Ring opening and cycloadditions of novel fused 1,2,4-triazines

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Dedicated to Professor Gábor Bernáth on his 70th birthday
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Abstract
Ring opening of two ring transformation products of furo[2,3-e]pyrido[1,2-b][1,2,4]triazinium salt, i.e. a pyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazine derivative and a zwitterionic pyrido[1,2-b]pyridazino[3,4-e][1,2,4]triazine compound has been investigated. The pyrrole-fused tricycle when reacted with some dienophiles resulted, unlike its zwitterionic pyridazine analogue, only in Michael addition and/or subsequent ring opening. Reaction of the methylated N-methylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazinium derivative and dimethyl pyrido[1,2-b]pyridazino[3,4-e][1,2,4]triazinium salt with secondary amines afforded new hetaryldienes which, in some cases, were successfully subjected to Diels-Alder reaction to give regular cycloadducts.

Keywords: Fused 1,2,4-triazines, zwitterion, hetaryldiene, cycloaddition, ring opening

Introduction

In the course of our activity in the area of ring transformation reactions of some polyfused triazines we have described that 2-arylfuro[2,3-e]pyrido[1,2-b][1,2,4]triazinium salts (1) readily react with nucleophiles and undergo ring transformations to a pyrrole-fused tricyclic ring system (2) or differently substituted pyridazines, e.g. to the zwitterionic pyrido[1,2-b]pyridazino[3,4-e]-[1,2,4]triazine (3)1. We have also reported that these tricyclic derivatives (2, 3) can be selectively alkylated to quaternary salts (4, and 5, respectively)2. Furthermore, reactivity of the zwitterionic 3 has also been studied in detail: we found that this compound when reacted with acetylenedicarboxylic ester can undergo dipolar cyclization. Reaction with tetracyanoethylene resulted in oxidative dimerization to yield a stable radical cation, whereas reaction with tosyl isocyanate yielded Michael addition products3. All these results prompted us to explore the
reactivity of the pyrrole-fused analogue 2 with particular respect to possible cycloaddition and ring opening transformations.

**Results and Discussion**

The pyrrole-fused tricyclic compound was reacted – for comparison with our earlier results with the analogous pyridazine derivative 3 – with dimethyl acetylenedicarboxylate, tosyl isocyanate and tetracyanoethylene. Interestingly enough, all these reagents resulted in Michael-additions and no cycloaddition or transformation of any other type was found. Thus, both with tetracyanoethylene and tosyl isocyanate the regular Michael adducts (6 and 7, respectively) were isolated in acceptable yields. A more interesting transformation was observed during the reaction of 2 and dimethyl acetylenedicarboxylate: although Michael addition also took place in this case, because of the presence of traces of water during the work up, the addition intermediate underwent hydrolytic ring opening to 8 which was obtained in good yield.
Both positively charged methylated salts (1-methyl-2-phenylfuro[2,3-e]pyrido[1,2-b][1,2,4]triazinium tetrafluoroborate 4 and 1,5-trimethylpyrido[1,2-b]pyridazino[3,4-e][1,2,4]triazinium tetrafluoroborate 5) reacted with secondary amines. In these transformations –like in several cases found by us earlier4,5 – the pyridine moiety underwent ring opening to yield new hetaryldienes, 9 and 10, respectively. The new dienes, in accordance with the general experience6-8, had a trans-trans geometry as supported unambiguously by the coupling constants of the diene protons in the 1H-NMR spectrum.

While our efforts to carry out cycloaddition reactions with 9 failed, diene 10 reacted relatively easily with N-phenylmaleinimide and fumaronitrile to yield regular cycloadducts containing a partially saturated benzene ring (11 and 12, respectively). Aromatization of the benzene moiety was carried out with both cycloadducts. In the case of cycloadduct 11 simple heating in toluene was enough to facilitate elimination of pyrrolidine and a subsequent spontaneous oxidation to give the corresponding isoindol-2,7-dione derivative 13. The similar
transformation with the fumaronitrile adduct was carried out by oxidation with DDQ to yield the hetarylphtalonitrile 14.

Conclusions

Transformations observed in these studies provided access to several new fused heterocyclic derivatives. These compounds seem to be promising candidates for biological (particularly DNA intercalation\(^9\) – determined by measurement of the \(T_m\) point\(^10\) - and multidrug resistance inhibitory\(^11\)) tests which are now in progress in the frame of COST B16 action.

Experimental Section

General Procedures. Melting points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet Magna 750 FT-IR, spectrophotometers; the NMR spectra were recorded with a Varian UNITY INOVA spectrometer (400 MHz for \(^1\)H and 100 MHz for \(^{13}\)C) and Varian VXR200 spectrometer (200 MHz for \(^1\)H).

**2-Cyano-3-(2-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazin-3-yl)but-2-enedinitrile (6).** Tetracyanoethylene (0.13 g, 1 mmol) was added to a suspension of 2-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazine (2, 0.25 g, 1 mmol) in dichloromethane (5 mL), and the mixture was stirred at rt for 1 h. A solid separated which was filtered off and recrystallized from acetonitrile to give 0.15 g (43%) of red crystals, mp 250-252 °C. IR (KBr): 2216, 1581, 1519, 1502, 1481, 1455, 1409, 1242, 1184, 1153, 1138, 1127, 1102, 782 cm\(^{-1}\); \(^1\)H NMR \(\delta\) (CDCl\(_3\)): 7.68 (m, 3H, H-phenyl), 7.71 (t, 1H, \(J = 7, 9\) Hz, H-7), 8.01 (m, 2H, H- phenyl), 8.18 (t, 1H, \(J = 9, 9.3\) Hz, H-8), 8.31 (d, 1H, \(J = 9.3\) Hz H-9), 9.11 (d, 1H, \(J = 7\) Hz, H-6); \(^{13}\)C NMR \(\delta\) (DMSO-d\(_6\)): 82.9(C=C), 99.3(C=C), 112.9(CN), 113.2(CN), 113.6(CN), 120.8(C-7), 126.7(C-9), 128.5(C-phenyl), 130.5(C-3), 130.6, 132.2 and 133.1(C-phenyl), 137.3(C-8), 138.1(C-6), 144.6(C-9a), 145.3 (C-2), 154.9(C-3a), 179.4(C-10a). Anal. Calcd. for C\(_{20}\)H\(_9\)N\(_7\) (347.35): C, 69.15; H, 2.61; N, 28.23. Found: C, 68.63; H, 2.68; N, 28.10.

**4-Methyl-N-(2-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazin-3-carbonyl)-benzenesulfonamide (7).** The reagent (p-toluenesulfonyl isocyanate, 1.0 mL, 6.6 mmol) was added to the compound of 2-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazine (2, 0.25 g, 1 mmol) and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with diethylether (10 mL) and a yellow solid separated which was filtered off and recrystallized from DMF to give 0.32 g (72%) of product, mp 275-278 °C. IR (KBr): 3261, 3069, 1678, 1581, 1485, 1412, 1429, 1346, 1333, 1161, 1140, 1131, 1078, 1020, 750, 666 cm\(^{-1}\); \(^1\)H NMR \(\delta\) (DMSO-d\(_6\)): 7.40 (d, 1H, H-9), 7.5 (m, 3H, H-phenyl), 7.55 (m, 1H, H-7), 7.76 (m, 1H, H-8), 7.92 (m, 4H, H-tolyl), 8.2 (m, 2H, H-phenyl), 9.26 (d, 1H, \(J = 7\) Hz, H-6), 11.5 (NH); \(^{13}\)C NMR \(\delta\) (DMSO-d\(_6\)): 21.8, 119.6, 126.8,
128.0, 128.2, 129.6, 130.5, 131.4, 134.5, 135.8, 137.2, 137.9, 144.1, 144.6, 146.5, 160.9, 162.6. Anal. Calcd. for C_{23}H_{17}N_{5}O_{3}S (443.50): C, 62.29; H, 3.86; N, 15.79. Found: C, 62.20; H, 3.95; N, 15.80.

**Dimethyl 2-(2-(3-oxo-3,4-dihydropyrido[1,2-b][1,2,4]triazin-2-ylideneamino)-2-phenylvinyl)-but-2-enedioate (8).** Dimethyl acetylenedicarboxylate (0.3 mL, 2.4 mmol) was added to a suspension of 2-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazine (2, 0.5 g, 2 mmol) in dichloromethane (10 mL), and the mixture was stirred at rt for 6 h. The reaction mixture was evaporated and the product was isolated by column chromatography (Aluminiunoxide, chloroform) and recrystallized from ethanol to give yellow crystals (0.15 g, 18%), mp 210-215 °C. IR (KBr): 3087, 3045, 2949, 1732, 1675, 1609, 1552, 1490, 1436, 1298, 1226, 1157, 1136, 770 cm⁻¹; ¹H NMR δ (CDCl₃): 3.19 (s, 3H, H-COME), 3.82 (s, 3H, H-COME), 5.60 (s, 1H, H-3'), 6.25 (s, 1H, H-5'), 6.95 (t, 1H, J = 7.2, 9 Hz, H-7), 7.40 (d, 1H, J = 9.3, Hz H-9), 7.60 (t, 1H, J = 9, 9.3, Hz H-8), 7.60-7.20 (m, 5H, H-phenyl), 8.32 (d, 1H, J = 7.2 Hz, H-6) 12.3 (NH); ¹³C NMR δ (CDCl₃): 51.7, 52.3, 98.0, 98.5, 113.5, 123.7, 128.1, 130.0, 136.4, 136.6, 137.2, 145.6, 151.0, 151.5, 152.5, 159.9, 164.1, 168.2. Anal. Calcd. for C₂₁H₁₈N₄O₅ (406.41): C, 62.06; H, 4.46; N, 13.79. Found: C, 61.84; H, 4.62; N, 13.43.

**1-Methyl-2-phenyl-6-(4-pyrrolidin-1-yl-buta-1,3-dienyl)-1H-pyrrolo[2,3-e][1,2,4]triazine (9).** Pyrrolidine (0.7 mL, 8.4 mmol) was added to a solution of 1-methyl-3-phenylpyrrolo[2,3-e]pyrido[1,2-b][1,2,4]triazinium tetrafluoroborate (4, 0.7 g, 2 mmol) in acetonitrile (10 mL), and the mixture was stirred at rt for 1 h. A solid separated which was filtered off and recrystallized from acetonitrile to give reddish crystals (0.34 g, 51%), mp 148-150 °C. IR (KBr): 2970, 1624, 1604, 1581, 1418, 1397, 1369, 1264, 1094, 980, 748 cm⁻¹; ¹H NMR δ (CDCl₃): 1.93 (m, 4H, H-pyrrolidine), 3.28 (m, 4H, H-pyrrolidine), 3.76 (s, 3H, H-1-Me), 5.28 (dd, 1H, J=12.8, 11.4 Hz, H-2'), 6.53 (d, 1H, J = 14.5 Hz, H-4'), 6.81 (s, 1H, H-3'), 6.90 (d, 1H, J = 12.8 Hz, H-1'), 7.78 (dd, 1H, J = 14.5, 11.4 Hz, H-3'), 7.50-7.55 (m, 5H, H-phenyl); ¹³C NMR δ (CDCl₃): 25.2, 29.0, 48.9, 98.7, 99.9, 115.8, 125.2, 128.9, 129.3, 130.7, 139.4, 143.6, 144.0, 146.6, 160.4. Anal. Calcd. for C₂₀H₂₁N₅ (331.41): C, 72.48; H, 6.39; N, 21.13. Found: C, 72.16; H, 6.21; N, 21.18.

**1,5-Dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-e]-[1,2,4]triazine (10).** Pyrrolidine (2 mL, 24 mmol) was added to a solution of 1,5-dimethyl-3-phenylpyrido[1,2-b]pyridazino[3,4-e][1,2,4]triazinium tetrafluoroborate 5 (4 g, 10.6 mmol) in acetonitrile (20 mL), and the mixture was stirred at rt. A violet solid separated which was filtered off and recrystallized from acetonitrile to give 2.56 g (67%) of product, mp 188-90 °C. ¹H NMR δ (CDCl₃): 1.88 (m, 4H, H-pyrrolidine), 2.82 (s, 3H, H-1-Me), 3.19 (m, 4H, H-pyrrolidine), 3.31 (s, 3H, H-5-Me), 4.75 (s, 1H, H-8), 5.04 (dd, 1H, J = 12.6, 11.5 Hz, H-2'), 5.41 (d, 1H, J = 14.5 Hz, H-4'), 6.70 (d, 1H, J = 12.6 Hz, H-1'), 7.03 (dd, 1H, J = 14.5, 11.5 Hz, H-3'), 7.33-7.60 (m, 5H, H-phenyl); ¹³C NMR δ (CDCl₃): 25.2, 39.1, 39.3, 48.8, 84.6, 98.3, 114.2, 125.2, 128.3, 129.1, 136.2, 136.8, 141.1, 142.4, 153.0, 158.3.

**4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-7-pyrrolidin-1-yl-3a,4,7,7a-tetrahydroisoindol-1,3-dione (11).** A mixture of N-pyromaleimide (110 mg, 0.64 mmol), 1,5-dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-
e][1,2,4]triazine (10, 200 mg, 0.55 mmol), and toluene (10 mL) was stirred at rt. Orange-red crystals separated which were filtered off and washed with ether to give 226 mg (76%) of product, mp 166-8 °C. \(^1\)H NMR \(\delta\) (CDCl\(_3\)): 1.85 (m, 4H, H-pyrrolidine), 2.72 (m, 4H, H-pyrrolidine), 2.79 (s, 3H, H-5'-Me), 2.90-2.96 (m, 2H, H-4, H-7), 3.20 (s, 3H, H-1'-Me), 3.54 (dd, 1H, \(J = 9.5, 7.0\) Hz, H-3a or H-7a), 3.86 (dd, 1H, \(J = 9.0, 6.0\) Hz, H-3a or H-7a), 4.63 (s, 1H, H-8'), 6.10 (dt, 1H, \(J = 9.5, 3.5\) Hz, H-6), 6.36 (dt, 1H, \(J = 9.5, 3.0\) Hz, H-5), 7.23-7.26, 7.29-7.42 and 7.50-7.54 (m, 10H, H-phenyl); \(^1^3\)C NMR \(\delta\) (CDCl\(_3\)): 24.5, 40.3, 40.4, 41.7, 43.9, 44.3, 54.7, 64.8, 86.2, 126.4, 127.7, 129.3, 129.5, 129.8, 130.4, 131.8, 133.1, 137.0, 143.3, 155.5, 158.4, 158.6, 175.5, 176.6. Anal. Calcd. for C\(_{31}\)H\(_{31}\)N\(_7\)O\(_2\) (533.62): C, 69.77; H, 5.86; N, 18.37. Found: C, 69.64; H, 5.86; N, 18.28.

3-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-6-pyrrolidin-1-yl-cyclohexene-1,2-dicarbonitrile (12). A mixture of 1,5-dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-e][1,2,4]triazine (10, 400 mg, 1.1 mmol), fumaronitrile (100 mg, 1.28 mmol) and dichloromethane (10 mL) was stirred at rt for 4 d. The mixture was evaporated and the residue subjected to column chromatography on silica (with chloroform as an eluent). The main fraction gave 220 mg (45 %) of pale yellow product, mp 220–222 °C. \(^1\)H NMR \(\delta\) (CDCl\(_3\)): 2.69 (m, 4H, H-pyrrolidine), 2.71 (s, 3H, H-1'-Me), 2.73 (m, 4H, H-pyrrolidine), 3.11 (dd, 1H, \(J = 11.0, 6.0\) Hz, H-1), 3.13 (s, 3H, H-5'-Me), 2.97 (ddd, 1H, \(J = 6.0, 4.5, 1.5\) Hz, H-6), 3.63 (ddd, 1H, \(J = 10.2, 4.5, 2.0\) Hz, H-3), 3.98 (dt, 1H, \(J = 10.3, 1.5\) Hz, H-4); \(^1^3\)C NMR \(\delta\) (CDCl\(_3\)): 24.4, 30.6, 32.1, 39.1, 40.1, 41.4, 48.4, 58.2, 86.3, 117.6, 119.7, 125.5, 127.6, 128.0, 128.7, 129.8, 135.7, 142.7, 155.4, 157.8, 158.5. Anal. Calcd. for C\(_{25}\)H\(_{26}\)N\(_8\) (438.53): C, 68.47; H, 5.98; N, 25.55. Found: C, 68.23; H, 5.92; N, 25.54.

4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-2-phenylisoindol-1,3-dione (13). A solution of 4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-7-pyrrolidin-1-yl-3a,4,7,7a-tetrahydroisoindol-1,3-dione (11, 300 mg, 0.56 mmol) in toluene (5 mL) was refluxed for 2 h. Evaporation of the mixture gave a residue which was crystallized from acetonitrile to give 182 mg (70 %) of dark gray crystals, mp 268–70 °C. \(^1\)H NMR \(\delta\) (CDCl\(_3\)): 2.83 (s, 3H, H-1'-Me), 3.20 (s, 3H, H-5'-Me), 4.78 (s, 1H, H-8'), 7.35-7.47 (m, 10H, H-phenyl), 7.73 (t, 1H, \(J = 7.5\) Hz, H-6), 7.88 (dd, 1H, \(J = 7.5, 1.0\) Hz, H-5), 7.92 (dd, 1H, \(J = 7.5, 1.0\) Hz, H-7); \(^1^3\)C NMR \(\delta\) (CDCl\(_3\)): 39.1, 39.6, 86.0, 123.9, 125.3, 126.7, 128.0, 128.5, 129.0, 129.6, 131.8, 132.8, 134.0, 134.2, 135.6, 135.7, 142.6, 154.9, 155.9, 157.8, 165.5, 166.7. Anal. Calcd. for C\(_{27}\)H\(_{20}\)N\(_8\)O\(_2\) (460.49): C, 70.42; H, 4.38; N, 18.25. Found: C, 70.31; H, 4.28; N, 18.31.

3-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)phthalonitrile (14). A mixture of 3-(1,5-dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-6-pyrrolidin-1-yl-cyclohexene-1,2-dicarbonitrile (12, 260 mg, 0.6 mmol), DDQ (297 mg, 1.3 mmol) and toluene (10 mL) was refluxed for 1 h. The mixture was evaporated, the residue treated with dichloromethane and the insoluble material was removed. The filtrate was evaporated and the residue was subjected to chromatography on silica (with a chloroform-
methanol 50:1 mixture as an eluent). The main fraction gave 110 mg (49 %) of green crystalline product, mp 239–41 °C. $^1$H NMR δ (CDCl$_3$): 2.90 (s, 3H, H-5'-Me), 3.55 (s, 3H, H-1'-Me), 4.80 (s, 1H, H-8'), 7.39 (m, 3H, H-phenyl), 7.56 (m, 2H, H-phenyl), 7.60 (t, 1H, $J$ = 8.0 Hz, H-5), 7.72 (dd, 1H, $J$ = 8.0, 1.5 Hz, H-6), 8.14 (dd, 1H, $J$ = 8.0, 1.5 Hz, H-4). Anal. Calcd. for C$_{21}$H$_{15}$N$_7$ (365.39): C, 69.03; H, 4.14; N, 26.83. Found: C, 68.90; H, 3.91; N, 26.78.

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