The Ritter reaction in the 5-cyano-1,2,4-triazine series

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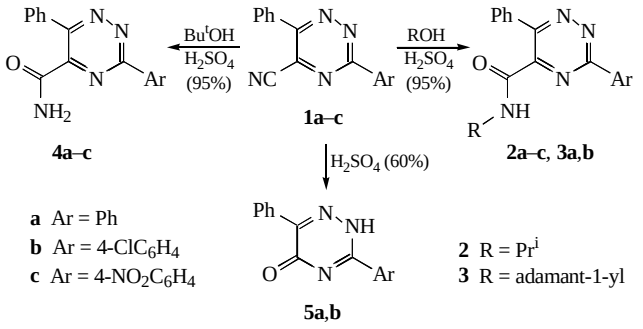
5-Cyano-1,2,4-triazines enter into the Ritter reaction with secondary and tertiary alcohols to form N-alkylated 1,2,4-triazine-5-carboxamides.

The cyano group at a 1,2,4-triazine ring does not undergo reactions accompanied by a nucleophilic attack on the carbon atom of CN (these reactions are typical of nitriles).[1–4] At the same time, the reactions of nucleophilic *ipso*-substitution for the cyano group with alcohols,[1] amines,[2] CH-active compounds and Grignard reagents[3,4] proceed very smoothly.

We found that the nitrile group in 5-cyano-1,2,4-triazines **1** can react with carbocations obtained *in situ* from alcohols under conditions of the Ritter reaction in spite of the electron-withdrawing properties of the heterocyclic ring. Thus, the reaction of 3-aryl-5-cyano-6-phenyl-1,2,4-triazines **1a–c** with the secondary alcohol propan-2-ol in 95% sulfuric acid leads to corresponding *N*-isopropyl-3-aryl-6-phenyl-1,2,4-triazine-5-carboxamides **2** in 45–60% yields.†

The reaction with the tertiary alcohol adamantanol proceeds in a similar manner to form *N*-(adamant-1-yl)-3-aryl-6-phenyl-1,2,4-triazine-5-carboxamides **3a**,**b** in higher yields (80–85%) (Scheme 1). Unexpectedly, compounds **1a–c** do not enter into the Ritter reaction with *tert*-butanol under the same conditions. Instead, the hydrolysis of the cyano group takes place yielding 3-aryl-6-phenyl-1,2,4-triazine-5-carboxamides **4a–c**. However, the treatment of cyano compounds **1** with concentrated H_2SO_4 at room temperature without *tert*-butanol does not afford any products. On the other hand, the use of dilute H_2SO_4 leads to nucleophilic displacement of the cyano group, and 3-aryl-6-phenyl-1,2,4-triazin-5(2*H*)-ones **5a**,**b** are formed.†



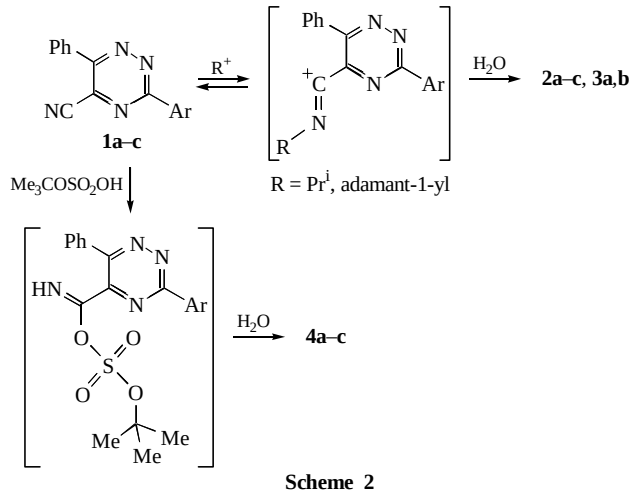
Scheme 1

The reaction with primary alcohols such as methanol, ethanol and benzyl alcohol does not take place because of the instability of intermediate carbocations.

The difference in reactivity between two tertiary alcohols, adamantan-1-ol and *tert*-butanol, can be explained by the following reasons. The rate of reaction of cyano-1,2,4-triazines **1** and the well-stabilised *tert*-butyl cation is lower than the rate of formation of *tert*-butyl sulfate (Me_3COSO_2OH). The ester reacts with compounds **1** at the nitrile carbon atom to form carboxamides **4** (Scheme 2), similarly to the reaction of aliphatic nitriles with olefins in sulfuric acid.[6] This reaction accompanied by a nucleophilic attack on the cyano carbon is a rare example for 1,2,4-triazine carbonitriles. However, the classical Ritter reaction mechanism seems to be preferable in the reaction of **1** with less stable adamantyl or isopropyl cations.

Thus, the presence of a nitrile group in 1,2,4-triazines provides an opportunity to perform various modifications of 1,2,4-triazines by both *ipso*-substitution and nucleophilic or electrophilic reactions of the cyano group.

The structures of the compounds obtained were confirmed by ^{1}H NMR spectroscopy;‡ the melting point of compound **5a** is equal to the published value.[7]



Scheme 2

† *Typical reaction procedure*: cyano-1,2,4-triazine **1a–c** (1 mmol) and a corresponding alcohol were dissolved in 2 ml of 95% sulfuric acid; the mixture was kept for 0.5–2 h at room temperature and then poured into ice water. The crystals of **2–4** were filtered off, washed with water and recrystallised from propan-2-ol.

Typical procedure for the synthesis of 3-aryl-6-phenyl-1,2,4-triazine-5(2H)-ones **5a**,**b**: cyano-1,2,4-triazine **1a**,**b** (1 mmol) was dissolved in 4 ml of 60% sulfuric acid at 40 °C, and the solution was kept for 2 h. The reaction mixture was diluted with water, and the crystals of **5a**,**b** were filtered off and recrystallised from ethanol.

‡ All the compounds obtained exhibited satisfactory analytical data (maximum differences between the calculated and found data were no more than 0.15% for C, 0.18% for H and 0.24% for N). The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer at a frequency of 250.137 MHz, the solvent was [$^2H_6$]DMSO. The mass spectra (electron impact ionization) were measured on a Varian MAT-311 spectrometer.

For **2a**: yield 45%, mp 196–198 °C. ^{1}H NMR, δ: 1.12 (d, 6H, 2Me, *J* 7 Hz), 4.02 (m, 1H, CH), 7.52 (m, 3H), 7.60 (m, 3H), 7.85 (m, 2H), 8.52 (m, 2H), 8.64 (br. d, 1H, NH, *J* 7 Hz).

For **2b**: yield 55%, mp 248–249 °C. ^{1}H NMR, δ: 1.13 (d, 6H, 2Me, *J* 7 Hz), 4.03 (m, 1H, CH), 7.54 (m, 3H), 7.62 (d, 2H), 7.91 (m, 2H), 8.54 (d, 2H), 8.66 (br. d, 1H, NH, *J* 7 Hz). MS, *m*/*z* (%): 354 (2), 352 (5) [M$^+$].

For **2c**: yield 60%, mp 292–263 °C. ^{1}H NMR, δ: 1.12 (d, 6H, 2Me, *J* 7 Hz), 4.03 (m, 1H, CH), 7.58 (m, 3H), 7.87 (m, 2H), 8.42 (d, 2H), 8.65 (br. d, 1H, NH, *J* 7 Hz), 8.78 (d, 2H).

For **3a**: yield 78%, mp 185–188 °C. ^{1}H NMR, δ: 1.63 (br. s, 6H, 3CH_2), 1.97 (br. s, 6H, 3CH_2), 2.03 (br. s, 3H, 3CH), 7.58 (m, 3H), 7.63 (m, 3H), 7.90 (m, 2H), 8.17 (br. s, 1H, NH), 8.49 (m, 2H). MS, *m*/*z* (%): 410 (58) [M$^+$].

For **3b**: yield 80%, mp 132–135 °C. ^{1}H NMR, δ: 1.63 (br. s, 6H, 3CH_2), 1.97 (br. s, 6H, 3CH_2), 2.03 (br. s, 3H, 3CH), 7.58 (m, 3H), 7.69 (d, 2H), 7.90 (m, 2H), 8.41 (br. s, 1H, NH), 8.50 (d, 2H). MS, *m*/*z* (%): 446 (12), 444 (34) [M$^+$].

For **4a**: yield 50%, mp 227–228 °C. ^{1}H NMR, δ: 7.51 (m, 3H), 7.60 (m, 3H), 7.86 (m, 2H), 7.95 (br. s, 1H, NH_2), 8.30 (br. s, 1H, NH_2), 8.57 (m, 2H).

For **4b**: yield 55%, mp 235–236 °C. ^{1}H NMR, δ: 7.58 (m, 3H), 7.70 (d, 2H), 7.86 (m, 2H), 7.98 (br. s, 1H, NH_2), 8.38 (br. s, 1H, NH_2), 8.58 (d, 2H). MS, *m*/*z* (%): 312 (4), 310 (11) [M$^+$].

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For **4c**: yield 58%, mp 277–280 °C. ^{1}H NMR, δ: 7.55 (m, 3H), 7.90 (m, 2H), 8.07 (br. s, 1H, NH_2), 8.40 (br. s, 1H, NH_2), 8.49 (d, 2H), 8.82 (d, 2H).

For **5a**: yield 90%, mp 271–273 °C (lit.,[7] 275 °C). ^{1}H NMR, δ: 7.4–7.7 (m, 6H), 8.1–8.3 (m, 4H), 14.2 (br. s, 1H, NH).

For **5b**: yield 95%, mp > 290 °C. ^{1}H NMR, δ: 7.5 (m, 3H), 7.7 (d, 2H), 8.1–8.2 (m, 4H), 14.3 (br. s, 1H, NH).

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