Oxidative Rearrangement of Tertiary Propargylic Alcohols

Arantxa Rodríguez,* Wesley J. Moran*

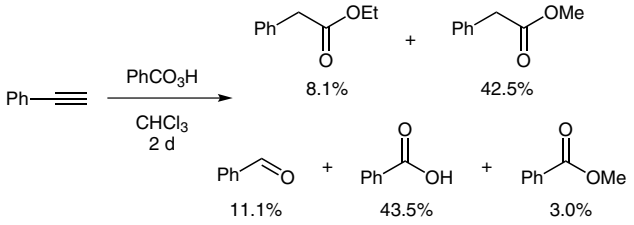
Department of Chemical & Biological Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK
Fax +44(1484)472182; E-mail: a.r.menendez@hud.ac.uk; E-mail: w.j.moran@hud.ac.uk

Received: 09.10.2012; Accepted after revision: 07.11.2012

Abstract: An oxidative rearrangement of tertiary alcohols mediated by *m*-CPBA is described that generates tetrasubstituted alkenes with a carboxylic acid substituent. The mechanism of the reaction is proposed to proceed through epoxidation of the alkyne to form an oxirene that undergoes a 1,2-aryl shift.

Key words: oxidation, rearrangement, propargylic alcohols, carboxylic acids, peroxy acid

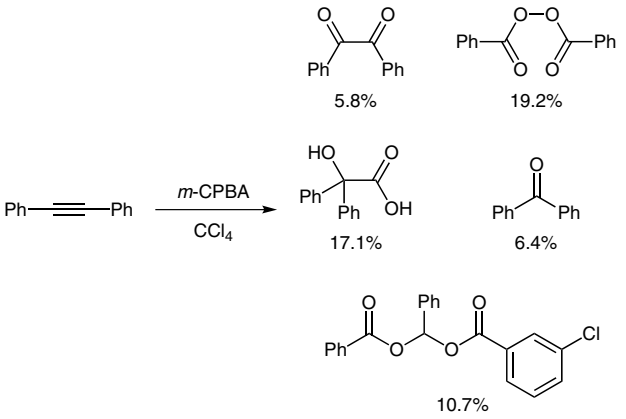
The oxidation of acetylenes with peroxy acids is capricious and can lead to the formation of a variety of products resulting from either oxidation, rearrangement, or addition depending on the reaction conditions used. In addition, only low yields of products have been reported in the scant number of examples on this topic. McDonald and Schwab reported that phenylacetylene was oxidised to five different compounds by perbenzoic acid: ethyl phenylacetate, methyl phenylacetate, benzaldehyde, benzoic acid, and methyl benzoate (Scheme 1).[1] The overall yield reported was greater than 100%, as the benzoic acid could also have come from reduction of the perbenzoic acid.



Scheme 1 McDonald and Schwab's oxidation reaction

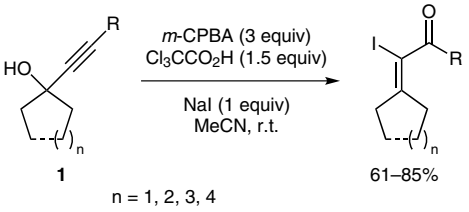
Stille and Whitehurst reported the oxidation of diphenylacetylene by perbenzoic acid and *m*-CBPA and obtained a mixture of products in both cases including benzil and benzoic peroxyanhydride with ratios which were found to be solvent dependent (Scheme 2).[2] The mechanism for the formation of these products was proposed to proceed through epoxidation of the alkyne followed by either ring opening or rearrangement to the ketene and subsequent addition or elimination processes.[3]

As part of a wider programme concerned with the reactivity of polyvalent iodine species, we became interested in the rearrangement of tertiary propargyl alcohols. Tertiary propargyl alcohols are useful synthetic intermediates that



Scheme 2 Stille and Whitehurst's oxidation reaction

have found widespread use in organic synthesis.[4] In particular, the rearrangement of these compounds has garnered significant attention.[5,6] During these studies we discovered a hypoiodite-induced rearrangement to α-iodoenones (Scheme 3)[7] as well as the reaction detailed herein.



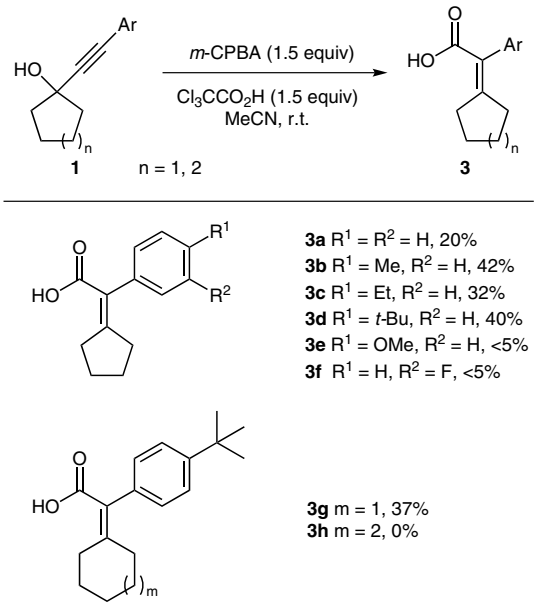
Scheme 3 Our group's hypoiodite-initiated rearrangement reaction

With the aim of extending our work utilising in situ generated iodine(III) species, we aimed to effect an oxidative rearrangement of propargyl alcohols **1** into diketones **2** through a semipinacol-type process. Accordingly, **1a** was treated with 20 mol% of iodobenzene, 1.5 equivalents of *m*-CPBA, and 1.5 equivalents of 4-toluenesulfonic acid monohydrate in acetonitrile at room temperature (Table 1).[8] However, instead of the anticipated oxidative rearrangement, elimination of water occurred to generate enyne **4** (Table 1, entry 1). Replacement of the strong acid with acetic acid led to no conversion whatsoever (Table 1, entry 2). However, treatment with trifluoroacetic acid also led to formation of enyne **4** (Table 1, entry 3). At this point, it was decided that an acid with a pK_a in between that of trifluoroacetic acid and acetic acid was necessary. Accordingly, trichloroacetic acid was tested, and a new product was formed (Table 1, entry 4). Analysis suggested

SYNLETT 2013, 24, 0102–0104
Advanced online publication: 04.12.2012
DOI: 10.1055/s-0032-1317711; Art ID: ST-2012-D0870-L

that this was not the anticipated product **2a** but that an alternative oxidative rearrangement had taken place to generate the enoic acid **3a**. This rearrangement is completely unprecedented for this substrate and involves a 1,2-aryl migration instead of the anticipated 1,2-alkyl migration. Only a low yield of **3a** was obtained, however the remainder of the mass balance was unreacted starting material. Attempts to improve the conversion, and hence the yield of the product, were unsuccessful. Using either 2- or 4-iodoanisole as the catalyst led to complete reaction inhibition (Table 1, entries 5 and 6), whereas 2-iodonitrobenzene led to complete conversion into enyne **4** (Table 1, entry 7). During these studies it became evident that iodobenzene was not required and that the reaction was mediated by *m*-CPBA and not a hypervalent iodine species (Table 1, entry 8). Changing the solvent from acetonitrile to dichloromethane, TFE, or nitromethane afforded the dehydrated product **4** whilst methanol gave a mixture of unidentifiable compounds. Using Oxone® instead of *m*-CPBA led to complete conversion into enyne **4**. Epoxidation of enyne **4** was not observed in any reactions.

The rearrangement of a few derivatives with these conditions was investigated in turn (Scheme 4).[9] With a 4-methyl substituent, substrate **1b** rearranged to provide 42% yield of isolated product **3b**. With a 4-ethyl group, 32% yield of **3c** was obtained and with a 4-*tert*-butyl group 40% yield of **3d** was obtained. Substrates **1e** and **1f** containing more strongly electron-donating and electron-withdrawing aromatic substituents, respectively, where synthesised and submitted to the same reaction conditions but no desired products could be isolated. The rearrangement of the cyclohexyl substrate **1g** proceeded with moderate efficiency furnishing 37% of the acid **3g**. However, cycloheptyl substrate **1h** failed to rearrange, and a mixture of unidentified products was obtained.

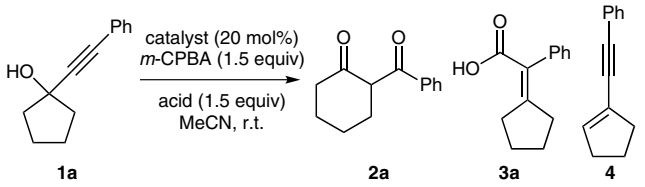


Scheme 4 Scope of the rearrangement reaction

The structure of the products was determined with the aid of NOESY and HMBC NMR experiments (Figure 1). The NOESY spectrum showed an interaction between the arene CH and a CH_2 in the aliphatic ring. The HMBC showed interactions between the alkene C and all four of the CH_2 groups in the ring. Subsequently, the methyl ester of compound **3a** was synthesised and the analytical data matched those in the literature.[10]

Methyl ether **5** was prepared and subjected to the reaction conditions, however, no reaction took place (Scheme 5),[11]

Table 1 Optimization of the Reaction Conditions



Entry	Acid	Catalyst	Yield (%)[a]
1	*p*-toluenesulfonic acid monohydrate	iodobenzene	**4** 83
2	acetic acid	iodobenzene	0
3	trifluoroacetic acid	iodobenzene	**4** 80
4	trichloroacetic acid	iodobenzene	**3a** 20
5	trichloroacetic acid	2-iodoanisole	0
6	trichloroacetic acid	4-iodoanisole	0
7	trichloroacetic acid	2-iodonitrobenzene	**4** 78
8	trichloroacetic acid	–	**3a** 20

[a] Yield of isolated product.

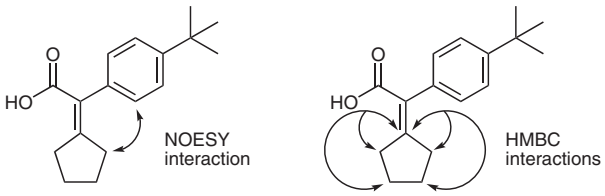
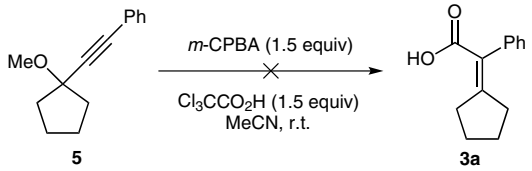


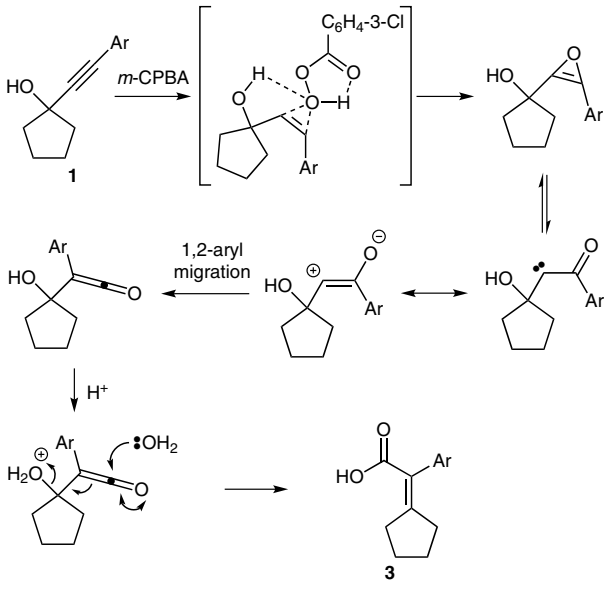
Figure 1 Structure determination by NMR experiments



Scheme 5 Mechanistic investigation

thus demonstrating that the presence of the hydroxyl group is crucial for the reaction to occur. Presumably, the hydroxyl group preorganises and directs the epoxidation of the alkyne through a hydrogen-bonding interaction.[12]

The mechanism of this rearrangement is proposed to proceed through hydroxyl-directed epoxidation of the alkyne to form an oxirene that undergoes a 1,2-aryl shift to form a ketene intermediate (Scheme 6). Addition of water followed by elimination of water generates the final product. An acid is required for the reaction to occur, however, a fine balance exists between formation of products **3** and **4**.



Scheme 6 Postulated rearrangement mechanism

In conclusion, an unprecedented oxidative rearrangement of tertiary propargylic alcohols to enoic acids is presented. This process converts readily accessible compounds into tetrasubstituted alkenes with a carboxylic acid substituent. The reaction likely proceeds through a hydrogen-bond directed alkyne epoxidation followed by a 1,2-aryl migration.

Acknowledgment

We thank the University of Huddersfield for funding.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) McDonald, R. N.; Schwab, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 4866.
(2) Stille, J. K.; Whitehurst, D. D. *J. Am. Chem. Soc.* **1964**, *86*, 4871.
(3) (a) Ortiz de Montellano, P. R.; Kunze, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 7373. (b) Crandall, J. K.; Conover, W. W. II. *J. Org. Chem.* **1978**, *43*, 1323. (c) Csizmadia, I. G.; Font, J.; Strausz, O. P. *J. Am. Chem. Soc.* **1968**, *90*, 7360.
(4) For a review, see: Bauer, E. B. *Synthesis* **2012**, *44*, 1131.
(5) For example, see: (a) Angara, G. J.; Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1992**, *33*, 2285. (b) Bovonsombat, P.; McNelis, E. *Tetrahedron* **1993**, *49*, 1525. (c) Chen, J.-M.; Huang, X. *Synthesis* **2004**, 2459. (d) Bovonsombat, P.; McNelis, E. *Synth. Commun.* **1995**, *25*, 1223. (e) Djuardi, E.; Bovonsombat, P.; McNelis, E. *Tetrahedron* **1994**, *50*, 11793. (f) Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1993**, *34*, 4277. (g) Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1993**, *34*, 8205.
(6) For a review of the Meyer–Schuster rearrangement, see: Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149.
(7) Moran, W. J.; Rodríguez, A. *Org. Biomol. Chem.* **2012**, *10*, 8590.
(8) Rodríguez, A.; Moran, W. J. *Org. Lett.* **2011**, *13*, 2220.
(9) **Typical Experimental Procedure**
1-[(4-*tert*-Butylphenyl)ethynyl]cyclopentanol (**1a**, 50 mg, 0.21 mmol), *m*-CPBA (54 mg, 0.31 mmol), and trichloroacetic acid (51 mg, 0.31 mmol) were dissolved in MeCN (1 mL) at r.t. under a nitrogen atmosphere. The mixture was stirred overnight until solid precipitation was evident (typically less than 15 h). The reaction mixture was quenched with sat. aq $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with sat. aq $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel; 20:1 PE–EtOAc) to afford 2-(4-*tert*-butylphenyl)-2-cyclopentylideneacetic acid (**3a**) as a pale yellow solid (22 mg, 40%); mp 193–195 °C. IR (neat): 1252 (s), 1284 (s), 1618 (m), 1674 (s), 2955 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (9 H, s), 1.58 (2 H, quin, *J* = 6.8 Hz), 1.76 (2 H, quin, *J* = 6.9 Hz), 2.23 (2 H, t, *J* = 7.2 Hz), 2.89 (2 H, t, *J* = 7.3 Hz), 7.10 (2 H, d, *J* = 8.4 Hz), 7.35 (2 H, d, *J* = 8.4 Hz), 11.35 (1 H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 27.1, 31.7 (3 C), 34.8, 34.9, 36.5, 125.1, 125.4 (2 C), 129.2 (2 C), 135.9, 149.9, 168.1, 173.0. MS: *m/z* = 281.2 [M + 23]. HRMS: *m/z* calcd for $C_{17}H_{22}NaO_2$: 281.1512; found: 281.1518.
(10) Martín-Vaca, B.; Rudler, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3119.
(11) Zhang, H.; Fu, X.; Chen, J.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 9351.
(12) For a review, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

