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2-(2-FURYL)IMIDAZO[1,2-*a*]PYRIMIDINE SYNTHESIS AND ELECTROPHILIC SUBSTITUTION REACTIONS

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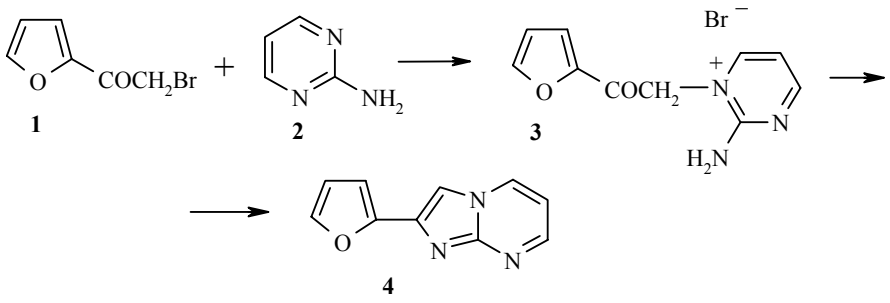
The synthesis of 2-(2-furyl)imidazo[1,2-a]pyrimidine has been carried out. Azocoupling, nitrosation, and bromination by 1 mole of bromine occur at position 3 of the bicycle. Reaction with 2 mol of bromine gives the 3,5'-disubstituted derivative. Bromination using 1 mol of bromine in 40% hydrobromic acid and sulfonation occur initially at the 5' position of the furyl group.

Keywords: 2-(2-furyl)imidazo[1,2-*a*]pyrimidine, azocoupling, bromination, nitrosation, sulfonation.

We have continued our study of the effect of the nature of heterocycles with a bridging nitrogen atom on the reactivity of hetarylfurans. The reaction of an ether solution of freshly prepared 2-bromoacetylfuran (**1**) (an unstable lachrymator) with 2-aminopyrimidine (**2**) gave 2-amino-1-(2-furoylmethyl)pyrimidinium bromide (**3**) which was converted to 2-(2-furyl)imidazo[1,2-*a*]pyrimidine (**4**) by subsequent heating with $NaHCO_3$ in water.



A study of the electrophilic substitution of compound **4** has shown that the reactions with *p*-nitrophenyldiazonium chloride and *n*-butylnitrite occur only at position 3 of the bicycle and give the corresponding 3-(*p*-nitrophenylazo)- (**5**) and 3-nitroso- (**6**) substituted compounds. The structure of the latter was proved by ^{1}H NMR spectroscopy.

Analogously to previously reported formylation reaction of compound **4**, which with 1 mol of reagent occurs selectively at position 3 whereas an excess of reagent reacts at positions 3 and 5' [1], the action of 1 mol of bromine on this compound in acetic acid gives the 3-bromo-substituted (**7**) and 2 mol of bromine the 3,5'-disubstituted **8**.

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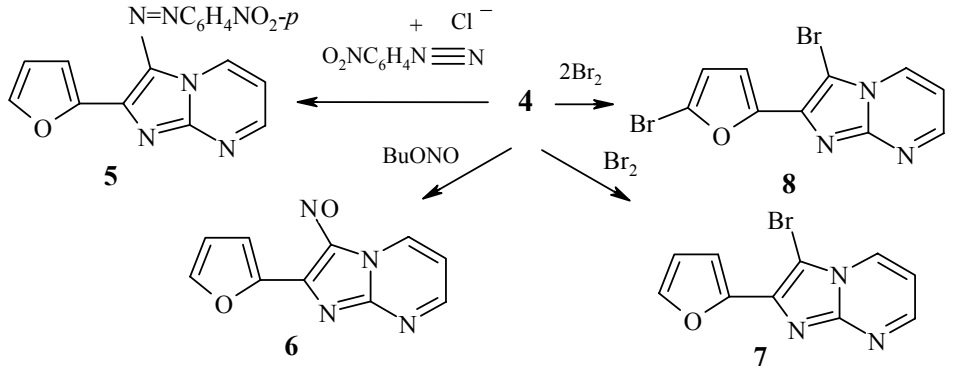
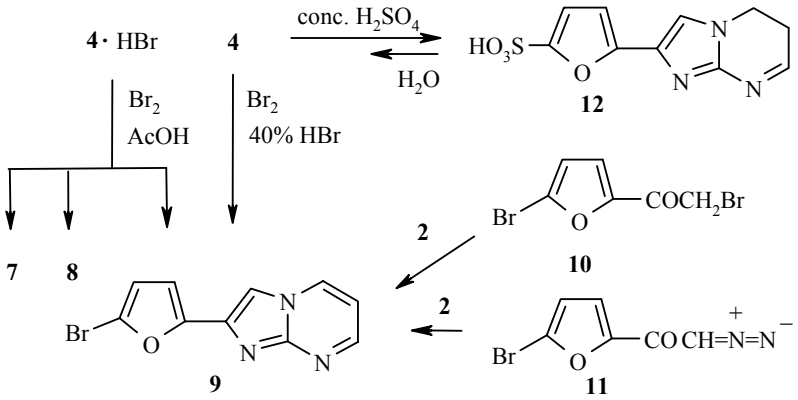


Hence an electrophilic substitution reaction of **4** in neutral or weakly acidic media occurs in the same way as in the case of its 8-desaza analog 2-(2-furyl)imidazo[1,2-*a*]pyrimidine [2, 3].

However, the action of 1 mole of bromine in acetic acid on the salt **4**·HBr gives a mixture of 3-bromo-, 3,5-'dibromo- and 5'-bromo-substituted **7-9** by contrast with 6-(2-furyl)imidazo[2,1-*b*]thiazole hydrobromide which is completely converted to the 5'-bromofuryl derivative under the same conditions [4].



From compound **4** it proved possible to obtain only the 5'-bromo derivative **9** by the action of 1 mol of bromine in 40% hydrobromic acid medium. The ^{1}H NMR spectrum of the reaction mixture after 1 h showed signals for the bromo-substituted **8** and **9** but after 24 h only compound **9** and the starting material in the ratio 1:1. This is likely to be the result of partial as well as complete debromination of compound **8**. The occurrence of debromination was previously reported when heating in DMF medium the furylimidazopyridine and furylimidazothiazole hydrobromides which were bromo-substituted in the imidazole ring [5].

The mixture of the bromo-substituted **7-9** with the starting material was separated on a silica gel column. A counter synthesis of the 5'-bromo-substituted **9** was carried out by the reaction of the 2-aminopyrimidine (**2**) with the bromo ketone **10** and also with the precursor in the preparation of this bromo ketone, the diazo ketone **11**.

The difference in reactivity of compound **4** and furylimidazopyridine was particularly clear in strongly acidic medium. It has previously been shown [6] that the nitration of compound **4** with 1 mol of HNO_3 in conc. H_2SO_4 occurs selectively to give the 5'-nitro derivative in 79% yield while the furylimidazopyridine these conditions forms, in low yield, a mixture of the 5'-nitro- and 3,5'-dinitro-substituted compound with a predominance of the latter [7]. Subsequent introduction of a nitro group in position 3 of compound **4** proves strongly hindering [6]. If the furylimidazopyridine forms the 3,5'-disulfoacid in 68% yield with conc. H_2SO_4 [7] then compound **4** is sulfonated only in the furyl group and the reaction occurs with greater difficulty. The ^{1}H NMR spectrum of the reaction mixture showed the presence of only 40% of the 5'-sulfoacid **12** which could not be separated.

TABLE 1. Characteristics of Compounds **3-9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield,% (method)
		C	H	N		
3	$C_{10}H_{10}BrN_3O_2$	42.41 / 42.27	3.64 / 3.80	14.48 / 14.79	220-222	89
4	$C_{10}H_7N_3O$	64.65 / 64.86	3.78 / 3.81	22.73 / 22.69	212-214	58
4·HBr·H_2O	$C_{10}H_{10}BrN_3O_2$	42.09 / 42.28	3.61 / 3.54	14.53 / 14.79	258-260	72
4·picrate	$C_{16}H_{10}N_6O_8$	46.09 / 46.39	2.51 / 2.43	20.09 / 20.28	238-239	—
5	$C_{16}H_{10}N_6O_3$	57.11 / 57.22	2.84 / 3.02	24.89 / 25.14	>300	99
6	$C_{10}H_6N_4O_2$	55.83 / 56.07	2.76 / 2.87	25.98 / 26.10	223-225	81
7	$C_{10}H_6BrN_3O$	45.23 / 45.48	2.21 / 2.29	16.14 / 15.91	184-186	81
7·HBr	$C_{10}H_7Br_2N_3O$	35.05 / 34.81	1.94 / 2.02	11.97 / 12.18	268-270	84
8	$C_{10}H_5Br_2N_3O$	34.78 / 35.00	1.57 / 1.46	12.27 / 12.25	281-283	80
9	$C_{10}H_6BrN_3O$	45.34 / 45.48	2.43 / 2.29	15.93 / 15.91	252-254	29 (A), 50 (B) 73 (C), 35 (D)
9·HBr	$C_{10}H_7Br_2N_3O$	34.67 / 34.81	2.13 / 2.02	12.26 / 12.18	269-271	83

* Compound **3** was purified by crystallization from a mixture of EtOH–ether; **5** from DMF–EtOH; **6** from benzene; **4b**, **4**·HBr, **4**·picrate, **7**, **7**·HBr from aqueous EtOH; **8, 9** from aqueous DMF.

This observation additionally confirms the lowering of the susceptibility of the imidazole ring to electrophilic substitution in acidic media with the increased π-deficiency of the heterocycle annelated *via* the bridging nitrogen atom.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) instrument using DMSO-d_6, CF_3COOH, 40% hydrobromic acid (internal standard HMDS, δ 0.055 ppm), or conc. H_2SO_4 (internal standard cyclohexane, δ 1.44 ppm). IR spectra were taken on a Perkin Elmer 580B instrument using vaseline oil (region 2000-600 cm^{-1}) and hexachlorobutadiene (regions 3600-2000 and 1500-1300 cm^{-1}). TLC was performed using Silufol UV-254 plates in the systems benzene–dioxane–acetic acid (20:4:1) , benzene–ethyl acetate (1:3), or acetone–chloroform (1:5) and were revealed using UV light. Mixture separation was carried out on a Woelm silica gel column (2.5 × 40 cm) with chloroform eluent (compounds **4, 7-9**). Melting points were measured on a Boetius instrument. For the determination of the C and H content a combustion catalyst was used or the carbon data obtained was too low.

2-Amino-1-(2-furoylmethyl)pyrimidinium Bromide (3). 2-Aminopyrimidine **2** (38 g, 400 mmol) was added to a solution of the bromo ketone **1** (75.6 g, 400 mmol) in ether (300 ml). The mixture was held for 5 days at room temperature and the precipitate was filtered off and washed with ether. Yield 101 g. IR spectrum, ν, cm^{-1}: 3400 and 3320 (NH_2), 2600-2500 ($NH_{assoc.}$), 1668 (C=O), 1620 (C=N, δ NH), 1515 ($COCH_2$).

TABLE 2. ^{1}H NMR Spectra of 2-(2-Furyl)imidazo[1,2-*a*]pyrimidine and Derivatives

Compound	Solvent	Chemical shifts, δ, ppm*						
		H-3	H-5	H-6	H-7	H-3'	H-4'	H-5'
4	DMSO-d_6	8.11	8.91	7.02	8.50	6.88	6.68	7.75
	CF_3COOH	8.23	9.17	7.79	9.10	7.26	6.72	7.71
4·HBr	DMSO-d_6	8.44	9.21	7.43	8.83	7.15	6.74	7.94
	40% HBr	8.52	9.20	7.65	8.96	7.30	6.73	7.92
4·H_2SO_4	H_2SO_4 conc.	8.55	9.67	8.38	9.33	7.52	6.87	7.92
6	DMSO-d_6	—	9.91	7.56	9.04	7.75	6.86	8.22
7	DMSO-d_6	—	8.95	7.57	9.00	7.79	6.90	7.85
	CF_3COOH	—	9.27	7.70	9.02	7.62	6.72	7.73
8	DMSO-d_6	—	8.95	7.30	8.70	7.87	7.38	—
	CF_3COOH	—	9.13	7.86	9.08	7.48	6.72	—
9	DMSO-d_6	8.15	8.90	7.02	8.52	6.91	6.69	—
	CF_3COOH	8.25	9.17	7.75	9.11	7.48	6.72	—
9·HBr*[2]	40% HBr	8.56	9.25	7.65	8.96	7.30	6.73	—
12*[2]	H_2SO_4 conc.	8.76	9.80	8.35	~9.5	6.87	~7.6	—

* Imidazopyrimidine signals: H-3 – s; H-5 – dd; H-6 – dd; H-7 – dd; $J_{5,6}$ = 6.4-6.7; $J_{5,7}$ = 1.6-2.0; $J_{6,7}$ = 4.1-4.4 Hz in DMSO-d_6 and CF_3COOH; $J_{5,6}$ = 7.0 Hz in conc. H_2SO_4; 2-substituted furan: H-3' – dd; H-4' – q; H-5' – dd; $J_{3,4}$ = 3.6-4.0; $J_{3,5}$ = 0.8-0.9; $J_{4,5}$ = 1.8 Hz; 2,5-disubstituted furan: 2d, $J_{3,4}$ = 3.6-4.0 Hz.

*[2] In a mixture with starting compound **4**.

2-(2-Furyl)imidazo[1,2-*a*]pyrimidine (4). The salt **3** (10 g, 35 mmol) in water (200 ml) with $NaHCO_3$ (10 g) was refluxed for 3 h. The precipitate formed on cooling was filtered off and washed with water. Yield 3.78 g. It was purified by crystallization from aqueous ethanol or acetone, octane, or by vacuum sublimation.

2-(2-Furyl)-3-(*p*-nitrophenylazo)imidazo[1,2-*a*]pyrimidine (5). A solution of the diazonium salt prepared from *p*-nitroaniline (1.52 g, 11 mmol), conc. HCl (3 ml), ice (50 g), and $NaNO_2$ (1 g, 15 mmol) was added at 0-5°C with stirring to a solution of compound **4** (1.85 g, 10 mmol) in pyridine (20 ml). The red-brown precipitate was filtered off and washed with water and ethanol. Yield 3.33 g.

2-(2-Furyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine (6). Freshly distilled butylnitrite (1.55 g, 15 mmol) was added with stirring to a solution of compound **4** (1.85 g, 10 mmol) in benzene (60 ml) cooled in ice. After 2 h the reaction mixture was diluted with petroleum ether (130 ml) and the green precipitate was filtered off and washed with petroleum ether. Yield 1.73 g.

3-Bromo-2-(2-furyl)imidazo[1,2-*a*]pyrimidine (7). A solution of bromine (0.51 ml, 10 mmol) in glacial acetic acid (8 ml) was added to a solution of compound **4** (1.85 g, 10 mmol) in the same solvent (50 ml) and stirred for 1 h. Ether (100 ml) was added and the precipitated **7**·HBr salt was washed with ether. Yield 2.90 g. Treatment of the salt (2.5 g) with a 20% aqueous NaOH solution gave compound **7** (1.55 g).

3-Bromo-2-(5-bromo-2-furyl)imidazo[1,2-*a*]pyrimidine (8) was prepared similarly from compound **4** (1.85 g, 10 mmol) and bromine (1.12 ml, 22 mmol). Yield of the base 2.74 g.

2-(5-Bromo-2-furyl)imidazo[1,2-*a*]pyrimidine (9), 3-Bromo-2-(2-furyl)imidazo[1,2-*a*]pyrimidine (7), and 3-Bromo-2-(5-bromo-2-furyl)imidazo[1,2-*a*]pyrimidine (8). A. A solution of bromine (0.51 ml, 10 mmol) in AcOH (15 ml) was added over 30 min to a stirred suspension of compound **4**·HBr·H_2O (2.84 g, 10 mmol) in AcOH (10 ml) and the temperature was held at 10-15°C. The product was stirred for 2 h, ether

(150 ml) was added, and the precipitate formed was filtered off, washed with ether, triturated with 10% aqueous NaOH solution, and then washed with water to give a mixture of compounds **4, 7-9** (2.04 g) in the ratio 2:2:1:4 (^{1}H NMR spectrum in CF_3COOH). The mixture was separated on a column to give a first fraction of compound **8** (0.065 g), second of **7** (0.12 g), and third of **9** (0.29 g).

2-(5-Bromo-2-furyl)imidazo[1,2-*a*]pyrimidine (9). B. A solution of bromine (0.13 ml, 2.5 mmol) in 40% hydrobromic acid (2 ml) was added portionwise with stirring to a solution of compound **4** (0.462 g, 2.5 mmol) in the same solvent (5 ml) and held for 24 h at room temperature. According to the ^{1}H NMR spectrum the mixture obtained was of **9** and **4** in the ratio 1:1.

C. A solution of 5-bromo-2-bromoacetylfuran **10** (2.68 g, 10 mmol) and the amine **2** (0.95 g, 10 mmol) in ethanol (30 ml) was refluxed for 7 h, diluted with ether (60 ml), and the precipitated hydrobromide **9** was filtered off. Yield 2.86 g.

This salt (2.0 g) was triturated with aqueous ammonia and the precipitate was filtered off and washed with water to give the base **9** (1.35 g).

D. The diazo ketone **11** (2.15 g, 10 mmol) and amine **2** (0.95 g, 10 mmol) in absolute ethanol (30 ml) were refluxed for 1 h and solvent was evaporated off. The residue was recrystallized from aqueous ethanol to give compound **9** (0.92 g).

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