*Chemistry of Heterocyclic Compounds, Vol. 40, No. 7, 2004*

# REGIOSELECTIVITY OF NUCLEOPHILIC ATTACK IN THE REACTIONS OF 1,2,4-TRIAZINE 4-OXIDES WITH CERTAIN C-NUCLEOPHILES

**D. N. Kozhevnikov[1], A. M. Prokhorov[1], V. L. Rusinov[1], and O. N. Chupakhin[2]**

*The addition of CH-active compounds to 6-aryl-1,2,4-triazine 4-oxide is reversible and occurs under conditions of kinetic control at position 5 of the heterocycle to form cyclic C(5)-$\sigma^H$ adducts. Under conditions of thermodynamic control the nucleophilic attack is directed to position 3 of the heterocycle and is accompanied by its opening to form the more stable open chain addition products. Attack of ethylmagnesium bromide is directed exclusively to the 5 position of the 6-aryl-1,2,4-triazine 4-oxides as a result of the irreversibility of the given reaction.*

**Keywords:** 1,3-diketones, organomagnesium compounds, 1,2,4-triazine, nucleophilic substitution of hydrogen.

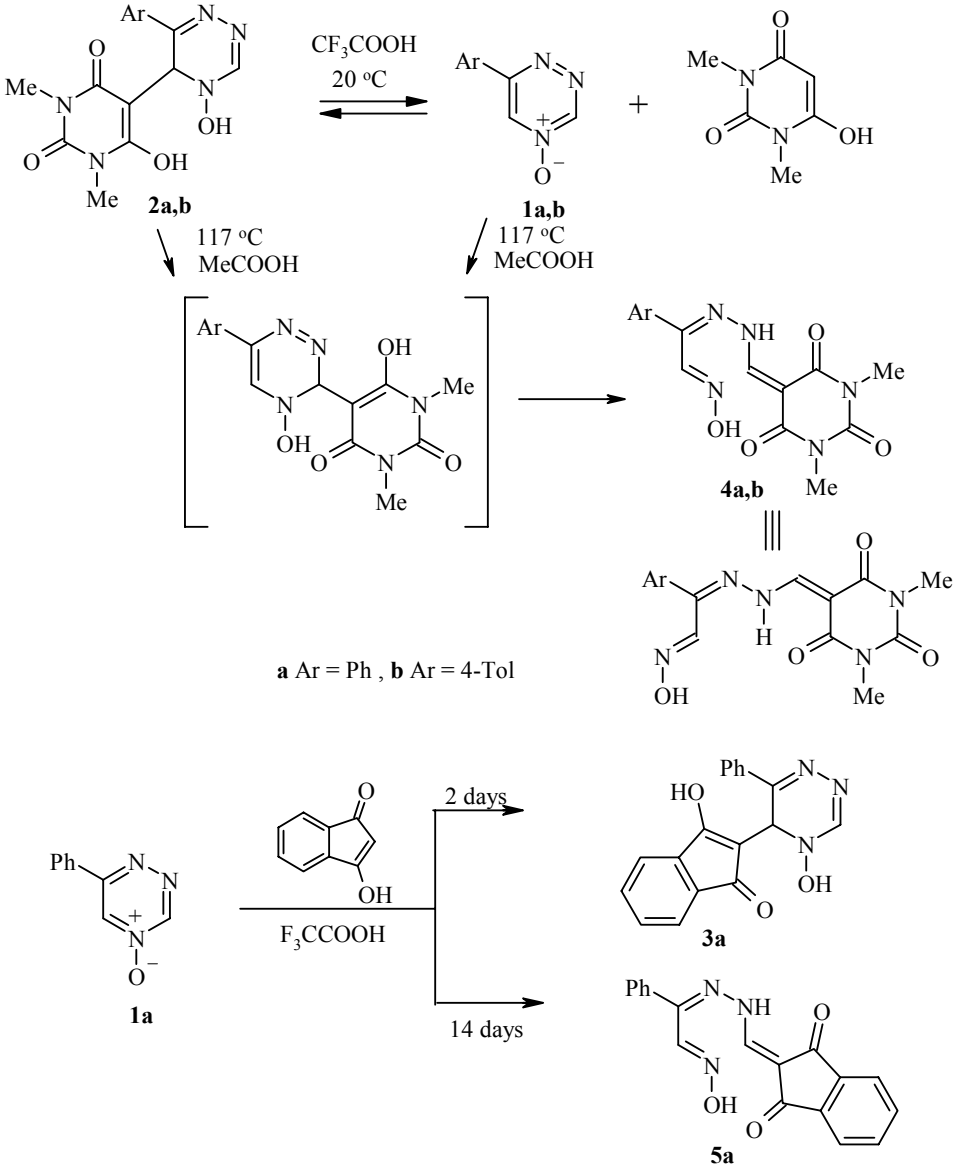
A study of the regioselectivity of the reaction of polydentate substrates is an important area in the chemistry of heterocycles and makes it possible to predict the ratio of regioisomers or, in preference, to direct the reaction [1]. This also applies to the reactions of 6-aryl-1,2,4-triazine 4-oxides which have proved themselves to be highly electrophilic substrates in the nucleophilic substitution reactions of hydrogen ($S_N^H$) with N-, S-, O-, and C-nucleophiles [2, 3]. Previously carried out investigations have shown that nucleophilic attack is directed to the 3 or 5 position of the 1,2,4-triazine ring, as determined by the nature of the reagents and the reaction conditions. Thus the reaction of 1,2,4-triazine 4-oxides with cyanamide [4], cyanide anion [5], water in the presence of benzoyl chloride [6], or indoles and phenols with trifluoroacetic acid [7, 8] occurs exclusively *via* addition of the nucleophile at the 5 position of the heterocycle. On the other hand, the reaction of individual CH-active compounds with 1,2,4-triazine 4-oxides occurs by the addition of the nucleophile at position 3 of the heterocycle and with subsequent opening [9, 10]. By aminating 1,2,4-triazine 4-oxides with ammonia or with primary and secondary aliphatic amines it has been shown that the addition of the amine at position 5 of the heterocycle is a kinetically controlled process whereas the addition at position 3 with ring opening is thermodynamically controlled [11].

In this connection we have studied the regioselectivity of the addition of C-nucleophiles to the 6-aryl-1,2,4-triazine 4-oxides **1** since the C–C bond formed in this way is more stable than the C–O, C–N, or C–S bonds and the reversible reactions of the regioisomers can occur more slowly, making their investigation easier. We chose cyclic 1,3-diketones as the C-nucleophiles. It has previously been reported that the reaction of 1,2,4-triazine 4-oxides **1** with 1,3-dimethylbarbituric acid and indane-1,3-dione at room temperature occurs with addition of these C-nucleophiles at position 5 of the heterocycle to form the C(5)-$\sigma^H$ adducts **2** and **3** [12]. In

[1] Ural State Technical University, Yekaterinburg 620002, Russia; e-mail: rusinov@htf.ustu.ru. [2] I. Ya. Postovsky Institute of Organic Synthesis, Ural Section, Russian Academy of Sciences, Yekaterinburg 620219; e-mail: chupakhin@ios.uran.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1060-1064, July, 2004. Original article submitted July 15, 2002.

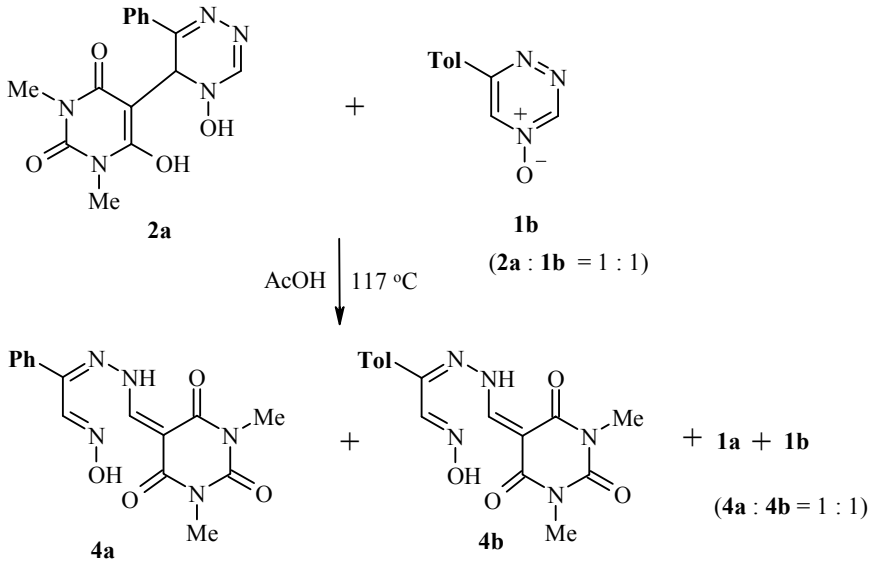
 

continuing our study of this reaction we have found that an increase in the temperature or the time changes the course of the nucleophilic attack. When the reaction is carried out in refluxing acetic acid the dimethylbarbituric acid addition occurs at position 3 of the triazine system with the formation of the opened products 1-hydroxy-6-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimid-5-ylidene)-1,4,5-triazahexa-1,3-dienes **4a,b** in 50-60% yields. The similar product 1-hydroxy-6-(1,3-dioxoindan-2-ylidene)-3-phenyl-1,4,5-triazahexa-1,3-diene (**5a**) was prepared in 55% yield by treating the 1,2,4-triazine 4-oxide **1a** with indanedione in the presence of trifluoroacetic acid over 14 days at room temperature.

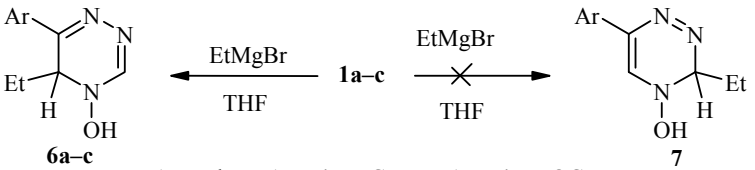



The change in reaction course with change in temperature and time is consistent with the proposal of kinetic control of nucleophilic attack at position 5 and thermodynamic at position 3 of the heterocycle. In the latter case a gain factor in energy is evidently achieved upon ring opening. For confirmation we have carried out the following experiment. The C(5)-adducts **2** were heated in acetic acid over 30 min. As a result, a complete conversion of the cyclic C(5)-$\sigma^H$ adducts **2** to the open chain triazahexadienes **4** was observed, these being obtained through the addition of the nucleophile at position 3 of the 1,2,4-triazine 4-oxide **1a**.

Such reactions can theoretically be accompanied by the formation of the starting substrate and nucleophile *via* the reversibility of the addition stage or by an intramolecular sigmatropic shift in the pyrimidine fragment. The latter variant seems less likely but, in order to exclude it completely, we carried out the transformation of the adduct **2a** reported above in the presence of an equimolar amount of 1,2,4-triazine 4-oxide as an external entrainment trap. A small difference in the aryl substituent at position 6 of the 1,2,4-triazine ring (phenyl and *p*-tolyl) did not prove to have a significant effect on the reaction course because of the remoteness of the latter from the reaction centers. After refluxing in acetic acid for 30 min the reaction mixture in this case consists of practically equal amounts of the open chain products **4a** and **4b** and also the 1,2,4-triazine 4-oxides **1a** and **1b** (according to $^1$H NMR spectroscopic data). This points to an intermolecular transfer of the nucleophilic fragment and hence to the reversibility of the formation of the C(5)-$\sigma^H$ adducts **2**.




To confirm the proposal of kinetic control of the nucleophilic attack at position 5 of the heterocycle the reaction of the 6-aryl-1,2,4-triazine 4-oxides **1** with such C- nucleophiles as organomagnesium compounds was investigated. It should be noted that the addition of the latter is an irreversible process [1, 13, 14] which, in turn, excludes the equilibria of interconverting regioisomers. It was found that the 1,2,4-triazine 4-oxides **1** react with ethylmagnesium bromide to give only the 6-aryl-5-ethyl-4-hydroxy-4,5-dihydro-1,2,4-triazine **6a-c** C(5) adducts. We point out that this is the first example of the reaction of 1,2,4-triazine 4-oxides with Grignard reagents. The $^1$H NMR spectroscopic data for compounds **6a-c** agrees with the proposed structure and differs markedly from the spectra of the 5-aryl-3-ethyl-4-hydroxy-3,4-dihydro-1,2,4-triazine **7** C(3)-$\sigma^H$ adducts prepared by a counter synthesis [15].




**a** Ar = Ph, **b** Ar = 4-MeC$_6$H$_4$, **c** Ar = 4-MeOC$_6$H$_4$

Hence it follows that, in the reactions of 1,2,4-triazine 4-oxides with nucleophiles, there are observed kinetic selectivity of addition of the nucleophile at position 5 of the heterocycle and thermodynamic selectivity at position 3 of the heterocycle with opening of the latter.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Bruker WM-250 (250 MHz) spectrometer with TMS as internal standard. Monitoring of the course of the reaction and the purity of the products was carried out by TLC on Silufol UV-254 plates with ethyl acetate eluent and revealed using UV light. The 1,2,4-triazine 4-oxides **1** were synthesized according to the method [16].

**Reaction of 1,2,4-Triazine 4-Oxides 1a,b with 1,3-Dimethylbarbituric Acid. (General Method).** A solution of the 6-aryl-1,2,4-triazine 4-oxide **1** (4 mmol) and 1,3-dimethylbarbituric acid (624 mg, 4 mmol) in acetic acid (30 ml) was refluxed for 30 min. The precipitate formed on cooling was filtered off and recrystallized from ethanol.

**1-Hydroxy-6-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidyl-5-idene)-3-phenyl-1,4,5-triazahexa-1,3-diene (4a).** Yield 1120 mg (85%); mp 255-257°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (3H, s, $NCH_3$); 3.20 (3H, s, $NCH_3$); 7.4 (3H, m); 7.8 (2H, m); 8.38 (1H, s); 8.44 (1H, d, *J* = 11.6); 12.80 (1H, s, OH); 14.13 (1H, d, *J* = 11.6, NH). Found, %: C 54.89; H 4.49; N 21.34. $C_{15}H_{15}N_5O_4$. Calculated, %: C 54.71; H 4.59; N 21.27.

**1-Hydroxy-6-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidyl-5-idene)-3-(4-tolyl)-1,4,5-triazahexa-1,3-diene (4b).** Yield 1100 mg (80%); mp >270°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, $CH_3$); 3.20 (3H, s, $NCH_3$); 3.23 (3H, s, $NCH_3$); 7.22 (3H, m); 7.67 (2H, m); 8.32 (1H, s); 8.46 (1H, d, *J* = 11.1); 12.68 (1H, s, OH); 14.15 (1H, d, *J* = 11.1, NH). Found, %: C 55.80; H 5.18; N 20.56. $C_{16}H_{18}N_5O_4$. Calculated, %: C 55.97; H 4.99; N 20.40.

**1-Hydroxy-6-(1,3-dioxoindan-2-ylidene)-3-phenyl-1,4,5-triazahexa-1,3-diene (5a).** A solution of the 6-phenyl-1,2,4-triazine 4-oxide **1a** (4 mmol) and indanedione (584 mg, 4 mmol) in trifluoroacetic acid was allowed to stand at room temperature for 14 days, after which it was diluted with water and the residue was recrystallized from ethanol. Yield 700 mg (55%); mp 180-181°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.4 (3H, m); 7.76 (s, 4H, indane); 7.8 (2H, m); 8.15 (1H, d, *J* = 11.0); 8.46 (1H, s); 12.9 (1H, s, OH); 14.0 (1H, d, *J* = 11.0, NH). Found, %: C 67.55; H 4.26; N 13.02. $C_{18}H_{13}N_3O_3$. Calculated, %: C 67.71; H 4.10; N 13.16.

**Reaction of the 1,2,4-Triazine 4-Oxides 1a,b with Ethylmagnesium Bromide. (General Method).** A solution of ethylmagnesium bromide in THF (obtained from 2 mmol of Mg and 2.5 mmol of bromoethane) was added to the triazine 4-oxide **1** (1 mmol) with vigorous stirring. The solution formed was evaporated, water (~20 ml) was added, and the mixture was refluxed for 5-10 min, cooled to room temperature, and the precipitate was filtered off.

**5-Ethyl-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazine(6a).** Yield 70 mg (35%); mp 195-197°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (3H, t, $C\underline{H}_3CH_2$); 1.65 and 2.05 (both 1H, m, $CH_3C\underline{H}_2$); 5.23 (1H, t, H-5); 7.43 (3H, m); 7.79 (2H, m); 8.35 (1H, s, H-3). Found, %: C 64.89; H 6.49; N 20.54. $C_{11}H_{13}N_3O$. Calculated, %: C 65.01; H 6.45; N 20.67.

**5-Ethyl-4-hydroxy-6-tolyl-4,5-dihydro-1,2,4-triazine(6b).** Yield 140 mg (65%); mp 250-253°C (decomp.). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (3H, t, $C\underline{H}_3CH_2$); 1.65 and 2.00 (both 1H, m, $CH_3C\underline{H}_2$); 2.36 (3H, s, $CH_3$); 5.41 (1H, t, H-5); 7.32 (2H, d); 7.78 (2H, d); 9.14 (1H, s, H-3). Found, %: C 66.21; H 7.09; N 19.18. $C_{12}H_{15}N_3O$. Calculated, %: C 66.34; H 6.96; N 19.34.

**5-Ethyl-4-hydroxy-6-(4-methoxyphenyl)-4,5-dihydro-1,2,4-triazine (6c).** Yield 120 mg (50%); mp 213-215°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, $C\underline{H}_3CH_2$); 1.65 and 2.05 (both 1H, m, $CH_3C\underline{H}_2$); 3.80 (3H, s, $CH_3$); 4.98 (1H, t, H-5); 6.93 (2H, d); 7.70 (2H, d); 8.12 (1H, s, H-3). Found, %: C 61.88; H 6.34; N 17.82. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

This work was carried out with financial support of the RFFI (grant No. 02-03-32627) and the Ural Science Research Center (grant CRDF REC-005).

**REFERENCES**


1. I. S. Poddubnyi, *Khim. Geterotsikl. Soedin.*, 774 (1995).
2. O. N. Chupakhin, V.N. Charushin, and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, New York, San Diego (1994), p. 367.
3. D. N. Kozhevnikov, V. L. Rusinov, and O. N. Chupakhin, *Adv. Heterocycl. Chem.*, **82**, 261 (2002).
4. V. N. Kozhevnikov, A. M. Prokhorov, D. N. Kozhevnikov, V. L. Rusinov, and O. N. Chupakhin, *Izv. Akad. Nauk, Ser. Khim.*, 1128 (2000).
5. O. N. Chupakhin, V. L. Rusinov, E. N. Ulomsky, D. N. Kozhevnikov, and H. Neunhoeffer, *Mendeleev Commun.*, 66 (1997).
6. H. Neunhoeffer and V. Böhnisch, *Liebigs Ann. Chem.*, 153 (1976).
7. V. L. Rusinov, D. N. Kozhevnikov, E. N. Ulomsky, O. N. Chupakhin, G. G. Aleksandrov, and H. Neunhoeffer, *Zh. Org. Khim.*, **34**, 429 (1998).
8. D. N. Kozhevnikov, E. N. Ulomsky, V. L. Rusinov, O. N. Chupakhin, and H. Neunhoeffer, *Mendeleev Commun.*, 116 (1997).
9. Yu. A. Azev, H. Neunhoeffer, S. Foro, H. J. Lindner, and S. V. Shorshnev, *Mendeleev Commun.*, 229 (1995).
10. Yu. A. Azev, O. V. Gryazeva, and S. V. Shorshnev, *Khim. Geterotsikl. Soedin.*, 564 (2001).
11. A. Rykowski, O. N. Chupakhin, D. N. Kozhevnikov, V. N. Kozhevnikov, V. L. Rusinov, and H. C. van der Plas, *Heterocycles*, **55**, 127 (2001).
12. D. N. Kozhevnikov, I. S. Kovalev, V. L. Rusinov, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 1239 (2001).
13. D. Doddi, G. Ercolani, and P. Mencarelli, *J. Org. Chem.*, **57**, 789 (1992).
14. T. -L. Ho, *Tetrahedron*, **41**, 3 (1985).
15. D. N. Kozhevnikov, V. N. Kozhevnikov, V. L. Rusinov, O. N. Chupakhin, E. O. Sidorov, and N. A. Klyuev, *Zh. Org. Khim.*, **34**, 423 (1998).
16. H. Neunhoeffer, F. Weischedel and V. Böhnisch, *Liebigs Ann. Chem.*, **750**, 12 (1971).