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2-Vinylpyrroles and Pyrrolo[3,2-*d*]pyrimidines from Direct Addition of Aldehydes to 4-Amino-pyrrole-2-carboxylate Derivatives

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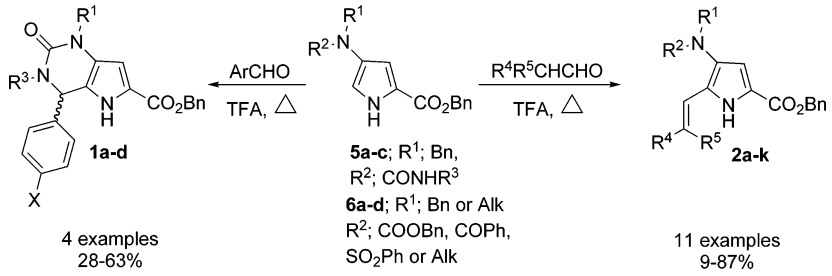
ABSTRACT



A new methodology for the direct preparation of 2-vinylpyrroles is presented. Treatment of 4-amino-pyrrole-2-carboxylates 5a–c and 6a–d with aliphatic aldehydes and TFA furnished 2-vinylpyrroles 2a–k in 9–87% yields. Under similar conditions ureidopyrroles 5a–c reacted with aryl aldehydes to provide pyrrolo[3,2-*d*]pyrimidines 1a–d in 28–63% yields.

2-Vinylpyrroles are valuable for the synthesis of natural products such as porphyrins and chlorophylls, as well as photo- and electroconducting materials.[1] They are usually prepared from *C*-formyl and *C*-acetylpyrroles by way of condensations onto malonates, esters, ketones, and alkylidenephosphoranes.[2] *C*-Vinypyrroles have also been synthesized from electrophilic substitution of pyrroles using acetylenes and electron-deficient alkenes.[2] In light of the propensity of pyrroles to form dipyrromethenes in reactions with aldehydes,[1−3] *N*-methylpyrroles have only been converted to vinylpyrroles by way of reactions with ketones onto osmium[4] and lithium[5] complexes. To the best of our knowledge, no method for the preparation of 2-vinylpyrrole from direct addition of aldehydes onto the pyrrole ring exists in the literature.

Pyrrolo[3,2-*d*]pyrimidines exhibit biological activity as receptor ligands,[6] and enzyme inhibitors.[7] Such deazapurine derivatives have typically been prepared by pyrrole annulation on properly substituted pyrimidines.[8] Recently, we have presented effective solution- and solid-phase methodol-

(1) Trofimov, B. A.; Sobenina, L. N; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004**, *104*, 2481 and references within.
(2) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. Chem. Rev.* **2002**, *71*, 563 and references within.
(3) Garabatos-Perera, J. R.; Rotstein, B. H.; Thompson, A. *J. Org. Chem.* **2007**, *72*, 7382.
(4) Hodges, L. M.; Spera, M. L.; Moody, M. W.; Harman, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 7117.
(5) Andersen, K. E.; Braestrup, C.; Grønenwald, F. C.; Jørgensen, S. A.; Nielsen, E. B.; Sonnewald, U.; Søerensen, P. O.; Suzdak, P. D.; Knutsen, L. J. S. *J. Med. Chem.* **1993**, *36*, 1716.
(6) Grahner, B.; Winiwarter, S.; Lanzner, W.; Muller, C. E. *J. Med. Chem.* **1994**, *37*, 1526.
(7) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Hanson, J. C.; Kicska, G. A.; Sauve, A. A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 155.
(8) Amarnath, V.; Mdhav, R. *Synthesis* **1974**, 837.

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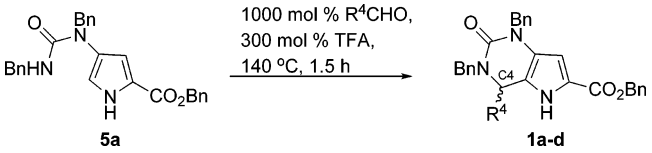
ogy for pyrrolopyrimidine synthesis starting from 4-amino-pyrrole-2-carboxylates.[9−11]

In the context of our program on the synthesis and screening of libraries of pyrrolo[3,2-*d*]pyrimidines, we have now explored a variation of the Pictet−Spengler[12] reaction featuring condensation of ureidopyrroles with aldehydes to introduce diversity at the C4 position (Table 1). The Pictet−Spengler reaction refers typically to the condensation of an aminoalkyl indole (i.e., tryptamine or tryptophan derivative) with an aldehyde or ketone to furnish *β*-carboline.[13] Aminoalkyl aromatic systems possessing relatively electron-rich aromatic rings (i.e., L-DOPA,[13,14] tyramine,[13] alkylamino-imidazoles,[15] and thiophenes[16]) have also served as substrates; however, few aminoalkyl pyrroles have been examined in Pictet−Spengler reactions. To the best of our knowledge, only three reports use primary aminoalkyl *N*-substituted pyrrole substrates in Pictet−Spengler reactions.[17−19] Ureas have been rarely used in Pictet−Spengler reactions relative to their aminoalkyl counterparts.[14,16] In such cases, electron-rich aryl derivatives (i.e., tryptophan, L-DOPA, thiophene, and furan analogues) served as the *C*-nucleophiles in intramolecular reactions in which only one urea nitrogen was incorporated into the heterocycle.[14,16]

The use of a pyrrole−urea combination has, to the best of our knowledge, no precedent in Pictet−Spengler chemistry. With the interest in preserving the pyrrole NH and 2-position carboxylate for potential hydrogen bonding in molecular recognition events, and for subsequent diversification, we have now explored the intramolecular Pictet−Spengler reaction of 4-ureidopyrrole 2-carboxylates and obtained pyrrolopyrimidines using aryl aldehydes. Employing aliphatic aldehydes in these conditions has also led to a new route to *C*-vinylpyrroles.

Table 1. Pyrrolopyrimidines from Heating Ureidopyrroles and Aromatic Aldehydes with Trifluoroacetic Acid

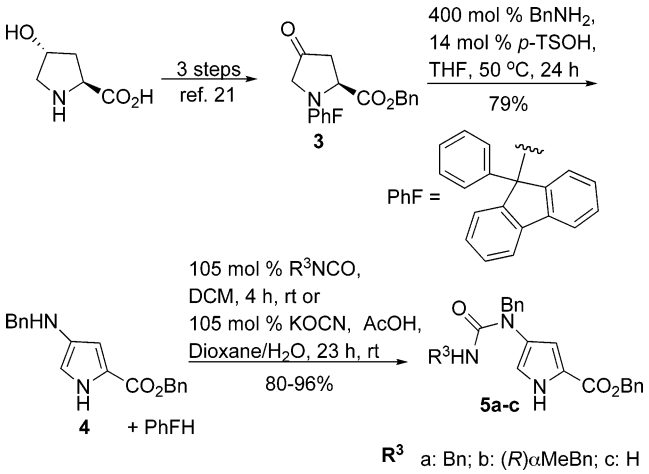


product	R^4	isolated yield %
1a	Ph	55
1b	*p*-MePh	63
1c	*p*-MeOPh	53
1d	*p*-NO_2Ph	28[a]

[a] 1000 mol % R^4CHO, 300 mol % TFA, toluene, 110 °C, 1.5 h.

N,*N*′-Dibenzylureidopyrrole **5a** was selected as the model substrate and prepared by our reported method[9] featuring acylation of benzyl 4-(benzylamino)-1*H*-pyrrole-2-carboxylate (**4**)[20] with benzyl isocyanate (Scheme 1). Ureidopyrrole **5a** was treated with different aldehydes under various conditions, including the common Pictet−Spengler reaction conditions of neutral and acidic media in hot toluene in a Dean−Stark apparatus,[13] as well as heating at reflux in the presence of TFA (up to 10% v/v) in alternative solvents (THF, acetonitrile, and DCM). However, in all cases, the desired products were obtained only in trace amounts as ascertained from LC/MS analyses, which gave mostly unreacted staring material. Pyrrolopyrimidines were obtained in better yield using solvent-free conditions. For example, heating ureidopyrrole **5a** (100 mol %) in benzaldehyde (1000 mol %) with TFA (300 mol %) at 140 °C for 1.5 h gave 55% yield of pyrrolopyrimidine **1a** after chromatography on silica gel (Table 1).

Scheme 1. Synthesis of Ureidopyrroles **5a**−**c**



Electron-rich aromatic aldehydes, *p*-tolualdehyde and *p*-anisaldehyde, reacted with **5a** under similar conditions to give pyrrolopyrimidines **1b** and **1c** in 63% and 53% yields, respectively (Table 1). The electron-defficient aryl aldehyde, *p*-nitrobenzaldehyde, reacted with ureidopyrrole **5a** to give pyrrolopyrimidine **1d** in only 28% yield. This reaction required heating in toluene at reflux due to inability to use *p*-nitrobenzaldehyde, a solid at rt, under standard conditions in neat aldehyde at 140 °C. The lower yield of **1d** may thus stem from using lower temperature and concentration, rather than electronic effects.

The scope of the reaction was next examined using isobutyraldehyde and ureidopyrrole **5a**. Considering high

(9) Marcotte, F.-A.; Rombouts, F. J. R.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6984.
(10) Rombouts, F. J. R.; Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 589.
(11) Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 977.
(12) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.
(13) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(14) Lee, S. C.; Park, S. B. *J. Comb. Chem.* **2006**, *8*, 50.
(15) De la Figuera, N.; Fiol, S.; Fernández, J.-C.; Forns, P.; Fernández-Forner, D.; Albericio, F. *Synlett* **2006**, *12*, 1903.
(16) Diness, F.; Beyer, J.; Meldal, M. *Chem. Eur. J.* **2006**, *12*, 8056.
(17) Rousseau, J. F.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 2731.
(18) Raiman, M. V.; Pukin, A. V.; Tyvorskii, V. I.; De Kimpe, N.; Kulinkovich, O. G. *Tetrahedron* **2003**, *59*, 5265.
(19) Xiang, J. B.; Zheng, L. Y.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765.
(20) Marcotte, F.-A.; Lubell, W. D. *Org. Lett.* **2002**, *4*, 2601.

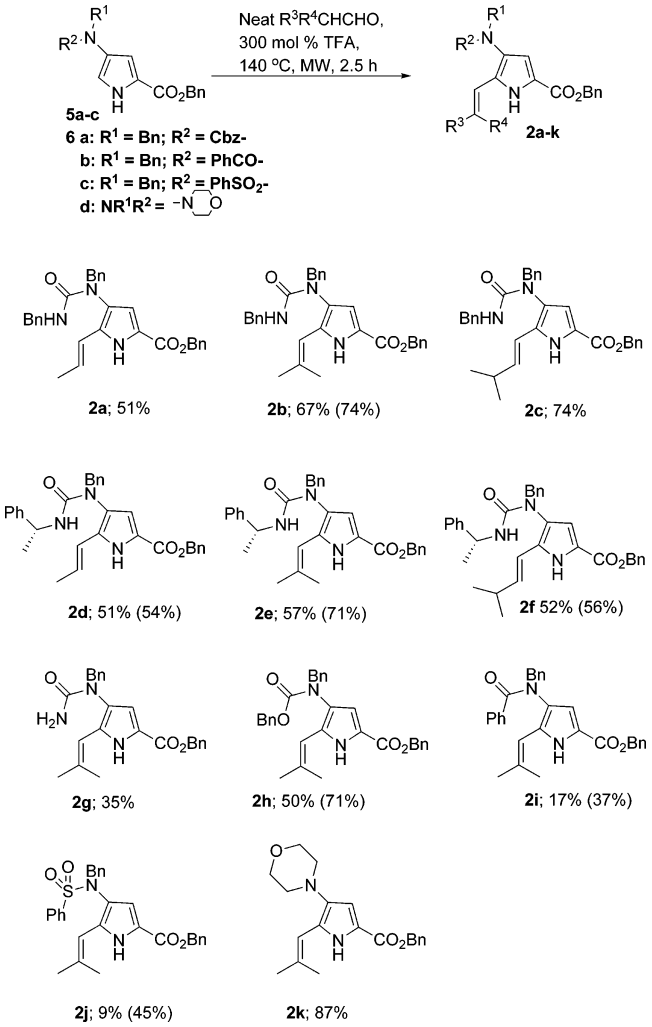


Figure 1. Isolated yields of 2-vinylpyrroles from microwave heating of 4-amino-pyrrole-2-carboxylates and aldehydes. Yields in parentheses are based on recovered starting material.

temperatures important for ring annulation, the lower-boiling aliphatic aldehyde and **5a** were heated in a sealed tube using microwave irradiation. Microwave heating of **5a** and isobutyraldehyde (0.02 M) at 140 °C for 2.5 h followed by chromatography on silica gel gave a major product in 67% yield with 14% yield of recovered starting material, which was recycled. Although the product's molecular ion corresponded to a C4 alkyl pyrrolopyrimidine,[22] examination of its ^{1}H- and ^{13}C NMR spectra revealed a structural isomer. The methyl groups of the isopropyl moiety appeared as singlets rather than doublets, no isopropyl CH proton was observed, and a new vinyl proton and urea NH proton were observed, indicating that no cyclization occurred and 2-vinylpyrrole **2b** was formed (Figure 1).

To widen this new entrance to vinylpyrroles, other ureidopyrroles and aliphatic aldehydes were examined. *N*-Benzyl *N*′-α-methylbenzylureidopyrrole **5b** was prepared from acylation of aminopyrrole **4** with α-methylbenzyl isocyanate in 96% yield, and *N*-benzylureidopyrrole **5c** was made in 80% yield by treating **4** in dioxane/water with potassium cyanate and AcOH. From the same conditions with isobutyraldehyde, ureidopyrroles **5b** and **5c** yielded 2-vinylpyrroles **2e** and **2g** in 57% and 35% yields, respectively, after chromatography. Ureidopyrroles **5a** and **5b** reacted similarly with propionaldehyde and isovaleraldehyde to provide 2-vinylpyrroles **2a**, **2c**, **2d**, and **2f** in 51−74% yields (Figure 1). The *trans*-olefin isomer was indicated in all cases by the large vinylic proton *J* coupling constant value (16.2−16.9 Hz). Ureidopyrrole **5a** failed to react with pivalaldehyde and acetone.

Crystals of vinylpyrrole **2e** were grown from EtOAc in hexanes and examined by X-ray diffraction (Figure 2). Other

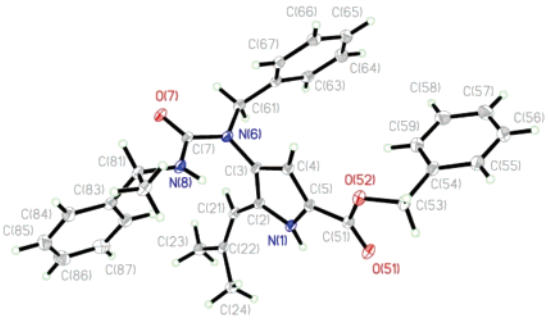


Figure 2. X-ray crystal structure of 2-vinylpyrrole, **2e**.

than 1,1,2,2-tetra(2-pyrrolyl)ethene,[23] to the best of our knowledge, the crystal structure of **2e** represents the first example of a pyrrole ring connected to a double bond. The olefin bond length (1.33 Å) was in agreement with the typical ethylene bond length (1.32 Å)[24] and in conjugation with the pyrrole as ascertained from their connecting bond length (1.45 Å) which corresponded with bond lengths in butadiene and biphenyl (1.48 Å).[24]

Considering the mechanism, two routes to vinylpyrrole appeared possible (Figure 3). In accord with the Pictet−Spengler mechanism,[13] initial condensation of the aldehyde onto the urea nitrogen would yield acyl imminium ion that is attacked by pyrrole with subsequent aromatization to form the pyrrolo[3,2-*d*]pyrimidine. Subsequently, *β*-elimination of the urea could provide the *C*-vinyl ureidopyrrole. Pyrrolopyrimidines from aryl aldehydes may be stable, because they cannot undergo *β*-elimination to *C*-vinylpyrrole. A second mechanism would involve attack of pyrrole directly onto the aldehyde to furnish an alcohol intermediate that eliminates water to afford *C*-vinylpyrrole (Figure 3).

To examine the Pictet−Spengler mechanism and the necessity for the urea nitrogen, benzyl 4-[*N*-(Cbz)-*N*-ben-

(21) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202.
(22) Blankenship, J.W.; Lubell, W.D. Synthesis of pyrrolo[3,2-d]-pyrimidines for application as *β*-sheet mimics. In *Peptides 2004: Proceedings 3rd International and 28th European Peptide Symposium*; Prague, Czech Republic, September 5−10, 2004; Flegel, M., Fridkin, M., Gilon, C., Slaninova, J., Eds.; Kenes International: Israel, 2005; p 746.
(23) Khoury, R.G.; Jaquinod, L.; Smith, K.M. *Chem. Commun.* **1997**, 1057.
(24) Smith, M.B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; Chapter 1, p 20.

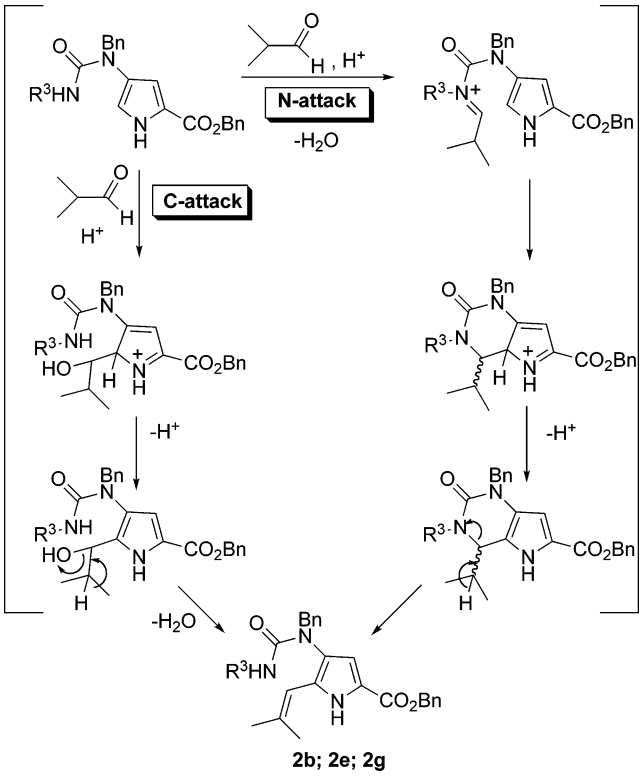


Figure 3. Possible mechanisms for vinylpyrrole formation

zylamino]pyrrole-2-carboxylate **6a** was synthesized in 67% yield by acylation of aminopyrrole **4** with benzylchloroformate, and then reacted with isobutyraldehyde under the same conditions as used with ureidopyrroles **5a**−**c**. After chromatography on silica gel, *C*-vinylpyrrole **2h** was isolated in 50% yield, and carbamatopyrrole **6a** was recovered in 30% yield and recycled. Although the Pictet−Spengler-like mechanism may not be totally excluded for ureas **5**, it is impossible for carbamate **6a**; thus, vinylpyrrole synthesis was extended to pyrroles bearing other ring substituents. Benzamido- and benzenesulphonamidopyrroles **6b** and **6c** were prepared respectively in 67% and 65% yields by acylation of **4** with benzoyl and benzenesulphonyl chloride, and reacted with isobutyraldehyde to give 2-vinylpyrroles **2i** and **2j** in 17% and 9% yields, respectively, with recovered starting material (54% and 80% for **6b** and **6c**). 4-Morpholinopyrrole[20] **6d** reacted qauntitatively with isobutyraldehyde to give 2-vinylpyrrole **2k** in 87% isolated yield. Multiple products were respectively obtained from reactions of pyrrole and benzyl 4-hydroxy-pyrrole-2-carboxylate with isobutyraldehyde under the same conditions. Vinylpyrrole yield correlated with the electron density of the aminopyrroles. Yields were typically >50% and comparable with alternative methods for making vinylpyrroles that usually require multiple steps.

2-Vinylpyrroles and pyrolo[3,2-*d]*pyrimidines were synthesized from acid-induced condensations of 4-ureido-pyrrole-2-carboxylates with aliphatic and aryl aldehydes, respectively. Mechanistic study revealed that *C*-vinylpyrrole arose from pyrrole reacting as a *C*-nucleophile onto the aliphatic aldehyde and indicated that other aminopyrrole analogues react to give vinylpyrrole under the reaction conditions. Considering the utility of *C*-vinylpyrroles and the biological activity of pyrrolo[3,2-*d*]pyrimidines, the scope of these reactions is under further investigation.

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Supporting Information Available: General experimental methods, copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **2**, **5** and **6**, and X-ray structure data of compound **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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