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$Hg(OAc)_2 \cdot 0.1Sc(OTf)_3$-Catalyzed Cycloisomerization of 2-(4-Pentynyl)furan

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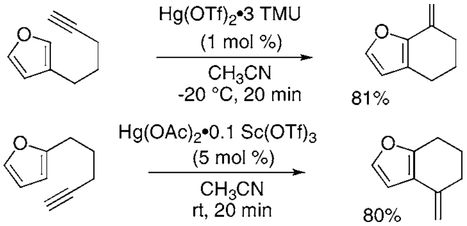
ABSTRACT



Although the $Hg(OTf)_2 \cdot 3TMU$-catalyzed Friedel–Crafts-type reaction of 3-(4-pentynyl)furan afforded the exo cyclization product, the reaction of 2-(4-pentynyl)furan furnished a very low yield. We found a 10:1 mixed reagent of $Hg(OAc)_2$ and $Sc(OTf)_3$ showed remarkable catalytic activity for the latter transformation. The actual reacting species is presumed to be Hg(OAc)(OTf), which is efficiently generated in situ by mixing the two reagents.

Transition-metal-catalyzed cycloisomerization of arylalkynes has been intensively studied and has played an important role in modern organic synthesis.[1] Electron-rich arenes react with alkynes in the presence of electrophilic metal halides or Brønsted acids.[2] We have also reported six-endo cycloisomerization of arylalkynes to give dihydronaphthalene derivatives.[3] Intramolecular reaction of furan with alkynes, however, mostly affords phenolic products via Diels−Alder reaction followed by a fragmentation.[4] Although an endo mode Friedel−Crafts-type cyclization of furanoalkynes affording benzofurans has been reported,[5] exo mode cyclization of alkynyl furans has not been recorded except for one example using $PtCl_2$ as catalyst, affording a benzofuran derivative.[4e] Therefore, the Friedel−Crafts-type cycloisomerization of alkynyl furans is an almost unknown area of research, and thus we have investigated the cycloisomerizations of 3-(4-pentynyl)furan (**1**) and 2-(4-pentynyl)furan (**3**) by using the reagent that we originated, mercuric triflate [$Hg(OSO_2CF_3)_2$, hereafter $Hg(OTf)_2$].[6−13] The latter type of cycloisomerization (**3** to **4**) is entirely unknown. The reaction

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(1) (a) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200−203. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328−2334. (c) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048−1052. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

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of 3-(4-pentynyl)furan (**1**) and 1 mol % of mercuric triflate·3tetramethylurea (hereafter TMU) complex afforded exo cyclization product **2** in 81% yield. However, the reaction of 2-(4-pentynyl)furan (**3**) with a variety of modified Hg(OTf)$_2$ reagents gave a very low yield of **4**. We found that a 10:1 mixed reagent of Hg(OAc)$_2$ and Sc(OTf)$_3$ showed remarkable catalytic activity for the latter transformation leading to **4**. The actual reacting species is presumed to be Hg(OAc)(OTf) efficiently generated in situ by mixing the two reagents. First, we examined the reaction of 3-(4-pentynyl)furan (**1**) with 1 mol % of Hg(OTf)$_2$ in CH$_3$CN at −20 °C for 3 h, and only a trace amount of **2** was detected along with 25% of starting material and some polymeric materials (Table 1, entry 1). This result suggested the existence of some catalyst suicide mechanism, probably by the reaction of Hg(OTf)$_2$ and the product **2**. Reaction with Hg(OTf)$_2$·TMU (1 mol %) for 20 min or 3 h also furnished disappointing results (entries 2 and 3). A 20 min reaction with Hg(OTf)$_2$·2TMU (1 mol %) afforded **2** in 50% yield (NMR yield using naphthalene as the internal standard) along with 20% of starting material; however, prolonged reaction for 3 h resulted in decomposition to give **2** in only 7% yield (entries 4 and 5). The best result was obtained by using Hg(OTf)$_2$·3TMU (1 mol %) in CH$_3$CN at −20 °C for 20 min, affording **2** in 81% yield (entry 6). However, prolonged reaction for 3 h again decreased the yield significantly as the result of some decomposition (entry 7). Neither 0.5 mol % catalyst nor 0.1 mol % catalyst afforded good results (entries 8 and 9). Reaction using AuCl$_3$ (1 mol %) resulted in complete decomposition of material (entry 10). In contrast, the reaction with PtCl$_2$ (1 mol %) at −25 °C for 1 h resulted in recovery of starting material (entry 11). Thus, not only the starting material **1** but also the product **2** were very sensitive to even mildly acidic conditions.

Scheme 1

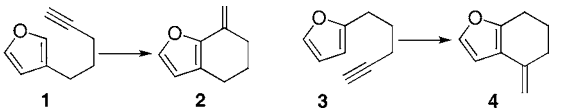


Table 1. Cycloisomerization of **1** in CH$_3$CN at −20 °C.

entry	catalyst	mol %	time	yield (%)[a] **2**	yield (%)[a] **1**
1	Hg(OTf)$_2$	1	3 h	tr	25
2	Hg(OTf)$_2$·TMU	1	20 min	5	57
3	Hg(OTf)$_2$·TMU	1	3 h	tr	52
4	Hg(OTf)$_2$·2TMU	1	20 min	50	20
5	Hg(OTf)$_2$·2TMU	1	3 h	7	16
6	Hg(OTf)$_2$·3TMU	1	20 min	81	tr
7	Hg(OTf)$_2$·3TMU	1	3 h	5	
8	Hg(OTf)$_2$·3TMU	0.5	3 h	8	36
9	Hg(OTf)$_2$·3TMU	0.1	3 h	10	78
10	AuCl$_3$	1	5 min		
11	PtCl$_2$	1	1 h		96[b]

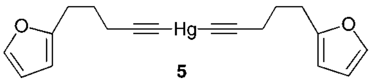
[a] NMR yield using naphthalene as the internal standard. [b] Reactions in acetone at −20 °C for 1 h afforded **2** in 2% yield along with 77% of **1**.

Next we examined the cycloisomerization of 2-(4-pentynyl)furan (**3**) by expecting a Friedel−Crafts type product such as **4**. As shown in Table 2, transformation of **3** to **4** is very difficult even by using Hg(OTf)$_2$·3TMU complex. A better result was obtained by the reaction of **3** with 1 mol % catalyst in CH$_3$CN at 25 °C for 20 min, but the yield was still 36% (Table 2, entry 3). Thus, we decided to examine other possibilities. Upon learning of the enyne cycloisomerization catalyzed by a mixed reagent of Au complex and AgSbF$_6$,[14] we tried the reaction of **3** with a 10:1 mixed reagent of Hg(OTf)$_2$·3TMU and AgSbF$_6$ in CH$_3$CN at 25

Table 2. Cycloisomerization of **3** in CH$_3$CN for 20 min

entry	Hg salt (mol %)	additive (mol %)	temp (°C)	yield (%)[a] **4**	yield (%)[a] **3**
1	Hg(OTf)$_2$ (1)		0	8	40
2	Hg(OTf)$_2$·3TMU (1)		0	17	55
3	Hg(OTf)$_2$·3TMU (1)		25	36	18
4	Hg(OTf)$_2$·3TMU (5)		0	30	*b*
5	Hg(OTf)$_2$·3TMU (5)	AgSbF$_6$ (0.5)	25	38	
6	Hg(OTf)$_2$ (5)	Sc(OTf)$_3$ (0.5)	25		
7	Hg(OTf)$_2$·3TMU (5)	Sc(OTf)$_3$ (0.5)	25	4	61
8	Hg(OAc)$_2$ (5)	AgSbF$_6$ (0.5)	25		90
9	Hg(OAc)$_2$ (5)	AgOTf (0.5)	25		86
10	Hg(OAc)$_2$ (5)	La(OTf)$_3$ (0.5)	25	19	60
11	Hg(OAc)$_2$ (5)	Eu(OTf)$_3$ (0.5)	25	26	60
12	Hg(OAc)$_2$ (5)	Yb(OTf)$_3$ (0.5)	25	39	37
13	Hg(OAc)$_2$ (5)	Sc(OTf)$_3$ (0.5)	25	80	
14	Hg(OAc)$_2$ (5)	Sc(OTf)$_3$ (5)	25	3	*b*
15	Hg(OAc)$_2$ (5)		25		90[c]
16		Sc(OTf)$_3$ (0.5)	25		94
17	Hg(OAc)$_2$ (5)	TfOH (0.5)	25	66	
18	Hg(OAc)$_2$ (5)	TfOH (5)	25		*b*
19	PtCl$_2$ (5)		25		*d*

[a] NMR yield using naphthalene as the internal standard. [b] Complex mixture was formed. [c] Small amount of **5** was detected. [d] A 10:1 mixture of phenol **6** and an unidentified product was obtained in 72% yield after 10 h at reflux in acetone.



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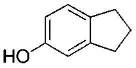

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°C for 20 min and obtained **4** in 38% yield (entry 5). Then we screened a variety of combinations of mercuric salts and additives in a 10:1 ratio. Because no promising results were obtained by using $Hg(OTf)_2$ or its TMU complex (entries 6 and 7), we switched to $Hg(OAc)_2$. Then, we found the combination of $Hg(OAc)_2$ and $La(OTf)_3$ (10:1) affords **4** in 19% yield along with 60% of starting material (entry 10). A 10:1 combination of $Hg(OAc)_2$ with $Eu(OTf)_3$ also afforded **4** in 26% yield, and with $Yb(OTf)_3$ gave a 39% yield of **4** together with significant quantities of starting material **3** (entries 11 and 12). Finally we found that the combination of $Hg(OAc)_2$ and $Sc(OTf)_3$ (10:1) gave rise to **4** in 80% yield (entry 13). However, the reaction using a 1:1 mixture of $Hg(OAc)_2$ and $Sc(OTf)_3$ afforded **4** only in 3% yield along with complex polymeric products (entry 14). The reaction with only $Hg(OAc)_2$ (5 mol %) did not afford **4** at all, and most of the starting material was recovered along with trace amounts of unstable byproduct that is dimeric mercury acetylide **5** (entry 15). Acetylide formation is a catalyst suicide mechanism. Reaction with 0.5 mol % of $Sc(OTf)_3$ resulted in complete recovery of starting material (entry 16). However, a 10:1 combination of $Hg(OAc)_2$ and TfOH afforded **4** in 66% yield (entry 17), and a 1:1 reagent did not afford **4**, instead producing complex mixtures (entry 18). When the reaction of **3** with $PtCl_2$ (5 mol %) in acetone was examined at reflux for 10 h, Diels−Alder and following fragmentation took place to give a 10:1 mixture of phenol **6** and an unidentified product in 72% yield.[4e,15]

The results suggested the actual reacting species to be Hg(OAc)(OTf) generated by the reaction of $Hg(OAc)_2$ and small amounts of $Sc(OTf)_3$ or TfOH (entries 13 and 17). When $Hg(OAc)_2$ and an equal amount of either $Sc(OTf)_3$ or TfOH were mixed, decomposition took place because of the partially formed $Hg(OTf)_2$ (entries 14 and 18). However, we failed to detect any occurrence of Hg(OAc)(OTf) or $Hg(OTf)_2$ by NMR experiment, probably due to too low concentration.

Therefore, we propose that the reaction is likely to be initiated from π-complex **7**, cyclized oxonium cation **9** is generated probably via the spirocyclic cation **8**, and the cation **9** produces the vinylmercury intermediate **10** by deprotonation. Then, the protonation of **10** by in situ generated TfOH leads to alternative oxonium cation **11** and upon demercuration regenerates the catalyst Hg(OAc)(OTf) and affords the product **4**. Probably Hg(OAc)(OTf) is inert against **4**. However, as shown in Table 2, $Hg(OTf)_2$ also reacts with the product **4**, generating cation **12**. Further reaction of **12** with **4** should lead to complex polymerization products. Occurrence of an sp^3-C−Hg bond formed by the deprotonation of polymeric products should be the alternative catalyst suicide mechanism.The procedure was applied to the reaction of 2-methyl-5-(4-pentynyl)furan (**13**). A reaction with 5 mol % of $Hg(OAc)_2{\cdot}0.1Sc(OTf)_3$ in CH_3CN at room temperature for 20 min afforded exo cyclization product **14** in 75% yield (Table 3). Malonate derivative **15** was converted to **16** in 91% yield. The reaction of 2-methyl-5-(4-nonynyl)furan (**17**) with 5 mol % of $Hg(OAc)_2{\cdot}0.1Sc(OTf)_3$ in CH_3CN required 60 °C and afforded endo cyclized seven-membered ring product **18** in 75% yield after 17 h. Although the reaction of 2-(4-nonynoyl)furan (**19**) afforded seven-membered ring product **20** in low yield (44%) even after 24 h reaction at 60 °C, the phenyl-substituted analogues **21** and **23** afforded endo cyclization products **22** (90% yield) and **24** (93% yield), respectively. Reaction of 2-(3-butynyl)-5-methyfuran (**25**) with $Hg(OAc)_2{\cdot}0.1Sc(OTf)_3$ at 25 °C for

Scheme 2

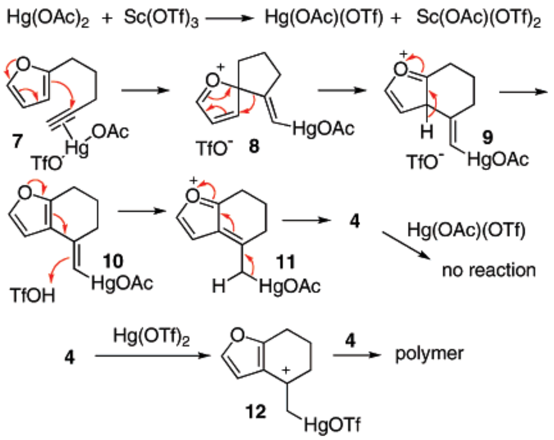
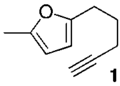
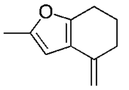
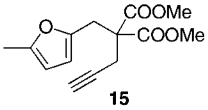
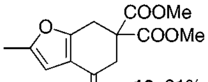
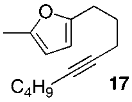
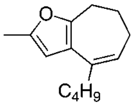
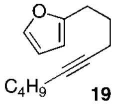
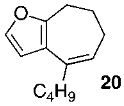
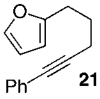
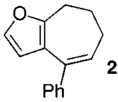
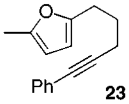
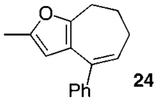
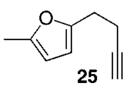
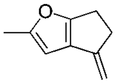


Table 3. Reaction of Alkynyfurans with 5 mol % of $Hg(OAc)_2{\cdot}0.1Sc(OTf)_3$ in CH_3CN.

substrate	temperature, time	product	isolated yield (%)
 **13**	rt, 20 min	 **14**	75%
 **15**	rt, 20 min	 **16**	91%
 **17**	60 °C, 17 h	 **18**	75%
 **19**	60 °C, 24 h	 **20**	44%
 **21**	60 °C, 17 h	 **22**	90%
 **23**	60 °C, 1.5 h	 **24**	93%
 **25**	rt, 24 h	 **26**	0%[a]

[a] Starting material was recovered in 88% yield.

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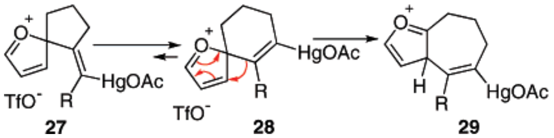
Scheme 3



24 h resulted in 88% recovery of starting material without forming **26**. Elevating the reaction temperature to 60 °C for 24 h led to decomposition. These results suggest that the rearrangement mechanism is from spirocyclic intermediate **8** to **9**, since the case of **25** has to generate a spirocyclic four-membered ring intermediate. It must be pointed out that internal alkynyl furans **17**, **19**, **21**, and **23** selectively afforded seven-membered ring products **18**, **20**, **22**, and **24**, respectively. The results reflect the stability of **28** over **27**, and the rearrangement to **29** was the only possible path (Scheme 3).

Thus, we have developed a new, mild catalytic system, $Hg(OAc)_2$•0.1Sc$(OTf)_3$, and achieved novel cycloisomerization of very sensitive substrates such as 2-(4-pentynyl)furan and analogues.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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