Mercury(II)-Catalyzed Synthesis of Spiro[4.5]decatrienediones in the Presence of Water

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Abstract

Treatment of the easily available p-methoxybenzyl allenyl ketone 2 or the (p-tert-butyldimethylsiloxybenzyl) allenyl ketone 9 with 1% Hg(ClO$_4$)$_2$ in acetonitrile/water provided good yields of the spiro[4.5]deca-3,6,9-triene-2,8-dione 6c. The Hg(II)-catalyzed addition of water to the allene was much slower, the 1,3-diketone 7 was only a minor side-product. The isomeric o-methoxybenzyl allenyl ketone 12 formed some spiro[4.5]deca-3,7,9-triene-2,6-dione 13, the side-reactions were the addition of water and a new spirocyclization/dimerization leading to 15.
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Numerous publications have been devoted to the synthesis of the spiro[4.5]decane terpene skeleton 1 from methoxy [1] or hydroxy [2] substituted arenes. This interest originates from the naturally occurring sesquiterpenes like spirovetivanes, acorones and alaskanes [1b,3] and the synthesis of aromatase inhibitors [1c,d]. Recently Nagao et al. [4] published an intriguing synthesis of spiro[4.5]deca-3,6,9-triene-2,8-diones 6. Treatment of the easily available allenyl ketones 2 with stoichiometric amounts of Lewis acids (LA) like BF$_3$·Et$_2$O, ZnI$_2$ or AlCl$_3$ delivered the spiro compounds 6. A major synthetic limitation of this method was the need of at least two methoxy substituents on the aromatic system. With only one methoxy group being present, the yield dropped from more than 80% to 8%.

1   R = Me,H
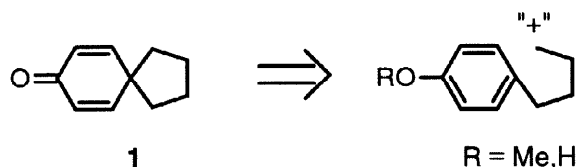
The reaction proceeds through an intial activation of enone by coordination to the Lewis acid (3) followed by electrophilic attack at the *ipso*-position of the electron rich aromatic ring (4). Now the

crutial step is the nucleophilic substitution at the methyl group (to **5**). In Nagao's reaction the nucleophile (Nu) is the halide anion set free from the Lewis acid. On the other hand Gajewski [1a] has demonstrated in his pioneering work that with water as nucleophile much better yields can be obtained even with only one hydroxyl group on the aromatic system, but he had to use concentrated sulfuric acid as a catalyst – conditions unsuitable for many organic compounds.
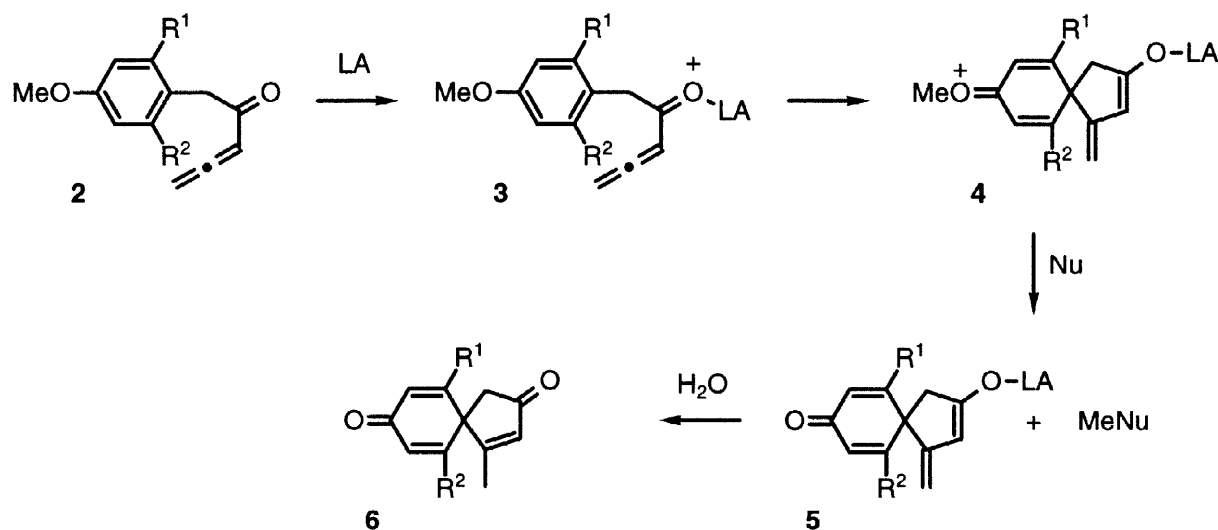

| 2-6:	R^1, R^2	LA	solv.	yield of **6** (%)
a	OMe,OMe	1.20 eq. $BF_3 \cdot Et_2O$	CH_2Cl_2	83 [a)]
b	OMe,H	1.20 eq. $BF_3 \cdot Et_2O$	CH_2Cl_2	80 [a)]
c	H,H	1.20 eq. $BF_3 \cdot Et_2O$	CH_2Cl_2	8 [a)]
c	H,H	0.01 eq. $Hg(ClO_4)_2$	$MeCN/H_2O$	80

a) see ref. [4].

For the cyclization of **2c**, we now tested several Lewis acids that tolerate water. When water acts as a nucleophile, methanol and a proton are formed. The latter is now capable to liberate the Lewis acid from the enolate complex, thus a catalytical cycle would be possible. While $InCl_3$ and $Tl(ClO_4)_3$ were inactive, $Hg(NO_3)_2$, $Hg(OAc)_2$, $HgSO_4$ and $Hg(ClO_4)_2$ showed catalytical activity, the latter being most active. The solvent of choice was acetonitrile (MeCN, containing 2 eqs. H_2O), in wet ethyl acetate, acetone or dichloromethane lower yields were obtained and the reaction was slower, in hexane no reaction was observed. Under these optimized and mild conditions with 1% of $Hg(ClO_4)_2$ in $MeCN/H_2O$ a 80% yield of **6c** was obtained. The structure of **6c** was unambiguously proven by an X-ray structure analysis (Figure 1) [5]. The only side-product was the 1,3-diketone **7** formed by the mercury(II)-catalyzed addition of water to the allene (as known for other allenes and alkynes) [6]. This demonstrates that the intramolecular spirocyclization is faster than the intermolecular addition of water to the allene. When only a small amount of water was present, the conversion to **6c** stopped as soon as the water was consumed. The subjection of **2** to 10mol% of perchloric acid in $MeCN/H_2O$ delivered an almost quantitative yield of **7** (quantitative by NMR, 94% isolated), not a trace of **6c** was detectable.

The difference between Hg(II) and the other Lewis acids might arise from the fact that the comparable soft [7] Hg^{2+} is not only capable to coordinate to the ketone but like in oxymercuration reactions it can coordinate to the double-bond as well. So the reaction might proceed via **8**.
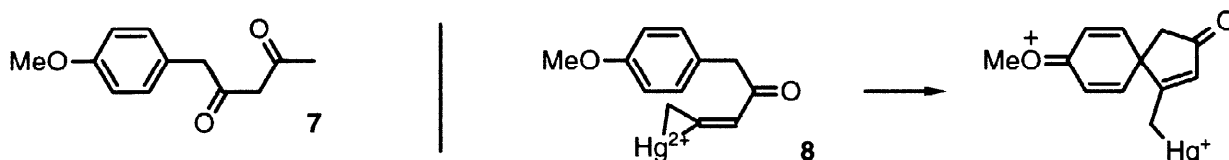

We then tested whether the corresponding silyl ether **9** could also be used. Again **6c** was formed, the yield was slightly higher (84%) than in the case of the methyl ether.
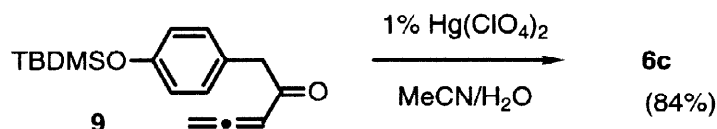
The related aryl allenyl ketone **10** and homobenzyl allenyl ketone **11** were also investigated. But here instead of a spirocyclization only a slow addition of water to the allene was observed.
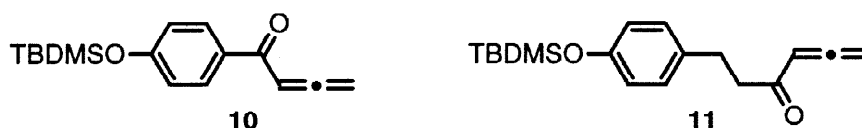

Finally we investigated the benzyl allenyl ketone **12** bearing an *ortho*-methoxy substituent. The reaction was much slower, after five days still some starting material was present (this explains why Nagao did not observe the ketone in *ortho*-position in the case of the 2,4-dimethoxy or 2,4,6-trimethoxy arenes **2a** and **2b**). Besides 24% of the spiro[4.5]deca-3,7,9-triene-2,6-dione **13** and the 1,3-diketone **14** also **15** could be isolated. Both **13** and **15** represent hitherto unknown structure-types. While the structure eludication for **13** was straightforward, for **15** besides ^1H and ^{13}C NMR spectra also $^1H,^1H$-COSY, $^{13}C,^1H$-COSY and $^{13}C,^1H$-HMBC spectra were necessary for an unambiguous proof of the connectivity [8]. The unexpected formation of **15** is still under investigation, we assume that the allenyl ketone part of **12** is first cycloisomerized to a furan (metal-catalyzed) [9] and the latter then forms the new C-C-bond by electrophilic attack of **13** (activated by the Lewis acid).
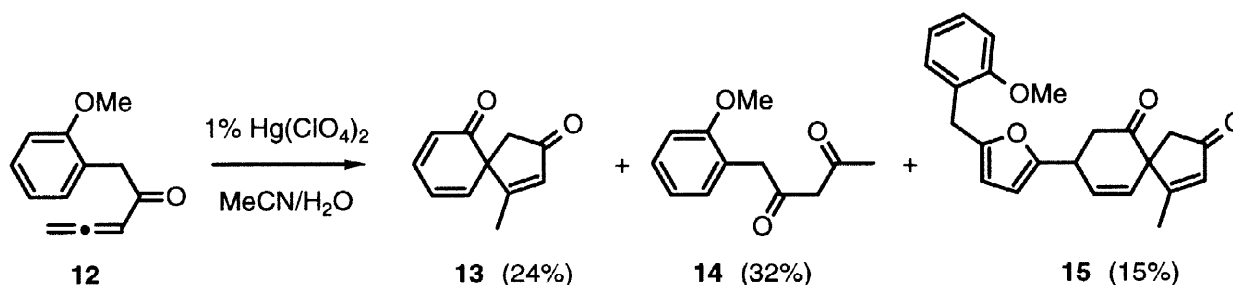
In order to use H^+ as a better leaving group we tried to prepare the *ortho*-hydroxy derivative **17** from **16**. Unfortunately, besides polymeric material only the seven-membered cyclic vinyl ether **18**

could be obtained in moderate yield, demonstrating that substrates like **17** undergo fast intramolecular addition of the hydroxyl group to the allene.
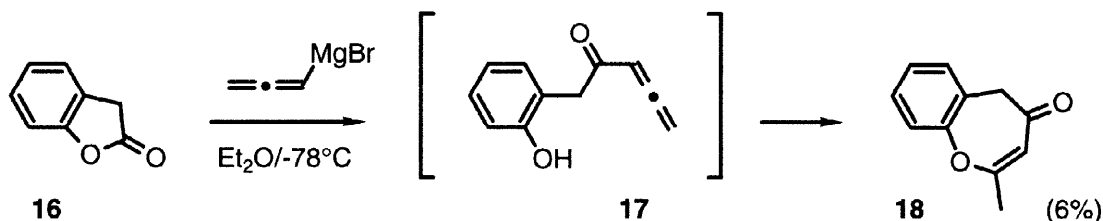
Again the structure was proven by an X-ray structure determination (Figure 2) [5]. There exists only one other example for a comparable formation of a seven-membered heterocycle [10].
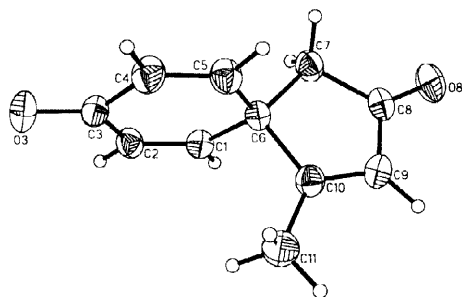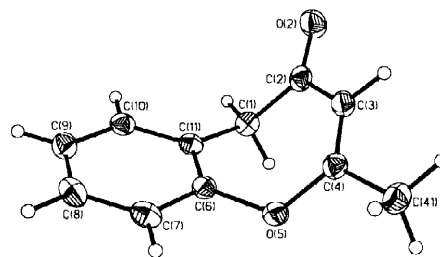

Figure 1. ORTEP-plot of **6c**

Figure 2. ORTEP-plot of **18**

References and Notes

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