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SHORT COMMUNICATIONS

One-Pot Synthesis of 2-Aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines

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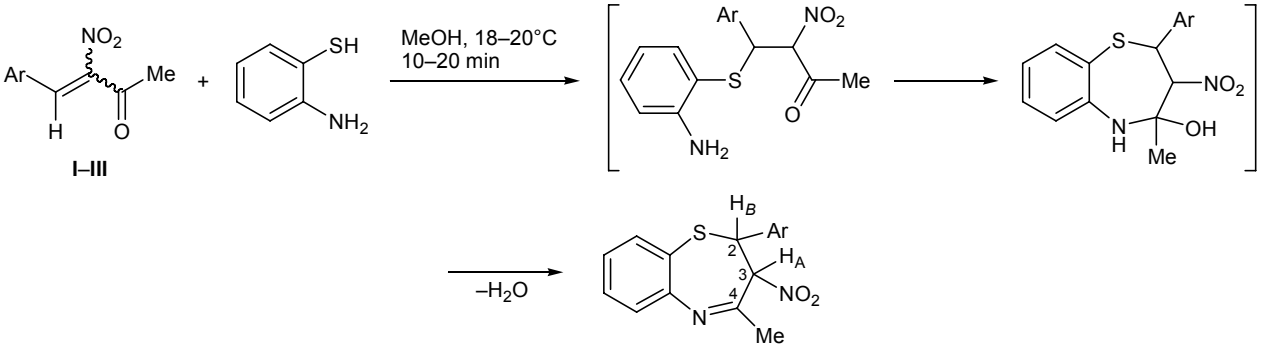
Wide application in medical practice of compounds whose molecules contain seven-membered thiazepine rings (examples are diltiazem which exhibits antianginal, hypotensive, and antiarrhythmic activity and neuroleptic quetiapine [1, 2]), strongly stimulated studies aimed at developing new methods of synthesis of thiazepine derivatives and extending their series.

With the goal of obtaining new nitro-substituted thiazepine structures we examined reactions of accessible and reactive 4-aryl-3-nitrobut-3-en-2-ones **I**–**III** [3] with *o*-aminobenzenethiol. Unlike other α,β-unsaturated ketones which react with *o*-aminobenzenethiol under fairly drastic conditions (heating in boiling methanol for several hours in the presence of acid [4] or base catalyst [5] or heating in higher-boiling solvents, such as toluene, in the absence of catalyst [6]) to produce seven-membered heterocycles, reactions of nitro enones **I**–**III** with *o*-aminobenzenethiol occurred very readily at 18–20°C in methanol (without a catalyst) and were complete in 10–20 min. Crystalline 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines **IV**–**VI** separated from the reaction solution, and their yields attained 98%. Presumably, the process follows nucleophilic addition pattern with subsequent heterocyclization of S-adducts.

Compounds **IV**–**VI** were isolated as colorless or yellowish crystalline substances which were diastereoisomerically pure. Their structure was confirmed by spectral methods. The IR spectra of functionally substituted 1,5-benzothiazepines **IV**–**VI** contained strong absorption bands due to stretching vibrations of unconjugated nitro group (1560, 1360 cm^{-1}), and C=N stretching vibrations had a frequency of 1645 cm^{-1}.

The ^1H NMR spectra of **IV**–**VI** were consistent with the assumed structure. Compound **V** displayed in the ^1H NMR spectrum ($CDCl_3$) two clearly defined doublets from H_A and H_B at δ 5.45 and 5.25 ppm, respectively, with a coupling constant $^3J_{AB}$ of 11.90 Hz; protons in the methyl and methoxy groups resonated as singlets at δ 2.43 and 3.76 ppm, respectively; aromatic protons appeared as doublets at δ 7.11 and 6.79 ppm and multiplets at δ 7.57, 7.52, 7.29, and 7.20 ppm. In



I, **IV**, Ar = Ph; **II**, **V**, Ar = 4-$MeOC_6H_4$; **III**, **VI**, Ar = 4-$Me_2NC_6H_4$.

the ^{13}C NMR spectrum of **V** (recorded with decoupling from protons), the downfield signal at δ_C 162.68 ppm was assigned to the C=N carbon atom (C^4), and signals at δ_C 58.43 and 91.30 ppm were attributed to C^2 and C^3. The assignment of signals in the ^1H and ^{13}C NMR spectra was proved by HMQC and HMBC correlation experiments.

Initial 4-aryl-3-nitrobut-3-en-2-ones **I**–**III** were synthesized according to the procedures reported in [3], and *o*-aminobenzenethiol was prepared as described in [7].

4-Methyl-3-nitro-2-phenyl-2,3-dihydro-1,5-benzothiazepine (IV). Yield 81%, colorless crystals, mp 136–137°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 1645 (C=N); 1560, 1360 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (3H, CH_3), 5.27 d (1H, H_B, $^3J_{AB}$ = 11.90 Hz), 5.52 d (1H, H_A, $^3J_{AB}$ = 11.90 Hz), 7.17–7.58 m (9H, H_{arom}). $^{13}C-\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 21.99 (CH_3), 58.70 (C^2), 90.98 (C^3); 120.50, 124.56, 126.39, 126.60, 129.02, 129.23, 131.04, 135.28, 139.89, 150.09 (C_{arom}); 162.76 (C=N). Found, %: C 64.61; H 4.91; N 9.15. $C_{16}H_{14}N_2O_2S$. Calculated, %: C 64.41; H 4.73; N 9.39.

2-(4-Methoxyphenyl)-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepine (V). Yield 98%, light yellow crystals, mp 132–134°C (from ethanol). IR spectrum, ν, cm^{-1}: 1645 (C=N); 1560, 1360 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.43 s (3H, CH_3), 3.76 s (3H, OCH_3), 5.25 d (1H, H_B, $^3J_{AB}$ = 11.90 Hz), 5.45 d (1H, H_A, $^3J_{AB}$ = 11.90 Hz), 6.79 d and 7.11 d (2H each, C_6H_4); 7.20 t, 7.29 d, 7.52 t, and 7.57 d (4H, 6-H, 7-H, 8-H, 9-H). $^{13}C-\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 22.05 (CH_3), 55.38 (OCH_3), 58.43 (C^2), 91.30 (C^3); 114.49, 120.59, 121.68, 124.54, 126.54, 127.69, 130.93, 132.11, 135.24, 150.00, 159.90 (C_{arom}); 162.68 (C=N). Found, %: N 8.80. $C_{17}H_{16}N_2O_3S$. Calculated, %: N 8.53.

2-(4-Dimethylaminophenyl)-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepine (VI). Yield 98%, light orange crystals, mp 144–146°C (from ethanol). IR spectrum, ν, cm^{-1}: 1645 (C=N); 1560, 1360 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.43 s (3H, CH_3), 2.91 s (6H, NCH_3), 5.23 d (1H, H_B, $^3J_{AB}$ = 11.90 Hz), 5.46 d (1H, H_A, $^3J_{AB}$ = 11.90 Hz), 6.57 d and 7.03 d (2H each, C_6H_4); 7.18 t, 7.28 d, 7.50 t, 7.58 d (4H, 6-H, 7-H, 8-H, 9-H). $^{13}C-\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 22.09 (CH_3), 40.41 (NCH_3), 59.01 (C^2), 91.46 (C^3); 112.41, 121.00, 124.44, 126.41, 126.29, 130.67, 135.30, 150.04, 150.70, 150.00 (C_{arom}); 162.74 (C=N). Found, %: N 12.01. $C_{18}H_{19}N_3O_2S$. Calculated, %: N 12.31.

The ^1H and ^{13}C NMR spectra, including HMQC and HMBC experiments, were recorded on a Jeol JNM-ECX400A spectrometer at 100.53 (^{13}C) and 399.78 MHz (^1H) using the residual solvent signal ($CHCl_3$) as internal reference. The IR spectra were measured from solutions in $CHCl_3$ (c = 0.1–0.001 M) on a Shimadzu IR Prestige-21 spectrometer with Fourier transform. The elemental compositions were determined on a EuroVector EA 3022 CHN Dual analyzer.

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