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Specific Example of the Mannich Reaction in the Series of 5-Acetyl-6-aminoacenaphthene and Its Derivatives

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Abstract—Reactions of 5-acetyl-6-aminoacenaphthene and 5-acetyl-6-acetylaminoacenaphthene with aromatic aldehydes under conditions of base and acid catalysis gave derivatives of a new *peri*-fused heterocyclic system, 2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]azepin-4(1*H*)-ones.

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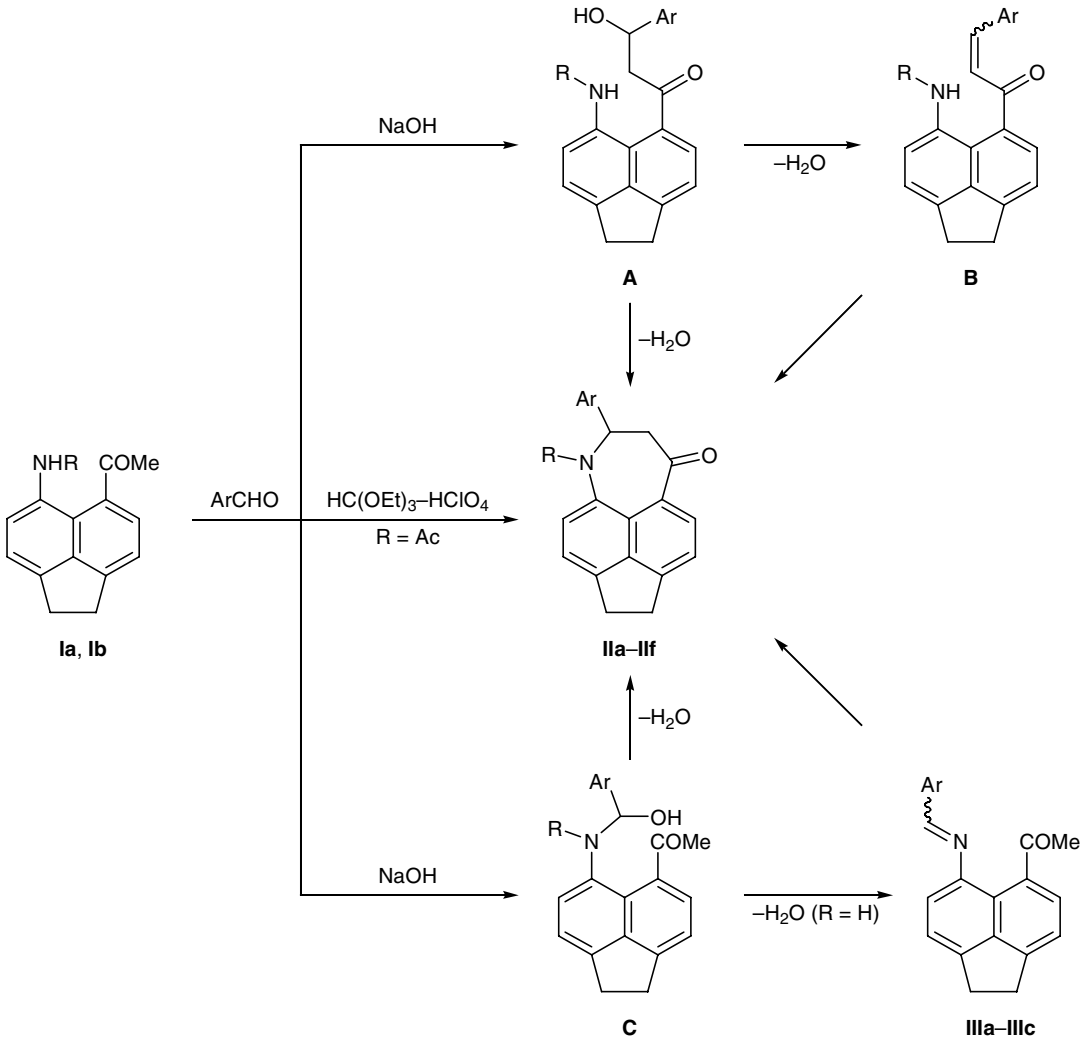
peri-Aminoacetylacenaphthene **I** and its *N*-acetyl derivative **Ib** were reported for the first time in 1966 [1]. These compounds attract interest as potential precursors of *peri*-fused nitrogen-containing heterocycles; however, their ability to undergo heterocyclization was not studied until present. *peri*-Amino ketones of the naphthalene series could not be isolated because of their fast intramolecular heterocyclization leading to benzo[*cd*]indoles [2]. The presence of an ethylene bridge connecting *peri* positions of the naphthalene core at the side opposite to the *peri*-aminocarbonyl moiety changes the molecular geometry so strongly that closure of five-membered heteroring becomes difficult. Therefore, derivatives of 5-amino-6-acylacenaphthene are sufficiently stable to exist as individual substances.

While performing studies on purposeful synthesis of *peri*-fused heterocyclic compounds of the naphthalene and acenaphthene series, we have found that aromatic aldehydes react with *peri*-aminoacetylacenaphthene **I** in alkaline medium to give acenaphtho[5,6-*bc*]-azepinones **II**. The reaction can follow four alternative pathways involving intermediate formation of β-hydroxy ketones **A**, chalcones **B**, amino alcohols **C**, or Schiff bases **III** (Scheme 1). In the reactions of amino ketone **Ia** with aldehydes, apart from azepinones **IIa**–**IIc**, we isolated small amounts of the corresponding Schiff bases **III**; therefore, the latter could mediate the transformation of compounds **I** into **II**. In fact, azepinones **II** are formed under analogous conditions from specially prepared Schiff bases **III**. On the other hand, these findings do not rule out the possibility for participation of three other intermediates **A**–**C**. Thus *N*-acetylazepinone **IIe** was obtained in the reaction of *p*-methoxybenzaldehyde with *N*-acetylaminoacenaphthene **Ib** despite the latter could not give rise to Schiff base like **III**. Azepinones **IId**–**IIf** can also be prepared from ketone **Ib** and aromatic aldehydes in triethyl orthoformate in the presence of perchloric acid.

Taking into account the character of final products **II** and probably one of the mechanisms shown in Scheme 1 (**I** → **C** → **II**), the examined transformations may be regarded as a specific example of the Mannich reaction. The classical Mannich reaction is a three-component condensation of an aldehyde with amine and carbanion generated from methyl (methylene) ketone by the action of a base [3]. In our case, the difference is that the hydroxyalkylamino and carbanion moieties formed during the process are fixed at the *peri* positions of a rigid aromatic framework (structure **C**). Presumably, just this factor is responsible for the reaction direction involving closure of seven-membered heteroring.

According to the ^{1}H NMR data, methylene protons neighboring to the asymmetric center in the azepine ring are magnetically nonequivalent, and they resonate as two one-proton doublets of doublets. The C**H**Ar proton gives a one-proton doublet of doublets at 4.7 (**IIa**–**IIc**) or 6.4 ppm (**IId**–**IIf**). The observed large difference in the chemical shifts of that proton between azepinones **IIa**–**IIc** and their *N*-acetyl derivatives **IId**–

Scheme 1.



I, R = H (**a**), Ac (**b**); **II**, R = H, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**); R = Ac, Ar = Ph (**d**), 4-$MeOC_6H_4$ (**e**), 3,4-$(MeO)_2C_6H_3$ (**f**); **III**, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**).

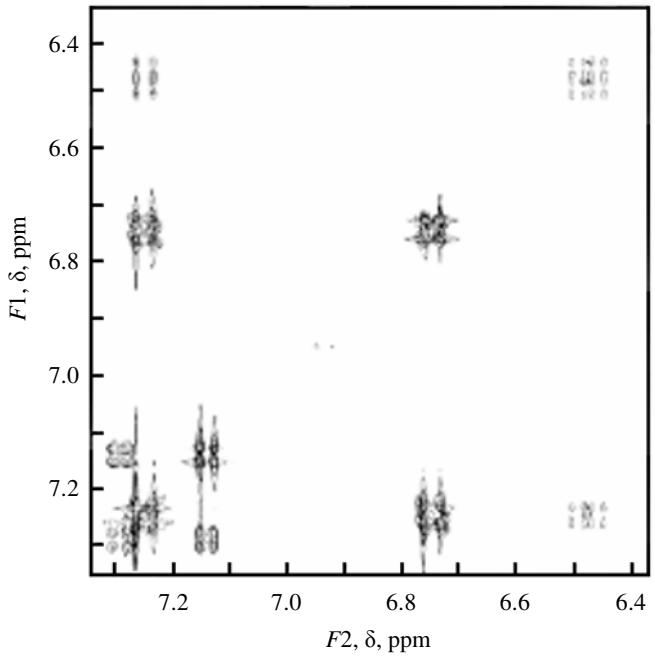
IIf may be rationalized in terms of electron-withdrawing effect of the acetyl group on the nitrogen atom.

The steric structure of heterocyclic compounds **II** was determined using homo- and heteronuclear correlation techniques (COSY, HETCOR). On the basis of these data we also assigned signals in the ^1H and ^{13}C NMR spectra. Analysis of cross couplings in the COSY spectra showed that, among the 2α-H, 3α-H, and 3β-H protons constituting a strongly coupled spin system, only the former (2α-H, δ 6.45 ppm) is characterized by a clearly defined spin–spin coupling with protons in the aromatic substituent (δ 7.25 ppm; see figure). The structure of the synthesized compounds was also confirmed by the IR and mass spectra and elemental analyses.

Unlike colorless *N*-acetyl derivatives **IId–IIf**, NH-azepinones **IIa–IIc** are yellow–orange both in solution and in crystal; this may be the result of the presence of small amounts of their open-chain tautomers, chalcones **B**, for the nitrogen atom in **IIa–IIc** is sufficiently basic to abstract proton from the methylene group.

EXPERIMENTAL

The IR spectra were measured from samples dispersed in mineral oil on a Specord IR-71 spectrometer. The NMR spectra were recorded on a Varian Unity-300 spectrometer in $CDCl_3$ using HMDS as internal reference. The mass spectra (70 eV) were run on a Kratos instrument with direct sample admission into the ion source (accelerating voltage 1.75 kV).



Fragment of the two-dimensional (COSY) ^{1}H NMR spectrum of compound **IIb**.

1-[6-(4-Methoxybenzylideneamino)acenaphthen-5-yl]ethanone (IIIb). Amino ketone **I**, 0.478 g (2.27 mmol), was dissolved on heating in 1 ml of ethanol, 0.31 ml (2.27 mmol) of *p*-methoxybenzaldehyde was added, the mixture was heated for 3–4 min under reflux and cooled, and the precipitate was filtered off. Yield 0.608 g (82%), yellow powder, mp 109–110°C (from EtOH). IR spectrum, ν, cm^{-1}: 1607, 1620 (C=N); 1687 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, COMe), 3.4 br.s (4H, CH_2CH_2), 3.9 s (3H, OMe), 6.9–7.9 (8H, H_{arom}), 8.5 s (1H, N=CH). Found, %: C 80.20; H 5.81; N 4.27. $C_{22}H_{19}NO_2$. Calculated, %: C 80.24; H 5.76; N 4.26.

Compounds **IIIa** and **IIIc** were synthesized in a similar way.

1-(6-Benzylideneaminoacenaphthen-5-yl)-ethanone (IIIa). Yield 83%, yellow powder, mp 133–134°C (from EtOH). IR spectrum: ν(C=O) 1673 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, COMe), 3.4 br.s (4H, CH_2CH_2), 7.22–7.24 d (1H, H_{arom}), 7.3–7.36 m (3H, H_{arom}), 7.48–7.52 m (3H, H_{arom}), 7.9–7.94 m (2H, H_{arom}), 8.6 s (1H, N=CH). Found, %: C 84.29; H 5.66; N 4.71. $C_{21}H_{17}NO$. Calculated, %: C 84.28; H 5.69; N 4.68.

1-[6-(3,4-Dimethoxybenzylideneamino)acenaphthen-5-yl]ethanone (IIIc). Yield 56%, yellow powder, mp 104–105°C (from EtOH). IR spectrum: ν(C=O) 1673 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, COMe), 3.45 br.s (4H, CH_2CH_2), 3.98 s (3H, OMe), 4.11 s (3H, OMe), 6.95–6.98 d (1H, H_{arom}), 7.29–7.36 m (5H, H_{arom}), 7.7 s (1H, H_{arom}), 8.6 s (1H, N=CH). Found, %: C 76.84; H 5.88; N 3.93. $C_{23}H_{21}NO_3$. Calculated, %: C 76.88; H 5.85; N 3.90.

2-(4-Methoxyphenyl)-2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]azepin-4(1*H*)-one (IIb). Amino ketone **Ia**, 0.162 g (0.77 mmol), was dispersed in 1 ml of ethanol, and 0.104 ml (0.77 mmol) of *p*-methoxybenzaldehyde and 0.4 ml of 30% aqueous sodium hydroxide were added to the suspension. The mixture was heated to 50–60°C, kept for 2 h at room temperature, and cooled, and the precipitate was filtered off. Yield 76%, orange–red powder, mp 109–110°C. IR spectrum, ν, cm^{-1}: 3420 (NH), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.16 d.d (1H, 3-H, J_1 = 16.7, J_2 = 2.34 Hz), 3.38 m (4H, 7-H, 8-H), 3.56 d.d (1H, 3-H, J_1 = 16.7, J_2 = 11.15 Hz), 3.84 s (3H, OMe), 4.36 br.s (1H, NH), 4.7–4.76 d (1H, 2-H, J_1 = 11.1, J_2 = 2.3 Hz), 6.8 d (1H, 10-H, J = 7.4 Hz), 6.93 d (2H, C_6H_4, J = 8.6 Hz), 7.15 d (1H, 6-H, J = 7.32 Hz), 7.34 d (1H, 5-H, J = 7.34 Hz), 7.35 (2H, C_6H_4, J = 8.6 Hz), 8.15 d (1H, 9-H, J = 7.4 Hz). Found, %: C 80.21; H 5.83; N 4.28. $C_{22}H_{19}NO_2$. Calculated, %: C 80.24; H 5.78; N 4.26.

Compounds **IIa** and **IIc** were synthesized in a similar way.

2-Phenyl-2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]-azepin-4(1*H*)-one (IIa). Yield 79%, yellow powder, mp 176–177°C. IR spectrum, ν, cm^{-1}: 3314 (NH), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.2 d.d (1H, 3-H, J_1 = 16.75, J_2 = 2.3 Hz), 3.42 m (4H, 7-H, 8-H), 3.6 d.d (1H, 3-H, J_1 = 16.5, J_2 = 11.24 Hz), 4.45 br.s (1H, NH), 4.8 d.d (1H, 2-H, J_1 = 11.1, J_2 = 2.4 Hz), 6.84 d (1H, 10-H, J = 7.4 Hz), 7.2 d (1H, 6-H, J = 7.4 Hz), 7.42–7.5 m (6H, H_{arom}), 8.2 d (1H, 9-H, J = 7.4 Hz). Found, %: C 84.30; H 5.64; N 4.70. $C_{21}H_{17}NO$. Calculated, %: C 84.28; H 5.69; N 4.68.

2-(3,4-Dimethoxyphenyl)-2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]azepin-4(1*H*)-one (IIIc). Yield 82%, orange–red powder, mp 154–155°C. IR spectrum, ν, cm^{-1}: 3354 (NH), 1677 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.18 d.d (1H, 3-H, J_1 = 16.75, J_2 = 2.45 Hz), 3.39 d.m (4H, 7-H, 8-H), 3.57 d.d (1H, 3-H, J_1 = 16.7, J_2 = 11.1 Hz), 3.85 s (3H, OMe), 3.9 s (3H, OMe), 4.4 br.s (1H, NH), 4.72 d.d (1H, 2-H, J_1 = 11.1, J_2 = 2.42 Hz), 6.82 d (1H, 10-H, J = 7.36 Hz), 6.86–7.0 m (3H, C_6H_3), 7.14 d (1H, 6-H, J = 7.36 Hz), 7.34 d (1H, 5-H, J = 7.36 Hz), 8.14 d (1H, 9-H, J = 7.36 Hz). Mass spectrum, *m/z* (I_{rel}, %): 359 (40) $[M]^+$, 208 (90), 195

(90), 180 (15), 166 (50), 164 (100), 151 (35), 149 (40), 139 (20), 121 (15), 91 (15), 77 (20), 65 (10), 43 (10). Found, %: C 76.86; H 5.82; N 3.7. $C_{23}H_{21}NO_3$. Calculated, %: C 76.88; H 5.85; N 3.4.

1-Acetyl-2-(4-methoxyphenyl)-2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]azepin-4(1*H*)-one (IIe). *a*. *N*-Acetylamino ketone **Ib**, 0.254 g (1 mmol), was dispersed in 3 ml of triethyl orthoformate, 0.136 ml (1 mmol) of *p*-methoxybenzaldehyde was added, and 0.15 ml of 70% perchloric acid was added dropwise. The mixture was kept for 3 h at room temperature, the solvent was evaporated, and the dry residue was dissolved in chloroform and subjected to chromatography on aluminum oxide. Yield 49%, pale yellow powder, mp 172–173°C. IR spectrum, ν, cm^{-1}: 1687 (C=O), 1647 (NC=O). ^{1}H NMR spectrum, δ, ppm: 1.6 s (3H, $NCOCH_3$), 3.2 d.d (1H, 3-H, J = 13.7, 6.5 Hz), 3.4–3.5 m (5H, 3-H, 7-H, 8-H), 3.7 s (3H, OMe), 6.47 d.d (1H, 2-H, J = 9.9, 6.6 Hz), 6.74 d (2H, C_6H_4, J = 8.75 Hz), 7.14 d (1H, 10-H, J = 7.25 Hz), 7.24 d (2H, C_6H_4, J = 8.75 Hz), 7.29 d (1H, 9-H, J = 7.25 Hz), 7.68 d (1H, 6-H, J = 7.25 Hz), 7.98 d (1H, 5-H, J = 7.25 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 30.0, 31.0, 48.0, 55.0, 56.5, 76.5, 77.0, 77.5, 113.6, 119.6, 119.8, 128.4, 130.2, 131.2, 131.6, 132.4, 132.8, 140.0, 146.0, 152.0, 158.5, 170.5, 200.0. Found, %: C 77.86; H 5.62; N 3.87. $C_{24}H_{21}NO_3$. Calculated, %: C 77.63; H 5.66; N 3.77.

Compounds **IId** and **IIf** were synthesized in a similar way.

b. A mixture of 0.3 g (1.2 mmol) of *N*-acetylamino ketone **Ib**, 0.16 ml (1.2 mmol) of *p*-methoxybenzaldehyde, 0.6 ml of 30% aqueous sodium hydroxide, and 2 ml of ethanol was stirred for 3 h at room temperature. The precipitate was filtered off. Yield 0.25 g (62%), mp 172–173°C.

1-Acetyl-2-phenyl-2,3,7,8-tetrahydroacenaphtho-[5,6-*bc*]azepin-4(1*H*)-one (IId). Yield 51%, pale yellow powder, mp 144–145°C. IR spectrum, ν, cm^{-1}: 1687 (C=O), 1647 (NC=O). ^{1}H NMR spectrum, δ, ppm: 1.65 s (3H, NCOMe), 3.1–3.2 d.d (1H, 3-H, J_1 = 13.6, J_2 = 6.4 Hz), 3.4–3.6 m (5H, 3-H, 7-H, 8-H), 6.48 d.d (1H, 2-H, J_1 = 10.1, J_2 = 6.5 Hz), 7.18–7.4 m (8H, H_{arom}), 8.0 d (1H, H_{arom}). Found, %: C 81.13; H 5.65; N 4.00. $C_{23}H_{19}NO_2$. Calculated, %: C 80.94; H 5.57; N 4.11.

1-Acetyl-2-(3,4-dimethoxyphenyl)-2,3,7,8-tetrahydroacenaphtho[5,6-*bc*]azepin-4(1*H*)-one (IIf). Yield 59%, pale yellow powder, mp 184–185°C. IR spectrum, ν, cm^{-1}: 1687 (C=O), 1647 (NCOMe). ^{1}H NMR spectrum, δ, ppm: 2.7 s (3H, NCOMe), 3.25 d.d (1H, 3-H, J_1 = 14.2, J_2 = 6.5 Hz), 3.4–3.6 m (5H, 3-H, 7-H, 8-H), 3.75 s (3H, OMe), 3.8 s (3H, OMe), 6.43 d.d (1H, 2-H, J_1 = 9.3, J_2 = 6.5 Hz), 6.66 d (1H, C_6H_3, J = 8.3 Hz), 6.8 s (1H, C_6H_3, J = 1.95 Hz), 6.85 d.d (1H, C_6H_3, J_1 = 8.3, J_2 = 1.95 Hz), 7.17 d (1H, 6-H, J = 7.3 Hz), 7.26 d (1H, 5-H, J = 7.3 Hz), 7.4 d (1H, 10-H, J = 7.25 Hz), 8.0 d (1H, 9-H, J = 7.25 Hz). Found, %: C 75.02; H 5.75; N 3.27. $C_{25}H_{23}NO_4$. Calculated, %: C 74.81; H 5.74; N 3.49.

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