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LETTERS TO THE EDITOR

Electrophilic Tropylation of 2-Aminopyridine

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Abstract—Electrophilic tropylation of 2-aminopyridine afforded *N*-(cyclohepta-2,4,6-trien-1-yl)pyridin-2-amine. The product was tested for antibacterial activity against *Staphylococcus aureus* no. 906 and *Candida albicans* ATSS 24433.

Keywords: 2-aminopyridine, tropylium chloride, tropylium tetrafluoroborate, tritylium tetrafluoroborate, X-ray analysis

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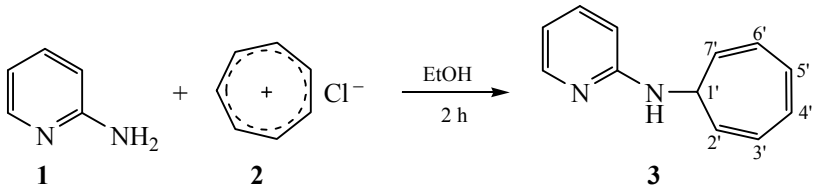
Interest in compounds containing a 1,3,5-cycloheptatriene (tropylidene) ring is related to their potential pharmacological activity [1, 2]; they can also be used for the synthesis of calixarenes that are promising for nanomedicine [3] and for studying mesomorphism [4].

The results of tropylation of primary and secondary aromatic amines with tropylium salts (chloride, perchlorate, and tetrafluoroborate) depend on the anion nature and solvent. The alkylation of aniline with tropylium perchlorate in THF [1] was shown to occur at the *para* position of the benzene ring with formation of stable 4-(cyclohepta-2,4,6-trien-1-yl)aniline possessing antimicrobial activity [2]. The tropylation of aniline with tropylium tetrafluoroborate in water involved the nitrogen atom [5] to produce unstable *N*-(cyclohepta-2,4,6-trien-1-yl)aniline which underwent dehydrogenation during the process with formation of more stable 8-phenyl-8-azaheptafulvenium salt. Analogous compounds were obtained from secondary aromatic amines and chlorotropylium perchlorate in methylene chloride [6]. It should be noted that, apart from dehydrogenation of N-alkylation product, reactions of aromatic amines with tropylium perchlorate can be accompanied by formation of aromatic Schiff bases via tropylidene contraction to benzylidene [2].

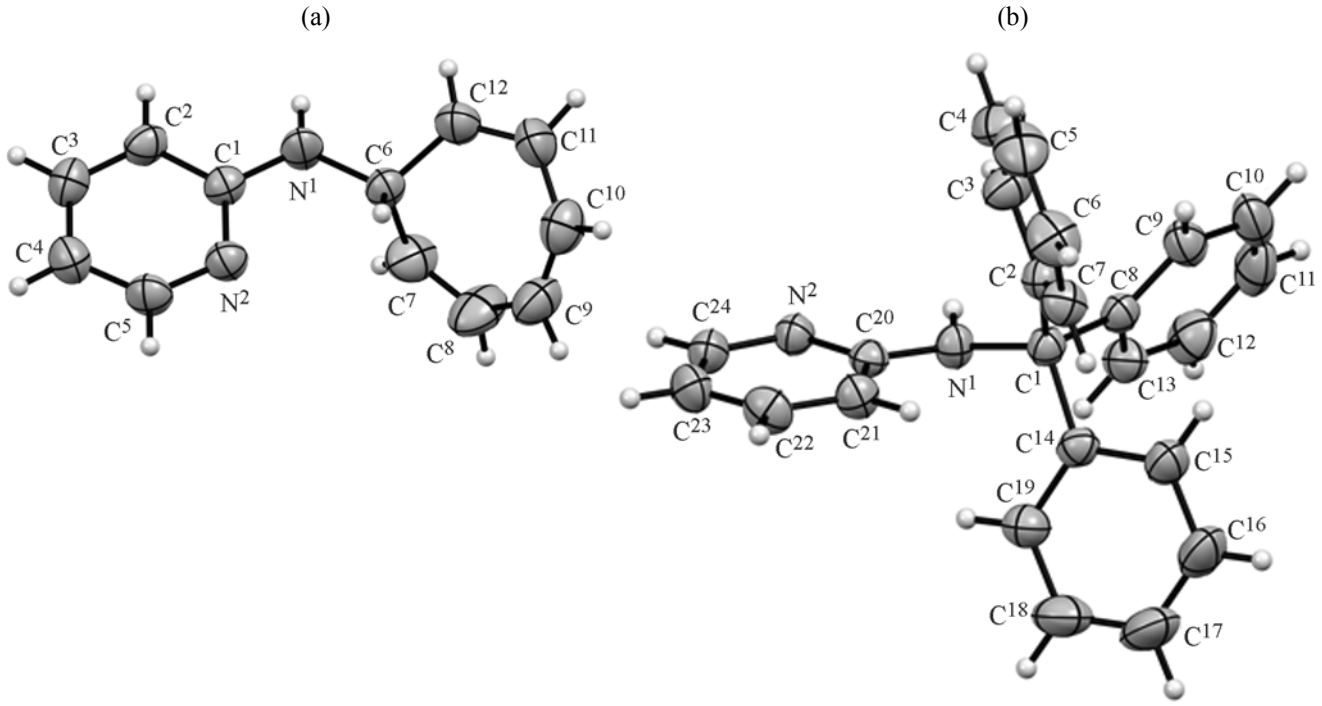
In continuation of our previous studies [1, 2], we now report electrophilic tropylation of 2-aminopyridine whose molecule possesses two nucleophilic centers, endocyclic nitrogen atom and nitrogen atom of the amino group. 2-Aminopyridine (**1**) reacted with tropylium chloride (**2**) in ethanol with selective formation of *N*-(cyclohepta-2,4,6-trien-1-yl)pyridin-2-amine (**3**) in 80% yield (Scheme 1). Unlike *N*-cycloheptatrienyl anilines [5], neither dehydrogenation of **3** with excess tropylium tetrafluoroborate (**4**) nor ring contraction to *N*-benzylidene derivative (as noted in [2]) was observed. When tritylium tetrafluoroborate (**5**) was used to effect dehydrogenation of **3**, the cycloheptatrienyl substituent was unexpectedly replaced by more electrophilic triphenylmethyl group with formation of *N*-tritylpyridin-2-amine **6** (Scheme 2).

The structure of **3** and **6** was confirmed by ^{1}H NMR and mass spectra and X-ray analysis (see figure).

Scheme 1.



1 **2** **3**



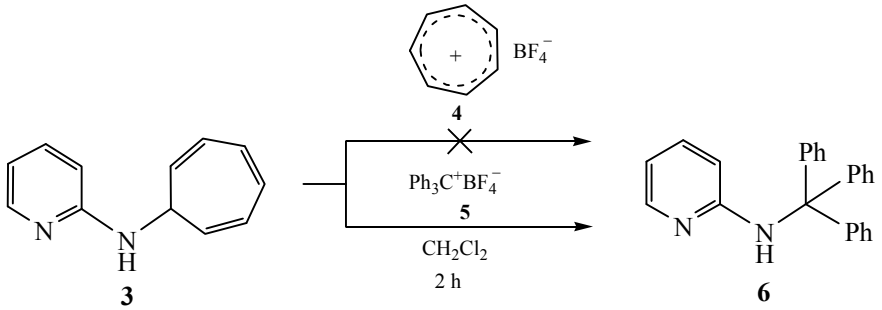
Structures of the molecules of (a) *N*-(cyclohepta-2,4,6-trien-1-yl)pyridin-2-amine (**3**) and (b) *N*-(triphenylmethyl)pyridin-2-amine (**6**) in crystal according to the X-ray diffraction data.

The antibacterial activity of compound **3** against *Staphylococcus aureus* № 906 and *Candida albicans* ATSS 24433 was assessed by the twofold serial dilution method [7]. Like 4-(cyclohepta-2,4,6-trien-1-yl)aniline [1], compound **3** at a concentration of 125.0 μg/mL showed a moderate bacteriostatic effect against the above bacterial strains. Bactericidal effect was observed at 125.0 and 250.0 μg/mL.

Tropylium chloride **2** was synthesized according to the procedure described in [8].

***N*-(Cyclohepta-2,4,6-trien-1-yl)pyridin-2-amine (3).** Pyridin-2-amine, 1.07 g (11 mmol), was added at room temperature to a solution of 0.96 g (5.5 mmol) of tropylium chloride (**2**) in 5 mL of ethanol. The mixture was stirred for 2 h, neutralized with 10% aqueous ammonia to pH 7, and left to stand for crystallization. The precipitate was filtered off and recrystallized from hexane. Yield 1.11 g (80%), white needles, mp 84–86° C (from hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.78–3.82 d.t (1H, 1′-H, J = 5.2, 5.2 Hz), 5.13 s (1H, NH), 5.48–5.52 d.d (2H, 2′-H, 7′-H, J = 9.2, 5.2 Hz), 6.26–6.30 m (2H, 3′-H, 6′-H), 6.37–6.40 d (1H, 3-H, J = 12.0 Hz), 6.61–6.64 m (2H, 4′-H, 5′-H), 6.75–6.76 t (1H, 5-H, J = 4.0, 4.0 Hz) , 7.41–7.46 m (1H, 4-H), 8.10–8.12 d (1H, 6-H, J = 6.0 Hz). Mass spectrum, m/z (I_{rel}, %): 184 (33.1) $[M]^+$, 183 (37.3), 106 (46.3), 91 (100), 78 (44.8).

Scheme 2.



***N*-(Triphenylmethyl)pyridin-2-amine (6).** Triphenylcarbenium perchlorate (**5**), 0.78 g (2.3 mmol), was added to a solution of 0.19 g (1 mmol) of *N*-(cyclohepta-2,4,6-trien-1-yl)pyridin-2-amine (**3**) in 7 mL of methylene chloride, and the mixture was refluxed for 2 h. The precipitate was filtered off and washed with methylene chloride (4 mL), the filtrate was neutralized with 10% aqueous ammonia to pH 7, and the precipitate was filtered off, washed with diethyl ether, and dried. Yield 0.20 g (60%), mp 146–148°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.79–5.82 d (1H, 3-H, J = 8.7 Hz), 6.14 s (1H, NH), 6.45–6.49 m (1H, 4-H), 6.99–7.04 m (1H, 5-H), 7.17–7.35 m (15N, Ph), 8.00–8.02 d (1H, 6-H, J = 6.0 Hz). Mass spectrum, m/z (I_{rel}, %): 336 (25.5) $[M]^+$, 243 (100.0), 165 (48.2), 78 (9.2).

The ^{1}H NMR spectra were recorded on Varian Mercury 300BB (300 MHz) and Bruker Avance III HD (400 MHz) spectrometers using hexamethyldisiloxane was internal standard. The mass spectra (electron impact, 70 eV) were obtained on an Agilent Technologies 6890N/5975B GC/MS system; HP-5ms column, 30 m × 0.25 mm, film thickness 0.25 μm; carrier gas helium; oven temperature 100°C, injector temperature 260, 270°C.

The X-ray diffraction data for compounds **3** and **6** were acquired on an Xcalibur R diffractometer. Corrections for absorption were applied empirically by the multiscan method using SCALE3 ABSPACK algorithm [9]. The structures were solved by the direct method and were refined by the full-matrix least-squares method using SHELX97 [10].

Compound **3**. Monoclinic crystal system, space group $I112/a$; $C_{12}H_{12}N_2$, M 184.24; unit cell parameters at 295(2) K: a = 33.356(13), b = 9.458(2), c = 6.4891(17) Å; β = 90.635(16)°; V = 2047.1(11) Å^3; d_{calc} = 1.196 g/cm^3; μ = 0.072 mm^{-1}; Z = 8; λ(Mo$K_α$) = 0.71073 Å. The structure was refined as twin with the twinnig matrix [–1 0 0, 0 1 0, 0 0 –1]. Final divergence factors: R_1 = 0.0494, wR_2 = 0.1037 [1624 reflections with $I > 2σ(I)$]; R_1 = 0.0732, wR_2 = 0.1203 (2348 independent reflections); goodness of fit S = 1.022; twin component ratio 0.616(2) : 0.384(2).

Compound **6**. Monoclinic crystal system, space group $P2_1/c$; $C_{24}H_{20}N_2$, M 336.42; unit cell parameters at 295(2) K: a = 13.376(3), b = 9.606(2), c = 14.772(4) Å; β = 103.24(3)°; V = 1847.6(8) Å^3; d_{calc} = 1.209 g/cm^3; μ = 0.071 mm^{-1}; Z = 4; λ(Mo$K_α$) 0.71073 Å. Final divergence factors: R_1 = 0.0489, wR_2 = 0.1199 [3137 reflections with $I > 2σ(I)$]; R_1 = 0.0725, wR_2 = 0.1338 (4366 independent reflections); goodness of fit S = 1.064.

The crystallographic data for compounds **3** and **6** were deposited to the Cambridge Crystallographic Data Centre [CCDC entry nos. 1 488 927 (**3**), 1 488 928 (**6**)].

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REFERENCES

1. Yunnikova, L.P. and Akent'eva, T.A., RU Patent no. 2 479 571, 2013; *Byull. Izobret*., 2013, no. 11.
2. Yunnikova, L. P., Akent'eva, T.A., and Esenbaeva, V.V., *Pharm. Chem. J*., 2015, vol. 49, no. 4, p. 243. doi 10.1007/s11094-015-1263-3
3. Fehlinger, M. and Abraham, W., *J. Inclusion Phenom. Macrocyclic Chem*. 2007, vol. 58, nos. 3–4, p. 263. doi 10.1007/s10847-006-9153-7
4. Esenbaeva, V.V., Smirnova, A.I., Usol'tseva, N.V., Yunnikova, L.P., and Akent'eva, T.A., *Zhidk. Kryst. Ikh Prakt. Ispol'z*., 2015, vol. 15, no. 2, p. 26.
5. Sanechika, K., Kajigaeshi, S., and Kanemasa, S., *Synthesis*, 1977, no. 3, p. 202. doi 10.1055/s-1977-24325
6. Föehlisch, B. and Haug, E., *Chem. Ber*., 1971, vol. 104, no. 7, p. 2324. doi 10.1002/cber.1971104073
7. *Rukovodstvo po eksperimental'nomu (doklinicheskomu) izucheniyu novykh farmakologicheskikh veshchestv* [Manual on Experimental (Preclinical) Testing of New Pharmacological Agents], Fisenko, V.P., Ed., Moscow: IIA Remedium, 2000.
8. Kursanov, D.N. and Vol'pin, M.E., *Dokl. Akad. Nauk SSSR*, 1957, vol. 113, no. 2, p. 339.
9. *CrysAlisPro. Version 1.171.37.33. CrysAlis171. NET*. Agilent Technologies.
10. Sheldrick, G.M., *Acta Crystallogr., Sect. A*, 2008, vol. 64, p. 112. doi: 10.1107/S0108767307043930