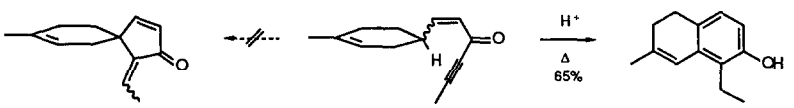
Tetrahedron Letters,Vol.29,No.52,pp 6873-6876,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENYNONES IN ORGANIC SYNTHESIS. III. A NOVEL SYNTHESIS OF PHENOLS

Peter A. Jacobi* and Joseph I. Kravitz
Hall-Atwater Laboratories, Wesleyan University
Middletown, Connecticut 06457

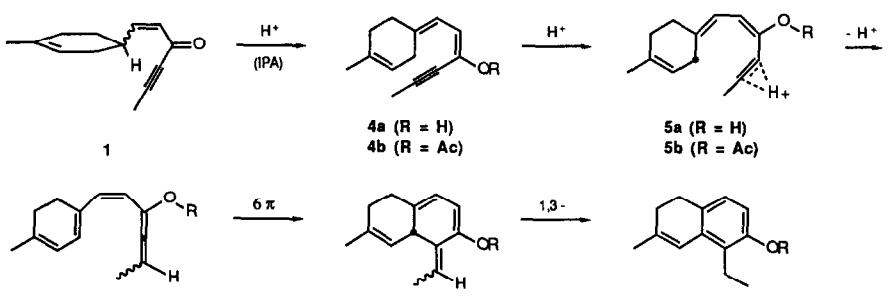
Summary: *Enynones are converted to phenols by an acid catalyzed process which can be controlled to give either of two regioisomeric series of products.*

During the course of efforts aimed at converting the acetylenic enone **1** to the acorone precursor **2**,[1,2] we were surprised to find that collidine *p*-toluenesulfonate (CPTS) catalyzed a very efficient transformation of **1** to the dihydronaphthol derivative **3a** at 250° C in mesitylene. None of the desired spirocycle **2** could be detected, and the



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

only other material isolated was a trace amount of the corresponding naphthol derivative formed by air oxidation of **3a**. This transformation works equally well with either the E- or Z-isomer of **1**, and mechanistic studies indicate that the initial step is an acid catalyzed enolization of **1** to give the dienyne derivative **4a** (Scheme 1). At this stage, we believe,



1

4a (R = H)
4b (R = Ac)

5a (R = H)
5b (R = Ac)

6a (R = H)
6b (R = Ac)

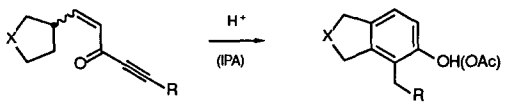
7a (R = H)
7b (R = Ac)

3a (R = H) 65%
3b (R = Ac) 71%

Scheme 1

a protonation-deprotonation sequence proceeding *via* the intermediacy of **5a** leads to the fully conjugated allene derivative **6a**, which upon 6π-electrocyclization followed by aromatization would afford the observed product **3a**. These last steps find excellent precedent in the work of Okamura *et al.*,[3] who have utilized similar allenyldiene electrocyclizations in the synthesis of drimatrienes. An alternative route from **4a** to **6a** involving a concerted 1,7-prototropic shift has been ruled out on the basis of studies conducted with the enolacetate derivative **4b**. Thus, in the absence of acid **4b** was completely stable at the temperatures required for cyclization, but with CPTS it was rapidly converted to the phenol acetate **3b**, which was identical with that obtained by acetylation of **3a**.

The scope of this reaction was initially explored with the acetylenic enones **8-E,Z**, and in each case modest yields of the phenols **9a** were obtained when only CPTS was employed as catalyst (Table 1).[4,5] However, we subsequently found

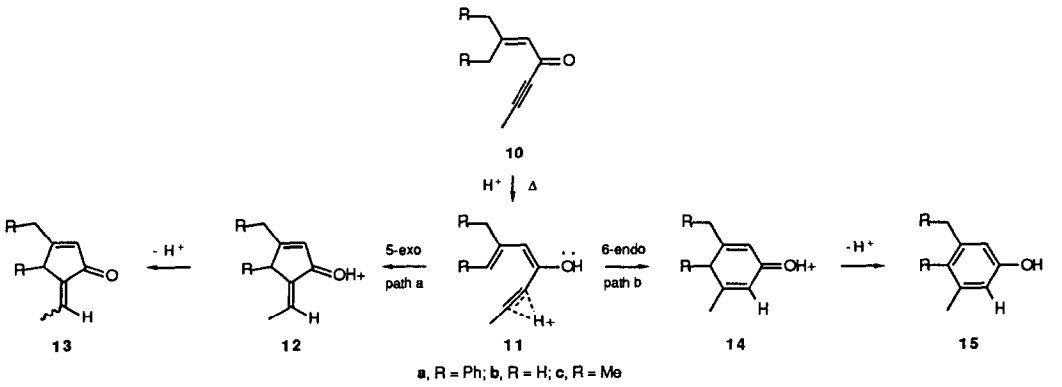


8-E,Z	9a (b)
1 : X = (CH_2), R = H	14% (30%)
2 : X = (CH_2), R = Me	4% (45%)
3 : X = $(CH_2)_2$, R = Me	19% (89%)

Table 1

that these conversions take place at a markedly enhanced rate in the presence of isopropenyl acetate (IPA), and yield the corresponding phenol acetates **9b** in much improved yield. Acetate cleavage with $NaBH_4$ in MeOH then provided the parent phenols **9a** in 85-100% yield.[6] These results are in accord with an expected stabilization of intermediates of type **4b** - **6b** (Scheme 1), as compared with the corresponding protic derivatives **4a** - **6a**.

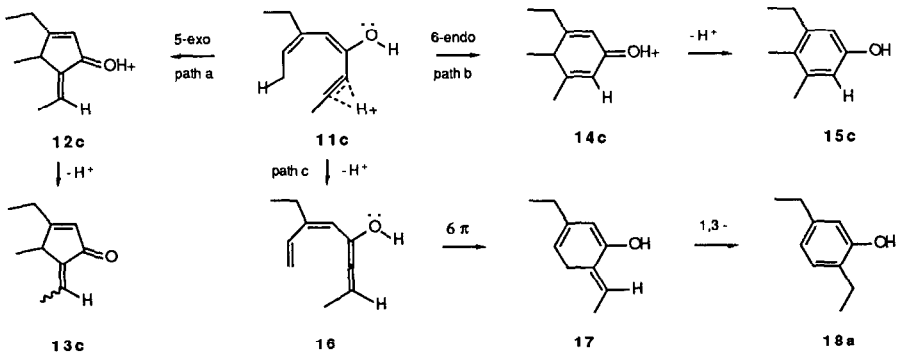
In view of the observations described above, it was of interest to explore the effect of similar reaction conditions on substrates which could not be transformed to allenyldienes of type **6a**. One such example was the dibenzylenynone **10a**, and we were interested to find that this material gave mixtures of the methylenecyclopentenone **13a** (10%) and the new phenol derivative **15a** (44%) under acid catalyzed conditions (Scheme 2). In similar fashion, dimethylenynone **10b**



Scheme 2

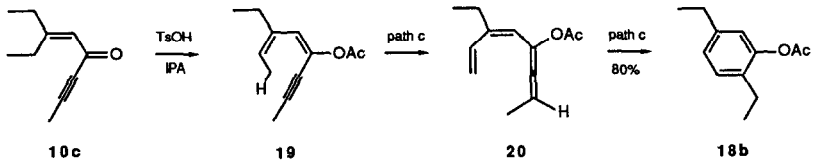
afforded 76% of the phenol derivative **15b**.[7] These results are consistent with a reaction pathway involving enolization and protonation to afford **11**, which might then collapse *via* a 5-*exo* transition state to **12** (path a), or *via* a 6-*endo* transition state to **14** (path b). Simple deprotonation would then provide the observed products.

Not surprisingly, complex mixtures of products were initially obtained with substrates which could undergo cyclization by any of the three reaction pathways thus far uncovered. For example, diethylenynone **10c** afforded the phenol **15c** (path b) and variable amounts of the isomeric phenol **18a** (path c) and methylenecyclopentenone **13c** (path a) upon heating with acid catalysts (Scheme 3). These product mixtures were solvent dependent, with significant quantities of **13c** only observed in 1,2-dichloroalkanes (CPTS) or HOAc (10% **13c**; 21% **15c**). With toluene as solvent, and CPTS as catalyst, **15c** was formed in 82% yield together with only 8% of **18a** (0% **13c**). However, these isomer ratios

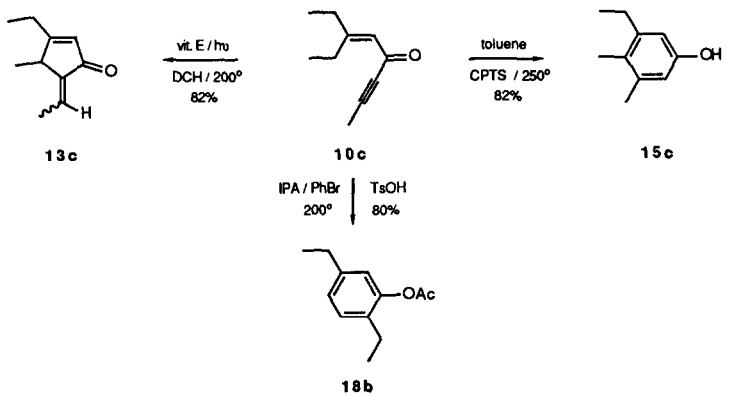


Scheme 3

were dramatically reversed in PhBr with high concentrations of isopropenyl acetate (IPA) and TsOH as catalyst, in which case the phenol acetate **18b** was formed in 80% yield with ~25:1 selectivity. Under these conditions, **10c** is rapidly converted to its enolacetate derivative **19**,[8] which is ideally suited for cyclization *via* path c (*vide supra*).



This last observation, taken together with our previously described results,[1] now allows for the highly efficient conversion of **10c** to any one of the products **13c**, **15c** or **18b** (Scheme 4). Thus, with CPTS in toluene, **10c** gave



Scheme 4

an 82% yield of the trisubstituted phenol **15c**, along with only trace amounts of the isomeric phenol **18a** and none of the methylenecyclopentenone **13c**. In complementary fashion, **10c** provided an 82% yield of **13c** under neutral conditions with vitamin E (1,2-dichlorohexane, hυ, photoassisted electron transfer),[1] and as just described, **10c** gave an 80% yield of **18b** in the presence of both isopropenyl acetate (IPA) and TsOH. Acetate **18b** was readily converted to the phenol **18a** with $NaBH_4$ in MeOH (90% yield).[6]

Analogous results were obtained with other enynones of general structure **10**. This methodology is clearly applicable to the synthesis of monocyclic phenol derivatives of the carvacrol class, and it should also be applicable to the synthesis of fused ring phenols such as juncusol,[9] and ring systems which have traditionally been prepared by phenolic coupling. These last possibilities are currently under active investigation.[10]

References and Notes

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4. All yields refer to isolated and purified materials. Phenol **9a1** had identical spectral data and physical properties as that reported by Tius *et al.*[5] Physical and chemical data for representative compounds: (a) **3b:** pale yellow oil, Rf 0.23 (10% EtOAc/hexanes, silica gel); mass spectrum, m/e 230 (M^+); IR($CHCl_3$) 1751, 1686, 1650, 1601 cm^{-1}; NMR($CDCl_3$) δ 1.02 (t, 3H, J = 7.1 Hz), 1.08 (s, 3H), 2.18 (t, 2H, J = 8.0 Hz), 2.30 (s, 3H), 2.54 (q, 2H, J = 7.1 Hz), 2.74 (t, 2H, J = 8.0 Hz), 6.39 (s, 1H), 6.70 (d, 1H, J = 8.4 Hz), 6.92 (d, 1H, J = 8.4 Hz). **Exact mass.** Calcd for $C_{15}H_{18}O_2$: 230.1307. Found 230.1306. (b) **15c:** Colorless crystalline solid, mp 76-77° C, Rf 0.24 (10% EtOAc/hexanes, silica gel); mass spectrum, m/e 150 (M^+); IR($CHCl_3$) 3600, 3400 br, 1615, 1603 cm^{-1}; NMR($CDCl_3$) δ 1.15 (t, 3H, J = 7.6 Hz), 2.09 (s, 3H), 2.21 (s, 3H), 2.57 (q, 2H, J = 7.6 Hz), 4.43 (s, 1H), 6.50 (s, 2H). **Anal.** Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.40. Found: C, 79.89; H, 9.45. (c) **18a:** Pale yellow oil, bp 50-54° C (0.125 mm), Rf 0.28 (10% EtOAc/hexanes, silica gel); mass spectrum, m/e 150 (M^+); IR($CHCl_3$) 3605, 3371 br, 1626, 1588 cm^{-1}; NMR($CDCl_3$) δ 1.19 (t, 3H, J = 7.5 Hz), 1.20 (t, 3H, J = 7.6 Hz), 2.52 (q, 2H, J = 7.6 Hz), 2.56 (q, 2H, J = 7.5 Hz), 4.61 (s, 1H), 6.71 (d, 1H, J = 7.8 Hz), 7.03 (d, 1H, J = 7.8 Hz). **Exact mass.** Calcd for $C_{10}H_{14}O$: 150.1045. Found 150.1056.

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10. Financial support of this work by the National Science Foundation, Grant No. CHE-8711922, is gratefully acknowledged.

(Received in USA 14 September 1988)