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Intramolecular *meta* Photocycloaddition of 3-Benzylazaprop-1-enes

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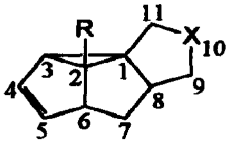
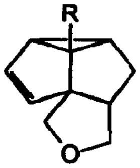
Abstract:. Photoinduced intramolecular electron transfer in 3-benzylazaprop-1-enes is inhibited by N-acetyl or N-carbomethoxy protecting groups: fluorescence is then observed from the arene chromophore and intramolecular *meta* photocycloaddition occurs to give the linear azatriquinane system with high selectivity

The intramolecular *meta* photocycloaddition of 5-phenylpent-1-ene derivatives has been shown to have appreciable application in complex molecule total synthesis and, in particular, to provide an elegant access to linear and angular triquinane skeleta of several naturally occurring cyclopentanoids.[1]

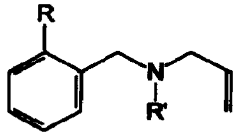
Our recently reported studies with 3-benzyloxyprop-1-enes have shown that oxatriquinane systems can also be obtained by this photochemical route, but with these bichromophores, *ortho* photocycloaddition is a significant process for some derivatives.[2] The intramolecular *meta* cycloadducts from 3-benzyloxyprop-1-enes, however, reflect high selectivity in the direction of formation of the cyclopropane ring since the linear oxatriquinane **1** is markedly favoured over its angular isomer **2**. This photochemical methodology cannot, however, be applied to gain access to the potentially more useful azatriquinanes and only low efficiency fragmentation reactions are induced photochemically from 3-benzylazaprop-1-enes **3** and the arene-amine-ethene trichromophores **4**.[3] The intramolecular *meta* cycloaddition arises from the S_1 state of the benzenoid compound,[4] and the absence of this process in these systems can be attributed to an efficient competing electron transfer reaction from the amine to the electronically excited arene moiety. Although this process is unproductive in the present systems, with styrene - amine systems[5] an intramolecular cyclisation is induced and benzazepine derivatives have been accessed by this route.[6] Support for photoinduced intramolecular electron transfer in the benzene-amine-ethene trichromophores **4** is provided by their fluorescence spectral characteristics,[3,7] but uniquely, 3-benzylazaprop-1-enes **3** exhibit essentially no fluorescence from either the arene or an intramolecular arene - amine exciplex: this feature may be rationalised in terms of formation of the species **5** as proposed much earlier to account for the lack of emission from the corresponding 1-naphthyl systems.[8] We have investigated the feasibility of promoting intramolecular arene-ethene photocycloaddition reactions of 3-benzylazaprop-1-enes **3** by inhibiting the electron transfer from the nitrogen in the tether, and now describe a convenient and effective methodology for accessing the linear azatriquinane system **6**: this overcomes the previously reported photoinertness of such systems and appreciably extends the potential and versatility of the intramolecular *meta* photocycloaddition of the arene-ethene bichromophores in complex molecule synthesis.[1]



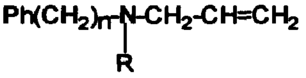
(1) X=O, R=Me or OMe
(6) X=N-R'
(9) R=Me, X=N-COMe
(10) R=OMe, X=N-COMe
(12) R=Me, X=N-CO$_2$Me
(14) R=OMe, X=N-CO$_2$Me
(17) R=H, X=N-CO$_2$Me



(2) R=Me or OMe
(18) R=H, X=N-CO$_2$Me

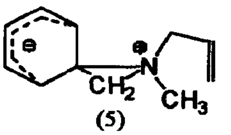


(3) R=H, R'=H or Me
(7) R=R'=Me
(8) R=H, Me, or OMe; R'=COMe
(11) R=Me, R'=CO$_2$Me
(13) R=OMe, R'=CO$_2$Me
(16) R=H, R'=CO$_2$Me



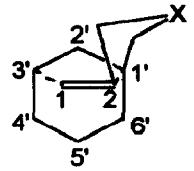
$Ph(CH_2)_n\underset{R}{N}CH_2CH{=}CH_2$

(4) n=2, 3, or 4, R=H or Me



(5)

The incorporation of electron donor substituents into the benzene ring may be expected to inhibit the photoinduced intramolecular electron transfer in 3-benzylazaprop-1-enes **3**, and, furthermore, such groups at the 2'-position will direct the *meta* photocycloaddition of an ethene specifically to the 1',3'-positions.[4] However, the 2'-methyl-derivative **7** neither displayed arene fluorescence nor yielded isomers on 254 nm irradiation.[9] Complete inhibition of the intramolecular electron transfer may be expected for **3** and **7** in acid solution and indeed, the protonated species did exhibit arene fluorescence, but again only fragmentation was induced photochemically. The presence of an electron-withdrawing protecting group on the nitrogen, however, provides a convenient and more effective method of moderating the electron transfer in these systems thereby permitting the S_1 state of the benzene chromophore to fluoresce and undergo intramolecular cycloaddition. Thus, 3-benzylazaprop-1-enes having an N-acetyl or N-carbomethoxy protecting group displayed fluoresence from the arene chromophore in the 280 - 290 nm region: the intensity of this emission was approximately 10% of that from the corresponding protected benzyl n-propylamine indicating that interaction between the S_1 arene and the S_0 ethene was occurring. Satisfyingly, irradiation[9] of the protected trichromophores did produce isomers. Although much polymeric material was obtained on irradiation of the N-acetyl compounds **8**, the *meta* cycloaddition from systems having a 2'-methyl or 2'-methoxy substituent to direct the reaction gave only the linear azatriquinane isomers **9** and **10** respectively in approximately 30% yield.[10] Thus during the photoreaction of both trichromophores, bond formation between the 2'6'-positions to give the cyclopropane ring must occur with high selectivity, otherwise the angular triquinane isomer from 2'4'-closure would be detected. Using carbomethoxy as the nitrogen protecting group greatly improved chemical yields of the photoisomers. Thus three photoisomers from the 2'-methyl-trichromophore **11** were produced in a combined yield of 95% and a selectivity of 18:2:1 with respective retention times relative to **11** of 1.3, 1.5, and 1.6. The major isomer (80% yield) was isolated by flash chromatography, and from spectral analysis was assigned the linear triquinane structure **12**.[11] Similar selectivity of the intramolecular *meta* photocycloaddition was noted for the 2'-methoxy-trichromophore **13** which again gave three photoisomers with the linear triquinane **14**[12] comprising 80% of the product yield. In both series, the protecting groups could be removed from the photoisomers by treatment with base.



(15)

The high selectivity for formation of the linear azatriquinanes can most conveniently be explained in terms of an unsymmetrical orientation **15** of the interacting S_1 arene and S_0 ethene as a result of smaller bond angle and shorter bond lengths of the CH_2-X-CH_2 tethering unit compared to that of hydrocarbon systems.[1,4] This "asymmetric effect" allows C_2-$C_{1'}$ bonding prior to C_1-$C_{3'}$ bonding and results in $C_{1'}$ attaining sp^3 hybridisation before $C_{3'}$ and so promotes the cyclisation between $C_{2'}$ and $C_{6'}$ to give the cyclopropane ring. However, while absence of a directing group on the benzene ring in **16** leads to an understandable lack of selectivity in the regiochemistry of *meta* photocycloaddition (2',6'- and 1',3'-), the formation of both azatriquinanes (ratio **17**:**18** of 1.0:3.2) is not consistent with the heteroatom-directed cyclopropane ring formation observed when the regiochemistry of addition is controlled by substitution on the arene, and, as for the similar results from 3-benzyloxyprop-1-ene,[2] remains unexplained. Nevertheless, this feature does not limit the synthetic application of these intramolecular photocycloadditions as the presence of such substitution on the benzene ring is essential to direct the photoaddition and obtain the specificity for triquinane formation, and as evidenced by the exploitation in the hydrocarbon series,[1] such substitution is generally required by the synthetic target.

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9. Cyclohexane or dioxane solutions (1% w/v) of the trichromophores in 50 cm x 1 cm (i.d.) quartz tubes were exposed to the emission from an array of eight 15w low pressure mercury arc lamps.
10. **9**: δ_H ($CDCl_3$, 400MHz) 5.64 (dt, $J_{4,5}$5.4, $J_{4,3}$2.1, $J_{4,6}$2.1, 4-H), 5.48 (dt, $J_{5,6}$2.7, $J_{3,5}$2.7, 5-H), 3.87-3.20 (m, 9-H, 9-H', 11-H, 11-H'), 2.95 (br. d, 6-H), 2.60-2.37 (m, 8-H), 2.07 (s, COMe), 1.80 (overlapping dd's, $J_{7endo,6}$5.3, $J_{7endo,7exo}$9.2, 7-H_{endo}; $J_{7exo,8}$5.3, 7-H_{exo}), 1.72 (br. d, 3-H), and 1.37 (s, 2-Me). (Found: M^+, 203.1314. Calc. for $C_{13}H_{17}NO$: *M*, 203.1311). **10**: δ_H ($CDCl_3$, 400MHz) 5.57 (dd, $J_{4,5}$5.7, $J_{4,3}$2.2, 4-H), 5.51 (ddd, $J_{5,6}$2.7, $J_{5,3}$1.2, 5-H), 3.89-3.22(m, 9-H, 9-H', 11-H, 11-H'), 3.35 (s, OMe), 3.24 (dd, $J_{6,7exo}$4.4, 6-H), 2.40-2.09 (m, 8-H), 1.97 (s, COMe), 1.91 (d, 3-H), and 1.86-1.69 (m, 7-H_{endo}, 7-H_{exo}). δ_C 169.0, 132.9, 126.8, 89.4, 56.7, 53.4, 52.6, 51.1, 44.1, 38.9, 37.7, 35.8, and 22.1. (Found: M^+, 219.1203. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1206).
11. **12**: δ_H ($CDCl_3$, 400MHz) 5.62 (dd, $J_{4,5}$5.4, $J_{4,3}$1.9 4-H), 5.44 (dd, $J_{5,6}$2.3, 5-H), 3.70 (s, CO_2Me), 3.59-3.15 (m, 9-H, 9-H', 11-H, 11-H'), 2.95 (dd, $J_{6,7exo}$5.0, 6-H), 2.44-2.37 (m, 8-H) 1.89 (dd, $J_{7endo,8}$6.3, $J_{7endo,7exo}$11.5, 7-H_{endo}), 1.75 (dt, $J_{7exo,8}$5.0, 7-H_{exo}), 1.62 (d, 3-H), and 1.30 (s, Me). δ_C 206.6, 133.1, 128.1, 57.5, 52.2, 48.8, 46.5, 46.0, 39.6, 37.5, 25.2, 20.9, and 13.9. (Found: M^+, 219.1258. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1260).
12. **14**: δ_H ($CDCl_3$, 400MHz) 5.64 (dd, $J_{4,5}$5.7, $J_{4,3}$2.4, 4-H), 5.55 (ddd, $J_{5,6}$2.9, $J_{5,3}$1.6, 5-H), 3.92-3.19 (m, 6-H, 9-H, 9-H', 11-H, 11-H'), 3.68 (s, CO_2Me), 3.37 (s, OMe), 2.35-2.32 (m, 8-H), 2.21 (d, 3-H), 1.76 (dd, $J_{7exo,7endo}$13.7, $J_{7exo,6}$6.2, 7-H_{exo}), and 1.54 (dd, $J_{7endo,8}$6.2). δ_C 205.6, 132.8, 127.3, 89.6, 56.8, 52.9, 52.3, 48.5, 47.3, 45.7, 37.9, 36.1, and 24.9. (Found: M^+, 235.1210. Calc. for $C_{13}H_{17}NO_3$: *M*, 235.1209).

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