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A new method for [*c*,*d*]pyridine *peri*-annelation: synthesis of azapyrenes from phenalenes and their dihydro derivatives

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Abstract

An effective synthesis of various azapyrenes from phenalenes and their dihydro derivatives has been developed using 1,3,5-triazines in polyphosphoric acid (PPA).

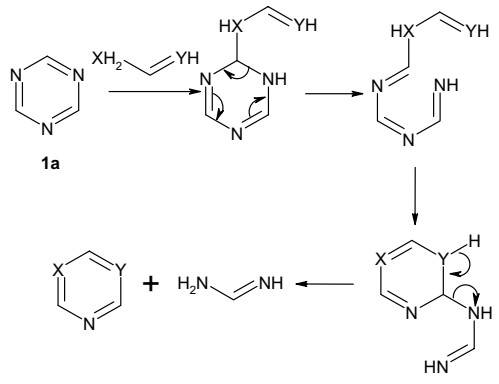
Keywords: Phenalenes; 1,3,5-Triazines; Polyphosphoric acid; Azapyrenes; *Peri*-Annelation

It is well known that 1,3,5-triazine can undergo ring cleavage upon treatment with nucleophilic reagents and serve as a formyl group precursor. This property has been extensively used in organic synthesis. Thus formamidines,[1a] perimidines,[1b] benzoimidazoles,[1b] benzothiazoles,[1b] benzoxazoles,[1b] purines,[1b] pyridines,[1c,d] pyrimidines,[1c,e,f] and [1,6]naphthyridines[1g–i] have been obtained utilizing different nucleophiles in reactions with 1,3,5-triazine (**1a**).

In the case of 1,3-binucleophiles, two aza-formyl groups of 1,3,5-triazine (**1a**) are involved in the reaction (Scheme 1). As a result of cyclization, a new six-membered ring is formed.

Currently, there exist four examples of 1,3,5-triazine reactions with 1,3-binucleophiles: syntheses of substituted triazines,[2a] 4-aminopyridines,[2b] 4-hydroxypyridines,[2c] and pyrimidines[1c] (Scheme 2). The common drawback of these methods is that they are limited to 1,3,5-triazine (**1a**) itself.

On the basis of the mechanism shown in Scheme 1, we presumed that 1,3,5-triazine would be a suitable reagent for *peri*-annelation of the [*c*,*d*]pyridine nucleus of azaphenalenes (X = Y = phenalenes *peri*-positions).



Scheme 1. Mechanism of the reaction of 1,3,5-triazine (**1a**) with 1,3-binucleophiles.

We chose the transformation of perimidines **2** to 1,3,7-triazapyrenes **3** as a test reaction. However, the reaction did not occur utilizing the conditions (HCl/MeCN or EtONa/EtOH) described in the above mentioned reports.[2] Therefore, we used PPA as a non-nucleophilic acid catalyst. Pleasingly, heating perimidines **2** with a 1.5-M excess of 1,3,5-triazines **1a**–**c** in the medium of PPA[3] (~3 g) yielded the previously unknown 1,3,7-triazapyrenes **3a**–**f** (Scheme 3, Table 1).[4]

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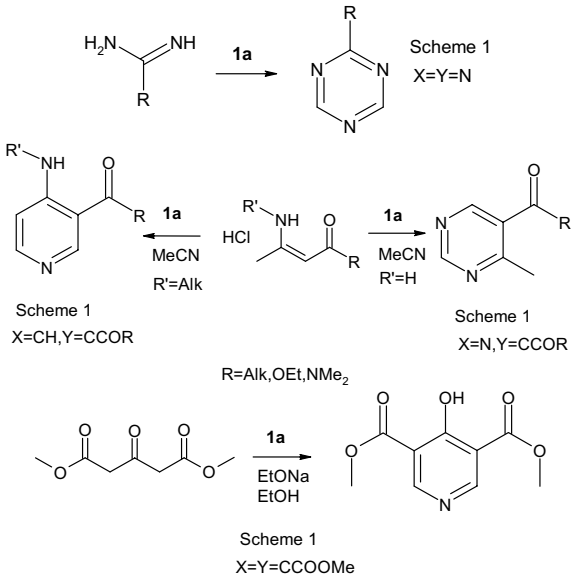
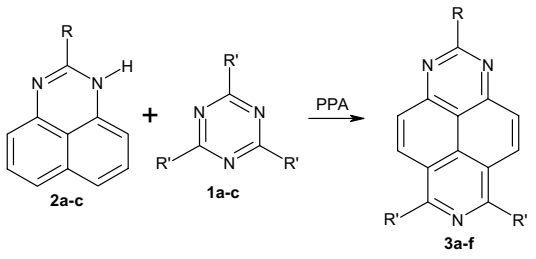


Scheme 2. Known reactions of 1,3,5-triazine (**1a**) with 1,3-binucleophiles.



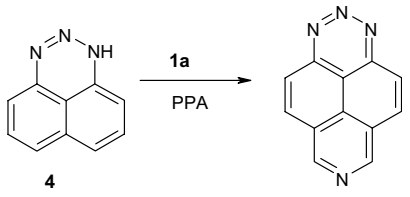
Scheme 3. Synthesis of 1,3,7-triazapyrenes (**3**).

Table 1
Synthesis of 1,3,7-triazapyrenes

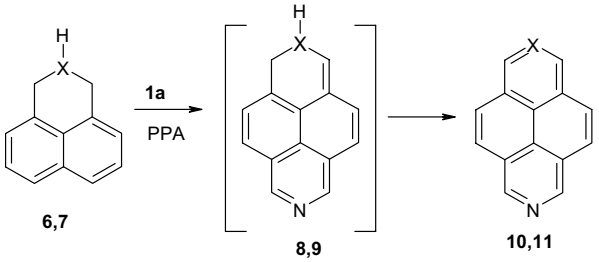
Entry	R	R′	Product	Yield (%)
1	H (**2a**)	H (**1a**)	**3a**	63
2	Me (**2b**)	H (**1a**)	**3b**	55
3	Ph (**2c**)	H (**1a**)	**3c**	56
4	H (**2a**)	Me (**1b**)	**3d**	71
5	Me (**2b**)	Me (**1b**)	**3e**	52
6	H (**2a**)	Ph (**1c**)	**3f**	78

In a similar way the reaction proceeded with 1*H*-naphtho[1,8-*de*][1,2,3]triazine (1,2,3-triazaphenalene, **4**) (Scheme 4). The yield of the previously unknown product 1,2,3,7-tetraazapyrene (**5**) was 68%.

Using the mechanism in Scheme 1, we further hypothesized that the reaction should be applicable to dihydrophenalenes and dihydroazaphenalenes. For the formation of azapyrenes an additional dehydrogenation step would be required. Indeed, heating dihydrophenalenes **6** and **7** in PPA gave rise to the corresponding 2-azapyrene (**10**)[4] and 2,7-diazapyrene (**11**)[4] in 74% and 55% yields, respectively. Presumably, intermediates **8** and **9** undergo spontaneous dehydrogenation during the reaction (Scheme 5).



Scheme 4. 1,2,3,7-Tetraazapyrene (**5**) synthesis.



6,8,10: X=CH, **7,9,11:** X=N

Scheme 5. Synthesis of 2-azapyrene (**10**) and 2,7-diazapyrene (**11**).

Table 2
Conditions for azapyrene syntheses

Product	Temperature (°C)	Reaction time (h)
3a	100	1.5
3b	100	1.5
3c	100	1.5
3d	140	1.5
3e	140	1.5
3f	180	1.5
5	60 and then	1
	100	3
10	100 and then	2
	140	3
11	100 and then	2
	140	3

In conclusion, the advantages of the method described for [*c*,*d*]pyridine cycle *peri*-annelation include reagent availability, experimental simplicity and its applicability to the synthesis of a broad range of substituted triazapyrenes.

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3. PPA containing 86% P_2O_5 was used; preparation according to: Uhlig, F. *Angew. Chem.* **1954**, *66*, 435.
4. *General procedure*: a mixture of compounds **2**, **4**, **6**, or **7** (1 mmol), corresponding 1,3,5-triazine (**1a**–**c**) (1.5 mmol), and PPA (2–3 g) was stirred under conditions according to Table 2. After cooling to 80–85 °C, the reaction mixture was poured into cold water (25 ml) with vigorous stirring and ammonia was added to pH ~ 8. The precipitate was filtered off, washed with water, and dried. Compounds **3**, **10**, and **11** were purified by recrystallization. Compound **5** was purified by flash chromatography on silica gel, eluting with ethyl acetate.

   Data for 1,3,7-triazapyrene (**3a**): yellow crystals; mp 240–242 °C (octane; with sublimation). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (2H, d, $J = 9.24$ Hz, 4/10-H); 8.63 (2H, d, $J = 9.24$ Hz, 5/9-H); 9.70 (2H, s, 6/8-H); 9.91 (1H, s, 2-H). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.26 (2H, d, $J = 9.22$ Hz, 4/10-H); 8.80 (2H, d, $J = 9.22$ Hz, 5/9-H); 9.72 (2H, s, 6/8-H); 9.76 (1H, s, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.81, 122.94, 125.00, 127.95, 133.29, 147.29, 153.90, 157.28. Anal. Calcd for $C_{13}H_7N_3$: C, 76.09; H, 3.44; N, 20.48. Found: C, 76.22; H, 3.01; N, 20.28.

   Data for 2-methyl-1,3,7-triazapyrene (**3b**): yellow crystals; mp 230–232 °C (octane; with sublimation). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.20 (3H, s, CH_3); 8.24 (2H, d, $J = 9.16$ Hz, 4/10-H); 8.62 (2H, d, $J = 9.16$ Hz, 5/9-H); 9.64 (2H, s, 6/8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.49, 111.95, 122.72, 125.17, 127.62, 133.22, 147.13, 154.22, 167.14. Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.47; H, 3.96; N, 19.41.

   Data for 2-phenyl-1,3,7-triazapyrene (**3c**): white crystals; mp 260–261 °C (octane; with sublimation). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (3H, m, *m*- and *p*-H C_6H_5); 8.40 (2H, d, $J = 9.25$ Hz, 4/10-H); 8.64 (2H, br d, *o*-H C_6H_5); 8.86 (2H, d, $J = 9.25$ Hz, 5/9-H); 9.68 (2H, s, 6/8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.20, 123.76, 126.48, 128.77, 129.12, 129.20, 130.53, 130.99, 133.85, 147.90, 155.30, 167.48. Anal. Calcd for $C_{19}H_{11}N_3$: C, 81.12; H, 3.94; N, 14.94. Found: C, 80.92; H, 3.77; N, 15.17.

   Data for 6,8-dimethyl-1,3,7-triazapyrene (**3d**): yellow crystals; mp 225–226 °C (octane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (6H, s, 6/8-CH_3); 8.19 (2H, d, $J = 9.14$ Hz, 4/10-H); 8.72 (2H, d, $J = 9.14$ Hz, 5/9-H); 9.80 (1H, s, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.64, 111.27, 118.48, 124.48, 124.63, 131.14, 152.96, 153.78, 165.46. Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.02; H, 4.65; N, 18.11.

   Data for 2,6,8-trimethyl-1,3,7-triazapyrene (**3e**): orange crystals; mp 206–208 °C (octane). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.98 (3H, s, 2-CH_3); 3.08 (6H, s, 6/8-CH_3); 7.92 (2H, d, $J = 9.4$ Hz, 4/10-H); 8.67 (2H, d, $J = 9.4$ Hz, 5/9-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.64, 25.80, 111.27, 118.48, 124.41, 124.63, 131.14, 152.96, 153.78, 165.46. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.87; H, 5.18; N, 16.72.

   Data for 6,8-diphenyl-1,3,7-triazapyrene (**3f**): yellow crystals; mp 257–259 °C (ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69 (6H, m, *m*- and *p*-H C_6H_5); 7.95 (4H, br d, $J = 7.4$ Hz, *o*-H C_6H_5); 8.31 (2H, d, $J = 9.50$ Hz, 4/10-H); 8.79 (2H, d, $J = 9.50$ Hz, 5/9-H); 9.86 (1H, s, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.48, 124.63, 127.42, 128.41, 128.69, 130.02, 132.10, 133.12, 133.38, 152.94, 153.67, 167.89. Anal. Calcd for $C_{25}H_{15}N_3$: C, 84.01; H, 4.23; N, 11.76. Found: C, 84.16; H, 4.18; N, 11.66.

   Data for 1,2,3,7-tetraazapyrene (**5**): yellow crystals; mp 212–214 °C (ethyl acetate; with dec.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.35 (2H, d, $J = 9.50$ Hz, 4/10-H); 8.92 (2H, d, $J = 9.50$ Hz, 5/9-H); 9.83 (2H, s, 6/8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.54, 122.37, 125.03, 128.88, 133.69, 149.24, 157.17. Anal. Calcd for $C_{12}H_6N_4$: C, 69.90; H, 2.93; N, 27.17. Found: C, 70.06; H, 2.86; N, 27.08.

   Data for 2-azapyrene (**10**): yellow crystals; mp 163–165 °C (ethanol/water; with sublimation). Lit.[5] mp 162–165 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (1H, t, $J = 7.96$ Hz, 7-H); 7.62 (2H, d, $J = 9.14$ Hz, 5/9-H); 7.82 (2H, d, $J = 7.96$ Hz, 6/8-H); 7.96 (2H, d, $J = 9.14$ Hz, 4/10-H); 9.12 (2H, s,1/3-H). Anal. Calcd for $C_{15}H_9N$: C, 88.65; H, 4.46; N, 6.89. Found: C, 88.79; H, 4.41; N, 6.80.

   Data for 2,7-diazapyrene (**11**): yellow crystals; mp 283–285 °C (octane). Lit.[6] mp 282–284 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (4H, s, 4/5/9/10-H); 9.38 (4H, s, 1/3/6/8-H). Anal. Calcd for $C_{14}H_8N_2$: C, 82.34; H, 3.95; N, 13.72. Found: C, 82.51; H, 3.86; N, 13.63.
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