ORGANIC LETTERS

2009
Vol. 11, No. 6
1233−1235

Synthesis of 2,4-Disubstituted Pyrroles by Rearrangements of 2-Furanyl Carbamates

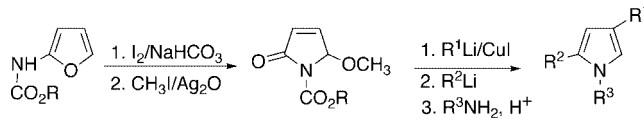
Sezgin Kiren, Xuechuan Hong, Carolyn A. Leverett, and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia, 30322

chemap@emory.edu

Received January 12, 2009

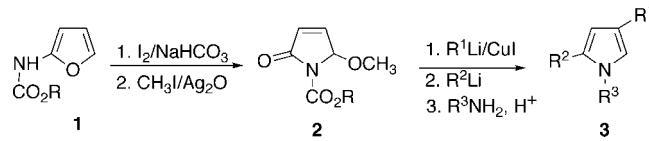
ABSTRACT



2,4-Disubstituted pyrroles were synthesized by an oxidative rearrangement of a furanyl carbamate followed by sequential reaction of the resulting 5-methoxypyrrol-2(5*H*)-one with different alkyl lithiates. The final step of the procedure involves heating the ring opened 1-methoxy-5-oxopentylcarbamate with a primary amine.

The biological activity of substituted pyrroles has made them a focus of medicinal chemistry over the years.[1] Pyrroles occur in numerous pharmacologically active natural and unnatural products.[2] Additionally, functionalized pyrroles represent building blocks of natural tetrapyrrole pigments, such as porphorobilinogen or bilirubin, and of various other natural products and their analogues.[3] For more than a century, many diverse methods have been developed to prepare pyrroles with various ring substitution patterns,[4] including the classical Hantzsch, Knorr and Paal-Knorr procedures.[5] We describe here, the details of a new method for preparing 2,4-disubstituted pyrroles starting from a furanyl carbamate (i.e., **1**) (Scheme 1). The advantage of this methodology is that various substituents can be selectively introduced at the C_2 and C_4-positions using alkyl lithiates and aromatization can be accomplished under nonaqueous conditions.

Scheme 1



Some years ago, we reported a useful protocol for the preparation of hydroxylated piperidine alkaloids[6] by making use of the aza-Achmatowicz oxidation.[7] This earlier work prompted us to explore the related oxidative rearrangement of furanyl carbamate **1** into 5-methoxypyrrol-2(5*H*)-one (**2**). 5-Alkoxypyrrol-2(5*H*)-ones (**4**) exhibit a wide range of interesting pharmacological properties,[8] have been used as key intermediates in the synthesis of various alkaloids,[9] and

(1) (a) Balme, G. *Angew Chem., Int. Ed.* **2004**, *43*, 6238. Pyrroles: (b) Jones, R. A., Ed. *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1996; Vol 48, Part 1.

(2) Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*; Springer: Wien, 1989; p 355.

(3) Sunberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheesemen, G. W. H., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 331.

(4) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol 2, p 207.

(5) (a) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095. (b) Ferreira, V. F.; deSouza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. C. *Org. Prep. Proced. Int.* **2001**, *33*, 413.

(6) (a) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371. (b) Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591.

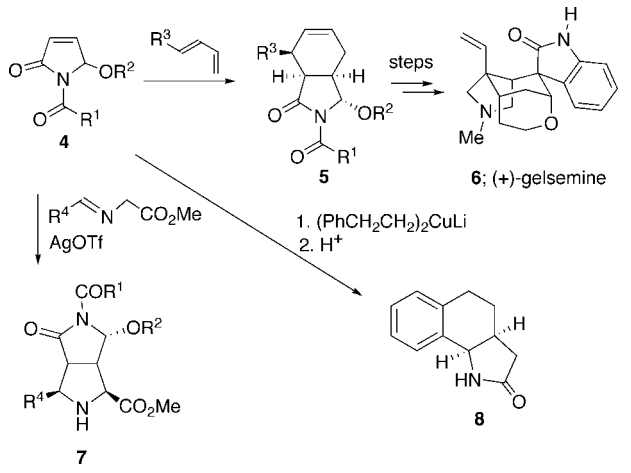
(7) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett.* **1998**, 105.

(8) (a) Wooldridge, T. A.; Lightner, D. A. *J. Heterocycl. Chem.* **1977**, *14*, 1283. (b) Vitillo, B.; Buniva, G.; Bernareggi, A.; Assandri, A.; Perazzi, A.; Fuccella, L. M.; Palumbo, R. *Int. Clin. Parmacol. Ther. Toxicol.* **1984**, *22*, 273.

10.1021/ol900059e CCC: $40.75
Published on Web 02/20/2009

are also suitable precursors for the preparation of unusual γ-amino acids such as statine and its analogues.[10] The chemistry of this unique pyrrolidinone ring has been explored by a number of research groups.[11] Because of its multifunctional core, this heterocyclic system can take part in several stereoselective transformations such as conjugate addition,[12] cycloadditions,[13] acyliminium ion chemistry,[14] and allylic substitutions[15] (Scheme 2).

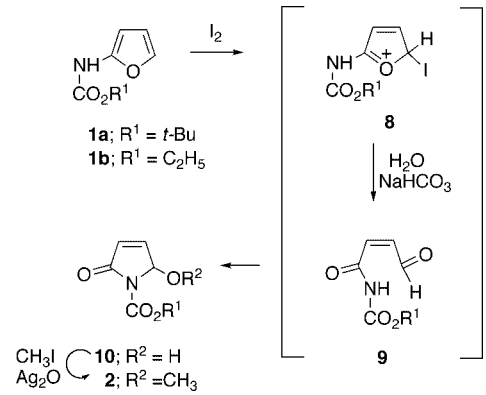
Scheme 2



Besides some specialized methodologies,[16] the majority of synthetic approaches used for the preparation of 5-alkoxypyrrol-2(5*H*)-ones are based on the cyclization of α,β-unsaturated keto amides,[17] amination reactions of the corresponding γ-lactones,[18] Grignard addition to maleimide derivatives,[19] and the photosensitized oxygenation of pyrroles,[20] diazepines[21] and 2-furyl carbamates.[22]

We now describe a four-step synthesis of 2,4-disubstituted pyrroles (**3**) involving (i) an oxidative rearrangement of a furanyl carbamate (**1**) to give 5-methoxypyrrol-2(5*H*)-one (**2**), (ii) conjugate addition of a cuprate reagent to the C_4 position of the heterocyclic ring, (iii) further reaction of the resulting 2-methoxy-5-oxopyrrolidine **11** with an alkyl lithium to furnish a ring-opened alkyl 1-methoxy-5-oxopentylcarbamate **12** and (iv) cyclization with a primary amine under microwave conditions to afford the pyrrole derivative. The 5-methoxypyrrol-2(5*H*)-one required for this methodology was readily prepared by the addition of I_2 to a solution of the furanyl carbamate **1** in aqueous acetone which contained a 2 mol excess of $NaHCO_3$. More than likely the reaction proceeds *via* intermediates **8** and **9** as indicated in Scheme 3. The initially formed 2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole **10** was smoothly converted into the corresponding methoxy derivative **2** by treatment with methyl iodide and silver (I) oxide in CH_2Cl_2 at 25 °C. The yield of the resulting 5-methoxypyrrol-2(5*H*)-one from the furanyl carbamate is quite good (*ca* 85%) and the final product is easily isolated by column chromatography on silica gel.

Scheme 3



The conjugate addition of various cuprates to the α,β-unsaturated lactam system of **2** proceeded in 60−92% yield with high stereoselectivity. The ^{1}H NMR spectra of the crude product only showed the presence of a single *trans*-addition product in all cases. The assignment was based on the ^{1}H NMR vicinal coupling constant of H_5. In a *trans*-lactam this coupling is 0−1 Hz, whereas a *cis*-lactam has a coupling of 5−6 Hz.[23] The products obtained from the cuprate additions

(9) (a) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588. (b) Newcombe, N. J.; Ya, F.; Vijin, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767. (c) Speckamp, W. N.; Newcombe, N. J.; Hiemstra, H.; Ya, F.; Vijin, R. J.; Koot, W. *J. Pure Appl. Chem.* **1994**, *66*, 2163. (d) Casiraghi, G.; Spanu, P.; Rassu, G.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1994**, *59*, 2906. (e) Griffart-Brunet, D.; Langois, N. *Tetrahedron Lett.* **1994**, *35*, 119.

(10) (a) Jouin, P.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. (b) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron Asymmetry* **1996**, *7*, 2365.

(11) (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. (c) Farina, F.; Martin, M. V.; Paredes, M. C. *Synthesis* **1973**, 167. (d) Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 3801.

(12) (a) Jimenez, M. D.; Ortega, R.; Tito, A.; Farina, F. *Heterocycles* **1988**, *27*, 173. (b) Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Asymmetry* **1993**, *4*, 1941.

(13) (a) Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 1059. (b) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791.

(14) Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969.

(15) Cuiper, A. D.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 655.

(16) (a) McKennis, H.; Bowman, E. R.; Quin, L. D.; Denney, R. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2046. (b) Veronese, A. C.; Callegari, R.; Basato, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1779. (c) Arzoumanian, H.; Jean, M.; Nuel, D.; Garcia, J. L.; Rosas, N. *Organometallics* **1997**, *16*, 2726.

(17) Lightner, D. A.; Low, L. K. *J. Heterocycl. Chem.* **1972**, *9*, 167.

(18) (a) Shiraki, R.; Sumino, A.; Tadano, K. I.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845. (b) Farina, F.; Martin, M. V.; Paredes, M. C. *Heterocycles* **1984**, *22*, 1733. (c) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567. (d) Kotera, M.; Roupioz, Y.; Defrancq, E.; Bourdat, A. G.; Garcia, J.; Coulombeau, C.; Lhomme, J. *Chem.−Eur. J.* **2000**, *6*, 4163.

(19) Bartfeld, H. D.; Flitsch, W. *Chem. Ber.* **1973**, *106*, 1423.

(20) Lightner, D. A.; Bisacchi, G. S.; Norris, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 802.

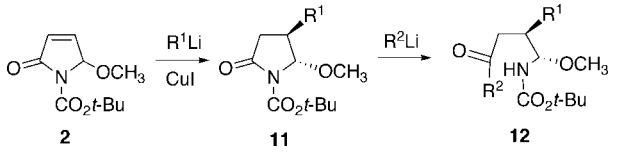
(21) (a) Kurita, J.; Kojima, H.; Tsuchiya, T. *Chem. Parm. Bull.* **1986**, *34*, 4871. (b) Kurita, J.; Kojima, H.; Tsuchiya, T. *Heterocycles* **1984**, *22*, 721.

(22) Kakushijin, K.; Suzuki, R.; Kawaguchi, N.; Tsuboi, Y.; Furakawa, H. *Chem. Pharm. Bull.* **1986**, *34*, 2049.

(23) Koot, W. J.; Van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401.

were then used in the next step which consisted of treating the 2-methoxy-3-alkyl substituted 5-oxopyrrolidinone **11** with an alkyl lithium reagent to give the ring opened 1-methoxy-5-oxopentylcarbamate **12**. The results for the conjugate addition-alkyl lithiation reaction of differently substituted systems in THF at −78 °C are summarized in Table 1. From

Table 1. Conjugate Addition-Alkyl Lithiation Reaction of 5-Methoxypyrrol-2(5*H*)-one (2)

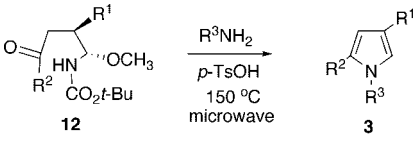


entry	R^1	yield of **11**	R^2	yield of **12**
a	$t-Bu$	80%	allyl	72%
b	Ph	75%	CH_3	70%
c	$n-C_4H_9$	92%	Ph	94%
d	$n-C_4H_9$	–	CH_3	85%
e	CH_3	80%	2−thienyl	86%
f	CH_3	–	$n-C_4H_9$	80%
g	$n-C_6H_{13}$	60%	C_2H_5	65%

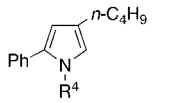
the table it can be seen that the reaction is quite general: R^2 = various alkyl, phenyl or 2-thienyl groups with yields ranging from 65% to 94%.

The 2,4-disubstituted pyrrole (**3**) system was then prepared by heating a mixture of the 1-methoxy-5-oxopentylcarbamate **12** and an appropriate primary amine in the presence of a trace amount of *p*-TsOH in a microwave reactor at 150 °C (Scheme 4). In all cases, the desired 2,4-disubstituted pyrrole

Scheme 4



12a $R^1 = n\text{-}C_4H_9$, $R^2 = Ph$



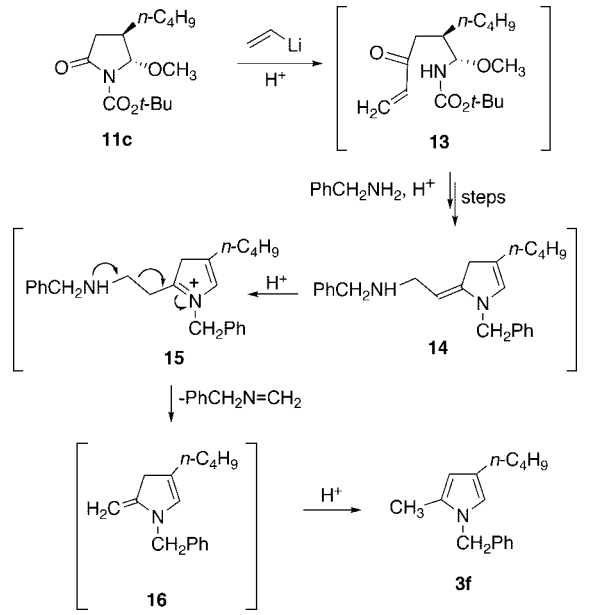
3a; $R^1 = n\text{-}C_4H_9$; $R^2 = Ph$; $R^3 = CH_2Ph$ (90%)
3b; $R^1 = n\text{-}C_4H_9$; $R^2 = R^3 = Ph$ (97%)
3c; $R^1 = n\text{-}C_4H_9$; $R^2 = Ph$; $R^3 = 2\text{-}CH_2$(furanyl) (65%)
3d; $R^1 = n\text{-}C_4H_9$; $R^2 = Ph$; $R^3 =$ cyclohexyl (90%)
3e; $R^1 = Ph$; $R^2 = CH_3$; $R^3 = CH_2Ph$ (70%)
3f; $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$; $R^3 = CH_2Ph$ (81%)
3g; $R^1 = CH_3$; $R^2 = 2$-thienyl; $R^3 = CH_2Ph$ (86%)
3h; $R^1 = n\text{-}C_6H_{13}$; $R^2 = C_2H_5$; $R^3 = CH_2Ph$ (42%)
3i; $R^1 = CH_3$; $R^2 = n\text{-}C_4H_9$; $R^3 = CH_2Ph$ (54%)

3j; $R^4 = H$ (98%)
3k; $R^4 = CO_2t\text{-}Bu$ (76%)

was obtained in good yield with no evidence of any products arising from simple hydrolysis or alternatively, by furan formation. On the other hand, heating an aqueous DMF solution of **12a** (R^1 = Ph; $R^2 = n\text{-}C_4H_9$) in a microwave reactor afforded an almost quantitative yield of the NH-pyrrole **3j**. However, when **12a** is heated in toluene in the presence of a CSA/quinoline catalyst, only the Boc-pyrrole **3k** was formed in 76% yield.

Interestingly, when the reaction was carried out in a one-pot fashion using 5-oxopyrrolidinone **11c** and vinyl lithium followed by heating with benzyl amine, the only product that could be isolated corresponded to *N*-benzyl-4-*n*-butyl-2-methyl-1*H*-pyrrole (**3f**). This surprising result can be explained by the series of reactions outlined in Scheme 5.

Scheme 5



More than likely, the transient vinyl oxypentylcarbamate **13** that is first formed reacts with excess benzyl amine to eventally give enamine **14**. Protonation of **14** to iminium ion **15** followed by loss of $PhCH_2N{=}CH_2$ under the reaction conditions furnishes **16** which is readily isomerized to pyrrole **3f**.

In summary, we have discovered a new and efficient approach to a variety of 2,4-disubstituted pyrroles based on an oxidative rearrangement of a furanyl carbamate followed by sequential reaction of the resulting 5-methoxypyrrol-2(5*H*)-one with alkyl lithiates. The final step of the procedure involves heating the ring opened 1-methoxy-5-oxopentyl-carbamate with a primary amine. The overall process can be carried out under mild conditions and complements existing methods to prepare substituted pyrroles.

Acknowledgment. We appreciate the financial support provided by the National Science Foundation (CHE-0742663).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900059E