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On cyclization of 2-chloro-*N*-phenacylpyridinium ylides by the action of aryldiazonium salts

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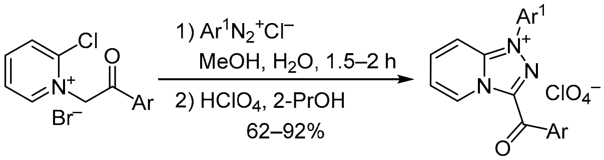


The reaction of 2-chloro-*N*-phenacylpyridinium salts with diazonium salts in the presence of bases was studied for the first time. It was demonstrated that this reaction leads to the formation of [1,2,4]triazolo[4,3-*a*]pyridinium salts. It was shown that substitution of the pyridine with a thiazole moiety leads to a similar cyclization.

Keywords: 2-chloro-*N*-phenacylpyridinium salts, diazonium salts, thiazolo[2,3-*c*][1,2,4]triazol-4-ium salt, [1,2,4]triazolo[4,3-*a*]pyridinium salts, cyclization.

The heterocyclic system [1,2,4]triazolo[4,3-*a*]pyridine (**I**) comprises the structure of the molecules of antiplatelet, antibacterial, antibiotic, as well as anti-neurodegenerative agents and is of high importance to pharmaceutical chemistry.[1] There are several routes to construct this system, which are shown in Figure 1.

The most common of them is route A, which involve cyclization of suitable α-pyridylhydrazides or -hydrazones.[2] Another one is the cyclization of 1,2,4-triazoles during the reaction with unsaturated halo ketones and subsequent action of a base.[3] Alkylation of the bases is used for the synthesis of triazolo[4,3-*a*]pyridinium salts.[4] Yet another method for preparing these salts is known, which constitutes the reaction of pyridines with nitrilimines (route C).[5] In the present work, we will focus on a new method of accessing triazolo[4,3-*a*]pyridinium salts which is based on the reaction of *N*-alkylpyridinium salts with diazonium salts (route D).

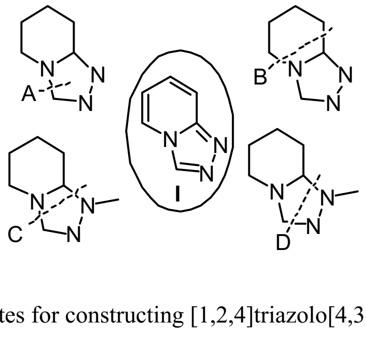


Figure 1. Routes for constructing [1,2,4]triazolo[4,3-*a*]pyridine.

The continued interest in the chemistry of pyridinium *N*-ylides containing a leaving group in position 2, such as a halogen,[6,7] prompted us to examine their reactivity toward diazonium salts. In the literature,[8] pyridinium ylides (not containing an active halogen) were generated with the aid of bases in aqueous medium. This method was unacceptable for us, since such treatment of 2-chloropyridinium salts **1** could lead to the formation of *N*-phenacylpyridin-2-ones. Meanwhile, an attempt to carry out the reaction of the ylides from salts **1** with aryldiazonium salts under anhydrous conditions (Et_3N, CH_2Cl_2) showed that the process is highly exothermic and with evolution of nitrogen.

Then we decided to reproduce the azo coupling conditions described in the literature,[9] i.e., using aqueous solutions and sodium acetate as the base. It turned out that in this case, the reaction proceeds without evolution of N_2 to form an individual crystalline compound. Initially, we believed that an adduct of the pyridinium ylide and diazonium salt in the form of hydrazone **2** forms during the reaction of salts **1** (Scheme 1). Meanwhile, the ^{1}H NMR spectrum of the resulting product **3a** (Table 1) contained a doublet at 9.63 ppm which is "too" downfield (in monocyclic pyridinium salts the chemical shifts of aromatic protons do not exceed 7.5 ppm), and it did not contain signals of the NH group. The mass spectrum of compound **3a** shows that the mass of the molecular ion is by 36 units of the mass number (the mass of a HCl molecule) less than that of the corresponding hydrazone **2**.

Scheme 1

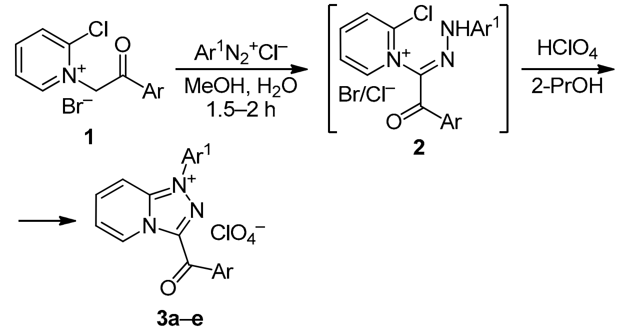


Table 1. Yields and characterization of triazolo[4,3-*a*]pyridinium salts **3a**–**e**

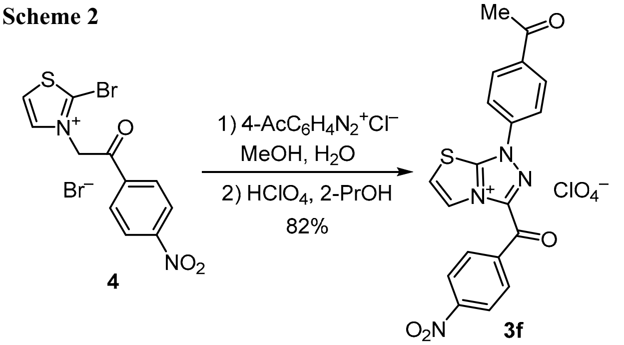
Compound	Ar	Ar^1	Yield, %	^{1}H NMR spectrum, δ (H-5), ppm
3a	4-ClC$_6$H$_4$	Ph	63	9.64
3b	4-ClC$_6$H$_4$	4-BrC$_6$H$_4$	92	9.62
3c	4-O$_2$NC$_6$H$_4$	4-MeC$_6$H$_4$	62	9.68
3d	4-O$_2$NC$_6$H$_4$	4-AcC$_6$H$_4$	86	9.68
3e	4-MeC$_6$H$_4$	4-BrC$_6$H$_4$	70	9.63

Thus, adduct **2** cyclizes with loss of a HCl molecule during the reaction, and the structure of the formed products corresponds to [1,2,4]triazolo[4,3-*a*]pyridinium salts **3a**–**e** (Table 1). Such outcome also explains the appearance of a downfield doublet attributed to the proton H-5 due to the *peri* effect of a magnetically anisotropic aroyl group. The obtained salts were converted to perchlorates, elemental analysis of which is fully confirmed to their assumed composition. The structure of the obtained perchlorates was also confirmed by ^{13}C NMR spectral data.

We decided to investigate whether 2-bromo-*N*-phenacylthiazolium salts undergo this reaction. It was found that an analogous reaction of salt **4** proceeds in 82% yield to form [1,2,4]triazolo[4,3-*a*]pyridinium salt **3f**, ^{1}H and ^{13}C NMR spectra of which does not conflict with the proposed bicyclic structure (Scheme 2).

To conclude, salts of 2-chloro-*N*-phenacylpyridinium react with diazonium salts with the closure of the triazolium ring; the thiazolium salt behaves similarly. In all cases, the reaction appears to begin with an attack of the diazonium salt at the CH$_2$ group of the pyridinium salt followed by cyclization of the resulting hydrazone with the expulsion of an α-halogen atom.

Scheme 2



Experimental

^{1}H and ^{13}C NMR spectra were registered on a Bruker AM 400 spectrometer (360 and 90 MHz, respectively) in DMSO-d_6 (internal standard TMC). Mass spectra were recorded on a Kratos MS-30 mass spectrometer with direct sample injection at 150–250°C, EI ionization, 70 eV. Elemental analysis was performed on a Vario multi cube apparatus. Melting points were determined on a Electrothermal IA910 apparatus. Purification and drying of solvents were done according to established routines. 2-Chloro-*N*-phenacylpyridinium salts **1**[7] and aryldiazonium salts[9] were prepared following published procedures.

3-Aroyl-1-aryl[1,2,4]triazolo[4,3-*a*]pyridin-1-ium salts 3a–**e** (General method). For the preparation of an aryldiazonium salt, a solution of the corresponding aniline (2 mmol) in a mixture of water (10 ml) and concentrated HCl (2 ml) was placed in a three-neck round-bottom flask equipped with magnetic stirring, a dropping funnel, thermometer, and cooling bath. The solution was cooled to –5°C, and a solution of NaNO$_2$ (0.138 g, 2 mmol) in water (10 ml) was added with stirring. The temperature of the reaction mixture was kept at –5–0°C. Then the mixture was kept at 5°C for 15 min. The respective 2-chloro-*N*-phenacylpyridinium salt **1** (2 mmol) was dissolved in MeOH–H$_2$O, 1:1 mixture (20–40 ml), then the previously prepared solution of the aryldiazonium salt and an excess of a saturated aqueous MeCO$_2$Na were added. The mixture was stirred for 1.5–2.0 h. The formed precipitate was filtered off and washed with diethyl ether (2×10 ml). The obtained salt was reprecipitated as a perchlorate. In order to do that, the precipitate was dissolved in a mixture of isopropanol (10 ml) and HClO$_4$ (10 ml), and the resulting solution poured into diethyl ether (50 ml) with vigorous stirring (*Warning! Highly exothermic reaction!*). The formed precipitate was filtered off, washed with diethyl ether (2×10 ml), and dried.

3-(4-Chlorobenzoyl)-1-phenyl[1,2,4]triazolo[4,3-*a*]pyridin-1-ium perchlorate (3a). Yield 1.12 g (63%), mp 244–245°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.63 (1H, d, *J* = 7.1, H-5); 8.48–8.50 (2H, m, H Ar); 8.33–8.36 (2H, m, H Ar); 7.96–7.98 (1H, m, H Ar); 7.92–7.94 (2H, m, H Ar); 7.75–7.77 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 179.8; 143.1; 141.0; 140.4; 140.0; 134.4; 133.0; 132.6; 131.3; 130.5; 129.6; 129.3; 124.9; 121.2; 111.5. Mass spectrum, *m/z* (I_{rel}, %): 334 [M$^+$] (21), 194 (100), 139 (77). Found, %: C 52.34; H 3.18; N 9.48. $C_{19}H_{13}Cl_2N_3O_5$. Calculated, %: C 52.55; H 3.02; N 9.68.

1-(4-Bromophenyl)-3-(4-chlorobenzoyl)[1,2,4]triazolo[4,3-*a*]pyridin-1-ium perchlorate (3b). Yield 0.92 g (92%), mp 285–286°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.62 (1H, d, *J* = 7.1, H-5); 8.50–8.52 (2H, m, H Ar); 8.32–8.34 (2H, m, H Ar); 7.98–8.00 (3H, m, H Ar); 7.88–7.90 (2H, m, H Ar); 7.77–7.79 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 179.7; 143.2; 141.1; 140.4; 140.1; 133.6; 133.4; 132.9; 132.6; 129.7; 129.3; 127.0; 124.5; 121.2; 111.5. Found, %: C 44.23; H 2.44; N 7.98. $C_{19}H_{12}BrCl_2N_3O_5$. Calculated, %: C 44.47; H 2.36; N 8.19.

1-(4-Methylphenyl)-3-(4-nitrobenzoyl)-1*H*-[1,2,4]triazolo[4,3-*a*]pyridinium perchlorate (3c). Yield 0.75 g

(62%), mp 300–302°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.68 (1H, d, *J* = 6.9, H-5); 8.48–8.50 (6H, m, H Ar); 7.99–8.01 (1H, m, H Ar); 7.82–7.84 (2H, m, H Ar); 7.58–7.60 (2H, m, H Ar); 2.48 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 180.4; 151.3; 143.6; 141.9; 141.6; 140.4; 139.5; 132.6; 132.4; 131.3; 130.1; 125.1; 124.5; 121.9; 112.1; 21.3. Found, %: C 52.50; H 3.34; N 12.10. $C_{20}H_{15}ClN_4O_7$. Calculated, %: C 52.36; H 3.30; N 12.21.

1-(4-Acetylphenyl)-3-(4-nitrobenzoyl)-1*H*-[1,2,4]triazolo[4,3-*a*]pyridinium perchlorate (3d). Yield 0.85 g (86%), mp 310–312°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.68 (1H, d, *J* = 6.9, H-5); 8.64 (1H, d, *J* = 9.3, H Ar); 8.56–8.58 (1H, m, H Ar); 8.53–8.55 (2H, m, H Ar); 8.49–8.51 (2H, m, H Ar); 8.29–8.31 (2H, m, H Ar); 8.12–8.14 (2H, m, H Ar); 8.03–8.05 (1H, m, H Ar); 2.70 (3H, s, CH_3CO). ^{13}C NMR spectrum, δ, ppm: 197.6; 180.2; 151.3; 143.6; 142.1; 140.8; 139.4; 138.8; 138.1; 132.7; 130.7; 130.3; 125.4; 124.5; 122.1; 112.3; 27.6. Found, %: C 51.43; H 3.17; N 11.42. $C_{21}H_{15}ClN_4O_8$. Calculated, %: C 51.81; H 3.11; N 11.51.

1-(4-Bromophenyl)-3-(4-methylbenzoyl)-1*H*-[1,2,4]triazolo[4,3-*a*]pyridinium perchlorate (3e). Yield 0.94 g (70%), mp 236–238°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.63 (1H, d, *J* = 6.9, H-5); 8.47–8.49 (2H, m, H Ar); 8.20–8.22 (2H, m, H Ar); 7.99–8.01 (2H, m, H Ar); 7.95–7.97 (1H, m, H Ar); 7.87–7.89 (2H, m, H Ar); 2.46 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 180.7; 147.0; 143.7; 141.5; 140.7; 134.1; 133.9; 132.2; 131.5; 130.2; 127.5; 124.9; 121.5 (2C); 111.9; 22.0. Found, %: C 48.70; H 2.93; N 8.78. $C_{20}H_{15}BrClN_3O_5$. Calculated, %: C 48.75; H 3.07; N 8.53.

1-(4-Acetylphenyl)-3-(4-nitrobenzoyl)-1*H*-[1,3]thiazolo[2,3-*c*][1,2,4]triazol-4-ium perchlorate (3f) was obtained in the same way from 2-bromo-*N*-(4-nitrophenacyl)thiazolium bromide (**4**) and 4-acetylphenyldiazonium chloride. Yield 0.33 g (82%), mp 285–287°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.84 (1H, d, *J* = 4.0, H-5(6)); 8.50–8.70 (4H, m, H Ar); 8.23 (1H, d, *J* = 4.0, H-6(5)); 7.84–8.03 (2H, m, H Ar); 7.58–7.60 (2H, m, H Ar); 2.46 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 178.5; 155.5; 151.4; 141.9; 141.4; 138.5; 132.9; 132.5; 131.6; 131.5; 127.3; 124.7; 122.0; 120.8; 21.3. Found, %: C 46.02; H 2.71; N 11.30. $C_{19}H_{13}ClN_4O_8S$. Calculated, %: C 46.30; H 2.66; N 11.37.

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