A One Step Synthesis of 4-Substituted Imidazoles. An Important Observation When *N*-Alkylating Imidazoles

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Imidazoles substituted in the 2-position with methyl, **1e**, phenyl, **1a**, 2-imidazole, **1b-d**, or *t*-butyldiphenylsilyl, **1f**, react with soft electrophiles **2** to give modest yields of 4(5)-*C*-alkylated-imidazoles **3** and *N*-alkylated products **5**. These two products are readily separated by flash chromatography.

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During our investigation of the chemistry and biology of novel imidazole derivatives [1], it was desired to have a short sequence to 4-alkylated-imidazoles **3**. *C*(4)-Alkylated-imidazoles are normally synthesized from natural products [2], by multiple step procedures [3], or by nonpreparative methods such as photolysis [4]. However, we have found that conditions which normally *N*-alkylate imidazoles [5] can predominantly *C*-alkylate to yield *C*-alkylated-imidazoles **3**. We believe this to be the first reported direct *C*(4)-alkylation of imidazole.

Direct carbon alkylation can occur in nitrogen heterocyclic systems with acidic NH groups, for instance indole, by generating their heterocyclic anions under basic conditions and subsequent reaction with suitable electrophiles [6]. This has not been observed with imidazoles [5], possibly due to the participation of *C*(2)-deprotonation in the transition stages. On blocking the 2-imidazole position we have made the important and unexpected observation that *C*(4)-alkylation can then occur under basic conditions as well as *N*-alkylation.

Treatment of 2-phenylimidazole (**1a**) with 3-thienylmethyl bromide (**2a**) [7] and sodium hydroxide yielded 45% of the mono-*C*-alkylated-4-(3-thienylmethyl)-2-phenylimidazole **3a**, 26% of the di-*C*-alkylated-4,5-bis-(3-thienylmethyl)-phenylimidazole **4a** [8] with only a trace of *N*-alkylated-imidazole **5a** (4%) (Table 1). Similarly 3-thienylmethyl bromide and 2,2'-bi-1*H*-imidazole **1b** [1e] yielded 34% of the 4-alkylated-2,2'-bi-1*H*-imidazole **3b** with a small amount of *N*-alkylation (Table 1).

The nature of the electrophile strongly influenced the reaction [9]. The harder electrophile benzyl bromide gave mainly *N*-alkylation on reaction with 2,2'-bi-1*H*-imidazole, and *C*-alkylation as a secondary product **3d**. However, the softer electrophile 4-methoxybenzyl chloride again gives mainly *C*-alkylation, **3c**, (Table 1).

As it was desired to have 4-alkylated-imidazoles with no *N*- or *C*(2)-substitution we synthesized the previously uncharacterized 2-*t*-butyldiphenylsilylimidazole **1f** as a crystalline stable *C*(2)-blocked imidazole. On treatment of **1f** with ethylmagnesium bromide and 4-methoxybenzyl chloride, 29% of the 4-substituted imidazole **3f** was isolated along with 21% of the *N*-alkylated product **5f**. Thus the use of the removable *t*-butyldiphenylsilyl group allows entry into a wide variety of *C*(4)-alkylated-imidazoles with or without *C*(2)-substituents.

The *C*- and *N*-alkylated-imidazoles have distinctive spectra. The ^{1}H nmr shifts for the methylene protons are consistently downfield for the *N*-alkylated-imidazoles. Also the mass spectra (ei) show characteristic fragmentation patterns. For the *N*-alkylated-imidazoles, the alkyl frag-

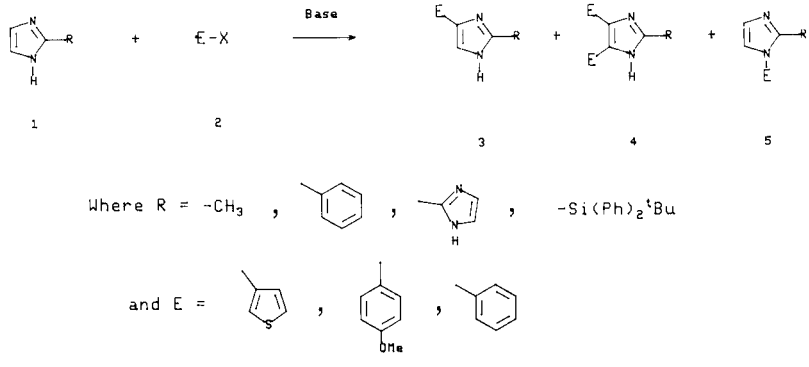

Table 1

Starting Material 1 R	Electrophile 2 EX	Product	Yield	MP °C	Molecular Analysis % Calcd./(Found) Formula	C	H	N
		3a	45% [a]	166-168	$C_{14}H_{12}N_2S$	69.97 (69.83)	5.03 (5.13)	11.66 (11.58)
phenyl	3-thienyl bromide	**4a**	26% [a]	163-165	$C_{19}H_{16}N_2S_2$	67.82 (67.60)	4.79 (4.85)	8.32 (8.35)
		5a	4%	180-184	$C_{14}H_{12}N_2S$	69.97 (69.77)	5.03 (4.98)	11.66 (11.38)
		3b	34% [g] [a]	225-226	$C_{11}H_{10}N_4S$	57.37 (56.82)	4.38 (4.39)	24.33 (24.12)
2-1*H*-imidazole	3-thienyl bromide	**5b**	7% (2%) [c] [a]	140-142	$C_{11}H_{10}N_4S$	57.37 (57.67)	4.38 (4.47)	24.33 (24.38)
		3c	31% [b]	204-205	$C_{14}H_{14}N_4O$	66.13 (66.03)	5.55 (5.65)	22.03 (21.73)
	4-methoxybenzyl chloride	**5c**	20% [b]	138-140	$C_{14}H_{14}N_4O$	66.13 (66.23)	5.55 (5.45)	22.03 (21.83)
		3d	16% [a]	208-210	$C_{13}H_{12}N_4$	69.62 (69.67)	5.39 (5.54)	24.99 (24.68)
	benzyl bromide	**5d**	23% (17%) [c] [a]	138-140	$C_{13}H_{12}N_4$	69.62 (70.00)	5.39 (5.49)	24.99 (24.66)
		3e	8% [a]	oil [d]	–	–	–	–
2-methyl	benzyl bromide	**5e**	20% [a]	oil [e]	–	–	–	–

[a] From toluene/hexane. [b] From toluene. [c] % Di-*N*-alkylated. [d] Reference [12]. [e] Reference [13]. [f] From ethanol. [g] Exact mass m/z Found: 230.0626; Calcd. for $C_{11}H_{10}N_4S$: 230.0628.

ment ion has a relative ion intensity near 100%, whereas in the *C*-alkylated compounds this fragment ion has a much lower intensity [10]. As an example the ^{1}H nmr spectrum of 4-benzyl-2,2′-bi-1*H*-imidazole **3d**, the methylene singlet is observed at δ 3.94, whereas for *N*-benzyl-2,2′-bi-1*H*-imidazole **5d** the methylene singlet is observed at δ 5.84. In the mass spectrum of the *N*-benzylated product **5d**, the benzyl ion (m/z 91) is the base peak whereas in the *C*-benzylated product **3d** the base peak is m/z 147 ($M^{+\cdot}$ -C6H5·) and the benzyl ion is 33% of the base peak.

In summary novel 4-alkylated-imidazoles with or without 2-substitution can be readily formed from soft electrophiles. This reaction should be of interest not only as the first reported direct C(4)-alkylation of imidazoles, but also should be borne in mind when *N*-alkylating imidazoles as *C*-alkylation could occur.

EXPERIMENTAL

Proton magnetic resonance (^{1}H nmr) spectra were recorded on a Varian EM-360 (60 MHz) spectrometer. All chemical shifts were reported in ppm (δ) from tetramethylsilane as an internal standard. Low-resolution mass spectra were recorded on a Finnigan 4500 GC/MS/ spectrometer. Infrared spectra were recorded on a Perkin-Elmer 710-B spectrophotometer using samples in potassium bromide pellets. Recrystallization solvents, mp and yields are given in Table 1.

Representative Example of the *C*-Alkylation of 2-Substituted Imidazoles **1** by Electrophiles **2**. The Synthesis of 2-Phenyl-4-(3-thienylmethyl)-1H-imidazole (**3a**).

A mixture of 2-phenylimidazole (**1a**) (7.2 g, 0.05 mole), 12 ml 5*M* sodium hydroxide and 100 ml of ethanol was refluxed for 1 hour. After cooling to room temperature, 3-thienyl bromide (7.1 g, 0.04 mole) was added and the reaction again heated to reflux. After 24 hours, the reaction was cooled and concentrated to give 23 g of a brown residue. The products were separated by flash chromatography (10% acetone/dichloromethane) to yield 2.6 g of **4a** (26%), 3.1 g of **3a** (45%), 0.3 g of **5a** (4%) and 2.3 g of **1a** (31%).

Compound **3a**.

This compound had ir: 3100 br cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.90 (s, 2H), 6.85-7.96 (m, 9H), 12.37 (br s, 1H); ms: (ei at 70 eV) m/z 240 (100) ($M^{+\cdot}$), 157 (9), 136 (62), 97 (8).

Compound **4a**.

This compound had ir: 3100 br cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.88 (s, 4H), 6.93-7.98 (m, 11H), 12.20 (br s, 1H); ms: (ei at 70 eV) m/z 336 (87) ($M^{+\cdot}$), 239 (50), 97 (100).

Compound **5a**.

This compound had ^{1}H nmr (DMSO-d$_6$); δ 5.42 (s, 2H), 6.95-7.90 (m, 10H); ms: (ei at 70 eV) m/z 240 (53) ($M^{+\cdot}$), 157 (1), 136 (2), 97 (100).

Compound **3b**.

This compound had ^{1}H nmr (DMSO-d_6): δ 3.90 (s, 2H), 6.75-7.50 (m, 6H); ms: (ei at 70 eV) m/z 230 (100) ($M^{+\cdot}$), 147 (27), 97 (10).

Compound **5b**.

This compound had ^{1}H nmr (DMSO-d_6): δ 5.85 (s, 2H), 7.02-7.48 (m, 7H); ms: (ei at 70 eV) m/z 230 (100) ($M^{+\cdot}$), 147 (18), 97 (98).

Compound **3c**.

This compound had ^{1}H nmr (DMSO-d_6): δ 3.71 (s, 3H), 3.95 (s, 2H), 6.77-7.26 (m, 7H); ms: (ei at 70 eV) m/z 254 (45) ($M^{+\cdot}$), 147 (100), 121 (81).

Compound **5c**.

This compound had ^{1}H nmr (DMSO-d_6): δ 3.75 (s, 3H), 5.85 (s, 2H), 6.71-7.43 (m, 8H); ms: (ei at 70 eV) m/z 254 (6) ($M^{+\cdot}$), 147 (3), 121 (100).

Compound **3d**.

This compound had ^{1}H nmr (DMSO-d_6): δ 3.94 (s, 2H), 6.81-7.34 (m, 8H); ms: (ei at 70 eV) m/z 224 (30) ($M^{+\cdot}$) 147 (100), 91 (33), 77 (44).

Compound **5d**.

This compound had ^{1}H nmr (DMSO-d_6): δ 5.84 (s, 2H), 6.99-7.28 (m, 9H); ms: (ei at 70 eV) m/z 224 (13) ($M^{+\cdot}$), 147 (40), 91 (100), 77 (9).

Compound **5e**.

The dibenzylated material had mp 132-134°; ms: (ei at 70 eV); m/z 314 (41) ($M^{+\cdot}$), 237 (23), 223 (69), 91 (100).

2-Methyl-4-phenylmethyl-1*H*-imidazole (**3e**) and 2-Methyl-1-phenylmethyl-1*H*-imidazole (**5e**).

2-(*t*-Butyldiphenylsilyl)-1*H*-imidazole (**1f**).

A solution of 1-diethoxymethylimidazole [11] (8.5 g, 0.05 mole) in 100 ml of THF was cooled to −40° and 44 ml of 1.13 *M* *n*-butyllithium was added. After 15 minutes *t*-butyldiphenylsilyl chloride (15.1 g, 0.055 mole) was added. The reaction was stirred for 24 hours and then 25.0 g of flash silica gel was added and the resulting mixture stirred for a further 4 hours. The mixture was poured directly onto a flash column and eluted with ethyl acetate to yield as a white solid (12.6 g 82%), (6): mp 170° (waxes), (toluene); ^{1}H nmr (carbon tetrachloride) δ 0.86 (s, 9H), 6.8-7.8 (br m, 12H); ms: (ei at 70 eV) m/z 307 (1) ($M^{+\cdot}$).

Anal. Calcd. for $C_{19}H_{22}N_2Si$: C, 74.46; H, 7.23; N, 9.14. Found: C, 74.35; H, 7.38; N, 8.91.

2-(*t*-Butyldiphenylsilyl)-4-(4-methoxybenzyl)-1*H*-imidazole (**3f**).

A solution of 2-(*t*-butyldiphenylsilyl)-1*H*-imidazole (**1f**) (4.0 g 0.013 mole) in 20 ml of dry tetrahydrofuran was cooled with an external water bath and 4.56 ml of 3.0 *M* ethylmagnesium bromide added dropwise over 5 minutes. The reaction was stirred for 0.5 hour at room temperature then 4-methoxybenzyl chloride (2.2 g, 0.014 mole) was added. The resulting mixture was refluxed for 4 hours then quenched with 100 ml water. The aqueous mixture was then extracted with ethyl acetate (3 x 100 ml). The extracts were combined, dried (magnesium sulfate), and evaporated. The residue was subjected to flash chromatography on silica gel (100 g) using a 5:1 mixture of hexane/ethyl acetate to give **3f** (1.6 g 29%); ^{1}H nmr (deuteriochloroform): δ 0.95 (s, 9H), 3.7 (s, 3H), 4.4 (s, 2H), 6.5-8.0 (bm, 15H); ms: (ei at 70 eV) m/z 426 (13) ($M^{+\cdot}$), 369 (100), 249 (60); hrms: (ei at 70 eV) exact mass m/z Found: 426.2123; Calcd. for $C_{27}H_{30}N_2OSi$: 426.2127; **5f** (1.1 g, 21%); ^{1}H nmr (deuteriochloroform): δ 0.95 (s, 9H), 3.7 (s, 3H), 3.9 (bs, 2H), 6.0-7.5 (bm, 15H); ms: (ei at 70 eV) m/z 426 (5) ($M^{+\cdot}$), 369 (60), 249 (100); hrms: (ei at 70 eV) exact mass m/z Found: 426.2132; Calcd. for $C_{27}H_{30}N_2OSi$: 426.2127.

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