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Synthesis of α-Diketones from Alkylaryl- and Diarylalkynes Using Mercuric Salts

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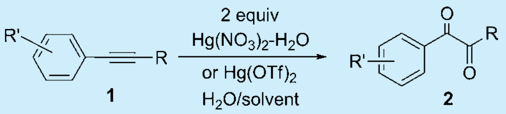
Supporting Information

ABSTRACT: Both alkylarylalkynes and diarylalkynes **1** are converted into the α-diketones **2** in good yield by the use of mercuric salts, e.g., mercuric nitrate hydrate or mercuric triflate, in the presence of water. Other mercuric salts, e.g., sulfate, chloride, acetate, or trifluoroacetate, do not provide the diketone product. A possible mechanism is proposed.

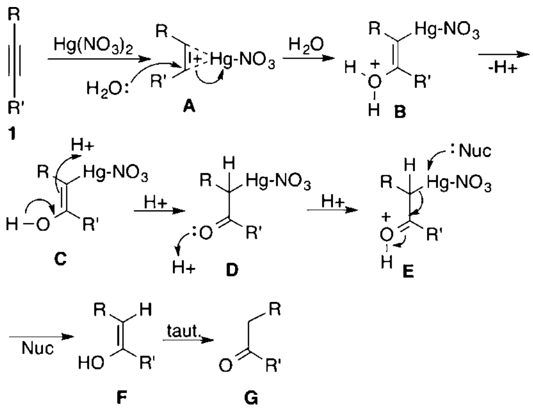


The oxidation of alkylarylalkynes and diarylalkynes **1** to furnish the corresponding α-diketones **2** is well-known in organic chemistry. A very large number of oxidants have been used for this process. For example, $KMnO_4$ has been employed often for this transformation[1] as has RuO_4 (often generated in situ or immobilized).[2] There are also several reports of the use of various DMSO-based oxidations, usually with an added electrophile[3] or in the presence of a palladium catalyst[4] for the formation of **2** from **1**. Finally, a large variety of other metal-based[5] and nonmetal-based[6] oxidations have been reported. For a project involving the synthesis of androgen receptor antagonists, we had need of a good method for converting alkylarylalkynes into α-diketones. We report here that methodology and its application to the conversion of several disubstituted alkynes **1** to the corresponding α-diketones **2**.

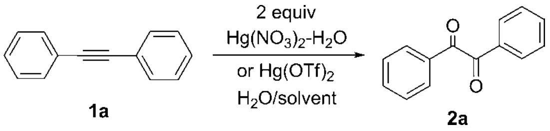
We hoped if it might be possible to intercept the well-known mechanism[7] for mercuric-catalyzed hydration of an alkyne (Scheme 1) by reaction of the α-mercurioketone intermediate **D** with another equivalent of the mercuric salt.

We examined this process using 1,2-diphenylacetylene **1a** as the substrate. Thus treatment of **1a** with 2 equiv of mercuric nitrate hydrate at 22 °C in aqueous THF for 12 h gave the expected α-diketone, benzil **2a**, in 52% yield (Scheme 2). We carried out several experiments on this test reaction to find the best set of conditions. Carrying out the reaction under air or under argon gave the same results, so oxygen is not required for the process. The use of anhydrous THF with an added equivalent of water afforded good yields. Other solvents worked well, e.g., methanol, DME, dioxane, acetonitrile, acetone, acetic acid, DMSO, and especially DMF. The best yields were obtained in methanol with 1 equiv of added water (22 °C, 20 min, 84%) and in DMF (22 °C, 24 h, 90%). The use of other mercuric salts, e.g., sulfate, chloride, acetate, and trifluoroacetate, did not give any **2a**. However, the use of mercuric triflate, $Hg(OTf)_2$, also produced good yields of the α-diketone **2a**.

Scheme 1. Mercuric Nitrate Catalyzed Hydration of an Alkyne



Scheme 2. Oxidation of 1a To Give 2a



We then applied this method to the synthesis of a wide variety of α-diketones using the following set of conditions, namely treatment of the alkyne **1** with 2 equiv of mercuric nitrate hydrate in DMF in air at 22 °C. The results are shown in Table 1. Arylalkynes generally gave good yields of the expected α-diketone products, e.g., **2b**,**d**–**f**,**m**,**n**, with yields ranging from 47 to 82%. In addition, most of the diarylacetylenes gave quite good yields of product. The presence of halogens (**1c**,**i**,**j**,**n**) did not hinder the oxidation nor did the more oxidizable or labile functionalities, such as phenols (**1l** and **1m**), esters (**1k** and **1o**), amines (**1e**, **1p**, and **1q**), or nitriles (**1f**), all of which gave reasonable yields of the desired products **2**. Substrates with electron-donating substituents (methoxy, **2g**, or methyl, **2h**) gave good yields, while the substrate having a 4-trifluoromethyl

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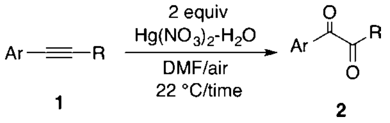
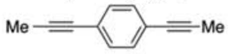
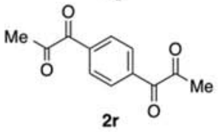
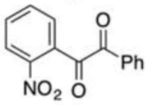
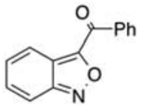
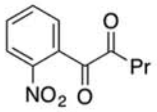
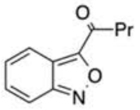
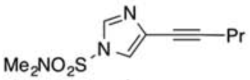
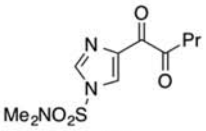
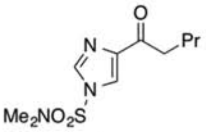
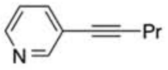
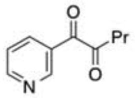
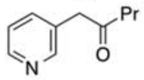
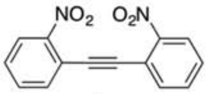
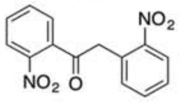
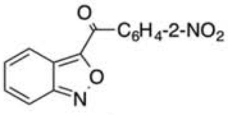
Table 1. Oxidation of Alkynes with Mercuric Nitrate Hydrate

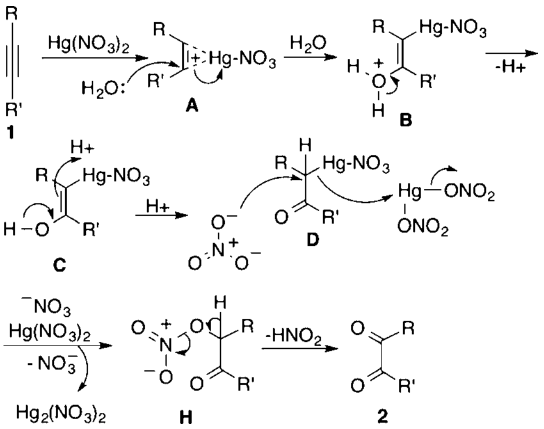


entry	Ar	R	time	product	byproduct	yield %
1	Ph	Ph	24 h	**2a**	none	90
2	Ph	Me	1 h	**2b**	none	78
3	3-FC_6H_4	Ph	2 h	**2c**	none	91
4	4-$CF_3C_6H_4$	Me	20 min	**2d**	none	47
5	4-$NH_2C_6H_4$	Bu	20 min	**2e**	none	79
6	4-$(NCC(Me)_2NH)C_6H_4$	Bu	20 min	**2f**	none	67
7	4-$MeOC_6H_4$	Ph	2 h	**2g**	none	76
8	4-MeC_6H_4	Ph	2 h	**2h**	none	69
9	2-ClC_6H_4	Pr	1 h	**2i**	none	57
10	3-FC_6H_4	Pr	1 h	**2j**	none	78
11	2-$(MeOOC)C_6H_4$	Ph	1 h	**2k**	none	66
12	4-HOC_6H_4	Ph	2 h	**2l**	none	81
13	4-HOC_6H_4	Pr	15 min	**2m**	none	64
14	4-ClC_6H_4	Pr	30 min	**2n**	none	82
15	4-$(AcO)C_6H_4$	Ph	2 h	**2o**	none	56
16	4-$(Bn_2N)C_6H_4$	Ph	2 h	**2p**	none	86
17	4-$(BnNH)C_6H_4$	Ph	2 h	**2q**	none	51
18	 **1r**		12 h	 **2r**	none	69
19	2-$(NO_2)C_6H_4$ **1s**	Ph	48 h (50 °C)	 **2s**	 **3s**	33/54
20	2-$(NO_2)C_6H_4$ **1t**	Pr	2 h	 **2t**	 **3t**	0/61%
21	 **1u**	Ph	1 h	 **2u**	 **3u**	69/20
22	 **1v**		20 min	 **2v**	 **3v**	49/38
23	 **1w**		1 h	 **3w**	 **3w'**	32/37

group **1d** gave the lowest yield among the successful substrates, perhaps due to lower electron density in the alkyne. The 1,4-di(propynyl)benzene **1r** afforded the bis(α-diketone) **2r** in good yield. A few substrates did not work well in this reaction, giving mixtures of products. Thus, the 2-nitrophenyl substrate **1s** gave the expected α-diketone **2s** in 33% yield along with the expected 3-benzoylanthranil **3s** in 54% yield. The analogous 2-nitrophenyl substrate with a propyl group on the end of the alkyne, **1t**, gave none of the α-diketone and only the anthranil **3t** in 61% yield. This cyclization of a 1-(2-nitrophenyl)alkynes such as **1s** and **1t** is well-known[8] and is usually carried out by treatment with either transition metals or Lewis acids. We also attempted the oxidation on two different heterocyclic alkyne substrates. Thus, the protected 4-pentynyl imidazole **1u** gave a relatively good yield of the desired α-diketone **2u** (69%) accompanied by the simple hydration product **3u** in 20% yield. The 3-pentynylpyridine **1v** likewise gave the desired α-diketone **2v** as the major product (49%) along with the opposite hydration product **3v** in 38% yield.[9] Finally the symmetrical (2-nitrophenyl)acetylene **1w** did not give any of the desired α-diketone product **2w** but rather the two byproducts, the simple hydration product **3w** in 32% yield and the anthranil **3w′** in 37% yield.[10]

We believe that the mechanism involves the steps shown in Scheme 3, namely attack of the alkyne **1** on the mercuric nitrate to give the cyclic mercuronium ion **A**, which is then attacked by water to give **B**, which loses a proton to give the α-mercurio enol **C**. Tautomerization would then give the α-mercurio ketone **D**. Up to this point, this is the same mechanism as for the simple hydration of the alkyne (as shown in Scheme 1). The key step is the attack of nitrate on the α-mercurio ketone **D**, with activation by the second equivalent of mercuric nitrate, to generate the α-nitrato ketone **H** and mercurous nitrate. The final step is the reductive elimination of nitrous acid from **H** to give the observed α-diketone product **2**.

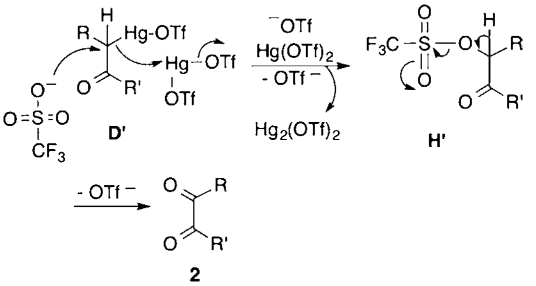
Scheme 3. Proposed Mechanism of Oxidation with Mercuric Nitrate



Perhaps the most unusual step in this proposed mechanism is the conversion of the α-mercurio ketone **D** to the α-nitrato ketone **H**, but this step has precedent in the literature since a similar conversion of 2-methoxy-1,2-diphenylethyl mercuric nitrate to the 2-methoxy-1,2-diphenylethyl nitrate is known.[11] There is also good precedent for the final step, since the conversion of α-nitrato ketones to α-diketones is well-known.[12]

This oxidation also proceeds, although less well, with 2 equiv of anhydrous mercuric triflate and 2 equiv of water in THF. We propose a very similar mechanism for the formation of the α-diketone **2** in this reaction (Scheme 4), namely the attack of triflate ion on the corresponding α-mercurio ketone **D′** activated by mercuric triflate to give the α-sulfonyloxy ketone **H′**. Elimination of trifluoromethanesulfinate from **H′** would then give the α-diketone **2**. This last step, the elimination of sulfinates to give ketones, is well precedented in the literature.[13]

Scheme 4. Proposed Mechanism of Oxidation with Mercuric Triflate



In summary, we have developed a new method for the oxidation of alkylarylalkynes and diarylalkynes **1** to give α-diketones **2** with mercuric salts. The reaction is limited to salts that can undergo facile subsequent elimination, namely nitrates and triflates. The use of this process in synthesis is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and proton and carbon NMR for all new compounds and those prepared by routes different from those in the literature. This material is free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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