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OXIDATIVE S_NH-ALKOXYLATION OF 1,3,7-TRIAZAPYRENES

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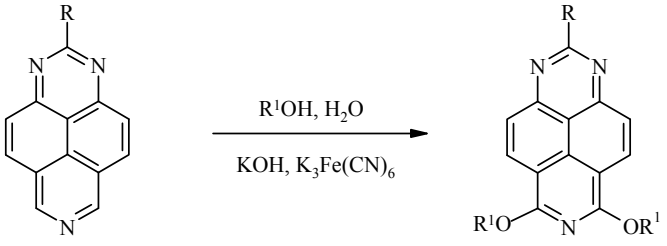
The classic strategies for synthesizing alkoxy derivatives of nitrogen heterocycles are based on the nucleophilic substitution of good leaving groups. Among these are also nonoxidative methods occurring *via* a *tele*-mechanism. Hence heteroarenes with di- or trichloromethyl substituents react with alkoxide anions to give products of substitution of hydrogen in the ring by an alkoxy group [1-4].

In the case of electron-deficient aza aromatic substrates a better alternative can be a direct oxidative nucleophilic substitution of hydrogen (ONSH [5]) by an alkoxy group since it does not need the preliminary introduction of good nucleofuges into the molecule. However, in the literature there are only individual examples of the successful alkoxylation of heterocycles *via* the ONSH process [6, 7].

In studying the reactivity of 1,3,7-triazapyrenes [8] relative to nucleophiles we unexpectedly found that they very readily undergo a double alkoxylation under unusual conditions. Reaction of 1,3,7-triazapyrene (**1a**) and its 2-methyl-substituted **1b** with excess KOH and $K_3Fe(CN)_6$ in aqueous methanol solution occurs at room temperature to give a high yield of the previously unknown 6,8-dimethoxy derivatives of this heterocycle (**2a** and **2b** respectively). A similar reaction with **1a** and ethyl or propyl alcohols gave the 6,8-diethoxy- (**2c**) and 6,8-dipropoxy-1,3,7-triazapyrene (**2d**).



1a,b **2a–d**

2 a R = H, R^1 = Me (98%), **b** R = R^1 = Me (89%), **c** R = H, R^1 = Et (91%), **d** R = H, R^1 = Pr (69%)

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Attempts to stop the reaction at the mono alkoxylation stage were not successful, the second alkoxylation evidently occurring no less readily than the first. With the donor effect of an alkoxy group in mind this fact does not agree with a traditional S_NAr mechanism. Consecutive exclusion of individual components of the reaction mixture showed that, in the absence of base or $K_3Fe(CN)_6$, the reaction does not occur. In the absence of water it is at least very strongly slowed down. Water is probably needed for increasing the solubility of the oxidant since the $K_3Fe(CN)_6$ is poorly soluble in alcohols. The limits of this alkoxylation method and its mechanism remain to be investigated.

The ^{1}H NMR spectra were taken on a Bruker-250 instrument (250 MHz) using DMSO-d_6 and ^{13}C NMR spectra on a Bruker DRX-500 (75 MHz) using $CDCl_3$ with TMS as internal standard. Mass spectra were obtained on an MX-1321A instrument (70 eV). Monitoring of the reaction course and the purity of the compounds synthesized was carried out by TLC on Silufol UV-254 plates.

Synthesis of Compounds 2a-d (General Method). A mixture of compound **1a** or **1b** (0.5 mmol), KOH (0.5 g, 9 mmol), $K_3Fe(CN)_6$ (1.0 g, 3 mmol), water (5 ml), and the corresponding alcohol (5 ml) was vigorously stirred at room temperature for 2 h (for the synthesis of **2a**), 3 h for **2b**, 5 h for **2c**, or for 16 h for **2d**. A further amount of $K_3Fe(CN)_6$ (1.0 g, 3 mmol) was added in the middle of the process. At the end of the reaction the mixture was poured into cold water (50 ml) and the precipitate formed was filtered off, washed with water, dried, and recrystallized from toluene.

6,8-Dimethoxy-1,3,7-triazapyrene (2a). Yield 0.13 g (98%). Yellow-green crystals; mp 260-261ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.32 (6H, s, 6,8-OCH_3); 7.78, 8.58 (4H, two d, ^3J = 9.3, AB system, H-4,5,9,10); 9.42 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 54.62, 106.46, 116.74, 122.58, 131.11, 131.25, 155.64, 157.70, 159.95. Mass spectrum, *m/z* (I_{rel}, %): 265 $[M]^+$ (100), 250 (23), 222 (25), 194 (10), 165 (14). Found, %: C 67.77; H 3.98; N 15.64. $C_{15}H_{11}N_3O_2$. Calculated, %: C 67.92; H 4.18; N 15.84.

6,8-Dimethoxy-2-methyl-1,3,7-triazapyrene (2b). Yield 0.124 g (89%). Yellow-green crystals; compound sublimes above 200ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.89 (3H, s, 2-CH_3); 4.30 (6H, s, 6,8-OCH_3); 7.75, 8.58 (4H, two d, ^3J = 9.3, AB system, H-4,5,9,10). Mass spectrum, *m/z* (I_{rel}, %): 279 $[M]^+$ (100), 263 (26), 236 (26), 208 (7). Found, %: C 68.56; H 4.89; N 15.22. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.04.

6,8-Diethoxy-1,3,7-triazapyrene (2c). Yield 0.133 g (91%). Yellow-green crystals; mp 235-236ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (6H, t, *J* = 6.9, 6,8-$OCH_2C\underline{H}_3$); 4.75 (4H, q, *J* = 6.9, 6,8-$OC\underline{H}_2CH_3$); 7.75, 8.57 (4H, two d, ^3J = 9.3, AB system, H-4,5,9,10); 9.40 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 14.57, 63.27, 106.11, 116.56, 122.08, 130.97, 131.07, 155.47, 157.60, 159.48. Mass spectrum, *m/z* (I_{rel}, %): 293 $[M]^+$ (83), 265 (10), 237 (100), 219 (31), 191 (35), 164 (19). Found, %: C 69.87; H 5.28; N 14.42. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.61; H 5.15; N 14.33.

6,8-Dipropoxy-1,3,7-triazapyrene (2d). Yield 0.111 g (69%). Yellow-green crystals; mp 167-168ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66 (6H, t, *J* = 7.2, 6,8-$OCH_2CH_2C\underline{H}_3$); 2.00 (4H, m, 6,8-$OCH_2C\underline{H}_2CH_3$); 4.61 (4H, t, *J* = 6.6, 6,8-$OC\underline{H}_2CH_2CH_3$); 7.72, 8.52 (4H, two d, ^3J = 9.3, AB system, H-4,5,9,10); 9.39 (1H, s, H-2). Mass spectrum, *m/z* (I_{rel}, %): 321 $[M]^+$ (44), 237 (100), 219 (21), 191 (21), 164 (10). Found, %: C 71.23; H 5.74; N 13.22. $C_{19}H_{19}N_3O_2$. Calculated, %: C 71.01; H 5.96; N 13.07.

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