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A Useful Benzannulation Reaction

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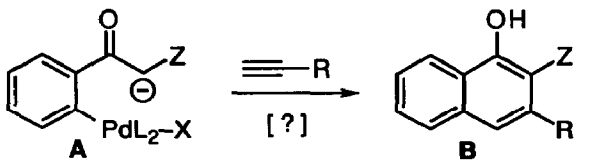
ABSTRACT: *[(2-Alkynyl)-benzoyl]-acetate esters undergo cycloaromatization in good yield upon treatment with CSA in refluxing chloroform.*

The preparation of fused polycyclic aromatic structures is often complicated by the inefficiency of the traditional methods that are commonly used to assemble the desired goals. It has become clear, in recent times, that protocols for *de novo* construction of already functionalized benzenoid rings (benzannulations) may resolve several of the foregoing difficulties. Indeed, the past few years have seen the development of a number of useful benzannulation techniques,[2] particularly elegant among which are those relying on the chemistry of Fischer carbene complexes[3] and of cyclobutenediones.[4]

A useful complement to established benzannulation reactions may be envisioned as shown in Eq. 1, wherein a palladated acetophenone derivative **A** condenses with an acetylene to furnish structures **B** (Eq. 1).[5] This reaction would possess the two-fold advantage of being fully catalytic in transition metal and of requiring readily available building blocks. However, important work by Goré[6] would lead one to question the possibility of reaching **B** from **A** in a single step, and indeed, despite numerous attempts, this goal remains elusive. Nonetheless a method to achieve a transformation of this general type has been found as described below.



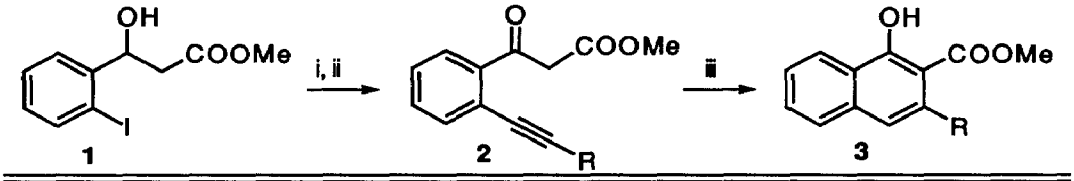
Eq. 1

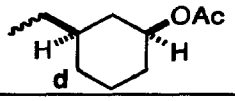
Hydroxyester **1**, prepared in a particularly convenient fashion by ozonolysis of the ene product of 2-iodobenzaldehyde with 2-methoxypropene,[7] underwent smooth alkynylation under Castro-Stephens conditions.[8,9] Subsequent PCC oxidation provided ketoesters **2**. These compounds, in crude form, slowly cyclize to naphthalenes **3** even upon standing at room temperature for prolonged periods of time, probably (*vide infra*) as a consequence of an interaction with Brønsted acidic contaminants carried over from the oxidation step.

A superficial analogy between the cycloaromatization of **2** and Bergman-type reactions is apparent. At this time, however, we are tend to regard the cyclization of **2** not as radical process, but rather an ionic, proton-catalyzed reaction, on the basis of the following observations. Thoroughly purified ketoesters **2** do not cyclize upon thermal or photochemical activation, whereas adsorption on silica gel at room temperature suffices to induce some conversion to **3**. Amine, alkoxide, or hydride bases are ineffective as cyclization catalysts. Lewis acids (e.g., $BF_3{\cdot}OEt_2$), likewise, are poor cyclization catalysts. By contrast, treatment with strong protonic acids dramatically accelerates the cyclization step, and while HCl gas in benzene (25° C) is satisfactory, best results are

obtained with 1 eq. of camphorsulfonic acid in refluxing chloroform. Under the latter conditions, complete cycloaromatization occurs in 8 – 12 hours. Table I summarizes representative examples of the new reaction.[10]

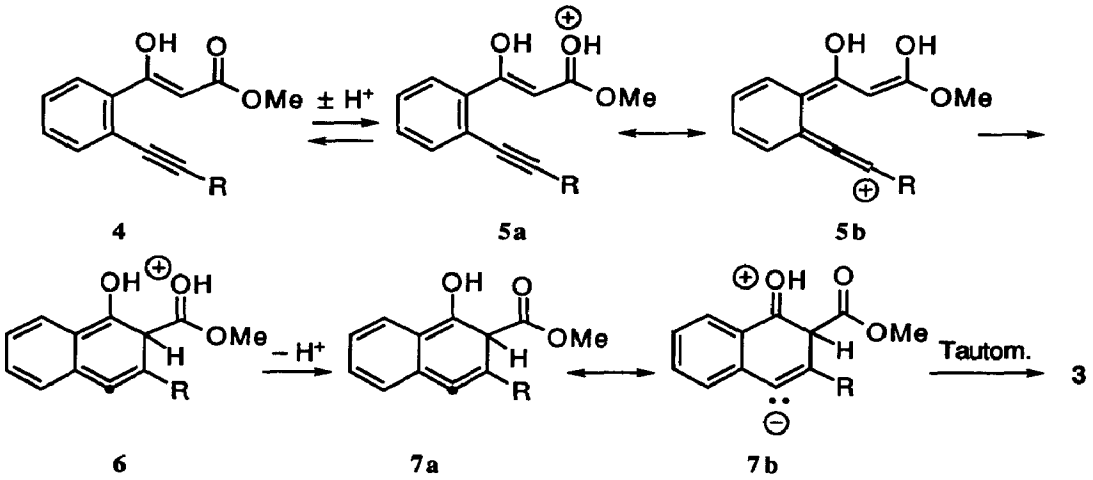
Table I: Representative Benzannulation Reactions.[a]



R =	n-C_6H_{13} **a**	CH_2OMe **b**	Ph **c**	 **d**
Yield % of Step				
i	90	65	97	48
ii	93	76	88	70
iii	90	82	89	75

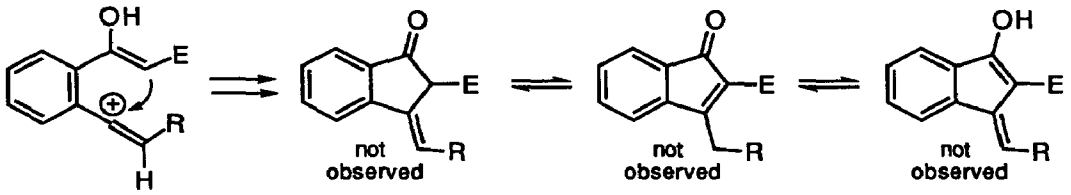
[a]*Reagents and conditions*: (i) R–C≡C–H, cat. CuCl, cat. $Pd(PPh_3)_4$, $tBuNH_2$, PhMe, RT; (ii) PCC,CH_2Cl_2, RT; (iii) $CHCl_3$, CSA, reflux.

The mechanism of the new reaction is not clear at this time, but it seems plausible that cyclization may commence with protonation of the ester carbonyl of the enol tautomer **4** of the starting ketoester **2**. The carbonyl group should be significantly more basic than the triple bond, and its protonation would activate the molecule toward cyclization through the electrocyclic process shown below.



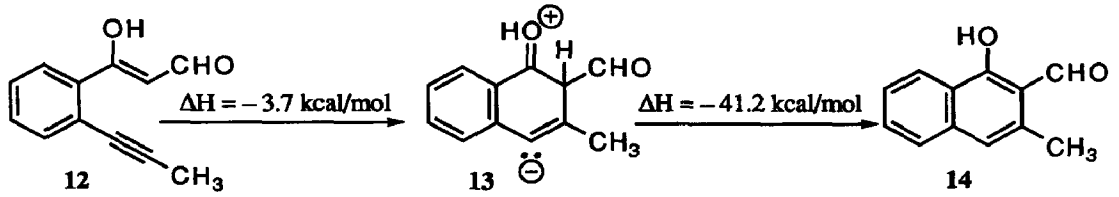
An alternative mechanism involving proton activation of the triple bond seems less likely, as almost certainly this would lead to an isomer of the observed product, *via* a benzylic vinyl cation **8**. The structures of hypothetical tautomeric compounds **9**, **10**, or **11** that would thus emerge are inconsistent with the ^1H NMR spectra of naphthalenes **3**.[10] These exhibit highly diagnostic singlets at ca. 12.5 and 7 ppm, assigned to the

phenolic OH and to the aromatic H *para* to the phenolic functionality, respectively, but no resonances between 5 and 7 ppm. None of the H atoms in the three tautomers would appear as a singlet at ca. 7 ppm; **9** and **11** would show the olefinic H as a triplet at about 6 ppm; **9** and **11** would exhibit no resonances at ca. 12.5 ppm.

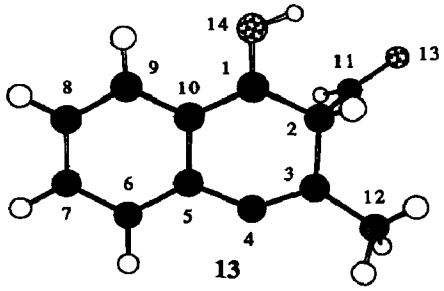


8 **9** **10** **11**

The proposed mechanism invokes a strained allenic intermediate **7a**. However, the enolic group present in **7a** allows it to resonate with a less strained dipolar ion **7b**, which could readily tautomerize to **3**. The cyclization of a simplified molecule of the type **2**, aldehyde **12**, was briefly examined computationally at the MNDO level (UHF). MNDO revealed that, indeed, the optimized geometry of an intermediate similar to **7**, compound **13**, best fits structure **7b**. The optimized structure of **13**, for which we calculate a healthy HOMO-LUMO gap ΔE = 9.182 eV (215 kcal/mol), is shown below, together with key bong lengths and angles. Remarkably, conversion of **12** to **13** is estimated to be mildly exothermic.[11]



12 **13** **14**



13

Bond	Length	Angle	Degrees
1-2	1.535	2-3-4	113.5
1-10	1.445	2-3-12	122.3
1-14	1.352	3-4-5	135.9
2-3	1.530	4-5-6	125.7
3-4	1.360	4-5-10	113.4
5-4	1.400	6-5-10	120.9
5-6	1.424	10-1-2	124.5
5-10	1.468	12-3-4	124.0

The new transformation should be particularly useful to assemble the aromatic frameworks of various antitumor agents, for instance, anthracyclins and related substances. Such applications are currently under intense investigation, and results in this area will be described in due course.

Acknowledgement. We are grateful to the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), and the Robert A. Welch Foundation (C-1007) for support of our research program.

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5. This reaction would proceed by *syn* carbopalladation of the acetylene and trapping of the intermediate vinyl-Pd by the enolate: Ciufolini, M. A.; Qi, H.-B., Browne, M. E., *J. Org. Chem.* **1988**, *53*, 4149.
6. Cf. (a) Fournet, G.; Balme, G.; Van Hemelryck, B.; Goré, J. *Tetrahedron Lett.* **1990**, *31*, 5147; (b) Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811.
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8. The Linstrumelle modification (Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811) of the Sonogashira protocol (Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467) for the Castro-Stephens reaction (Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313) was particularly effective in the present context.
9. The Castro-Stephens reaction failed with the ketoester obtained by oxidation of **1**.
10. Spectral data for compounds **3** (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS). **a**: 12.69 (s, 1H); 8.38 (br. d, 1H, J = 8.4 Hz); 7.66 (br. d, J = 8.1 Hz); 7.57 (br t, 1H, app. J = 6.8 Hz); 7.45 (br t, 1H, app. J = 8.0 Hz); 7.11 (s, 1H); 4.01 (s, 3H); 3.00 (br. t, 2H, J = 7.5 Hz); 1.59 (m, 2H); 1.35 (m, 6H); 0.92 (br. t, 3H, J = 6.9 Hz). 172.9; 162.5; 139.7; 136.0; 129.5; 126.5; 124.9; 124.0; 123.6; 120.2; 105.6; 52.1; 37.1; 32.0; 31.8; 29.6; 22.6; 14.1. 3300-2800 (w, br); 3057; 1651; 1338; 1255. 286 (M^+); 254; 226; 216; 215; 212, 184 (100 %); 183. Calc. for $C_{18}H_{22}O_3$: 286.1569; obs.: 286.1568. **b**: 12.14 (s, 1H); 8.43 (d, 1H, J=8.5 Hz); 7.74 (d, 1H, J = 8.3 Hz); 7.63 (br. t, 1H, app. J = 7.6 Hz); 7.54 (br. t, 1H, app. J = 7.7); 7.43-7.29 (m, 5H); 7.21 (s, 1H); 3.57 (s, 3H). 172.2; 161.2; 143.3; 139.2; 135.6; 129.8; 128.3; 127.5; 127.4; 126.5; 125.8; 123.9; 121.4; 105.8; 51.7. 3300-2800 (w, br); 3050; 1656; 1324; 1264. 278 (M^+); 246; 218; 189 (100%); 163. Calc. for $C_{18}H_{14}O_3$: 278.0943; obs.: 278.0943. **c**: 12.41 (s, 1H); 8.19 (d, 1H, J = 8.9 Hz); 7.54 (d, 1H, J = 7.9 Hz); 7.41 (br t, 1H, app J = 7.7 Hz); 7.30 (br t, 1H, app. J = 7.6 Hz); 7.06 (s, 1H); 4.61 (s, 2H); 3.82 (s, 3H); 3.30 (s, 3H). 172.5; 162.5; 135.9; 134.6; 129.8; 127.3; 125.7; 124.4; 124.0; 118.0; 104.3; 74.3; 58.6; 52.3. 3300-2800 (w, br); 1652; 1345; 1260. 246(M^+); 214; 199 (100%); 185; 171. Calc. for $C_{14}H_{14}O_4$: 246.0892; obs.: 246.0897. **d**: 12.71 (s, 1H); 8.37 (br. d, 1H, J = 8.4 Hz); 7.65 (br. d, J = 7.8 Hz); 7.58 (br. t, 1H, app J_1 = 7.8 Hz); 7.46 (br. t, 1H, app. J_1 = 8.8 Hz); 7.02 (br s, 1H); 4.65 (br. m); 2H; 4.02 (s, 3 H); 2.96 (m, 2H); 2.00 (s, 3H); 2.0-1.2 (m, 9H). 172.8; 170.5; 162.9; 136.8; 135.7; 129.7; 126.6; 125.2; 124.1; 123.9; 121.5; 105.5; 73.2; 52.3; 44.5; 38.7; 38.1; 32.0; 31.8; 23.8; 21.4. 3300-2800 (w, br, OH); 3057; 1736; 1649; 1257. 356 (M^+); 324; 296; 216; 212; 183; 141 (100 %). Calc. for $C_{21}H_{24}O_5$: 356.1624; obs.: 356.1617.
11. Computational work was carried out with the HYPERCHEM® package, available from Autodesk, Inc, Sausalito, CA, and running on a Windows® -based 486 PC system.

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