

REACTIONS OF DIHYDROPYRIDINES WITH BENZYNE

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Abstract

Reactions of 1,2-dihydropyridines (**1a-c**) and 1,4-dihydropyridines (**2a-c**) in the presence of benzyne (**3**) under thermal conditions, and in the case of (**2c**) under photochemical conditions, have been investigated. Benzyne acts as an oxidizing agent to convert dihydropyridine (**1a**) and (**2a**) to the corresponding pyridine (**4**) or adds as a dienophile to (**1b-c**).

Introduction

Earlier investigations concerning cycloaddition reactions of substituted 1,4-dihydropyridines have been reported with dimethyl acetylenedicarboxylate (DMAD), under thermal conditions via a formal unconcerted [2+2]-mechanism [1]. Lewis acid catalyzed [4+2]-cycloaddition of 1,4-dihydropyridines with various kinds of dienophiles such as styrene, cyclopentadiene, etc. [2-4] and also 1,3-dipolar cycloaddition of 1,4-dihydropyridines with nitrile oxides have been observed [5].

1,2-Dihydropyridines behave as dienes in [4+2]-cycloaddition reactions [6-12]. Only a few examples of cycloaddition reactions of 1,2-dihydropyridines via [2+2]-pathway have been reported [13,14].

We now wish to report reactions of some 1,2- and 1,4-dihydropyridine derivatives with benzyne, under thermal and also photochemical conditions.

Results and Discussion

Cycloaddition reactions of 1,2-dihydropyridines (**1a-c**) and 1,4-dihydropyridines (**2a-c**) with benzyne (**3**) under

thermal conditions and reactions of 1,4-dihydropyridine (**2c**) with (**3**) under photochemical conditions were investigated.

1,2-Dihydropyridine (**1a**) was oxidized to corresponding pyridine (**4**) on heating in the presence of benzyne under a nitrogen atmosphere, whereas (**1b**) reacted with benzyne to give adduct (**5**), via a [4+2]-cycloaddition mechanism.

The IR spectrum of compound (**5**) showed two $\bar{\nu}$ (C=O) bands at 1710 and 1680 cm^{-1} indicative of saturated and conjugative ester groups, respectively. More confirmation was obtained from ^1H - and ^{13}C -NMR spectra (see Experimental Section). Compound (**5**) could exist in exo- and endo-forms in relation to nitrogen lone pair with respect to benzene ring. The endo/exo selectivity in similar systems has been rationalized by CNDO/2M6 molecular orbital calculations [15]. It has been shown that the endo-form is more stable due to the interaction between the nitrogen lone pair and π -orbital.

On the basis of the above results, it may be suggested that the endo-conformation (**5**) is preferred due to more interaction of nitrogen lone pair with π -orbitals of benzene ring in comparison to interaction with conjugated olefinic π -bond.

1,2-Dihydropyridine (**1c**) reacted with benzyne under

Keywords: Benzyne; Cycloaddition; 1,2-Dihydropyridine; 1,4-Dihydropyridine

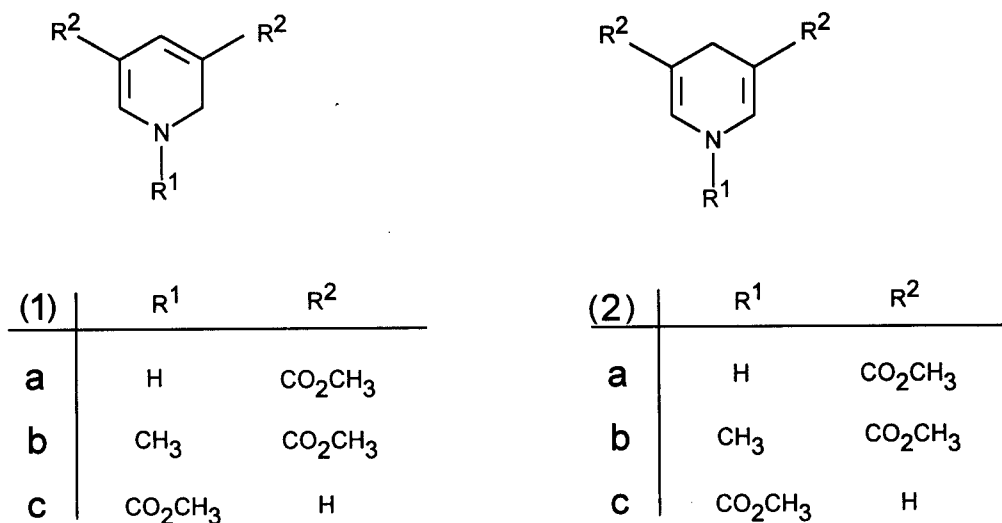


Figure 1.

thermal conditions to give naphthalene probably through the intermediacy of compound (6). Similar results have been obtained using 1,3-disubstituted 1,2-dihydropyridines with DMAD [12]. Apparently, compound (1c) reacts with benzyne via [4+2]-cycloaddition to give intermediate (6) which converts to

to corresponding pyridine (4), while (2b) and (2c) remained unchanged under similar conditions.

More interesting results have been obtained on irradiation of (2c) under an oxygen or nitrogen atmosphere and in the presence or absence of benzyne. Compound (2c) was oxidized to pyridine under an oxygen atmosphere,

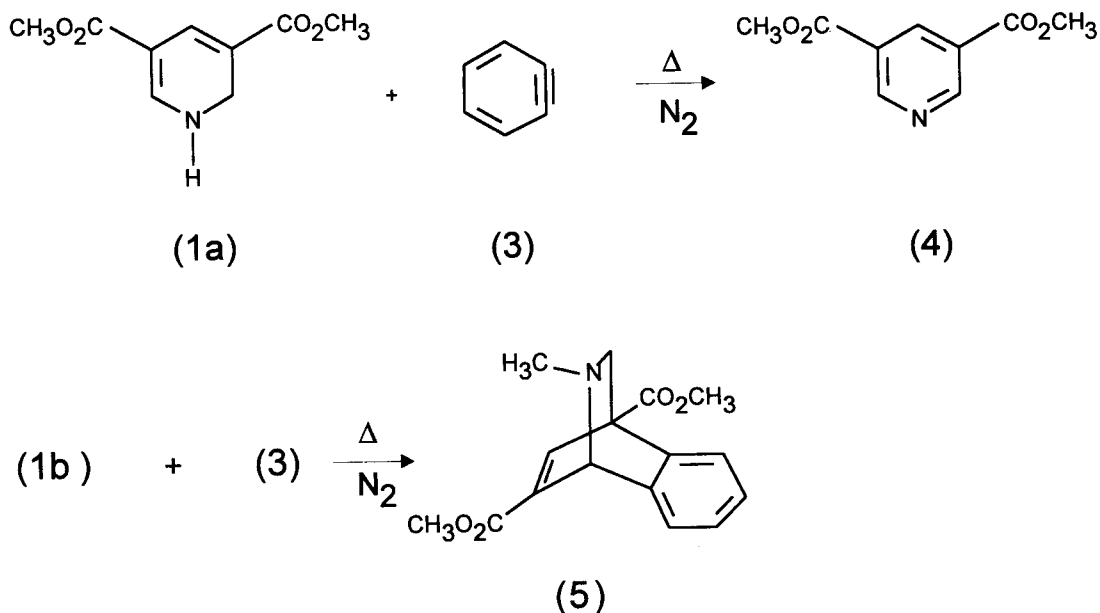


Figure 2.

a more stable product, naphthalene, after elimination of $\text{CH}_2=\text{N}-\text{CO}_2\text{CH}_3$ via a retro-Diels-Alder reaction.

It is interesting to compare the results of 1,4-dihydropyridines (2a-c) in reaction with benzyne (3) under thermal conditions. Compound (2a) was oxidized

whereas photolysis of the same compound under an atmosphere of nitrogen resulted in the formation of 2,2'-bipyridil (7) which was identified by its spectroscopic data and elemental analysis. Irradiation of compound (2c) in the presence of benzyne under a nitrogen atmosphere

yielded the expected dimers (7) (30%) and a second compound (14.2%) to which we assign the structure (8) on the basis of its spectroscopic properties.

¹H-NMR spectrum of compound (8) showed aromatic hydrogens around δ 6.6-6.8 ppm and olefinic hydrogens at 6.3 ppm. The structure of the compound was confirmed by spectroscopic data and elemental analysis. The mechanism of the formation of compound (8) is described below.

Experimental Section

Melting points were determined with a Mettler-PF5 and are uncorrected. IR spectra: Philips, PU-9716. ¹H NMR spectra: Bruker AW-80 MHz. ¹³C NMR spectra:

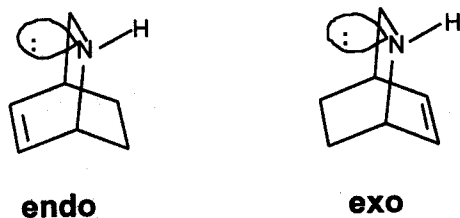


Figure 3.

Jeol-EX (22.4 MHz). UV spectra: Shimadzu UV-160. Mass spectra (EI mode, 70 eV): INCOS-50. Elemental analysis: Heraeus CHN-O-RAPID. Preparative layer chromatography (PLC) was carried out on 20×20 cm² plates, coated with a 1-mm layer of Merck silica gel PF₂₅₄, prepared by applying the silica as a slurry and drying in air. Silica gel used for column chromatography was Mesh 70-

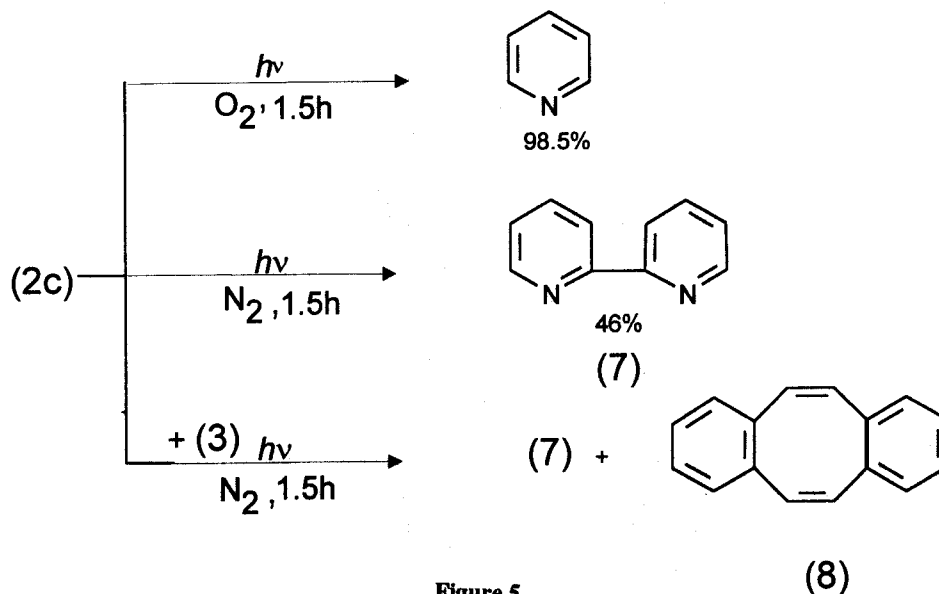


Figure 5.

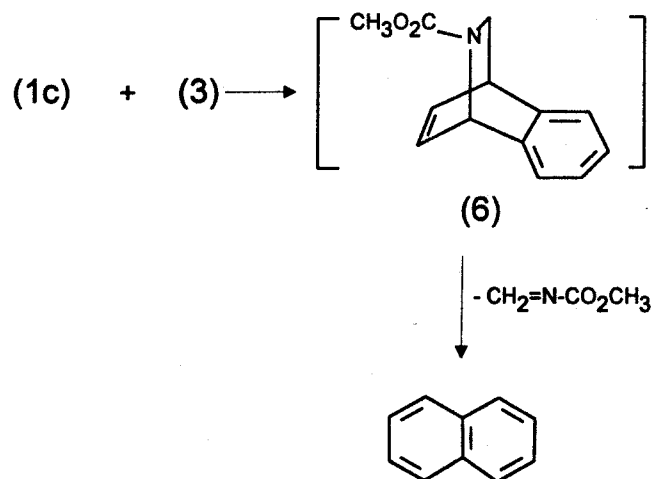


Figure 4.

230 μ from Merck. All irradiations were carried out using a LTI LPS 200X, AMKO LIGHT TECHNOLOGY instrument Hg-100W. Starting materials (1a-c), (2a-c) and (3) were prepared according to known procedures [16-18]. Controlled experiments have been carried out in order to verify the results. The known compounds were identified by comparing with authentic samples.

Reaction of 1,2-dihydropyridine (1a-c) with Benzyne under Thermal Conditions

A solution of (1a) (200 mg, 1.0 mmol) in 1,2-dichloroethane (10 ml) contained in a 100-ml, three-necked, round-bottomed flask equipped with a condenser was heated to reflux under red light and nitrogen atmosphere. Two additional funnels attached to the flask contained anthranilic acid (150 mg, 1.1 mmol) dissolved

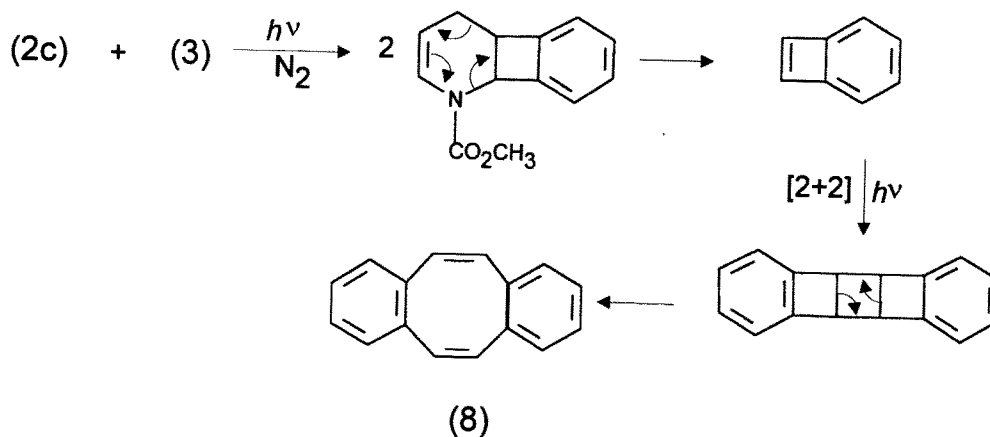


Figure 6.

in 1,2-dichloroethane (10 ml)/diglyme (5 ml) and iso-amylnitrate (120 mg, 1.02 mmol) in 1,2-dichloroethane (10 ml), respectively. Anthranilic acid and iso-amylnitrate were added simultaneously dropwise to the refluxing solution within 30 min. The solution was refluxed for 2 h, then stirred at room temperature for 13 h. The reaction mixture was filtered off and the solvent evaporated *in vacuo* to dryness. The crude product was separated by PLC, using toluene/ethyl acetate (4:1) as eluent. The corresponding pyridine (4) was obtained as a white solid, $R_f = 0.62$, 192 mg, 96%.

To a solution of (1b) (100 mg, 4.7 mmol) in 1,2-dichloroethane (5 ml) were added anthranilic acid (64 mg, 0.467 mmol) in 1,2-dichloroethane (5 ml)/diglyme (2 ml) and iso-amylnitrate (50 mg, 0.43 mmol) in 1,2-dichloroethane (5 ml). The reaction was carried out as above and the mixture was separated by PLC, using *n*-hexane/ethyl acetate (2:1) as eluent. The product was obtained as a white solid, $R_f = 0.51$, 56 mg, 56%, m.p. 42°C.

Dimethyl 5,6-benzo-2-methylbicyclo [2,2,2]-2-azacyclooct-7-ene-4,7-dicarboxylate (5)

IR (KBr): $\bar{\nu} = 3050$ (CH aromatic), 1710 (C=O), 1680 cm^{-1} (C=O). $^1\text{H-NMR}$ (CDCl_3): $\delta = 1.2$ (s, 2H, 3-H), 3 (s, 3H, N- CH_3), 3.6 (s, 3H, C=C- CO_2CH_3), 3.8 (s, 3H, $\text{CO}_2\text{-CH}_3$), 6.1 (s, 1H, 1-H), 7.2-7.8 ppm (m, 5H, aromatic hydrogens and 8-H). $^{13}\text{C-NMR}$ (CDCl_3): $\delta = 49.4$ (N- CH_3), 51.0 (O- CH_3), 53.3 (O- CH_3), 62.3 (3-C), 67.1 (4-C), 79.2 (1-C), 127.5, 129, 129.5, 131.1, 133, 136.7 (C-aromatic), 140 (8-C), 162 (7-C), 170.3 (=C-C=O), 173.2 (-C-C=O). EI-MS (70 eV): $m/e = 287$ (M^+ , 58%), 272 (51), 244 (39), 228 (90), 185 (86). UV (methanol): λ_{max} ($\lg \epsilon$) = 396 nm (3.537), 280 (4.195).

To a solution of (1c) (320 mg, 2.3 mmol) in 1,2-dichloroethane (5 ml) were added anthranilic acid (340 mg, 2.48 mmol) in 1,2-dichloroethane (10 ml)/diglyme (4

ml) and iso-amylnitrate (270 mg, 2.32 mmol) in 1,2-dichloroethane (10 ml). The mixture was separated by PLC using *n*-hexane/ethyl acetate (10:1) as eluent. The product was obtained (naphthalene) as a white solid, $R_f = 0.71$, 94 mg, 29.5%.

Reaction of 1,4-dihydropyridine (2a) with Benzyne under Thermal Conditions

To a solution of (2a) (200 mg, 1.0 mmol) in 1,2-dichloroethane (10 ml) were added anthranilic acid (150 mg, 1.1 mmol) dissolved in 1,2-dichloroethane (10 ml)/diglyme (5 ml) and iso-amylnitrate (120 mg, 1.02 mmol) in 1,2-dichloroethane (10 ml), respectively.

The reaction was carried out as the reaction of 1,2-dihydropyridine (1a) with benzyne under thermal conditions and the mixture was separated by PLC, using toluene/ethyl acetate (5:2) as eluent. The corresponding pyridine (4) was obtained as a white solid, $R_f = 0.57$, 141 mg, 70.5%.

Irradiation of 1,4-dihydropyridine (2c)

1,4-Dihydropyridine (2c) (100 mg, 0.719 mmol) in 1,2-dichloroethane (5 ml) was irradiated under oxygen atmosphere for 1.5 h. TLC of the reaction mixture, using *n*-hexane/ethyl acetate (5:1) showed only one spot. Solvent was evaporated *in vacuo* at 40°C, the product (pyridine) was obtained as a colorless liquid, 56 mg, 98.5%.

The same mixture was irradiated under a nitrogen atmosphere for 1.5 h. The crude product was purified by PLC, using cyclohexane/chloroform (3:1) as eluent. The product (7) was obtained as a white solid, $R_f = 0.59$, 52 mg, 46%, m.p. 70-73°C.

Irradiation of 1,4-dihydropyridine (2c) with Benzyne

A solution of anthranilic acid (200 mg, 1.46 mmol) in 1,2-dichloroethane (40 ml)/diglyme (2 ml) was added to a photochemical cell. The mixture was cooled to 0°C,

then 1,4-dihydropyridine (2c) (200 mg, 1.44 mmol) in 1,2-dichloroethane (5 ml) was added to the mixture under a nitrogen atmosphere and was irradiated by UV light. During the irradiation iso-amyl nitrite (160 mg, 1.38 mmol) was added slowly and irradiation was continued for 1.5 h. The temperature was maintained at about 30°C. The solvent was evaporated and the mixture was separated by PLC using *n*-hexane/ethyl acetate (10:1) as eluent. Two major products (7) and (8) were separated. Compound (7) was obtained as a white solid, 89 mg, 30% and compound (8) was as liquid 42 mg, 14.2%.

1,2,5,6-Dibenzo-1,3,5,7-cyclooctatetraene (8)

IR (KBr): $\bar{\nu}$ = 3040 (CH aromatic), 1600 (C=C), 1470 (C=C) 880, 750, 690 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): δ = 6.35-6.40 (d, 4H, H-C=olefinic), 6.6-6.8 (t, 4H, H-C=aromatic), 7.05-7.25 ppm (t, 4H, H-C=aromatic). $^{13}\text{C-NMR}$ (CDCl_3): δ = 115.249 (10-C), 118.519 (9-C), 129.418 (8-C), 146.750 ppm (1-C). EI-MS (70 eV): m/e = 205 (M^{0+} , 1.2%), 128 (69), 127 (10), 102 (9), 76 (7), 52 (100), 51 (52). UV (cyclohexane): λ_{max} ($\lg \epsilon$) = 222.4 nm (4.497), 224.4 (4.460), 231.2 (4.756), 268.8 (3.381). $\text{C}_{16}\text{H}_{12}$ (204.27): Calcd. C 94.1, H 5.9; Found. C 94.8, H 5.3.

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