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Transformations of 1,2,4-triazine 4-oxides to pyridazines and triazolo[4,3-*b*]pyridazines by the action of substituted acetonitriles

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Two types of ring transformations of 1,2,4-triazine to pyridazine were found: 1,2,4-triazine 4-oxides bearing *ortho*-halophenyl in the 3-position react with phenylacetonitrile under basic conditions to form 3-(2-oxyphenyl)[1,2,4]triazolo[4,3-*b*]pyridazines, while the reactions of 3,6-diaryl-1,2,4-triazin 4-oxides with sodium ethyl cyanoacetate afforded 2-aminopyridazines.

The reactions of carbanions generated from substituted acetonitriles with various heterocyclic compounds yield products of ring transformation. The resulting new heterocyclic systems involve usually a C,C-fragment of the starting nitrile. Such reactions can proceed by two general pathways. The first one is by way of addition of nucleophile, ring opening, ring closure (ANRORC),[1] *e.g.*, the reaction of 3-chloro-1,2,4-triazines with phenylacetonitrile or ethyl cyanoacetate resulting in 3-aminopyridazine.[2] An alternative way involves 1,4-dipolar cycloaddition of the acetonitrile carbanion to a heterocycle, *e.g.*, the reaction of nitrotriazolopyrimidine with ethyl cyanoacetate.[3] In general, ring transformations can be an unusual and sufficient method for the synthesis of various heterocyclic systems.

Recently,[4] we reported that 3,6-diaryl-1,2,4-triazine 4-oxides **1** easily react with carbanions of arylacetonitriles or malonodinitrile yielding products of nucleophilic substitution of hydrogen, corresponding 5-cyanomethylene-1,2,4-triazines **2**. Unexpectedly, attempts to provide the same well-studied reaction of 3-(2,4-dichlorophenyl)-6-phenyl-1,2,4-triazine 4-oxide with phenylacetonitrile **1a** resulted in product **3a**. The molecular composition of product **3a** was in agreement with the product of the chlorine substitution with phenylacetonitrile residue, which was not confirmed by NMR spectroscopy. It was impossible to obtain single crystals of **3a** suitable for X-ray crystallography. Fortunately, the alkylation of product **3a** with EtBr in the presence of Bu^tOK gave a well-crystallised compound, whose structure was defined by X-ray analysis to be 3-(4-chloro-2-ethoxyphenyl)-6,8-diphenyl[1,2,4]triazolo[4,3-b]pyridazine **4** (Figure 1).†

The X-ray data show that the endocyclic bond angle at N(1) is 113.49(16)°, and the angles at N(3) and N(4) are 106.85(17) and 109.10(16)°, respectively. The N(1)–N(2) bond distance is 1.359(2) Å, shorter than N(3)–N(4) [1.376(3) Å]. The whole molecule of **4** is basically planar, with the exception of the ethoxyphenyl moiety, which is perpendicular to the mean molecular plane. A characteristic feature of the crystal packing is the

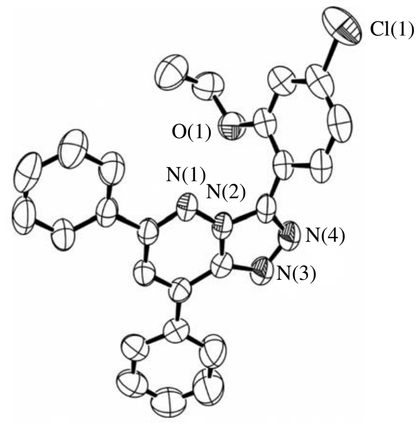


Figure 1 Crystal structure of **4** (ORTEP representation with 50% probability).

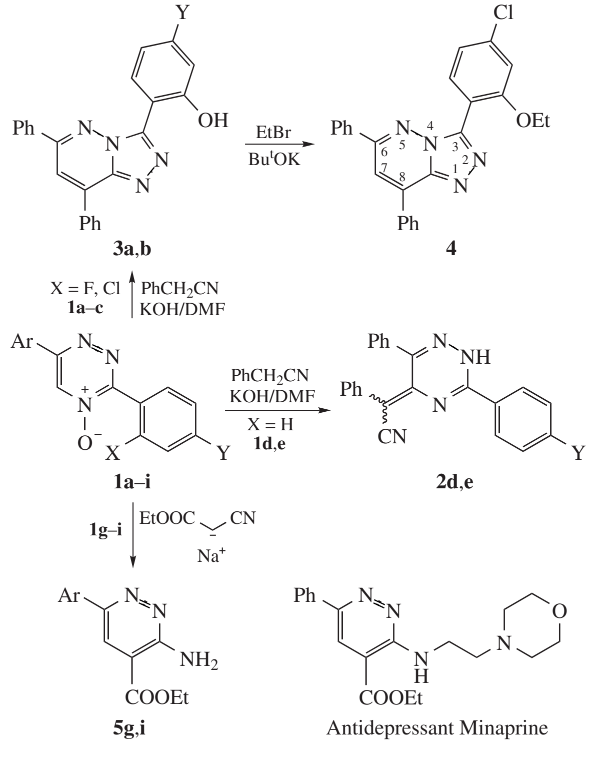
stacking with strong π ring interactions. The centroids of the 6-phenyl ring at (*x*, *y*, *z*) and the pyridazine ring at (1 + *x*, *y*, *z*) are 3.50 Å apart (the dihedral angle is 0.28°).

NMR spectroscopy data conform to the structure of triazolopyridazine **4**. The ^{1}H NMR spectra‡ of compounds **3a** and **4** are similar (excluding, of course, the signals of protons of ethyl and OH group). It means that the alkylation has not change the basic structure of molecule. Hence the reaction of **1a** with the anion of phenylacetonitrile resulted in 3-(4-chloro-2-oxyphenyl)-5,8-diphenyl[1,2,4]triazolo[4,3-*b*]pyridazine **3a** (Scheme 1). The reaction proceeded *via* cleavage of two C,N- and N,O-bonds in the starting triazine ring and formation of three new C,C-, C,N- and N,N-bonds accompanied with chlorine substitution.

The reaction proceeded with other triazines **1**; however, a necessary condition in this case is the presence of an *ortho*-halogen (chlorine or fluorine) in the phenyl substituent. Thus, 1,2,4-triazine 4-oxides **1b**,**c** when treated with phenylacetonitrile under the above conditions underwent the same transformation yielding 3-(2-oxyphenyl)-6,8-diphenyl[1,2,4]triazolo[4,3-*b*]pyridazine **3b**. Any position of the halogen atom in starting triazine **1** other than the *ortho*-position did not provide the ring transformation, while the substitution of hydrogen reaction proceeded very well yielding expected[3] 5-phenylcyanomethylene-1,2,4-triazines **2d**,**e** as a mixture of two *Z*- and *E*-isomers (Scheme 1).

The pyridazine ring was found to form in the reaction of 1,2,4-triazine 4-oxides **1** with sodium ethyl cyanoacetate. However, in this case, the C(3),N(4)-fragment and the aryl substituent in the 3-position were completely removed from the starting 1,2,4-triazine ring. The treatment of triazines **1g**–**i** with a mixture obtained by dissolving an excess of sodium metal in pure ethyl cyanoacetate at 60 °C resulted in 3-amino-4-ethoxycarbonylpyridazines **5g**,**i** (Scheme 1). This reaction did not depend on the aryl substituent in starting heterocycle **1**, but it is very sensitive to the nucleophile nature and did not proceed with phenylacetonitrile.

Both of the above ring transformations lead to involving the same C,C-fragment of the nitriles into resulting heterocyclic systems. Obviously, in both cases, the reactions proceed *via* the same step of dipolar 1,4-cycloaddition of the nitrile carbanion to 1,2,4-triazine ring of **1** to give cycloadduct **A** (Scheme 2). Further elimination of benzonitrile oxide from adduct **A** *via* a retrodiene synthesis affords aminopyridazines **5**. However, the presence of an *ortho*-halogen atom in the aromatic substituent



a Ar = Ph, X = Y = Cl
b Ar = Ph, X = Cl, Y = H
c Ar = Ph, X = F, Y = H
d Ar = Ph, X = H, Y = Cl
e Ar = Ph, X = H, Y = F
f Ar = Ph, X = Y = H
g Ar = 4-ClC$_6$H$_4$, X = Y = H
h Ar = 4-ClC$_6$H$_4$, X = H, Y = Cl
i Ar = 4-BrC$_6$H$_4$, X = Y = H

Scheme 1

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† *Crystal data for* **4**: $C_{25}H_{19}ClN_4O\cdot 0.5EtOH$, *M* = 426.91, triclinic, *a* = 10.824(3), *b* = 10.881(3) and *c* = 11.558(3) Å, α = 102.33(2)°, β = = 107.42(2)°, γ = 109.88(2)°, *V* = 1143.5(5) Å^3, *T* = 293(2) K, space group $P\bar{1}$, *Z* = 2, μ(MoKα) = 0.198 mm^{-1}, 5515 reflections measured, 5514 unique (R_{int} = 0.0560) which were used in all calculations. The final wR_2 was 0.2014 (all data).

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 232441. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.

‡ *General procedure.* Phenylacetonitrile (0.23 ml, 2 mmol) and, after 1 min, corresponding 1,2,4-triazine 4-oxide **1** (1 mmol) were added to a mixture of finely powdered KOH (0.5 g) in 5 ml of DMF with stirring. The reaction mixture was kept for 3 h at room temperature, poured into water and acidified with acetic acid. The crystals formed were filtered off and recrystallised from DMF.

2e: mp > 300 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 6.82 (dd, 2H, *Z*-), 6.99 (s, 5H, Ph of *Z*-), 7.2–7.6 (m, 4H of *Z*- and 7H of *E*-), 7.75 (dd, 2H, *E*-), 7.90 (m, 2H, *E*-), 8.09 (dd, 2H, *E*-), 8.28 (dd, 2H, *Z*-), 13.60 (br. s, 1H, NH *E*- and *Z*-). MS, *m*/*z* (*I*, %): 384 (60) [M$^+$]. Found (%): C, 56.09; H, 4.28; N, 15.00. Calc. for $C_{23}H_{15}ClN_4O$ (277.71) (%): C, 56.23; H, 4.36; N, 15.13.

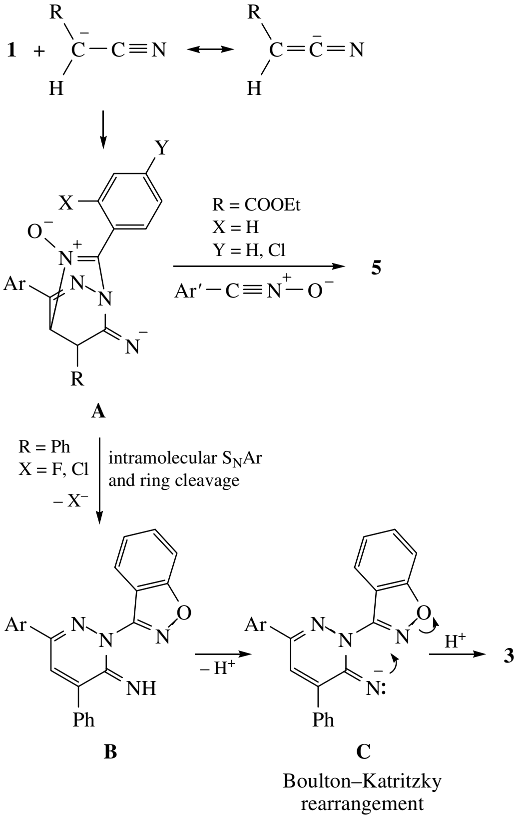
3a: mp 278–279 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.11 (dd, 1H), 7.12 (d, 1H), 7.6 (m, 6H), 8.19 (s, 1H, H-7), 8.2 (m, 2H), 8.44 (d, 1H), 8.5 (m, 2H), 11.61 (br. s, 1H, NH). MS, *m*/*z* (*I*, %): 398 (100) and 400 (29) [M$^+$]. Found (%): C, 69.14; H, 3.87; N, 14.08. Calc. for $C_{23}H_{15}ClN_4O$ (398.86) (%): C, 69.26; H, 3.79; N, 14.05.

3b: mp 223–224 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.11 (m, 2H), 7.43 (ddd, 1H), 7.6 (m, 6H), 8.20 (m, 2H), 8.21 (s, 1H, H-7), 8.52 (m, 2H), 11.03 (br. s, 1H, NH). MS, *m*/*z* (*I*, %): 364 (100) [M$^+$]. Found (%): C, 75.93; H, 4.57; N, 15.25. Calc. for $C_{23}H_{16}N_4O$ (364.41) (%): C, 75.81; H, 4.43; N, 15.37.

4: mp 174–176 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.12 (t, 3H), 4.15 (q, 2H), 7.15 (dd, 1H), 7.26 (d, 1H), 7.5 (m, 3H), 7.6 (m, 4H), 8.1 (m, 2H), 8.13 (s, 1H, H-7), 8.6 (m, 2H). Found (%): C, 69.54; H, 5.05; N, 12.21. Calc. for $C_{25}H_{19}ClN_4O\cdot 0.5EtOH$ (%): C, 69.41; H, 4.93; N, 12.45.

5g: mp 160–163 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.41 (t, 3H), 4.40 (q, 2H), 7.35 (br. s, 2H, NH$_2$), 7.46 (m, 2H), 7.96 (m, 2H), 8.11 (s, 1H, H-5). MS, *m*/*z* (*I*, %): 279 (33) and 277 (100) (M$^+$). Found (%): C, 56.09; H, 4.28; N, 15.00. Calc. for $C_{13}H_{12}ClN_3O_2$ (277.71) (%): C, 56.23; H, 4.36; N, 15.13.

5i: mp 189–192 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.41 (t, 3H), 4.40 (q, 2H), 7.36 (br. s, 2H, NH$_2$), 7.60 (m, 2H), 7.92 (m, 2H), 8.12 (s, 1H, H-5). Found (%): C, 48.59; H, 3.82; N, 12.90. Calc. for $C_{13}H_{12}BrN_3O_2$ (322.16) (%): C, 48.47; H, 3.75; N, 13.04.



Scheme 2

causes intramolecular nucleophilic substitution of the halogen resulting in an isoxazole ring accompanied by triazine ring cleavage to give 2-benzisoxazolylpyridazine **B**. The latter, under basic conditions, forms anion **C**, which undergoes the Boulton–Katritzky[5] rearrangement yielding triazolopyridazines **3** after protonation.

The ring transformations described here may provide an alternative route to useful compounds of the pyridazine series, *e.g.*, the transformation of readily available[6–8] 1,2,4-triazine 4-oxides **1** leads to aminopyridazine **5**, which is a structural moiety of the antidepressant Minaprine, 4-ethoxycarbonyl-3-(2-morpholinoethylamino)-6-phenylpyridazine.[9]

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