S_N^H-REACTIONS OF 1,2,4-TRIAZINE DERIVATIVES WITH ACETOPHENONES

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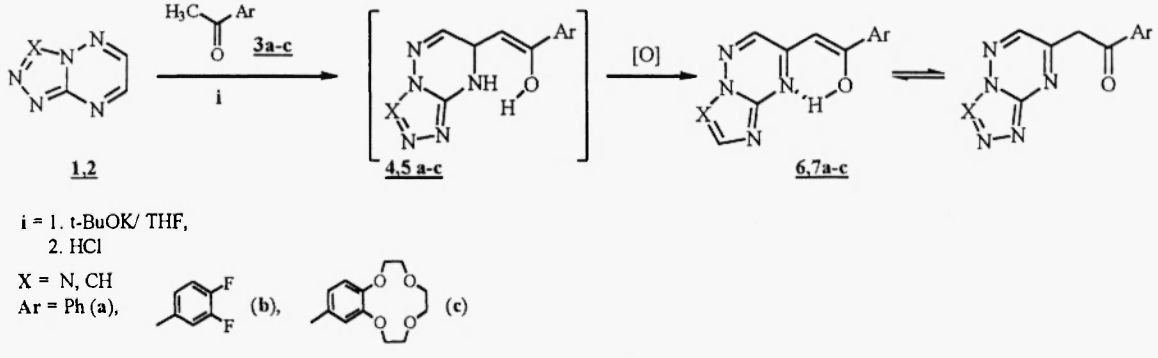
Abstract. S_N^H-products were obtained by the reaction of azoloannelated 1,2,4-triazines and 3-substituted 1,2,4-triazin-5(2H)-ones with acetophenones. The reasons of extraordinary readily aromatization of σ^H-adducts have been discussed.

Introduction. It has been known that most approaches used for functionalization of 1,2,4-triazines and their azoloannelated analogues are based on the reaction of nucleophilic substitution of good leaving groups (1). However, according to the modern conceptions of nucleophilic substitution in aromatic systems the nucleophilic attack first of all takes place at the unsubstituted carbon atom of triazine ring even if good leaving group is in the cycle. σ^H-Adducts obtained by interaction of aza-aromatic compounds with nucleophiles can undergo dissociation or take part in the further transformations, such as aromatization by oxidizing or *auto*-aromatization (S_N^H-processes), ring opening or recyclization. As a rule the σ^H-adducts obtained from 1,2,4-triazines are stable compounds. The main difficulty of realizing S_N^H-process consists in the aromatization of σ^H-adducts (2).

Discussion. In present work the extraordinary readily oxidation of σ^H-intermediates obtained by the reaction of 1,2,4-triazines (azoloannelated 1,2,4-triazines **1,2** and 1,2,4-triazin-5(2H)-ones **8-10**) with acetophenones **3a-c** has been found. Thus, such σ^H-adducts **4,5 a-c** were oxidized very readily by the action of oxygen contained in a solvent and in air (Scheme 1).

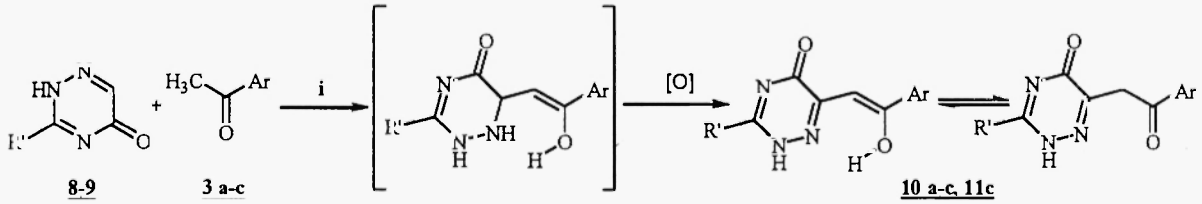


Scheme 1

Attempts to detect σ^H-adducts in that reactions by both thin-layer chromatography and UV spectroscopy failed. To our mind the readily oxidation of σ^H-adducts **4,5** is due to the tendency to fix preferred conformation for oxidation in which the oxidized bond tends to be located in the ring plane. It is likely due to the formation of H-bond between N4-H and oxygen atom of carbonyl group. This bond is not formed in the products of addition of CH-active compounds to 3-substituted 1,2,4-triazines which N2-H isomer is more energy preferred. So, the products prepared by the interaction of unannelated 3-substituted 1,2,4-triazines with carbaniones generated *in situ* from CH-active compounds are stable and their oxidation is possible only under more rigid condition (3). The products of nucleophilic substitution of hydrogen **6,7 a-c** were isolated with 30-60% yields. According to the ^{1}H-NMR and IR data it is evident that the reaction products exist as two tautomeric forms, with a predominance of an enol form.

Introduction of oxo-group into the 5-position of triazine ring decreases its reactivity substantially. The attempts to isolate products of addition of acetophenones to 1,7-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7(1H)-one or S_N^H-products both in the presence of base and using protonation of nitrogen atoms of triazine ring – the frequently used approach to activation of triazines - failed.

It has been known that in the presence of acids the unannelated 1,2,4-triazinones are more active then their annelated analogues (4). Introduction of acetophenones to 6-position of triazine ring was realize using 3-substituted 1,2,4-triazin-5(2H)-ones as a substrate. Lewis acid was the better activating agent in combination of 3-substituted 1,2,4-triazin-5(2H)-ones with acetophenone's derivatives. As in the case of the reaction of azolotriazines this interaction is not stopped on the stage of the σ^H-adducts formation and results in S_N^H-products **10a-c, 11c**. In the case of acetophenone **3c** the formation of C-C bond between unsubstituted carbon atom of triazine and unsubstituted aromatic carbon of acetophenone would be expected as it is in the reaction of 1,2,4-triazin-5(2H)-ones with benzoannelated crown ethers (5). However, an electron withdrawing substituents (acyl group) in aromatic ring decreases the nucleophilicity of acetophenone aromatic ring and the addition products had not obtained. The only products of this reaction were compounds **10 a-c, 11c** (Scheme 2).



i = BF_3•Et_2O, MeOH

R' = Ph (**8**, **10**), 4-Tol (**9**, **11**)

Scheme 2

According to the ^{1}H-NMR and IR data it has been established that obtained compounds as well as products **6,7 a-c** exist in an enol form predominantly.

The IR-study of H-bonds in **10, 11** has shown that in **10a** the intramolecular H-bond between OH-group and N1 of triazine ring is realized in the formation of six-member cycle. IR spectra of **10b** and **11c** showed lamellar absorption with several maximums (3600, 3450, 3170 cm^{-1}) and shift of C=O band to the far infrared region. The C=O absorption was observed at 1590 cm^{-1} and its intensity was increased by 24 times. So it can be concluded that

introduction of substituents in aromatic ring of acetophenone promotes formation of H-bond between OH-group and C=O fragment of triazine ring.

Conclusion. It has been shown that the S_N^H-process proceeds smoothly without adding any oxidizers when triazines and traizinones react with acetophenones. This process not only makes it possible to introduce acetophenone's moieties but can be used for synthesis of triazine containing crown ethers. Two different complexation centers are combined in compounds **6,7,10** and **11**, promissing agents for the use as receptors of bipolar organic compounds.

Experimental

^{1}H-NMR spectra were measured on Bruker DRX-400 in the DMSO-D6 solutions, TMS was used as a standard: mass spectra (EI, 70eV) were recorded on Varian MAT311-A; IR spectra were recorded on Specord IR-75 instrument; melting points (uncorrected) were obtained on a Boetius apparatus.

General procedure for the preparation of 1-Ar-2-azolo[1,2,4]triazin-7-yl-1-ethen-1-ol (6, 7).

To a solution of acetophenone in THF an equimolar amount of potassium *tert*-butoxide was added. The reaction mixture was stirred to salt formation. Then an equivalent of azolo[1,2,4]triazine was added to the stirred solution portionwise. The mixture was stirred at room temperature. The solvent was removed *in vacuo*, the residue was dissolved in water, the dilute HCl was added to the obtained solution. The precipitate was filtered off and recrystallized from methanol. **6b** (46%): m.p. 176-178^{0}C. Found, %: C- 47.44; H- 2.07; N- 30.17. Calculated for $C_{11}H_6N_6O_1F_2$, %: C- 47.83; H- 2.19; N- 30.43. MS m/z (relative intensity): 276 (M^+, 12), 141 (100), 113 (55), 79 (26), 63 (17). ^{1}H NMR (δ, ppm): 8.48 (b.s., 0.93H), 9.15 (s, 0.07H) (C_{triaz}-H); 6.96 (s, 0.93H), 5.01 (s, 0.14H) ($C_{acetophenne}$-H); 7.40-7.54 (m, 3H, Ar). **6c** (30%): m.p. 166-168^{0}C. Found, %: C- 52.98; H- 4.36; N- 21.76. Calculated for $C_{17}H_{18}N_6O_5$, %: C- 52.71; H- 4.69; N- 21.75. MS m/z (relative intensity): 386 (M^+, 19), 251 (39), 163 (100), 135 (33), 79 (17).^{1}H NMR (δ, ppm): 8.52 (s., 0.87H), 9.13 (s, 0.13H) (C_{triaz}-H); 6.92 (s, 0.87H), 4.98 (s, 0.26H) ($C_{acetophenone}$-H); 7.2 (m, 1H, Ar), 7.58-7.75 (m,1.99H, Ar), 4.18-4.21 (m, 4H, Ar), 3.67-3.82 (m, 4H, Ar), 3.62 (b.s., 4H, Ar). **7a** (41%): m.p. 239-241^{0}C. Found, %: C- 59.92; H- 4.05; N- 29.65. Calculated for $C_{12}H_9N_5O_1$, %: C- 60.25; H- 3.79; N- 29.27. MS m/z (relative intensity): 239 (M^+,13), 184 (25), 105 (100), 77 (58). ^{1}H NMR (δ, ppm): 9.04 (s, 0.87H), 9.56 (s, 0.13H) (C_{azol}-H); 8.37 (s., 0.87H), 8.73 (s, 0.13H), (C_{triaz}-H); 6.77 (s, 0.87H), 4.86 (s, 0.26H) ($C_{acetophenone}$-H), 7.92-8.04 (m, 2H, Ar), 7.49-7.58 (m,3.06H, Ar). **7c** (32%): m.p. 232-233^{0}C. Found, %: C- 55.86; H- 5.01; N- 17.99. Calculated for $C_{18}H_{19}N_5O_5$, %: C- 56.11; H- 4.95; N- 18.18. MS m/z (relative intensity): 385 (M^+,39), 367 (26), 279 (100), 264 (37), 163 (97), 135 (39), 79 (22). ^{1}H NMR (δ, ppm): 9.09 (s, 0.77H), 9.64 (s, 0.23H) (C_{azol}-H); 8.26 (s., 0.77H), 8.76 (s, 0.23H) (C_{triaz}-H); 6.77 (s, 0.77H), 4.81 (s, 0.46H) ($C_{acetophenone}$-H), 7.12-7.21 (m, 1H, Ar), 7.65-7.79 (m, 2H, Ar), 4.20-(b.s., 4H, Ar), 3.69-3.76 (m, 4H, Ar), 3.62 (b.s., 4H, Ar).

General procedure for the preparation of 6-(2-hydroxy-2-Ar-1-ethynyl)-3-R-2,5-dihydro-1,2,4-triazin-5-ones (10a-c, 11c)

3-R-1,2,4-Triazin-5(2H)-one was dissolved in methanol. An equimolar amount of acetophenone and catalytic amount of $BF_3{\cdot}Et_2O$ were added to reaction mixture. The mixture was stirred at room temperature. The precipitate was filtered off and recrystallized from methanol. **11a** (56%): m.p. 228-230^{0}C. Found, %: C- 70.16; H- 4.79; N- 14.39. Calculated for

$C_{17}H_{13}N_3O_2$, %: C- 70.09; H- 4.50; N- 14.42. MS m/z (relative intensity): 291 (M^+,100), 144 (21), 105 (50), 77 (42). ^{1}H NMR (δ, ppm): 6.58 (s, 0.77H), 4.34 (s, 0.23H) ($C_{acetophenone}$-H); 13.88 (b.s., 0.77H), 14.07 (b.s., 0.11H) (NH); 12.52 (b.s., 0.77H, OH), 7.97-7.99 and 7.4-7.94 (m, 8.7H, 3-R, Ar). **11b** (40%): m.p. 188-190^{0}C. Found, %: C- 62.55; H- 3.23; N- 12.44. Calculated for $C_{17}H_{11}N_3O_2F_2$, %: C- 62.39; H- 3.39; N- 12.84. MS m/z (relative intensity): 327 (M^+,100), 180 (24), 141 (52), 104 (51), 77 (31). ^{1}H NMR (δ, ppm): 6.56 (s, 0.8H), 4.41 (s, 0.2H) ($C_{acetophenone}$-H); 13.88 (b.s., 0.8H), 14.11 (b.s., 0.12H) (NH); 12.65 (b.s., 0.8H, OH), 7.90-8.08 and 7.49-7.66 (m, 7.2H, 3-R, Ar). **11c** (58%): m.p. 239-240^{0}C. Found, %: C- 63.47; H- 5.03; N- 9.25. Calculated for $C_{23}H_{23}N_3O_6$, %: C- 63.15; H- 5.30; N- 9.60. MS m/z (relative intensity): 437 (M^+,100), 251 (39), 163 (74), 104 (40), 77 (25). ^{1}H NMR (δ, ppm): 6.51 (s, 1H, $C_{acetophenone}$-H), 13.79 (b.s., 1H, NH_{enol}), 12.66 (b.s., 0.9H, OH), 7.52-7.91 (m, 8H, 3-R, Ar), 4.15-4.19 (b.s., 4H, $\mathbf{CH_2}CH_2O$), 3.66-3.82 (m, 8H, $CH_2\mathbf{CH_2}O\mathbf{CH_2}$). **12c** (42%): m.p. 215-216^{0}C. Found, %: C- 63.97; H- 5.56; N- 9.27. Calculated for $C_{24}H_{25}N_3O_6$, %: C- 63.84; H- 5.58; N- 9.31. M^+=451. ^{1}H NMR (δ, ppm): 6.49 (s, 1H, $C_{acetophenone}$-H), 13.79 (b.s., 1H, NH_{enol}), 12.41 (b.s., 1H, OH), 7.61 (dd, 1H, J=2Hz, J'=8.4Hz, Ar), 7.56 (d, 1H, J=2Hz, Ar), 7.05 (d, 1H, J=8.4Hz, Ar), 4.16-4.19 (b.s., 4H, $\mathbf{CH_2}CH_2O$), 3.73-3.79 (m, 4H, $CH_2\mathbf{CH_2}O$), 3.64-3.70 (m, 4H, $CH_2CH_2O\mathbf{CH_2}$), 8.00 (d, 2H, J=8.24Hz, pTol), 7.26 (d, 2H, J=8.24Hz, pTol), 2.49 (s, 3H, CH_3).

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