One-Pot Three-Component Synthesis of N-Arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines

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Received April 2, 2013; revised April 30, 2013; accepted May 3, 2013

ABSTRACT

We report a one-pot three-component synthesis of N-arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines by using various aromatic imines, tropylium tetrafluoroborate, and sodium tetrahydroborate in the presence of imidazole as activator.

Keywords: Imines; Tropylium Tetrafluoroborate; Sodium Tetrahydroborate; N-Arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines

1. Introduction

Nitrogen-containing compounds with the 1,3,5-cycloheptatriene fragment have a marked biological action [1, 2]. The use of tropylium salts (tetrafluoroborate or perchlorate) is a method to introduce the 1,3,5-cycloheptatriene cycle into aniline molecules and into its substituted molecules. Anion in a tropylium salt influences the N-[3] or C-[1] tropylation process of aniline, of arylamines or of N-substituted anilines, and a yield of final products.

Interaction between tropylium tetrafluoroborate and aniline or arylamines proceeds as N-tropylation of amino-group with subsequent transformation to 8-aryl-8-azaheptafulvenes [3]. Reaction with N,N-dimethylaniline proceeds as C-tropylation; however, the expected 7-(4-N,N-dimethylaminophenyl)-1,3,5-cycloheptatriene was not educed. Its isomer, namely 3-(4-N,N-dimethylaminophenyl)-1,3,5-cycloheptatriene (18% yield), was identified from a mixture of reaction products [4].

A good result was obtained after replacement of tetrafluoroborate with tropylium perchlorate to react with N, N-dimethylaniline or with aniline; this reaction is known to proceed as C-tropylation and enables educing 7-(4-N,N-dimethylaminophenyl)-1,3,5-cycloheptatriene (up to 76% yield), or 7-(4-aminophenyl)-1,3,5-cycloheptatriene (up to 82% yield). The latter compound has a marked antimycobacterial action against Staphylococcus aureus, Staphylococcus epidermis, Staphylococcus saprophyticus bacteria, and Candida albicans fungi [1].

Earlier [5], we had reported the reducing reaction of imine hydrotropylation in the “tropylium perchlorate—sodium tetrahydroborate” system resulting in unstable tertiary amines, namely N-phenyl-N-arylmethyl-N-(7-cyclohepta-1,3,5-trienyl)anilines. However, direction of this reaction changes after addition of imidazole to the reaction mass. Imidazole promotes a shift of the tropylium moiety from the nitrogen atom to para-position of the aniline ring and, thus, leads to formation of such stable products as N-arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines. The educed products contain two important biogenic moieties, namely tropilidene cycle and NH-group. The NH-group—in accordance with investigations in modeling and in predicting properties of active heterocyclic compounds based on the “structure-action-toxicity” link [6]—promotes an increase in pharmacological action and a decrease in toxicity of compounds, so important for investigations in growth control of crops.

Thus, the use of tropylium perchlorate enabled educing para-tropylated aniline [1] which had been inaccessible earlier [7], as well as secondary tropylated amines by using the ionic imine-hydrotropylation reaction [5]. A disadvantage of these methods is the use of explosive tropylium perchlorate.

2. Results and Discussion

Our investigation aims at the one-pot three-component synthesis of N-arylmethyl-4-(7-cyclohepta-1,3,5-trienyl) anilines by using the method [5] with tropylium tetrafluoroborate instead of explosive tropylium perchlorate.

The conducted investigation has shown that ionic hydrotropylation of imines in the “tropylium perchlorate—sodium tetrahydroborate” system in the presence of imidazole as activator leads to formation of N-arylmethyl-
4-(7-cyclohepta-1,3,5-trienyl)anilines (3a-e) with the 23.3% - 51.4% yield (Scheme 1). It is worth noting that, in the absence of activator, the yield of tropylation products (3a-e) is only 1.5% - 8%, N-arylmethylanilines (4a-e) being the main reaction products; these results correspond with the data in [5].

Optimal ratio of reagents, namely the Schiff base: Tropylium tetrafluoroborate: Sodium tetrahydroborate: Imidazole = 1:1:1:0.5, is ascertained. The reaction proceeds in the absence of activator, the yield of tropylation products (3a-e) is only 1.5% - 8%, N-arylmethylanilines (4a-e) being the main reaction products; these results correspond with the data in [5].

A role of the activator is, probably, to form the B complex promoting a shift of the cycloheptatriene cycle to the para-position of the aniline fragment of the A intermediate (Scheme 2).

3. Experimental Part

The FTIR spectra were registered by using the IR Fourier spectrometer (Bruker, Germany), registration condition: suspension in vaseline oil. The $^1$H NMR spectra were registered by using the Mercury 300 device (300 MHz), with hexamethyldisiloxane (HMDSO) as internal standard. Chromatograph mass spectrum was recorded by using the Agilent Technologies 689ON/597B device, the HP-5ms column (30 x 0.25 mm, helium as carrier gas, 70 eV electron shock, 100°C temperature of the column’s thermostat, 250°C, 270°C temperature of evaporator); CHNS-932 (Carbon, Hydrogen, Nitrogen and Sulfur Determinator), LECO Corporation (USA).

General Preparation Procedure for the 3a-e Compounds

Imine (1 mmol) is dissolved in 5 ml of tetrahydrofuran, whereupon tropylium tetrafluoroborate (1 mmol), sodium tetrahydroborate (1 mmol), and imidazole (0.5 mmol) are added at one go. The reaction mass is then stirred for 2.5 h at room temperature, diluted with water, and neutralized to pH 7.

1) N-Benzyl-4-(7-cyclohepta-1,3,5-trienyl)aniline (3a)

The yield of the 3a compound: 0.07 g (25%), appearance: white crystals with m.p. 69°C - 70°C (hexane), (ref. 69°C - 70°C [5]). IR (vas): $\nu$N= 3391, $\delta$NH 1611, 820 cm$^{-1}$. $^1$H NMR (CDCl$_3$), $\delta$, ppm, (J, Hz): 2.58 (1 H, t, J 5.4, C1H in C7H); 4.05 (1 H, br.s, NH); 4.34 (2 H, s, CH$_2$); 5.36 - 5.41 (2 H, dd, J 5.4, C1,6H in C7H); 6.19 - 6.24 (2 H, m, C2,5H in C7H); 6.65 (2 H, d, J 8.7, ortho-C6H$_4$-NH); 6.71 - 6.73 (2 H, m, C3,4H in C7H); 7.17 (2 H, d, J 8.4, meta-C6H$_4$-NH); 7.27 - 7.40 (5 H, m, Ph). MS (EI)$^+$: m/z 273 (100) [M]+. Anal. Calcd for C$_{20}$H$_{19}$N (273.38): C, 87.58; H, 6.95; N, 5.12. Found: C, 87.58; H, 6.95; N, 5.10.

2) N-(4-Bromphenylmethyl)-4-(7-cyclohepta-1,3,5-trienyl)aniline (3b)

The yield of the 3b compound: 0.26 g (74.3%), appearance: white crystals with m.p. 107°C - 108°C (hexane). $^1$H NMR (CDCl$_3$), $\delta$, ppm, (J, Hz): 2.59 (1 H, t, J 5.1, J$_{1,2}$ 5.1, J$_{2,3}$ 5.4, C1H in C7H); 4.06 (1 H, br.s, NH); 4.29 (2 H, s, CH$_2$); 5.34 - 5.39 (2 H, dd, J 5.4, C1,6H in C7H); 6.19 - 6.23 (2 H, m, C2,5H in C7H); 6.65 (2 H, d, J 8.1, ortho-C6H$_4$-NH); 6.70 - 6.72 (2 H, m, C3,4H in C7H); 7.16 (2 H, d, J 8.4, meta-C6H$_4$-NH); 7.25 (2 H, d, J 8.1 ortho-C6H$_4$-NH); 7.45 (2 H, d, J 8.4, meta-C6H$_4$-CH$_2$). MS (EI)$^+$: m/z 352 (32) [M]$^+$. Anal. Calcd for C$_{20}$H$_{18}$NBr (352.27): C, 67.95; H, 5.05; N, 3.83. Found: C, 68.16; H, 5.15; N, 3.97.

3) N-(4-Chlorophenylmethyl)-4-(7-cyclohepta-1,3,5-trienyl)aniline (3c)

The yield of the 3c compound: 0.25 g (83.3%), appearance: white crystals with m.p. 94°C - 95°C (hexane), (ref. 94°C - 95°C [5]). $^1$H NMR (CDCl$_3$), $\delta$, ppm, (J, Hz): 2.59 (1 H, t, J 5.4, C1H in C7H); 4.07 (1 H, br.s, NH); 4.30 (2 H, s, CH$_2$); 5.34 - 5.39 (2 H, dd, J 5.4, C1,6H in C7H); 6.19 - 6.22 (2 H, m, C2,5H in C7H); 6.63 (2 H, d, J 8.4, ortho-C6H$_4$-NH): 6.70 - 6.72 (2 H, m, C3,4H in C7H); 7.16 (2 H, d, J 8.4, meta-C6H$_4$-NH); 7.23 - 7.30 (4 H, m, C4,5H in C7H).

Scheme 1. One-pot synthesis of N-arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines (3a-e) in the presence of imidazole.

Scheme 2. The role of the B complex in the reducing imine hydrotropylation process.
4. Conclusions

Thus, the one-stage synthesis route of n-arylmethyl-4-(7-cyclohepta-1,3,5-trienyl)anilines through ionic hydro-tropilation of imines in the “tropolium perchlorate—sodium tetrafluoroborate” system in the presence of imidazole as activator has been designed.

The advantage of this method is the use of safe-to-handle tropolium tetrafluoroborate (instead of tropolium perchlorate), and the increased yield of the 3b-d compounds.

The advantage of the use of tropolium tetrafluoroborate is that higher yields for the 3b-d compounds are achieved as compared with tropolium perchlorate [5].

The educed compounds contain two biogenic moieties, namely NH group and tropilidene cycle.

5. Acknowledgements

This work was financially supported by the Ministry of Education of Perm Region Administration (Russian Federation).

REFERENCES


