

α -Methyl Functionalization of Electron-Poor Heterocycles¹: Free Radical Chlorination

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We reported recently that α -methyl functionalization of 6,6'-dimethyl-2,2'-dipyridine gave 6,6'-bis[chloromethyl]-2,2'-dipyridine in high yield (65%) via a free radical reaction using *N*-chlorosuccinimide (NCS)². Our interest in halomethylpyridines stems from their diverse potential as pivotal starting compounds for the incorporation of pyridine as a sub-unit within polyfunctional ligands³ and macrocycles⁴. In addition to (di)pyridine, we have found that this same general procedure is capable of giving high yields of other substituted chloromethylpyridines through minor modification of reaction conditions. The utility of this one-step functionalization procedure is of timely value since it circumvents lengthy, albeit good overall yield, procedures commonly employed to obtain the same synthetic intermediates⁵⁻¹².

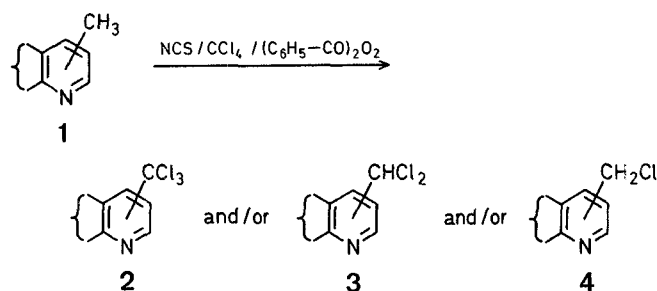
There are few literature examples which have dealt specifically with the free radical α -halogenation of side chain substituents in heterocyclic systems using NCS, as the chlorine source. In a report¹³ on the NCS chlorination of 2-methyl-, 2,5-dimethyl-, and 2,6-dimethyl-pyrazine, most of the intermediate chloro-compounds were not isolated due to their instability. Later, investigations of these dialkylpyrazines indicated that it is also possible to prepare 2,3-bis[chloromethyl]pyrazine in 75% yield by an analogous procedure¹⁴.

From our work in functionalizing methylpyridines by this method, we have found that there is an indirect but real relationship between the ease of chlorination and the electronic environment of the methyl substituent. For example, when 2,9-dimethyl-1,10-phenanthroline is treated with 6 equivalents of NCS, benzoyl peroxide, and refluxed for 4 hours in carbon tetrachloride, the 2,9-bis-trichloromethyl derivative

is obtained in quantitative yield^{15,16}. However, treatment of 6,6'-dimethyl-2,2'-dipyridine under identical conditions yields only a minor percentage of halogenated material none of which is the bis-trichloromethyl derivative. Further, dimethyl-dipyridine can be driven to the bis-dichloromethyl compound under only the most stringent conditions. As one might expect, such differences in reactivity are of paramount importance since the reactivity of the substituent will dictate the necessary conditions for product optimization.

We herein report a comparative evaluation of the NCS free radical chlorination procedure for a series of heterocyclic systems **1** to products **2** and/or **3** and/or **4** (Table). The reaction conditions were standardized for all substrates thereby enabling the establishment of general trends in the reactivity for the various heterocycles. These trends can be extended to

other heteroaromatics, which bear similarity to those reported herein, thus allowing one to predict conditions for product optimization.



Reagent grade compounds **1** are dried and distilled immediately prior to use.

Table. Free Radical Chlorination of Methyl-*N*-heteroarenes **1**

Reactant	Product(s)	Yield [%] ^a	m.p. [°C] or b.p. [°C]/torr	Molecular Formula ^b or Lit. Data	¹ H-N.M.R. (CDCl ₃ /TMS) ^c δ [ppm]	M.S. ^d <i>m/e</i> M ⁺ (%)
1a		20	55–57°/1	C ₆ H ₆ Cl ₂ N (127.6)	6.78 (s, 1H, CHCl ₂)	161 (51)
		25	39–42°/1	C ₆ H ₇ ClN (127.6)	4.64 (s, 2H, CH ₂ Cl)	127 (98)
1b		26	— ^e	C ₆ H ₆ ClN (127.6)	4.58 (s, 2H, CH ₂ Cl)	127 (20)
1c		16	58–60°/1	C ₇ H ₈ ClN (141.1)	2.37 (s, 3H, CH ₃); 4.63 (s, 2H, CH ₂ Cl)	141 (100)
		13	— ^e	C ₇ H ₆ Cl ₃ N (210.6)	2.66 (s, 3H, CH ₃)	209 (29)
		7	— ^e	C ₇ H ₅ Cl ₂ N (245.0)	4.68 (s, 2H, CH ₂ Cl)	243 (12)
		29	44–46°	C ₇ H ₇ Cl ₂ N (176.1)	4.60 (s, 2H, CH ₂ Cl); 4.68 (s, 2H, CH ₂ Cl)	175 (18)
1d		4	— ^e	C ₇ H ₆ Cl ₃ N (210.6)	4.71 (s, 2H, CH ₂ Cl); 6.77 (s, 1H, CHCl ₂)	209 (16)
		4	— ^e	C ₇ H ₆ Cl ₃ N (210.6)	4.62 (s, 2H, CH ₂ Cl); 6.75 (s, 1H, CHCl ₂)	209 (20)
		4	— ^e	C ₇ H ₇ Cl ₂ N (176.1)	4.60 (s, 2H, CH ₂ Cl); 4.68 (s, 2H, CH ₂ Cl)	175 (18)
1e		16	40–43°/1	C ₁₂ H ₁₂ ClN ₂ (242.1)	2.55 (s, 3H, CH ₃); 4.63 (s, 2H, CH ₂ Cl)	141 (100)
		33	73–75°	C ₁₂ H ₁₀ Cl ₂ N ₂ (274.1)	4.66 (s, 4H, CH ₂ Cl)	175 (100)
		12	— ^e	C ₁₂ H ₁₁ Cl ₂ N ₂ (274.1)	2.57 (s, 3H, CH ₃); 6.69 (s, 1H, CHCl ₂)	175 (10)
		14	— ^e	C ₁₂ H ₁₀ Cl ₃ N ₂ (306.1)	4.66 (s, 2H, CH ₂ Cl); 6.72 (s, 1H, CHCl ₂)	209 (15)

Table. (Continued)

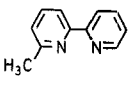
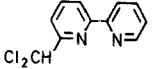
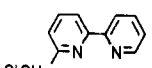
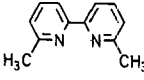
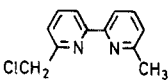
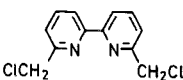
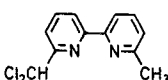
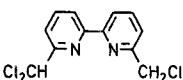
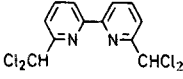

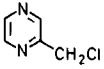
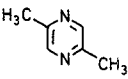
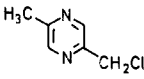

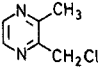
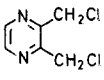
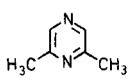
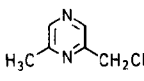
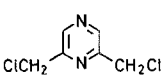
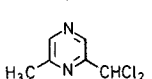
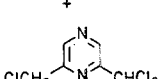
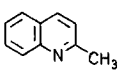
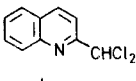
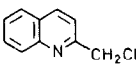



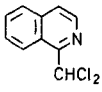
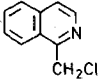
Reactant	Product(s)	Yield [%] ^a	m.p. [°C] or b.p. [°C]/torr	Molecular Formula ^b or Lit. Data	¹ H-N.M.R. (CDCl ₃ /TMS) ^c δ [ppm]	M.S. ^d m/e M ⁺ (%)
1f 		25	— ^e	not reported ²	6.83 (s, 1H, CHCl ₂)	240 (36)
		60	— ^e	not reported ²	4.75 (s, 2H, CH ₂ Cl)	204 (100)
1g 		37	63.5–65°	61–63° ²	2.63 (s, 3H, CH ₃); 4.75 (s, 2H, CH ₂ Cl)	218 (100)
		10	158–160°	157–158° ²	4.75 (s, 4H, CH ₂ Cl)	252 (100)
		6	63.5–65°	C ₁₂ H ₁₀ Cl ₂ N ₂ (253.3)	2.62 (s, 3H, CH ₃); 6.81 (s, 1H, CHCl ₂)	252 (72)
		6	93–95°	C ₁₂ H ₉ Cl ₃ N ₂ (287.7)	4.75 (s, 2H, CH ₂ Cl); 6.81 (s, 1H, CHCl ₂)	286 (62)
		1	115–117°	C ₁₂ H ₈ Cl ₄ N ₂ (322.1)	6.81 (s, 2H, CHCl ₂)	320 (30)
1h 		89	— ^e	not reported ^{13,18}	4.68 (s, 2H, CH ₂ Cl)	—
1i 		70	— ^e	not reported ^{13,19}	2.53 (s, 3H, CH ₃); 4.70 (s, 2H, CH ₂ Cl)	—
1j 		10	— ^e	not reported ^{14,19}	2.59 (s, 3H, CH ₃); 4.70 (s, 2H, CH ₂ Cl)	—
		60	— ^e	not reported ¹⁴	4.73 (s, 4H, CH ₂ Cl)	—
1k 		25	— ^e	not reported ¹⁹	2.65 (s, 3H, CH ₃); 4.68 (s, 2H, CH ₂ Cl)	—
		20	— ^e	not reported ¹³	4.70 (s, 4H, CH ₂ Cl)	—
		10	— ^e	C ₆ H ₆ Cl ₂ N ₂ (177.2)	2.61 (s, 3H, CH ₃); 6.73 (s, 1H, CHCl ₂)	180 (1)
		12	— ^e	C ₆ H ₅ Cl ₃ N ₂ (211.6)	4.75 (s, 2H, CH ₂ Cl); 6.78 (s, 1H, CHCl ₂)	—
1l 		12	79–81°	82–83° ^{12,20}	6.89 (s, 1H, CHCl ₂)	211 (37)
		36	52–54°	54–55° ^{12,20}	4.48 (s, 2H, CH ₂ Cl)	177 (1)
1m 		23	52–53°	C ₁₀ H ₈ ClN (177.7)	5.35 (s, 2H, CH ₂ Cl)	177 (58)

Table. (Continued)

Reactant	Product(s)	Yield [%] ^a	m.p. [°C] or b.p. [°C]/torr	Molecular Formula ^b or Lit. Data	¹ H-N.M.R. (CDCl ₃ /TMS) ^c δ [ppm]	M.S. ^d m/e M ⁺ (%)
1n 		20	— ^e	C ₁₀ H ₇ Cl ₂ N (212.1)	7.54 (s, 1H, CHCl ₂)	211 (52)
	+ 	38	65–66.5 ^o	C ₁₀ H ₈ ClN (177.7)	5.16 (s, 2H, CH ₂ Cl)	177 (100)

^a Yield of isolated product.^b Satisfactory microanalyses obtained: C ± 0.2, H ± 0.3, N ± 0.2).^c IBM NR-80 NMR spectrometer.^d Hewlett-Packard HP 5985 G.L.C./M.S.^e Product is too unstable for microanalysis and is immediately transformed to the stable dimethyl malonate derivative.**Free Radical Chlorination of Methyl-N-heteroarenes 1; General Procedure:**

A solution of the methyl-N-heteroarene **1** (10 mmol), N-chlorosuccinimide (1 equivalent per methyl group), and benzoyl peroxide (50 mg) in carbon tetrachloride (50 ml) is refluxed for 24 h under argon. The mixture is cooled in an ice bath, filtered, and the filtrate is concentrated in vacuum. The residue is subjected to preparative T.L.C. on silica gel using 5 : 1 cyclohexane/ethyl acetate to give the products (Table).

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