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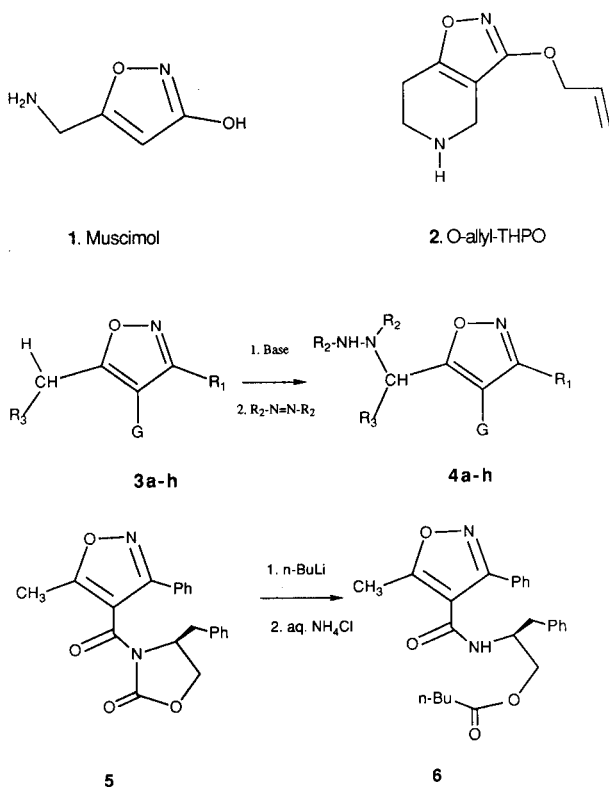
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C-5 Lithio-alkylisoxazoles were quenched with dialkyl azodicarboxylates to form the C-5 alkylhydrazine derivatives in synthetically useful yields.

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Isoxazoles functionalized with an additional nitrogen containing group have seen application [1], notably in the area of geriatric memory dysfunction. For example, muscimol (**1**), an isoxazole derivative with an aminomethylene functional group in the C-5 position, represents a rigid structural analog of gamma amino butyric acid (GABA) [2,3], can pass the blood-brain barrier and exert a profound effect on the central nervous system [4]. Tetrahydropyridine (THP) fused isoxazoles, such as *O*-allyl-THPO (**2**), are currently under investigation as agents for the treatment of Alzheimer's disease [5].

#### Schemes



The lateral metalation of isoxazoles is a useful tactic for the regioselective introduction of electrophiles in the C-5

position of functionally complex isoxazole derivatives [6,7]. Previous workers have reported that enolates of active methylene groups [8] and chiral carboximides [9,10,11] can be used as nucleophiles with dialkylazodicarboxylates [12]. We now report that the quenching of the lithio-vinyllogous imidates, produced by selective lateral metalation of **3**, with dialkylazodicarboxylates produces 5-alkylhydrazine derivatives **4** in excellent yield, and represents a synthetically useful tactic for the direct introduction of nitrogen electrophiles in functionally complex systems of potential biological relevance.

The typical experimental procedure is mild and convenient. Metalation was accomplished at  $-78^{\circ}$ , followed by treatment at low temperature with one equivalent of diazodicarboxylate for a few minutes, after aqueous work up and purification by chromatography (Table 1) the products **4** were obtained as viscous oils or glasses, which are stable at or below room temperature under a nitrogen atmosphere. Attempted distillation, however, produced oligomeric by-products, as evidenced by mass spectrometry, presumably by intermolecular acyl-transfer processes. The characterization data is given in Tables 1, 2, and 3. The thermal lability of the products **4**, precluded the removal of the last traces of chromatography solvent in some cases, thus, several products were characterized by high resolution mass spectrometry. The yields, after isolation and purification to homogeneity, were uniformly excellent, for both isoxazole (Table 1, Entries **4a-d**) and tertiary amide (Table 1, Entries **4e-h**) groups in the C-4 position. This is in contrast to the usual situation with alkyl halides and aldehyde electrophiles, for which the tertiary amide G groups normally give only moderate yields compared to the oxazoline [7e]. A limitation was found for the 3-phenyl-4-carboximide **5**, in which the *n*-butyllithium attacked the oxazolidone carbonyl to produce the pentanoate ester **6**.

Thus, the lateral metalation and electrophilic quenching of C-4 functionalized isoxazoles with dialkylazodicarboxylates proceeds under mild and convenient conditions, to produce synthetically useful yields of isoxazole

Table 1  
Characterization Data for Dialkyl Azodicarboxylate-quenched Isoxazoles 4

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	G	Yield (%)	tlc, silica gel R <sub>f</sub> (solvent)	Empirical Formula	Mass Spectrum [g] m/e(%)	Exact Mass or Elemental Analysis Found(Calcd.)		
									C	H	N
4a	Me	-CO <sub>2</sub> Et	H	[a]	75	0.5 (hexane-ethyl acetate, 1.4:1)	C <sub>16</sub> H <sub>24</sub> N <sub>4</sub> O <sub>6</sub>	369 (100)	368.1695 (368.1695) [i]		
4b	Ph	-CO <sub>2</sub> Et	H	[a]	80	0.3 (hexane-ethyl acetate, 1.4:1)	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	431 (100)	430.1853 (430.1852) [i]		
4c	Ph	-CO <sub>2</sub> Et	H	[b]	95	0.4 (ethyl acetate-hexane, 1:1)	C <sub>27</sub> H <sub>30</sub> N <sub>4</sub> O <sub>7</sub>	523 (100)	62.23 (62.06)	5.79 (5.78)	10.92 (10.72)
4d	Me	-CO <sub>2</sub> Et	H	[b]	74	0.39 (ethyl acetate-hexane, 1:1)	C <sub>22</sub> H <sub>28</sub> N <sub>4</sub> O <sub>7</sub>	461 (100)	57.44 (57.38)	6.07 (6.13)	12.24 (12.17)
4e	Me	-CO <sub>2</sub> Et	H	[c]	96	0.23 (hexane-ethanol, 6:1)	C <sub>18</sub> H <sub>30</sub> N <sub>4</sub> O <sub>6</sub>	399 (100)	399.2236 (399.2243)		
4f	Me	-CO <sub>2</sub> Et	H	[d]	78	0.25 (hexane-ethyl acetate-ethanol, 6:1:2)	C <sub>17</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	399 (100)	51.14 (51.24)	6.73 (6.58)	13.83 (14.06)
4g	Me	-CO <sub>2</sub> t-Bu	H	[c]	81	0.53 (hexane-ethyl acetate-ethanol, 5:2:0.2)	C <sub>22</sub> H <sub>38</sub> N <sub>4</sub> O <sub>6</sub>	455 (14.51) [h]	455.2870 (455.2869) [g] 57.60 8.41 12.46 (58.13) (8.42) (12.32)		
4h	Me	-CO <sub>2</sub> Et	H	[c]	84	0.39 (hexane-ethanol, 3:1)	C <sub>18</sub> H <sub>29</sub> N <sub>4</sub> O <sub>7</sub>	413 (100)	55.57 (55.33)	8.06 (7.82)	13.31 (13.58)
5	Ph-	...	H	[e]	83	0.13 (hexane-methylene chloride-ethyl acetate, 6:4:1) m.p. 130-132)	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	362 (22.4) [i]	69.54 (69.60)	4.92 (5.01)	7.78 (7.73)
6	Ph-	...	H	[f]	56	0.08 (hexane-methylene chloride-ethyl acetate, 6:4:1)	C <sub>25</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub>	421 (35) 319 (100, M-BuCO <sub>2</sub> H) [g]	421.2135 (421.2127) [g]		

[a] 4-[4',4'-Dimethyl- $\Delta^2$ -oxazoline]-. [b] 4-[4'S-Methoxymethyl-5'S-phenyl- $\Delta^2$ -oxazoline]-. [c] 4-[N,N-Diisopropyl]carboxamide-. [d] 4-Carboxamide of (S)-prolinol. [e] 4-[Oxazolidone]-. [f] 4-Carboxamide-. [g] Chemical ionization, corresponding to [M+1]<sup>+</sup>, unless otherwise noted. [h] Fast Atom Bombardment, corresponding to [M+1]<sup>+</sup>. [i] Electron Impact, 70 EV, corresponding to [M]<sup>+</sup>.

C-5 alkylhydrazine derivatives **4**. The method tolerates amide and oxazoline functional groups conjugated with the isoxazole, and provides a direct entry to a new class of vinylogous hydrazino acid functional equivalents.

We continue to explore the utility and scope of the lateral metalation of isoxazoles, and we will report on our progress in due course.

## EXPERIMENTAL

General Procedure for the Reaction of Isoxazoles **3** with Dialkyl-diazocarboxylates. Preparation of 5-[N,N'-Diethylformyl]hydrazinomethyl-4-(2'-[4'S-methoxymethyl-5'S-phenyl]- $\Delta^2$ -oxazoliny)-3-phenylisoxazole (**4c**).

All of these reactions were carried out under a nitrogen atmos-

Table 2  
Infrared and Proton NMR Spectroscopic Data for Compounds in Table 1

Entry	IR, cm <sup>-1</sup>	<sup>1</sup> H NMR, deuteriochloroform
4a	3298 (N-H), 1724 (C=O) 1678 (C=O)	4.95 (s, 2H, N-CH <sub>2</sub> -), 4.1 (m, 4H, CH <sub>2</sub> -O), 3.96 (s, 2H, oxazoline CH <sub>2</sub> -O), 2.31 (s, 3H, isoxazole C-3 CH <sub>3</sub> ), 1.22 (s, 6H, oxazoline gem CH <sub>3</sub> 's), 1.1 (m, 6H, CH <sub>3</sub> )
4b	3298 (N-H), 1740 (C=O) 1713 (C=O), 1612	7.66 (m, 2H, Ar-H), 7.44 (m, 3H, Ar-H), 5.07 (s, 2H, N-CH <sub>2</sub> ), 4.2 (m, 4H, CH <sub>2</sub> -O), 3.91 (s, 2H, oxazoline CH <sub>2</sub> -O), 1.33 (s, 6H, oxazoline gem CH <sub>3</sub> 's), 1.22 (m, 6H, CH <sub>3</sub> )
4c	3291 (N-H), 1720 (C=O) 1678 (C=O)	7.79 (br s, 1H), 7.1-7.6 (m, 10H, Ar-H), 5.38 (d, 1H), 5.13 (br s, 2H), 4.39 (br s, 1H), 4.17 (q, 4H), 3.64 (m, 2H), 3.46 (s, 3H, OCH <sub>3</sub> ), 1.23 (t, 6H)
4d	3290 (N-H), 1743 (C=O) 1722 (C=O), 1676 (oxazoline)	7.62 (br s, 1H), 7.3-7.4 (m, 5H, Ar-H), 5.41 (d, 1H), 5.1 (br s, 2H), 4.27 (m, 1H), 4.17 (q, 4H), 3.65 (m, 2H), 3.45 (s, 3H, OCH <sub>3</sub> ), 2.48 (s, 3H, isoxazole C-3 CH <sub>3</sub> ), 1.24 (t, 6H)
4e	3291 (N-H), 1740 (C=O) 1721 (C=O), 1624 (amide)	7.78 (br s, 1H), 5.31 (br s, 2H), 4.18 (q, 4H), 3.63 (br s, 1H), 2.28 (s, 3H), 1.46 (br s, 6H), 1.23-1.36 (m, 6H), 1.16 (br s, 6H)
4f	3434 (O-H), 3283 (N-H) 1721 (C=O), 1616 (amide)	7.9 (br s, 1H), 4.89 (m, 2H), 4.36 (br s, 2H), 4.17 (q, 4H), 3.88 (br s, 1H), 3.63 (br s, 1H), 3.35 (m, 2H), 2.6 (s, 1H), 2.32 (s, 3H), 1.8-2.1 (m, 4H), 1.26 (t, 6H)
4g	3290 (N-H), 1746 (C=O) 1726 (C=O), 1626 (amide)	7.3 (br s, 1H), 5.2 (br s, 2H), 3.7 (br s, 2H), 2.25 (s, 3H), 1.1-1.5 (m, 30H)
4h	3282 (N-H), 1749 (C=O) 1713 (C=O), 1678 (amide)	7.69 (br s, 1H), 5.74 (br s, 1H), 4.17 (m, 4H), 3.43 (br s, 1H), 3.49 (m, 1H), 2.27 (s, 3H), 1.62 (d, 3H), 1.47 (dd, 6H), 1.28 (t, 6H), 1.16 (dd, 6H)
5	1807 (oxazolidone), 1687 (C=O)	7.1-7.6 (m, 10H, Ar-H), 4.3 (m, 1H, N-CH-), 4.0 (d, 2H, CH <sub>2</sub> -O), 3.5 (dd, 1H, Ph-CH-, J = 2, 12 Hz), 2.6 (m, 1H, Ph-CH-), 2.0 (s, 3H, isoxazole C-5 CH <sub>3</sub> )
6	1730 (ester), 1649 (C=O)	7.6 (br s, 5H, Ar-H), 7.1-7.4 (m, 5H, Ar-H), 5.75 (br d, 1H, N-H), 4.7 (m, 1H, N-CH), 4.0 (d, 2H, J = 7 Hz, CH <sub>2</sub> -O), 2.85 (d, 2H, J = 8 Hz, PhCH <sub>2</sub> -), 2.8 (s, 3H, isoxazole C-5 CH <sub>3</sub> ), 2.3 (t, 2H, J = 7 Hz, CO-CH <sub>2</sub> -), 1.3-1.7 (m, 4H, -(CH <sub>2</sub> ) <sub>2</sub> -), 1.0 (t, 3H, J = 7 Hz, CH <sub>3</sub> )

phere. To a stirred and cooled ( $-78^{\circ}$ ) solution of isoxazole **4c** (304 mg, 0.87 mmole) in dry THF (8 ml), *n*-butyllithium (0.42 ml of a 2.26 M solution in hexanes) was added dropwise. After two hours at that temperature, a precooled solution of diethyl azodicarboxylate (0.165 ml, 1 mmole) in THF (2 ml) was added. After a reaction time of two hours, glacial acetic acid was added (0.11 ml), and the reaction mixture concentrated *in vacuo*. To the residue was added methylene chloride (10 ml), and the resulting mixture was washed with aqueous sodium bicarbonate (2 x 50 ml). The aqueous layers were back extracted with methylene chloride (2 x 30 ml), and the combined organic layers washed with water (250 ml) and dried over anhydrous sodium sulfate. Filtration and concentration produced a yellow viscous oil, which was purified by preparative tlc (conditions as shown in Table 1) to give the product **4c** (432 mg, 95%). The characterization data is presented in Tables 1-3.

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Table 3  
<sup>13</sup>C NMR (Deuteriochloroform/tetramethylsilane)

Entry	C-3	C-4	C-5	Lateral CH	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	G	ref
3a	155.7	105.7	159.3	12.7	11.5	...	...	171.3 78.0 67.1 28.2	[7f]
4a	155.25	107.1	159.66	46.55	11.64	155.79 155.61 61.99 14.38	...	168.96 67.53 62.94 28.27	[a]
3b	154.8	104.5	160.6	11.9	129.4 128.9 128.1 127.3	...	...	171.98 77.6 27.4	[7f]
4b	154.71	106.27	155.25	45.48	129.34 128.14 127.66	160.91 155.13 61.27 13.78	...	169.31 67.23 62.29 27.37	[a]
4c	154.7	105.31	156.35	45.68	129.0 127.84 127.46 127.26	161.00 62.08 61.13 13.5	...	169.48, 138.84 128.14, 127.68 124.72, 82.86 73.44, 72.67 58.33 (-OCH <sub>3</sub> )	[a] [13]
4d	154.66	105.4	156.45	46.8	13.14	158.82 61.97 61.07 14.52	...	168.95, 139.3 128.516, 127.45 124.5, 82.19 73.22, 72.39 58.37	[a]
4e	154.08	113.57	155.22	50.73	9.19	161.74 156.51 62.07 60.91 13.43, 13.33	...	163.35 45.42, 44.95 44.61 19.98, 19.18 18.8	[a]
3f	164.06	113.5	167.17	12.14	10.10	...	...	157.85(amide) 65.7, 60.47 49.46 28.03, 24.6	[7b]
4f	161.81	113.65	163.81	44.55	9.09	156.97 62.96 62.03 13.21	...	155.42 60.89, 59.06 48.44, 26.62 23.41	[a]
4g	153.23	114.08	153.78	50.51	9.17	162.08 156.55 81.09 80.16 27.28 27.08	...	163.9 45.33, 44.7 19.94	[a]
4h	154.6	112.92	155.54	50.78	9.28	162.13 156.79 61.89 60.91 13.55 13.33	13.03	166.1 45.49 27.1, 20.31 19.96, 19.22	[a]

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