Bromination of Diimidazo[1,2-*b*;2′,1′-*f*]pyridazine; A Reinvestigation

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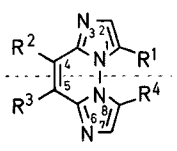
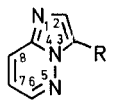
As a result of our continuous interest in fused pyridazines with a bridgehead nitrogen atom, especially in imidazo[1,2-*b*]pyridazines and other azoloazines[1,2], a report[3] about the synthesis of diimidazo[1,2-*b*;2′,1′-*f*]pyridazine **(1a)** and the reactivity of this new heterocyclic system has attracted our attention. Namely, it has been claimed, that bromination with bromine or *N*-bromosuccinimide in chloroform is taking place in pyridazine nucleus at position 4 to give **1b** and that further bromination under essentially the same reaction conditions is taking place again in the pyridazine part of the molecule affording thus the 4,5-dibromo derivative **1c.**

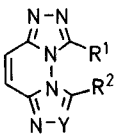


1	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	Br	H	H
c	H	Br	Br	H
d	Br	H	H	H
e	Br	H	H	Br

These results are surprising, since there are no other examples, known in the literature, in which electrophilic substitution is taking place in the pyridazine part of the molecule. To the contrary, according to the common experience, all electrophilic substitutions, including bromination, of imidazo[1,2-*b*]pyridazine **(2a)** are taking place in the imidazole ring at position 3, next to the bridgehead nitrogen atom[1,2]. Furthermore, it has been also shown, and confirmed by an independent synthesis, that bromination of a tricyclic system, 1-phenylimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine **(3a)** is taking place in imidazole ring, next to the bridgehead nitrogen atom, affording 8-bromo-1-phenylimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine **(3b)**[4]. Therefore, in view of these results, it seems, that reinterpretation of the findings reported[3] is justified.



2a R = H
2b R = Br



3	R^1	R^2	Y
a	C_6H_5	H	CH
b	C_6H_5	Br	CH
c	C_6H_5	H	N
d	C_6H_5	C_6H_5	N

When the high resolution ^{1}H-N.M.R. spectrum of **1a** was rerun in $CDCl_3$, we obtained essentially the same chemical shift values as reported[3] [three singlets at $\delta = 7.37$ (4-H, 5-H), 7.48 (1-H, 8-H) and 7.65 ppm (2-H, 7-H)]. On the other hand, the spectrum of **1a** in DMSO-d_6 is much more informative, since we observed three groups of signals; a doublet of doublets at $\delta = 8.58$ for 1-H and 8-H, a doublet at $\delta = 7.61$ for 2-H and 7-H, and a doublet at $\delta = 7.58$ ppm for 4-H and 5-H, with the coupling constants $J_{1\text{-H},2\text{-H}} = J_{7\text{-H},8\text{-H}} = 1.4$ Hz and $J_{1\text{-H},4\text{-H}} = J_{5\text{-H},8\text{-H}} = 0.4$ Hz, as expected because of the high symmetry of the molecule. The magnitudes of the coupling constants for *ortho*-protons in the imidazole ring $J_{1\text{-H},2\text{-H}}$ and $J_{7\text{-H},8\text{-H}}$ corresponding to $J_{7\text{-H},3\text{-H}} = 1$ Hz in imidazo[1,2-*b*]pyridazines **(2a)**[5,6] and the long-range coupling constants $J_{1\text{-H},4\text{-H}}$ and $J_{5\text{-H},8\text{-H}}$ corresponding to $J_{3\text{-H},8\text{-H}} = 0.8$ Hz in imidazo[1,2-*b*]pyridazines **(2a)**[5,6] make the assignment of signals in diimidazo[1,2-*b*;2′,1′-*f*]pyridazine **(1a)** unambiguous. This assignment is supported also by base-catalyzed hydrogen-deuterium exchange. In 0.1 normal sodium deuteroxide in a mixture of D_2O/DMSO-d_6 (10:90), the doublet of doublets at low field corresponding to 1-H and 8-H disappears at room temperature in few minutes. At the same time, the doublet for 2-H and 7-H and the doublet for 4-H and 5-H transform into singlets. At elevated temperatures (100 °C) also protons 4-H and 5-H are slowly exchanging. This is in agreement with the hydrogen-deuterium exchange of the corresponding 3-H and 8-H in imidazo[1,2-*b*]pyridazines, observed earlier[7].

The ^{1}H-N.M.R. spectrum of monobromo derivative of diimidazo[1,2-*b*;2′,1′-*f*]pyridazine in $CDCl_3$ as reported in Ref.[3] shows a multiplet at $\delta = 7.55$–7.62 corresponding to 1-H, 2-H, 7-H, and 8-H, and a singlet at $\delta = 8.91$ ppm for 5-H. On the other hand, we obtained in DMSO-d_6 solution a well-resolved spectrum showing a singlet at $\delta = 7.44$ (2-H), a doublet at $\delta = 7.40$ (4-H), and a doublet of doublets at $\delta = 7.33$ ppm (5-H) with the coupling constants $J_{4\text{-H},5\text{-H}} = 8.0$ Hz, which is of the same order of magnitude as the corresponding coupling constant $J_{7\text{-H},8\text{-H}} = 9$ Hz in imidazo[1,2-*b*]pyridazines[4,5,6], a doublet at $\delta = 7.60$ (7-H) and a doublet of doublet at $\delta = 8.88$ ppm (8-H) with the coupling constants $J_{7\text{-H},8\text{-H}} = 1.4$ and $J_{5\text{-H},8\text{-H}} = 0.4$ Hz. The presence of the large coupling constant (8 Hz), which excludes bromination either at position 4 or 5, the long-range coupling constant $J_{5\text{-H},8\text{-H}} = 0.4$ Hz, which makes possible to assign protons 5-H and 8-H, and the absence of the long-range coupling constant $J_{1\text{-H},4\text{-H}}$ is consistent only with 1-bromodiimidazo[1,2-*b*;2′,1′-*f*]pyridazine **(1d),** and not with te 4-bromo derivative **(1b),** as reported earlier[3]. This is further supported by the formation of the pseudocontact complex with Eu(fod)$_3$ shift reagent. Again a well-resolved AX pattern at $\delta = 11.05$ (d) and $\delta = 12.55$ ppm (d) (4-H, 5-H) is observed with coupling constants $J_{4\text{-H},5\text{-H}} = 9$ Hz, and three singlets at $\delta = 11.15$ (2-H), $\delta = 11.65$ (8-H), and $\delta = 13.0$ ppm (7-H). The greater chemical shift difference for 7-H in comparison to the chemical shift difference for 8-H indicates, that the pseudocontact complex is formed preferentially at N-6, since the nucleophilic character of N-3 is diminished as a result of bromination at position 1.

The ^{1}H-N.M.R. spectrum of the dibromo derivative in $CDCl_3$ solution shows two singlets at $\delta = 7.39$ and $\delta = 7.51$ ppm, and, in DMSO-d_6, two singlets at $\delta = 7.37$ (2-H, 7-H) and $\delta = 7.25$ ppm (4-H, 5-H) indicating the high symmetry of the product. The absence of the *ortho* coupling constants $J_{1\text{-H},2\text{-H}}$ and $J_{7\text{-H},8\text{-H}}$ and long-range coupling constants $J_{1\text{-H},4\text{-H}}$ and $J_{5\text{-H},7\text{-H}}$ is consistent only with 1,8-dibromodiimidazo[1,2-*b*;2′,1′-*f*]pyridazine **(1e)** and not with the 4,5-dibromo derivative **1c** as reported previously[3].

Further attempts to brominate 1,8-dibromodiimidazo[1,2-*b*;2′,1′-*f*]pyridazine, and some derivatives of some other tricyclic systems, such as 1-phenyl-8-bromoimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine **(3b),** 1-phenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-

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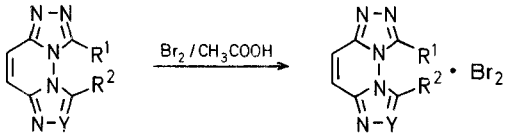
f]pyridazine **(3c)** and 1,8-diphenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine **(3d)** on the pyridazine part of the molecule with bromine in acetic acid, even under forced conditions, i.e. several hours under reflux, were unsuccessful. Instead, only complexes with bromine are formed. In comparison to the imidazo[1,2-*b*]pyridazine/bromine complexes which are well-defined and have been recently used for bromination of various classes of organic compounds, including ergot alkaloids[8,9], these complexes are relatively unstable. 1-Phenyl-8-bromoimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine/bromine complex decomposes in few hours while standing in an open atmosphere, while others decompose after few days at room temperature, by attempted crystallization from acetic acid, or when gently heated under diminished pressure.



3 a-d **3 a-d** · Br_2

The following compounds were prepared in essentially the same way as reported in literature: diimidazo[1,2-*b*;2′,1′-*f*]pyridazine[3], 1-phenyl-8-bromoimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine[4], 1-phenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine[10], and 1,8-diphenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine[10].

8-Bromo-1-phenylimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine/Bromine Complex (3b · 2Br₂)

To a suspension of 8-bromo-1-phenylimidazo[1,2-*b*]-*s*-triazolo[3′,4′-*f*]pyridazine (**3b**; 100 mg) in glacial acetic acid (4 ml), a solution of bromine (1 ml) in glacial acetic acid (2 ml) is added dropwise. The precipitate which is formed immediately is collected by filtration and crystallized from acetic acid containing few drops of bromine; yield (after crystallization): 188 mg (95%). The complex decomposes at elevated temperatures into **3b** and bromine.

$C_{13}H_8BrN_5 \cdot 2Br_2$	calc.	N 11.05
(633.8)	found	11.17

^{1}H-N.M.R. (DMSO-d_6): $\delta = 7.78$ (d); 8.0 (d, 4-H, 5-H); 7.70 (s, 7-H, partially overlapped with C_6H_5); 7.5–7.8 ppm (m, 5 H_{arom}).

1-Phenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine/Bromine Complex (3c · Br₂):

From 1-phenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine and bromine; yield (after crystallization): 84%. The complex decomposes at elevated temperatures into **3c** and bromine.

$C_{12}H_8N_6 \cdot Br_2$	calc.	C 36.39	H 2.04	N 21.22
(396.1)	found	36.21	2.45	20.93

^{1}H-N.M.R. (DMSO-d_6): $\delta = 8.60$ (s, 1 H, 8-H); 8.15 (s, 2 H, 4-H, 5-H); 7.8–7.5 ppm (m, 5 H_{arom}).

1,8-Diphenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine/Bromine Complex (3d · Br₂):

From 1,8-diphenyl-bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine and bromine; yield (after crystallization): 71%. The complex decomposes at evelated temperatures into **3d** and bromine.

$C_{18}H_{12}N_6 \cdot 3/2\,Br_2$	calc.	C 39.16	H 2.19	N 15.22
(552.1)	found	39.55	2.48	15.48

^{1}H-N.M.R. (DMSO-d_6): $\delta = 7.85$ (s, 2 H, 4-H, 5-H); 7.50–6.90 ppm (m, 10 H_{arom}).

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