SYNTHESIS OF 5-(4-PYRAZOLYL AND 4-ISOXAZOLYL)-1,3-DIHYDRO-2H-1,4-BEZODIAZEPIN-2-ONES

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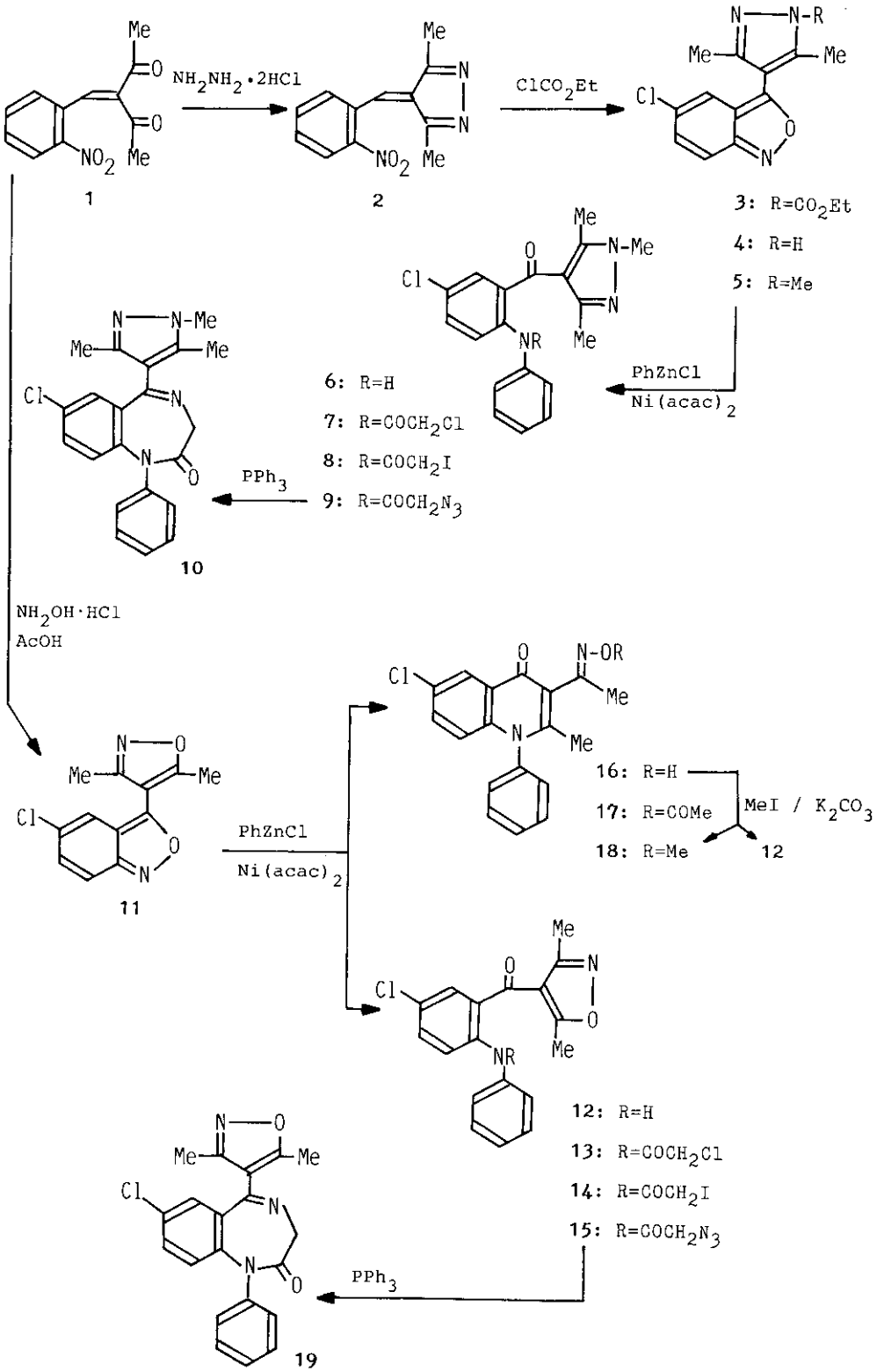
Abstract ----- Reaction of 3-(4-pyrazolyl)anthranil (**5**) with phenylzinc chloride in the presence of nickel acetylacetonate gave 4-(2-anilinobenzoyl)pyrazole (**6**). 3-(4-Isoxazolyl)anthranil (**11**) gave a mixture of 4-(2-anilinobenzoyl)isoxazole (**12**) and 1-phenyl-4-quinolone (**16**). The compounds **6** and **12** were readily transformed to the azidoacetanilides (**9** and **15**), which were cyclized to 1,4-benzodiazepin-2-ones (**10** and **19**), respectively, via aza-Wittig reaction at room temperature. Treatment of azido derivative (**25**) with triphenyl phosphine gave the phosphinimine (**26**), which was eventually cyclized to the 1,4-benzodiazepine (**27**) in refluxing toluene. In contrast, the phosphinimine (**41**) prepared from 4-(2-azidoacetamido-3-theonyl)isoxazole (**40**) failed to cyclize to the condensed thieno-1,4-diazepine (**42**).

We have previously reported that 2-nitrobenzylideneacetylacetone (**1**) reacts with hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) in acetonitrile or acetic acid at 50 °C to give the isoxazoloanthranil (**11**) in good yield.[1] An analogous cyclization was observed upon treatment of 4-(2-nitrobenzylidene)-3,5-dimethylisopyrazole (**2**)[2] with acetyl chloride, benzoyl chloride, and ethyl chloroformate to yield 3-(1-acyl- or 1-ethoxycarbonyl-3,5-dimethyl-4-pyrazolyl)anthranils such as compound (**3**).[3] Recently, it has been reported that anthranils undergo a novel transformation into N-arylaminobenzoyl compounds upon treatment with arylzinc chloride in the presence of nickel catalyst.[4] These are convenient precursors of 1,4-benzodiazepine skeletons, which have attracted attention because of their potential pharmacological activity.[5] For this reason, we investigated the conversion of 3-(4-pyrazolyl- and 4-isoxazolyl)anthranils (**5** and **11**) and related compounds (**22**,


NH2NH2·2HCl
ClCO2Et
1
2
3: R=CO2Et
4: R=H
5: R=Me
PhZnCl
Ni(acac)2
6: R=H
7: R=COCH2Cl
8: R=COCH2I
9: R=COCH2N3
PPh3
10
NH2OH·HCl
AcOH
11
PhZnCl
Ni(acac)2
16: R=H
17: R=COMe
18: R=Me
MeI / K2CO3
12
12: R=H
13: R=COCH2Cl
14: R=COCH2I
15: R=COCH2N3
PPh3
19

37) into 1,4-diazepine derivatives.

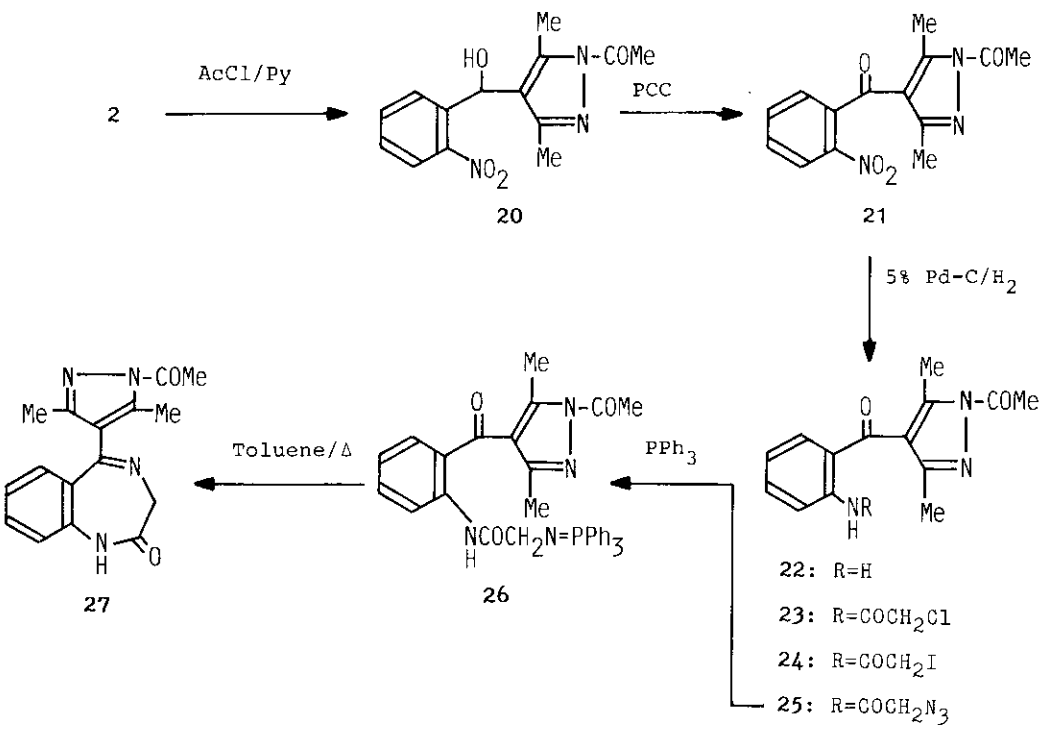
Hydrolysis of **3** with sodium hydroxide[6] followed by methylation with methyl iodide (MeI) gave 5-chloro-3-(1,3,5-trimethyl-4-pyrazolyl)anthranil (**5**) in 78% yield. When **5** was treated with phenylzinc chloride (PhZnCl), prepared in situ from phenyllithium (PhLi) and anhydrous zinc chloride ($ZnCl_2$) at 0°C, in the presence of nickel acetylacetonate [$Ni(acac)_2$] at room temperature for 6 h, 4-(2-anilino-5-chlorobenzoyl)-1,3,5-trimethylpyrazole (**6**) was produced in 77% yield. Acetylation of **6** with chloroacetyl chloride under refluxing conditions gave a quantitative yield of the amide (**7**), which was converted into the corresponding azido derivatives (**9**) via the iodide (**8**) by successive treatment with sodium iodide (NaI) and sodium azide (NaN_3). Cyclization of **9** via an intramolecular aza-Wittig reaction was then accomplished by treatment with triphenylphosphine (PPh_3) at 25 °C, yielding the desired 7-chloro-1,3-dihydro-1-phenyl-5-(1,3,5-trimethyl-4-pyrazolyl)-2H-1,4-benzodiazepin-2-one (**10**).

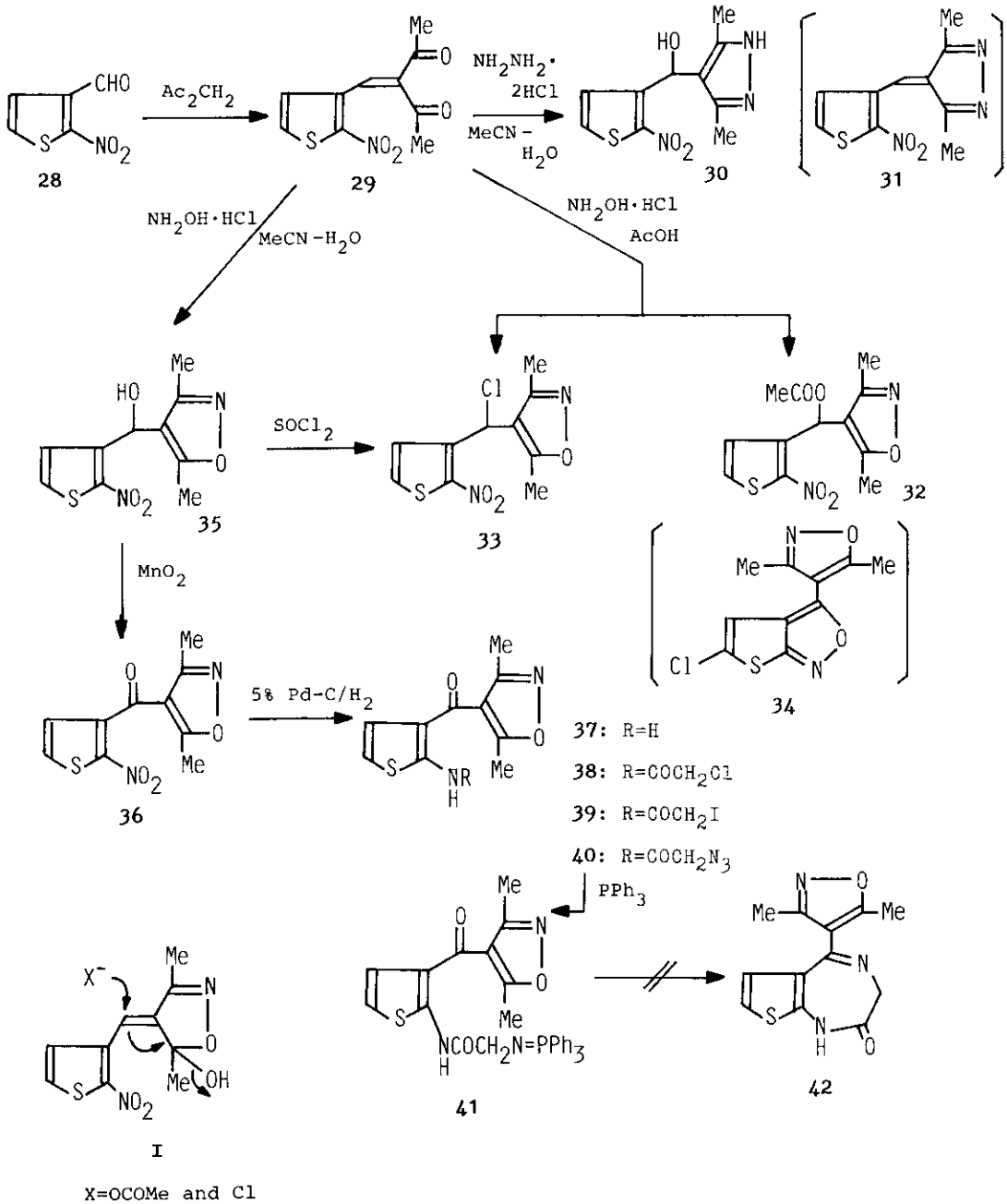
On the other hand, treatment of the isoxazoloanthranil (**11**) with two equivalents of PhZnCl at room temperature for 1 h gave a mixture of anilinobenzoylisoxazole (**12**) (49%) and a highly polar product (**16**) (41%). When an excess of PhZnCl was used, the reaction proceeded faster (even under ice cooling) and gave **12** as a sole product in a yield of over 85%. The structure of **16** was determined to be 6-chloro-1,4-dihydro-3-(α-hydroxyimino)ethyl-2-methyl-1-phenylquinolin-4-one on the basis of its spectral data and by the following chemical reactions. Heating **16** with acetic anhydride and pyridine gave the acetate (**17**), the ir spectrum of which exhibited a strong absorption band at 1765 cm^{-1} due to NOCOMe group.[6] When **16** was heated with MeI and potassium carbonate in acetone in a sealed tube, the methyl ether (**18**) was formed in 73%, accompanied with a small amount of **12**. Transformation of **16** into **12** can presumably be explained by nucleophilic addition of an iminoxy anion at the C-2 position followed by cleavage of the C-N bond. The anilide (**12**) was analogously transformed to the azidoacetamide (**15**) through the chloroacetamide (**13**) and the iodoacetamide (**14**). The ring closure of **15** to the 5-isoxazolyl-1,4-benzodiazepine (**19**) was also readily performed by aza-Wittig reaction in 88% yield.

Another approach to produce 1,4-benzodiazepine derivatives was then examined. Oxidation of **20**[6] with pyridinium chlorochromate (PCC) in $CHCl_3$ gave the ketone (**21**), which was hydrogenated over 5% palladium on carbon (Pd-C) in EtOAc to give the amino ketone (**22**). Without isolation, **22** was successively treated with

chloroacetyl chloride, NaI, and NaN_3 to give the azidoacetamide (**25**) in a similar way. Treatment of **25** with Ph_3P resulted in the formation of intermediate phosphinimine (**26**) in a high yield of 90%. Although **26** was rather stable and resisted the intramolecular cyclization under usual conditions, the desired 5-(1-acetyl-4-pyrazolyl)-1,4-benzodiazepine (**27**) was obtained in 25% yield by refluxing in toluene for 7 h.

Finally, synthesis of the condensed thieno-1,4-diazepine was attempted. Knoevenagel condensation of 2-nitrothiophene-3-carbaldehyde (**28**)[7] with acetylacetone gave the nitrothienylmethyleneacetylacetone (**29**) in 52% yield. The reaction of **29** with hydrazine dihydrochloride ($NH_2NH_2 \cdot 2HCl$) in aqueous acetonitrile did not give the expected isopyrazole (**31**)[2] corresponding to **2**, but only the pyrazole (**30**) was formed in good yield. Furthermore, heating **29** with $NH_2OH \cdot HCl$ in glacial acetic acid also did not give the anthranil (**34**) corresponding to **11**, and instead gave a mixture of the acetate(**32**) and the chloride (**33**) via a intermediate **I**. However, the alcohol (**35**) was obtained by the reaction of **29** with $NH_2OH \cdot HCl$ in aqueous acetonitrile. Attempts to obtain **34** by treatment of **35** with thionyl chloride were also unsuccessful,[8] and the chloride (**33**) was isolated as the sole product. Subsequently, **35** was oxidized with active manganese dioxide in $CHCl_3$ to afford the




CHO
NO2
28
Ac2CH2
Me
O
29
NH2NH2·
2HCl
MeCN –
H2O
HO
NH
N
30
31
NH2OH·HCl
MeCN–H2O
NH2OH·HCl
AcOH
35
SOCl2
Cl
33
MeCOO
32
MnO2
36
5% Pd-C/H2
NR
H
34
37: R=H
38: R=COCH2Cl
39: R=COCH2I
40: R=COCH2N3
PPh3
NCOCH2N=PPh3
41
42
X⁻
OH
I
X=OCOMe and Cl

ketone (**36**) in 96% yield. Catalytic hydrogenation of **36** over 5% Pd-C in EtOAc, followed by treatment with chloroacetyl chloride gave the chloroacetamide (**38**) in a 36% yield from **36**. Treatment of the azide (**40**), prepared via the iodide (**39**), with PPh_3 gave the phosphinimine (**41**) in 37% yield. Taking account of the above-mentioned reaction of **26**, we attempted cyclization of the phosphinimine (**41**) by refluxing toluene or xylene, but the desired product (**42**) was not isolated at all. None of compounds tested (**10**, **19**, **27**, and **16**) had any significant pharmacological activity.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were determined using a Shimadzu IR-435 spectrophotometer. ^1H and ^{13}C nmr spectra were obtained using a Varian XL-300 spectrometer with TMS as the internal standard. Mass spectra were measured with a Hitachi M-80 instrument. For column chromatography, SiO_2 (Merck Art 7734) was used.

5-Chloro-3-(1,3,5-trimethyl-4-pyrazolyl)anthranil (**5**)

A mixture of **4**[6] (1.04 g, 4.2 mmol), MeI (1.2 g, 8.4 mmol), and K_2CO_3 (1.16 g, 8.4 mmol) in acetone (10 ml) was heated at 65 °C for 15 h in a sealed tube. The reaction mixture was poured into water, and extracted with EtOAc. The extract was washed with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from ligroin to give **5** (855 mg, 78%) as colorless needles, mp 125-126 °C; ^1H nmr ($CDCl_3$) δ 2.36 and 2.39 (each 3H, each s, 2 x Me), 3.84 (3H, s, NMe), and 7.20-7.60 (3H, m, Ar-H). Anal. Calcd for $C_{13}H_{12}ClN_3O$: C, 59.65; H, 4.62; N, 16.05. Found: C, 59.82; H, 4.61; N, 15.97.

4-(2-Anilino-5-chlorobenzoyl)-1,3,5-trimethylpyrazole (**6**)

To a solution of $ZnCl_2$ (2.73 g, 20 mmol) in THF (5 ml), 0.97 mol benzene-ether solution of PhLi (16 mmol) was added under ice cooling, and the mixture was stirred at room temperature for 5 min. To the resulting phenylzinc chloride solution cooled to 0 °C, a solution of **5** (2.1 g, 8 mmol) in THF (15 ml) was added, followed by addition of $Ni(acac)_2$ (208 mg, 0.8 mmol) in THF (3 ml). The reaction mixture was stirred for 6 h at room temperature under N_2, poured into ice-water, and then extracted with ether. The extract was washed with brine, dried over anhyd. $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from diisopropyl ether to give **6** (2.08 g, 77%) as yellow needles, mp 140-141 °C; ir (KBr) 3280 (NH) and 1600 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.21 and 2.29 (each

3H, each s, 2 x Me), 3.90 (3H, s, NMe), 7.00-7.50(8H, m, Ar-H), and 9.78 (1H, s, NH); ms m/z 341 (M^++1). Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.33; N, 12.36. Found: C, 67.46; H, 5.23; N, 12.51.

Reaction of Anthranil (**11**) with Phenylzinc Chloride

Method A ----- As described for the preparation of **6**, **11**[1] (249 mg, 1 mmol) was treated with PhZnCl, prepared from PhLi (2 mmol) and $ZnCl_2$ (2.4 mmol), in the presence of $Ni(acac)_2$ (0.1 mmol). After being stirred for 1 h at room temperature, the reaction mixture was poured into ice-water and extracted with EtOAc. The extract was washed with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was triturated with benzene, and the resulting solid was collected by filtration, washed with benzene and recrystallized from MeOH to give 6-chloro-1,4-dihydro-3-(α-hydroxyimino)ethyl-2-methyl-1-phenylquinolin-4-one (**16**) (135 mg, 41%) as colorless needles, mp 252-254 °C; ir (KBr) 3200 (=NOH) and 1580-1600 (N-C=C-CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.88 and 2.08 (each 3H, each s, 2 x Me), 6.68 (1H, d, J=8.5 Hz, 8-H), 7.10 (1H, dd, J=8.5, 3.3 Hz, 7-H), 7.45-7.75 (5H, m, Ar-H), and 8.12 (1H, d, J=3.3 Hz, 5-H); ^{13}C nmr (DMSO-d_6) δ 172.3 (4-C); ms m/z 326 (M^+). Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.15; H, 4.62; N, 8.57. Found: C, 66.05; H, 4.62; N, 8.34. The filtrate was condensed and the residue was purified by column chromatography using benzene as eluent to give 4-(2-anilono-5-chlorobenzoyl)-3,5-dimethylisoxazole (**12**) (161 mg, 49%), which was recrystallized from diisopropyl ether, yellow needles, mp 125-127 °C; ir (KBr) 3280 (NH) and 1630 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.34 and 2.43 (each 3H, each s, 2 x Me), 7.00-7.50(8H, m, Ar-H), and 10.0 (1H, bs, NH); ms m/z 326 (M^+). Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.15; H, 4.62; N, 8.57. Found: C, 65.76; H, 4.52; N, 8.84.

Method B ----- A solution of **11** (1.49 g, 6 mmol) in THF (10 ml) was added to a solution of PhZnCl, prepared from PhLi (24 mmol) and $ZnCl_2$ (30 mmol), in the presence of $Ni(acac)_2$ (0.6 mmol) at -40 °C, and the reaction mixture was stirred for 30 min at 0 °C, quenched by the addition of 5% HCl and water, and extracted with Et_2O. The extract was washed with brine, dried over anhyd. $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography using benzene as eluent to give **12** (1.67 g, 85%), which was identical with a sample obtained by Method A.

3-(α-Acetoxyimino)ethyl-6-chloro-1,4-dihydro-2-methyl-1-phenylquinolin-4-one (**17**) A solution of **16** (326 mg, 1 mmol) and pyridine (1 drop) in Ac_2O (5 ml) was heated at 60 °C overnight. The reaction mixture was poured into ice-water, made alkaline

with $NaHCO_3$, and extracted with EtOAc. The extract was washed with water, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using benzene as eluent to give **17** (236 mg, 64 %) as a viscous oil, ir (Neat) 1765 (CO) and 1585-1605 (N-C=C-CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.90 and 2.10 (each 3H, s, 2 x Me), 2.38 (3H, s, COMe), 6.60 (1H, d, J=8.5 Hz, 8-H), 7.35 (1H, dd, J=8.5, 3.3 Hz, 7-H), 7.20-7.70 (5H, m, Ar-H), and 8.40 (1H, d, J=3.3 Hz, 5-H); ms m/z 368 (M^+).

Methylation of **16**

A mixture of **16** (653 mg, 2 mmol), MeI (568 mg, 4 mmol), and K_2CO_3 (552 mg, 4 mmol) in acetone (10 ml) was heated in a sealed tube at 80°C for 24 h. The reaction mixture was diluted with water, and extracted with EtOAc. The extract was washed with water, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using benzene as eluent. The First fraction afforded **12** (77 mg, 12%). The second fraction gave 6-chloro-1,4-dihydro-3-(α-methoxyimino)ethyl-2-methyl-1-phenylquinolin-4-one (**18**) (500 mg, 73%), which was recrystallized from MeOH, colorless needles, mp 185-187°C; ir (Nujol) 1580-1615 (N-C=C-CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.95 and 2.20 (each 3H, each s, 2 x Me), 3.32 (3H, s, OMe), 6.60 (1H, d, J=8.5 Hz, 8-H), 7.30 (1H, dd, J=8.5, 3.3 Hz, 7-H), 7.20-7.65 (5H, m, Ar-H), and 8.38 (1H, d, J=3.3 Hz, 5-H); ms m/z 340 (M^+). Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.74; H, 5.07; N, 8.07.

General Procedure for Reaction of Anilides (**6** and **12**) with Chloroacetyl Chloride

A mixture of anilides (1 mmol) and chloroacetyl chloride (10 mmol) was heated under reflux for 10 min and treated according to the procedure reported by Baum[4] to give the chloroacetanilides (**7** and **13**).

4-[5-Chloro-2-(N-chloroacetyl-N-phenyl)aminobenzoyl]-1,3,5-trimethylpyrazole (**7**)

Yield 98%, pale yellow needles, mp 146-147°C (from diisopropyl ether-ligroin); ir (KBr) 1680 and 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.25 (6H, s, 2 x Me), 3.70 (3H, s, NMe), 3.85 (2H, s, CH_2), and 7.00-7.65 (8H, m, Ar-H); ms m/z 416 (M^+). Anal. Calcd for $C_{21}H_{19}Cl_2N_3O_2$: C, 60.58; H, 4.60; N, 10.09. Found: C, 60.77; H, 4.64; N, 10.18.

4-[5-Chloro-2-(N-chloroacetyl-N-phenyl)aminobenzoyl]-3,5-dimethylisoxazole (**13**)

Yield 93%, pale yellow needles, mp 128-130°C (from MeOH); ir (KBr) 1680 and 1590 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.35 and 2.45 (each 3H, each s, 2 x Me), 3.90 (2H, s, CH_2), and 7.05-7.70 (8H, m, Ar-H); ms m/z 402 (M^+). Anal. Calcd for $C_{20}H_{16}Cl_2N_2O_3$:

C, 59.56; H, 3.99; N, 6.94. Found: C, 59.75; H, 3.85; N, 7.01.

General Procedure for the Preparation of Iodoacetanilides (**8** and **14**)

Reaction of the chlorides (1 mmol) and NaI (1.1 mmol) in acetone (10 ml) was carried out according to the method of Baum.[4]

4-[5-Chloro-2-(N-iodoacetyl-N-phenyl)aminobenzoyl]-1,3,5-trimethylpyrazole (**8**)

Yield 86%, pale yellow needles, mp 199-200°C (from CH_2Cl_2-hexane); ir (KBr) 1660 and 1630 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.28 and 2.30 (each 3H, each s, 2 x Me), 3.62 (3H, s, NMe), 3.75 (2H, s, CH_2), and 7.05-7.75 (8H, m, Ar-H); ms m/z 507 (M^+). Anal. Calcd for $C_{21}H_{19}ClIN_3O_2$: C, 49.67; H, 3.77; N, 8.27. Found: C, 49.82; H, 3.69; N, 8.37.

4-[5-Chloro-2-(N-iodoacetyl-N-phenyl)aminobenzoyl]-3,5-dimethylisoxazole (**14**)

Yield 88%, pale yellow needles, mp 174-175°C (from EtOAc); ir (KBr) 1640 and 1590 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.39 and 2.42 (each 3H, each s, 2 x Me), 3.60 (2H, s, CH_2), and 7.05-7.70 (8H, m, Ar-H); ms m/z 494 (M^+). Anal. Calcd for $C_{20}H_{16}ClIN_2O_3$: C, 48.55; H, 3.26; N, 5.66. Found: C, 48.62; H, 3.30; N, 5.49.

General Procedure for the Preparation of Azidoacetanilides (**9** and **15**)

Reaction of the iodides (1 mmol) with NaN_3 (2 mmol) in DMSO (4 ml) was carried out according to the method of Baum.[4]

4-[2-(N-Azidoacetyl-N-phenyl)amino-5-chlorobenzoyl]-1,3,5-trimethylpyrazole (**9**)

Yield 97% as a pale yellow viscous oil; ir (Neat) 2200 (N_3), 1680 and 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.25 (6H, s, 2 x Me), 3.70 (2H, s, CH_2), 3.76 (3H, s, NMe), and 7.05-7.60 (8H, m, Ar-H); ms m/z 422 (M^+). Calcd for $C_{21}H_{19}ClN_6O_2$: M^+, 422.1256. Found: 422.1245.

4-[2-(N-Azidoacetyl-N-phenyl)amino-5-chlorobenzoyl]-3,5-dimethylisoxazole (**15**)

Yield 95%, beige prisms, mp 124-125°C (from MeOH), ir (KBr) 2200 (N_3), 1660 and 1600 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.38 and 2.48 (each 3H, each s, 2 x Me), 3.80 (2H, s, CH_2), 7.10-7.60 (8H, m, Ar-H); ms m/z 409 (M^+). Anal. Calcd for $C_{20}H_{16}ClN_5O_3$: C, 58.16; H, 3.93; N, 17.09. Found: C, 58.33; H, 4.14; N, 17.24.

General Procedure for the Preparation of 1,3-Dihydro-2H-1,4-benzodiazepin-2-ones (**10** and **19**)

A solution of the azide (1 mmol) in THF (2 ml) and a solution of PPh_3 (1.1 mmol) in Et_2O (4 ml) were mixed, and the mixture was stirred under N_2 at 25°C for 17h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography using EtOAc as eluent.

7-Chloro-1,3-dihydro-1-phenyl-5-(1,3,5-trimethyl-4-pyrazolyl)-2H-1,4-benzodiaze-

pin-2-one (10)

Yield 98%, colorless needles, mp 200-204°C (from EtOH); ir (KBr) 1680 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ2.0 and 2.30 (each 3H, each s, 2 x Me), 3.80 (3H, s, NMe), 3.94 and 4.91 (each 1H, each d, J=10.4 Hz, 3-H_2), 6.88 (1H, d, J=8.4 Hz, 9-H), and 7.20-7.45 (7H, m, Ar-H); ms m/z 378 (M^+). Anal. Calcd for $C_{21}H_{19}ClN_4O$: C, 66.57; H, 5.05; N, 14.78. Found: C, 66.62; H, 5.00; N, 14.89.

7-Chloro-1,3-dihydro-5-(3,5-dimethyl-4-isoxazolyl)-1-phenyl-2H-1,4-benzodiazepin-2-one (19)

Yield 88%, colorless needles, mp 205-207°C (from benzene); ir (KBr) 1685 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ2.20 and 2.35 (each 3H, each s, 2 x Me), 3.95 and 4.95 (each 1H, each d, J=10.5 Hz, 3-H_2), 6.90 (1H, d, J=8.4 HZ, 9-H), and 7.15-7.47 (7H, m, Ar-H); ms m/z 365 (M^+). Anal. Calcd for $C_{20}H_{16}ClN_3O_2$: C, 65.66; H, 4.40; N, 11.48. Found: C, 65.84; H, 4.31; N, 11.32.

1-Acetyl-4-(2-nitrobenzoyl)-3,5-dimethylpyrazole (21)

To a stirred suspension of PCC (2.8 g, 14.3 mmol) in CH_2Cl_2 (30 ml), a solution of **20** (3.76 g, 13 mmol) in CH_2Cl_2 (65 ml) was added in one portion at room temperature. Then, two 2.8 g portions of PCC were added at 40 min intervals, and the reaction mixture was stirred for additional 1 h. The mixture was diluted with Et_2O (65 ml) and filtered through Celite. The filtrate was then passed through the SiO_2 column to remove the colored complexes and concentrated under reduced pressure. The residue was recrystallized from EtOH to give **21** (3.14 g, 84%) as pale yellow needles, mp 110-111°C; ir (KBr) 1740 and 1650 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ2.10 and 2.49 (each 3H, each s, 2 x Me), 2.68 (3H, s, COMe), and 7.35-8.15 (4H, m, Ar-H); ms m/z 288 (M^+). Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.50; H, 4.45; N, 14.75.

1-Acetyl-4-(2-chloroacetamidobenzoyl)-3,5-dimethylpyrazole (23)

A solution of **21** (3.11 g, 10.8 mmol) in EtOAc (40 ml) was hydrogenated using a Skita apparatus (initial pressure: 1.5 Kg/cm^2) with 5% Pd-C (770 mg) for 4 h. After disappearance of the starting material by tlc, catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (20 ml) was added Et_3N (3.27 g, 32.4 mmol) followed by chloroacetyl chloride (3.66 g, 32.4 mmol) under ice cooling, and the mixture was stirred at room temperature for 4 h. The reaction mixture was poured into a vigorously stirred mixture of $NaHCO_3$ (5 g) and ice-water (50 ml), and the organic layer was separated, washed with saturated $NaHCO_3$ solution, water,

and dried over anhyd. Na_2SO_4. The EtOAc solution was concentrated, and the residue was purified by column chromatography using EtOAc-benzene (1:99) as eluent to give **23** (3.09 g, 86%) as a pale yellow viscous oil; ir (Neat) 1735, 1675, and 1625 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.20, 2.48, and 2.70 (each 3H, each s, 2 x Me and COMe), 4.20 (2H, s, CH_2), 7.10-7.65 (3H, m, Ar-H), 8.65 (1H, dd, J=8.5, 3.3 Hz, 6-H), and 11.80 (1H, s, NH); ms m/z 335 (M^+). Calcd for $C_{16}H_{16}ClN_3O_3$: M^+, 335.0850. Found: 335.0850.

1-Acetyl-3,5-dimethyl-4-(2-iodoacetamidobenzoyl)pyrazole **(24)**

Reaction of **23** (3.09 g, 9.25 mmol) and NaI (1.39 g, 10.2 mmol) in acetone (25 ml) was carried out as described for the preparation of **14**. The crude solid was recrystallized from EtOH to give **24** (3.72 g, 95%) as beige needles, mp 114-116°C ; ir (Nujol) 1735, 1660, and 1625 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.20, 2.46, and 2.70 (each 3H, each s, 2 x Me and COMe), 3.88 (2H, s, CH_2), 7.10-7.60 (3H. m, Ar-H), 8.61 (1H, dd, J=8.5, 3.3 Hz, 6-H), and 11.65 (1H, s, NH); ms m/z 425 (M^+). Anal. Calcd for $C_{16}H_{16}IN_3O_3$: C, 45.19; H, 3.79; N, 9.88. Found: C, 45.00; H, 3.85; N, 9.49.

1-Acetyl-4-(2-azidoacetamidobenzoyl)-3,5-dimethylpyrazole **(25)**

Reaction of **24** (3.12 g, 7.3 mmol) and NaN_3 (0.95 g, 14.6 mmol) in DMSO (15 ml) was carried out as described for the preparation of **15**. The crude solid was recrystallized from EtOH to give **25** (2.29 g, 92%) as pale yellow needles, mp 88-89°C ; ir (Nujol) 2200 (N_3), 1735, 1665, and 1620 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.20, 2.48, and 2.72 (each 3H, each s, 2 x Me and COMe), 4.15 (2H, s, CH_2), 7.15-7.60 (3H, m, Ar-H), 8.67 (1H, dd, J=8.5, 3.3 Hz, 6-H), and 11.65 (1H, s, NH); ms m/z 340 (M^+). Anal. Calcd for $C_{16}H_{16}N_6O_3$: C, 56.46; H, 4.74; N, 24.70. Found: C, 56.55; H, 4.69; N, 24.67.

1-Acetyl-3,5-dimethyl-4-(2-triphenylphosphiniminoacetamidobenzoyl)pyrazole **(26)**

A solution of **25** (1.81 g, 5.32 mmol) in THF (21 ml) and a solution of PPh_3 (1.54 g, 5.85 mmol) in Et_2O (21 ml) were mixed and the mixture was allowed to stand for 42 h under N_2. The resulting solid was collected by filtration and the filtrate was concentrated under reduced pressure. The combined solid was recrystallized from acetone to give **26** (2.74 g, 90%) as beige needles, mp 94-94.5°C ; ir (Nujol) 1740, 1680, and 1638 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.15 and 2.42 (each 3H, each s, 2 x Me), 2.70 (3H, s, NCOMe), 3.80-3.90 (2H, m, CH_2), and 7.10-7.90 (19H, m, Ar-H); ms m/z 574 (M^+). Anal. Calcd for $C_{31}H_{31}N_4O_3P$: C, 71.07; H, 5.44; N, 9.76. Found: C, 71.17; H, 5.36; N, 9.85.

5-(1-Acetyl-3,5-dimethyl-4-pyrazolyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**27**)

A solution of **26** (547 mg, 1mmol) in dry toluene (5 ml) was refluxed for 7 h under N_2. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using $CHCl_3$-MeOH (30:1) as eluent to give **27** (75 mg, 25%) as an amorphous colorless powder, ir (Nujol) 3350 (NH), 1735, and 1645 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.08 (3H, s, COMe), 2.13 (6H, s, 2 x Me), 4.03 (2H, q, J=15 Hz, CH_2), and 7.20-7.70 (4H, m, Ar-H); ms m/z 296 (M^+).

2-Nitro-3-thienylmethyleneacetylacetone (**29**)

A mixture of 2-nitrothiophene-3-carbaldehyde (**28**) (5.13 g, 32.7 mmol) and acetylacetone (3.27 g, 32.7 mmol) containing 10 drops of piperidine was allowed to stand for 2 days. Resulting solid was recrystallized from EtOH to give **29** (6.99 g, 52%) as yellow prisms, mp 90-91 °C ; ir (KBr) 1710 and 1690 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.28 and 2.51 (each 3H, each s, 2 x Me), 7.08 (1H, d, J=5.6 Hz, 2-H of thiophene ring), 7.51 (1H, d, J=5.6 Hz, 3-H of thiophene ring), and 8.10 (1H, s, =CH); ms m/z 240 (M^++1). Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.19; H, 3.79; N, 5.85. Found: C, 50.06; H, 3.72; N, 5.69.

1-(3,5-Dimethyl-4-pyrazolyl)-1-(2-nitro-3-thienyl)methanol (**30**)

A solution of **29** (2.39 g, 10 mmol) and $NH_2NH_2 \cdot 2HCl$ (1.05 g, 10 mmol) in 70% aqueous acetonitrile (100 ml) containing conc. HCl (0.5 ml) was heated at 60°C for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot water (80 ml). The aqueous solution was decolorized by Nolite and filtered through Celite. The filtrate was cooled, and neutralized with 15% aqueous ammonia. The resulting precipitate was collected by filtration, washed with cold acetone, and recrystallized from EtOAc to give **30** (2.04 g, 81%) as colorless needles, mp 170-171 °C ; ir (KBr) 3400-3200 (OH and NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.97 (6H, s, 2 x Me), 5.57 (1H, d, J=4 Hz, OH), 6.14 (1H, d, J=4 Hz, CH), 7.51 (1H, d, J=5.6 Hz, 3-H of thiophene ring), and 7.95 (1H, d, J=5.6 Hz, 2-H of thiophene ring); ms m/z 253 (M^+). Anal. Calcd for $C_{10}H_{11}N_3O_3S$: C, 47.41; H, 4.37; N, 16.60. Found: C, 47.50; H, 4.33; N, 16.64.

Reaction of **29** with Hydroxylamine Hydrochloride in Acetic Acid

A solution of **29** (478 mg, 2 mmol) and $NH_2OH \cdot HCl$ in glacial AcOH (8 ml) was heated at 60 °C for 20 h. The solvent was evaporated under reduced pressure, and the residue was stirred with a mixture of saturated $NaHCO_3$ solution and EtOAc. The organic layer was separated, washed with water, dried over anhyd. Na_2SO_4, and concentrated. The residue was purified by column chromatography using EtOAc-hexane

(1:1) as eluent. The former fraction gave 1-(3,5-dimethyl-4-isoxazolyl)-1-(2-nitro-3-thienyl)methyl chloride (**33**) (202 mg, 37%), which was recystallized from benzene-ligroin, mp 108-109 °C as colorless needles, ^{1}H nmr ($CDCl_3$) δ 2.21 and 2.38 (each 3H, each s, 2 x Me), 6.72 (1H, s, CH), and 7.60 (2H, q, J=5.6 Hz, 2-H and 3-H of thiophene ring); ms m/z 272 (M^+). Anal. Calcd for $C_{10}H_9ClN_2O_3S$: C, 44.03; H, 3.32; N, 10.27. Found: C, 44.30; H, 3.33; N, 10.43. The second fraction afforded 1-(3,5-dimethyl-4-isoxazolyl)-1-(2-nitro-3-thienyl)methyl acetate (**32**) (208 mg, 36%), which was recrystallized from benzene-ligroin, mp 112-113 °C as colorless needles; ir (KBr) 1720 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.12 (6H, s, 2 x Me), 2.44 (3H, s, MeCO), 7.35 (1H, s, CH), 7.36 (1H, d, J=5.5 Hz, 3-H of thiophene ring), and 7.55 (1H, d, J=5.5 Hz, 2-H of thiophene ring); ms m/z 297 (M^+). Anal. Calcd for $C_{12}H_{11}N_2O_5S$: C, 48.81; H, 3.75; N, 9.49. Found: C, 48.68; H, 4.05; N, 9.48.

1-(3,5-Dimethyl-4-isoxazolyl)-1-(2-nitro-3-thienyl)methanol (**35**)

A solution of **29** (478 mg, 2 mmol) and $NH_2OH \cdot HCl$ (139 mg, 2 mmol) in acetonitrile (12 ml) was heated at 60 °C for 14 h. The solvent was evaporated under reduced pressure, and the residue was stirred with a mixture of saturated $NaHCO_3$ solution and EtOAc. The organic layer was separated, washed with water, dried over anhyd. Na_2SO_4, and concentrated. The residue was recrystallized from benzene-ligroin to give **35** (324 mg, 64%) as colorless prisms, mp 162-164 °C ; ir (KBr) 3400 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.17 and 2.39 (each 3H, each s, 2 x Me), 2.79 (1H, d, J=4 Hz, OH), 6.35 (1H, d, J=4 Hz, CH), 7.34 (1H, d, J=5.6 Hz, 3-H of thiophene ring), and 7.54 (1H, d, J=5.6 Hz, 2-H of thiophene ring); ms m/z 255 (M^++1). Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H,3.96; N, 11.02. Found: C, 47.17; H, 3.91; N, 11.12.

Reaction of **35** with Thionyl Chloride

A mixture of **35** (254 mg, 1 mmol) and thionyl chloride (3.57 g, 30 mmol) in $CHCl_3$ (5 ml) was refluxed for 15 h under N_2. After concentration of the mixture, the residue was dissolved in benzene (20 ml), and the solution was again concentrated under reduced pressure. The residue was recrystallized from benzene-ligroin to give **33** (231 mg, 85%), which was identical with an above sample.

3,5-Dimethyl-4-(2-nitro-3-thenoyl)isoxazole (**36**)

A mixture of **35** (1.85 g, 7.3 mmol) and MnO_2 (19 g) in $CHCl_3$ (120 ml) was vigorously stirred at room temperature for 7 h and filtered through Celite to remove MnO_2. The filtrate was concentrated and the residue was recrystallized from benzene-ligroin to give **36** (1.78 g, 96%) as pale yellow needles, mp 101-101.5 °C ; ir (KBr) 1650 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.27 and 2.33 (each 3H, each s, 2 x Me),

7.05 (1H, d, J=5.0 Hz, 3-H of thiophene ring), and 7.65 (1H, d, J=5 Hz, 2-H of thiophene ring); ms m/z 252 (M^+). Anal. Calcd for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.74; H, 3.20; N, 11.16.

4-(2-Chloroacetamido-3-thenoyl)-3,5-dimethylisoxazole (**38**)

A solution of **36** (1.26 g, 5 mmol) in EtOAc (10 ml) was hydrogenated using Skita apparatus (initial pressure: 1.5 Kg/cm^2) with 5% Pd-C (0.5 g) for 4 h. Catalyst was removed by filtration through Celite, and the filtrate was treated with chloroacetyl chloride (0.96 g, 8.5 mmol) and Et_3N (0.83 g, 8.5 mmol) as described for the preparation of **23**. The crude solid was recrystallized from benzene-ligroin to give **38** (537 mg, 36%) as pale yellow needles, mp 158-160°C; ir (KBr) 3420 (NH), 1675 and 1610 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.31 and 2.43 (each 3H, each s, 2 x Me), 4.30 (2H, s, CH_2), 6.88 (2H, d and d, J=5.5 Hz, 2-H and 3-H of thiophene ring); ms m/z 298 (M^+). Anal. Calcd for $C_{12}H_{11}ClN_2O_3S$: C, 48.24; H, 3.69; N, 9.38. Found: C, 47.77; H, 3.63; N, 9.13.

3,5-Dimethyl-4-(2-iodoacetamido-3-thenoyl)isoxazole (**39**)

A mixture of **38** (537 mg, 1.8 mmol) and NaI (285 mg, 1.9 mmol) in acetone (20 ml) was treated as described for the preparation of **24**. The crude solid was recrystallized from benzene-ligroin to give **39** (690 mg, 98%) as beige needles, mp 171-173 °C ; ir (KBr) 3420 (NH), 1670 and 1610 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.30 and 2.43 (each 3H, each s, 2 x Me), 3.98 (2H, s, CH_2), 6.85 (2H, d and d, J=5.5 Hz, 2-H and 3-H of thiophene ring); ms m/z 390 (M^+). Anal. Calcd for $C_{12}H_{11}IN_2O_3S$: C, 36.92; H, 2.82; N, 7.18. Found: C, 37.18; H, 2.84; N, 6.85.

4-(2-Azidoacetamido-3-thenoyl)-3,5-dimethylisoxazole (**40**)

A mixture of **39** (267 mg, 0.68 mmol) and NaN_3 in DMSO (5 ml) was treated as described for the preparation of **25**. The crude solid was rerystallized from benzene-ligroin to give **40** (179 mg, 86%) as beige prisms, mp 113-115°C; ir (KBr) 2200 (N_3), 1675 and 1610 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.31 and 2.42 (each 3H, each s, 2 x Me), 4.28 (2H, s, CH_2), 6.88 (2H, d and d, J=5.6 Hz, 2-H and 3-H of thiophene ring); ms m/z 305 (M^+). Anal. Calcd for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.61; N, 22.95. Found: C, 47.37; H, 3.58; N, 23.14.

3,5-Dimethyl-4-(2-triphenylphosphiniminoacetamido-3-thenoyl)isoxazole (**41**)

A solution of **40** (481 mg, 1.58 mmol) in THF (5 ml) and a solution of PPh_3 (456 mg, 1.74 mmol) in Et_2O (7 ml) were mixed, and the mixture was allowed to stand under N_2 overnight. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using a mixture of $CHCl_3$-MeOH (5:1) as

eluent to give **41** (311 mg, 37%) as a glassy solid, ^{1}H nmr ($CDCl_3$) δ 2.28 and 2.40 (each 3H, each s, 2 x Me), 4.15 (2H, q, J=7.5 Hz, CH_2), 6.70 and 6.81 (each 1H, each d, J=5.5 Hz, 2-H and 3-H of thiophene ring), and 7.60-8.0 (15H, m, Ar-H); MS m/z 539 (M^+).

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