FACILE SYNTHESIS OF 4*H*,6*H*-PYRROLO[3,4-*c*]ISOXAZOLES

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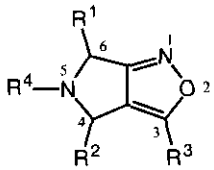
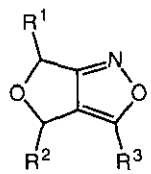
Abstract - Various 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazoles (**I**) were prepared in good yields from the corresponding 4*H*,6*H*-furo[3,4-*c*]isoxazoles (**II**) by a ring cleavage and cyclization reaction.

It is well known that substituted isoxazole derivatives have a variety of biological activities in pharmaceutical and agricultural areas.[1] For example, isoxazolylmethanols have antiinflammatory and analgesic activities,[2] haloisoxazolylureas have acaricidal and insecticidal properties,[3] and 3-hydroxy-5-methylisoxazole and 4*H*,6*H*-furo[3,4-*c*]isoxazoles (**II**) show high fungicidal activities against plant pathogens.[4,5] In a previous report,[5] we described the successful preparation of 4*H*,6*H*-furo[3,4-*c*]isoxazoles (**II**) and their fungicidal activities.

In continuation of this research, we designed the 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (**I**), [5,5] fused ring system like furoisoxazole (**II**), which enables us to provide a diverse structural modification at 5-position. To our best knowledge, the synthetic methodology for 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole has not been reported yet. Herein we report a synthesis of 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazoles (**I**) from the corresponding 4*H*,6*H*-furo[3,4-*c*]isoxazoles (**II**).

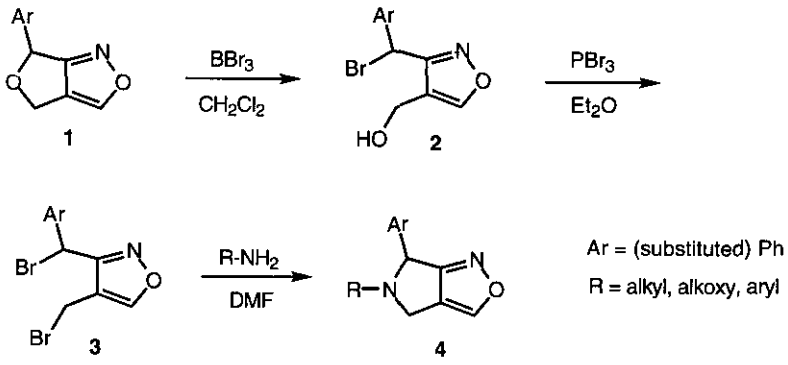


I



II

R^1= alkyl, aryl;
R^2= H, alkyl, aryl;
R^3= H, alkyl;
R^4 = alkyl, aryl, alkoxy.



Scheme 1

Based on our previous work,[5] 4*H*,6*H*-furo[3,4-*c*]isoxazole (**1**) was reacted with BBr_3 to give 3,4-disubstituted isoxazoles (**2**) which could be highly functionalized as shown in **Scheme 1**.

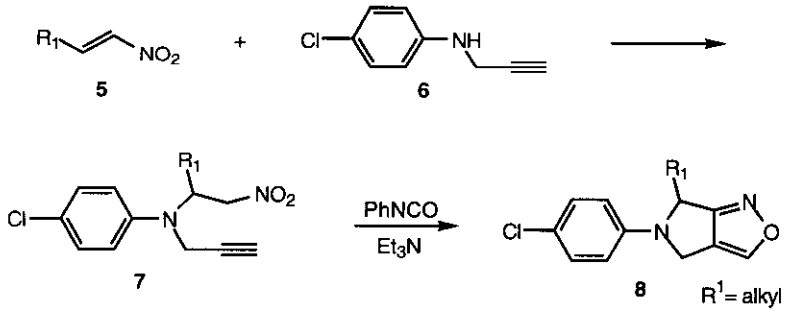
Bromo alcohol (**2**) was treated with PBr_3 in ether at 0 °C to give the dibromide (**3**) in quantitative yield. Then, the dibromide (**3**) was reacted with the appropriate primary amine in DMF to afford 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (**4**) in good yields. The results are summerized in **Table**. The cyclization reaction of **3** with RNH_2 readily proceeded within 3 h in the presence of two equivalents of potassium carbonate with a slow addition of RNH_2 at around 80 °C. The yields of **4** were high when RNH_2 was alkylamine (**4a**, **4b**, **4c**, **4g**, **4j** and **4k**), while the yields of cyclization were low with aryl-and benzylamine (**4d**, **4e**, **4h** and **4i**). It is noteworthy that *N*-alkoxy-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazoles (**4f** and **4l**) can be also prepared when the alkoxyamines are used instead of $R\text{-}NH_2$.

Meanwhile, the similar way to the synthesis of 4*H*,6*H*-furo[3,4-*c*]isoxazole[5] was applied to prepare 4*H*,6*H*-pyrrolo[3,4-c]isoxazole (**I**) *via* the nitro amine intermediate (**7**), which is thought to be readily transformed into the 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (**8**) by the intramolecular nitrile oxide-alkyne cycloaddition process[6] (**Scheme 2**). However, the Michael addition of the secondary arylamine (**6**) to the nitro olefin (**5**) was very sluggish in various reaction conditions. Actually, the nitro amine intermediate (**7**) was obtained in only 20% yield when R^1 was isopropyl group. When R^1 was phenyl or substituted phenyl group, the adduct (**7**) was never produced.

Thus, this addition-intramolecular cyclization process was not applicable to the preparation of pyrrolo[3,4-*c*]isoxazole (**I**).

Table. Yields of 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (**4**) from dibromide (**3**)

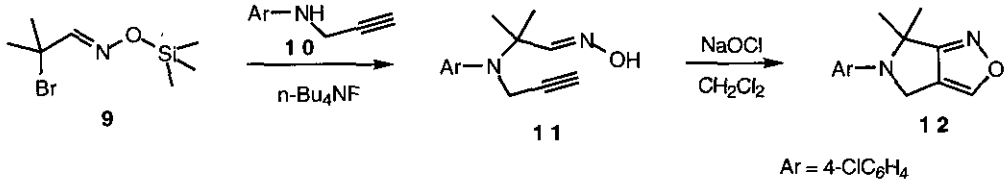
No.	Ar	R	Reaction Time (h)	Yield(%)
a	2-Cl-C_6H_4	n-Pr	1.5	76
b	2-Cl-C_6H_4	t-Bu	1.5	58
c	2-Cl-C_6H_4	n-C_5H_{11}	1.5	72
d	2-Cl-C_6H_4	Ph	1.5	50
e	2-Cl-C_6H_4	4-Cl-C_6H_4	2	42
f	2-Cl-C_6H_4	MeO-	3	39
g	Ph	n-Pr	1.5	61
h	Ph	4-Cl-$C_6H_4CH_2$-	3	40
i	Ph	3-Cl-$C_6H_4CH_2$-	3	34
j	4-Cl-C_6H_4	n-Pr	1.5	55
k	2,4-Cl_2-C_6H_3	n-Pr	1.5	67
l	2,4-Cl_2-C_6H_3	EtO	3	38



Scheme 2

In addition, 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (**12**) was prepared from amino aldoxime (**11**) which was obtained from the corresponding α-bromo-*O*-silyloxime (**9**) and *N*-propargyl aniline (**10**) by the modification of the reported method[7] as shown in **Scheme 3**. But the overall yield was less than 20% and the preparation of the secondary amine (**10**) was usually difficult. Furthermore, introduction of aryl group

to 6-position of 4H,6H-pyrrolo[3,4-c]isoxazole (**I**) based on this method was limited because the corresponding α-bromo-*O*-silyloxime (R^1 = Ar, R^2 = H) is not readily obtainable.[8]



Scheme 3

In summary, we efficiently prepared new 4*H*,6*H*-pyrrolo[3,4-*c*]isoxazoles (**4**) from the corresponding 4*H*,6*H*-*furo*[3,4-*c*]*isoxazoles in three steps.* The starting material 4*H*,6*H*-furo[3,4-*c*]isoxazole (**II**) is readily obtained by the well known procedure[5] and all the primary amines (RNH_2) are commercially available.

EXPERIMENTAL

Infrared spectra were obtained on a Shimadzu IR-435 spectrophotometer. ^{1}H Nmr spectra were obtained in $CDCl_3$ at 60 or 300 MHz. ^{13}C Nmr spectra were obtained at 75.5 MHz. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane at 0. Column chromatography was performed using Merck Kieselgel 60 (230-400 mesh) as a stationary phase.

General Procedure for the Preparation of Dibromide 3a-l. To a stirred solution of alcohol (**2**) (10 mmol) dissolved in anhydrous Et_2O (20 ml) was slowly added PBr_3 (12 mmol) at 0 °C and then stirred for 30 min. The reaction solution was poured into cold water (20 ml) and the layers separared. The organic solution was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using an n-hexane/EtOAc (5:1) eluent.

3-[Bromo(2-chlorophenyl)methyl]-4-bromomethylisoxazole (3a). Yield 95%, a brown oil; ir (neat) 3090, 1595, 1460, 1430, 1105, 1035, 835, 745 cm^{-1}; ^{1}H nmr (300 MHz) 4.18 (dd, J = 11.8, 0.5 Hz, 1H, C*H*HBr), 4.37 (dd, J = 11.8, 0.6 Hz, 1H, CH*H*Br), 6.75 (s, 1H, CHBr), 7.26-7.38 (m, 3H, Ar), 7.76-7.80 (m, 1H, Ar), 8.47 (br s, 1H, isoxazole); ^{13}C nmr 18.2, 36.9, 115.5, 127.5, 129.6, 130.3, 131.5, 132.5, 134.4, 158.3, 160.2; Anal. Calcd for $C_{11}H_8NOBr_2Cl$: C, 36.15; H, 2.21; N, 3.83. Found: C, 36.37; H, 2.17; N, 3.90.

3-[Bromo(4-chlorophenyl)methyl]-4-bromomethylisoxazole (3b). Yield 94%, a clear oil; ir (neat) 1590, 1480, 1395, 1215, 1105, 1085, 835, 775 cm^{-1}; ^{1}H nmr (300 MHz) 4.14 (dd, J = 11.8, 0.6 Hz, 1H, C*H*HBr),

4.36 (dd, J = 11.8, 0 9 Hz, 1H, CH*H*Br), 6.25 (s, 1H, CHBr), 7.33-7.53 (m, 4H, Ar), 8.47 (br s, 1H, isoxazole); ^{13}C nmr 18.4, 40.3, 115.6, 128.9, 129.9, 135.0, 135.1, 158.6, 160.4; Anal. Calcd for $C_{11}H_8NOBr_2Cl$: C, 36.15; H, 2.21; N, 3.83. Found: C, 36. 29; H, 2.10; N, 3.93.

3-[Bromo(phenyl)methyl]-4-bromomethylisoxazole (3c). Yield 98%, a clear oil; ir (neat) 1595, 1400, 1215, 1105, 690; ^{1}H nmr (300 MHz) 4.06 (dd, J = 11.8, 0.7 Hz, 1H, C*H*HBr), 4.31 (dd, J = 11.8, 0.8 Hz, 1H, CH*H*Br), 6.28 (s, H, CHBr), 7.33-7.56 (m, 5 H, Ar), 8.43 (br s, 1H, isoxazole); ^{13}C nmr 18.5, 41.4, 115.6, 128.4, 128.7, 129.1, 136.6, 158.6, 160.6; Anal. Calcd for $C_{11}H_9NOBr_2$: C, 39.93; H, 2.74; N, 4.23 Found: C, 40.07; H, 2.70; N, 4.01.

3-[Bromo(2,4-dichlorophenyl)methyl]-4-bromomethylisoxazole (3d). Yield 92%, mp 77-78 °C (n-hexane/EtOAc); ir (KBr) 1595, 1455, 1410, 1375, 1105, 845, 780; ^{1}H nmr (300 MHz) 4.25 (dd, J = 11.8, 0.6 Hz, 1H, C*H*HBr), 4 42 (dd, J = 11.8, 0.9 Hz, 1H, CH*H*Br), 6.70 (s, 1H, CHBr), 7.26-7.80 (m, 3H, Ar), 8.49 (br s, 1H, isoxazole); ^{13}C nmr 18.1, 36.1, 115.6, 127.9, 129.4, 132.7, 133.1, 133.2, 135.7, 158.3, 160.1; Anal. Calcd for $C_{11}H_7NOBr_2Cl_2$: C, 33.04; H, 1.76; N, 3.50. Found: C, 33.23; H, 1.70; N, 3.42.

General Procedure for the Preparation of Pyrroloisoxazole 4a-l. To a mixture of dibromide (**3**) (2 mmol) and anhydrous K_2CO_3 (276 mg, 2 mmol) in DMF (18 ml) was slowly added a solution of R-NH_2 (3 mmol) in DMF (2 ml) for 1 h using a syringe pump at 80 °C. After being stirred for 0.5 h, the reaction mixture was poured into water (10 ml), then extracted with CH_2Cl_2 (10 ml x 2). The extract was dried ($MgSO_4$), concentrated and purified with column chromatography (n-hexane/EtOAc = 8:1).

6-(2-Chlorophenyl)-5-n-propyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4a) Oil; ir (neat) 2930, 2785, 1625, 1455, 1435, 1165, 1050, 750; ^{1}H nmr (300 MHz) 0 88 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.46-1.55 (m, 2H, $CH_3CH_2CH_2$), 2.65 (t, J = 7.2 Hz, 2H, NCH_2CH_2), 3.54 (dt, J = 12.4, 1.4 Hz, 1H, NC*H*H), 4.27 (dd, J = 12.4, 0.7 Hz, 1H, NCH*H*), 5.32 (s, 1H, ArCH), 7.20-7.63 (m, 4H, Ar), 7.80 (t, J = 1.1 Hz, 1H, isoxazole); ^{13}C nmr 11.5, 21.2, 47.9, 55.4, 61.7, 120.3, 126.91, 128.9, 129.2, 129.4, 133.8, 136.4, 148.2, 171.1; HRms Calcd for $C_{14}H_{15}N_2OCl$: 262.0873. Found: 262.0859.

6-(2-Chlorophenyl)-5-*tert*-butyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4b). Mp 95-97 °C (n-hexane/EtOAc). Ir (KBr) 1590, 1495, 1345, 1060, 745; ^{1}H nmr (300 MHz) 1.06 (s, 9H, $C(CH_3)_3$), 3.96 (dt, J = 13.1, 0.6 Hz, 1H, NC*H*H), 4.22 (dt, J = 13.1, 1.4 Hz, 1H, NCH*H*), 5.77 (s, 1H, ArCH), 7.09-7.72 (m, 4H, Ar), 7.92 (t, J = 1.3 Hz, 1H, isoxazole); ^{13}C nmr 26.6, 43.1, 53.9, 55.8, 120.1, 126.5, 128.1, 129.1, 131.5, 141.7, 148.4, 172.1; HRms Calcd for $C_{15}H_{17}N_2OCl$: 276.1063. Found: 276.1046.

6-(2-Chlorophenyl)-5-n-pentyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4c). Oil; ir (neat) 2895, 1625, 1455,

1435, 1060, 750; ^{1}H nmr (300 MHz) 0.85 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.16-1.35 (m, 4H, $CH_3CH_2CH_2$), 1.49 (t, J = 7.2 Hz, 2H, NCH_2CH_2), 2.59-2.74 (m, 2H, $NCH_2CH_2CH_2$), 3.52 (dt, J = 12.4, 1.5 Hz, 1H, NCHH), 4.25 (d, J = 12.4 Hz, 1H, NCHH), 5.30 (s, 1H, ArCH), 7.16-7.60 (m, 4H, Ar), 7.97 (t, J = 1.0 Hz, 1H, isoxazole); ^{13}C nmr 13.8, 22.2, 27.6, 29.0, 47.9, 53.4, 61.7, 120.3, 126.9, 128.8, 129.2, 129.3, 136.5, 148.1, 171.2; HRms Calcd for $C_{16}H_{19}ClN_2O$: 290.1186. Found: 290.1184.

6-(2-Chlorophenyl)-5-phenyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4d). Mp 153-155 °C (n-hexane/EtOAc). Ir (KBr) 1590, 1495, 1060, 745; ^{1}H nmr (300 MHz) 4.53 (dd, J = 12.4, 1.1 Hz, 1H, NCHH), 4.83 (dt, J = 12.4, 1.4 Hz, 1H, NCHH), 6.64 (d, J = 1.5 Hz, 1H, ArCH), 6.52-7.46 (m, 9H, Ar), 8.13 (t, J = 1.1 Hz, 1H, isoxazole); ^{13}C nmr 45.6, 57.9, 112.5, 117.7, 118.1, 127.3, 127.4, 129.2, 129.3, 130.2, 132.5, 136.4, 145.5, 149.3, 169.9; HRms Calcd for $C_{17}H_{13}N_2OCl$: 296.0717. Found: 296.0692.

6-(2-Chlorophenyl)-5-(4-chlorophenyl)-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4e). Mp 142-144 °C (n-hexane/EtOAc). Ir (KBr) 1590, 1490, 1350, 1060, 755; ^{1}H nmr (300 MHz) 4.52 (dd, J = 12.3, 1.2 Hz, 1H, NCHH), 4.82 (dt, J = 12.3, 1.6 Hz, 1H, NCHH), 6.31 (d, J = 1.8 Hz, 1H, ArCH), 7.09-7.47 (m, 8H, Ar), 8.18 (t, J = 1.2 Hz, 1H, isoxazole); ^{13}C nmr 45.9, 58.0, 113.6, 118.0, 122.8, 127.4, 127.5, 129.2, 129.5, 130.4, 132.6, 136.0, 144.0, 149.4, 169.8; HRms Calcd for $C_{17}H_{12}N_2OCl_2$: 330.0327. Found: 330.0327.

6-(2-Chlorophenyl)-5-methoxy-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4f). Mp 59-61 °C (n-hexane/EtOAc). ir (CCl_4) 2910, 1625, 1455, 1435, 1395, 1050; ^{1}H nmr (300 MHz) 3.51 (s, 3H, CH_3), 3.96 (dd, J = 13.5, 1.4 Hz, 1H, NCHH), 4.43 (dd, J = 13.5, 1.0 Hz, 1H, NCHH), 5.72 (s, 1H, ArCH), 7.20-7.45 (m, 4H, Ar), 8.07 (dd, J = 1.4, 1.0 Hz, 1H, isoxazole); ^{13}C nmr 51.6, 61.6, 65.6, 118.8, 126.8, 129.1, 129.4, 129.6, 134.2, 134.4, 149.4, 168.6; HRms Calcd for $C_{12}H_{11}N_2OCl$: 250.0509. Found: 250.0505.

6-Phenyl-5-n-propyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4g). Mp 77-77.5 °C (n-hexane/EtOAc). Ir (KBr) 2785, 1145, 1050, 750; ^{1}H nmr (300 MHz) 0.87 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.42-1.57 (m, 2H, $CH_3CH_2CH_2$), 2.54-2.72 (m, 2H, NCH_2CH_2), 3.50 (dt, J = 12.4, 1.5 Hz, 1H, NCHH), 4.23 (d, J = 12.4 Hz, 1H, NCHH), 4.75 (s, 1H, ArCH), 7.29-7.46 (m, 5H, Ar), 7.99 (t, J = 1.2 Hz, 1H, isoxazole); ^{13}C nmr 11.5, 21.3, 48.0, 55.3, 65.4, 120.3, 127.9, 128.0, 128.4, 138.9, 148.2, 172.3; HRms Calcd for $C_{14}H_{16}N_2O$: 228.1263. Found: 228.1237.

5-(4-Chlorobenzyl)-6-phenyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4h). Mp 149-151 °C (n-hexane/EtOAc). Ir (KBr) 3070, 2785, 1480, 1400, 1145, 1080, 1060, 840, 815, 750; ^{1}H nmr (300 MHz) 3.48 (dt, J = 12.4, 1.4 Hz, 1H, NCHH), 3.61 (d, J = 12.4 Hz, 1H, NCHH), 3.96 (d, J = 12.4 Hz, 1H, ArCHHN), 4.01 (d, J = 12.4 Hz, 1H, ArCHHN), 4.89 (s, 1H, PhCH), 7.21-7.50 (m, 9H, Ar), 7.98 (t, J = 1.2 Hz, 1H, isoxazole); ^{13}C nmr

48.0, 56.3, 64.9, 120.1, 128.2, 128.4, 128.5, 128.7, 129.8, 132.9, 136.7, 138.2, 148.4, 172.0; HRms Calcd for $C_{18}H_{15}N_2OCl$: 310.0873. Found: 310.0901.

5-(3-Chlorobenzyl)-6-phenyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4i). Mp 89-90 °C (n-hexane/EtOAc). Ir (KBr) 3065, 2785, 1590, 1395, 1250, 1145, 1060, 750; ^{1}H nmr (300 MHz) 3.49 (dt, J = 12.4, 1.4 Hz, 1H, NC*H*H), 3.63 (d, J = 12.4 Hz, 1H, NCH*H*), 3.99 (d, J = 12.4 Hz, 1H, ArC*H*HN), 4.02 (d, J = 12.4 Hz, 1H, ArCH*H*N), 4.90 (s, 1H, PhCH), 7.20-7.51 (m, 9H, Ar), 8.00 (t, J = 1.1 Hz, 1H, isoxazole); ^{13}C nmr 48.1, 56.5, 65.0, 120.1, 126.6, 127.4, 128.2, 128.4, 128.5, 128.7, 129.7, 134.3, 138.0, 140.3, 148.4, 172.0; HRms Calcd for $C_{18}H_{15}N_2OCl$: 310.0873. Found: 310.0881.

6-(4-Chlorophenyl)-5-n-propyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4j). Mp 79-80 °C (n-hexane/EtOAc). Ir (KBr) 2930, 2780, 1480, 1395, 1080, 1055, 795; ^{1}H nmr (60 MHz) 0.88 (t, J = 7 Hz, 3H, CH_2CH_3), 1.50 (m, 2H, $CH_3CH_2CH_2$), 2.65 (t, J = 7 Hz, 2H, NCH_2CH_2), 3.55 (dt, J = 12, 1 Hz, 1H, NC*H*H), 4.25 (dd, J = 12, 1 Hz, 1H, NCH*H*), 4 77 (s, 1H, ArCH), 7.25 (m, 4H, Ar), 8.02 (t, J = 1 Hz, 1H, isoxazole); HRms Calcd for $C_{14}H_{15}N_2OCl$: 262.0873. Found: 262.0885. Anal. Calcd for $C_{14}H_{15}N_2OCl$: C, 64.00; H, 5.75; N, 10.66. Found: C, 63.89; H, 5.70; N, 10.72.

6-(2,4-Dichlorophenyl)-5-n-propyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4k). Oil; ir (neat) 2925, 2785, 1580, 1455, 1375, 1060, 1040, 800; ^{1}H nmr (60 MHz) 0.89 (t, J = 7 Hz, 3H, CH_2CH_3), 1.50 (m, 2H, $CH_3CH_2CH_2$), 2.65 (t, J = 7 Hz, 2H, NCH_2CH_2), 3.55 (dt, J = 12, 1 Hz, 1H, NC*H*H), 4.27 (dd, J = 12, 1 Hz, 1H, NCH*H*), 5.32 (s, 1H, ArCH), 7.20-7.71 (m, 4H, Ar), 8.08 (t, J = 1 Hz, 1H, isoxazole); Anal. Calcd for $C_{14}H_{14}NOCl_2$. C, 168.14; H, 14.11; N, 28.02. Found: C, 168.29; H, 14.00; N, 28.34.

6-(2,4-Dichlorophenyl)-5-ethoxy-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (4l). Oil; ir (neat) 2945, 1500, 1460, 1375, 1095, 1045, 775; ^{1}H nmr (300 MHz) 1.05 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.67 (m, 2H, CH_2CH_3), 4.00 (dt, J = 12.4, 1.4 Hz, 1H, NC*H*H), 4.49 (d, J = 12.4 Hz, 1H, NCH*H*), 5.67 (s, 1H, ArCH), 7.22-7.46 (m, 3H, Ar), 8.11 (dd, J = 1.5, 0.9 Hz, 1H, isoxazole); ^{13}C nmr 14.1, 52 4, 65.2, 69.5, 118.5, 127.2, 129.4, 130.6, 133.5, 134.6, 135.0, 149.5, 168.1; HRms Calcd for $C_{13}H_{12}N_2O_2Cl_2$: 298.0276. Found: 298.0273.

4-Chloro-*N*-propargyl-*N*-(1-isopropyl-2-nitroethyl)aniline (7). A mixture of 3-methyl-1-nitrobutene (518 mg, 4.50 mmol) and 4-chloro-*N*-propargylaniline (3.73 g, 22.51 mmol) dissolved in dry THF (5 ml) was stirred for 1 day at room temperature. The mixture was concentrated under reduced pressure and purified by column chromatography (n-hexane/EtOAc = 5/1) to afford **7** (276 mg, 21%) as a brown oil; ir (neat) 3266, 2945, 1590, 1540, 1490, 810; ^{1}H nmr (60 MHz) 0.92 (d, J = 7 Hz, 3H, $CH(CH_3)_2$), 1.07 (d, J = 7 Hz, 3H, $CH(CH_3)_2$), 2.10 (m, 1H, $CH(CH_3)_2$), 2.25 (t, J = 2 Hz, 1H, CCH), 4.00 (d, J = 3 Hz, 2H,

NCH_2CC), 4.52 (m, 1H, $NCHCH_2NO_2$), 4.76 (m, 2H, $NCHCH_2NO_2$), 6.58-7.30 (m, 4H, Ar); Anal. Calcd for $C_{14}H_{17}N_2O_2Cl$: C, 59.89; H, 6.10; N, 9.99. Found: C, 59. 98; H, 6.12; N, 9.91.

5-(4-Chlorophenyl)-6-isopropyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (8). To a mixture of **7** (260 mg, 0.926 mmol) and *p*-chlorophenylisocyanate (356 mg, 2.316 mmol) dissolved in dry benzene (20 ml) was added Et_3N (10 mg, 0. 099 mmol), and the resulting mixture was stirred overnight at room temperature. Water (1 ml) was added, and the mixture was stirred for 2 h at which time the solids were removed by vacuum filtration. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by column chromatography (n-hexane/EtOAc = 6/1) to give **8** (205 mg, 84%) as a brown oil; ir (neat) 2930, 2845, 1710, 1590, 1480, 1350, 1135, 1090, 1066; ^{1}H nmr (60 MHz) 0.68 (d, J = 7 Hz, 3H, $CH(CH_3)_2$), 1.23 (d, J = 7 Hz, 3H, $CH(CH_3)_2$), 2.53 (m, 1H, $CH(CH_3)_2$), 4.42 (m, 1H, NCH_2), 4.91 (m, 1H, NCHCH), 6.50-7.41 (m, 4H, Ar), 8.17 (t, J = 1 Hz, 1H, isoxazole); Anal. Calcd for $C_{14}H_{15}N_2OCl$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.11; H, 5.80; N, 10.52.

2-(4-Chloro-*N*-propargylanilino)-2-methylpropanal oxime (11). To a stirred solution of bromo-*O*-(trimethylsilyl)aldoxime[6] (**9**) (2.38 g, 10 mmol) and 4-chloro-*N*-propargylaniline (**10**) (4.97 g, 30 mmol) in THF (30 ml) was added tetrabutylammonium fluoride (1.0 M THF solution, 12 ml) at room temperature. After being stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure and redissolved in CH_2Cl_2 (50 ml). The organic soution was washed with water, brine and dried ($MgSO_4$). The concentrated residue was purified by column chromatography (n-hexane/EtOAc = 4:1) to give **11** (1.48 g, 59%) as a clear oil; ir (neat) 3255, 2950, 1480, 1150, 1090, 935; ^{1}H nmr (60 MHz) 1.35 (s, 6H, CH_3), 2.27 (t, J = 2 Hz, 1H, CH_2CCH), 3.92 (d, J = 2 Hz, 2H, CH_2CC), 7.26 (m, 4H, Ar), 7.64 (s, 1H, CH=N), 7.99 (br s, 1H, OH); Anal. Calcd for $C_{13}H_{15}N_2OCl$: C, 62.27; H, 6.03; N, 11.18. Found: C, 62.30; H, 6.01; N, 11.10.

5-(4-Chlorobenzyl)-6,6-dimethyl-4*H*,6*H*-pyrrolo[3,4-*c*]isoxazole (12). To a stirred solution of aldoxime (**11**) (1.0 g, 4.0 mmol) in CH_2Cl_2 (20 ml) was slowly added NaOCl solution (4%, 15 ml) at 0 °C, and then stirred for *ca.* 1 h at room temperature until all starting materials disappeared. The mixture was extracted with CH_2Cl_2 and the combined extracts were dried ($MgSO_4$), then concentrated under reduced pressure. The residue was purified by column chromatography (n-hexane/EtOAc = 5:1) to afford **12** (576 mg, 58%) as a clear oil; ir (neat) 3275, 1595, 1485, 1305, 1250, 1090; ^{1}H nmr (60 MHz) 1.82 (s, 6H, CH_3), 4.36 (d, J = 1 Hz, 2H, NCH_2), 6.72-7.36 (m, 4H, Ar), 8.25 (t, J = 1 Hz, 1H, isoxazole); Anal. Calcd for $C_{13}H_{13}N_2OCl$: C, 62.78; H, 5.27; N, 11.27. Found: C, 62.75; H, 5.15; N, 11.40.

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