DDQ-Promoted Functionalization of Phenylalkylacetylenes at the Propargylic Carbon

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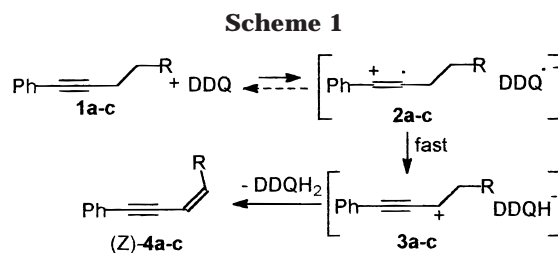
The oxidation of activated carbon−hydrogen σ bonds represents a useful protocol for the functionalization of hydrocarbons linked to activating π systems, particularly aryl and alkenyl groups.[1] In contrast, the oxidation of alkynes has received much less attention as a method for functionalizing the propargylic carbon.[2] The hitherto known methods are mainly confined to the oxidative transformation of the CC triple bond to diketones or carboxylic acids.[1a]

Our interest in the chemistry of the CC triple bond[3] prompted us to investigate the oxidative functionalization of alkylacetylenes at the propargylic carbon atom as a possible route to conjugated enynes. Conjugated enynes are useful intermediates as building blocks for the synthesis of natural products[4] and are generally obtained by alkyne/alkene coupling.[4,5]

Herein, we report results obtained from DDQ-promoted oxidation of phenylalkylacetylenes. DDQ (2,3-dicyano-5,6-dichloro-1,4-benzoquinone) is a well-known dehydrogenating oxidant that has been used for the aromatization of dihydrobenzene derivatives,[6] dehydrogenation of steroids and lactones,[7] and the oxidation of vinyl sulfides.[8]

Results and Discussion

In a typical experiment, a fluorobenzene solution (0.1 M) of phenylpentyne **1a** was refluxed for 2 h in the presence of an excess of DDQ (1.5 molar equiv). The resulting mixture was filtered to separate a black solid, consisting mainly of hydroquinone (DDQH$_2$). GC−MS and ^{1}H NMR analysis of the filtrate showed the absence

(1) Oxidations of activated C−H bonds have been extensively reviewed. See: (a) Hudlicky M. *Oxidations in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, DC, 1990. (b) Bulman Page, P. C.; McCarthy, T. J. Oxidation Adjacent to C=C Bonds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K., 1991; Vol. 7, Chapter 2.1. For electrochemical oxidations of hydrocarbons, see: Lund, H.; Baizer, M. M. *Organic Electrochemistry*, 3rd ed.; Marcel Dekker: New York, 1991.

(2) Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4202.

(3) Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1997**, *62*, 5600. Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1998**, *63*, 537 and references therein.
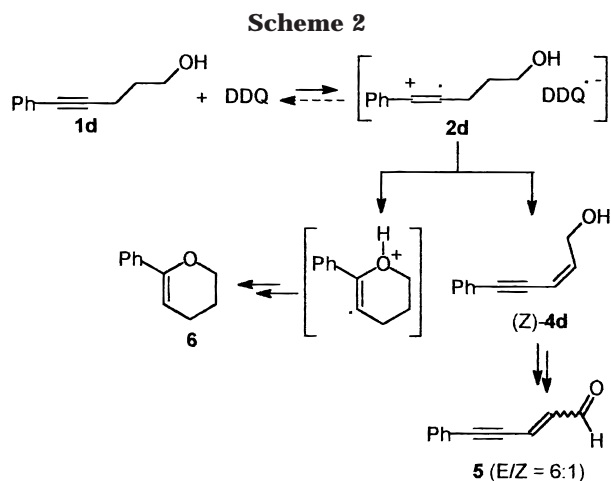
(4) A class of insect pheromones belongs to the conjugated enynes family; see: Mori, K. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: New York, 1992; Vol. 9.

(5) Normant, J. F. *Mod. Synth. Methods* **1983**, *3*, 139. Luh, T.-Y.; Wong, K.-T. *Synthesis* **1993**, 349. Sonogashira, K. Coupling Reactions between sp^2 and sp Carbon Centers. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K., 1991; Vol. 3, Chapter 2.4.2. Clough, J. M. The Ramberg-Backlund Rearrangement. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K., 1991; Vol. 3, Chapter 3.8.9.

(6) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. Foster, R.; Foreman, M. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; John Wiley and Sons: New York, 1974; Part 1, pp 257−423.

(7) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

(8) Capella, L.; Montevecchi, P. C.; Nanni, D. *J. Org. Chem.* **1994**, *59*, 7379.

Scheme 1

a: R = Me; b: R = Et; c: R = Hex

of starting alkyne **1a** and the exclusive presence of the enyne **4a** as a 95:5 *Z/E* mixture. The filtrate and the solid were dissolved in acetone and chromatographed on a silica gel column to give the enyne **4a** (48%) and hydroquinone (DDQH$_2$). Elution with methanol gave unidentifiable black solid material. Performing the reaction at 120 °C in a sealed tube gave identical results, while the use of boiling acetonitrile (2 h) similarly gave (*Z*)-**4a** in 50% yield (based on reacted **1a**), but alkyne **1a** was recovered in 70% yield. Similar results were obtained with phenylhexyne (**1b**) and phenyldecyne (**1c**), which reacted with 1.5 equiv of DDQ in boiling fluorobenzene to give the corresponding (*Z*)-enynes **4b,c** in a stereoselective mode (45% and 27% yields, respectively; 100% conversion) (Scheme 1). In contrast, neither 1-decyne or 5-decyne reacted under the general conditions suggesting that terminal acetylenes and dialkylacetylenes are unreactive to DDQ in refluxing fluorobenzene.

The effect of the 1-phenyl substituent in promoting the oxidation of acetylenes **1a**−**c** is likely related to the lower oxidation potential of the CC triple bond of arylalkylacetylenes as compared with dialkylacetylenes. Cyclic voltammetry experiments (see the Experimental Section) showed an oxidation anodic peak at +2.1 V for alkyne **1a**, while 5-decyne did not undergo electrochemical oxidation within 2.5 V.

From a mechanistic standpoint, the first step of the reaction leading to enynes **4** should be a single-electron-transfer (SET) process between the alkyne triple bond and DDQ generating the radical ion pair **2**. The latter should give the ion pair **3** through hydrogen transfer from the alkyne radical cation to DDQ$^{\bullet-}$. A proton transfer from **3** to DDQH$^-$ will then generate the enyne **4** and DDQH$_2$ (Scheme 1). The key step of the entire process is the SET reaction. The reduction potential for DDQ was reported to be $E° = +0.51$ V in acetonitrile.[9] If the SET process was an equilibrium, the resultant equilibrium constant ($K \approx 10^{-22}$ at 84 °C) is far too low to take into account the observed completion of the reaction within 2 h. Evidently, the driving force for the SET reaction is the subsequent hydrogen transfer to DDQ$^{\bullet-}$ that should be fast enough to make the electron transfer irreversible. We might infer that these two reactions could occur in a quasiconcerted mechanism; that is, the radical ion pair **3** is a transition state and not an intermediate.

Compelling evidence for the role played by the presence of propargylic hydrogen atoms in the oxidation of the CC triple bond was obtained by reacting diphenylacetylene and DDQ in boiling fluorobenzene. We observed the immediate formation of a deep green color at room

Scheme 2

temperature that is likely a charge-transfer complex, but alkyne and DDQ were recovered unchanged after 2 h.[10]

However, some evidence (although nonconclusive) that the radical ion pair **2** might be an actual intermediate arose from results obtained by reacting 5-phenylpent-4-yn-1-ol (**1d**) with DDQ (1.2 molar equiv). In fact, the ^{1}H NMR spectrum of the reaction mixture showed the presence of the (Z)-enyne **4d** and the enynaldehyde **5** in a ca. 1:1 ratio together with comparable amounts of an unidentified product. The unknown showed multiplets at δ 2.4 and 4.1 (this signal collapsed to a two-proton AB system upon irradiation at δ 2.4) and a triplet due to a vinylic proton at δ 6.50 (this signal collapsed to a singlet upon irradiation at δ 2.4) in addition to aromatic protons. We suspected that this product was 1-phenyldihydropyran (**6**), which might arise through electrophilic attack of the radical cation **2d** at the oxygen atom (Scheme 2). Unfortunately, the possible pyran **6** was not isolated by subsequent column chromatography, which only separated the (Z)-enyne (Z)-**4d** (12%) and the enynaldehyde **5** (16%, 6:1 *E/Z* mixture) (Scheme 2). The aldehyde **5** was formed by subsequent oxidation of the enyne **4d** at the allylic position, as evidenced by independent experiments.[11]

Formation of enynes **4a**−**c** from phenylalkylacetylenes **1a**−**c** is of particular interest due to the high *Z* stereoselectivity. Noteworthy is the observation that the *Z/E* ratio changed from 95:5 to 50:50 on standing the enyne **4a** at room temperature for 2 days in CDCl$_3$ solution, indicating that the stereoselectivity is not due to thermodynamic factors. The reason for predominant formation of the (Z)-enyne remains an open question. Possibly, the (E)-enyne might be selectively removed by DDQ to give tarry, unidentifiable products. This suggestion comes from our previous findings that DDQ, probably owing to steric factors, selectively oxidized vinyl sulfides only in the *E* configuration.[8] Supporting evidence arose from results obtained by carrying out the reaction of **1a**

with a 2-fold excess of DDQ. Under these conditions, no traces of the (E)-enyne (E)-**4a** were detected by ^{1}H NMR analysis of the reaction mixture, while the (Z)-enyne (Z)-**4a** was still isolated in 50% yield. The oxidation appears to proceed nonstereoselectively, generating both (E)- and (Z)-enynes from which the (E)-enyne is selectively removed by further oxidation with DDQ, as shown by results obtained from reactions of **1a** carried out at different DDQ concentrations (0.25, 0.5, and 1.0 molar equiv). Under these conditions, we found a ca. 20%, 40%, and 80% conversion yield, respectively, but in all cases, the enyne **4a** was formed in ca. 45−50% yield (on the basis of reacted alkyne) as a 93:7 *Z/E* mixture. Only trace amounts of other (unidentified) products could be revealed in the ^{1}H NMR spectrum of the crude mixture.

The 1-phenyl substituent was also necessary for the DDQ oxidation of propargylic alcohols. In fact, 1-phenylpropynol (**7**) gave, under the usual conditions, phenylpropynal **8** in 52% yield as the only identifiable product, together with DDQH$_2$. In contrast, 1-octyn-3-ol, hex-5-yn-1-ol, and oct-3-yn-1-ol did not undergo any DDQ-oxidation to the corresponding carbonyl compounds.
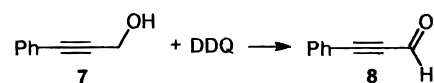
This study has been extended to 1-sulfanyl- and 1-silyl-substituted alkylacetylenes to provide a route to functionalized enynes that could be useful building blocks in organic synthesis. 1-(Phenylthio)hex-1-yne (**1e**) was reacted with DDQ (1.5 molar equiv) under the usual reaction conditions and at room temperature for 7 h to give the corresponding (Z)-enyne (Z)-**4e** in 32% and 48% yield, respectively, whereas 1-(trimethylsilyl)dec-1-yne did not react at all. The marked reactivity of **1e**, and the complete nonreactivity of the 1-silyl derivative, were not surprising in the light of the postulated requirement for the α-substituent to stabilize the positively charged intermediate by delocalization.
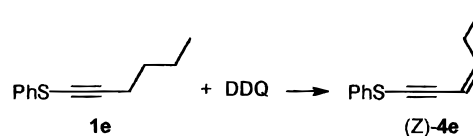
In conclusion, we have reported that the DDQ oxidation of phenylalkylacetylenes carried out in boiling fluorobenzene provides a potentially useful method to obtain synthetically interesting conjugated (Z)-enynes in a highly stereoselective mode. The reaction fails with 1-decyne or 5-decyne, likely as a consequence of the higher oxidation potential of dialkylacetylenes and terminal alkynes. The importance of an α-substituent capable of stabilizing the proposed positively charged intermediate is further seen in the DDQ oxidation of 1-(phenylthio)hex-1-yne that occurs even at room temperature.

Experimental Section

Phenylpentyne (**1a**), 1-octyn-3-ol (**9**), hex-5-yn-1-ol, oct-3-yn-1-ol, and oct-1-yn-3-ol are commercially available. Phenylalkylacetylenes **1b**,[12] **1c**,[12] **1d** [^{1}H NMR δ 1.85 (3H; 2H multiplet superimposed to a 1H broad singlet), 2.5 (2H, t, *J* = 7.0 Hz),

(9) Peover, M. E. *J. Chem. Soc.* **1962**, 4540.

(10) It appears that the alkyne radical cation is not willing to be trapped at alkynic carbon by the DDQ$^{\bullet-}$ counterion. Instead, covalent complexes between quinones and diarylacetylenes are formed under photochemical conditions in the solid state; see: Bosch, E.; Hubig, S. M.; Lindeman, S. V.; Kochi, J. K. *J. Org. Chem.* **1998**, *63*, 592.

(11) We also found that, under our conditions, allylic alcohols such as 1-octen-3-ol can be oxidized by DDQ to the corresponding aldehydes in good yields. The DDQ oxidation of allylic alcohols has been already reported in a few cases (see: Braude, E. A.; Linstead, R. P.; Wooldridge, K. R. *J. Chem. Soc.* **1956**, 3070. Burn, D.; Petrow, V.; Weston, G. O. *Tetrahedron Lett.* **1960**, 14).

(12) Ward, H. R. *J. Am. Chem. Soc.* **1967**, *89*, 5517.

3.80 (2H, t, $J = 6.2$ Hz), 7.2–7.5 (5H, m); MS m/z (rel inten) 160 (M^+, 40) 159 (20), 141 (80), 128 (60), 115 (100), 104 (80); HRMS calcd for $C_{11}H_{12}O$ 160.0888; found 160.0885], and **7**[13] were obtained in ca. 80–90% yield through tetrakis(triphenylphosphine)palladium-catalyzed coupling of iodobenzene with the corresponding terminal alkyne, according to a procedure reported in the literature.[14]

1-(Phenylthio)pent-1-yne (**1e**)[15] and 1-(trimethylsilyl)dec-1-yne [^{1}H NMR δ 0.1 (9H, s), 0.85 (3H, t, $J = 7$ Hz), 1.2–1.5 (12H, m), 2.2 (2H, t, $J = 7.0$ Hz); MS m/z (rel inten.) 210 (M^+, 0.1), 195 (60), 73 (100), 59 (80)] were obtained in 70–80% yield as follows. To a THF solution (80 mL) of the appropriate alkyne (1-hexyne or 1-decyne) (20 mml) was added a 1.6 M solution of butyllithium in *n*-pentane (12.5 mL) at 0–5 °C. The solution was stirred for 15 min, and then diphenyl disulfide (20 mmol) or trimethylsilyl chloride (20 mmol) in THF (10 mL) was added dropwise at 0 °C. The resulting mixture was refluxed for 2 h and then cooled and filtered. The filtrate was evaporated and the residue chromatographed on silica gel column.

^{1}H NMR spectra were recorded at 200 (or 300) MHz with Me$_4$-Si as an internal standard. Mass spectra (MS and HRMS) were recorded using electron-impact ionization.

Reaction of Alkynes 1a–e, 7, and 9 with DDQ. General Procedure. A solution of the appropriate alkyne **1a–e**, or **7** (3 mmol) and DDQ (1.0 g, 4.5 mmol; 0.8 g in the case of **1d**) in fluorobenzene (30 mL) was refluxed for 2 h. The reaction mixture was cooled and the black solid filtered off. The filtrate was evaporated and the residue analyzed by GC–MS and then chromatographed on a silica gel column by elution with petroleum ether (bp 40–60 °C), unless otherwise stated. The following reaction products were obtained as oily products:

From 1a. 1-Phenylpent-3-en-1-yne (**4a**) (48%; 95:5 Z/E mixture): ^{1}H NMR δ [*Z* isomer] 1.95 (3H, dd, $J_1 = 7.0$ Hz, $J_2 = 1.7$ Hz), 5.70 (1H, dq, $J_d = 10$ Hz, $J_q = 1.7$ Hz), 6.0 (1H, dq, $J_d = 10$ Hz, $J_q = 7.0$ Hz), 7.1–7.4 (5H, m); δ [*E* isomer] 1.85 (3H, dd, $J_1 = 7.0$ Hz, $J_2 = 2.0$ Hz), 5.72 (1H, dq, $J_d = 15$ Hz, $J_q = 2.0$ Hz), 6.25 (1H, dq, $J_d = 15$ Hz, $J_q = 7.0$ Hz), 7.1–7.4 (5H, m); MS m/z (rel inten) 142 (M^+, 50), 141 (100), 115 (100); HRMS calcd for $C_{11}H_{10}$ 142.0782, found 142.0784. In a repeated experiment, the filtrate and the black solid were collected and chromatographed to give enyne **4a**. Elution with diethyl ether gave hydroquinone (DDQH$_2$; yield not determined). Further elution with methanol gave black tarry material.

From 1b. (*Z*)-6-Phenylhex-3-en-1-yne ((*Z*)-**4b**) (45%): ^{1}H NMR δ 1.05 (3H, t, $J = 7$ Hz), 2.40 (2H, d quintuplet, $J_q = 7.0$ Hz, $J_d = 2$ Hz), 5.65 (1H, dt, $J_d = 10$ Hz, $J_q = 2$ Hz), 5.97 (1H, dt, $J_d = 10$ Hz, $J_t = 7.0$ Hz), 7.1–7.4 (5H, m); MS m/z (rel inten) 156 (M^+, 80), 155 (40), 141 (80), 115 (100); HRMS calcd for $C_{12}H_{12}$ 156.0939, found 156.0936.

From 1c. (*Z*)-1-Phenyldec-3-en-1-yne ((*Z*)-**4c**) (27%): ^{1}H NMR δ 0.85 (3H, t, 7.5 Hz); 1.2–1.6 (10H, m), 2.35 (2H, dq, $J_q = 7.5$ Hz, $J_d = 1.4$ Hz), 5.65 (1H, B part of an ABX$_2$ system, $J_{AB} = 10.5$ Hz, $J_{AX} = 1.4$ Hz), 5.95 (1H, A part of an ABX$_2$ system, J_{AB}

= 10.5 Hz, $J_{AX} = 7.5$ Hz), 7.2–7.6 (5H, m); MS m/z (rel inten) 212 (M^+, 80), 155 (700), 141 (80), 128 (90), 115 (100); HRMS calcd for $C_{16}H_{20}$ 212.1565, found 212.1568.

From 1d. Gradual elution with petroleum ether/diethyl ether mixtures gave (*Z*)-5-Phenylpent-2-en-4-yn-1-ol ((*Z*)- **4d**) (12%, based on reacted **1d**) ^{1}H NMR δ 1.9 (OH, broad signal), 4.50 (2H, dd, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz), 5.8 (1H, dt, $J_1 = 10.5$ Hz, $J_2 = 1.5$ Hz), 6.15 (1H, dt, $J_1 = 10.5$ Hz, $J_2 = 6.5$), 7.2–7.5 (5H, m) Hz); MS m/z (rel inten) 158 (M^+, 20), 157 (25), 129 (100), 128 (90), 155 (100); HRMS calcd for $C_{11}H_{10}O$ 158.0732, found 158.0734], 5-phenylpent-2-en-4-yn-1-al (**5**) (6:1 E/Z mixture) (16%, based on reacted **1d**) [^{1}H NMR δ (*E* isomer) 6.45 (1H, B part of an ABX system, $J_{AB} = 15.5$ Hz, $J_{AX} = 7.7$ Hz), 6.75 (1H, A part of an AB system, $J_{AB} = 15.5$ Hz), 7.1–7.5 (5H, m), 9.55 (1H, d, $J = 7.7$ Hz); δ (*Z* isomer) 6.25 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 8.5$ Hz), 6.80 (1H, d, $J = 10.5$ Hz), 7.1–7.5 (5H, m), 10.20 (1H, d, $J = 8.5$ Hz); MS m/z (rel inten) 156 (M^+, 100), 128 (80), 127 (60), 102 (100); HRMS calcd for $C_{11}H_8O$ 156.0575, found 156.0578], and starting alkyne **1d** (25%). The ^{1}H NMR spectrum of the reaction mixture showed, in addition to compounds **1d**, **4d**, and **5**, signals at δ 2.4 (m), 4.1 (2H, m; collapsing to AB system, $J_{AB} = 10.6$ Hz, inner line separation = 11 Hz, upon irradiation at δ 2.4), 6.50 (1H, t, $J = 6.0$ Hz; collapsing to singlet upon irradiation at δ 2.4), and 7.1–7.5 (m) ascribable to the dihydropyran **6**. Products **4d**, **5**, and **6** were found to be in a ca. 1:1:1 ratio.

From 7. Phenylpropynal **8** exhibited spectral properties identical to those reported[16] (52%).

From 1e. (*Z*)-1-(Phenylthio)hex-3-en-1-yne ((*Z*)-**4e**) (32%): ^{1}H NMR δ 1.05 (3H, t, $J = 7.5$ Hz), 2.35 (2H, d quintuplet, $J_q = 7.5$ Hz, $J_d = 1.5$ Hz), 5.60 (1H, dt, $J_d = 11$ Hz, $J_q = 1.5$ Hz), 5.95 (1H, dt, $J_d = 11$ Hz, $J_t = 7.5$ Hz), 7.15–7.5 (5H, m); MS m/z (rel inten) 188 (M^+, 80), 173 (70), 77 (100); HRMS calcd for $C_{12}H_{12}S$ 188.0660, found 188.0663. This reaction, repeated by stirring **1e** and DDQ at room temperature for 6–7 h, gave the (*Z*)-enyne (*Z*)-**4e** in 48% yield.

Electrochemical Experiments. Cyclic voltammetry experiments were carried out at 25 °C in acetonitrile/0.1 M LiClO$_4$. CV curves, recorded on Pt electrode vs saturated calomel electrode (SCE), showed an irreversible oxidation for 1-phenylpentyne **1a**, with an anodic peak at 2.1 V. No anodic peak was observed within 2.5 V for dec-5-yne.

Supporting Information Available: ^{1}H NMR spectra for all new compounds (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(14) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(15) Casson, S.; Kocienski, P.; Reid, G.; Smith, N.; Street, J. M.; Webster, M. *Synthesis* **1994**, 1301.

(16) Noro, M.; Masuda, T.; Ichimura, A. S.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1994**, *116*, 6179.