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NOVEL APPROACH TO THE SYNTHESIS OF 1,3-DIAZAPYRENES

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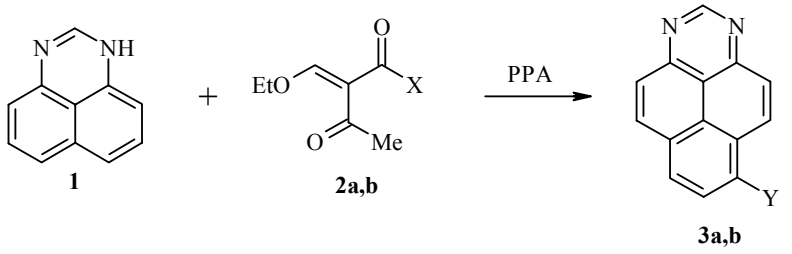
Methods have been developed for the synthesis of 1,3-diazapyrenes based on the reactions of perimidines with ethoxymethylene-1,3-dicarbonyl compounds and also 6(7)-benzoyl(acetyl, formyl)perimidines with carbonyl compounds in PPA.

Keywords: 6(7)-acetylperimidine, 6(7)-benzoyl(acetyl)perimidines, 1,3-diazapyrenes, carbonyl compounds, perimidine-6(7)-carbaldehyde, perimidines, polyphosphoric acid (PPA), cyclization.

A series of methods has been developed previously for the synthesis of 1,3-diazapyrenes **3** based on the *peri*-annelation of a carbocyclic ring to a perimidine using α,β-dicarbonyl compounds in PPA [1-4]. The overall drawback of these methods is their restriction to just acrolein prepared *in situ* from glycerine and to unsaturated ketones containing an aryl substituent in a β-position. The use of 1,3-dicarbonyl compounds (e.g. acetylacetone) also failed to give the desired result [4] hence it was of interest to develop a more universal method for synthesis of these compounds.

We have proposed that such a method limitation is associated with the lack of high alkylating activity in both unsaturated aldehydes and ketones and in 1,3-dicarbonyl compounds. As a result the use of more active alkylation reagents such as ethoxymethyleneacetoacetic ester (**2a**) and ethoxymethyleneacetylacetone (**2b**) broadens the scope of the method.



1 **2a,b** **3a,b**

2 a X = OEt, **b** X = Me; **3 a** Y = OH, **b** Y = Me

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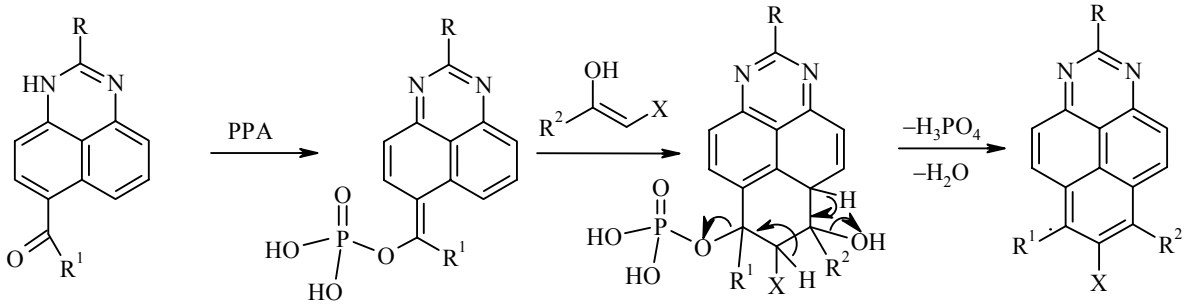
In fact, compounds **2a,b** react with perimidine **1** in PPA* at 75-80ºC unexpectedly to give 6-hydroxy-1,3-diazapyrene (**3a**, 28%) and 6-methyl-1,3-diazapyrene (**3b**, 34%) respectively. Desacetylation was observed along with the *peri*-cyclization.

We have previously shown [6] that the perimidine type carbonyl compounds **4a-d** react with 1,3,5-triazines to give 1,3,7-triazapyrenes. The ease of the electrophilic substitution of these compounds at position 7 can be rationalized by their possible phosphorylation to give compounds **5** in which the free *peri*-position is activated towards electrophile attack. We have proposed that the enol forms of the carbonyl compounds will react with compounds **5** to give the diazapyrenes **3** as a result of cyclocondensation or successive electrophilic attack.



4a–d **5a–d** **3b–h**

3 b–g R = H, **b** R^1 = X = H, R^2 = Me; **c** R^1 = X = H, R^2 = Ph; **d** R^1 = H, R^2 = Me, X = COOEt; **e** R^1 = R^2 = Me, X = H, **f** R^1 = Me, X = H, R^2 = Ph; **g** R^1 = R^2 = Ph; X = H; **h** R = R^1 = R^2 = Ph, X = H; **4, 5 a** R = R^1 = H, **b** R = H, R^1 = Me, **c** R = H, R^1 = Ph; **d** R = R^1 = Ph

In fact, the reaction of compounds **4a-d** with carbonyl compounds in PPA gives the diazapyrenes **3b-h** in 21-67% yield. It should be noted that, by contrast to acetylacetone, the reaction in the case of acetoacetic ester is not accompanied by desacylation and gives the product **3d**.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AS-200 (200 and 50 MHz respectively) instrument using $CDCl_3$ and with TMS as internal standard. Mass spectra were taken on an MAT-311A instrument. Monitoring of the reaction course and purity of the synthesized compounds was carried out on Silufol UV-254 plates with ethyl acetate as solvent. Column chromatography was carried out on L 40/100 silica gel with ethyl acetate as eluent.

Synthesis of 1,3-Diazapyrenes 3a,b Using Ethoxymethyleneacetoacetic Ester (2a) and Ethoxymethyleneacetylacetone (2b) (General Method A). A mixture of perimidine (0.168 g, 1 mmol), compound **2** (1.5 mmol), and PPA (4 g) was vigorously stirred for 5 h at 80-90ºC. The reaction mixture was poured into water (30 ml) and basified using ammonia solution to pH ~ 7-8. The mother liquor was refluxed to full evaporation of the ammonia and the crystals precipitated after cooling were extracted with ethyl acetate (3×50 ml). Solvent was evaporated and the residue was chromatographed.

6-Hydroxy-1,3-diazapyrene (3a, $C_{14}H_8N_2O$). Yield 0.062 g (28%); mp 303-305ºC (ethanol) (mp 303-305ºC [7]). A sample mixed with a known sample did not show a melting point depression and the ^{1}H NMR spectra were identical [7].

* The PPA used had an 86% P_2O_5 content and was prepared by method [5].

Synthesis of 1,3-Diazapyrenes 3b-h from the Perimidine Series Carbonyl Compound 4a-d (General Method B). A mixture of the corresponding compound **4a-d** (1 mmol), the corresponding carbonyl compound (3 mmol or 10 mmol in the case of acetone), and PPA (4 g) was vigorously stirred for 5 h at 70-80ºC. The reaction mixture was poured into water (30 ml), basified with an ammonia solution to pH ~ 7-8, and the crystals or oil formed after cooling were extracted with ethyl acetate (3×50 ml). Solvent was evaporated and the residue was chromatographed.

6-Methyl-1,3-diazapyrene (3b). A. Prepared from ethoxymethyleneacetylacetone in 0.074 g (34%) yield. B. Prepared from perimidine-6(7)-carbaldehyde and acetone in 0.052 g (24%) yield. B. Prepared from perimidine-6(7)-carbaldehyde and acetylacetone in 0.107 g (49%) yield; mp 178-179ºC (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 (3H, s, CH_3); 8.04 (1H, d, $J_{7,8}$ = 7.7, H-7); 8.20 (1H, d, $J_{9,10}$ = 9.5, H-9); 8.30 (1H, d, $J_{4,5}$ = 9.5, H-5); 8.37 (1H, d, $J_{7,8}$ = 7.7, H-8); 8.55 (1H, d, $J_{9,10}$ = 9.5, H-10); 8.82 (1H, d, $J_{4,5}$ = 9.5, H-4); 9.80 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 19.23 (1C), 125.97 (1C), 126.54 (1C), 127.61 (1C), 128.90 (1C), 129.16 (1C), 129.49 (1C), 131.00 (1C), 132.60 (1C), 134.41 (1C), 136.35 (1C), 138.62 (1C), 152.76 (1C), 153.28 (1C), 155.91 (1C). Found, %: C 82.67; H 4.56; N 12.77. $C_{15}H_{10}N_2$. Calculated, %: C 82.55; H 4.62; N 12.83.

6-Phenyl-1,3-diazapyrene (3c). B. Prepared from perimidine-6(7)-carbaldehyde and acetophenone in 0.118 g (42%) yield; mp 193-195ºC (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.59-7.64 (5H, m, C_6H_5); 8.15 (1H, d, $J_{7,8}$ = 7.7, H-7); 8.32 (1H, d, $J_{4,5}$ = 9.4, H-5); 8.41 (1H, d, $J_{7,8}$ = 7.7, H-8); 8.48 (1H, d, $J_{9,10}$ = 9.4, H–9); 8.76 (1H, d, $J_{4,5}$ = 9.4, H-4); 8.98 (1H, d, $J_{9,10}$ = 9.4, H-10); 9.76 (1H, s, H-2). Found, %: C 85.82; H 4.25; N 8.93. $C_{20}H_{12}N_2$. Calculated, %: C 85.69; H 4.32, N 9.99.

Ethyl 6-Methyl-1,3-diazapyrene-7-carboxylate (3d). B. Prepared from perimidine-6(7)-carbaldehyde and acetoacetic ester in 0.16 g (55%) yield; mp 153-154ºC (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (3H, t, *J* = 6.9, C<u>H</u>$_3$CH$_2$); 3.26 (3H, s, CH_3); 4.55 (2H, q, *J* = 6.9, CH_3C<u>H</u>$_2$); 8.22 (1H, d, $J_{9,10}$ = 9.5, H-9); 8.31 (1H, d, $J_{4,5}$ = 9.5, H-5); 8.55 (1H, d, $J_{9,10}$ = 9.5, H-10); 8.85 (1H, s, H-8); 8.93 (1H, d, $J_{4,5}$ = 9.5, H-4); 9.80 (1H, s, H-2). Found, %: C 74.58; H 4.81; N 9.58. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.47; H 4.86; N 9.65.

6,8-Dimethyl-1,3-diazapyrene (3e). B. Prepared from 6(7)-acetylperimidine and acetone in 0.049 g (21%) yield. B. Prepared from 6(7)-acetylperimidine and acetylacetone in 0.155 g (67%) yield; mp 207-209ºC (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 (6H, s, CH_3); 7.88 (1H, s, H-7); 8.19 (2H, d, *J* = 9.5, H-5,9); 8.74 (2H, d, *J* = 9.5, H-4,10); 9.73 (1H, s, H-2). Found, %: c 82.89; H 5.15; N 11.96. $C_{16}H_{12}N_2$. Calculated, %: C 82.73; H 5.21; N 12.06.

6-Methyl-8-phenyl-1,3-diazapyrene (3f, $C_{21}H_{14}N_2$). B. Prepared from 6(7)-benzoylperimidine and acetone in 0.082 g (28%) yield. B. Prepared from 6(7)-acetylperimidine and acetophenone in 0.165 g (56%) yield. B. Prepared from 6(7)-benzoylperimidine and acetylacetone in 0.153 g (52%) yield; mp 198-199ºC (benzene), (mp 198-199ºC [4]). A sample mixed with a known sample did not give a melting point depression and the ^{1}H NMR spectra were identical [4].

6,8-Diphenyl-1,3-diazapyrene (3g, $C_{26}H_{16}N_2$). B. Prepared from 6(7)-benzoylperimidine and acetophenone in 0.171 g (48%) yield; mp 175-176ºC (ethyl acetate) (mp 175-176ºC [4]). A sample mixed with a known sample did not give a melting point depression and the ^{1}H NMR spectra were identical [4].

2,6,8-Triphenyl-1,3-diazapyrene (3h, $C_{32}H_{20}N_2$). B. Prepared from 2-phenyl-6(7)-benzoylperimidine and acetophenone in 0.229 g (53%) yield; mp 267-268ºC (a mixture of benzene and hexane) (mp 267-268ºC [4]). A sample mixed with a known sample did not give a melting point depression and the ^{1}H NMR spectra were identical [4].

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