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Alkylation of 1-(Prop-2-ynyl)piperidine with CH-Acids in ihe Presence of Mercury(II) Acetate

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Abstract—General regilarities of the reaction of C-nucleophiles with 1-(prop-2-ynyl)piperidine in the presence of mercuty(II) acetate to form mono-and dicarbonyl derivatives of piperidine and bis[3-(piperidin-1-yl)prop-1-ynyl]mercury. Conditions of these reactions were optimized.

Keywords: alkylatione, acetylacetone, acetoacetic ester, prototropic isomers

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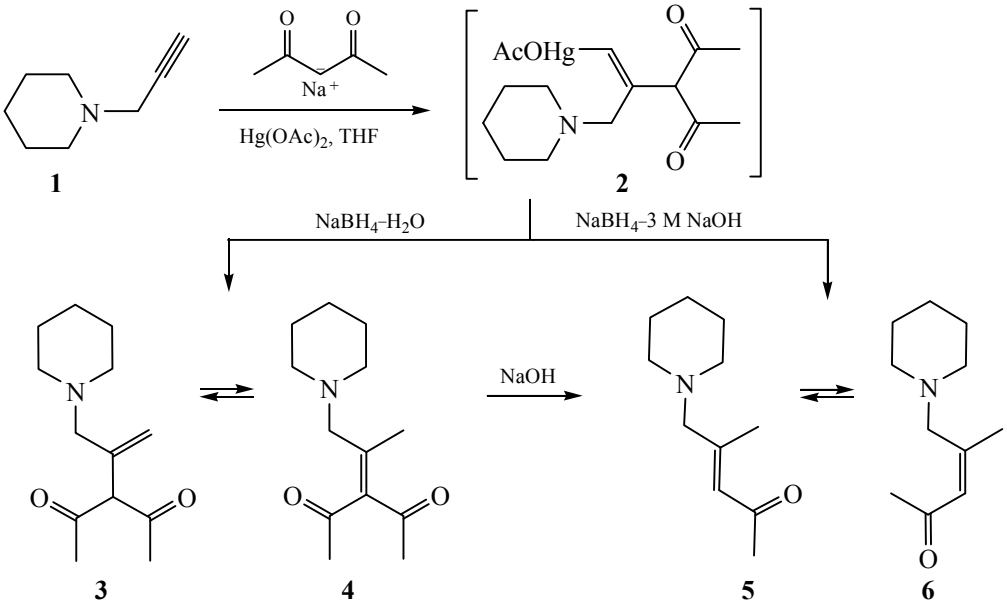
We earlier studied the functionalization of terminal acetylenic derivatives with various C-, N-, and O-nucleophiles in the presence of mercury(II) acetate and provided evidence for the formation of hydration adducts, alkylation by the substituted carbon atom of the triple bond, and subsequent prototropic isomerizations and intramolecular cyclization [1–3]. It was shown that acetylacetone and acetoacetic ester are readily alkylated with diethynylamine and propynylmorpholine in the presence of mercury(II) acetate to form 1,3- and 1,5-diketoenol derivatives via direct vinylation followed by protropic isomerization.

Proceeding with the research in this field we have studied the behavior of 1-(prop-2-ynyl)piperidine **1** as the propargyl substrate in the alkylation with various CH-acids in the presence of mercury(II) acetate. It was found that the reaction of compound **1** with sodium acetylacetonate in the presence of mercury(II) acetate in THF forms a mixture of linear regioisomers 3-[3-(piperidin-1-yl)prop-1-en-2-yl]pentane-2,4-dione **3** and 3-[1-(piperidin-1-yl)propan-2-ylidene]pentane-2,4-dione **4** after the demercurization of intermediate **2** with aqueous sodium borohydride. The reduction of the intermediate mercury derivative with the $NaBH_4$–3 M NaOH system alters the reaction route, and demercurization is accompanied by alkaline cleavage of intermediate **2**. Elimination if acetic acid forms a mixture of unsaturated aminoketones: (*E*)- and (*Z*)-4-methyl-5-(piperidin-1-yl)pent-3-en-2-ones **5** and **6.** It should be noted that the alkaline cleavage of the mixture of linear regioisomers **3** and **4** with 3 M NaOH, too, provides a 1 : 1 mixture of (*E*)- and (*Z*)-pentenones **5** and **6** (Scheme 1).

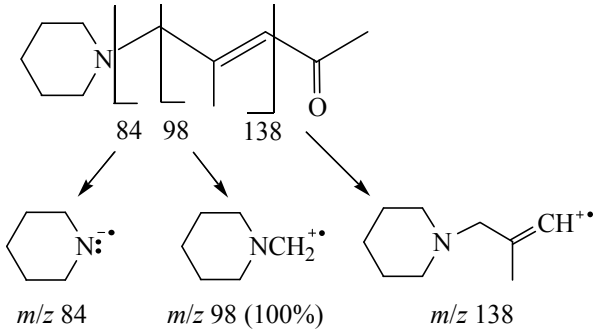
The structure of compounds **5** and **6** was proved by ^{1}H NMR spectroscopy and mass spectrometry. The characteristic vinyl proton signals of isomers **5** and **6** appear in their ^{1}H NMR spectra at 6.22 and 6.40 ppm, respectively. The mass spectra of these compounds contain a molecular ion peak at *m*/*z* 181 and peaks of the most stable fragment ions (Scheme 2).

Further on we reacted 1-(prop-2-ynyl)piperidine **1** with sodium acetoacetate in the presence of mercury(II) acetate in THF (Scheme 3). It was found that the reduction of intermediate **7b** with aqueous $NaBH_4$ or the $NaBH_4$–3 M NaOH system forms a dialkynylmercury derivative—bis[3-(piperidin-1-yl)prop-1-ynyl]-mercury **8**, which can be explained by the prevalence of O-alkylation over C-alkylation, when acetoacetic ester is used as the CH-acid. Thus, the intermediate obtained by O-alkylation of **7b** splits under the action of hydride ion to form acetoacetic ester and alkynylmercury acetate, and the latter undergoes a radical reaction to form bis[3-(piperidin-1-yl)prop-1-ynyl]-mercury **8** (Scheme 4).

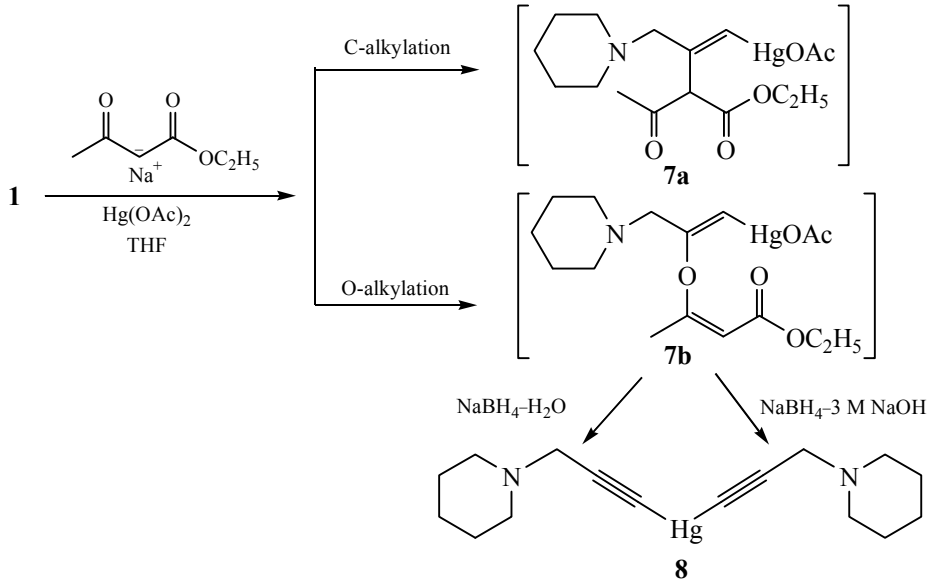
Scheme 1.



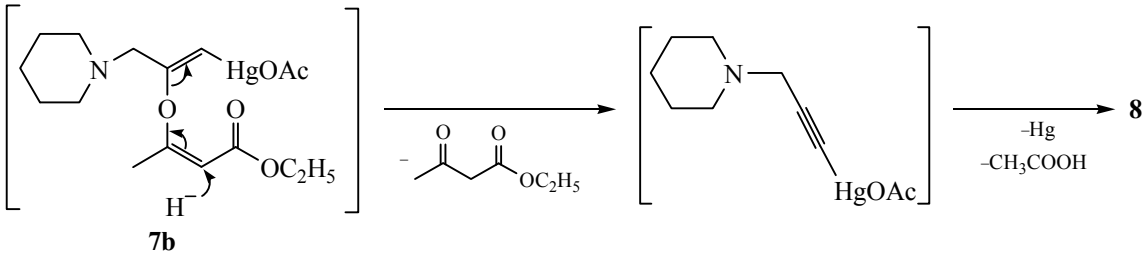
Scheme 2.



Scheme 3.



Scheme 4.



It should be noted that the demercurization products of intermediate **7a** were not detected. The structure of compound **8** was confirmed by ^{1}H and ^{13}C NMR spectroscopy [4, 5]. The ^{1}H NMR spectrum of this compound contains three types of characteristic signals at 1.4–1.6 (CH_2), 2.4 (CH_2N), and 3.2 ppm (≡C–CH_2–N). The ^{13}C NMR spectrum displays a characteristic doublet from the *sp*-carbon atoms linked to mercury at 116.0 ppm ($^{1}J_{CHg}$ = 2540 Hz). Evidence for the presence of the ≡C–Hg group in compound **8** comes from the observation of characteric IR absorption bands at 440 and 520 cm^{-1}. The formation of bis[3-(piperidin-1-yl)prop-1-ynyl]mercury and lack of complex formation between the acetylene fragment and mercury are also confirmed by the absence of characteristic maxima from the UV-vis spectra.

We also studied the effect of the solvent on the regiochemistryof the reaction of propargylpiperidine with CH-acids in the presence of mercuty(II) acetate. The C-alkylations of acetylacetone with 1-(prop-2-ynyl)piperidine were performed in THF, 1,4-dioxane, and DMSO. The yield of the target products in the reaction in THF was 52%, whereas the reactions of 1,4-dioxane and DMSO gave a lot of unidentified compounds. With acetoacetic ester, bismercury derivative **8** formed in all the solvents, but the highest yield was, too, obtained in THF.

The effect of the reducer on the regiochemistry of this reaction was also studied. Thus, with sodium borohydride, the mercury intermediates derived from acetylacetone underwent acid cleavage to form amines, which was accompanied by tarring of the reaction mixture. It should be noted that bis[3-(piperidin-1-yl)-prop-1-ynyl]mercury was cleaved with HCl to form the starting propargylamine but proved to be insensitive to sodium borohydride.

Thus, we have studied the regularities of the C- and O-alkylation of acetyacetone and acetoacetic ester with 1-(prop-2-ynyl)piperidine in the presence of $Hg(OAc)_2$.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on a Varian Mercury-300 VX spectrometer (300.1 and 75.5 MHz, respectively). The chemical shifts were measure against internal TMS at 303 K for solutions in DMSO-d_6–CCl_4, 1 : 3. Reaction progress was monitored by TLC on Silufol UV-254 plates, development with $KMnO_4$ and iodine vapor. Gas chromatography was performed on an LKhM-80M (model 3) chromatograph on a 1.5-m column packed with 10% of Carbowax-20M on Inerton AW-NMDC, helium (40 mL/min), detector and injector temperatures 200°C and 250°C, respectively. The IR spectra were obtained on a Nicolet AVATAR 330FT-IR spectrometer. The UV spectra were run on a Helios γ UV-VIS instrument. The mass spectra were measured on a MX-1321A mass spectrometer.

Commercial 1-(prop-2-ynyl)piperidine (Aurum Pharmatech) was used.

Synthesis of compounds 3–6. *a.* 1-(Prop-2-ynyl)-piperidine, 6.2 g (0.05 mol), and 50 mL THF were added to 16 g (0.05 mol) of mercury(II) acetate at –5 to –7°C. The resulting complex of 1-(prop-2-ynyl)piperidine and mercury(II) acetate was added to sodium acetylacetonate prepared by the reaction of 1.2 g (0.05 mol) of Na with 10 mL of acetylacetone in THF. Sodium borohydride 0.95 g (0.025 mol), 50 mL of water, and 50 mL of diethyl ether were then added, and the reaction mixture was stirred for 2 h. The amorphous mercury precipitate was filtered off, the filtrate was extracted with ether, the extract was dried over magnesium sulfate, and the solvent was removed to obtain 5.8 g (52%) of a mixture of 3-[3-(piperidin-1-yl)prop-1-en-2-yl]pentane-2,4-dione **3** and 3-[1-(piperidin-1-yl)propan-2-ylidene]pentane-2,4-dione **4**, bp 89°C (2 mmHg).

3-[3-(Piperidin-1-yl)prop-1-en-2-yl]pentane-2,4-dione (3). ^{1}H NMR spectrum, δ, ppm: 1.35–1.45 m

(2H, γ-CH_2), 1.51–1.60 m (4H, β-CH_2), 2.15 s (6H, $COCH_3$), 2.39–2.44 m (4H, α-CH_2), 3.03 s (2H, CH_2), 3.91 s (1H, CH), 5.15 d.d (1H, =CH_2 J = 2.3, 1.5 Hz), 5.48 d.d (1H, =CH_2, J = 2.1, 1.9 Hz). Mass spectrum, m/z: 181 $[M]^+$.

3-[1-(Piperidin-1-yl)propan-2-ylidene]pentane-2,4-dione (4). ^{1}H NMR spectrum, δ, ppm: 1.35–1.45 m (2H, γ-CH_2), 1.51–1.60 m (4H, β-CH_2), 1.8 s (3H, C=C–CH_3), 2.23 s (6H, $COCH_3$), 2.39–2.44 m (4H, α-CH_2), 3.03 s (2H, CH_2).

b. 1-(Prop-2-ynyl)piperidine, 6.2 g (0.05 mol), and 50 mL THF were added to 16 g (0.05 mol) of mercury(II) acetate at –5 to –7°C. The resulting complex of 1-(prop-2-ynyl)piperidine and mercury(II) acetate was added to sodium acetylacetonate prepared by the reaction of 1.2 g (0.05 mol) of Na with 10 mL of acetylacetone in THF. Sodium borohydride, 0.95 g (0.025 mol), 50 mL of 3 M NaOH, and 50 mL of diethyl ether were then added, and the reaction mixture was stirred for 3 h. The amorphous mercury precipitate was filtered off, the filtrate was extracted with ether, the extract was dried over magnesium sulfate, and the solvent was removed to obtain 4.35 g (48.6%) of a mixture of (*E*)- and (*Z*)-4-methyl-5-(piperidin-1-yl)pent-3-en-2-ones **5** and **6**, bp 79–81°C (3 mmHg).

(*E*)-4-Methyl-5-(piperidin-1-yl)pent-3-en-2-one (5). ^{1}H NMR spectrum, δ, ppm: 1.35–1.45 m (2H, γ-CH_2), 1.51–1.60 m (4H, β-CH_2), 1.82 s (3H, C=C–CH_3), 2.23 s (3H, $COCH_3$), 2.39–2.44 m (4H, α-CH_2), 3.03 s (2H, CH_2), 6.22 br.s (1H, =CH).

(*Z*)-4-Methyl-5-(piperidin-1-yl)pent-3-en-2-one (6). ^{1}H NMR spectrum, δ, ppm: 1.35–1.45 m (2H, γ-CH_2), 1.51–1.60 m (4H, β-CH_2), 1.82 s (3H, C=C–CH_3), 2.23 s (3H, $COCH_3$), 2.39–2.44 m (4H, α-CH_2), 3.03 s (2H, CH_2), 6.4 br.s (1H, =CH).

Bis[3-(piperidin-1-yl)prop-1-ynyl]mercury (8). 1-(Prop-2-ynyl)piperidine, 2.0 g (0.016 mol), and 50 mL of 1,4-dioxane were added to 5.1 g (0.016 mol) of mercury(II) acetate at –5 to 0°C. The resulting mixture was stirred for 30 min at 25°C. Sodium acetoacetate prepared from 0.016 mol of sodium ethylate and 0.016 mol of acetoacetic ester was added dropwise to the reaction mixture, which was stirred for 10 h at 25°C and, after addition of 0.3 g (0.008 mol) of $NaBH_4$, 50 mL of 3 M of aqueous NaOH (or 50 mL of water), and 50 mL of diethyl ether, stirring was continued for an additional 3 h. The mercury metal precipitate was filtered off, the filtrate was extracted with ether, the extracts were dried over sodium sulfate, the solvent was removed by distillation, and the residue was washed with CCl_4 and dried. Yield 2.6 g (73%), mp 105°C, R_f 0.56 (hexane–ether, 2 : 1). IR spectrum, ν, cm^{-1}: 2150, 440, 520. ^{1}H NMR spectrum, δ, ppm: 1.35–1.60 m (12H, γ-CH_2, β-CH_2), 2.39–2.5 m (8H, α-CH_2), 3.17 s (4H, CH_2 C≡). ^{13}C NMR spectrum, δ_C, ppm: 23.5 (γ-CH_2), 25.3 (β-CH_2), 47.8 (NCH_2), 52.3 (α-CH_2), 99.9 (C≡), 116.0 (≡C).

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