# SYNTHESIS OF PYRIMIDINE AND 1,3-BISHYDROXYLAMINE DERIVATIVES FROM ENONE MANNICH BASE METHIODIDES

Vadim K. Khlestkin*, Alexsei Ya. Tikhonov
Novosibirsk Institute of Organic Chemistry, prosp. Lavrent'eva, 9, Novosibirsk, 630090, RUSSIA
Fax +7-3832-344-752; E-mail vadim@nioch.nsc.ru

**Abstract:** Reaction of the bis(aminomethylated) alkylaromatic ketones with methyl iodide gave the enone Mannich base methiodides. Subsequent reaction with two equivalents of methoxyamine or sodium *anti*-benzaldoximate resulted in 1,3-bismethoxyamine or dinitrone correspondingly. Partial hydroxylaminolyses of dinitrones led to 5-aroyl-1,3-dihydroxy-2-phenylperhydropyrimidines. Reaction of the enone Mannich base methiodides with cyclic paramagnetic amidine gave nitroxides of imidazopyrimidine series.

## Introduction

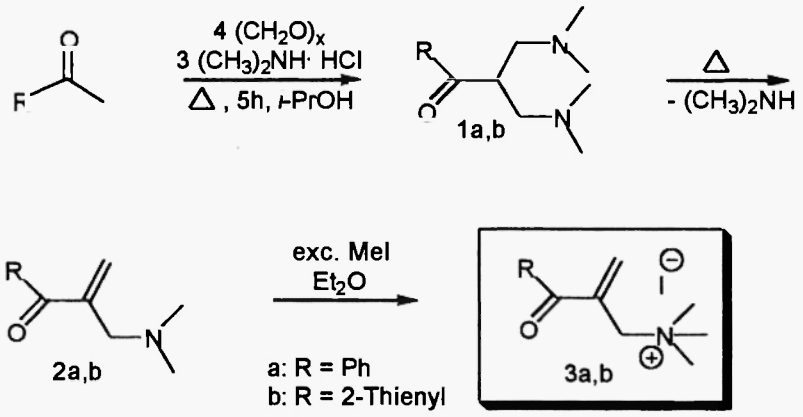
Aryl methyl ketones are known to give twice aminomethylated products under Mannich reaction conditions (1). Resulting β,β'-diaminoketones are quite able to eliminate the molecule of amine to form appropriate enone Mannich bases. The latter are known for their capability for the reaction with two equivalents of the same or different nucleophiles (2). Reports about their reaction with ambident nucleophiles with formation of heterocycles have also been published (3).

On the other hand the quaternary salts obtained via alkylation of β-aminoketones with methyl iodide appear to be more reactive compounds in reactions with nucleophiles. The preparation of enone Mannich base methiodides allows the preparation of reactive building blocks for the synthesis of polyfunctional acyclic and heterocyclic compounds.

We report a convenient method for preparation of enone Mannich base methiodides and their reactions with some *N*-nucleophiles to obtain pyrimidine and 1,3-bishydroxylamine derivatives.

## Results and discussion

Heating of acetophenone or 2-acetylthiophene under reflux with an excess of paraformaldehyde and three equivalents of dimethylamine hydrochloride in *i*-PrOH for 5 hours gave mixtures of the diaminoketones **1a** and **b** and the enone Mannich bases **2a** and **b** in a 1:2 ratio respectively according to the NMR $^1$H spectra. Alkylation of the mixture of compounds **1a,b** and **2a,b** with MeI without separation lead to the formation of the only product - enone Mannich bases methiodides **3a,b** (Scheme 1).



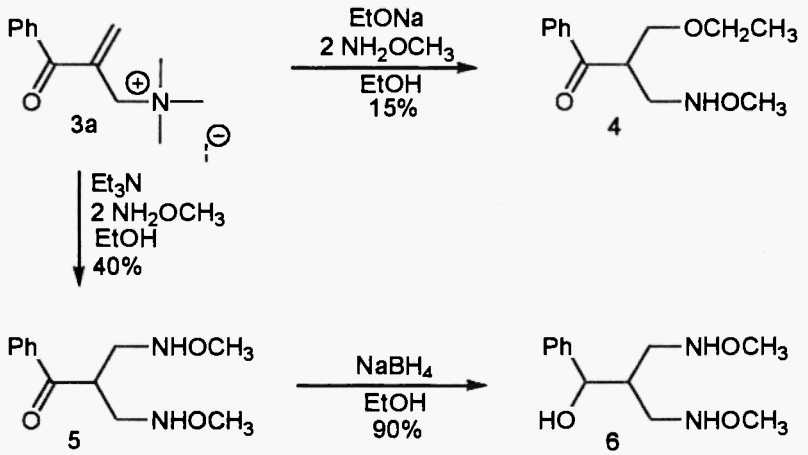

**Scheme 1**

Although the methiodides **3a** and **b** obtained contained impurities of trimethylamine hydroiodide and tetramethylammonium iodide (~10%, chem. shift 2.94 and 3.20 ppm in $CD_3OD$), they were used without purification.

To develop an approach to 1,3-bishydroxylamine derivatives that are expected to be an analogue of 1,2-bishydroxylamines - useful intermediates in heterocyclic *N*-oxides synthesis (4,5) - we studied the reactions of the Mannich base methiodides **3** with $CH_3ONH_2$ and *anti*-benzaldoxime.

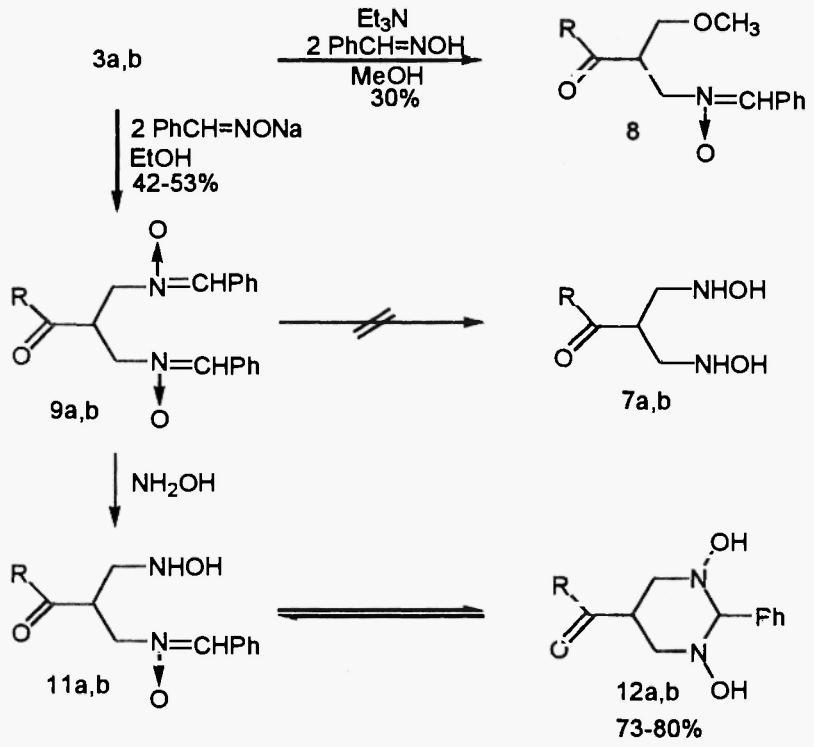
Reaction of the methiodide **3a** with two equivalents of $CH_3ONH_2$ in abs. EtOH in the presence of EtONa gave the ketone **4** in 15% yield.

Reaction of the methiodide **3a** with $CH_3ONH_2$ in the presence of $Et_3N$ gave 1,3-bismethoxyamine **5** in a 40% yield. Reduction of the ketone group of **5** with $NaBH_4$ resulted in the formation of the alcohol **6** (Scheme 2). Synthesis of the nitroso derivatives of bismethoxyamines **5** and **6** and their possibility to undergo intramolecular cyclization (5) are in progress.




**Scheme 2**

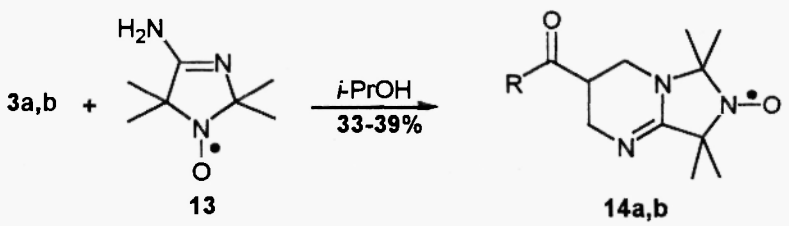
Reaction of **3a** and **b** in abs. EtOH with sodium *anti*-benzaldoximate gave the dinitrones **9a** and **b**. Carrying out the reaction of the methiodide **3a** with two equivalents of *anti*-benzaldoxime in MeOH in the presence of $Et_3N$ as the base led to the nitronoketone **8** with methoxy group in 30% yield.




**Scheme 3**

Treatment of the nitrones **9a** and b with an excess of free hydroxylamine in ethanol led to the hydroxylaminolyses of only one nitrone group and the 1,3-dihydroxypyrimidines **12a** and **b** formation (Scheme 3). It should be noted that the nitrone form **11** presents in a solid state (UV: strong band at 296 nm, KBr), but in MeOH or DMSO solutions only cyclic form **12** exists.

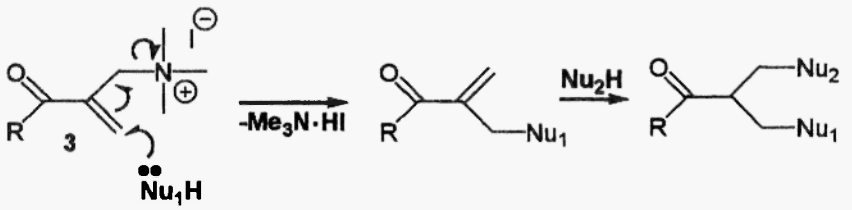
The amidine fragment of the nitroxide **13** is known to show a lower nucleophilic properties then usual amidines due to the strong electron withdrawing influence of the nitroxyl group. There are no data concerning direct modification of the amidine group of compound **13**. At the same time the nitroxide **13** and its derivatives are known to be a perspective spin probes and labels (6). We found the methiodides **3a** and b to react with compound **13** at room temperature in absolute ethanol or *i*-PrOH to give the imidazopyrimidines **14a** and b in 33 and 39% yield (Scheme 4).




**Scheme 4**

Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center (7).

We suppose the reaction of the methiodides **3** with nucleophiles to proceed via the addition-elimination route (as suggested in ref. 3) or via the concerted *tele*-substitution (Scheme 5).




**Scheme 5**

**Conclusion**

Thus enone Mannich base methiodides appear to be a convenient building blocks for synthesis of aroyl substituted pyrimidines as well as 1,3-bifunctional nitrogen compounds. An investigation of their reactions with other nucleophiles is under progress.

**Acknowledgement**

Authors thank the Russian Foundation for Basic Research (grant No. 99-03-33113) for financial support.

**Experimental**

*Typical procedure for 3.* Acetophenone (10 ml, 85.7 mmol), paraform (10.28 g, 342.7 mmol), *i*-PrOH, saturated with HCl (3 ml) and dimethylamine hydrochloride (20.94 g, 257.1 mmol) in *i*-PrOH (50 ml) were refluxed for 2 h. Then additional amount of paraform (2.57g, 85.7 mmol) was added and mixture was refluxed for 3 h. After cooling solvent was removed in vacuo, water (100 ml) was added, resulted solution extracted with EtOAc (2×10 ml). 30% solution of NaOH was added until the aqueous solution was pH 8. Mixture was extracted with $Et_2O$ (3×50 ml), organic layer separated, dried with $MgSO_4$, filtered and evaporated in vacuo to give 20.0 g of aminoketones **1a** and **2a**. To a solution of 11.0 g of mixture of **1a** and **2a** in dry $Et_2O$ (55 ml) MeI (5 ml, 80.2 mmol) was added. After 2 days white precipitate was filtered, washed with $Et_2O$ (2×10 ml) immediately and with acetone (2×10 ml) 12h after, then dried to give 16 g of **3a**.

*Data for 3a*: $^1$H-NMR (200 MHz, DMSO-$d_6$) $\delta_H$: 3.12 (s, 9H, $N(CH_3)_3$)), 4.44 (s, 2H, $NCH_2$), 6.39 (s, 1H, $=CH_a$), 6.77 (s, 1H, $=CH_b$), 7.50-7.72 (m, 3H, *m,p*-Ph), 7.82-7.92 (m, 2H, *o*-Ph); $^{13}$C-NMR (200 MHz, DMSO-$d_6$, j-mod) $\delta_C$: 44.17 (+, $N(CH_3)_3$), 63.31 (-, $NCH_2$), 128.40, 129.30, 132.84 (+, Ph), 135.22, 135.39, 141.28 (-, *i*-Ph, $C=CH_2$), 194.67 (-, CO); IR (KBr): ν, cm$^{-1}$ = 1670.

*Data for 3b*: $^1$H-NMR (200 MHz, DMSO-$d_6$) $\delta_H$: 3.08 (s, 9H, $N(CH_3)_3$), 4.41 (s, 2H, $NCH_2$), 6.58 (s, 1H, $=CH_a$), 6.61 (s, 1H, $=CH_b$), 7.33 (dd, 1H, J = 5, 3.8, $H(4)_{arom}$), 8.12 (dd, 1H, J = 1.5, 3.8, $H(3)_{arom}$ or $H(5)_{arom}$), 8.19 (dd, 1H, J = 5, 1.5, $H(5)_{arom}$ or $H(3)_{arom}$); IR (KBr): ν, cm$^{-1}$ = 1642.

*General procedure for nucleophilic addition to* ***3***. Mixture of **3** (10 mmol), solvent (20 ml) (MeOH for **8**, abs. EtOH for **4, 5,** 9**a,b** and **14a,b**), base (10 mmol of EtONa for **4** and **9a,b**, 10 mmol of $Et_3N$ for **5**, **8** and **14a,b**) and nuclcophile (20 mmol of $NH_2OMe$ for **4** and **5**, 20 mmol of *anti*-benzaldoxime for **8** and **9a,b**, 10 mmol of **13** for **14a,b**) was stirred for 12-48 h and filtered. After evaporation of the solvent the residue was treated with soln. of $NaHCO_3$, mixture was extracted with $CHCl_3$. Organic layer was dried ($MgSO_4$) and solvent removed in vacuo. For **9a,b** the residue was triturated with $Et_2O$ and filtered. For **4, 5, 8** and **14a,b** the residue was purified by column chromatography (for **4, 5, 8** silica gel, light petroleum-*t*-BuOMe, for **14a,b** $Al_2O_3$, $CHCl_3$).

*Data for* ***4***: colorless oil; $^1$H-NMR (200 MHz, $CCl_4$, HMDS) $\delta_H$: 1.10 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 3.00 (dd, 1H, J = 13.5, 5.8, $NC\underline{H}_aH_b$), 3.25 (dd, 1H, J = 13.5, 6.5, $NCH_a\underline{H}_b$), 3.34 (s, 3H, $OCH_3$), 3.39 (q, 2H, J = 7, $C\underline{H}_2CH_3$), 3.59 (m, 2H, $CHC\underline{H}_2OEt$), 3.97 (m, 1H, CH), 5.58 (br. s, 1H, NH), 7.30-7.60 (m, 3H, *m,p*-Ph), 7.9-8,05 (m, 2H, *o*-Ph); IR (neat): ν, $cm^{-1}$ = 1675; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 244 (4.19); $C_{13}H_{19}NO_3$ calc.: C 65.80, H 8.07, N 5.90; found: C 65.33, H 8.01, N 6.28.

*Data for* ***5***: colorless oil; $^1$H-NMR (200 MHz, $CCl_4$, HMDS) $\delta_H$: 3.05 (dd, 2H, J = 13.5, 6, $C\underline{H}_aH_b$), 3.25 (dd, 2H, J = 13.5, 6, $CH_a\underline{H}_b$), 3.39 (s, 3H, $OCH_3$), 4.03 (m, 1H, CH), 5.64 (br. s, 2H, 2NH), 7.35-7.50 (m, 3H, Ph), 7.90-8.00 (m, 2H, Ph); IR (neat): ν, $cm^{-1}$ = 1675; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 244 (4.18); $C_{12}H_{18}N_2O_3$×2HCl calc.: C 46.31, H 6.48, N 9.00, Cl 22.79; found: C 46.27, H 6.45, N 9.16, Cl 22.75.

*Data for* ***6***. colorless oil; $^1$H-NMR (500 MHz, $CCl_4$, $C_6D_{12}$) $\delta_H$: 2.11 (m, 1H, CH), 2.86 (dd, 1H, J = 12.9, 5.6, $C\underline{H}_aH_b$), 2.88 (dd, 1H, J = 12.8, 6.3, $C\underline{H}'_aH'_b$), 2.88 (dd, 1H, J = 12.9, 5.6, $CH_a\underline{H}_b$), 2.98 (dd, 1H, J = 12.8, 6.3, $CH'_a\underline{H}'_b$), 3.41 (s, 3H, $OCH_3$), 3.43 (s, 3H, $OCH_3$'), 4.32 (br.s., 1H, OH), 4.74 (d, 1H, J = 5, CHOH), 5.72 (br.s., 2H, NH), 7.13-7.20, 7.22-7.27 (2m, 5H, Ph); $^{13}$C-NMR (200 MHz, $CDCl_3$) $\delta_C$: 41.59 (d, CH), 50.85 (t, $CH_2$), 52.62 (t, $CH_2$), 61.38 (q, $CH_3$), 76.09 (d, CHOH), 126.04, 127.12, 128.16 (d, Ph), 143.15 (s, Ph); $C_{12}H_{20}N_2O_3$ calc.: C 59.98, H 8.39, N 11.66; found: C 59.80, H 8.24, N 11.69.

*Data for* ***8***. m.p. 101-103 °C (chromat. $SiO_2$, EtOAc:petroleum); $^1$H-NMR (200 MHz, $CDCl_3$) $\delta_H$: 3.24 (s, 3H, $OCH_3$), 3.68 (d, 2H, J = 5, $CH_2$), 4.24 (dd, 1H, J = 12, 7, $C\underline{H}_aH_b$), 4.60 (m, 2H, $CH_a\underline{H}_b$+CH), 7.47 (s, 1H, CH=N), 7.30-7.65, 7.90-8.00, 8.13-8.24 (3m, 10H, 2Ph); IR (KBr): ν, $cm^{-1}$ = 1680; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 245 (4.21), 294 (4.27); $C_{18}H_{19}NO_3$ calc.: C 72.71, H 6.44, N 4.71; found: C 72.80, H 6.37, N 4.69.

*Data for* ***9a***×*1/2H₂O*: m.p. 125-126 °C (chromatogr. $SiO_2$, *t*-BuOMe:MeOH, 15:1); $^1$H-NMR (200 MHz, $(CD_3)_2CO$) $\delta_H$: 4.42 (dd, 2H, J = 12.5, 5.5 $C\underline{H}_aH_b$), 4.54 (dd, 2H, J = 12.5, 7.2, $CH_a\underline{H}_b$), 5.10 (m, 1H, CH), 7.30-7.50 (m, 9H, Ph), 7.77 (s, 2H, CH=N), 8.00-8.30 (m, 6H, Ph); $^{13}$C-NMR (200 MHz, $(CD_3)_2CO$, j-mod) $\delta_C$: 43.73 (+, CH), 66.34 (-, $CH_2$), 129.03, 129.14, 129.21, 129.36, 130.78, 133.80, 135.47 (+, $CH_{Ph}$ and CH=N), 131.97 (-, $CH_{Ph}$), 137.83 (-, $CH_{Ph}$), 199.19 (-, CO); IR (KBr): ν, $cm^{-1}$ = 1675; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 246 (4.47), 290 (4.30); $C_{24}H_{22}N_2O_3$×1/2$H_2O$ calc.: C 72.89, H 5.86, N 7.08; found: C 73.22, H 5.83, N 6.95.

*Data for* ***9b***: m.p. 113-115 °C (chromatogr. *t*-BuOMe:MeOH, 15:1); $^1$H-NMR (200 MHz, $(CD_3)_2CO$) $\delta_H$: 4.38 (dd, 2H, J = 12.5, 5.5, $C\underline{H}_aH_b$), 4.55 (dd, 2H, J = 12.5, 7.6, $CH_a\underline{H}_b$), 5.02 (m, 1H, CH), 7.76 (s, 2H, CH=N), 7.14 (m, 1H, 4-$H_{Th}$), 7.25-7.42 (m, 6H, *m,p*-$H_{2Ph}$), 7.83 (m, 1H, 5-$H_{Th}$), 8.11 (m, 1H, 3-$H_{Th}$), 8.15-8.30 (m, 4H, *o*-$H_{2Ph}$); IR (KBr): ν, $cm^{-1}$ = 1640; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 225 (4.12), 297 (4.62); $C_{22}H_{20}N_2O_3S$×1/2$H_2O$ calc.: C 65.81, H 5.27, N 6.98, S 7.99; found: C 66.06, H 4.98, N 6.94, S 8.00.

*Data for* ***12a***: m.p. 169-171 °C (MeOH); $^1$H-NMR (200 MHz, DMSO-$d_6$, 60°C) $\delta_H$: 2.84 (dd, 2H, J = 11.5, 11.5, $2CH_aH_b$), 3.43 (dd, 2H, J = 11.5, 3, $2CH_aH_b$), 4.03 (br. s, 1H, NCHN), 4.35 (m, 1H, CCHC), 7.15-8.05 (m, 12H, 2Ph, 2OH); IR (KBr): ν, cm$^{-1}$ = 1655; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 245 (4.14), 286 (3.62); $C_{17}H_{18}N_2O_3$ calc.: C 68.44, H 6.08, N 9.39; found: C 68.23, H 6.02, N 9.29.

*Data for* ***12b***. m.p. 171-172 °C (MeOH); $^1$H-NMR (200 MHz, DMSO-$d_6$, 60°C) $\delta_H$: 2.88 (dd, 2H, J = 11.4, 11.4, $2CH_aH_b$), 3.43 (dd, 2H, J = 11.4, 3, $2CH_aH_b$), 4.03 (br. s, 1H, NCHN), 4.21 (m, 1H, CCHC), 7.15-7.33 (m, 4H, *m,p*-Ph, 4-$H_{Th}$), 7.42-7.52 (m, 2H, *o*-Ph), 7.63 (s, 2H, OH), 7.95 (m, 1H, 3- or 5-$H_{Th}$), 8.02 (m, 1H, 5- or 3-$H_{Th}$); IR (KBr): ν, cm$^{-1}$ = 1625; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 263 (3.86), 288 (3.82); $C_{15}H_{16}N_2O_3S$ calc.: C 59.19, H 5.30, N 9.20, S 10.54; found: C 59.14, H 5.34, N 9.02, S 10.40.

*Data for* ***14a***$\times H_2O$: m.p. 61-65 °C (EtOAc:hexane); IR (KBr): ν, cm$^{-1}$ = 1665; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 243 (4.21); $C_{17}H_{22}N_3O_2\times H_2O$ calc.: C 64.13, H 7.60, N 13.20; found: C 64.11, H 7.66, N 13.25.

*Data for* ***14b***. m.p. 147-149 °C (EtOAc:hexane); IR (KBr): ν, cm$^{-1}$ = 1634, 1666; UV (EtOH): $\lambda_{max}$, nm (lg ε) = 261 (3.96), 288 (3.87); $C_{15}H_{20}N_3O_2S$ calc.: C 58.80, H 6.58, N 13.71; found: C 58.81, H 6.56, N 13.59.

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