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Mercuric Triflate-Catalyzed Synthesis of 2-Methylfurans from 1-Alkyn-5-ones

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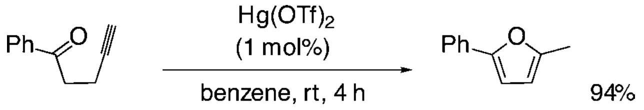
ABSTRACT



2-Methylfurans were prepared by an effective cyclization of 1-alkyn-5-ones in the presence of mercuric triflate as the catalyst under very mild reaction conditions with high catalytic turnover up to 100 times. Benzene, toluene, or dichloromethane was the solvent of choice.

We have developed mercury(II) trifluoromethanesulfonate, mercuric triflate [hereafter Hg(OTf)$_2$], as a highly efficient olefin cyclization agent[1] and applied it to the synthesis of polycyclic terpenoids.[2] Recently, we found that the Hg(OTf)$_2$ and Hg(OTf)$_2$-tetramethylurea (hereafter TMU) complex showed highly efficient catalytic activity for the hydration of terminal alkynes to give methyl ketones,[3] hydroxylative 1,6-enyne cyclization to give exomethylene five-membered ring products,[4] and ω-arylalkyne cyclization leading to dihydronaphthalene derivatives.[5] The reaction should involve a protodemercuration step of the vinylmercury intermediate induced by TfOH that is generated in situ.[6] We describe herein the Hg(OTf)$_2$-catalyzed keto alkyne cyclization leading to 2-methyl furan in excellent yields. Although many methods have been devised for the synthesis of the furan ring,[7] catalytic cyclization of 1-alkyne-5-one leading to 2-methylfuran has rarely been reported. PdCl$_2$-catalyzed cyclization of 6-phenylhex-5-yn-2-one has been achieved leading to 2-benzyl-5-methylfuran after 2 h at 100 °C.[8] A strong base or H$_3$PO$_4$-induced similar cyclization has also been recorded.[9,10] On the other hand, cyclization of alkyne with enolizable β-ketoesters is well-known.[11] The present furan synthesis is advantageous

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(2) (a) Nishizawa, M.; Takenaka, H.; Hirotsu, K.; Higuchi, T.; Hayashi, Y.*J. Am. Chem. Soc.* **1984**, *106*, 4290−4291. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522−523. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806−813. (d) Nishizawa, M.; Yamada, H.; Hayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 187−190. (e) Nishizawa, M.; Yamada, H.; Hayashi, Y. *J. Org. Chem.* **1987**, *52*, 4878−4884. (f) Nishizawa, M.; Takao, H.; Kanoh, N.; Asoh, K.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett.* **1994**, *35*, 5693−5696. (g) Nishizawa, M.; Morikuni, E.; Takeji, M.; Asoh, K.; Hyodo, I.; Imagawa, H.; Yamada, H. *Synlett* **1996**, 927−928. (h) Nishizawa, M.; Takao, H.; Iwamoto, Y.; Yamada, H.; Imagawa, H. *Synlett* **1998**, 76−78. (i) Nishizawa, M.; Imagawa, H.; Hyodo, I.; Takeji, M.; Morikuni, E.; Asoh, K.; Yamada, H. *Tetrahedron Lett.* **1998**, *39*, 389−392. (j) Imagawa, H.; Shigaraki, T.; Suzuki, T.; Takao, H.; Yamada, H.; Sugihara, T.; Nishizawa, M. *Chem. Pharm. Bull.* **1998**, *46*, 1341−1342. (k) Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **1999**, *40*, 1153−1156.

(3) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12−13.

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(7) (a) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Uchimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655−3661. (b) Padwa, A.; Ishida, M.; Muller, C. L.; Murphree, S. S. *J. Org. Chem.* **1992**, *57*, 1170−1178. (c) Kataoka, Y.; Tezuka, M.; Takai, K.; Uchimoto, K. *Tetrahedron* **1992**, *48*, 3495−3502. (d) Ji, J.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 764−765. (e) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem.* **2003**, *42*, 2681−2684. (f) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861−1864.

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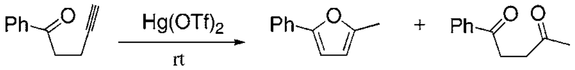
Table 1. $Hg(OTf)_2$-Catalyzed Cyclization of **1**

entry	$Hg(OTf)_2$ (mol%)	solvent	time (h)	yield (%)[a] **2**	yield (%)[a] **3**
1	10	CH_2Cl_2	0.25	87	3
2	10	CH_3CN	0.25	15	67
3	10	CH_3NO_2	0.25	30	39
4	10	Et_2O	1	86	4
5	10	hexane	40	82	7
6	10	C_6H_6	0.5	100	0
7	3	C_6H_6	2	95	5
8	2	C_6H_6	3	95	5
9	1	C_6H_6	4	94	6
10	1	$C_6H_5CH_3$	5	91	9
11[b]	1	C_6H_6	4	20[c]	29
12[d]	1	C_6H_6	4	0	0
13[e]	1	C_6H_6	4	9	0

[a] NMR yield using dibromomethane as an internal standard. [b] Reaction with $Hg(OTf)_2$−TMU. [c] Starting material 48% was recovered. [d] Reaction with $Hg(OAc)_2$. [e] Reaction with $Hg(OTFA)_2$.

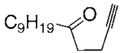
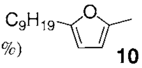
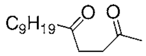
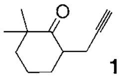
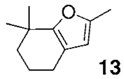
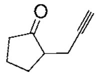
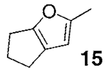
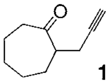
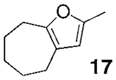
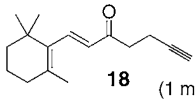
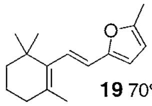
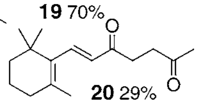
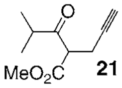
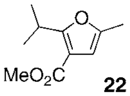
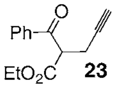
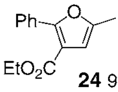
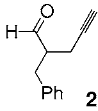
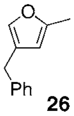
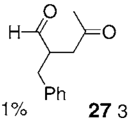
in that the reaction is carried out under very mild conditions with high catalytic turnover up to 100 times.



1 **2** **3**

When the reaction of 1-phenylpent-4-yn-1-one (**1**) with 10 mol % $Hg(OTf)_2$ in CH_2Cl_2 was carried out at room temperature for 15 min, clean cyclization took place to give 2-methyl-5-phenylfuran (**2**) in 87% yield along with 3% yield of diketone **3** (entry 1 in Table 1). Reaction in a polar solvent such as CH_3CN and CH_3NO_2 afforded poor results, and diketone formation predominated (entries 2 and 3). Although ether and hexane gave comparable results with CH_2Cl_2, benzene provided the best result, affording **2** in quantitative yield, and no trace of **3** was detected (entry 6).[12] Since $Hg(OTf)_2$ is not soluble in benzene, it is necessary to make a fine powder by sonication after exchange of the solvent from CH_3CN that is the requisite solvent for the preparation of $Hg(OTf)_2$. Using 3, 2, and 1 mol % of the catalyst also afforded **2** in acceptable yield along with 5−6% yield of diketone **3** requiring some longer reaction period (entries 7−9). Toluene was also acceptable as a solvent, affording **2** in 91% yield with 8% yield of **3** by using 1 mol % catalyst (entry 10). The occurrence of diketone **3** cannot be helped considering the participation of moisture, although we employed rather vigorous nonaqueous conditions. The $Hg(OTf)_2$−TMU complex (1 mol %) is not effective enough for this cyclization, affording **2** in 20% yield along with diketone **3** (29%), with 48% recovery of the starting material after 4 h (entry 11). Both $Hg(OAc)_2$ and $Hg(OTFA)_2$ were ineffective for the furan synthesis (entries 12 and 13).

Table 2. $Hg(OTf)_2$-Catalyzed Cyclization of Alkynylketones

substrate	$Hg(OTf)_2$ (mol %)	product, yield (%)[a]
 **9**	(1 mol%)	 **10**  **11** in C_6H_6, 5h 80% 20% in CH_2Cl_2, 1 h 85% 12%
 **12**	(5 mol%) in C_6H_6, 0.5 h	 **13** 98%
 **14**	(5 mol%) in C_6H_6, 4 h	 **15** 0%
 **17**	(1 mol%) in C_6H_6, 4 h	 **17** 98%
 **18**	(1 mol%) in C_6H_6, 2 h	 **19** 70%  **20** 29%
 **21**	(1 mol%) in C_6H_6 4 h	 **22** 99%
 **23**	(1 mol%) in C_6H_6, 6 h	 **24** 99%
 **25**	(1 mol%) in C_6H_6, 20 h	 **26** 21%  **27** 34%

[a] NMR yield using dibromomethane as an internal standard.

The reaction should be initiated by π-complexation of an alkynyl group with $Hg(OTf)_2$ as seen in **4**, and participation of a carbonyl group should lead to oxonium cation **5**. Deprotonation of **5** should provide vinyl mercury intermediate **6**. Protonation by in situ-generated TfOH leads to alternative oxonium cation **7**, which following demercuration is able to provide **8** and $Hg(OTf)_2$. Isomerization of **8** to 2-methylfuran **2** should be familiar.

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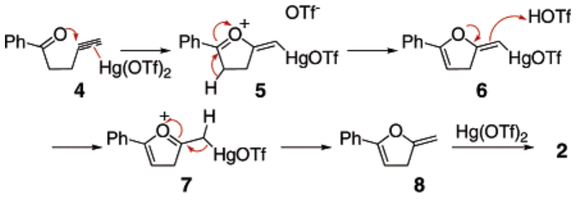
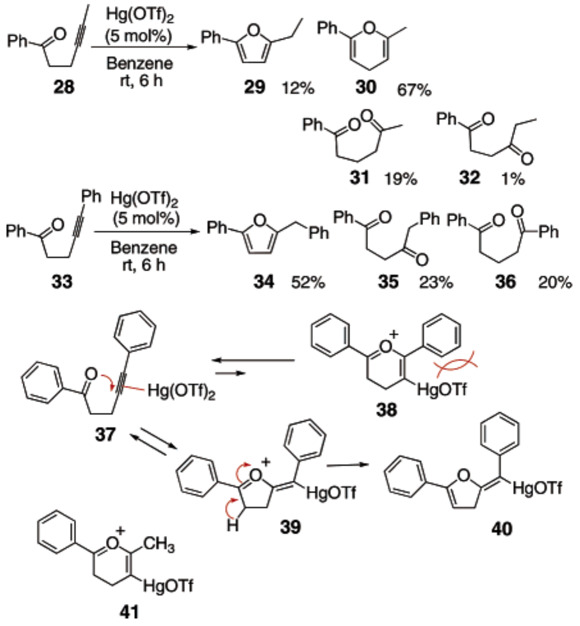
(11) (a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450−3451. (b) Marshall, J. A.; Zou, D. *Tetrahedron Lett.* **2000**, *41*, 1347−1350. (c) Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787−1790.

(12) Typical experimental procedure is as follows. A stock solution of $Hg(OTf)_2$ in CH_3CN (0.01 M solution, 0.63 mL, 0.0063 mmol) was transferred to two-necked flask under an argon atmosphere, and the solvent was replaced with benzene (3.3 mL) after removal of CH_3CN under reduced pressure. The suspension of $Hg(OTf)_2$ in C_6H_6 was sonicated to form a fine powder; to this was added a solution of 1-alkyne-5-one (100 mg, 0.63 mmol) in C_6H_6 (3 mL), and the mixture was stirred at room temperature until all of the starting material was consumed. The reaction was quenched by the addition of an aqueous NaCl−$NaHCO_3$ solution. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The resulting crude material was purified by column chromatography on silica gel using hexane−EtOAc as an eluent.



It is also possible for the alkyl ketone **9** to give furan **10** in 80% yield along with diketone **11** (20%) by using 1 mol % Hg(OTf)$_2$ in benzene.[12] Although extremely anhydrous conditions (substrate, solvent, and catalyst) were employed, we could not reduce the formation of diketone **11** to below 20%, and the result suggests the existence of another reaction mechanism such as decomposition of an unknown precursor to diketone during the aqueous workup stage. Dichloromethane is also acceptable for the reaction to give **10** in 85% yield after 1 h reaction period. Cyclohexanone derivative **12** afforded fused 2-methylfuran **13** in 98% yield by using 5 mol % catalyst in benzene at room temperature. However, the reaction of cyclopentanone derivative **14** with 5 mol % Hg(OTf)$_2$ provided a complicated mixture and the occurrence of furan **15** was not detected. Cycloheptanone derivative **16** was cleanly converted to methylfuran **17** in excellent yield by using 1 mol % catalyst. Cyclization of $\alpha,\beta,\gamma,\delta$-unsaturated ketone **18** is also possible, affording conjugated furan **19** in 70% yield along with diketone **20** (29%). Enolizable β-ketoesters **21** and **23** were also excellent substrates to give furans **22** and **24**, respectively, in excellent yields by using 1 mol % catalyst as described by Marshall and Wipf using Pd complex.[11] Application of this method to alkyne aldehyde **25**, however, resulted in a very poor yield of furan **26** (21%), and diketone **27** (34%) was the major product after 20 h of reaction.

Next, we examined the cyclization of internal alkynyl ketones **28** and **33**. The reaction of 1-phenylhex-4-yn-1-one (**28**) with 5 mol % Hg(OTf)$_2$ in benzene at room temperature afforded 2-ethylfuran **29** in only 12% yield, and the major product was the unstable disubstituted 4*H*-pyran **30** in 67% yield along with 1,5-diketone **31** (19%) and 1,4-diketone **32** (1%).[13−15] In contrast, 1,5-diphenylpent-4-yn-1-one (**33**) afforded 2-benzyl-5-phenylfuran (**34**) as the major product in 52% yield along with 1,4-diketone **35** (23%) and 1,5-diketone **36** (20%). The severe steric repulsion between the phenyl group and the HgOTf group of the cationic intermediate of **38** should bring about equilibrium to form cation **39** predominantly. Protodemercuration of **40** should result in **34** as the major product. Interaction of the methyl and HgOTf groups of **41** is not significant, and a 6-endo mode cyclization resulted, leading to **29**.



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

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[13] Separation of diketone from cyclization products was easily achieved by short-pass chromatography on silica gel (pretreated with Et_3N) using hexane as an eluent to give a 5.6:1 mixture of **29** and **30**. Attempted separation of **30** from **29** was unsuccessful due to the instability of **30**, that decomposed to **31**. Major peaks of ^1H and ^{13}C NMR are as follows. ^1H HMR (200 MHz in $CDCl_3$) δ 1.85 (dd, $J = 2.6$, 1.4 Hz, 2H), 2.86 (m, 3H), 4.58 (m, 1H), 5.31 (dt, $J = 4.0$, 2.0 Hz, 1H), 7.20−7.40 (m), 7.52−7.66 (m); ^{13}C NMR (50 MHz in $CDCl_3$) δ 19.28 q, 21.48 t, 95.32 d, 96.48 d, 123.32 d, 124.24 d, 126.71 d, 127.94 d, 128.14 d, 128.56 d, 134.82 s, 148.33 s, 149.12 s.

[14] Although 2-methyl-6-phenylpyrylium salts ($SnCl_5^-$ and ClO_4^-) are reported, 2-methyl-6-phenylpyran is not yet recorded. See: Dorofeenko, G. N.; Pyshchev, A. I. *Khim. Geterotsikl. Soedin.* **1974**, 1031−1035.

[15] 2,5-Dimethylpyran was prepared by the $NaBH_4$ reduction of the corresponding pyrylium salt. See: Safieddine, A.; Royer, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 2510−2513.