CROATICA CHEMICA ACTA CCACAA 54 (2) 211—216 (1981)

CCA-1276

YU ISSN 0011-1643
UDC 547.78
Original Scientific Paper

Synthesis of New Formyl Halo *N*-methylimidazole Derivatives

M. El Borai, A. H. Moustafa, M. Anwar, and A. G. Ghattas

Department of Chemistry, Faculty of Science, University of Tanta and University of Ain Shams, Egypt

Received December 25, 1979

Bromo-formyl imidazoles 16—20 have been prepared by three different ways. The first consisted of conversion of bromo or iodo imidazoles 1—6 into diethyl acetals 13—15, and subsequent hydrolysis into formyl derivatives 7—9. In the second, bromination of formyl imidazoles with NBS afforded compounds 16—18 in 45—70% yield. The third method used direct formylation of bromo imidazoles 10—12 with *n*-BuLi/DMF reagent into compounds 16, 19, and 20.

INTRODUCTION

Imidazole compounds are proving to be of vital importance for the function of biological systems[1-2]. This research was carried out to investigate the effect of some of these compounds in that respect. Iversen et al.[3] reported the preparation of 2-formyl *N*-methylimidazole (NMI) by addition of DMF to the relevant lithium compound. Mattews et al.[4] reported the preparation of 5-formyl NMI by manganese dioxide oxidation of methyl-1-methyl-5-imidazole carboxylate. Also 2-diethylacetal NMI was prepared in 45% yield by the action of ethyl ortho formate on 2-formyl-*N*-methylimidazole.

RESULTS AND DISCUSSION

Synthesis. — Conventional methods for the preparation of 2,4, and 5-diethylacetal NMI derivatives 13, 14, and 15 were used starting from the corresponding bromo or iodo compounds 1—6. The hydrolysis of these acetals leads to the formation of 2, 4, and 5-formyl imidazole compounds 7—9. (Scheme 1.)

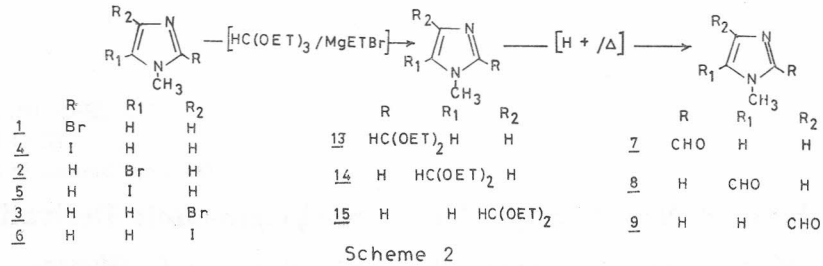
The bromo-formyl imidazoles 16—20 were prepared in two ways: firstly, bromination of 2, 4, and 5-formyl derivatives 7—9 with NBS and secondly, by direct formylation of 2,5 & 4,5-dibromo and 2,4,5-tribromo imidazole derivatives by *n*-BuLi/DMF reagent. (Scheme 2.)

EXPERIMENTAL

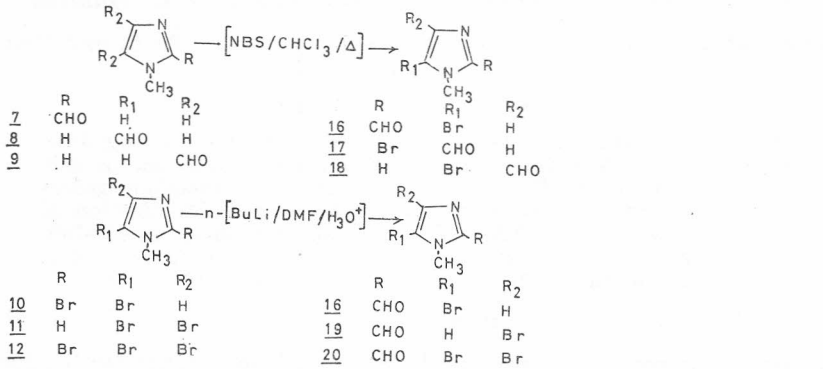
^{1}H NMR spectra were obtained on a Varian A-60 spectrometer in $CDCl_3$ with TMS as the internal reference, IR spectra were determined with a Unicam-SP 200G using the KBr Wafer technique. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

The usual procedure consisted of diluting with water, extracting with chloroform, washing the extract with water, drying over magnesium sulphate, removing the solvent and purification by column chromatography over silica G 60 (Merck) (Table II); or by crystallization from the appropriate solvents (Table III).

Scheme 1



Scheme 2



The starting compounds were prepared according to the methods cited in the literature: 2, & 5-bromo NMI[5]; 4-bromo NMI[6]; 4,5-dibromo NMI[7]; 2,5-dibromo, & 2,4,5-tribromo NMI[8]; 4-iodo NMI & 5-iodo NMI[8]; and 2-iodo NMI[9].

Method a: Formation of acetals.

To a solution of ethyl magnesium bromide (0.12 mol), the halo NMI derivative (0.1 mol) was added slowly at room temperature, the reaction mixture was refluxed for 2 hrs, 200 ml dry benzene was added and the ether was distilled off. The ethyl ortho formate was then added (0.2 mol) and the reaction mixture was refluxed for another 4 hrs. At 0 °C the reaction mixture was hydrolysed with 10% NH_4Cl solution and treated as described above. The experimental results were grouped in Table I.

TABLE I

Experimental Results of 2, 4, and 5-Diethylacetal NMI Compounds

Position of acetal	Halogen	Yield %	B. P. °C		Analysis % C	H	N
				Calc'd	58.68	8.75	15.21
2[3]	Br	56	78—80/	Found	58.52	8.81	15.16
	I	65	0.1 mm				
4	Br	48	118—120/	Found	58.50	8.83	15.20
	I	57	0.1 mm				
5	Br	60	98—100/	Found	58.54	8.76	15.15
	I	87	0.1 mm				

Hydrolysis of acetals: Formation of formyl NMI derivatives

To a solution of the diethyl acetal (0.1 mol) in 100 ml of chloroform under efficient stirring, 30 ml of 6N HCl was added dropwise and the reaction mixture was refluxed for 1 hr, cooled to 0 °C and neutralized with 50% NaOH solution and worked-up as usual. The products were recrystallized from ether-hexane 1 : 2 . The experimental results were grouped in Table II.

TABLE II

Experimental Results of 2, 4, and 5-Formyl NMI Derivatives

Position of CHO	Eluent	Yield %	IR data ν C=O cm^{-1}	Obs.	M. P °C Litt.
2	Ether	72	1680	35—36	34—37[3]
4	Ether-Acetone (4 : 1)	95	1686	66	66—66,5[4]
5	Ether-Acetone (2 : 1)	93	1682	54	53—54[4]

Method b: Bromination of formyl NMI derivatives

To a solution of 11 g (0.1 mol) of formyl NMI in 300 ml dry chloroform 19,5 g (0.11 mol) of NBS was added in little aliquots under vigorous stirring and the reaction mixture was refluxed for 2 hrs. At 0 °C 100 ml of saturated sodium carbonate solution was added, and the reaction mixture was worked-up as usual. The experimental results were grouped in Table III.

Method c: Formylation of di and tri bromo NMI derivatives

At —70 °C a solution of (0.05 mol) of halo NMI in 30 ml dry ether was treated by an equimolecular quantity of *n*-BuLi. The organo lithium intermediate was treated by 4,7 g (0.063 mol) of DMF in 20 ml dry ether and the temperature was kept at —70 °C for another one hour. At 0 °C the reaction mixture was hydrolysed and worked-up as usual.

REFERENCES

1. B. R. Rabin, C. M. Cuchillo, A. Deavin, C. M. Kemp, and A. P. Mathias, *Metabolic Regulation and Enzyme Action*, A. Sols and S. Gisolia (Eds.) Vol. 19, New York, Academic Press, 1970, p. 203.
2. R. M. Stroud, *Sci. Amer.* **231** (1974) 74.
3. P. Iversen and H. Lund, *Acta Chem. Scand.* **20** (1966) 2649.
4. P. Martin, H. R. Mattews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem.* **33** (1968) 3458.
5. G. B. Barlin, *J. Chem. Soc. B* (1967) 641.
6. M. Hoffer, V. Toome, and A. Brossi, *J. Heterocycl. Chem.* **3** (1966) 454.
7. V. Calo, F. Ciminale, L. Lopez, F. Naso, and P. E. Todesco, *J. Chem. Soc. Perkin I* (1972) 2567.
8. M. EL Borai, A. H. Moustafa, M. Anwar, and F. I. Abdel Hay, *Egypt. J. Chem.* (1980) in press.
9. M. S. Shvartsberg, L. N. Bizhan, E. E. Zave, and I. L. Kotlyarevskii, *Izv. Akad. Nauk. USSR, Ser. Khim.* (1972) 472. *C. A.* **77** (1972) 34422.

TABLE III

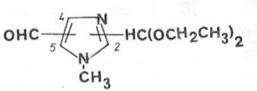
Experimental Results of Bromo-formyl NMI

Comp.	Method	Reaction conditions	Solvent of crystall.	Yield %	M. P °C	Formula Mol. Wt.		Analysis % C	H	N	Br
16	b	NBS on 2-formyl-NMI	A—B (2 : 1)	45	73—74	$C_5H_5N_2OBr$ (188.97)	Calc'd	31.77	2.67	14.82	42.28
							Found	31.84	2.64	14.70	42.10
17	b	NBS on 5-formyl-NMI	C—B (2 : 1)	46	135	$C_5H_5N_2OBr$ (188.97)	Found	32.00	2.60	14.96	42.20
18	b	NBS on 4-formyl-NMI	A—B (2 : 1)	70	111	$C_5H_5N_2OBr$ (188.97)	Found	31.82	2.60	14.70	42.40
16	c	*n*-BuLi/DMF on 2,5-dibromo NMI	A—B (2 : 1)	57	73—74	$C_5H_5N_2OBr$ (188.97)	Found	31.79	2.58	14.73	42.31
19	c	*n*-BuLi/DMF on 4,5-dibromo NMI	A—B (2 : 1)	52	95—96	$C_5H_5N_2OBr$ (188.97)	Found	30.70	2.60	14.89	42.22
20	c	*n*-BuLi/DMF on 2,4,5-tribromo NMI	A—B (3 : 1)	60	167	$C_5H_4N_2OBr_2$ 267.87)	Calc'd	22.41	1.50	10.46	59.65
							Found	22.24	1.42	10.62	59.80

A: Benzene; B: Hexane; C: Methylene chloride.

TABLE IV

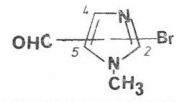
NMR Spectral Data of Formyl and Diethylacetal NMI Compounds



Compound	H_2		H_4		H_5		H_{CHO}		H_{Acetal}		CH_2		CH_3		N_{CH_3}	
	m/i	δ	m/i	δ	m/i	δ	m/i	δ	m/i	δ	m/i	δ	m/i	δ	m/i	δ
7	—	—	s/1	7.58	s/1	7.36	s/1	9.52	—	—	—	—	—	—	s/3	4.02
8	s/1	7.52	s/1	7.42	—	—	s/1	9.68	—	—	—	—	—	—	s/3	3.94
9	s/1	7.68	—	—	s/1	7.32	s/1	9.78	—	—	—	—	—	—	s/3	3.96
13	—	—	s/1	7.63	s/1	7.44	—	—	s/1	5.85	q/4	3.65	t/6	1.22	s/3	3.92
14	s/1	7.62	s/1	7.54	—	—	—	—	s/1	5.80	q/4	3.54	t/6	1.20	s/3	3.86
15	s/1	7.49	—	—	s/1	7.39	—	—	s/1	5.82	q/4	3.62	t/6	1.22	s/3	3.92

TABLE V

NMR Spectral Data of Bromo-formyl NMI Compounds



Compound	CHO	Br	H_2		H_4		H_5		H_{CHO}		N_{CH_3}	
			m/i	δ	m/i	δ	m/i	δ	m/i	δ	m/i	δ
16	2	5	—	—	s/1	7.26	—	—	s/1	9.54	s/3	4.01
17	5	2	—	—	s/1	7.68	—	—	s/1	9.58	s/3	3.96
18	4	5	s/1	7.65	—	—	—	—	s/1	9.82	s/3	3.69
19	2	4	—	—	—	—	s/1	7.26	s/1	9.76	s/3	4.02
20	2	4&5	—	—	—	—	—	—	s/1	9.68	s/3	3.96

m: multiplicity; i: intensity; s: singlet; d: doublet; t: triplet; q: quadriplet.

SAŽETAK

Sinteza novih formil halo *N*-metilimidazol derivata

M. El Borai, A. H. Moustafa, M. Anwar i A. G. Ghattas

Opisana su tri načina sinteze bromformil imidazola. Prvi se sastoji u prevođenju brom ili jod imidazola u dietilacetale i naknadnoj hidrolizi u formil derivate. U drugom načinu su bromiranjem formil imidazola s NBS dobiveni spojevi 16—18 u 45—70 postotnom iskorištenju. Treća metoda je direktno formiliranje brom imidazola s *n*-BuLi/DMF reagensom.

KEMIJSKI ODJEL
UNIVERZITET TANTA
i
UNIVERZITET AIN SHAMS
EGIPAT

Prispjelo 25. prosinca 1979.