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Practical Method for Transforming Alkynes into α-Diketones

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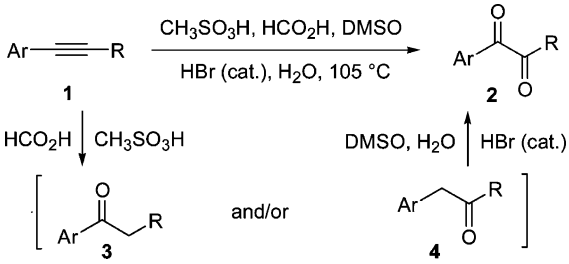
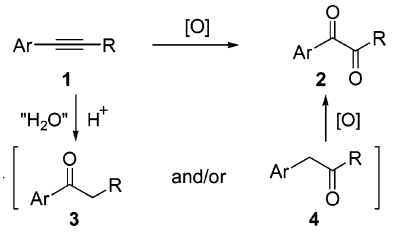


Oxidation of alkynes to α-dicarbonyl derivatives through a convenient one-pot procedure via a Brønsted acid-promoted "hydration" and a DMSO-based oxidation sequence has been achieved in high yields. The scope and limitations of the reaction have also been investigated.

α-Dicarbonyl derivatives are versatile building blocks capable of undergoing a variety of chemical transformations,[1] especially for the synthesis of biologically active heterocyclic compounds.[2] Several approaches[3] have been reported to prepare the α-dicarbonyl derivatives. The direct oxidation of properly substituted alkynes, which are easily accessible via Sonogashira coupling,[4] appears to be the most straightforward method to synthesize the α-dicarbonyl derivatives. However, the frequently used potassium permanganate oxidation[5] is neither environmentally benign nor operatively efficient, the DMSO-based oxidations[6] require high temperature (usually >150 °C) and are thus considered potentially hazardous, transition-metal-catalyzed oxidations[7] have their substrate limitations, and oxidation via ozonolysis[8] requires cryogenic reaction conditions. Obviously, as a result of these drawbacks and limitations of the existing methods, a practical and general method for oxidizing alkynes to α-dicarbonyl derivatives is highly desirable. Such a method should utilize mild reaction conditions and avoid the use of stoichiometric inorganic oxidants as well as toxic transition-metal catalysts.

SCHEME 1. Possible Stepwise Oxidation of Alkynes to α-Dicarbonyl Derivatives



Our approach is based on the consideration outlined in Scheme 1. We envisioned that the difficulty associated with the direct oxidation of an alkyne triple bond to the α-dicarbonyls can be circumvented by a stepwise approach, such as the possibility of first hydrating an alkyne **1** to the monoketone **3** and/or **4**, followed by oxidizing **3** and/or **4** into the dicarbonyl **2**.

In the literature, there are numerous reports of alkyne hydration under either acid[9] or transition-metal catalysis.[10] In our case, the most attractive result was reported by Shvo and Menashe.[11] They found that electron-rich alkynes **1** could be "hydrated" to form monoketones **3** and/or **4** by pure formic acid without any catalyst, while electron-poor alkynes needed transition-metal catalysis. These results indicated the role of formic acid serving as a formal and efficient "water donor" for alkyne hydrations. There are also numerous methods[12] to transform the monoketones **3** and/or **4** to the dicarbonyls **2**. We were particularly intrigued by the DMSO-based oxidations reported by Kornblum and co-workers[13] and further developed by Floyd and co-workers,[14] which appear to fit the criteria set forth for this method development effort and appear to be compatible with the alkyne hydration conditions.

(1) (a) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahadron Lett*. **1995**, *40*, 7305−7308 and references cited therein. (b) De Kimpe, N.; Stanoeva, E.; Boeykens, M. *Synthesis* **1994**, 427−431 and references cited therein.

(2) (a) Barta, T. E.; Stealey, M. A.; Collins, P. W.; Weier, R. M. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3443−3448. (b) Callahan, J. M.; Burgess, J. L.; Fornwald, J. A.; Gaster, L. M.; Harling, J. D.; Harrington, F. P.; Heer, J.; Kwon, C.; Lehr, R.; Mathur, A.; Olson, B. A.; Weinstock, J.; Laping, N. J. *J. Med. Chem.* **2002**, *45*, 999−1001. (c) McKenna, J. M.; Halley, F.; Souness, J. E.; McLay, I. M.; Pickett, S. D.; Collis, A. J.; Page, K.; Ahmed, I. *J. Med. Chem*. **2002**, *45*, 2173. (d) Singh, S. K.; Saibaba, V.; Ravikumar, V.; Rudrawar, S. V.; Daga, P.; Rao, C. S.; Akhila, V.; Hegde, P.; Rao, Y. K. *Bioorg. Med. Chem*. **2004**, *12*, 1881−1893.

(3) Katritzky, A. R.; Zhang, D.; Kirichenko, K. *J. Org. Chem*. **2005**, *70*, 3271−3274 and references therein.

(4) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, *8*, 627−630.

(5) (a) Srinvasan, N. S.; Lee, D. G. *J. Org. Chem*. **1979**, *44*, 1574. (b) Lee, D. G.; Chang, V. S.; Chandler, W. D. *J. Org. Chem*. **1985**, *50*, 4306.

(6) (a) Wolfe, S.; Pilgrim, W. R.; Garrad, T. F.; Chamberlain, P. *Can. J. Chem*. **1971**, *49*, 1099−1015. (b) Yusubov, M. S.; Filimonov, V. D.; Vasilyeva, V. P.; Chi, K. W. *Synthesis* **1995**, 1234−1236.

(7) (a) Zhu, Z. L.; Espenson, J. H. *J. Org. Chem*. **1995**, *60*, 7728−7732. (b) Yusubov, M. S.; Zholobova, G. A.; Vasilevsky, S. F.; Tretyakov, E. V.; Knight, D. W. *Tetrahedron* **2002**, *58*, 1607−1610 and references therein.

(8) Favino, T. F.; Fronza, G.; Fuganti, C.; Fuganti, D.; Grasselli, P.; Mele, A. *J. Org. Chem*. **1996**, *61*, 8975−8979.

(9) (a) Kozhevnikov, I. V. *Chem. Rev*. **1998**, *98*, 171. (b) Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* **2000**, *12*, 1777−1778.

(10) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563−4565 and references therein.

(11) (a) Menashe, N.; Shvo, Y. *J. Org. Chem*. **1991**, *56*, 2912−2914. (b) Menashe, N.; Shvo, Y. *J. Org. Chem*. **1993**, *58*, 7434−7439.

(12) (a) Rabjohn, N. *Org. React*. **1949**, *5*, 331. (b) Rabjohn, N. *Org. React*. **1976**, *24*, 261. (c) Wentzel, B. B.; Donners, M. P. J.; Alsters, P. L.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron* **2000**, *56*, 7797−7803. (d) Tatsugi, J.; Izawa, Y. *J. Chem. Res., Miniprint* **1988**, *11*, 2747−2763. (e) Bonadies, F.; Bonini, C. *Synth. Commun.* **1988**, *18*, 1573−1580.

(13) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.

(14) Floyd, M. B.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem*. **1985**, *50*, 5022−5027.

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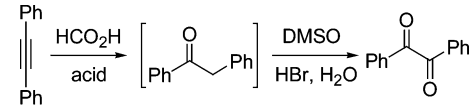
TABLE 1. Acid-Promoter Screen[a]



1a **3a** **2a**

entry	acid[b] (equiv)		time[c] (h)	yield of **2a**[d] (%)
1	CF_3SO_3H	0.50	10	84
2	$(CF_3SO_2)_2NH$	0.50	10	82
3	CH_3SO_3H	0.25	15	71
4	CH_3SO_3H	0.50	15	75
5	CH_3SO_3H	1.00	15	82
6	CH_3SO_3H	2.00	10	60
7	H_2SO_4	0.25	15	78
8	H_2SO_4	0.50	15	75
9	H_2SO_4	1.00	10	69
10	H_3PO_4	0.50	15	50
11	CF_3CO_2H	0.50	15	63

[a] All reactions were run with different acid promoters under the same conditions: 1.0 mmol of diphenylacetylene, 1.0 mL of 88% formic acid, 5.0 mmol of DMSO, and 0.10 mmol of 48% HBr. The reactions were heated at ~105 °C using a short path to distill off any volatiles. [b] Acid equivalent to diphenylacetylene. [c] Actual time, not the optimal time. [d] Isolated yield.

Our investigation began with a stepwise sequence by first screening commonly used strong Brønsted acids (see Table 1) in either a catalytic or a stoichimetric amount for the "hydration" of diphenylacetylene **1a** to form 1,2-diphenylethanone **3a**, using commercially available 88% formic acid as both "water donor" and solvent. After the "hydration" of diphenylacetylene **1a** to form 1,2-diphenylethanone **3a** was completed, DMSO and a catalytic amount of HBr were added to oxidize **3a** to form the desired dibenzyl **2a**.

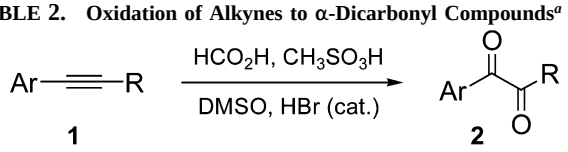
To our delight, a variety of strong Brønsted acids promoted the "hydration" of diphenylacetylene **1a** to form 1,2-diphenylethanone **3a** in 88% formic acid, and the ensuing hydrobromic acid-catalyzed DMSO oxidation afforded the desired dicarbonyl **2a** in high yields.

More conveniently, we found that even though the reaction is stepwise in nature, all the reagents could be added at the same time at the beginning. Typically, heating a mixture of diphenylacetylene **1a** (1.0 equiv), 88% formic acid (~5.0−10 vol), DMSO (~5.0−10 equiv), aqueous 48% HBr (~0.10−0.15 equiv), and a variety of strong Brønsted acids (0.25−1.0 equiv) at about 105 °C using a short path to distill off the volatiles, which contains the reaction-generated dimethyl sulfide and some solvent, afforded the desired dicarbonyl **2a** in high yields.[15] The best results (Table 1) were obtained from reactions using trifluoromethanesulfonic acid (entry 1), trifluoromethane sulfonimide (entry 2), methanesulfonic acid (entry 5), and sulfuric acid (entry 7) as promoters. When the cost, the effectiveness, and the operational convenience of these acids are considered, methanesulfonic acid appeared to be the Brønsted acid promoter choice.

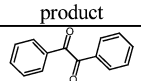
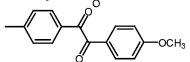
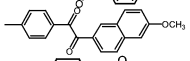
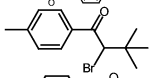
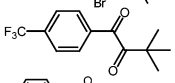
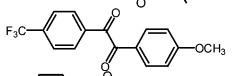
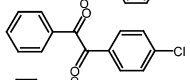
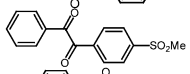
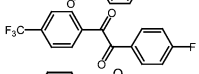
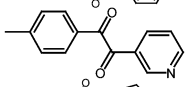
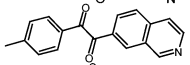
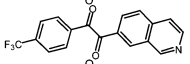
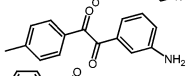
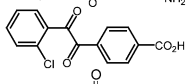
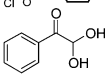
Encouraged by the diphenylacetylene oxidation results, we then attempted to oxidize alkynes bearing a variety of substituents with the general structure **1** to the dicarbonyls **2** (Table 2). Alkynes with electron-rich (entries a−c) or electron-poor (entries f−i) diaryl substituents, heteroaryls (entries j−l), an aryl with an unprotected free amine (entry m), or a free acid (entry n) all underwent a smooth transformation to form the corresponding α-dicarbonyl derivatives in good to excellent yields. An aryl terminal alkyne (entry o) formed the corresponding glyoxal derivative. It is surprising to notice the different reactivities of the substrates with tertial alkyl substituents (entries d and e). The reaction of **1d** stopped at the α-bromoketone stage as the isolated product (entry d), while the corresponding trifluoromethyl analogue, **1e**, gave the α-dione product, **2e**, with good yield (entry e). We assume that the relative electron-rich property of **1d** contributed to the lower reactivity of the intermediate α-bromoketone. α-Unbranched alkyl-substituted alkynes are not valid substrates for this oxidation reaction as a result of the continuous α-oxidation to form multiple carbonyl derivatives, which are not stable under the reaction conditions.

We briefly studied the alkyne oxidation reaction mechanism by detecting the off gas with headspace GC-MS and the reaction intermediates with liquid chromatography mass spectrometry (LC-MS). We found that CO and Me_2S evolved from the

TABLE 2. Oxidation of Alkynes to α-Dicarbonyl Compounds[a]



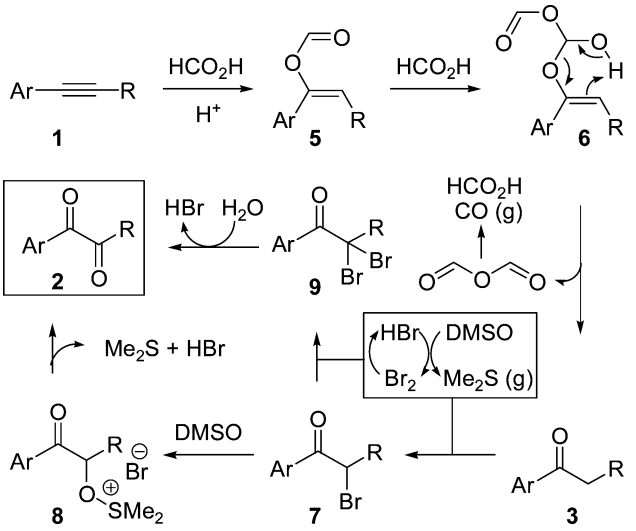
1 **2**

entry	product	time (h)	yield (%)[b]
a		10	82
b		15	56
c		15	66
d		50	75[c]
e		15	79
f		15	57
g		15	80
h		15	66
i		15	93
j		15	76
k		15	83
l		15	53
m		15	59
n		15	75
o		20	48

[a] All reactions were under the same conditions: 2.0 mmol of the substituted acetylene, 2.0 mL of 88% formic acid, 10.0 mmol of DMSO, and 0.20 mmol of 48% HBr. The reactions were heated at ~105 °C until complete conversion. [b] Isolated yields. [c] Stoichiometric amount of HBr was used.

(15) The efficient removal of the generated dimethyl sulfide by distillation from the reaction system is crucial for reaction completion. See Supporting Information.

SCHEME 2. Possible Reaction Pathway



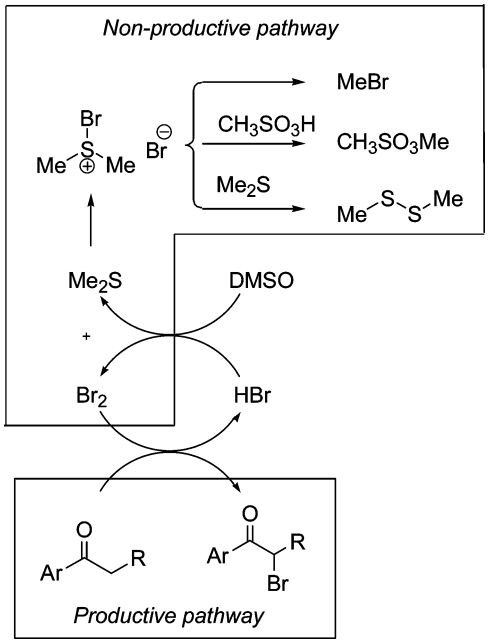
reaction media, and the amount of CO and Me_2S evolution is proportional to the conversion. We also detected reaction intermediates, such as the monoketone **3** and the bromoketone **7**, by LC-MS (Scheme 2). The results indicated the reaction does indeed proceed through the sequence of a formic acid addition to an alkyne to form the vinyl formate **5**, which decomposes to form the monoketone **3** by liberating CO, as reported by Shvo and Menashe;[11] the ensuing DMSO-based oxidation of **3** using HBr/Br_2 as a catalyst affords the expected dicarbonyl **2** by liberating Me_2S gas via either the Kornblum et al.[13] alkoxydimethyl sulfonium salt **8** or the Floyd et al.[14] α-dibromoketone **9**. It is also plausible that enol formate **5** undergoes bromination directly to afford the bromoketone **7**, which would readily undergo the DMSO oxidation.

We also found bromomethane and dimethyl disulfide in the off gas and methyl methanesulfonate in the reaction mixture, and the higher the concentrations of these byproducts, the lower the dione product yields. A rationale for this phenomenon is illustrated in Scheme 3. If too much dimethyl sulfide remains in the reaction system, it will deplete both the reaction catalyst bromine and the reaction reagent DMSO by reacting with the in situ generated bromine catalyst to form dimethyl bromosulfonium bromide[16] first, which is then converted to the byproducts, bromomethane, methyl methane sufonate, and dimethyl disulfide, through a nonproductive pathway. It is clear that efficient removal of dimethyl sulfide out of the reaction system is important for achieving fast, complete, and high yielding reactions.

In conclusion, we have developed a practical and convenient method for oxidizing aryl alkynes to α-dicarbonyl derivatives using inexpensive 88% formic acid as both the reagent and the solvent, hydrobromic acid as the catalyst, and DMSO as the stoichiometric oxidant. The new procedure is efficient and high-

(16) Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, *60*, 2268−2273.

SCHEME 3. Dimethyl Sulfide Involved Nonproductive Pathway



yielding and also has circumvented the use of stoichiometric inorganic oxidants and toxic transition-metal catalysts.

Experimental Section

General Procedure for the Oxidation of Alkynes to α-Diketones. Typical experimental procedures for the oxidation of alkynes to α-diketones, as exemplified by the formation of 1-(4-fluorophenyl)-2-(4-trifluoromethylphenyl)-ethane-1,2-dione (**2i**) are as follows: (4-Fluorophenyl)-ethynyl-4-trifluoromethylbenzene (530 mg, 2.0 mmol) was mixed with 2.0 mL of 88% formic acid, 2.0 mmol of methanesulfonic acid, 12.0 mmol of DMSO, and 0.20 mmol of 48% HBr in a 10 mL flask. The reactions were heated to ∼105−110 °C using a short path to distill off the volatiles (mostly dimethyl sulfide generated from the reaction and some solvents) for 15 h until complete conversion. The reaction was cooled to room temperature. The crude product was extracted into ethyl acetate after an aqueous workup. Flash chromatography on silica gel using 15% ethyl acetate in hexanes as the eluent afforded the title compound (552 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 2H), 7.80 (d, J = 7.5 Hz, 2H), 8.04 (m, 2H), 8.10 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 116.5 (d), 126.1, 130.3, 132.8, 132.9, 135.5, 166.0, 168.0, 191.5, 192.5. HRMS (M + H)$^+$ calcd for $C_{15}H_9F_4O_2$, 297.0539; found, 297.0547. IR (KBr, cm^{-1}): 1670, 1664, 1598.

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

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