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The 10-halo (Cl or Br) anthracene-9-nitrile oxides (**1a,b**) were obtained directly from the treatment of 9-anthracenylaldoxime with *N*-halosuccinimide (NCS or NBS) in DMF. The 3-(10'-halo-9'-anthracenyl)-5-isoxazolecarboxylic esters (**5a,b** and **6a,b**) were prepared *via* 1,3-dipolar cycloaddition between the obtained nitrile oxides **1a** (or **1b**) and two different dipolarophiles: ethyl β-pyrrolidinocrotonate (an enamine of ethyl acetoacetate) or dimethyl acetylenedicarboxylate (DMAD) respectively. The 10 (or 10')- position of the anthracene in either anthracene-9-nitrile oxide or 3-(9'-anthracenyl) isoxazole molecules (**3,4**) is readily halogenated by *N*-halosuccinimide in DMF. X-ray studies showed that **5a** possesses two aromatic ring systems that lie at 74.4° from coplanarity. The bond linking the two ring systems is 1.4893(18) Å, indicating only partial conjugation between the two ring systems. The crystal lattice showed unique head-to-tail intermolecular stacking of anthracene rings.

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Introduction.

Our work on the preparation of anti-tumor DNA-binding lexitropsin molecules [1] included ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate [2], an intercalating isoxazole molecule, of which the anthracene ring was assumed to be able to intercalate between DNA base pairs. The halogenated intercalating molecules may show special clinical importance, since halogenated anti-tumor B-DNA intercalators such as iododoxorubincin [3] have demonstrated significantly reduced levels of cardiotoxicity in comparison with currently employed anthracyclines [4,5]. Studies on iododoxorubincin's interaction with DNA indicate that the existence of a halogen atom in the DNA minor grooves affects the hydration of the drug-DNA complex [3].

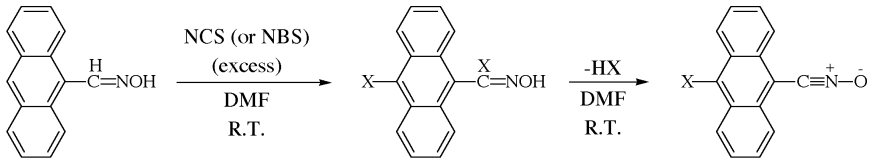
Telomerase, which is activated especially in most tumor cells, is believed to help tumor cells to replicate indefinitely [6]. The formation and stabilization of telomeric G-quadruplex DNA structures have been demonstrated to inhibit telomerase [7]. In our recent studies on the design and synthesis of a novel class of G-quadruplex DNA ligands, dimethyl 3-(9'-anthracenyl)-4,5-isoxazoledicarboxylate (**4**) was introduced as a new scaffold for a series of G-quadruplex DNA binding agents [8]. In order to further elaborate an aryl or alkyl substituent on the 10-position of anthracene ring, a halogen atom has to be added to this position, followed by a highly efficient catalytic Suzuki coupling reaction [9] or Stille reaction [10]. Therefore, we sought the 10-halogenated anthracenyl isoxazole derivatives for their intrinsic biological activity, as well as for their usefulness in future development of the Structure Activity Relationship (SAR) for potential anti-cancer agents.

Results and Discussion.

The 3-(10'-halo-9'-anthracenyl)-5-methyl isoxazolecarboxylic esters were prepared *via* 1,3-dipolar cycloaddition between 10-haloanthracene-9-nitrile oxide and dipolarophiles (DMAD or the enamine of ethyl acetoacetate). The anthracene-9-nitrile oxide was first studied in mid-1960's and is considered to be a relatively stable intermediate [11]. A great number of efforts have been made to optimize the formation of aryl nitrile oxides, including Liu's method [12], in which *N*-chlorosuccinimide (NCS) in DMF was used to generate aryl hydroximoyl chloride, the precursor of aryl nitrile oxide. In our study, the expected 9-anthracenyl hydroximoyl chloride was not detected when 9-anthraldehyde oxime was treated with NCS (1 eq) in DMF. Instead anthracene-9-nitrile oxide was obtained directly [6] as the oxidation product of 9-anthraldehyde oxime. It was suggested that a spontaneous elimination of hydrogen chloride occurs after the formation of the hydroximoyl chloride *via* electrophilic substitution in NCS-DMF system. In the studies of this paper, treatment of 9-anthraldehyde oxime with excessive NCS in DMF gave 10-chloroanthracene-9-nitrile oxide (1a). The nitrile oxide moiety formed directly and a chlorine atom was added to the 10-position of anthracene. Similarly, treatment of 9-anthraldehyde oxime with excessive NBS in DMF afforded 10-bromo-9-anthracenyl nitrile oxide (1b). *N*-Halosuccinimide-DMF has been recognized as a convenient system for the electrophilic halogenation [13] and oxidation towards the formation of nitrile oxide [14]. It was therefore believed that NCS (or NBS) serves as a strong electrophilic source and induces the formation of anthracene-9-nitrile oxides in non-protonic polar solvent like DMF.

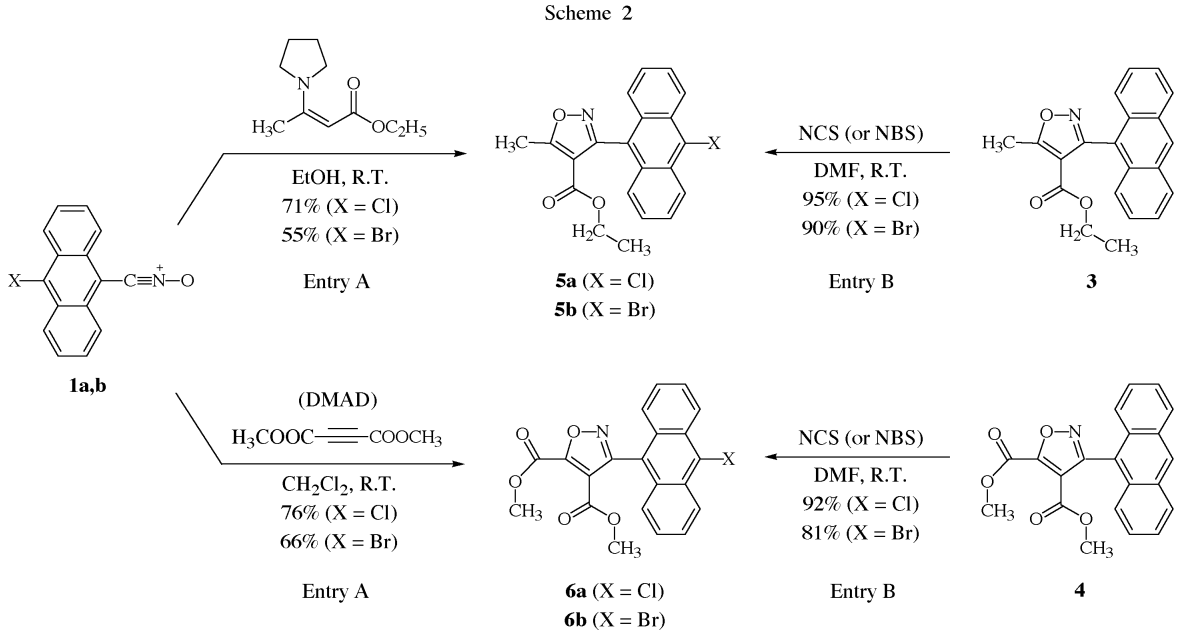
The syntheses of our target isoxazole molecules (**5a,b** and **6a,b**) were performed through “entry A” (1,3-dipolar cycloaddition). The 1,3-dipolar cycloaddition reactions of nitrile oxides (**1a,b**) with two different dipolarophiles were achieved individually with satisfactory yields of the

Scheme 1



Formation of 10-haloanthracene-9-nitrile oxides (**1a,b**).

Scheme 2



Preparation of 3-(10'-halo-9'-anthracenyl)-5-methyl isoxazolecarboxylic esters (**5a,5b,6a,6b**).

products (**5a,b** and **6a,b**). Since ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (**3**) and dimethyl 3-(9'-anthracenyl)-4,5-isoxazoledicarboxylate (**4**) can be prepared according to a previous method we developed [2,8], the direct halogenation of **3** or **4** with NCS (or NBS) in DMF was found in "entry B" to afford the desired products (**5a,b** and **6a,b)** with almost quantitative yields.

The crystal structure of ethyl 3-(10'-chloro-9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (**5a**) was obtained. It possesses similar bond lengths and angles as the previously reported isoxazole ester, ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (**3**). The crystal structure of **3** [15] showed that the anthracene ring and the isoxazole ring are almost orthogonal (torsion angle: C9 C8 C15 C16, 72.5°). The dihedral angle between the mean planes of the two aromatic rings of **5a** was found to be 74.43° (see Figure 1). This conformation could be a vital factor in the study of the binding of this species in the drug-DNA complex in further research.

Studies on intermolecular interactions (see Figure 2) of compound **5a** show that, the anti-parallel stacking is

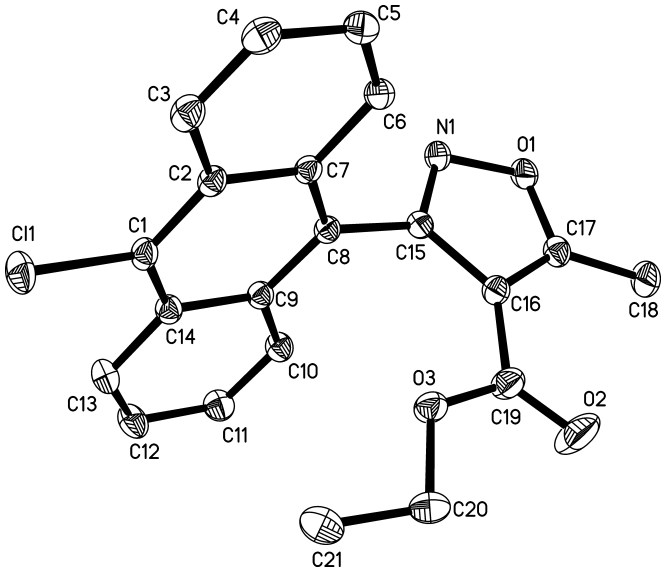


Figure 1. ORTEP diagram of **5a**. The thermal ellipsoids are shown at 30% probability.

formed by two anthracene rings (see **Figure 3**), and the average distance between the two stacked anthracene rings is *ca*. 3.61 Å (measured from C1 to a centroid in the central aromatic ring (C1 C2 C7 C8 C9 C14) in a symmetry related molecule). In contrast, the crystal structure of **3** [13] does not show this stacking.

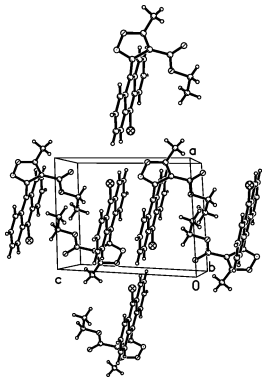


Figure 2. A ball and stick packing diagram of **5a** that shows the unit cell.

The formation of an anti-parallel stacking may arise from the intermolecular electric interaction between two molecules with substantial zwitterionic character (see Scheme 3). The strong electron-withdrawing effect of isoxazole ring is believed to induce the π-electron donating effect of chlorine atom, leading to the formation of temporary zwitterions. In Scheme 3, **B** and **D** are believed to make bigger contribution to the resonance structures of compound (**5a**) than **A** and **C**.

Therefore the δ+ on the 10'-position and δ- on the 9'-position of anthracene ring could explain the formation of this intermolecular alignment through a favorable electronic attraction (see Scheme 3).

The other previously published X-ray structures of 3-(9'-anthracenyl)-isoxazole compounds, 3-(9-anthracenyl)-4,5-dihydro-isoxazole-C60-fullenrene carbon disulfide solvate [16] and 3-(9-anthryl)-(C60) fullereno (1,2-d) isoxazole toluene solvate [17] did not show this intermolecular stacking. The packing diagram of compound **5a** reported in this paper is the first example of this intermolecular

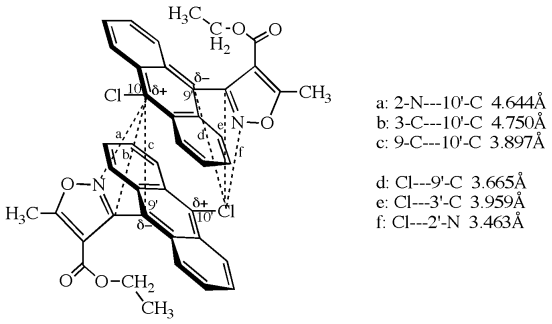


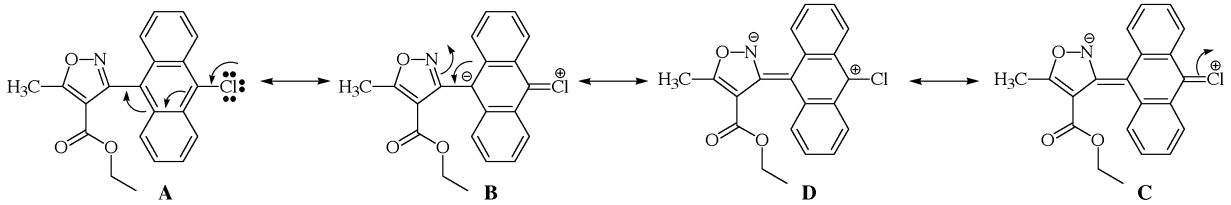
Figure 3. Intermolecular distances in bimolecular packing diagram of **5a**.

stacking, to the best of our knowledge, among the reported structures of 3-(9'-anthracenyl)-isoxazole compounds. The capacity for this type of intermolecular interaction is expected to be a critical factor in the biological effects observed for this class of compounds.

EXPERIMENTAL

Mass spectra were obtained on a JEOL JMS-AX505 HA. The NMR spectra (^{1}H and ^{13}C) were obtained on a Bruker AVANCE 500 Digital NMR (500 MHz) using SGI-IRIX 6.5. Elemental analyses were performed by Desert Analytics Laboratory, PO BOX 41838, Tucson, ARIZONA 85717. All reactions were performed under an inert atmosphere of nitrogen or argon. Tetrahydrofuran was distilled from sodium-benzophenone immediately before use. Flash chromatography was performed on silica gel (Merck 60 Å, 230-400 mesh) with freshly distilled solvents. Ethyl β-pyrrolidinocrotonate (enamine of ethyl acetoacetate) was prepared according to previously reported methodology [18,19]. Ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (3) and dimethyl 3-(9'-anthracenyl)-4,5-isoxazoledicarboxylate (4) were synthesized *via* the route developed by our laboratory [2,8].

Scheme 3



Resonance structures of **5a**.

Ethyl 3-(10'-Chloro-9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (5a) and Dimethyl 3-(10'-Chloro-9'-anthracenyl)-4,5-isoxazoledicarboxylate (6a).

Entry A.

To a vigorously stirred solution of 9-anthraldehyde oxime (2.30 g, 10.40 mmol) in DMF (15 mL), was added *N*-chlorosuc-

Table 1

Crystal Data and Structure Refinement for 10-Chloro-anthrylisoxazole Ester **5a**

Empirical formula	$C_{21}H_{16}ClNO_3$
Formula weight	365.80
T (K)	203(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
a (Å)	a = 8.7175(10)
b (Å)	b = 9.3982(11)
c (Å)	c = 11.7692(13)
a (°)	67.410(2)
β (°)	79.590(2)
γ (°)	76.659(2)
Volume (Å^3); Z	861.67(17); 2
Density (calc.) (Mg/m^3)	1.410
Absorption coefficient	0.243 mm^{-1}
F(000)	380
Crystal size (mm^3)	0.42 x 0.38 x 0.19
Crystal color and habit	pale green block
Theta range for data collection (°)	1.88 to 28.29
Index ranges	-11<=h<=11, -12<=k<=12, -15<=l<=15
Reflections collected	9178
Independent reflections	4059 [R(int) = 0.0243]
Completeness to theta = 28.29°	94.8 %
Max. and min. transmission	0.9553 and 0.9049
Data/restraints/parameters	4059/0/237
GOF	1.044
Final R indices [I>2σ(I)]	R1 = 0.0389, wR2 = 0.1087
R indices (all data)	R1 = 0.0475, wR2 = 0.1138
Largest diff. peak and hole (e.Å^{-3})	0.293 and -0.311

Table 2

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for bt204. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	2200(1)	7354(1)	3790(1)	41(1)
N(1)	8414(1)	1412(1)	3718(1)	31(1)
O(1)	9648(1)	617(1)	3091(1)	34(1)
O(2)	8866(2)	3821(2)	-537(1)	80(1)
O(3)	6984(1)	5018(1)	507(1)	37(1)
C(1)	3806(2)	5964(2)	3576(1)	28(1)
C(2)	3546(2)	4487(2)	3719(1)	26(1)
C(3)	2004(2)	4066(2)	4039(1)	33(1)
C(4)	1801(2)	2619(2)	4167(1)	36(1)
C(5)	3113(2)	1491(2)	3985(1)	33(1)
C(6)	4596(2)	1843(2)	3675(1)	29(1)
C(7)	4881(2)	3349(2)	3526(1)	25(1)
C(8)	6397(2)	3753(2)	3180(1)	25(1)
C(9)	6639(2)	5234(2)	3062(1)	26(1)
C(10)	8174(2)	5660(2)	2722(1)	31(1)
C(11)	8387(2)	7106(2)	2595(2)	36(1)
C(12)	7085(2)	8224(2)	2798(2)	40(1)
C(13)	5599(2)	7874(2)	3119(1)	36(1)
C(14)	5317(2)	6375(2)	3263(1)	27(1)
C(15)	7759(2)	2643(2)	2853(1)	25(1)
C(16)	8514(2)	2712(2)	1650(1)	30(1)
C(17)	9674(2)	1417(2)	1872(1)	32(1)
C(18)	10901(2)	747(2)	1067(2)	46(1)
C(19)	8172(2)	3887(2)	423(1)	39(1)
C(20)	6550(2)	6287(2)	-636(2)	46(1)
C(21)	5384(2)	7517(2)	-265(2)	53(1)

Table 3

Bond Lengths [Å] and Angles [°] for bt204

Cl(1)-C(1)	1.7350(13)	C(1)-C(2)-C(3)	122.76(12)
N(1)-C(15)	1.3048(17)	C(1)-C(2)-C(7)	118.63(12)
N(1)-O(1)	1.4232(14)	C(3)-C(2)-C(7)	118.61(12)
O(1)-C(17)	1.3391(18)	C(4)-C(3)-C(2)	120.99(13)
O(2)-C(19)	1.1988(19)	C(3)-C(4)-C(5)	120.59(13)
O(3)-C(19)	1.3224(19)	C(6)-C(5)-C(4)	120.38(13)
O(3)-C(20)	1.4554(18)	C(5)-C(6)-C(7)	121.49(13)
C(1)-C(2)	1.3996(19)	C(8)-C(7)-C(6)	122.60(12)
C(1)-C(14)	1.4040(19)	C(8)-C(7)-C(2)	119.45(12)
C(2)-C(3)	1.4336(19)	C(6)-C(7)-C(2)	117.94(12)
C(2)-C(7)	1.4377(18)	C(7)-C(8)-C(9)	121.09(12)
C(3)-C(4)	1.359(2)	C(7)-C(8)-C(15)	119.86(11)
C(4)-C(5)	1.416(2)	C(9)-C(8)-C(15)	118.92(11)
C(5)-C(6)	1.3592(19)	C(8)-C(9)-C(10)	121.84(12)
C(6)-C(7)	1.4317(19)	C(8)-C(9)-C(14)	119.92(12)
C(7)-C(8)	1.4053(18)	C(10)-C(9)-C(14)	118.23(12)
C(8)-C(9)	1.4059(18)	C(11)-C(10)-C(9)	121.19(13)
C(8)-C(15)	1.4893(18)	C(10)-C(11)-C(12)	120.46(14)
C(9)-C(10)	1.4293(18)	C(13)-C(12)-C(11)	120.49(14)
C(9)-C(14)	1.4348(18)	C(12)-C(13)-C(14)	121.09(14)
C(10)-C(11)	1.361(2)	C(1)-C(14)-C(13)	123.27(13)
C(11)-C(12)	1.412(2)	C(1)-C(14)-C(9)	118.18(12)
C(12)-C(13)	1.361(2)	C(13)-C(14)-C(9)	118.55(12)
C(13)-C(14)	1.426(2)	N(1)-C(15)-C(16)	111.25(12)
C(15)-C(16)	1.4332(18)	N(1)-C(15)-C(8)	120.31(12)
C(16)-C(17)	1.362(2)	C(16)-C(15)-C(8)	128.43(12)
C(16)-C(19)	1.474(2)	C(17)-C(16)-C(15)	104.52(12)
C(17)-C(18)	1.489(2)	C(17)-C(16)-C(19)	125.72(13)
C(20)-C(21)	1.499(3)	C(15)-C(16)-C(19)	129.76(13)
		O(1)-C(17)-C(16)	109.58(12)
C(15)-N(1)-O(1)	105.60(11)	O(1)-C(17)-C(18)	116.34(13)
C(17)-O(1)-N(1)	109.05(10)	C(16)-C(17)-C(18)	134.08(15)
C(19)-O(3)-C(20)	117.54(12)	O(2)-C(19)-O(3)	123.83(15)
C(2)-C(1)-C(14)	122.69(12)	O(2)-C(19)-C(16)	124.49(15)
C(2)-C(1)-Cl(1)	118.98(10)	O(3)-C(19)-C(16)	111.67(12)
C(14)-C(1)-Cl(1)	118.33(11)	O(3)-C(20)-C(21)	106.40(13)

cinimide (6.24 g, 46.8 mmol) in DMF (15.0 mL) over 15 minutes under nitrogen atmosphere at 0°. The reaction was allowed to warm up to room temperature and was stirred at room temperature for 8 hours. The reaction mixture was then cooled to 0° with an ice bath. The yellow precipitate was collected by filtration and washed with cold DMF (2 × 10 mL). The solid was dried *in vacuo* to give 10-chloroanthracene-9-nitrile oxide 1a, 0.66 g (25 %). The filtrate was poured into ice water (100 mL) and was then stirred for 1 hour. The therefore formed solid was collected by filtration and washed by water (3 × 25 mL). The crude product was dried *in vacuo* and purified by silica gel chromatography with hexane/ethyl acetate (20:1) to give another portion (R_F = 0.43) of 1a, 0.26 g (10 %), mp 185-187° (dec.); ^{1}H nmr (deuteriochloroform): δ 7.72-7.35 (m, 6H), 8.49 (dd, J = 1.10, 8.20 Hz, 2H); ir (Nujol): ν 2290 (C≡N→O) cm^{-1}.

A mixture of 10-chloroanthracene-9-nitrile oxide 1a (0.3 g, 1.18 mmol) and ethyl β-pyrrolidinocrotonate (enamine of ethyl acetoacetate) (0.40 g, 1.41 mmol) was dissolved in absolute ethanol (30 mL). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 hours. Solvent was evaporated and the residue was purified on silica gel with hexane/ethyl acetate (10:1). The pure product 5a (R_F = 0.32) was obtained as a yellow solid, 0.32 g (71.2 %), mp 119-120°; ^{1}H nmr (deuteriochloroform): δ 0.41 (t, 3H, J=7.10 Hz), 2.95 (s,

Table 4
Anisotropic displacement parameters ($Å^2 x 10^3$) for bt204. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	31(1)	37(1)	53(1)	-22(1)	-2(1)	7(1)
N(1)	27(1)	27(1)	35(1)	-13(1)	0(1)	2(1)
O(1)	28(1)	28(1)	40(1)	-13(1)	-1(1)	4(1)
O(2)	84(1)	84(1)	33(1)	-11(1)	12(1)	28(1)
O(3)	39(1)	36(1)	27(1)	-7(1)	-5(1)	1(1)
C(1)	25(1)	29(1)	27(1)	-12(1)	-3(1)	4(1)
C(2)	23(1)	29(1)	24(1)	-9(1)	-3(1)	0(1)
C(3)	24(1)	38(1)	35(1)	-14(1)	-1(1)	-1(1)
C(4)	25(1)	44(1)	38(1)	-13(1)	1(1)	-9(1)
C(5)	33(1)	32(1)	35(1)	-11(1)	-1(1)	-10(1)
C(6)	28(1)	27(1)	30(1)	-10(1)	-1(1)	-3(1)
C(7)	23(1)	26(1)	23(1)	-8(1)	-2(1)	-2(1)
C(8)	23(1)	25(1)	24(1)	-8(1)	-3(1)	0(1)
C(9)	25(1)	26(1)	25(1)	-9(1)	-3(1)	-2(1)
C(10)	25(1)	30(1)	36(1)	-13(1)	-2(1)	-3(1)
C(11)	32(1)	36(1)	43(1)	-15(1)	-1(1)	-10(1)
C(12)	42(1)	29(1)	53(1)	-19(1)	-4(1)	-9(1)
C(13)	37(1)	28(1)	43(1)	-17(1)	-5(1)	0(1)
C(14)	27(1)	26(1)	26(1)	-10(1)	-5(1)	0(1)
C(15)	21(1)	25(1)	30(1)	-11(1)	-1(1)	-4(1)
C(16)	25(1)	30(1)	33(1)	-13(1)	2(1)	-3(1)
C(17)	26(1)	32(1)	40(1)	-17(1)	2(1)	-5(1)
C(18)	39(1)	44(1)	52(1)	-25(1)	10(1)	0(1)
C(19)	37(1)	42(1)	30(1)	-10(1)	2(1)	-2(1)
C(20)	56(1)	40(1)	31(1)	-3(1)	-11(1)	-4(1)
C(21)	57(1)	39(1)	51(1)	-7(1)	-15(1)	3(1)

Table 5
Hydrogen Coordinates ($x 10^4$) and Isotropic Displacement Parameters ($Å^2 x 10^3$) for bt204

	x	y	z	U(eq)
H(3)	1120	4801	4163	40
H(4)	780	2365	4378	43
H(5)	2958	493	4079	40
H(6)	5454	1081	3557	35
H(10)	9053	4929	2584	37
H(11)	9407	7361	2371	43
H(12)	7246	9218	2710	48
H(13)	4744	8633	3248	43
H(18A)	10600	-168	1036	68
H(18B)	11914	448	1403	68
H(18C)	10987	1524	239	68
H(20A)	6070	5911	-1134	55
H(20B)	7487	6711	-1122	55
H(21A)	4484	7068	245	79
H(21B)	5025	8374	-999	79
H(21C)	5888	7905	201	79

3H), 3.74 (q, 2H, J = 7.10 Hz), 7.41-7.65 (m, 4H), 7.67 (dd, 2H, J = 1, 8.5 Hz), 8.61 (dd, 2H, J = 1, 8.5 Hz); ^{13}C nmr (deuteriochloroform): δ 12.9, 13.4, 60.2, 111.5, 122.6, 125.1, 125.9, 126.5, 126.7, 128.3, 131.0, 131.2, 160.2, 161.3, 176.3; ms-EI: m/z 365 (M^+, 100), 277 (23.94), 253 (24.04), 237 (10.55), 214 (14.18), 176 (15.53).

Anal. Calcd. for $C_{21}H_{16}ClNO_3$: C 68.93, H 4.41, N 3.83. Found: C 69.12 H 4.57, N 3.90.

To a well-stirred solution of 10-chloroanthracene-9-nitrile oxide 1a (0.3 g, 1.18 mmol) in CH_2Cl_2 (20 mL), was added drop-wise a solution of dimethyl acetylenedicarboxylate (DMAD) (0.218 g, 1.51 mmol) in CH_2Cl_2 (10 mL) over 10 minutes. The reaction was stirred under nitrogen atmosphere at room temperature for 1 hour. Solvent was evaporated and the residue was purified on silica gel with hexane/ethyl acetate (4:1). The pure product 6a (R_F = 0.20) was obtained as a pale yellow solid, 0.354 g (76.6 %), mp 175.0-176.5°; ^1H nmr (deuteriochloroform): δ 3.39 (s, 3H), 4.09 (s, 3H), 7.45-7.65 (m, 4H), 7.68 (dd, 2H, J = 1, 8.5 Hz), 8.58 (dd, 2H, J = 1, 8.5 Hz); ^{13}C nmr (deuteriochloroform): δ 53.0, 54.1, 118.2, 120.2, 125.7, 125.8, 127.3, 127.5, 128.8, 131.6, 132.6, 157.2, 160.4, 160.9, 161.5; ms-EI: m/z 395 (M^+, 100), 336 (24.84), 276 (24.65), 237 (12.54), 214 (13.08), 176 (14.90).

Anal. Calcd. for $C_{21}H_{14}ClNO_5$: C 63.73, H 3.57, N 3.54. Found: C 63.71, H 3.55, N 3.54.

Entry B.

To a solution of ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (3) (0.3 g, 0.91 mmol) in DMF (5 mL), was added a solution of *N*-chlorosuccinimide (0.145 g, 1.1 mmol) in DMF (5 mL) for 10 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then poured into ice water (50 mL). The resulting turbid mixture was stirred for 1 hour. The crude product was collected by filtration and washed with water (2 × 5 mL). Recrystallization from cyclohexane gave pure 5a as pale yellow prisms, 0.32 g (95 %).

To a solution of dimethyl 3-(9'-anthracenyl)-4,5-isoxazoledicarboxylate (4) (0.3 g, 0.83 mmol) in DMF (5 mL), was added a solution of *N*-chlorosuccinimide (0.133 g, 1.0 mmol) in DMF (5 mL) for 10 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then poured into ice water (50 mL). The resulting turbid mixture was stirred for 30 minutes. The crude product was collected by filtration and washed with water (2 × 5 mL). Recrystallization from cyclohexane gave pure 6a as pale yellow prisms, 0.29 g (92 %).

Ethyl 3-(10'-Bromo-9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (5b) and Dimethyl 3-(10'-Bromo-9'-anthracenyl)-4,5-isoxazoledicarboxylate (6b).

Entry A.

To a vigorously stirred solution of 9-anthraldehyde oxime (2.3 g, 10.4 mmol) in DMF (15 mL), was added *N*-bromosuccinimide (8.0 g, 45.0 mmol) in DMF (25 mL) over 15 minutes under nitrogen atmosphere at 0°. The reaction was allowed to warm up to room temperature and was stirred at room temperature for 8 hours. The reaction mixture was cooled to 0°. The orange precipitate was collected by filtration and washed with cold DMF (2 × 10 mL). The solid was dried *in vacuo* to give 10-bromoanthracene-9-nitrile oxide 1b, 0.62 g (20 %). The filtrate was poured into ice water (100 mL) and was then stirred for 1 hour. The therefore formed solid was collected by filtration and washed by water (3 × 25 mL). The crude product was dried *in vacuo* and purified by silica gel chromatography with hexane/ethyl acetate (20:1) to give another portion (R_F = 0.50)

of 1b, 0.31 g (10 %), mp 195-199° (dec.); ^{1}H nmr (deuteriochloroform): δ 7.66-7.32 (m, 6H), 8.56 (dd, J = 1.10, 8.20 Hz, 2H); ir (Nujol): ν 2301 (C≡N→O) cm^{-1}.

A mixture of 10-bromoanthracene-9-ntrile oxide 1b (0.36 g, 1.2 mmol) and ethyl β-pyrrolidinocrotonate (enamine of ethyl acetoacetate) (0.40 g, 1.41 mmol) was dissolved in absolute ethanol (30 mL). The reaction mixture was stirred at room temperature for 10 hours. Solvent was evaporated and the yellow residue was purified on silica gel with hexane/ethyl acetate (10:1). The pure 5b (R_F = 0.30) was obtained as a yellow solid, 0.27 g (55 %), mp 123-124°; ^{1}H nmr (deuteriochloroform): δ 0.36 (t, 3H, J = 7.10 Hz), 2.95 (s, 3H), 3.69 (q, 2H, J = 7.10 Hz), 7.40-7.64 (m, 6H), 8.60 (dd, 2H, J = 1, 8.5 Hz); ^{13}C nmr (deuteriochloroform): δ 13.3, 13.8, 60.6, 111.9, 124.1, 125.6, 126.3, 126.9, 127.5, 128.5, 130.5, 131.8, 160.7, 161.7, 176.7; ms-EI: m/z 411 (M+2, 82.80), 409 (M$^+$, 100), 322 (29.02), 320 (22.09), 298 (21.58), 296 (19.85), 214 (25.97), 176 (28.48).

Anal. Calcd. for $C_{21}H_{16}BrNO_3$: C 61.48, H 3.93, N 3.41. Found: C 61.73 H 3.75, N 3.36.

To a well-stirred solution of 10-bromoanthracene-9-nitrile oxide 1b (0.36 g, 1.2 mmol) in CH_2Cl_2 (20 mL), was added dropwise a solution of dimethyl acetylenedicarboxylate (DMAD) (0.22 g, 1.52 mmol) in CH_2Cl_2 (10 mL) over 10 minutes. The reaction was stirred under nitrogen atmosphere at room temperature for 1 hour. Solvent was evaporated and the residue was purified on silica gel with hexane/ethyl acetate (4:1). The pure product 6b (R_F = 0.17) was obtained as a pale yellow solid, 0.35 g (66 %), mp 177-178°; ^{1}H nmr (deuteriochloroform): δ 3.39 (s, 3H), 4.09 (s, 3H), 7.44-7.65 (m, 6H), 8.60 (dd, 2H, J = 1, 8.5 Hz); ^{13}C nmr (deuteriochloroform): δ 53.0, 54.1, 118.2, 121.2, 125.8, 127.0, 127.5, 127.7, 128.7, 130.5, 131.8, 157.2, 160.4, 161.0, 161.5; ms-EI: m/z 441 (M+2, 99.28), 439 (M$^+$, 100), 382 (24.61), 322 (28.81), 320 (21.98), 214 (23.95), 176 (37.64).

Anal. Calcd. for $C_{21}H_{14}BrNO_5$: C 57.29, H 3.21, N 3.18. Found: C 57.09, H 3.04, N 3.26.

Entry B.

To a solution of ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (3) (0.3 g, 0.91 mmol) in DMF (5 mL), was added a solution of *N*-bromosuccinimide (0.19 g, 1.08 mmol) in DMF (5 mL) for 10 minutes at room temperature. The reaction mixture was stirred at room temperature for 4 hours and then poured into ice water (50 mL). The resulting turbid mixture was stirred for 1 hour. The crude product was collected by filtration and washed with water (2 × 5 mL). Recrystallization from cyclohexane gave pure 5b as pale yellow prisms, 0.335 g (90 %).

To a solution of dimethyl 3-(9'-anthracenyl)-4,5-isoxazoledicarboxylate (4) (0.3 g, 0.83 mmol) in DMF (5 mL), was added a solution of *N*-bromosuccinimide (0.19 g, 1.08 mmol) in DMF (5 mL) for 10 minutes at room temperature. The reaction mixture was stirred at room temperature for 4 hours and then poured into ice water (50 mL). The resulting turbid mixture was stirred for 30 minutes. The crude product was collected by filtration and washed with water (2 × 5 mL). Recrystallization from cyclohexane gave pure 6b as pale yellow prisms, 0.30 g (81 %).

X-Ray Crystal Structure Determination of Ethyl 3-(10'-Chloro-9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate (5a).

Crystals of compound 5a were removed from the flask and covered with a layer of hydrocarbon oil. A suitable crystal was selected, attached to a glass fiber and placed in the low-temperature nitrogen stream [20]. Data for 5a were collected at 203(2) K using a Bruker/Siemens SMART 1K instrument (Mo Kα radiation, λ = 0.71073 Å) equipped with a Siemens LT-2A low temperature device. Data were measured using omega scans of 0.3° per frame for 10 seconds, and a full sphere of data was collected. A total of 2132 frames were collected with a final resolution of 0.75 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART [21] software and refined using SAINTPlus [22] on all observed reflections. Data reduction and correction for Lp and decay were performed using the SAINTPlus software. Absorption corrections were applied using SADABS [23]. The structure was solved by direct methods and refined by least squares methods on F^2 using the SHELXTL program package [24]. The structure was solved in the space group P-1 (# 2) by analysis of systematic absences. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added geometrically and refined with a riding model with their parameters constrained to the parent atom site. No decomposition was observed during data collection. Details of the data collection and refinement are provided in the tables.

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