Synthesis of a new tricylic ring system: [1,2,3]triazolo[1,5-*b*]cinnolinium salt

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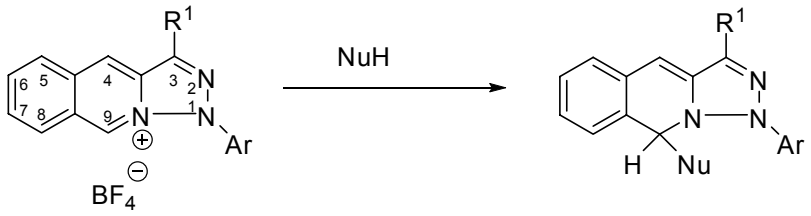
Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract
Synthesis of the first representative of the linearly fused [1,2,3]triazolo[1,5-*b*]cinnolinium heteroaromatic cation as a quaternary salt is reported. Improved reaction conditions for preparation of some precursors have been elaborated. Reaction of the new heteroaromatic salt with nucleophiles resulted in regioselective formation of zwitterionic products.

Keywords: Ring closure, cinnoline, nucleophilic addition, bridge-head nitrogen atom, zwitterions, negative solvatochromy

Introduction

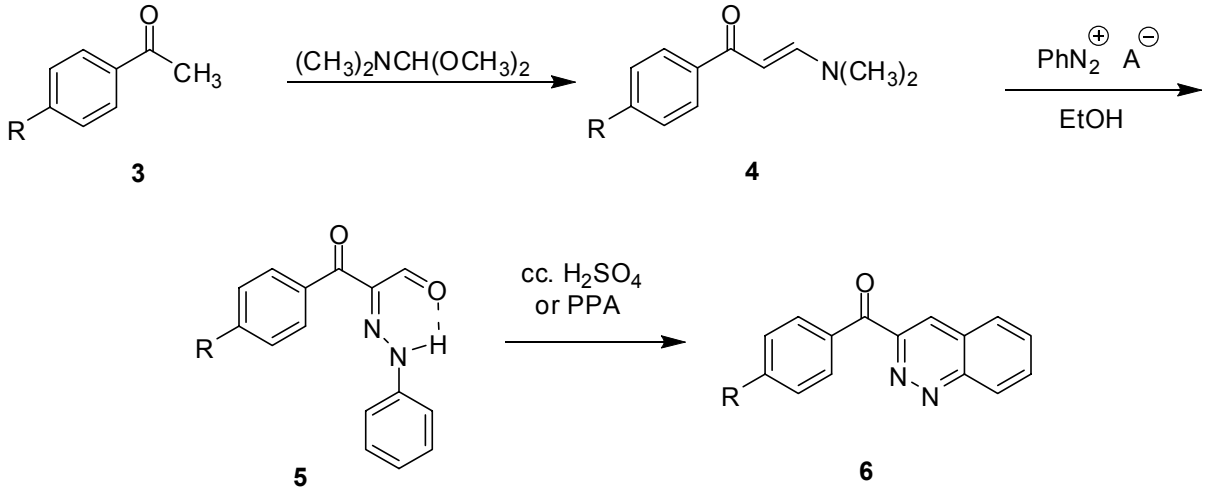
In the frame of our investigations on bridge-head nitrogen containing fused azolium salts we reported the synthesis of the linearly fused [1,2,3]triazolo[1,5-*b*]isoquinolinium salt (**1**, R^1 = alkyl and aryl group, Ar = phenyl or substituted phenyl group)[1]. Study of the reactivity of this quaternary salt (**1**) revealed that in reactions with various nucleophiles (*e.g.* with NuH = morpholine) regioselective addition at C-9 takes place to yield stable pseudobase-type products (**2**). This finding prompted us to extend the investigations to an aza-derivative of **1** containing a nitrogen atom in position 9. This structural change excludes the possibility of an attack of the nucleophile in this particular position. In this paper we report our efforts to synthesize this designed [1,2,3]triazolo[1,5-*b*]cinnolinium salt and to explore its reactivity with nucleophilic reagents.



1 **2**

Results and Discussion

According to the earlier established protocol[2], the synthesis of the desired model compound was planned by oxidative cyclization of cinnoline-3-ketones. Our literature survey indicated that very few procedures leading to such ketones were published[3,4], among which the method described by Al-Alwadi *et al.*[4] a few years ago seemed the most suitable for our purpose. These authors found that such ketones (**6**) can be obtained *via* a 3-step pathway starting from substituted benzophenones (**3**). Thus, **3** was reacted first with dimethylformamide dimethylacetal to give an aminoenone (**4**), this compound was then reacted with phenyldiazonium salt to afford the hydrazone **5** and, finally, cyclization reaction under strongly acidic conditions resulted in formation of the cinnoline ketone (**6**).



3 **4** **5** **6**

While reproduction of the first reaction step (*i.e.* **3** → **4**) took place in excellent yield,[5] we had to encounter some difficulties with the subsequent two reaction steps: rather low yields and intensive decompositions were experienced. As a result of an ongoing search for suitable reaction conditions for the desired synthesis, however, we have found that by the help of two modifications both transformations can be carried out in satisfactory and well reproducible yields.

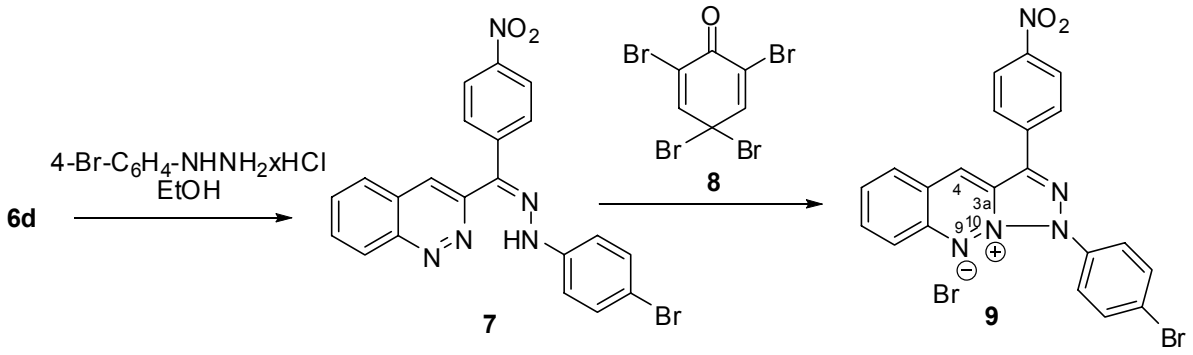
The first modification was that instead of *in situ* preparation of the diazonium salt in the second reaction step, crystalline phenyldiazonium fluoroborate (A = BF_4)[6] was used and, thus, hydrazones **5a-d** were obtained in high yields. As to the final ring closure reaction we have found, furthermore, that extenstion of the reaction time to 40 min and exclusive application of polyphosphoric acid results in a dramatic increase of the yields of **6a-d**. This successful preparative result allowed also the synthesis of two new compounds: the *p*-bromo substituted **5e** and **6e**. Some data (yield, mp) of the products prepared by the improved methodology are compiled in Table 1., whereas the modified reaction conditions are described in the Experimental Section for the new derivatives **5e** and **6e**

Table 1. Improved reaction conditions and yields with the synthesis of the hydrazones **5** and ketones **6**

5	R	Yield (%)	Mp (^oC)	Literature Mp (^oC)
a	H	80	96-98	82-84
b	Cl	80	136-138	135-137
c	OMe	70	139-140	141-143
d	NO_2	82	188-190	173-175
e	Br	84	143-144	-

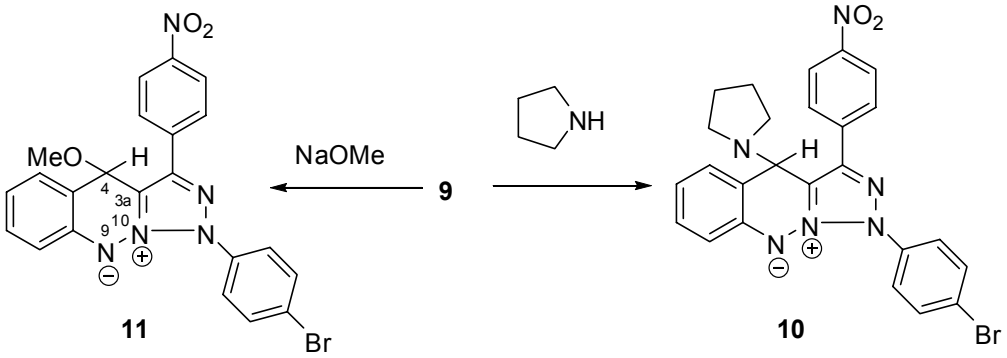
6	R	Yield (%)	Mp (^oC)	Literature Mp (^oC)
a	H	71	135-136	138-139
b	Cl	71	151-152	152-154
c	OMe	47	190-191	189-191
d	NO_2	91	214-216	210-212
e	Br	77	150-152	-

Treatment of *p*-nitrophenyl ketone (**6d)** with p-bromophenylhydrazine hydrochloride in ethanolic hydrochloric acid afforded arylhydrazone **7** as orange crystals. Oxidative cyclization of other related hydrazones to triazolium salts are generally carried out by *N*-bromosuccinimide[2]. While application of this reagent in the present case, unfortunately, failed, treatment of **7** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (**8**) - easily obtainable by bromination of 1,3,5-tribromophenol and also commercially available - successfully resulted in the desired cyclization and gave the fused triazolium bromide **9** as yellow crystals in modest yield.



Comparison of the UV spectra of **7** and **9** revealed that a significant change of the absorbances occurred (blue shift of the first maximum by 35 nm) which clearly indicates the substantial change of the chromophore. Appearance of the downfield ^{1}H-NMR shift (singlet at 10.64 ppm) is also in accordance with the presence of the positively charged heteroaromatic pyridazine moiety.

Two nucleophilic reagents: pyrrolidine and sodium methoxide have been selected for investigation of reactivity of the new heteroaromatic salt **9**. These reactions have been carried out in acetonitrile at room temperature. In both cases a zwitterionic addition product (**10** and **11**, respectively) separated from the reaction mixture. The most significant spectral property of these products was the presence of a proton attached to the saturated carbon atom in position 4 appearing at 5.8 and 6.6 ppm, respectively, whereas all routine analytical data (elemental analysis, MS) were in entire agreement with these structures.



An interesting spectroscopic feature of zwitterionic compounds is the negative solvatochromy[7], *i.e.* a significant red shift of the first maximum in UV/VIS when changing a polar solvent for an apolar one. This has also been detected for derivative **10** as shown in Fig 1.
The interesting finding of this regioselective addition reveals that position 4 as indicated by the strongly downfield NMR shift of the attached proton is electron-withdrawn enough to accept the nucleophilic heteroatom and to form a new *sigma* bond. The addition is obviously facilitated by the presence of N-9 atom which is able to bear two lone electron pairs and, thus, to become negatively charged. In other words, it is the C4-C3a-N10-N9 1,2-diazadiene structural moiety in

9 that plays an important role in this selective nucleophilic addition; there are several literature records that 1,2-diazadienes easily react with nucleophiles at the terminal C4 atom[8].

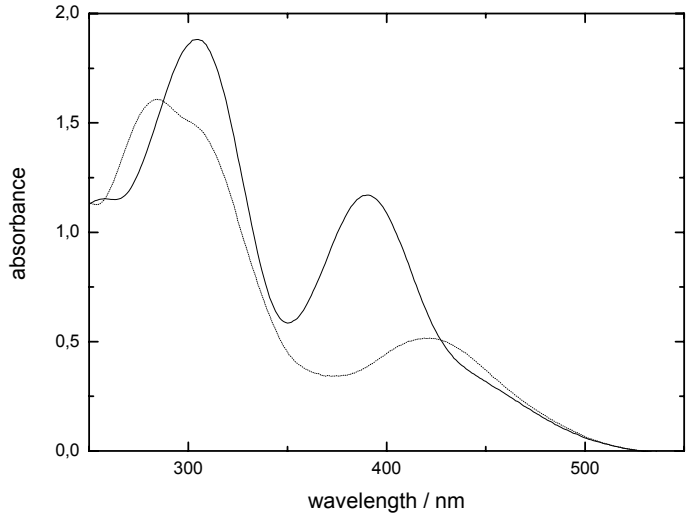


Figure 1. UV spectrum of **10**: a red shift of 29 nm, approximately appears in the spectrum recorded in a dichloromethane solution (----) compared to that of the acetonitrile solution (──).

Although the title new tricyclic heteroaromatic salt has been synthesized successfully, extenstion of this methodology to ketones bearing substituents other than nitro group on the phenyl moiety failed. In these cases the hydrazones related to **7** can not be isolated from the reaction mixture because subsequent rapid spontaneous conversions. Study of these transformations is in progress and the results will be published later.

Experimental Section

General Procedures. Melting Points were determined on a Kofler apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer and the UV spectra were measured on a ThermoSpectronic Unicam UV 500 spectrophotometer. The NMR spectra were determined on a Varian Unity Inova spectrometer (200 MHz and 400 MHz for ^{1}H and 100 MHz for ^{13}C). The elemental analysis has been carried out with an Elementar Vario EL III apparatus.

(*E*)-3-(4-Bromophenyl)-3-oxo-2-(2-phenylhydrazono)propanal (5e). A solution of (*E*)-1-(4-bromophenyl)-3-(dimethylamino)prop-2-en-1-one (**4e**) (9.7 g, 38.2 mmol) in EtOH (110 mL)

was cooled down to 0-(-5) ^{o}C and stirred with a mechanical stirrer. To this solution a cold suspension of phenyldiazonium fluoroborate (8.03 g, 42 mmol, in 50% aqueous EtOH, 140 mL) was added in portions so that the temperature of the reaction mixture remained below 0 ^{o}C. After complete addition of the diazonium salt the reaction mixture was stirred at 0 ^{o}C for 10 min, and allowed to warm up to room temperature. It was then stirred for additional 4 h, the precipitated product was filtered off and recrystallized from acetonitrile to give orange yellow crystals: 12.65 g (84%). mp: 143-144 ^{o}C. IR (KBr, cm^{-1}): 3129, 2863, 1650, 1633, 1589, 1518, 1271; ^{1}H NMR δ ($CDCl_3$): 7.22 (m, 1H, H4"), 7.37 (m, 2H, H2", H6"), 7.41 (m, 2H, H3", H5"), 7.63 (m, 2H, H3', H5'), 7.82 (m, 2H, H2', H6'), 10.2 (s, 1H, H1), 14.8 (s, 1H, NH); ^{13}C NMR δ ($CDCl_3$): 116.8 (2C), 126.9, 127.4, 130.1 (2C), 131.4 (2C), 131.6, 132.1 (2C), 132.3, 136.0, 189.6, 190.2. Anal. Calcd for $C_{15}H_{11}BrN_2O_2$ (331.16): C, 54.40; H, 3.35; N, 8.46; Found: C, 54.15; H, 3.42; N, 8.40.

(4-Bromophenyl)(cinnolin-3-yl)methanon (6e). To preheated polyphosphoric acid (45 g, inner temperature 100 ^{o}C) (*E*)-3-(4-bromophenyl)-3-oxo-2-(2-phenylhydrazono)propanal (**5e**, 3.79 g, 11.45 mmol) was added. The mixture was heated to 118-120 ^{o}C (inner temperature) and stirred for 40 min. The reaction mixture was poured onto ice water (200 mL) and extracted with chloroform (3x100 mL). The organic layer was dried over sodium sulphate, filtered and evaporated. The residue was recrystallized from acetonitrile to give yellow crystals: 2.77 g (77%). mp: 150-152 ^{o}C. IR (KBr, cm^{-1}): 3041, 2924, 1655, 1588, 1324, 1249, 1226; ^{1}H NMR δ ($CDCl_3$): 7.69 (m, 2H, H3', H5'), 7.88 (dd, 1H, *J* = 8.5, 8 Hz, H6), 8.04 (m, 2H, H7, H5), 8.2 (m, 2H, H2', H6'), 8.65 (d, 1H, *J* = 8 Hz, H8), 8.68 (s, 1H, H4); ^{13}C NMR δ ($CDCl_3$): 125.7, 126.2, 128.3, 129.0, 130.2, 131.8 (2C), 132.2, 133.1, 133.3 (2C), 135.2, 151.2, 151.9, 191.4. Anal. Calcd for $C_{15}H_9BrN_2O$ (313.15): C, 57.53; H, 2.90; N, 8.95; Found: C,57.21; H,2.98; N,9.03.

(*E*)-3-((2-(4-Bromophenyl)hydrazono)(4-nitrophenyl)methyl)cinnoline (7). A mixture of cinnolin-3-yl(4-nitrophenyl)methanone (**6d**, 1.18 g, 4.24 mmol), ethanol (50 mL), (4-bromophenyl)hydrazine hydrochloride (1.42 g, 6.37 mmol), and hydrochlorid acid in ethanol 5N (1 mL) was refluxed for 4.5 hours. The mixture was cooled down and the solid precipitate was collected. The crystals were boiled in ethanol and, after cooling, filtered off to give 1.14 g yellow crystals, 2.56 mmol (60%) of product, mp > 300^{o}C. IR (KBr, cm^{-1}): 3264, 3074, 1602, 1523, 1484, 1346, 1523, 1111; UV λ (nm) in acetonitrile: 342, 228; ^{1}H NMR δ (DMSO): 7.24 (m, 2H, H-2", H-6"), 7.44 (m, 2H, H-3", H-5"), 7.72 (m, 2H, H-2', H-6'), 7.97 (dd, 1H, *J*=7.5, 7 Hz, H-6), 8.09 (dd, 1H, *J*=8.7, 7 Hz, H-7), 8.18 (d, 1H, *J*=7.5 Hz, H-5), 8.2 (m, 2H, H-3', H-5'), 8.48 (s, 1H, H-4), 8.62 (d, 1H, *J*=8.7 Hz, H-8), 10.3 (s, 1H, NH); ^{13}C NMR δ (DMSO): 112.6, 116.2 (2C), 124.5 (2C), 126.8, 127.5 (2C), 128.5, 129.1, 129.8, 132.5 (2C), 132.6(2C), 132.7(2C), 138.3, 144.5, 145.0, 147.0, 149.0, 150.5; Anal. Calcd for $C_{21}H_{14}BrN_5O_2$ (448.27): C, 56.27; H, 3.15; N, 15.62; Found: C, 56.29; H, 2.79; N, 15.61.

1-(4-Bromophenyl)-3-(4-nitrophenyl)-1*H*-[1,2,3]triazolo[1,5-*b*]cinnolin-10-ium bromide (9). A mixture of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (**8**, 3.07 g, 7.5 mmol), and dry dichloromethane (70 ml) was heated to reflux temperature and was added (*E*)-3-((2-(4-

bromophenyl)hydrazono)(4-nitrophenyl)methyl)cinnoline (**7**, 1.12 g, 2.5 mmol). The reaction mixture was heated under reflux for 1 additional hour. The separated solid was filtered off, it was suspended in nitromethane and heated to reflux and the mixture was filtered. The filtrate was cooled down, cyclohexene (3 mL) was added whereupon yellow crystals separated which were filtered off to give 360 mg, 0.683 mmol (27%) of product, mp > 300°C. IR (KBr, cm^{-1}): 3021, 1523, 1485, 1340, 1000, 848; UV λ (nm) in acetonitrile: 307, 285, 222; ^{1}H NMR δ (DMSO): 8.09 (m, 2H, H-2", H-6"), 8.13 (m, 2H, H-3", H-5"), 8.18 (ddd, 1H, *J*=8, 7.5, 2 Hz, H-7), 8.37 (ddd, 1H, *J*=8.2, 7.5, 2.5 Hz, H-6), 8.42 (dd, 1H, *J*=8.2, 2 Hz, H-5), 8.55 (m, 3H, H-2', H-6', H-8), 8.63 (m, 2H, H-3', H-5'), 10.64(s, 1H, H-4); ^{13}C NMR δ (DMSO): 125.7 (2C), 126.3, 126.7, 127.4, 128.7 (2C), 129.3, 129.6, 130.0 (2C), 132.9, 133.1, 133.6, 133.9, 134.0 (2C), 139.3, 140.5, 147.1, 149.8; Anal. Calcd for $C_{21}H_{13}Br_2N_5O_2$ (527.17): C, 47.85; H, 2.49; N, 13.28; Found: C, 45.00; H, 2.59; N, 11.92.

1-(4-Bromophenyl)-3-(4-nitrophenyl)-4-(pyrrolidin-1-yl)-1,4-dihydro-[1,2,3]triazolo[1,5-*b*]cinnolin-10-ium-9-ide (10). Pyrrolidine (80 μl, 69 mg, 0.96 mmol) was added to a solution of 1-(4-bromophenyl)-3-(4-nitrophenyl)-1*H*-[1,2,3]triazolo[1,5-*b*]cinnolin-10-ium bromide (**9**, 100 mg, 0.19 mmol) in dry acetonitrile (7 mL), and the mixture was stirred at room temperature 5 hours. Orange-red crystals separated which were filtered off to give 81 mg, 0.156 mmol (82%) of product, mp > 300°C. IR (KBr, cm^{-1}): 2970, 2801, 1603, 1519, 1486, 1454, 1344, 1263; UV λ (nm) in acetonitrile: 390 (log ε = 4.1358), 304 (log ε = 4.350), in dichloromethane: 419 (log ε = 4.1638), 294 (log ε = 4.497); ^{1}H NMR δ ($CDCl_3$): 1.6 (m, 4H, H-pyrrolidine), 2.38 (m, 4H, H-pyrrolidine), 5.78 (s, 1H, H-4), 7.0 (dd, 1H, *J*=8.2, 8 Hz, H-6), 7.12-7.18 (m, 2H, H-8, H-5), 7.31 (dd, 1H, *J*=8.5, 8 Hz), 7.7 (m, 2H, H-2", H-6"), 8.1 (m, 2H, H-3", H-5"), 8.32 (m, 2H, H-2', H-6'), 8.38 (m, 2H, H-3', H-5'); ^{13}C NMR δ ($CDCl_3$): 23.1, 47.4, 53.7, 110.1, 116.8, 119.7, 121.2, 123.0, 124.4, 125.6, 128.8, 129.0, 129.7, 132.4, 135.6, 136.3, 142.9, 146.8, 148.5; Anal. Calcd for $C_{25}H_{21}BrN_6O_2$ (517.38): C, 58.04; H, 4.09; N, 16.24; Found: C, 57.70; H, 4.04; N, 16.38.

1-(4-Bromophenyl)-4-methoxy-3-(4-nitrophenyl)-1,4-dihydro-[1,2,3]triazolo[1,5-*b*]cinnolin-10-ium-9-ide (11) A 2M alcoholic sodium methoxide solution (75 μl, 3.5 mg, 0.06 mmol) was added to a solution of 1-(4-bromophenyl)-3-(4-nitrophenyl)-1*H*-[1,2,3]triazolo[1,5-*b*]cinnolin-10-ium bromide (**9**, 100 mg, 0.19 mmol) in dry acetonitrile (7 mL), and the mixture was stirred at room temperature 5 hours. Orange-red crystals separated which were filtered off to give 63 mg, 0.132 mmol (70%) of product, mp > 300°C. IR (KBr, cm^{-1}): 3095, 2937, 1603, 1524, 1488, 1461, 1345, 1053; ^{1}H NMR δ ($CDCl_3$): 2.9 (s, 3H, OMe), 6.6 (s, 1H, H-4), 7.1 (ddd, 1H, *J*=9, 8, 2 Hz, H-6), 7.21 (dd, 1H, *J*=8.3, 2 Hz, H-8), 7.4 (ddd, 1H, *J*=8.3, 8, 2 Hz, H-7), 7.47 (dd, 1H, *J*=9, 2 Hz, H-5), 7.72 (m, 2H, H-2", H-6"), 8.1 (m, 2H, H-3", H-5"), 8.32 (m, 2H, H-2', H-6'), 8.41 (m, 2H, H-3', H-5'); ^{13}C NMR δ ($CDCl_3$): 51.2, 69.2, 111.2, 116.0, 120.6, 122.5, 123.9, 124.6 (2C), 125.7 (2C), 128.5 (2C), 129.8, 130.1, 130.6, 132.5 (2C), 133.0, 135.1, 135.5, 145.7.

Acknowledgements

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