Synthesis of Halogenated Hydrazone Derivatives and Their Applicability in the Preparation of 4-Chloropyrazoles

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Reaction of hydrazonic derivatives **1** with N-chlorosuccinimide affords monohalogenated hydrazones **3** with nearly quantitative yields. When **3** is treated with mineral acids or trifluoroacetic acid 4-chloropyrazoles are isolated.

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In previous papers we have reported the versatility of azadiene derivatives in the synthesis of pyrazoles [1,2]. On the other hand, *N*-chlorosuccinimide reacts with 4-amino-1-azabutadienes to yield halogenated azabutadienes which are precursors of 4-chloropyrazoles [3].

In our continuing interest in developing new routes to heterocyclic compounds we have studied the behavior of hydrazonic derivatives **1** [2] towards NCS and investigated the synthetic utility of the resulting products in the preparation of pyrazoles.

Hydrazonic derivatives **1** react with NCS **2** at room temperature in toluene to afford monohalogenated hydrazones **3** in high yields (Table 1). The halogenation is regiospecific and occurs at the Cβ-enamine carbon when stoicheiometric amounts of **1** and **2** are used.

Compounds **3** were characterized on the basis of their elemental analyses and spectral data. All of them display in their ir spectra a clear absorption at *ca.* 3400 cm^{-1} (NH). The ^{13}C-nmr spectra show one singlet centered at 96-100 ppm which is attributed to the sp^2 hybridized carbon atom linked to halogen. The behavior of compounds **3** towards acids was studied in order to obtain regiospecific 4-chloropyrazoles. Thus, heterocycles **4** are obtained when a solution of **3** in THF is treated with 4*N* sulfuric acid at room temperature. The formation of pyrazoles **4** can be rationalised in terms of the nucleophilic attack of the sp^2 hybridised nitrogen at the carbon-nitrogen double bond [2]. Compounds **4** are alternatively synthesized by halogenating pyrazoles **5** with NCS. (Scheme I).

On the other hand, when monohalogenated hydrazonic

Table 1

Monohalogenated Hydrazones **3** and 4-Chloropyrazoles **4** and **6**

Product	R	R'	Yield (%)	Mp (°C)
3a	H	*p*-$CH_3C_6H_4$	87	oil
3b	H	C_6H_5	75	95-97
3c	H	*p*-ClC_6H_4	80	119-121
3d	CH_3	*p*-$CH_3C_6H_4$	77	88-90
3e	CH_3	*p*-ClC_6H_4	70	114-115
4a	–	*p*-$CH_3C_6H_4$	68	139-141
4b	–	C_6H_5	75	105-107
4c	–	*p*-ClC_6H_4	66	138-140
6a	H	*p*-$CH_3C_6H_4$	85	oil
6b	H	C_6H_5	78	oil
6c	H	*p*-ClC_6H_4	80	oil
6d	CH_3	*p*-$CH_3C_6H_4$	85	oil

Scheme I

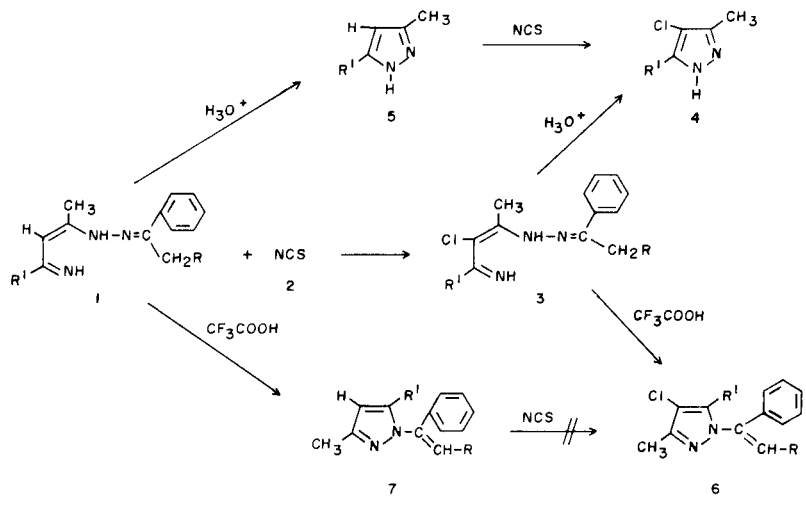


Table 2

^{13}C-NMR Spectral Data for Products **3**, **4** and **6** [a]

Product	*p*-CH_3	1-C	2-C	3-C	4-C	5-C	6-C	7-C
3a	21.90 (q)	17.94 (q)	152.80 (s)	100.11 (s)	167.54 (s)	158.84 (s)	15.58 (q)	
3b		16.95 (q)	151.08 (s)	99.48 (s)	166.15 (s)	157.93 (s)	14.68 (q)	
3c		17.10 (q)	149.81 (s)	99.98 (s)	166.10 (s)	158.42 (s)	14.93 (q)	
3d	20.99 (q)	16.99 (q)	151.27 (s)	99.30 (s)	166.25 (s)	162.59 (s)	21.50 (t)	11.03 (q)
3e		17.23 (q)	149.57 (s)	109.15 (s)	163.14 (s)	152.90 (s)	21.80 (t)	11.31 (q)
4a	21.15 (q)	9.86 (q)	143.48 (s)	105.99 (s)	141.76 (s)			
4b		9.60 (q)	143.66 (s)	106.54 (s)	141.48 (s)			
4c		9.68 (q)	146.22 (s)	106.64 (s)	143.08 (s)			
6a	20.56 (q)	10.90 (q)	144.63 (s)	108.64 (s)	145.86 (s)	112.07 (t)		
6b		11.16 (q)	145.09 (s)	107.24 (s)	146.36 (s)	112.20 (t)		
6c		10.95 (q)	144.68 (s)	109.17 (s)	146.15 (s)	112.25 (t)		
6d	20.41 (q)	10.70 (q)	139.23 (s)	108.14 (s)	144.91 (s)	124.56 (d)	13.26 (q)	

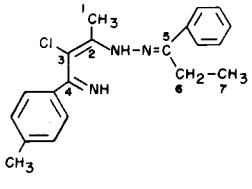
[a] δ From Internal TMS.

Numbering System for Products

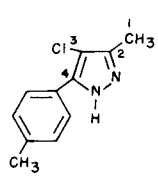
Table 3

Microanalytical, IR and ^{1}H-NMR Spectral Data for Compounds **3**, **4**, and **6**

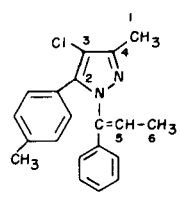
Compound	Formula	Molecular weight	Analyses Calcd. (Found) C	H	N	IR ν max (Nujol)/cm^{-1}	^{1}H-NMR (δ from TMS)
3a	$C_{19}H_{20}ClN_3$	325.85	70.03 (69.87)	6.19 (6.23)	12.90 (12.75)	3450 (NH) 1580 (CN)	2.3 (s, 9H), 7.8-8.0 (m, HAr, NH)
3b	$C_{18}H_{18}ClN_3$	311.82 M$^+$, 311	69.33 (69.37)	5.82 (5.89)	13.48 (13.46)	3450 (NH) 1590 (CN)	2.2 (s, 3H), 2.4 (s, 3H), 6.7-8.1 (m, HAr, NH)
3c	$C_{18}H_{17}Cl_2N_3$	346.27 M$^+$, 345	62.43 (62.40)	4.95 (4.50)	12.14 (12.20)	3480 (NH) 1590 (CN)	2.3 (s, 3H), 2.4 (s, 3H), 6.9-8.2 (m, HAr, NH)
3d	$C_{20}H_{22}ClN_3$	339.88	70.68 (70.66)	6.52 (6.49)	12.36 (12.31)	3450 (NH) 1590 (CN)	1.1 (t, 3H), 2.4 (m, 8H), 6.6-8.2 (m, HAr, NH)
3e	$C_{19}H_{19}Cl_2N_3$	360.30 M$^+$, 359	63.34 (63.36)	5.31 (5.33)	11.66 (11.69)	3460 (NH) 1590 (CN)	1.1 (t, 3H), 2.4 (s, 3H), 2.8 (q, 2H), 6.5-8.1 (m, HAr, NH)
4a	$C_{11}H_{11}ClN_2$	206.68	63.92 (63.88)	5.36 (5.33)	13.55 (13.59)	3200 (NH) 1600 (CN)	2.1 (s, 3H), 2.3 (s, 3H), 7.0-7.8 (m, HAr), 9.9 (m, 1H)
4b	$C_{10}H_9ClN_2$	192.65 M$^+$, 192	62.34 (62.37)	4.71 (4.71)	14.54 (14.60)	3200 (NH) 1590 (CN)	2.0 (s, 3H), 6.9-7.9 (m, HAr)
4c	$C_{10}H_8Cl_2N_2$	227.10 M$^+$, 226	52.89 (52.85)	3.55 (3.56)	12.34 (12.38)	3100 (NH) 1590 (CN)	2.2 (s, 3H), 7.1-7.9 (m, HAr), 9.3 (m, 1H)
6a	$C_{19}H_{17}ClN_2$	308.82	73.88 (73.85)	5.55 (5.35)	9.07 (9.17)	1650 (CN)	2.2 (s, 3H), 2.3 (s, 6H), 5.0 (s, 1H), 5.4 (s, 1H), 6.7-7.9 (m, HAr)
6b	$C_{18}H_{15}ClN_2$	294.81	73.33 (73.29)	5.13 (5.11)	9.59 (9.47)	1600 (CN)	2.2 (s, 3H), 5.6 (s, 1H), 5.4 (s, 1H), 6.9-7.5 (m, HAr)
6c	$C_{18}H_{14}Cl_2N_2$	329.24	65.67 (65.66)	4.29 (4.33)	8.51 (8.56)	1660 (CN)	2.2 (s, 3H), 5.1 (s, 1H), 5.5 (s, 1H), 6.9-7.5 (m, HAr)
6d	$C_{20}H_{19}ClN_2$	322.84 M$^+$, 322	74.41 (74.39)	5.93 (5.95)	8.53 (8.51)	1660 (CN)	1.7 (d, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 5.9 (q, 1H), 6.7-7.9 (m, HAr)



3d



4a



6d

derivatives **3** are treated with equimolecular amounts of anhydrous trifluoroacetic acid in dry THF, *N*-alkenyl-4-chloropyrazoles **6** are formed. The reaction is carried out at 50° and no traces of **4** are detected. In this case, pyrazoles **6** are not available from the corresponding unchlorinated *N*-alkenylpyrazoles **7** [4] and NCS.

The structure proposed for compounds **6** is fully consis-

tent with their elemental analyses and spectral data. Thus, ^{1}H-nmr spectra show two signals centered at δ 5.0 and 5.5 ppm (when R = H) corresponding to the non-cyclic enaminic hydrogens. In ^{13}C-nmr the cyclic and non cyclic β-enamine carbon atoms resonate at *ca.* 108 (singlet) and 112 (triplet, when R = H) ppm, respectively, thus centered in the typical enamine range [5].

Although, chlorination at position 4 in *N*-unsubstituted pyrazoles is readily achieved [6], the transformation of *N*-alkenylpyrazoles into *N*-alkenyl-4-chloropyrazoles is not a simple matter. On the other hand, the simplicity and regioselectivity of the procedure described herein, combined with the great availability of the starting materials, make this method a facile entry to 4-chloropyrazole derivatives.

EXPERIMENTAL

Melting points were taken on samples in open capillary tubes in a Buchi melting point apparatus and are uncorrected. The nmr spectra were obtained using a Varian FT-80 spectrometer using deuterated chloroform as solvent and shifts are reported in parts per million downfield (δ) from an internal tetramethylsilane (TMS) standard. Infrared spectra were recorded in nujol suspension on a Pye Unicam SP-1000 spectrophotometer. Microanalyses were performed on a Perkin-Elmer Model 240.

Preparation of Monohalogenated Hydrazonic Derivatives **3**. General Procedure.

N-Chlorosuccinimide (1.35 g, 10 mmoles) was added to a solution of **1** (10 mmoles) in toluene (60 ml) at room temperature. After being stirred for 5 hours, the mixture was poured into 3*N* potassium hydroxide and extracted with ether. The organic layer was dried (sodium sulfate), filtered and evaporated. The residue was purified by recrystallization from hot hexane/chloroform. Data for the products are given in Tables 1,2 and 3.

Synthesis of *N*-Unsubstituted-4-chloropyrazoles **4**. General Procedure.

To a solution of **3** (10 mmoles) in THF, 4*N* sulfuric acid (50 ml) was added and the solution stirred for 4 hours at room temperature. It was then poured into ice-water and extracted with ether. The dry organic layer was evaporated and the residue recrystallised from hot hexane. Data for products are given in the Table.

N-Alkenyl-4-chloropyrazoles **6**. General Procedure.

Trifluoroacetic acid (0.8 ml, 10 mmoles) was added to a solution of **3** (10 mmoles) in dry THF (40 ml) and the mixture heated at 50° for 15 hours. After cooling the solution was hydrolyzed with ice-water and extracted with ether. The organic layer was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvents, the residue was purified by column chromatography using CH_2Cl_2 as eluent. Data for products are given in the Table.

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