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SYNTHESIS OF 1H-1,5,7-TRIAZACYCLOPENTA[*c,d*]PHENALENES BY THE ELECTROPHILIC AMINATION OF PERIMIDINES USING SODIUM AZIDE IN PPA

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A method was developed for the synthesis of 1H-1,5,7-triazacyclopenta[c,d]phenalenes by the electrophilic amination of perimidines using the new sodium azide/PPA reagent system and a subsequent one-pot reaction with 1,3,5-triazines. A multicomponent variant of this reaction is possible in the case of 2,4,6-trimethyl- and 2,4,6-triphenyl-1,3,5-triazines.

Keywords: sodium azide, perimidines, PPA, 1H-1,5,7-triazacyclopenta[*c,d*]phenalenes, 1,3,5-triazines, amination.

It is difficult to overstate the importance of indole derivatives among biologically active compounds. Benzo[*c,d*]indoles occupy a special position and include efficient thymidylate synthase inhibitors [1].

The standard methods for the synthesis of such compounds involve annelation of a benzene [2] or pyrrole ring [3] starting from 1-naphthylamines containing a carbonyl [3] or cyano group [1, 3] in the neighboring *peri* position. When there is an electron-donor group at position 5, the carbonyl group may be introduced in reaction [3, 4].

Prior to our work benzo[*c,d*]indole derivatives of perimidine had not been reported. This was primarily a consequence of the lack of availability of perimidines containing an amino group in the *peri* position due to the low yield of the corresponding nitro derivatives [5]. We have recently proposed a method for the preparation of such compounds based on the Schmidt reaction and thermal cyclization of the intermediate amide [6]. However, this method does not yield 1H-1,5,7-triazacyclopenta[*c,d*]phenalenes **3** lacking substituents in the pyrrole ring.

In the present work, we propose a method of synthesis for such compounds involving electrophilic amination [7, 8] by means of the sodium azide/PPA reagent system recently discovered in our laboratory and subsequent reaction with 1,3,5-triazines. The PPA sample used containing 87% P_2O_5 was obtained according to Uhlig [9].

As noted in our previous work [7, 8], the reaction of perimidines **1a-c** with a threefold excess of sodium azide in PPA at 80-90°C leads to the corresponding 6(7)-aminoperimidines **3a-c** in high yield. The mechanism proposed in our previous work [7, 8] involves formation of intermediates **2**, which subsequently undergo hydrolysis.

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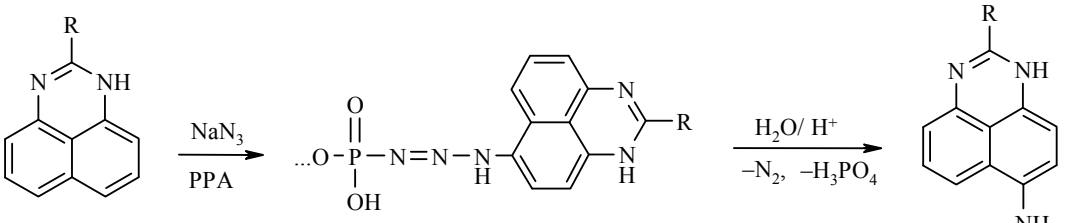
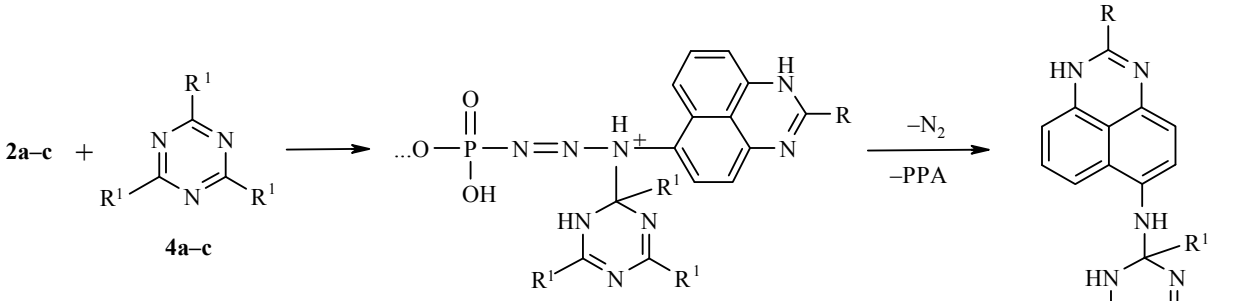


1a–c **2a–c** **3a–c**

1–3 a R = H, **b** R = Me, **c** R = Ph

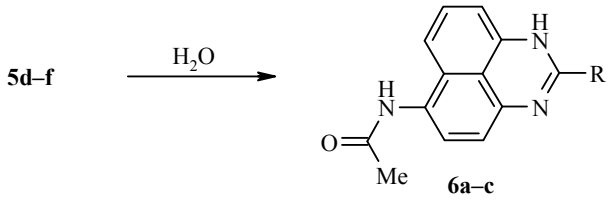
We proposed that intermediates **2a-c** may not only undergo protonation but also react with two electrophilic reagents such as 1,3,5-triazines. In this case, the reaction should proceed as in the following scheme.



4a–c **5a–i**

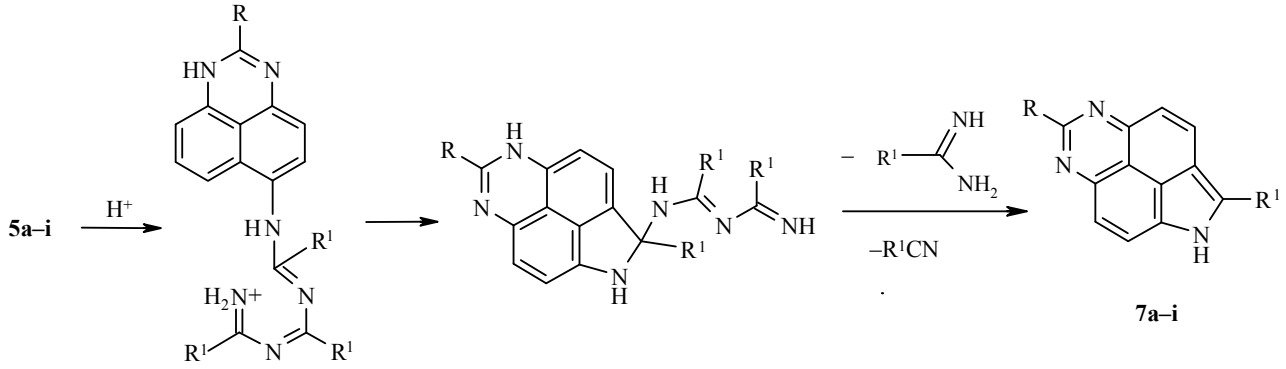
4 a R^1 = H, **b** R^1 = Me, **c** R^1 = Ph; **5 a** R = R^1 = H, **b** R = Me, R^1 = H, **c** R = Ph, R^1 = H, **d** R = H, R^1 = Me, **e** R = R^1 = Me, **f** R = Ph, R^1 = Me, **g** R = H, R^1 = Ph, **h** R = Me, R^1 = Ph, **i** R = R^1 = Ph

The subsequent fate of compounds **5a-i** depends on the reaction conditions. If, after addition of triazines **4**, the reaction mixture is maintained for 2 h at 70-80°C and treated with water, the reaction product will be the corresponding amide **6a-c**.



6a–c

6 **a** R = H, **b** R = Me, **c** R = Ph

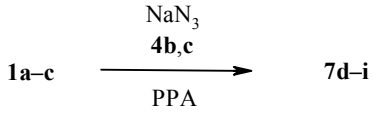


7a–i

7 a R = R^1 = H, **b** R = Me, R^1 = H, **c** R = Ph, R^1 = H, **d** R = H, R^1 = Me, **e** R = R^1 = Me, **f** R = Ph, R^1 = Me, **g** R = H, R^1 = Ph, **h** R = Me, R^1 = Ph, **i** R = R^1 = Ph

The five-membered ring is closed if the reaction temperature is raised to 100-110°C and the reaction time extended to 5 h to give 1H-1,5,7-triazacyclopenta[*c,d*]phenalenes **7a-i**.

A multicomponent reaction may occur in the case of triazines **4b**,**c**, while yield decreases insignificantly.



Thus, the feasibility of the *peri*-annelation of the pyrrole ring to give perimidines by means of electrophilic amination using sodium azide in PPA was demonstrated in this work.

EXPERIMENTAL

The ^{1}H NMR spectra were taken for **7b**,**e**,**g**,**i** on a Bruker WP-200 spectrometer at 200 MHz, while ^{1}H and ^{13}C NMR spectra were taken for **7a**,**f** on a JNM-ECX 400 spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with ethyl acetate or 3:1 ethyl acetate–ethanol as the eluent.

Commercial samples of 1,3,5-triazine (**4a**) and 2,4,6-triphenyl-1,3,5-triazine (**4c**) were obtained from Aldrich. 2,4,6-Trimethyl-1,3,5-triazine (**4b**) was prepared according to Schaefer and Peters [10].

Synthesis of Amides 6a-c (General Method). A mixture of corresponding perimidine **1a-c** (1 mmol) and sodium azide (0.195 g, 3 mmol) in PPA (2-3 g) was heated for 5 h at 80-90°C with stirring. Then, the temperature was lowered to 70-80°C and 2,4,6-trimethyl-1,3,5-triazine (**4b**) (0.135 g, 1.1 mmol) was added. The reaction mixture was stirred at this temperature for 2 h, then treated with 50 ml water, and neutralized by adding ammonium hydroxide. The precipitate formed was filtered off and purified by recrystallization from ethyl acetate.

6(7)-Acetaminoperimidine (6a) was obtained in 72% yield (0.162 g); mp 225-226°C (ethyl acetate) (mp 225-226°C [8]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [8].

6(7)-Acetamino-2-methylperimidine (6b) was obtained in 77% yield (0.184 g); mp 247-248°C (ethyl acetate) (mp 247-248°C [8]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [8].

6(7)-Acetamino-2-phenylperimidine (6c) was obtained in 79% yield (0.238 g); mp 302-303°C (ethyl acetate) (mp 302-303°C [8]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [8].

Synthesis of 1H-1,5,7-triazacyclopenta[*c,d*]phenalenes 7a-i (General Method). A. A mixture of corresponding perimidine **1a-c** (1 mmol) and sodium azide (0.195 g, 3 mmol) in PPA (2-3 g) was heated with stirring for 5 h at 80-90°C. Then, corresponding 1,3,5-triazine **4a-c** (1.1 mmol) was added, the temperature was raised to 100-110°C, and the mixture was stirred at this temperature for 5 h. The reaction mixture was then poured into water (30 ml) and neutralized by adding ammonium hydroxide. The precipitate formed was filtered off. The solution was extracted with six 30-ml toluene portions. The precipitate was extracted with 100 ml toluene in a Soxhlet apparatus for 5 h. The toluene solutions were combined and the solvent was evaporated off. The residue was purified by recrystallization.

B. The reaction was carried out analogously to method A but with the simultaneous mixing of all the components: corresponding perimidine **1a-c** (1 mmol), sodium azide (0.195 g, 3 mmol), and corresponding 1,3,5-triazine **4b** or **4c** (1.1 mmol) in PPA (2-3 g). The reaction mixture was treated similarly to the previous procedure.

1H-1,5,7-Triazacyclopenta[*c,d*]phenalene (7a) was obtained in 38% yield (0.073 g); mp 207-209°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.70 (1H, d, *J* = 9.0, H-3); 7.91 (1H, d, *J* = 8.7, H-9); 8.45 (1H, d, *J* = 8.7, H-8); 8.46 (1H, s, H-2); 8.51 (1H, d, *J* = 9.0, H-4); 9.48 (1H, s, H-6); 13.20 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 111.87, 112.86, 116.34, 120.09, 120.42, 120.56, 124.88, 131.06, 136.44, 147.82, 154.91, 163.04. Found, %: C 74.71; H 3.58; N 21.64. $C_{12}H_7N_3$. Calculated, %: C 74.60; H 3.65; N 21.75.

6-Methyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7b) was obtained in 41% yield (0.085 g) (method A); mp 237-238°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.93 (3H, s, CH_3); 7.65 (1H, d, *J* = 9.0, H-3); 7.82 (1H, d, *J* = 8.7, H-9); 8.42 (1H, d, *J* = 8.7, H-8); 8.46 (1H, s, H-2); 8.50 (1H, d, *J* = 9.0, H-4); 13.10 (1H, br. s, NH). Found, %: C 75.51; H 4.33; N 20.16. $C_{13}H_9N_3$. Calculated, %: C 75.35; H 4.38; N 20.28.

6-Phenyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7c) was obtained in 47% yield (0.085 g) (method A); mp 201-203°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57-7.63 (3H, m, H-3,4,5 Ph); 7.78 (1H, d, *J* = 8.4, H-3); 7.96 (1H, d, *J* = 8.5, H-9); 8.39 (1H, s, H-2); 8.43 (1H, d, *J* = 8.5, H-8); 8.51 (1H, d, *J* = 8.4, H-4); 8.73 (2H, d, *J* = 7.3, H-2,6 Ph); 13.10 (1H, br. s, NH). Found, %: C 80.43; H 4.03; N 15.54. $C_{18}H_{11}N_3$. Calculated, %: C 80.28; H 4.12; N 15.60.

2-Methyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7d) was obtained in 44% yield (0.091 g) (method A) and 43% yield (0.089 g) (method B); mp 259-260°C (benzene), (mp 259-260°C [6]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [6].

2,6-Dimethyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7e) was obtained in 47% yield (0.104 g) (method A) and 44% yield (0.097 g) (method B); mp 271-272°C (benzene), (mp 271-272°C [6]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [6].

2-Methyl-6-phenyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7f) was obtained in 45% yield (0.127 g) (method A) and 41% yield (0.116 g) (method B); mp 245-246°C (benzene–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.93 (3H, s, 6-CH_3); 7.48-7.58 (3H, m, H-3,4,5 Ph); 7.62 (1H, d, *J* = 9.0, H-3); 7.82 (1H, d, *J* = 8.7, H-9); 8.29 (1H, d, *J* = 8.7, H-8); 8.43 (1H, d, *J* = 9.0, H-4); 8.71 (2H, d, *J* = 8.4, H-2, H-6 Ph); 13.10 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 12.38, 112.66, 112.94, 117.12, 120.54, 120.61, 120.65, 124.85, 128.05 (2C), 128.22 (2C), 129.36, 130.88, 136.20, 140.09, 147.88, 155.12, 159.64. Found, %: C 80.66; H 4.56; N 14.78. $C_{19}H_{13}N_3$. Calculated, %: C 80.55; H 4.62; N 14.83.

2-Phenyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7g) was obtained in 41% yield (0.110 g) (method A) and 38% yield (0.102 g) (method B); mp 263-265°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.54 (3H, m, H-3,4,5 Ph); 7.66 (1H, d, *J* = 9.0, H-3); 7.79 (1H, d, *J* = 8.7, H-9); 8.18 (2H, d, *J* = 7.7, H-2,6 Ph); 8.33 (1H, d, *J* = 8.7, H-8); 8.69 (1H, d, *J* = 9.0, H-4); 9.33 (1H, s, H-6); 13.3 (1H, br. s, NH). Found, %: C 80.39; H 4.04; N 15.57. $C_{18}H_{11}N_3$. Calculated, %: C 80.28; H 4.12; N 15.60.

6-Methyl-2-phenyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7h) was obtained in 42% yield (0.119 g) (method A) and 39% yield (0.110 g) (method B); mp 291-202°C (benzene) (mp 291-292°C [6]). The ^{1}H NMR spectrum was identical to the spectrum given in our previous work [6].

2,6-Diphenyl-1H-1,5,7-triazacyclopenta[*c,d*]phenalene (7i) was obtained in 37% yield (0.128 g) (method A) and 34% yield (0.117 g) (method B); mp 169-171°C (benzene–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57-7.63 (3H, m, H-3,4,5 Ph); 7.78 (1H, d, *J* = 8.4, H-3); 7.96 (1H, d, *J* = 8.5, H-9); 8.39 (1H, s, H-2); 8.43 (1H, d, *J* = 8.5, H-8); 8.51 (1H, d, *J* = 8.4, H-4); 8.73 (2H, d, *J* = 7.3, H-2,6 Ph); 13.1 (1H, br. s, NH). Found, %: C 83.62; H 4.29; N 12.09. $C_{24}H_{15}N_3$. Calculated, %: C 83.46; H 4.38; N 12.17.

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