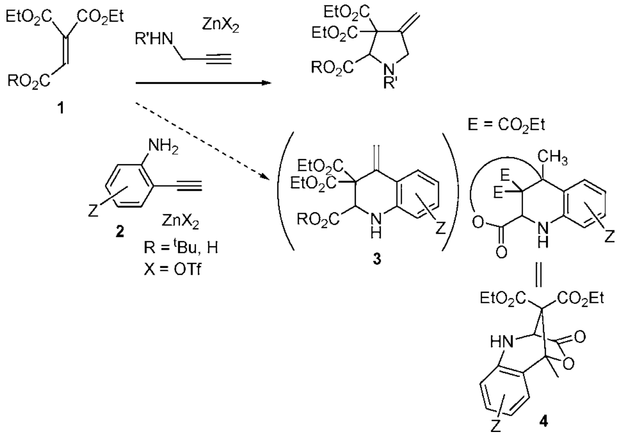
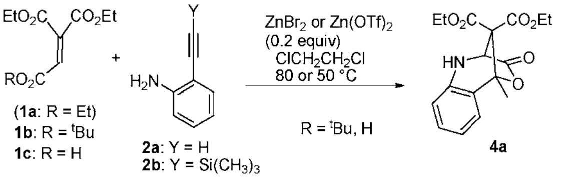
1).[5] In these reactions, the Lewis acid possibly coordinates to both carbonyl groups and alkynes. The highly electrophilic reactivity of ethenetricarboxylates **1** led to an efficient one-pot reaction. In this study, 2-ethynylanilines **2** were examined to extend this method to six-membered rings **3**, and as a result a new reaction to give bridged quinoline derivatives **4** has been found (Scheme 1).

Scheme 1





(1)

Table 1. Reaction of **1b**,**c** with 2-Ethynylanilines **2a**,**b**

entry	R		Y	Lewis acid	temp (°C)[a]	reaction time (h)[a]	4a (yield %)
1	**1b** ^{t}Bu	**2a**	H	$ZnBr_2$	80	16	35
2	**1b** ^{t}Bu	**2a**	H	$Zn(OTf)_2$	80	3	50
3	**1b** ^{t}Bu	**2b**	$Si(CH_3)_3$	$ZnBr_2$	80	19	38
4	**1b** ^{t}Bu	**2b**	$Si(CH_3)_3$	$Zn(OTf)_2$	80	3	58
5	**1c** H	**2a**	H	$ZnBr_2$	50	7	43
6	**1c** H	**2a**	H	$Zn(OTf)_2$	50	7	58

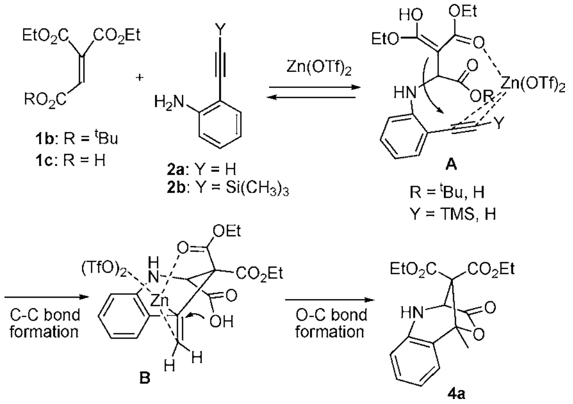
[a] Optimum reaction condition is shown.

The reaction of ethenetricarboxylates **1** and 2-ethynylanilines **2** as the one-carbon homologues for propargylamines was examined in the presence of zinc Lewis acids (0.2 equiv) (eq 1).[5] Reaction of triethyl ethenetricarboxylate **1a** and 2-ethynylaniline **2a** in the presence of $ZnBr_2$ or $Zn(OTf)_2$ at 80 °C in $ClCH_2CH_2Cl$ or 110 °C in toluene gave no cycloadducts such as **3** (in Scheme 1) efficiently and gave a complex mixture, possibly containing a noncyclized aniline adduct. Then, a Lewis acid-catalyzed cyclization of ethenetricarboxylate derivative **1a** with 2-(trimethysilylethynyl)aniline **2b** was examined, since Zn-catalyzed reaction of **1a** and silyl substituted propargyl alcohols gave tetrahydrofurans efficiently.[6] However, $ZnBr_2$ or $Zn(OTf)_2$ catalyzed reaction of **1a** with **2b** also gave a complex mixture containing a noncyclized adduct. Next, the reaction of *tert*-butyl ester **1b** and **2a**−**b** was examined. The $ZnBr_2$ and $Zn(OTf)_2$ catalyzed reaction of **1b** and **2a** in $ClCH_2CH_2Cl$ at 80 °C gave an unexpected compound **4a** as a major isolable product in 35 and 50% yields, respectively (eq 1 and Table 1, entries 1−2). Interestingly, the $ZnBr_2$ and $Zn(OTf)_2$ catalyzed reaction of **1b** and **2b** also gave **4a** in 38 and 58% yields, respectively (entries 3−4).

The structure of **4a** was determined by spectroscopic techniques and confirmed on the basis of the X-ray diffraction analysis of its 4-chloro analogue **4c** (see the Supporting Information for details). Apparently, ^{t}Bu and TMS groups were lost under the reaction conditions.

To obtain some insights into the mechanism, reactions between a substrate bearing a free CO_2H **1c**[7] and 2-ethynylaniline **2a** were examined. In the reactions, the compound **4a** was obtained in 43−58% yield (Table 1, entries 5−6). The results suggest that the free acid (or its anion) is the real reaction intermediates in the formation of **4a** (Scheme 2). It is difficult to predict when ^{t}Bu or TMS groups are removed precisely in the reaction of **1b** with **2a** or **2b**, since amine addition may be fast and reversible. In any case, intermediate **B** is formed from intermediate **A**, and then C−C bond formation occurs, followed by O−C bond formation.

Scheme 2



The reaction of 2-(phenylethynyl)aniline or 2-(1-hexynyl)aniline with **1b** in the presence of $Zn(OTf)_2$ was also examined. However, it gave a complex mixture.

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(4) For recent examples of synthesis of indoles, see: (a) Cui, S.-L.; Wang, J.; Wang, Y.-G. *J. Am. Chem. Soc.* **2008**, *130*, 13526. (b) El Kaim, L.; Gizzi, M.; Grimaud, L. *Org. Lett.* **2008**, *10*, 3417. (c) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.

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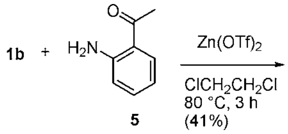
(7) (a) Kelly, T. R. *Tetrahedron Lett.* **1973**, 437. (b) Yamazaki, S.; Ohmitsu, K.; Ohi, K.; Otsubo, T.; Moriyama, K. *Org. Lett.* **2005**, *7*, 759.

Next, the reaction of **1b** and 2′-aminoacetophenone **5**, as another possible reaction intermediate for eq 1, was also examined (eq 2). The reaction **1b** and **5** in the presence of Zn(OTf)$_2$ (0.2 equiv) at 80 °C in $ClCH_2CH_2Cl$ for 3 h also gave **4a** in 41% yield. A possible reaction path including stepwise C−C and O−C bond formations is shown in Scheme 3. The yield of **4a** is lower than that of the reaction of **1b** and **2a**. The reactions of **2a** or **2b** with Zn(OTf)$_2$ at 80 °C in $ClCH_2CH_2Cl$ gave complex mixtures, possibly containing a small amount of **5**.[8] The amine adduct of **5** to **1b** (**C**, in Scheme 3) may also be a reaction intermediate in Scheme 2.[9]



(2)

Considering that the compounds **1c** and **2a** are prepared from **1b**[7] and **2b**,[10] respectively, and comparing the yields, the use of **1b** and **2b** is an effective way in view of reducing synthesis steps. Preparation of functionalized 2-(trimethylsilylethynyl)anilines are also conveniently prepared using a Sonogashira-coupling reaction.[3d,10,11] On the other hand, functionalized 2′-aminoacetophenones are not easily accessible,[1b] although 2′-aminoacetophenone **5** is commercially available.

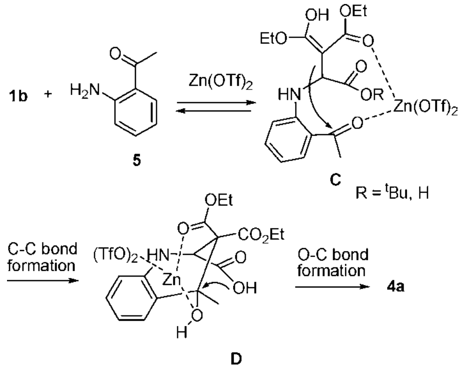
The reaction of various 2-ethynylaniline derivatives **2** was also examined and they also gave the bridged quinoline products **4** (eq 3, Table 2). 4-CN-Derivative **2d** gave the product **4b** in up to 85% yield, and it seems that aniline substituted with electron-withdrawing groups give somewhat better yields (entries 2−5, 7). They might suppress side reactions such as aromatic substitutions.

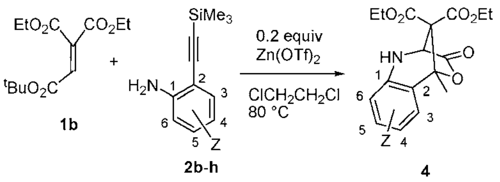
Table 2. Reaction of **1b** with 2-(Trimethylsilylethynyl)-anilines **2**

entry		Z	reaction time (h)[a]		yield (%)
1	**2b**[b]	H	3	**4a**	58
2	**2c**	4-Cl	16	**4c**	77[c]
3	**2d**	4-CN	18	**4d**	85
4	**2e**	4-CO_2Me	3	**4e**	69
5	**2f**	4-NO_2	18	**4f**	61
6	**2g**	4-Me	18	**4g**	43
7	**2h**	5-Cl	16	**4h**	62

[a] Optimum reaction time is shown. [b] In Table 1. [c] Reaction of **1b** and **2c** in the presence of 0.2 equiv $ZnBr_2$ for 3 h in $ClCH_2CH_2Cl$ at 80 °C also gave **4c** in 76% yield.

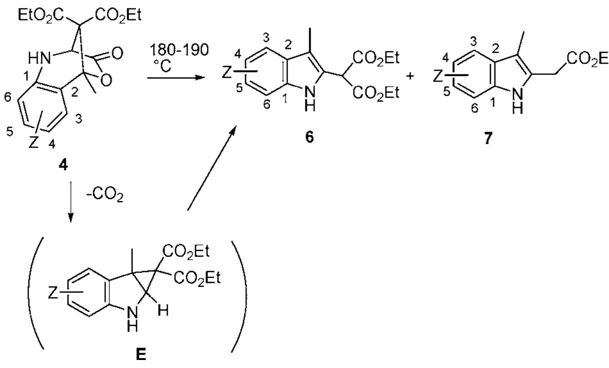
Scheme 3





(3)

Next, the thermal reaction of the bridged compounds **4** was examined. Heating **4** at 180−190 °C without solvent gave decarboxylated diesters **6** along with further decarboxylated monoesters **7** (eq 4, Table 3). The first formation of cyclopropane intermediates **E** by loss of CO_2 is assumed. Then, the resulting cyclopropylindolines **E** may be transformed to alkylated indoles **6**, similar to the reported examples for rhodium catalyzed carbenoid insertion.[12] Formation of byproducts **7** may occur by contaminated H_2O in situ.[13] Thus, heating compound **4c** and 1 equiv of water gave compound **7c** as a major product (entry 2).[14]



(4)

Table 3. Thermal Reaction of **4**

entry		Z	temp (°C)	reaction time (h)		**6** (%)	**7** (%)
1	**4c**	4-Cl	180	18	[a]	**6c** (68)	**7c** (8)
2	**4c**	4-Cl	180	18	[b]		**7c** (83)
3	**4d**	4-CN	190	16	[a]	**6d** (56)	**7d** (12)
4	**4e**	4-CO_2Me	180	5	[a]	**6e** (43)	**7e** (8)
5	**4h**	5-Cl	180	5	[a]	**6h** (49)	**7h** (12)

[a] Compound **4** (0.5−0.8 mmol) was heated in a closed vessel (50 mL). [b] Compound **4c** and 1 equiv of water were heated under nitrogen.

In summary, the zinc triflate-catalyzed reaction of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate **1b** or 1,1-diethyl 2-hydrogen ethenetricarboxylate **1c** with 2-ethynylanilines **2a,b** gave a bridged quinoline derivative **4a**.[15] The reaction of **1c** with 2′-aminoacetophenone also gave **4a**. Reaction of **1b** with various 2-(trimethylsilylethynyl)aniline substrates **2** in the presence of Zn(OTf)$_2$ gave bridged quinoline derivatives **4**. Furthermore, thermal reaction of **4** gave indole derivatives **6**.

Thus, a new reaction to construct bridged quinoline derivatives **4** was studied. Investigation of the detailed reaction mechanism and further transformation of the products to potentially useful compounds are ongoing.

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Supporting Information Available: Additional experimental procedure, spectral data and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The ^{1}H NMR spectra of the product mixtures show the peaks of **5**. However, isolation of **5** was unsuccessful. The efficiency of zinc catalysts in promoting the loss of TMS in the reaction conditions was also examined. The reaction of 4-(trimethylsilylethynyl)aniline with Zn(OTf)$_2$ gave 4′-aminoacetophenone in 47% isolated yield. On the other hand, the reaction of (trimethylsilylethynyl)benzene did not change under the reaction conditions. The detailed mechanism of loss of TMS is under investigation.

(9) 2′-Aminoacetophenone **5** and the amine adduct **C** are possibly formed in situ from Zn-catalyzed water addition to the triple bond of 2-ethynylanilines. The effect of water in situ will be investigated in due course.

(10) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581.

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(12) (a) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247. (b) Salim, M.; Capretta, F. *Tetrahedron* **2000**, *56*, 8063.

(13) Krapcho, A. P. *Synthesis* **1982**, *805*, 893.

(14) For a recent example of synthesis of indole-2-acetic esters, see: Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971.

(15) Typical experimental procedure (Table 1, Entry 4). To a solution of **1b** (107 mg, 0.39 mmol) in 1,2-dichloroethane (0.72 mL) was added 2-(trimethylsilylethynyl)aniline (**2b**) (74 mg, 0.39 mmol) and Zn(OTf)$_2$ (29 mg, 0.08 mmol). The mixture was heated at 80 °C and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched with water. The mixture was diluted with dichloromethane and then saturated aqueous NaHCO$_3$ was added. The organic phase was extracted with dichloromethane, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel with hexane-ether as eluent to give **4a** (76 mg, 58%). **4a**: $R_\mathrm{f} = 0.1$ (hexane-ether = 1 : 1); Colorless crystals; mp 124−125 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.02 (t, $J = 7.1$ Hz, 3H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.98 (s, 3H), 3.77−4.05 (m, 1H), 4.07−4.15 (m, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.48 (bd, $J = 1.8$ Hz, 1H), 4.80 (bs, 1H), 6.61 (dd, $J = 8.1$ Hz, 1.1 Hz, 1H), 6.81 (td, $J = 7.6$, 1.2 Hz, 1H), 7.17 (ddd, $J = 8.1$, 7.3, 1.5 Hz, 1H), 7.34 (dd, $J = 7.9$, 1.3 Hz, 1H). Selected NOEs are between δ 4.80 (N*H*) and δ 4.48 (C*H*N), 6.61 (Ar) and between δ 1.98 (C*H*$_3$) and δ 7.34 (Ar).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.67 (q), 14.06 (q), 17.64 (q), 58.58 (d), 60.62 (s), 61.87 (t), 63.08 (t), 84.49 (s), 115.10 (d), 119.17 (d), 123.87 (s), 124.69 (d), 130.48 (d), 139.93 (s), 165.02 (s), 167.70 (s), 169.65 (s). Selected HMBC correlations are between δ 4.48 (C*H*N) and δ 60.62 (*C*(CO$_2$Et)$_2$), 139.93 (Ar), 84.49 (O*C*Me), between δ 1.98 (C*H*$_3$) and δ 84.49 (O*C*Me), 123.87 (Ar), 60.62 (*C*(CO$_2$Et)$_2$), and between δ 7.34 (C*H*(Ar)) and δ 84.49 (O*C*Me).; IR (KBr) 3380, 2981, 1791, 1756, 1733, 1612, 1483, 1391, 1367, 1287, 1241, 1196, 1036 cm^{-1}; MS (EI) *m/z* 333 (M$^+$, 85), 26 (41), 216 (100%); HRMS M$^+$ 333.1214 (calcd for C$_{17}$H$_{19}$NO$_6$ 333.1212); Anal. Calcd for C$_{17}$H$_{19}$NO$_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.00; H, 5.61; N, 4.22.