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Technical Notes

Practical One-Pot Syntheses of Ethyl 4-Substituted-1*H*-Pyrrole-3-Carboxylates from Aldehydes†

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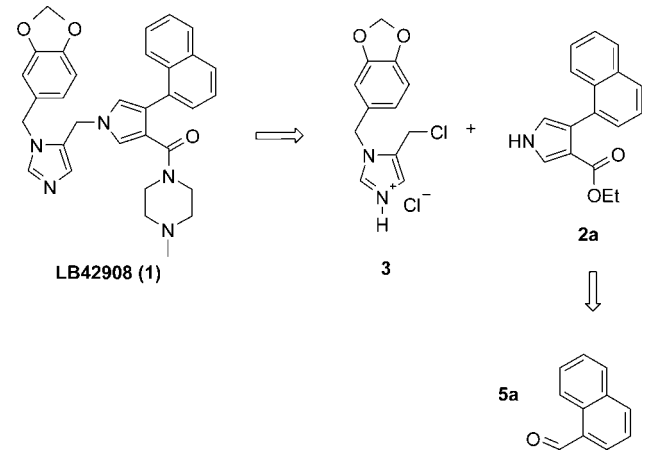
Abstract:

Ethyl 4-substituted-1*H*-pyrrole-3-carboxylates were prepared in a one-pot manner starting from aromatic or aliphatic aldehydes via a Horner−Wadsworth−Emmons reaction and subsequent reaction with tosylmethylisocyanide (TosMIC) in the presence of sodium *tert*-amylate in toluene. Judicious selection of base and solvent led to the use of a single solvent, i.e., toluene, for reactions as well as for crystallization to render the one-pot process more practical and greener than the stepwise version.

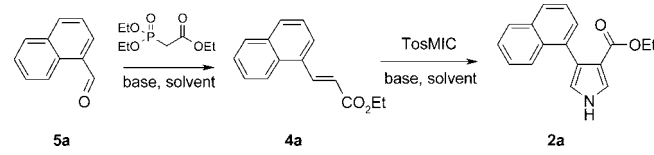
In search of a potent and selective farnesyltransferase (FTase) inhibitor, our discovery team identified LB42908 (**1**) having an ethyl 4-(1-naphthyl)-1*H*-pyrrole-3-carboxylate fragment as a development candidate[1] (Scheme 1). For its expeditious development, it became prerequisite to set up a large-scale viable synthesis of the pyrrole fragment **2a** and its coupling partner **3**.[2] Herein, we describe a practical and green, one-pot preparation of **2a** from aldehyde **5a**.[3]

In the literature there are limited synthetic methods for the construction of this class of compounds. Most frequently reaction of α,β-unsaturated ester with tosylmethylisocyanide (TosMIC) in the presence of base is used as developed by van Leusen et al.[4] Alternatively, reaction of β-aminoacrylate with α-aminoarylketone[5] or Michael addition of β-aminoacrylate towards nitroalkene followed by Nef reaction,[6] or oxidation of pyrrolidine by excess manganese dioxide[7] could be a possible route towards 4-substituted-1*H*-pyrrole-3-carboxylates. Based on readily accessible starting materials, α,β-unsaturated ester and TosMIC, a modified version of the first method was investigated for the synthesis of pyrrole compounds via two separate steps: (1) conversion of an aldehyde to an α,β-unsaturated ester with triethylphosphonoacetate in the presence of lithium chloride and DBU in acetonitrile and (2) its reaction with TosMIC in the presence of potassium *tert*-butoxide in THF (Scheme 2). However, we quickly realized that this route was not viable for a large-scale operation because water-miscible solvents, acetonitrile and THF, should be removed for efficient extractive workups, thus increasing effluent as well as the number of operations such as distillations. These shortcomings led us to consider a one-pot synthesis which not only obviates a number of operations but also reduces the amount of effluent. To this end, we ran the Horner−Wadsworth−Emmons reaction of aldehyde **5a** with sodium *tert*-butoxide in DME to form **4a**, into which TosMIC and additional sodium *tert*-butoxide was added to provide pyrrole **2a**. After the addition of water and toluene, most of DME was removed by distillation, and the organic phase was separated at 80 °C. Crystallization from toluene afforded highly pure product **2a**. Although this change is superior to the stepwise version, there is still room for further

Scheme 1



Scheme 2



† This paper is dedicated to Dr. Hokoon Park on the occasion of his 61st birthday.

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(1) Lee, H.; Lee, J.; Lee, S.; Shin, Y.; Jung, W.; Kim, J.-H.; Park, K.; Kim, K.; Cho, H. S.; Ro, S.; Lee, S.; Jeong, S. W.; Choi, T.; Chung, H.-H.; Koh, J. S. *Biorg. Med. Chem. Lett.* **2001**, *11*, 3069.

(2) (a) For the synthesis of **3**, please refer to: (a) ref 1. (b) Chang, J. H.; Lee, K. W.; Nam, D. H.; Kim, W. S.; Shin, H. *Org. Process Res. Dev.* **2002**, *6*, 674.

(3) The content of this paperhas been published as a part of patent. See: Shin, H.; Oh, S. T.; Chang, J. H.; Lee, K. U. WO 01/62727, 2001.

(4) (a) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, 5337. (b) Pavri, N. P.; Trudell, M. L. *J. Org. Chem.* **1997**, *62*, 2649. (c) For the use of benzotriazol-1-yl-methyl isocyanide (BetMIC) as a TosMIC surrogate, see Katritzky, A. R.; Cheng, D.; Musgrave, P. *Heterocycles* **1997**, *44*, 67.

(5) Alberola, A.; Andres, J. M.; Gonzalez, A.; Pedrosa, R.; Vicente, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2681.

(6) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263.

(7) Menasra, H.; Kedjadja, A.; Debaches, A.; Rhouati, S.; Belfaitah, A. *Synth. Commun.* **2005**, *35*, 2779.

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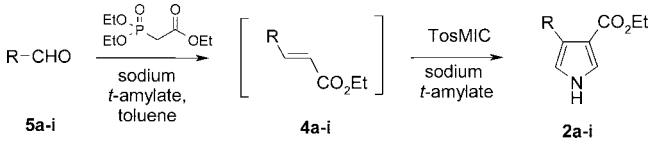
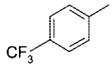
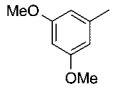
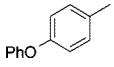
Table 1. **Substrate scope of one-pot pyrrole synthesis**



5a-i 4a-i 2a-i

Entry	R	aldehyde	Product	Yield
1		**5a**	**2a**	62%
2		**5b**	**2b**	55%
3		**5c**	**2c**	39%
4		**5d**	**2d**	47%[b] (38%[c])
5		**5e**	**2e**	37%
6		**5f**	**2f**	43%
7		**5g**	**2g**	52%
8		**5h**	**2h**	23%[d]
9		**5i**	**2i**	53%[d]

[a] Except **2a**, all the reactions were tested with 5 mmol of aldehydes. [b] At the first step, sticky oil was formed as reaction progressed to make stirring difficult. [c] Yield using MeTHF as a solvent; homogeneous reaction mixture was observed. [d] Although products solidified in toluene, they were purified by column chromatography.

improvement if we could use toluene as a solvent *for the reactions as well as for recrystallization*.[8] However, it was found that the Horner−Wadsworth−Emmons reaction of aldehyde **5a** in toluene with sodium *tert*-butoxide as a base was very sluggish. We speculated that the slow reaction might be caused by low solubility of sodium *tert*-butoxide in toluene and an alternative base having better solubility profile would solve this problem. Happily, replacement of sodium *tert*-butoxide with sodium *tert*-amylate[9] caused smooth conversion to α,β-unsaturated ester **4a** as well as to pyrrole **2a**. At the end of reaction, water was added, phases were separated at 80 °C, the organic phase was cooled, and product was filtered to provide highly pure (better than 95% by HPLC) **2a** as a crystalline solid.

To test the generality of the established method, we tested various aromatic aldehydes substituted by electron-withdrawing and -donating groups, revealing that electronic influence was negligible (Table 1). Products **2a**, **2c**, **2e**, and **2f** (entries 1, 3, 5, and 6) were isolated as a good solid from toluene without any chromatographic separation. Compounds **2b**, **2d**, and **2g** (entries 2, 4, and 7) were purified by column chromatography. Aliphatic aldehydes are also acceptable substrates for our protocol: trimethylacetaldehyde and isovaleraldehyde (entries 8 and 9) were converted to corresponding pyrroles **2 h** and **2i** in 23% and 53% yield, respectively.

In summary, by considering both operational efficiency as well as reduction of effluent, we devised a one-pot process towards ethyl 4-substituted-1*H*-pyrrole-3-carboxylates which features the use of a single solvent, i.e., toluene, for both reactions and crystallization.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Jeol 500 MHz spectrometer. HPLC analyses were carried out on a Hewlett-Packard 1100 system and a Waters 490E detector and 616 pump system. Mass spectra were collected using a Finnigan LCQ mass spectrometer system and a Jeol JMX-700 mass spectrometer.

Ethyl 4-(1-Naphthyl)-1*H*-pyrrole-3-carboxylate (2a). 1-Naphthaldehyde (2.8 kg, 18 mol) and triethylphosphonoacetate (4.04 kg, 18 mol) were introduced into a 50 L reactor and diluted with 18 L of toluene. The reaction mixture was cooled to about 0−5 °C, and sodium *tert*-amylate (2.38 kg, 21.6 mol) was added slowly in order to maintain the reaction temperature below 20 °C. After the addition was completed, the reaction mixture was stirred for 1 h at ambient temperature and cooled to 0−5 °C. TosMIC (3.69 kg, 18.9 mol) and sodium *tert*-amylate (2.38 kg, 21.6 mol) were added slowly in sequence, maintaining the reaction temperature below 20 °C. After the addition was completed, the reaction mixture was stirred for 5 h at ambient temperature, and 25 L of distilled water was added. The resulting mixture was heated at about 80 °C, and the organic layer was separated and washed once again with 25 L of distilled water at the same temperature. Roughly one-third of the separated organic layer was subjected to azeotropic distillation to remove the residual moisture. Then, the concentrate was cooled to about 50 °C with slow stirring. After the crystal was precipitated, the reaction temperature was further lowered to 25 °C and stirring was continued for 15 h. The formed solid was filtered, washed twice with 3 L of toluene and dried with nitrogen purge to give 2.96 kg (HPLC Purity 96% PAR, Yield 62%) of **2a** as a white solid. Physical and spectral data: mp 164−165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, br, 1H), 7.80 (m, 3H), 7.59 (dd, J = 3.2, 2.3 Hz, 1H), 7.41 (m, 4H), 6.79 (t, J = 2.3 Hz, 1H), 3.91 (q, J = 6.9 Hz, 2H), 0.71 (t, J = 6.9 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 133.8, 133.51, 133.50, 128.0, 127.5, 127.3, 126.7, 125.5, 125.4, 125.2, 124.7, 123.9, 119.3, 115.9, 59.5, 13.7.

Ethyl 4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (2b): ^{1}H NMR (500 MHz, CDCl3) δ 9.22 (s, br, 1H), 7.41 (dd, J = 8.5, 5.5 Hz, 2H), 7.34 (t, J = 2.3 Hz, 1H), 7.00 (t, J = 8.5 Hz, 2H), 6.59 (t, J = 2.3 Hz, 1H), 4.22 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 161.9 (d, J = 243 Hz), 131.0 (d, J = 8.3 Hz), 125.8, 125.5, 118.7, 114.7 (d, J = 21 Hz), 113.2, 59.9, 14.4.

Ethyl 4-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-car-

(8) One reviewer reminded us of a reference which describes the general concept of our approach as a "bottom-up" approach to the development of direct-drop process. Please refer to Chen, C.-K.; Singh, A. K. *Org. Process Res. Dev.* **2001**, *5*, 508.

(9) Sodium *tert*-butoxide and *tert*-amylate have 6 wt % and 41 wt % solubility in toluene at 25 °C, respectively. For general information on metal alkoxides, please visit http://www.alcoholates.com.

boxylate (2c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, br, 1H), 7.59 (s, 4H), 7.50 (t, J = 2.4 Hz, 1H), 6.81 (t, J = 2.4 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 138.5, 129.6, 128.7, 128.4, 125.7, 125.6, 125.5, 124.7, 124.6, 118.8, 113.9, 59.9, 14.4; HRMS (ESI) for [M + H$^+$] $C_{14}H_{13}F_3NO_2$: calcd, 284.0892; found, 284.0891.

Ethyl 4-[3-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxylate (2d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, br, 1H), 7.72 (s, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.52 (m, 1H), 7.50 (t, J = 2.3 Hz, 1H), 7.44 (m, 1H), 6.79 (t, J = 2.3 Hz, 1H), 4.20 (q, J = 7.4 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 135.6, 132.8, 130.1 (q, J = 31 Hz), 128.1, 126.2, 125.8, 125.5, 123.3, 118.7, 114.1, 59.9, 14.2; HRMS (ESI) for [M + H$^+$] $C_{14}H_{13}F_3NO_2$: calcd, 284.0892; found, 284.0891.

Ethyl 4-(2-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (2e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, br, 1H), 7.40 (t, J = 2.3 Hz, 1H), 7.27 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.72 (t, J = 2.3 Hz, 1H), 4.14 (q, J = 7.4 Hz, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 157.3, 131.2, 128.2, 124.4, 124.2, 121.9, 120.9, 118.7, 115.5, 110.4, 59.6, 55.5, 14.3; HRMS (ESI) for [M + H$^+$] $C_{14}H_{16}NO_3$: calcd, 246.1124; found, 246.1125.

Ethyl 4-(3,5-dimethoxyphenyl)-1*H*-pyrrole-3-carboxylate (2f): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, br, 1H), 7.47 (s, 1H), 6.79 (s, 1H), 6.66 (s, 2H), 6.40 (s, 1H), 4.22 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 160.1, 136.7, 126.5, 125.4, 118.5, 114.1, 107.7, 98.9, 59.8, 55.4, 14.4; HRMS (ESI) for [M + H$^+$] $C_{15}H_{18}NO_4$: calcd, 276.1230; found, 276.1231.

Ethyl 4-(4-phenoxyphenyl)-1*H*-pyrrole-3-carboxylate (2g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, br, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.36 (s, 1H), 7.28 (t, J = 8.0 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.4 Hz, 2H), 6.62 (s, 1H), 4.22 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 157.4, 156.0, 130.8, 130.2, 129.9, 125.9, 123.3, 118.9, 118.6, 118.4, 113.2, 59.9, 14.5; HRMS (ESI) for [M + H$^+$] $C_{19}H_{18}NO_3$: calcd, 308.1281; found, 308.1280.

Ethyl 4-*tert*-butyl-1*H*-pyrrole-3-carboxylate (2h): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, br, 1H), 7.46 (d, J = 2.5 Hz, 1H), 6.54 (d, J = 2.5 Hz, 1H), 4.24 (q, J = 7.4 Hz, 2H), 1.38 (s, 9H), 1.27 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 135.7, 126.8, 115.4, 113.9, 59.5, 31.4, 30.4, 14.5; HRMS (ESI) for [M + H$^+$] $C_{11}H_{18}NO_2$: calcd, 196.1332; found, 196.1331.

Ethyl 4-*iso*-butyl-1*H*-pyrrole-3-carboxylate (2i): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, br, 1H), 7.37 (d, J = 1.9 Hz, 1H), 6.50 (d, J = 1.9 Hz, 1H), 4.24 (q, J = 7.3 Hz, 2H), 2.56 (d, J = 7.3 Hz, 2H), 1.86 (m, 1H), 1.33 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 125.0, 124.7, 117.8, 114.4, 59.5, 35.4, 29.1, 22.6, 14.5; HRMS (ESI) for [M + H$^+$] $C_{11}H_{18}NO_2$: calcd, 196.1332; found, 196.1331.

Supporting Information Available

^{1}H and ^{13}C NMR spectra of **2a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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