THE PREPARATION OF THIOPHENE APPENDED VINYLOGOUS IMINIUM SALTS AND THEIR APPLICATION TO THE REGIOSELECTIVE SYNTHESIS OF THIENYLPYRIMIDINES AND THIENYLPYRROLES[1]

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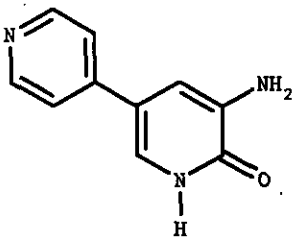
Abstract- The synthesis of two, vinylogous iminium salts, which contain an appended thiophene group, are described along with their conversion to thiophene substituted pyrimidines and pyrroles.

Reactions that result in the overall formation of biheterocyclic molecules represent important synthetic methodology for medicinal chemists as well as other practitioners who are responsible for the discovery of new bioactive substances.[2] Amrinone (**1**) is a simple example[3] of this class of molecules and it represents a regiospecifically oriented pyridylpyridone which has

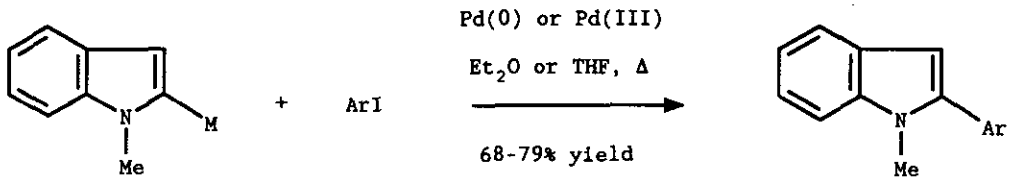
found important applications as a cardiotonic agent.



1

Many of the recent reactions[2] which have been applied to the synthesis of biheterocyclic compounds involve cross-coupling between heterocyclic organometallic species and heterocyclic halides. Kalinin has recently reviewed[2] this area and the following reaction (Scheme 1) is typical of such procedures.

Scheme 1



2

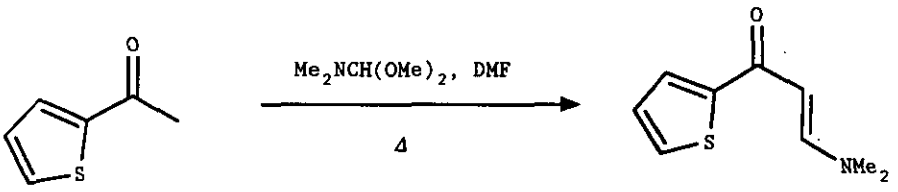
M = Li, MgBr, $B(OH)_2$

3

An alternative method[4] for the regioselective formation of biheterocyclic systems can involve the construction of a heterocycle appended synthon which could be used to form the second heterocyclic moiety. Our research group has been interested in developing vinamidinium salts and related compounds[5] as three carbon building blocks in organic synthesis. If an appropriate heterocycle could be appended to the vinamidinium salt

backbone, the resulting molecule could serve as the precursor to a variety of biheterocyclic systems. This approach has not received significant attention[4] and we have embarked on a long term project to evaluate this strategy for the synthesis of a variety of biheterocyclic systems. We would now like to report the synthesis and some preliminary findings for a thiophene appended vinamidinium salt and a thiophene appended chloropropeniminium salt. The starting material for the synthesis was 2-acetylthiophene (**4**) which was converted to the corresponding enaminone (**5**) by reaction with *N,N*-dimethylformamide dimethyl acetal (DMF acetal) (Scheme 2).

Scheme 2



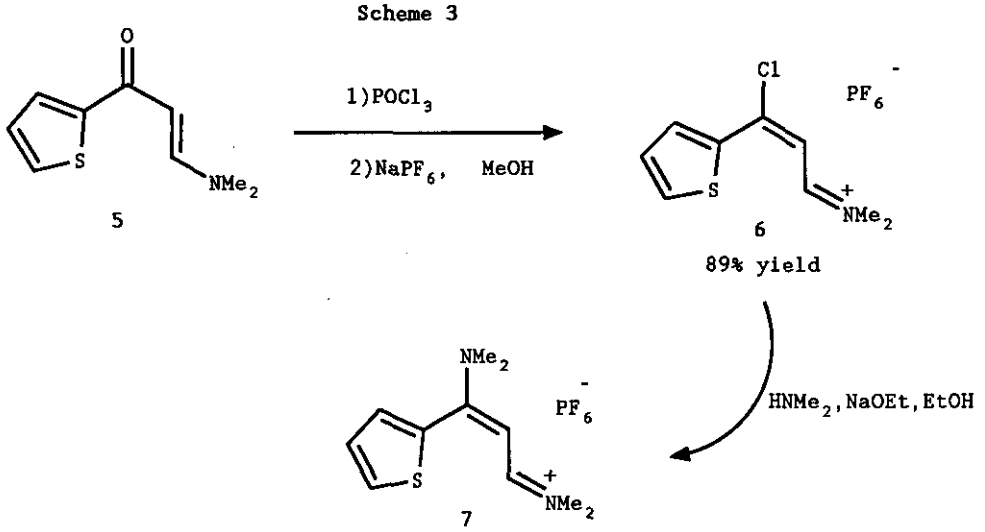
4 5

95% yield

The enaminone was reacted with phosphorous oxychloride to give the chloropropeniminium salt (**6**) which was crystallized in good yield with the use of the hexafluorophosphate anion. Subsequently, the chloropropeniminium salt was transformed to the unsymmetrical vinamidinium salt (**7**) by reaction with dimethylamine (Scheme 3).

This sequence of reactions has, therefore, provided a 2-thiophene group appended to either a chloropropeniminium salt (**6**) or vinamidinium salt (**7**) in a regiospecific fashion. To initially test the utility of these

Scheme 3



heterocycle appended synthons (**6** and **7**), both salts were reacted with guanidine under basic conditions to give the 2-amino-4-(2-thienyl)-pyrimidine (**8a**) (Scheme 4). The ^{1}H nmr of the pyrimidine product (**8a**) clearly demonstrated the presence of the thiophene group as well as the two adjacent pyrimidine hydrogens.

It is interesting to note that the vinamidinium salt (**7**) gives somewhat better yields of the thienylpyrimidine (**8a**) than does the chloropropeniminium salt (**6**) and this may be due to the greater reactivity of the latter. A variety of amidines were then reacted with the vinamidinium salt (**7**) in the presence of sodium hydride in DMF and a summary of the reaction yields are given in Table 1.

All of the amidines studied were found to react effectively with the thiophene appended vinamidinium salt (**7**) to produce the corresponding

Scheme 4

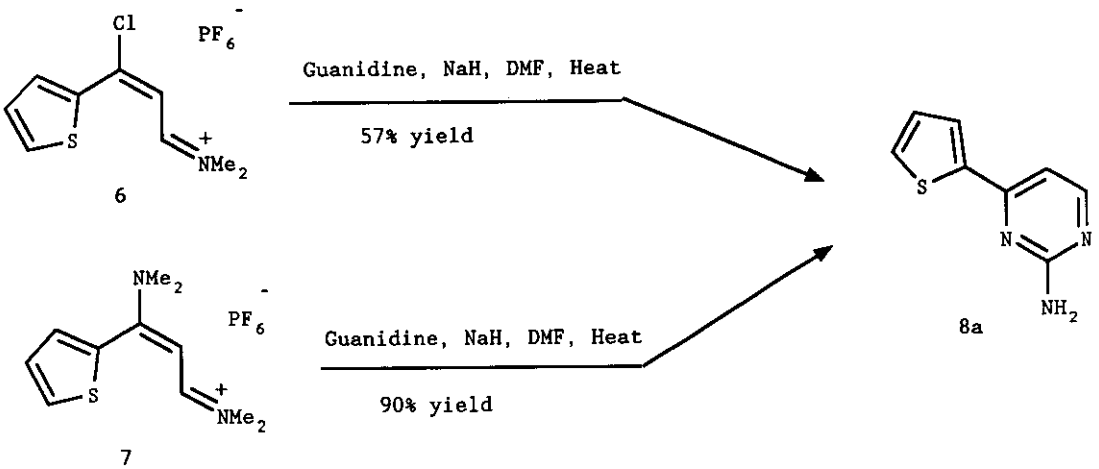
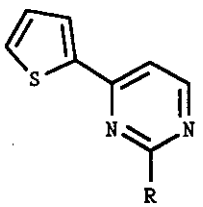


TABLE 1

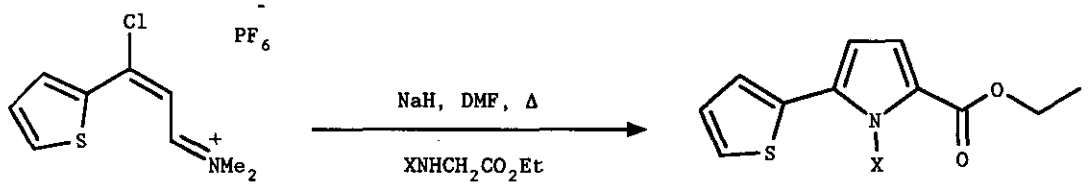


Compound	R	% Yield
8a	NH_2	90
8b	Ph	83
8c	Me	85
8d	H	81

4-(2-thienyl)pyrimidines (**8**) in good yield.

We have recently reported[6] that 3-aryl-3-chloropropeniminium salts react with either sarcosine ethyl ester or glycine ethyl ester under basic conditions to give the corresponding 5-aryl-2-carbethoxypyrroles in good yield. When these conditions were extended to the thienylchloropropeniminium salt (**6**), the corresponding 2,5-disubstituted thienylpyrroles were also obtained in yields ranging from 55-75% (Scheme 5). The ^{1}H nmr spectra of the thiophene appended pyrroles were consistent with those reported[6] for the aryl analogs and the proton coupling constants were clearly indicative of a 2,5-disubstitution pattern.[6]

Scheme 5



6

9

X = H 75% yield

X = Me 55% yield

We assume that these reactions proceed by the amino group of the amino acid ester displacing the chlorine of the salt (**6**) to give a new vinylogous iminium salt. This new vinylogous salt can then undergo a base mediated cyclization to the corresponding 2,5-disubstituted pyrrole (**9**). This procedure represents a novel and efficient entry into biheteroaryl systems which contain two five membered rings.

In summary, we have established the feasibility for preparing a thiophene appended vinamidinium salt (**7**) and chloropropeniminium salt (**6**) in a regiochemically defined manner. These materials were then used as synthons for the conversion to pyrimidines and pyrroles where a specific regiochemistry was established between the two heterocyclic groups. This methodology should be applicable to the regioselective synthesis of a wide variety of biheterocyclic systems and current work in our laboratory is focused in this direction.

EXPERIMENTAL

The following procedures are typical of the experimental conditions used for the preparation of the vinylogous iminium salts and their subsequent conversion to thienylpyrimidines and thienylpyrroles. All melting points and boiling points are uncorrected and all purified compounds gave a single spot on tlc analysis on silica gel 7GF with an ethyl acetate /hexane mixture as the eluant.

E-3-Dimethylamino-1-(2-thienyl)propenone (5): A mixture of 2-acetylthiophene (**4**) (10.0 g, 0.079 mol) and *N,N*-dimethylformamide dimethyl acetal (37.8 g, 0.317 mol) was placed in a round-bottomed flask equipped with a reflux condenser and a magnetic stirrer and was heated at reflux overnight. After cooling to room temperature, the solvent was removed via rotary evaporator and the resulting red-orange solid was dried in vacuo to yield 14.3 g (95% yield) of material. This material was sufficiently clean that additional purification was normally not required. An analytical sample can be prepared by radial chromatography of a 0.5 g sample of product on a 2 mm-thick plate of silica gel on a Harrison Chromatotron. Elution with a

60/40 mixture of hexane/ethyl acetate affords a major fraction which contains compound **(5)**. The solid **(5)** exhibited the following properties: mp 121-123 °C; ^{1}H nmr ($CDCl_3$) δ 2.90 (s, 3 H), 3.29 (s, 3 H), 5.78 (d, J = 12.5 Hz, 1 H), 7.15 (m, 1 H) and 7.60 - 7.90 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 38.9, 46.3, 92.4, 129.8, 130.3, 132.7, 149.9, 155.3 and 180.8; Ir (KBr) 1635 cm^{-1}; mass spectrum, m/z 181 (M^+). Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.47; H, 6.02; N, 7.58.

3-Chloro-3-(2-thienyl)prop-2-en-1-ylidendimethyliminium Hexafluorophosphate (6): Into a dry 250 ml three-necked flask is placed 100 ml of dry dichloromethane and compound **(5)** (14.0 g, 0.077 mol). Phosphorous oxychloride (11.8 g, 0.077 mol) is added to the reaction mixture in a dropwise fashion with stirring and the resulting solution is stirred for approximately 30 min. The solvent is removed in vacuo and a cold solution of methanol, containing 26 g (0.154 mol) of sodium hexafluorophosphate is carefully added to the residue. The resulting yellow solid which forms is isolated by filtration (23.7 g, 89% yield) and can be recrystallized from methanol if desired. This solid exhibited the following properties: mp 177-178 °C; ^{1}H nmr (DMSO-d_6) δ 3.64 (s, 3 H), 3.74 (s, 3 H), 7.43 (t, J = 4 Hz, 1 H), 7.62 (d, J = 6 Hz, 1 H), 8.26 (m, 2 H) and 8.85 (d, J = 6 Hz, 1 H); ^{13}C nmr ($CDCl_3$) δ 43.9, 50.9, 113.8, 132.1, 135.6, 138.8, 141.5, 151.2 and 166.2; Ir (KBr) 1656 cm^{-1}; mass spectrum, m/z 200, 202 (M^+). Anal. Calcd for $C_9H_{11}NClF_6PS$: C, 31.27; H, 3.21; N, 4.05. Found: C, 31.29; H, 3.17; N, 3.96.

2-(2-Thienyl)-1,1,5,5-tetramethyl-1,5-diazapentadienium Hexafluorophosphate (7): Into a dry 250 ml flask was placed 75 ml of anhydrous ethanol. Sodium

metal (3.0 g, 0.13 mol) was carefully added to the flask and after the ensuing reaction was completed, the mixture was cooled in an ice bath and dimethylamine hydrochloride (10.6 g, 0.13 mol) was added. Compound **(6)** (5.2 g, 0.015 mol) was added to the solution with stirring and cooling and after several hours the resulting pale-yellow solid (3.8 g, 71% yield) was removed by filtration and dried under vacuum. This material can be recrystallized from methanol if desired. The solid exhibited the following properties: mp 180-181 ^{0}C; ^{1}H nmr (DMSO-d_6) δ 3.17 (s, 3 H), 3.22 (s, 3 H), 3.36 (br s, 6 H), 5.65 (d, J = 11 Hz, 1 H), 7.20 (d, J = 11 Hz, 1 H), 7.35 (m, 2 H) and 8.02 (d, J = 5 Hz, 1 H); ^{13}C nmr ($CDCl_3$) δ 40.6, 43.5, 45.6, 49.1, 95.8, 130.2, 132.4, 132.5, 134.5, 163.5 and 167.1; ir (KBr) 1634 cm^{-1}; mass spectrum, m/z 209 (M^+); Anal. Calcd for $C_{11}H_{17}N_2F_6PS$: C, 37.29; H, 4.84; N, 7.91. Found: C, 37.29; H, 4.85; N, 7.88.

2-Amino-4-(2-thienyl)pyrimidine (8a): A 100 ml, round-bottomed flask was equipped with a magnetic stirring bar, reflux condenser and was placed under a nitrogen atmosphere. Into the flask was placed 0.28 g (.0070 mol) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed with a small amount of hexane and the washings were removed via cannula. Dry DMF (40 ml) was added to the flask along with 0.38 g (0.0028 mol) of guanidine carbonate and the resulting solution was stirred for 5 min. Compound **(7)** (1.00 g, 0.0028 mol) was then added to the flask and the resulting mixture was heated at 100 ^{0}C overnight. Subsequently, the solvents were removed in vacuo and the residue was partitioned between water and chloroform. The aqueous phase was extracted with additional chloroform and the combined chloroform extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude material was dissolved in a

small amount of ethyl acetate and filtered through a small plug of silica gel. The filtrate was concentrated to approximately 2-4 ml and subjected to radial chromatography with a 2 mm-thick plate of silica gel on a Harrison Chromatotron. Elution with a 60/40 mixture of hexane/ethyl acetate afforded 0.44g (90% yield) of a tan solid which exhibited the following properties: mp 194-196 ^{0}C; ^{1}H nmr (DMSO-d_6) δ 6.68 (br s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.19 (m, 1 H), 7.74 (d, J = 5.4 Hz, 1 H), 7.89 (d, J = 3.7 Hz, 1 H), and 8.25 (d, J = 5.2 HZ, 1 H); ^{13}C nmr (DMSO-d_6) δ 106.1, 129.4, 130.2, 131.7, 144.7, 160.5, 160.7 and 165.3; mass spectrum, m/z 177 (M^+); ir (KBr) 3323 and 3180 cm^{-1}; Anal. Calcd for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71. Found: C, 53.96, H, 3.91; N, 23.42. When the chloropropeniminium salt (**6**) was substituted for the vinamidinium salt (**7**), the reaction and purification was conducted in the same manner and a 57% yield of compound (**8a**) was obtained.

2-Phenyl-4-(2-thienyl)pyrimidine (8b): This compound was prepared in 83% yield in a manner similar to the preparation of compound **8a** with the exception that benzamidine was used as one of the starting materials. The purified product of this reaction exhibited the following properties: bp 116-117 ^{0}C at 0.2 torr; ^{1}H nmr (DMSO-d_6) δ 7.29 (t, J = 3.8 Hz, 1 H), 7.57 (m, 3 H), 7.93 (t, J = 5.3 Hz, 2 H), 8.16 (d, J = 3.8 Hz, 1 H), 8.46 (m, 2 H) and 8.89 (d, J = 5.3 Hz, 1 H); ^{13}C nmr (DMSO-d_6) δ 115.1, 129.5, 130.3, 130.5, 130.7, 132.8, 133.1, 138.7, 143.8, 160.0, 160.3 and 165.0; mass spectrum, m/z 238(M^+); Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76. Found: C, 70.32; H, 4.41; N, 11.74.

2-Methyl-4-(2-thienyl)pyrimidine (8c): This compound was prepared in 85%

yield in a manner similar to the preparation of compound **(8a)** with the exception that acetamidine was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 81-83 °C; ^{1}H nmr (DMSO-d_6) δ 2.62 (s, 3 H), 7.25 (t, J = 4.5 Hz, 1 H), 7.82 (m, 2 H), 8.05 (d, J = 4.5 Hz, 1 H) and 8.67 (d, J = 5.5 Hz, 1 H); ^{13}C nmr (DMSO-d_6) δ 27.5, 114.1, 130.4, 130.6, 132.8, 143.7, 159.5, 160.0 and 169.6; mass spectrum m/z 176 (M^+); Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.08; H, 4.47; N, 15.47.

4-(Thienyl)pyrimidine (8d): This compound was prepared in 81% yield in a manner similar to the preparation of compound **(8a)** with the exception that formamidine was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 70-71 °C; ^{1}H nmr (DMSO-d_6) δ 7.27 (t, J = 3.8 Hz, 1 H), 7.86 (d, J = 3.8 Hz, 1 H), 8.01 (d, J = 5.2 Hz, 1 H), 8.09 (d, J = 3.8 Hz, 1 H), 8.79 (d, J = 5.2 Hz, 1 H) and 9.10 (s, 1 H); ^{13}C nmr (DMSO-d_6) δ 117.1, 130.7, 130.8, 133.2, 143.4, 159.4, 159.8 and 160.5; mass spectrum m/z 162 (M^+); Anal. Calcd for $C_8H_6N_2S$: C, 59.24; H, 3.73; N, 17.27. Found: C, 58.87; H, 3.73; N, 17.05.

2-Carbethoxy-1-methyl-5-(2-thienyl)pyrrole (9a): This compound was prepared in 55% yield in a manner similar to the preparation of compound **(8a)** with the exception that *N*-methylglycine ethyl ester was used as one of the starting materials in place of the amidine. The product was purified by radial chromatography in a manner similar to that described for compound **(8a)**. The purified product exhibited the following properties: bp 81-82 °C at 0.2 torr ; ^{1}H nmr (DMSO-d_6) δ 1.29 (t, J = 7.0 Hz, 3 H), 3.94 (s, 3 H), 4.25 (q, J = 7.0 Hz, 2 H), 6.35 (d, J = 4.0 Hz, 1 H), 6.93 (d, J = 4.0 Hz,

1 H), 7.21 (t, J = 3.6 Hz, 1 H), 7.35 (d, J = 3.6 Hz, 1 H), and 7.68 (d, J = 3.6 Hz, 1 H); ^{13}C nmr (DMSO-d_6) δ 16.1, 35.7, 61.4, 111.6, 119.1, 125.3, 128.9, 129.2, 129.9, 134.1, 135.4 and 162.2; Ir (thin film) 1687 cm^{-1}; Hrms for $C_{12}H_{13}NO_2S$ calcd 235.0667, found 235.0674.

2-Carbethoxy-5-(2-thienyl)pyrrole (9b): This compound was prepared in 75% yield in a manner similar to the preparation of compound **(8a)** with the exception that glycine ethyl ester was used as one of the starting materials in place of the amidine. The product was purified by radial chromatography in a manner analogous to the purification of **(8a)**. The purified product exhibited the following properties: mp 118-120 ^{0}C; ^{1}H nmr (DMSO-d_6) δ 1.31 (t, J = 7.0 Hz, 3 H), 4.27 (q, J = 7.0 Hz, 2 H), 6.40 (m, 1 H), 6.82 (m, 1 H), 7.10 (t, J = 4.0 Hz, 1 H), 7.48 (d, J = 4.0 Hz 1 H), 7.64 (d, J = 4.0 Hz, 1 H) and 12.3 (br s, 1 H); ^{13}C nmr (DMSO-d_6) δ 16.2, 61.5, 109.7, 118.3, 124.6, 125.7, 126.7, 129.8, 133.4, 136.1 and 162.0; ir (KBr) 3247 and 1669 cm^{-1}; Hrms for $C_{11}H_{11}NO_2S$ calcd 221.0511, found 221.0517.

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