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An Effective New Synthesis of 4-Aminopyrrole-2-carboxylates†

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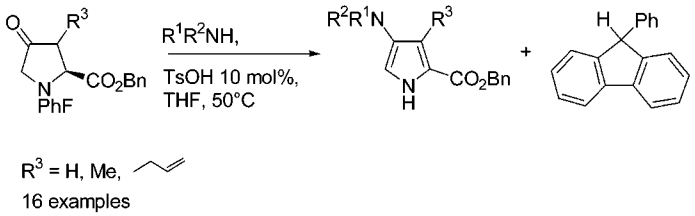
ABSTRACT



A series of 4-amino-1*H*-pyrrole-2-carboxylic acid benzyl esters has been synthesized in 61−84% yields on treatment of *N*-PhF-4-oxoproline benzyl ester and its 3-alkyl-substituted derivatives with different primary and secondary amines and a catalytic amount of TsOH in THF. 4-Hydroxy-1*H*-pyrrole-2-carboxylic acid benzyl esters were prepared in 59 and 70% yields by treatment of *N*-PhF-4-oxoproline benzyl esters with ammonium hydroxide in THF.

As constituents of cytotoxic drugs, such as netropsin and distamycin, 4-aminopyrrole-2-carboxylates have served as principle components for constructing a diverse series of DNA-binding ligands exhibiting antibiotic, antiviral, and oncolytic properties.[1] The related 3-aminopyrroles have also exhibited anticonvulsant activity by blocking sodium ion channels.[2] Effective methodology for synthesizing 3- and 4-aminopyrroles is thus essential for furthering their application in medicinal and biological chemistry. Drawbacks inherent in previous routes for their preparation have, however, limited the molecular diversity produced by existing aminopyrrole synthesis methods.[2,3]

The most commonly used method for the synthesis of 4-aminopyrrole-2-carboxylates involves Friedel−Crafts acylation of *N*-methylpyrrole with trichloroacetyl chloride followed by nitration and subsequent reduction of the nitro group.[1f] This route has furnished *N*-methyl-4-aminopyrrole-2-carboxylate in suitably protected form for oligomer synthesis.[1e,f] However, the harsh reaction conditions for installing the amine and carboxylate limits greatly the introduction of diverse functional groups. Alternative methods for aminopyrrole synthesis have recently been reviewed[2] and do not provide easy access for adding functionality to the 1- and 3-positions as well as onto the 4-amino substituent.

We have developed effective syntheses of enantiopure pyrrolidine-2-carboxylates from 4-hydroxyproline as an inexpensive chiral educt.[4] In particular, alkylation and triflation of enolates of 4-oxo-*N*-(PhF)prolinates **2** and **4** have

† Dedicated to the memory of Professor Henry Rapoport, deceased March 7, 2002.

(1) (a) Wang, C. C. C.; Dervan P. B. *J. Am. Chem. Soc.* **2001**, *123*, 8657. (b) Woods, C. R.; Ishii, T.; Bair, K. W.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 2148. (c) Wellenzohn, B.; Wolfgang, F.; Winger, R. H.; Hallbrucker, A.; Mayer, E.; Liedl, K. R. *J. Am. Chem. Soc.* **2001**, *123*, 5044, and refs 1−33 therein. (d) Sharma, S. K.; Tandon M.; Lown, J. W. *J. Org. Chem.* **2001**, *66*, 1030. (e) Wurtz, N. R.; Turner, J. M.; Baird, E. E.; Dervan, P. B. *Org. Lett.* **2001**, *3* (*8*), 1201. (f) Baird, E. E.; Dervan, P. B. *J. Am. Chem. Soc.* **1996**, *118*, 6141. (g) Dyatkina, N. B.; Roberts, C. D.; Keicher, J. D.; Dai, Y.; Nadherny, J. P.; Zhang, W.; Schmitz, I.; Kongpachith, A.; Fung, K.; Nokikov, A. A.; Lou, L.; Velligan, M.; Khorlin, A. A.; Chen, M. S. *J. Med. Chem.* **2002**, *45*, 805.

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(4) (a) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202. (b) Rondeau, D.; Gill, P.; Chan, M.; Curry, K.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 771. (c) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658.

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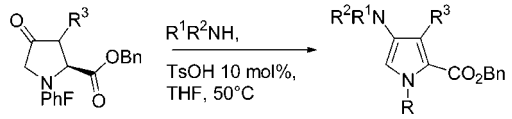
provided effective means for introducing substituents at the proline 3- and 4-positions (PhF = 9-(9-phenylfluorenyl)).[4,5] Enolization and alkylation of *N*-PhF protected 4-oxoproline **2** is complementary to the alkylation of enamines derived from the corresponding *N*-acyl 4-oxoprolines.[6] We now report that reaction with pyrrolidine and *p*-toluenesulfonic acid in benzene at reflux did not produce the respective enamine. Instead, benzyl 4-pyrrolidino-1*H*-pyrrole-2-carboxylate **1a** was isolated in 62% yield after purification by chromatography (Scheme 1). The formation of **1a** provided

Scheme 1



2 : R^3 = H
4 : R^3 = Alkyl

1 : R = H
3 : R = PhF

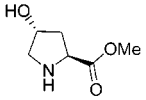
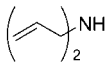
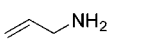
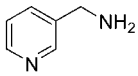
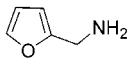
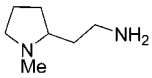
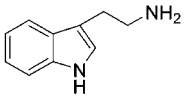
a novel entry into the 4-aminopyrrole system and was clearly demonstrated by a dramatic transformation of the aromatic region of the ^{1}H NMR spectrum in which the signals for the PhF protons were lost and new pyrrole protons at 6.4 and 6.5 ppm were detected.[7] Heating the reaction to 50 °C in THF increased the yield of **1a** and diminished the reaction time. TsOH (10 mol %) catalyzed the generation of **1a**. Excess amine (400 mol %) was necessary for reaction completion.

The influence of a 3-position substituent was examined by similarly treating 3-methyl- and 3-allyl-4-oxoprolines **4a** and **4b** with pyrrolidine, which produced respectively 3-alkyl pyrroles **1n** and **1o** in 73% and 61% yields. No double bond migration was observed during the synthesis of 3-allylated analogue **1o**.

Best conditions were employed with a variety of amines and **2** to provide a series of pyrroles **1** in 61−84% (Table 1).[7] The sterically hindered diisopropylamine failed to yield 4-aminopyrrole after 12 h and aside for some loss of the PhF group, **2** was recovered. Treatment of **2** with amines bearing remote amine and carboxylate functionality was well tolerated (entries d, j−m).

Allylamine reacted by two different oxidation pathways undergoing either loss of phenylfluorene to give 1*H*-pyrrole **1** or hydrogen to provide the *N*-(PhF)pyrrole counterpart **3**. *N*-(PhF)Pyrrole **3i** could be minimized by using acetonitrile as solvent. For example, allylamine reacted with proline **2** in THF at 50 °C to give a 1:1 ratio of *N*-(PhF)pyrrole **3i** and 1*H*-pyrrole **1i**. In acetonitrile at 50 °C, this ratio was reduced to 1:2.5; at room temperature, after 8 h, a 1:4 ratio of **3i** and

Table 1. Synthesis of 4-Aminopyrrole **1**

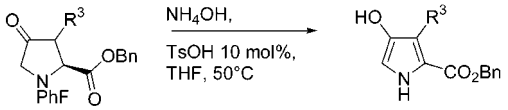
entry	R^1R^2NH	R^3	isolated yield (%)
a	Pyrrolidine	H	79
b	Piperidine	H	79
c	Morpholine	H	81
d		H	62
e		H	76
f	$BnNH_2$	H	84
g	$EtNH_2$	H	69
h	n-$PrNH_2$	H	62
i		H	75[a]
j		H	72
k		H	64
l		H	82
m		H	78
n	Pyrrolidine	Me	73
o	Pyrrolidine	Allyl	61

[a] Reaction performed in MeCN at room temperature.

1i was obtained, and 4-allylamino-1*H*-pyrrole **1i** was isolated in 75% yield after chromatography.

Attempts to synthesize 4-aminopyrrole **1p** by reacting **2** and TsOH in THF with aqueous ammonium hydroxide, and in THF and in dioxane with ammonia, all provided 4-hydroxypyrrole 2-benzyl ester **5** (Scheme 2). Similarly, treatment of 3-methyl-4-oxoproline **4a** with TsOH and ammonium hydroxide in THF furnished the corresponding 3-methyl-4-hydroxypyrrole **6** in 59% yield. 4-Aminopyrrole-2-carboxylate **1p** could be isolated in 75% yield after deprotection of allylaminopyrrole **1i** (Scheme 3).

Scheme 2



2 : R^3 = H
4a : R^3 = Me

5 : R^3 = H (70 %)
6 : R^3 = Me (59 %)

When the importance of the 2-carboxylate substituent was explored using *N*-(PhF)pyrrolidin-3-one, the corresponding

(5) For related methods see (a) Blanco, M.-J.; Paleo, R. P.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786. (b) Koskinen, A. M. P.; Schwerdtfeger, J.; Edmonds, M. *Tetrahedron Lett.* **1997**, *38*, 5399.

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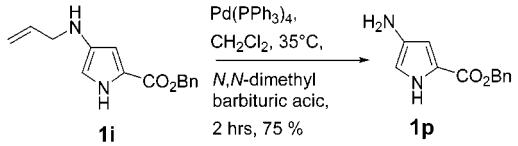
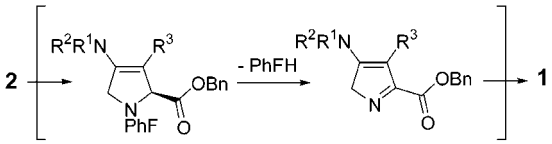
Scheme 3



Scheme 4



3-aminopyrrole was not isolated from the reaction with pyrrolidine and TsOH in THF at 50 °C. Instead, enamine formation was identified by the presence of vinylic protons at δ 6.51 (m, J = 7.6 Hz, 1H) and 5.90 (d, J = 15.9 Hz, 1H) ppm in the crude ^{1}H NMR spectrum.

A plausible mechanism for the formation of 4-aminopyrrole 2-carboxylate may thus involve condensation of the amine with the ketone to form an imminium ion. Tautomerization toward the 3-position provides an enamine,[8] which loses the aromatic phenylfluorenyl anion[9] to form an azadiene intermediate that aromatizes to pyrrole **1** (Scheme 4).

A series of 4-amino-1*H*-pyrrole-2-carboxylic acid benzyl esters have been synthesized in 61−84% yields on treatment of *N*-PhF-4-oxoproline benzyl esters **2** and **4** with different primary and secondary amines and a catalytic amount of TsOH in THF. 4-Hydroxy-1*H*-pyrrole-2-carboxylic acid benzyl esters **5** and **6** were respectively prepared in 70 and 59% yields by treatment of **2** and **4a** with ammonium hydroxide in THF. In light of their importance as components of drugs, polymers, and materials, this new synthesis of pyrrole analogues should provide a practical means for making novel libraries of these valuable compounds.

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Supporting Information Available: Experimental details for the preparation of aminopyrroles **1a**−**p** and hydroxypyrroles **5** and **6** and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) A stirred solution of benzyl *N*-PhF-4-oxo-prolinate (**2**, 300 mg, 0.653 mmol) in 30 mL of THF was treated with pyrrolidine (185 mg, 2.61 mmol) followed by TsOH (12 mg, 0.07 mmol), heated to 50 °C, stirred 4 h, and treated with a solution of saturated aqueous NH_4Cl followed by 30 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (30 mL × 2). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to a residue that was purified by column chromatography on silica gel using 10% ethyl acetate in hexanes as eluant. Evaporation of the collected fractions yielded pyrrole **1a** (139 mg, 0.514 mmol, 79%) as a green solid: mp 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.44−7.34 (m, 5H), 6.47 (s, 1H), 6.35 (s, 1H), 5.30 (s, 2H), 3.09 (t, J = 6.2 Hz, 4H), 1.96 (t, J = 3.1 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 140.1, 136.7, 129.0, 128.6, 128.5, 121.0, 107.2, 103.4, 66.3, 51.1, 25.2. HRMS: calcd for $C_{16}H_{18}N_2O_2$: 270.1371; found: 270.1368. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.79; H, 6.77; N, 10.17.

(8) Enolization of *N*-alkylpyrrolidin-3-one occurs predominantly away from the nitrogen-bearing carbon: Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

(9) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.