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REACTIONS OF 1-SUBSTITUTED BENZO[4,5]IMIDAZO[1,2-*a*]PYRIDINES

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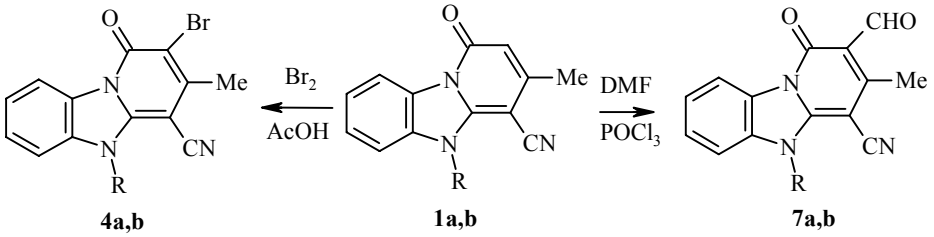
Bromination of 1-oxo(imino, amino)benzo[4,5]imidazo[1,2-a]pyridines gave the corresponding 2-bromo derivatives. Acylation using the Vilsmeier complex in acetic anhydride gave the N-formyl and N-acetyl derivatives. The reaction of the amine with the Vilsmeier complex, acetyl acetone, ethyl acetoacetate, and 2,5-dimethoxytetrahydrofuran occurs at the amino group.

Keywords: benzo[4,5]imidazo[1,2-*a*]pyridine, acylation, bromination.

Interest in benzo[4,5]imidazo[1,2-*a*]pyridines is due to their potential biological activity [1] and to the fluorescent properties of this class of compound [2]. We have previously described a simple method for the synthesis of certain 1-substituted benzo[4,5]imidazo[1,2-*a*]pyridines [3]. In this study we report a comparison of the chemical properties of the oxo compounds **1a,b** (Scheme 1) , the imine **2**, and the amine **3** (Schemes 2 and 3).

Scheme 1



4a,b **1a,b** **7a,b**

4 a R = H, **b** R = Me

Compounds **1a** and **3** are characterized by an electrophilic substitution reaction which occurs at position 2 of the heterocyclic system. Thus there are reports of an aza coupling reaction in which compounds **1a** and **3** take part as aza component [4, 5] and of the Vilsmeier formylation of compound **1a** leading to the aldehyde **7a** [2, 6].

Treatment of compounds **1-3** with bromine in acetic acid gave the 2-bromo derivatives **4-6** (Schemes 1-3). The reaction course is identified by the absence in the ^{1}H NMR spectra of the bromination products **4-**6 of the typical one proton singlet in the range 6-7 ppm.

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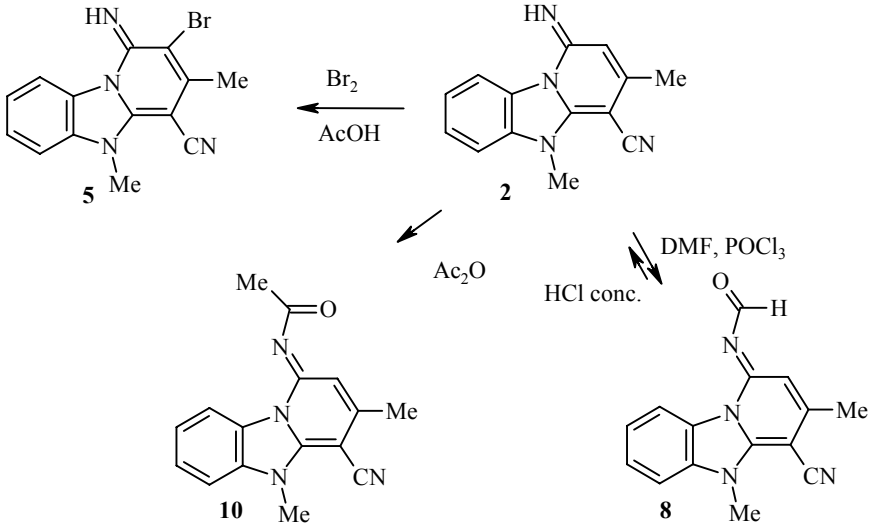
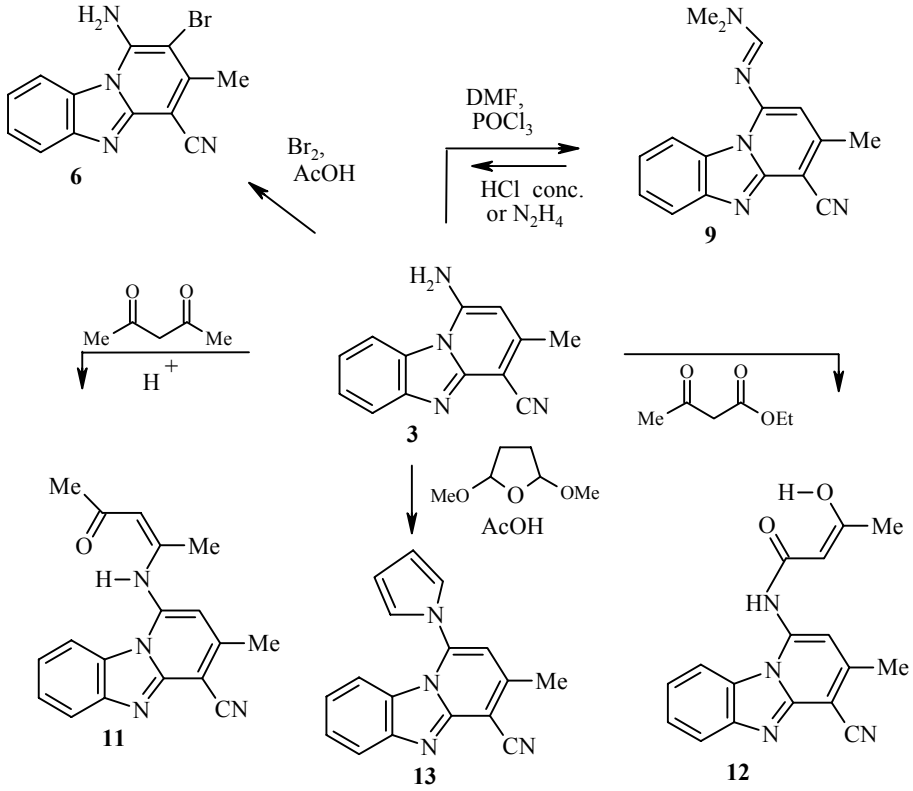
Scheme 2



The Vilsmeier formylation of the 5-methyl derivative **1b** gave the aldehyde **7b,** whose ^{1}H NMR spectrum showed the absence of the singlet for the 2-H proton and the presence of an aldehyde proton at 10.29 ppm. The IR spectrum of compound **7b** showed a stretching band for the aldehyde group at 1675-1650 cm^{-1}. The shift of the absorption band is due to the conjugation of the aldehyde group with the π-donor imidazole fragment.

Scheme 3



In contrast to the oxo compounds **1a,b**, the compounds **2** and **3** are formylated at the imino and amino group to give the N-formyl derivative **8** and the amidine **9** respectively (Schemes 2 and 3).

Both compounds are hydrolyzed by warm, concentrated hydrochloric acid to give the starting materials. In addition, the amidine **9** is converted to the starting amine **3** using hydrazine in acetonitrile. The ^{1}H NMR spectrum of compound **8** (DMSO-d_6 solvent) shows one proton singlets at 7.10 and 9.26 ppm. The first is assigned to the 2-H proton and the second to the formyl proton.

In the IR spectrum of this compound the absorption band for the N–H bond near 3300 cm^{-1} is absent and a carbonyl group absorption is observed at 1655 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) of amidine **9** shows a six proton singlet at 3.31 ppm which is assigned to the dimethylamino group protons. The use of CF_3CO_2D as solvent leads to deuteration of compound **9** and fixing of the configuration of the amidine fragment with non-equivalent methyl groups (observed as two, three proton singlets at 3.61 and 3.54 ppm). In the same spectrum, the two, one proton singlets at 6.64 and 8.60 ppm are assigned to the 2-H and formamidine protons.

We have found that nucleophilic reagents such as hydrazine and benzylamine do not react with the carbonyl and imine groups of compounds **1** and **2** respectively. This is explained by a lowering of the multiplicity of the bond in these groups as a result of the π-donor effect of the imidazole ring. For the same reason, the imine is not hydrolyzed either in acidic or in alkaline medium to the oxo compound **1b** but reacts with acetic anhydride to give the N-acetyl derivative **10**, a homolog of the N-formyl derivative **8** (Scheme 2). In the ^{1}H NMR spectrum of compound **10** in DMSO-d_6 the 2-H proton signal is shifted by 0.27 ppm to low field (7.37 ppm) of the position of this singlet in the spectrum of the N-formyl derivative **8**. This is explained by an increase in compound **10** (as a result of the greater steric bulk of the methyl group) of the statistical contribution of the conformation with the carbonyl group situated close to the 2-H proton.

TABLE 1. Physical Parameters for Prepared Compounds

Compound	Empirical formula	Found, % / Calculated, %		mp, °C* (solvent)	Yield, %
		N	Br		
4a	$C_{13}H_8BrN_3O$	13.91 / 14.26	26.45 / 26.21	>300 (BuOH)	87
4b	$C_{14}H_{10}BrN_3O$	13.52 / 13.29	25.52 / 25.28	261-262 (dioxane)	70
5	$C_{14}H_{11}BrN_4$	17.62 / 17.78	25.42 / 25.36	230-231 (BuOH)	52
6	$C_{13}H_9BrN_4$	18.23 / 18.60	26.52 / 26.54	261-262 (DMF/H_2O)	37
7b	$C_{15}H_{11}N_3O_2$	15.84 / 16.10		276-277 (BuOH)	84
8	$C_{15}H_{12}N_4O$	21.50 / 21.20		268-269 (BuOH)	97
9	$C_{16}H_{15}N_5$	25.45 / 25.25		>300 (DMF/H_2O)	87
10	$C_{16}H_{14}N_4O$	20.13 / 20.73		263-264 (BuOH)	87
11	$C_{18}H_{16}N_4O$	18.59 / 18.41		194-195 (BuOH)	49
12	$C_{17}H_{14}N_4O_2$	18.29 / 17.91		285-286 (BuOH)	36
13	$C_{17}H_{12}N_4$	20.57 / 20.69		>300 (BuOH)	55

***** Compounds **4b**, **5**, **6**, **7b**, **8**, **10**, and **12** melted with decomposition.

TABLE 2. Spectroscopic Parameters for Compounds **4-6, 7b-13**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm, spin-spin coupling (*J*), Hz
4a	2195 (CN) 1652 (CO)	8.53 (1H, d, *J* = 7.5, 9-H); 7.56-7.38 (3H, s, 6-,7-,8-H); 2.52 (3H, s, 3-CH_3)
4b	2200 (CN) 1667 (CO)	8.63 (1H, dd, *J* = 7.5, 1.5, 9-H); 7.74 (1H, dd, *J* = 7.5, 2.0, 6-H); 7.61 (1H, m, 8-H); 7.44 (1H, m, 7-H); 4.09 (3H, s, 5-CH_3); 2.56 (3H, s, 3-CH_3)
5	3300 (NH) 2175 (CN)	8.90 (1H, d, *J* = 7.5, 9-H); 7.59 (1H, m, 6-H); 7.54 (1H, s, NH); 7.48 (1H, m, 8-H); 7.31 (3H, m, 7-H); 3.97 (3H, s, 5-CH_3); 2.37 (3H, s, 3-CH_3)
6	3445, 3275 (NH_2) 2200 (CN) 1630 (C=N)	8.49 (1H, d, *J* = 8.0, 9-H); 7.81 (1H, d, *J* = 7.5, 6-H); 7.81 (2H, s, NH_2); 7.56 (1H, m, 8-H); 7.34 (1H, m, 7-H); 2.63 (3H, s, 3-CH_3)
7b	2190 (CN) 1675 (CO) 1655 (CO)	10.29 (1H, s, CHO); 8.66 (1H, dd, *J* = 7.5, 1.0, 9-H); 7.90 (1H, dd, *J* = 8.0, 1.5, 6-H); 7.68 (1H, m, 8-H); 7.53 (1H, m, 7-H); 4.17 (3H, s, 5-CH_3); 2.73 (3H, s, 3-CH_3)
8	2190 (CN) 1655 (CO)	9.26 (1H, s, CHO); 9.12 (1H, d, *J* = 8.0, 9-H); 7.84 (1H, m, 6-H); 7.66 (1H, m, 8-H); 7.46 (1H, m, 7-H); 7.10 (1H, s, 2-H); 4.15 (3H, s, 5-CH_3); 2.55 (3H, s, 3-CH_3)
9	2195 (CN) 1622 (C=N)	8.76 (1H, d, *J* = 8.0, 9-H); 8.60 (1H, s, CH amidine); 7.75 (1H, d, *J* = 7.5, 6-H); 7.53 (1H, m, 8-H); 7.32 (1H, m, 7-H); 6.64 (1H, s, 2-H); 3.31 (6H, s, $N(CH_3)_2$); 2.5 (3H, s, 3-CH_3) [8.99 (1H, d, *J* = 8.0, 9-H); 8.58 (1H, s, CH amidine); 7.9-7.6 (3H, m, 6-,7-,8-H); 7.02 (1H, s, 2-H); 3.61 (3H, s, NCH_3); 3.54 (3H, s, NCH_3); 2.84 (3H, s, 3-CH_3)]*
10	2180 (CN)	9.15 (1H, d, *J* = 8.0, 9-H); 7.81 (1H, d, *J* = 8.0, 6-H); 7.65 (1H, m, 8-H); 7.45 (1H, m, 7-H); 7.37 (1H, s, 2-H); 4.15 (3H, s, 5-CH_3); 2.46 (3H, s, 3-CH_3); 2.23 (3H, s, CH_3CO)
11	2210 (CN)	12.96 (1H, s, NH); 8.07 (1H, d, *J* = 8.0, 9-H); 7.88 (1H, d, *J* = 8.0, 6-H); 7.57 (1H, m, 8-H); 7.34 (1H, m, 7-H); 6.94 (1H, s, 2-H); 5.68 (1H, s, CH aliphatic) 2.61 (3H, s, 3-CH_3); 2.19 (3H, s, CH_3 aliphatic residue); 2.14 (3H, s, CH_3 aliphatic residue)
12	2200 (CN) 1680 (CO)	12.66 (1H, s, NH); 8.50 (1H, d, *J* = 8.0, 9-H); 7.90 (1H, d, *J* = 7,5, 6-H); 7.59 (1H, m, 8-H); 7.36 (1H, m, 7-H); 7.30 (1H, s, 2-H); 6.57 (1H, s, CH aliphatic) 2.66 (3H, s, 3-CH_3); 2.38 (3H, s, CH_3 aliphatic residue)
13	2225 (CN) 1632 (C=N)	7.89 (1H, d, *J* = 7.5, 6-H); 7.51 (1H, m, 8-H); 7.26 (3H, m, 2-CH+α-CH pyrrole); 7.19 (1H, m, 7-H); 6.54 (2H, m, β-CH pyrrole); 6.11 (1H, d, *J* = 8.5, 9-H); 2.69 (3H, s, 3-CH_3)

* in CF_3CO_2D.

The basicity of the amino group in compound **3** and its reactivity are strongly decreased by the conjugation with the heterocyclic system, hence its derivatives are formed under forcing conditions. Refluxing amine **3** in acetylacetone in the presence of catalytic amounts of *p*-toluenesulfonic acid gave compound **11** (Scheme 3). The ^1H NMR spectrum, recorded in DMSO-d_6, corresponds to the enamino ketone form with the signal of NH proton at 12.96 ppm and a one proton singlet at 5.68 ppm which is assigned to the proton on the double bond of the aliphatic residue.

Prolonged heating of the amine **3** in ethyl acetoacetate gave compound **12**. The ^1H NMR spectrum of this derivative corresponds to the enol form with a signal for the amidine proton at 12.66 ppm and the double bond proton in the aliphatic residue at 6.57 ppm. Prolonged refluxing of compound **3** with 2,5-dimethoxytetrahydrofuran in acetic acid gave pyrrole **13** (Scheme 3) whose ^1H NMR spectrum in DMSO-d_6

showed typical two proton multiplets at 6.54 and 7.26 ppm, assigned to the pyrrole ring protons. Compound **13** has a non planar structure, which is evident from the ^{1}H NMR spectrum where shielding of the 9-H proton (6.11 ppm) occurs above the plane of the pyrrole ring together with deshielding of the 2-H proton (7.26 ppm).

EXPERIMENTAL

Monitoring of the reaction course and the purity of the synthesized compounds was carried out by TLC using Silufol UV-254 plates. IR Spectra were recorded on a Pye Unicam SP-300 instrument for KBr tablets. ^{1}H NMR spectra were taken using DMSO-d_6 or CF_3CO_2D solvent on a Bruker WP-100 (100 MHz) instrument using TMS internal standard.

General Method for Bromination of Compounds 1-3. Bromine (0.1 ml, 1.9 mmol) was added with stirring to a suspension (solution) of compounds **1-3** (0.4 g, 1.7-1.8 mmol) in acetic acid (10-20 ml). Stirring was continued for 20 min and the precipitated 2-bromo derivatives **4-6** were filtered off and washed with acetic acid and water.

2-Formyl-3,5-dimethyl-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (7b). $POCl_3$ (0.62 ml, 6.65 mmol) was added to a suspension of compound **1b** (0.4 g, 1.69 mmol) in DMF (8.5 ml). The reaction mixture was heated at 70°C for 6 h, cooled, and water (100 ml) was added. The precipitate was filtered off, washed with water, and recrystallized.

N'-(4-Cyano-3,5-dimethyl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-1-ylidene)formamide (8). $POCl_3$ (2.7 ml, 28.8 mmol) was added stepwise to a cooled suspension of imine **2** (1.7 g, 7.2 mmol) in DMF (25 ml). The reaction mixture was heated at 60-65°C for 1.5 h, cooled, and water (50 ml) was added. The reaction medium was taken to neutrality by addition of sodium carbonate. The precipitate was filtered off, washed with water, and recrystallized.

N'-(4-Cyano-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridin-1-yl)-N,N-dimethylaminoformamide (9). $POCl_3$ (2.52 ml, 27 mmol) was added to a cooled suspension of amine **3** (2 g, 9 mmol) in DMF (40 ml). The reaction mixture was heated at 70°C for 3 h, cooled, and water (50 ml) was added. The reaction medium was taken to neutrality by addition of sodium carbonate. The precipitate was filtered off, washed with water, and recrystallized.

N'-(4-Cyano-3,5-dimethyl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-1-ylidene)acetamide (10). A solution of imine **2** (0.4 g, 1.7 mmol) in acetic anhydride (9 ml) was held at 70-80°C for 1 h. The crystalline precipitate of compound **10** was filtered off. The filtrate was evaporated in vacuo and the residue was recrystallized.

3-Methyl-1-[(1-methyl-3-oxo-1-butenyl)amino]benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (11). A suspension of amine **3** (0.5 g, 2.25 mmol) was refluxed for 10 h in acetylacetone (35 ml) together with a catalytic amount of p-toluenesulfonic acid. The solution formed was evaporated in vacuo. The residue was treated with water, and the precipitate was filtered off, washed with water, and recrystallized.

N'-(4-Cyano-3-methylbenzo[4,5]imidazo[1,2-*a*]pyridin-1-yl)-3-hydroxy-2-butenamide (12). A suspension of amine **3** (0.3 g, 1.35 mmol) in ethyl acetoacetate (5 ml) was heated at 180-185°C for 12 h. The mixture was cooled, butanol (15 ml) was added and the product was refluxed for about 0.5 h. The crystalline precipitate was filtered off, washed with alcohol, and recrystallized.

3-Methyl-1-(1H-1-pyrrolyl)benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile (13). 2,5-Dimethoxy-tetrahydrofuran (0.2 ml, 1.54 mmol) was added to a refluxing solution of amine **3** (0.3 g, 1.35 mmol) in acetic acid (20 ml). The reaction mixture was refluxed for 16 h. The solvent was evaporated in vacuo and the residue was treated with water. The precipitate was filtered off, washed with water, and recrystallized.

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