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THE REACTION OF ARYNES WITH ENAMINES: A NEW RING EXPANSION LEADING TO BENZOCYCLOHEPTENONE

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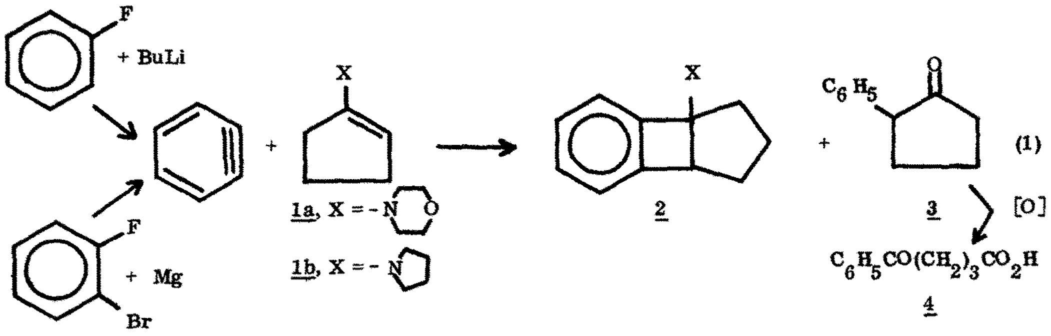
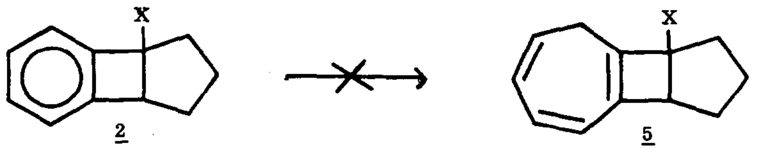
The recent literature reflects a resurgence in interest in the synthesis of polycyclic conjugated systems containing fused four-membered rings.[1] In connection with our continuing interest in this general area and our desire to synthesize tricyclo[7.3.0.0]dodecahexalene[2] we have investigated further the addition of arynes to cyclic enamines, a reaction first described in 1962.[3]

We wish to report that treatment of an ethereal solution of either the morpholine or pyrrolidine enamine of cyclopentanone (1) and fluorobenzene with n-butyllithium[3] affords 2a and 2b, respectively, in moderate yield[4] (30-38%) [equation (1)]. The aminobenzocyclobutene 2b (15% yield) and 2-phenylcyclopentanone (3) are also obtained upon treatment of enamine 1b with o-bromofluorobenzene and magnesium. The cyclopentanone 3, mp 30-32°, is oxidized spontaneously upon exposure to air to 4-benzoylbutyric acid (4), mp 122-124°.[5]



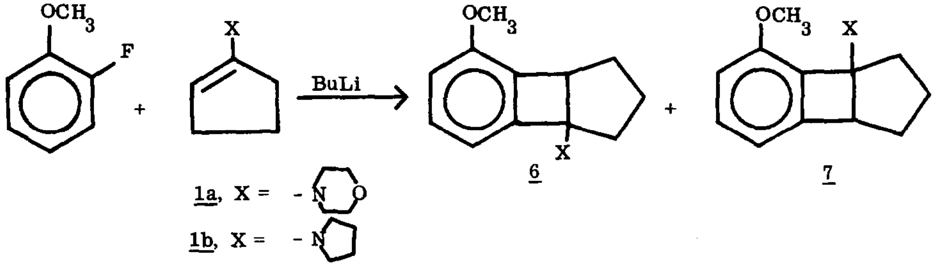
(1)

It was hoped that tricyclo[7.3.0.0]dodecahexalene could be obtained from the benzocyclobutene derivatives, but to date our efforts to achieve the required initial ring expansion of the aromatic nucleus of 2 by treatment with a variety of methylene transfer reagents have failed to give 5 [equation (2)].



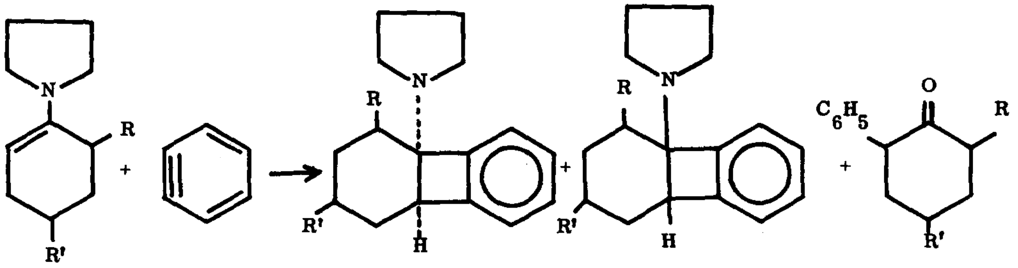
(2)

In an attempt to increase the reactivity of the aromatic nucleus toward expansion, the corresponding methoxy-substituted benzocyclobutenes 6 and 7 were prepared by treatment of ethereal solutions of the enamines 1 and o-fluoroanisole with n-butyllithium (32-34% yield) [equation (3)]. That "head-to-tail" and "head-to-head" isomers 6 and 7 are formed from 1a and 1b is apparent from the nmr spectra of the purified but unseparated products, which show doublet signals of unequal intensity for the methoxy protons at τ 6.18 and 6.25 (7:1) for the morpholine derivatives and τ 6.21 and 6.26 (4.3:1) for the pyrrolidine products. The fact that the nmr signal of the major peaks in the mixture of 6a and 7a as well as 6b and 7b is unperturbed in acid solution suggests that the "head-to-tail" isomer 6 predominates in each instance. Significantly, the signal of weaker intensity is broadened under these conditions. Ring expansion studies on 6 and 7 are in progress.



(3)

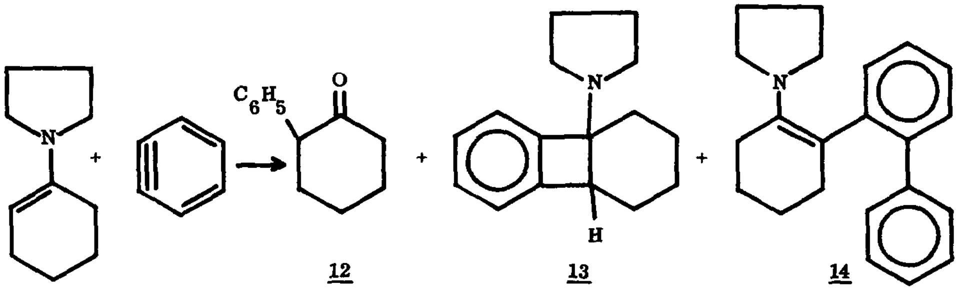
Addition of the pyrrolidine enamine of 2-methylcyclohexanone to benzyne generated from o-bromofluorobenzene and magnesium [equation (4)] gives aminocyclobutenes 8a and 8b (56% yield) and a small amount of 2-methyl-6-phenylcyclohexanone (9) (4.5% yield), isolated as a mixture of isomeric oximes (mp 165-185°). While the aminocyclobutene fraction appeared to be homogeneous on the basis of tlc and picrate melting point, it is apparent from 100 mc nmr spectra that both the free base and the picrate are mixtures of two isomeric compounds. The spectrum of the free base shows doublet methyl signals at τ 8.76 and 8.90 (J=8 cps). Relative intensities of all peaks (including the apparent methyl triplet) in a 60 mc nmr spectrum remain constant over a variable temperature range of 40-150°. It has now been shown that the two isomeric bases can be separated by glpc. The results obtained with the enamine of 2-methylcyclohexanone, in which predominant formation of the benzocyclobutene products 8 is observed, may be contrasted with the behavior noted with unsubstituted cyclohexanone enamine itself, where 2-phenylcyclohexanone (12) (28% yield) and aminocyclobutene 13 (21% yield) are obtained in about equal amounts [equation (5)]. This difference in product ratios may reflect the formation of epimeric zwitterionic cis-1,3-diaxially substituted chair, or trans-substituted boat intermediates in which the otherwise favored 1,5-proton transfer is hindered by a methyl substituent. It is noteworthy that an additional product, namely 2-o-biphenylpyrrolidinocyclohexene (14) (2% yield) is also formed. This may arise by attack on the initial zwitterionic intermediate by benzyne. Alternatively this result may be rationalized by assuming electrophilic addition of a 1,4-dipolar benzyne coupling adduct to the enamine followed by a 1,5-proton transfer to give the conjugated enamine product. Under the same reaction conditions, 4-t-butylpyrrolidinocyclohexene also gives two isomeric aminocyclobutenes 10a and 10b in about equal amounts, as well as an oily ketone fraction (11).



(4)

8a R = CH_3, R' = H 8b 9 R = CH_3, R' = H

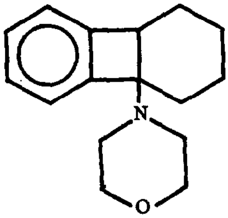
10a R = H, R' = t-butyl 10b 11



(5)

12 13 14

Finally, aminobenzocyclobutenes 15 and 16 derived from the morpholine enamines of cyclohexanone and cycloheptanone, respectively, were synthesized by treatment of the corresponding enamines with fluorobenzene and butyllithium. However, the yields of these products were lower (25-30%) than those obtained with the corresponding cyclopentanone enamines.



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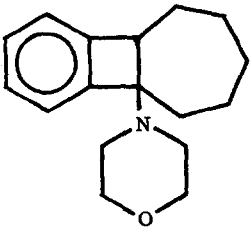

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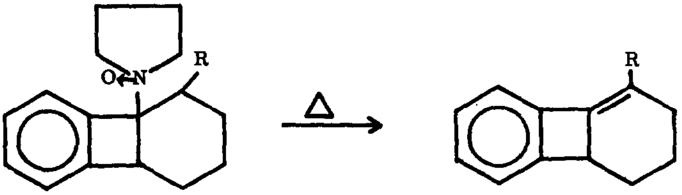
Thermolysis of amine oxides 17 and 18 gave benzocyclobutenes 19 and 20, respectively [equation (6)]. In connection with the synthetic sequence being considered for tricyclo[7.3.0.0]dodecahexalene (which would require a similar elimination on 5) it was of interest to establish if the amine oxides from 2a and 2b could be converted to 21 on pyrolysis. In this instance we also might obtain a precursor for 22 which in turn is related to the [4]-radialenes whose properties we continue to study.[6] Furthermore, an alternative route to the recently synthesized anion 23[1c] also might become available.



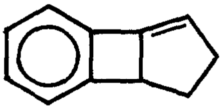
17, R = H

18, $R = CH_3$

19, R = H

20, $R = CH_3$

(6)



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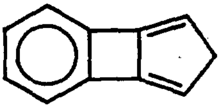

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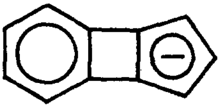

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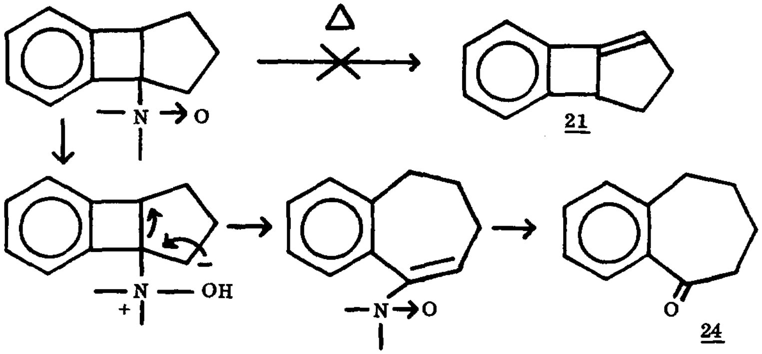
To our dismay none of the benzocyclobutene 21 was isolated. In both cases a ketone was obtained which was identified as benzocycloheptenone 24 on the basis of spectral data and the melting point of the dinitrophenylhydrazone derivative.[7] The formation of 24 may be rationalized in the manner shown in equation (7). Other synthetic routes to 21 are presently being explored.



(7)

TABLE I

2a	mp 59.5-61.5° (methiodide d. 190°)	τ 2.83 (m,4), 6.22 (t,4), 7.33 (t,4), 8.0-8.6 (m,7)	m/e 229 (M, 45%) 143 (base peak, 100%)
2b	bp 108-112° (1 mm) (picrate mp 135-137°)	τ 2.95 (m,4), 6.6 - 7.8 (m with strong absorption at 7.3,8), 7.8-8.7 (m,7).	
6a, 7a	mp 71.5-73°	τ 2.65-3.15 and 3.2-3.6 (m,3), 6.18 and 6.25 (d,3, $OC\underline{H}_3$), 6.43 (t,4), 7.4 (t,4) 8.0-8.7 (m,7).	m/e 281 (M, 2%) 173 (base peak, 100%).
6b, 7b	mp 76.5-78° (picrate mp 196-97°d)	τ 2.7-3.2 and 3.3-3.6 (m,3), 6.21 and 6.26 (d,3, $OC\underline{H}_3$), 7.07-7.6 (m,8), 7.8-8.8 (m,7).	
8a, 8b	bp 95-100° (0.2 mm) (picrate mp 162-164°) (hydrochloride mp 203-207°	τ 2.8 (m,4), 6.3 (t,1), 7.0-7.5 (m,4), 7.8-8.6 (m,9), 8.76 (d,4/5), 8.90 (d,6/5), 100 mc	
10a,10b	bp 110-120° (0.2 mm)	τ 2.8 (m,4), 6.3 (t,1), 7.1-7.4 (m,4), 7.7-8.9 (m,11), 9.2 (s,9).	
14	mp 153-155°	τ 2.7 (m,9), 7.1-7.5 (m,4), 7.6-8.2 (m,4), 8.3-8.8 (m,8).	
15	bp 142-150° (1 mm)	τ 2.85 (m,4), 6.28 (t,4), 7.28 (m,4), 7.8-8.8 (m,9).	
16	bp 135-150° (0.25 mm)	τ 2.83 (m,4), 6.32 (t,4), 7.32 (m,4), 7.8-8.8 (m,11).	
19	mp 21-24°	τ 3.0 (s,4), 4.3 (t,1), 6.3-6.7 (m), 7.6-9.0 (m). λmax. 225 (7,175), 248 (15,550), 260 (13,160), 288 (5,080), 297 (5,300). λ min. 229 (6,400), 268 (2,075), 293 (3,590). m/e 156.	

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