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The application of vinamidinium salts to the synthesis of 1,2,4-trisubstituted pyrroles

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ABSTRACT

The synthesis of 1-methyl-2-cyano-4-arylsubstituted pyrroles by the condensation of symmetrical vinamidinium salts with methyl aminoacetonitrile has been accomplished for the first time. Simple experimental conditions were used to prepare seven different pyrroles, six of which are not reported in the literature.

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Introduction

Vinamidinium salts are examples of push–pull alkenes with enhanced stability and will undergo condensation reactions with bifunctional nucleophiles to form heterocycles.[1] 2-Aryl vinamidinium salts are prepared under Vilsmeier–Haack conditions from the corresponding aryl acetic acid.[1,2] While it would seem more efficient to isolate these salts as the chloride this is usually not done. While stable the chloride salt is quite hygroscopic and therefore not very appealing. The vinamidinium salts are generally isolated as the perchlorate or the hexafluorophosphate as these salts are stable and not nearly as hygroscopic as the chloride.[3] The ease of preparation and stability of vinamidinium salts make them a suitable precursor for the synthesis of heterocycles such as isoxazoles,[1] pyrazoles,[1] pyrimidines,[1] and pyrroles.[2]

Pyrroles are important heterocycles and have attracted much interest due to their diverse and widespread nature.[4] In addition to the classic Paal-Knorr[5] and Hantzsch[6] synthesis of pyrroles some recent synthetic strategies include iron (III) mediated Paal-Knorr[7] reaction, phosphine-mediated reaction between an acid chloride and α,β-unsaturated imines,[8] nitroolefins reacting with α-isocyanoesters,[9] and condensation of 3-alkoxyacroleins with glycine derivatives.[10]

Of specific interest in this Letter is the synthesis of 2-cyanopyrroles, which are important intermediates for the synthesis of porphyrins.[11] The three main strategies for incorporating a cyano group on the ring are direct cyanation, functional group manipulation, and condensation reactions to form the ring with the cyano group in place. Several routes exist for direct cyanation of the pyrrole ring which include a modified Vilsmeier reaction,[12] reaction with 1-cyanobenzotrizole,[13] and a hypervalent iodine mediated reaction with TMSCN.[14] Condensation reactions to form 2-cyanopyrroles include condensation of isocyanoacetonitrile with α-acetoxynitro compounds[15,16] and condensation of 3-alkoxyacroleins with aminoacetonitrile.[10] The route by Adamczyk[15,16] prepared 2-cyano-3,4-substituted pyrroles in good yield where the substituents at the 3 and 4 positions are primarily alkyl groups with one example of an aromatic group. The route reported by Walizei and Breitmaier[10] prepared 2-cyano-4-substituted pyrroles in low to moderate yield where the substituents at the 4-position are exclusively alkyl groups.

The work reported here expands upon the previous strategies and allows synthesis of a 2-cyanopyrrole with an aromatic group at the 4-position. Due to the symmetrical nature of the 2-arylvinamidinium salts used in this study only the 4-arylpyrroles can be formed.[2] The 3-aryl or 5-arylpyrroles would arise from an unsymmetrical vinamidinium salt undergoing a condensation reaction with *N*-methylaminoacetonitrile. Also due to the nature of this reaction only the 2-cyanopyrroles can be synthesized; other regiochemical outcomes for placement of the cyano-group are not possible. These reactions proceed in good yield under relatively mild conditions.

Results and discussion

The vinamidinium salts (**1a–g**) used in this study were prepared by the standard Vilsmeier–Haack reaction of the appropriate aryl

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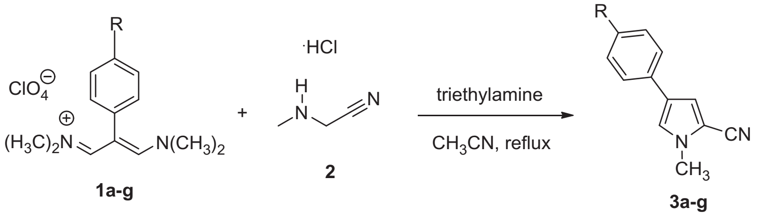

R	%CrudeYield	%Purity by GC/MS
H, **3a**	81	91
Br, **3b**	59	94
Cl, **3c**	85	88
OCH_3, **3d**	70	72
CH_3, **3e**	93	68
NO_2, **3f**	88	77
C_6H_5, **3g**	67	90

Scheme 1. Preparation of 2-cyanopyrroles.

acetic acid.[1] Walizei and Breitmaier[10] report higher yields with *N*-methylaminoacetonitrile than with aminoacetonitrile so it was decided to keep the scope of this study limited to the synthesis of *N*-methylpyrroles with *N*-methylaminoacetonitrile. In a typical procedure[17] to prepare the 2-cyanopyrrole the vinamidinium salt was allowed to react with 1 equiv of *N*-methylaminoacetonitrile hydrochloride (**2**) in refluxing acetonitrile in the presence of 2.1 equiv of triethylamine overnight (Scheme 1). After extractive workup the pyrroles were isolated in reasonable yield; the table of results is also shown in Scheme 1. Pyrroles **3a**, **3b**, **3c**, **3e**, **3f**, and **3g**, are all new compounds and were characterized by NMR, GC/MS, HRMS, and FTIR. Pyrrole **3d** is a known compound and is reported in the patent literature.[18] This pyrrole was also characterized by NMR, GC/MS, HRMS, and FTIR. The type of vinamidinium salt (**1**) did not substantially affect the yield. Analytical samples of the pyrroles could be obtained by column chromatography. The geometry of the pyrrole ring was established by the C-3 and C-5 proton NMR signal ($CDCl_3$) $\delta = 6.97$ and 7.01 ($J = 2.0$ Hz), respectively, for compound **3a**. Similar resonances were also observed for the C-3 and C-5 hydrogens of the other pyrroles. The chemical shift was dependent on the choice of NMR solvent with acetone causing a downfield shift of approximately 0.2–0.5 ppm. The experimental HRMS data of **3a–g** matched the calculated data.

Conclusion

In summary, it has been demonstrated that vinamidinium salts can be effectively used for the regioselective preparation of 4-aryl-2-cyano-*N*-methylpyrroles using simple experimental conditions in a minimum number of steps from commercially available starting materials.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.080.

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17. Representative procedure for pyrrole synthesis
    A dry one neck 50 mL round bottomed flask equipped with magnetic stirring, reflux condenser, and nitrogen atmosphere (or drying tube) was charged with the 2-phenyl-vinamidinium salt (1.00 g, 3.30 mmol), methylaminoacetonitrile hydrochloride (0.355 g, 3.33 mmol) and triethylamine (0.97 mL, 6.95 mmol). Anhydrous acetonitrile (10 mL) was added and the mixture was allowed to stir at reflux overnight. The flask was cooled to room temperature and the volatiles were removed in vacuo. The remaining solid was partitioned between water and ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and concentrated in vacuo to give 0.487 g (81%) of a solid.
    2-Cyano-1-methyl-4-phenylpyrrole [**3a**]
    Mp = 128–131 °C; ^1H NMR ($CDCl_3$) δ 7.38 (d, 2H, $J = 7.2$ Hz), 7.29 (t, 2H, $J = 7.6$ Hz), 7.17 (t, 2H, $J = 6.6$ Hz), 7.01 (d, 1H, $J = 2.0$ Hz), 6.97 (d, 1H, $J = 2.0$ Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 132.47, 127.86, 125.66, 124.82, 124.24, 123.10, 116.02, 112.57, 104.35, 34.56; LREIMS 182 (100), 181 (19), 188 (48), 154 (6), 140 (28), 114 (9), 77 (3); IR (solid) 2217 cm^{-1}; HRMS m/z calcd for $C_{12}H_{10}N_2$, 182.0844; found 182.0843.
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