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Synthesis of alkylpyrroles by use of a vinamidinium salt

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ABSTRACT

The synthesis of alkyl-substituted 2-pyrrolecarboxylate esters has been accomplished by the condensation reaction of a symmetrical vinamidinium salt and glycine ester derivatives.

1. Introduction

Symmetrical vinamidinium salts undergo condensation reactions, similar to malonaldehyde derivatives, with bifunctional nucleophiles to form heterocycles. These organic salts have been used to prepare many different monocyclic heterocycles including isoxazoles,[1] pyrazoles,[1] pyrimidines,[1] and pyrroles.[2] Most of these studies have used an aryl vinamidinium salt to synthesize an aryl-appended heterocycle. Aryl vinamidinium salts are easily prepared under Vilsmeier–Haack conditions from the corresponding aryl acetic acid.[1,2] Using alkyl acetic acids to synthesize alkyl vinamidinium salts does not work effectively. Davies has reported that alkyl vinamidinium salts could be prepared from alkyl acetic acids in low yield.[3] Other methods to prepare alkyl vinamidinium salts usually involve multiple steps and start with material other than carboxylic acids.[4–6] Because of the more involved procedures to make alkyl vinamidinium salts these compounds are not typically used in synthetic studies.

Two examples that use a condensation reaction to produce alkyl pyrroles have been reported by Walizei[7] and Barton.[8] In the report by Walizei[7] 2-carboxy-4-alkyl-substituted pyrroles have been prepared in average yield by the condensation of 3-alkoxyacroleins with glycine derivatives; sacrosine derivatives will produce an *N*-methylpyrrole. In the report by Barton[8] the procedure involves the condensation of an α-isocyanoester and a nitroolefin. By the nature of the traditional Barton–Zard procedure, the product will be an N–H pyrrole. The Barton–Zard method gives pyrroles that are 2,3,4-trisubstituted with a carbonyl at the 2-position in the form of an ester, but the carbonyl group could also belong to an amide. The substituents on pyrrole in the Barton–Zard reaction at the 3- and 4-position are typically alkyl or aryl groups, but it is possible for the 3-position to be unsubstituted.

Alkyl pyrroles have some important uses in organic chemistry. Some examples of their utility include, but are not limited to the following: used as building blocks preparing the pharmaceutically important pyrrolo[1,2-*a*]quinoxalines[9] structural core; compound **3f** has been used to prepare intermediates for compounds tested to treat multiple sclerosis;[10] compound **3b** has been used to prepare pyrazolylpyrrole ERK inhibitors.[11] Pyrroles **3a** and **3b** have been used to prepare ring-annulated pyrroles.[12] Pyrrole **3e** is an ant trail pheromone of *Atta Texana* and was first reported by Tumlinson in 1971.[13,14] Most of these simple alkyl pyrroles were synthesized starting with the pyrrole ring already present. Because of the limited use of alkyl vinamidinium salts and the fact that alkyl pyrroles can be important synthetic building blocks a new synthesis of alkyl pyrroles was explored by using alkyl vinamidinium salts. This route is expected to complement the existing procedures by Walizei and Barton.

2. Results and discussion

The vinamidinium salts used in these experiments were prepared by the 1996 procedure according to Arnold.[15] Ethyl vinyl ether was subjected to Vilsmeier–Haack conditions to prepare the unsubstituted vinamidinium salt (**1**, R = H). In a similar fashion the use of ethyl propenyl ether prepared the 2-methylvinamidinium salt (**1**, R = CH_3) and the use of 1-butenyl ethyl ether produced the 2-ethylvinamidinium salt (**1**, R = CH_2CH_3). All of these symmetrical vinamidinium salts were isolated as the perchlorate in good

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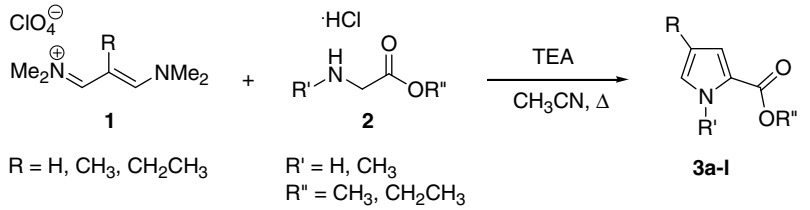

Compound	R	R'	R"	% crude yield	% purity*
3a	H	H	CH_3	86	77
3b	H	H	CH_2CH_3	68	82
3c	H	CH_3	CH_3	83	>95
3d	H	CH_3	CH_2CH_3	67	>95
3e	CH_3	H	CH_3	60	80.6
3f	CH_3	H	CH_2CH_3	75	>95
3g	CH_3	CH_3	CH_3	85	93
3h	CH_3	CH_3	CH_2CH_3	93	>95
3i	CH_2CH_3	H	CH_3	69	>95
3j	CH_2CH_3	H	CH_2CH_3	66	88.0
3k	CH_2CH_3	CH_3	CH_3	92	>95
3l	CH_2CH_3	CH_3	CH_2CH_3	98	91
3m	C_6H_5	H	CH_3	49	>95
3n	C_6H_5	CH_3	CH_3	81	>95

* as indicated by GC/MS

Scheme 1. Synthesis of alkyl pyrroles.

yield and good purity and were used without further purification for the synthesis of pyrroles.

In a typical procedure[16] the vinamidinium salt was allowed to react with 2 equiv of the glycine ester hydrochloride derivative (**2**) with 2 equiv of triethylamine while refluxing in acetonitrile 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**,[12] **3b**,[12] **3c**,[17] **3d**,[18] **3e**,[7] **3f**,[10] **3g**,[19] **3h**,[7] **3i**,[7] and **3l**[7] are all known compounds and the synthesized pyrroles were in good agreement with the reported literature spectroscopic data. Pyrroles **3j**[20] and **3k**[21] are new compounds and were characterized by NMR, GC/MS, HRMS, and FTIR. The regiochemistry of the pyrrole ring was confirmed by the C-3 and C-5 proton NMR signals δ = 6.70 and 6.51 (J = 2.0 Hz), respectively, for compound **3k**. Similar resonances (within 0.1 ppm) were also observed for the C-3 and C-5 hydrogens of pyrroles such as **3e**, **3h**, **3i**, and **3l**.[7]

Generally the crude yields were quite good and the reaction products looked relatively clean by TLC. The type of vinamidinium salt (**1**, R = H, CH_3, or CH_2CH_3) did not substantially affect the yield; nor did the fact that some of the glycine derivatives were methyl or ethyl esters (where R″ = CH_3 or CH_2CH_3). A slight trend might be present when sarcosine (**2**, R′ = CH_3) derivatives were used. The yields were generally higher and the pyrroles more pure by GC/MS when a sarcosine derivative was used, but it is not completely conclusive with our data. By comparison to the Walizei[7] method using 3-alkoxyacroleins for the synthesis of compounds **3e**, **3h**, **3i**, and **3l** the yields by our procedure were approximately twice as high in some cases.

To determine the influence of the substituent of the vinamidinium salt similar experiments were conducted with the 2-phenylvinamidinium salt (**1**, R = C_6H_5). The phenyl vinamidinium salt was allowed to react under the same conditions with the appropriate glycine derivatives to prepare pyrroles **3m** and **3n**. The yields and % purity were consistent with the results for the 4-alkyl pyrroles, therefore showing that the substituent on the vinamidinium salt was not a major factor in these experiments.

3. Conclusion

In summary, a dozen different alkyl pyrroles, including two new compounds, has been efficiently synthesized by a new route involving the condensation of a symmetrical vinamidinium salt and a glycine ester under simple experimental conditions.

Acknowledgments

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16. *General experimental procedure*: All reagents and solvents were obtained from Aldrich, ACROS, or Fluka and used without further purification. To a flame dried one-necked round-bottomed flask equipped with magnetic stirring, reflux condenser, and nitrogen atmosphere (or drying tube) was added the vinamidinium salt (1.0 mmol) and glycine ester hydrochloride (2.0 mmol). Anhydrous acetonitrile (5 mL) was added via a syringe. Triethylamine (2.0 mmol) was added via a microliter syringe. The mixture was allowed to reflux overnight (15–18 h) under a nitrogen atmosphere (or drying tube). The flask was cooled to room temperature and the solvent was removed by rotary evaporation. The residue was partitioned between methylene chloride and water. The aqueous layer was extracted with fresh methylene chloride, and the combined organic layers were then dried over sodium sulfate. The drying agent was filtered and the solvents were removed in vacuo to give the crude material. The crude material was run through a short pad of silica gel with methylene chloride and the organic solvent was removed in vacuo. At this point the crude yield and percent purity were obtained. Analytical samples were obtained by either column chromatography with hexanes and ethyl acetate or low pressure distillation.
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20. *Ethyl 4-ethyl-1H-pyrrole-2-carboxylate* (**3j**): mp = 115 °C; ^{1}H NMR ($CDCl_3$) δ 8.86 (br s, 1H), 6.71 (m, 1H), 6.67 (m, 1H), 4.43 (q, 2H, J = 7.2 Hz), 4.23 (q, 2H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 161.46, 128.54, 122.75, 120.19, 114.62, 60.42, 20.09, 15.43, 14.71; FTIR (neat) 3321, 1701 cm^{-1}; LREIMS 167 (56), 152 (61), 122 (32), 106 (100), 94 (20), 78 (10); HRMS calcd for $C_9H_{13}NO_2$ M+1 168.1019, obsd 168.1039.
21. *Methyl 4-ethyl-1-methyl-1H-pyrrole-2-carboxylate* (**3k**): bp = 101–102 °C (1 mmHg); ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1H, J = 2.0 Hz), 6.51 (d, 1H, J = 2.0 Hz), 3.79 (s, 3H), 3.71 (s, 3H), 2.36 (q, 2H, J = 7.6 Hz), 1.09 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 160.72, 126.22, 124.59, 120.66, 115.73, 49.87, 35.50, 18.63, 14.21; FTIR (neat) 1708 cm^{-1}; LREIMS 167 (32), 152 (100), 136 (11), 108 (10), 93 (6), 65 (4); HRMS calcd for $C_9H_{13}NO_2$ M+1 168.1019, obsd 168.0924.