Organic Process Research & Development **2009,** *13,* 1199–1201

Green *N*-Methylation of Electron Deficient Pyrroles with Dimethylcarbonate

Michael L. Laurila, Nicholas A. Magnus,* and Michael A. Staszak*

Eli Lilly and Company, Chemical Product Research and Development Division, Indianapolis, Indiana 46285, U.S.A

Abstract:

The *N*-methylation of electron-deficient pyrroles was affected using dimethyl carbonate in the presence of DMF and catalytic DABCO. This alkylation methodology has proven useful for the alkylation of a variety of pyrroles in 72−98% yields and is considered to be green chemistry relative to the more common use of methyl halides or dimethyl sulfate.

Introduction

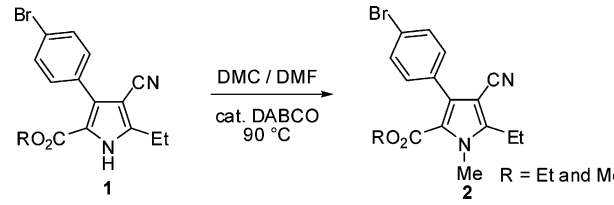
Nitrogen-containing heterocycles such as indoles and pyrroles are ubiquitous building blocks for pharmaceutical chemistry. The *N*-methylation of such heterocycles has traditionally been accomplished using toxic reagents such as dimethyl sulfate or methyl iodide in the presence of a strong base.[1] The past several years have seen the increased use of the "green reagent" dimethyl carbonate (DMC) as a viable alternative to these toxic alkylating agents.[2]

To support a neuroscience program at Eli Lilly and Company, the *N*-methylation of tetra-substituted pyrrole derivative **1** was required (Scheme 1).[3] Although classical conditions (MeI, K_2CO_3, acetone) afforded the *N*-methylated product in good yield, a less toxic method to achieve this alkylation was desired. The literature provides examples using dimethyl carbonate to *N*-methylate indoles. Surprisingly, there was far less information in the literature available on the subject of *N*-methylating pyrrole compounds.[5] In this report, the procedures concerning *N*-methylation of indoles using DMC by Jiang and, subsequently, Shieh[4] have been extrapolated to pyrroles. Herein, the *N*-methylation of compound **1** along with a number of commercially available pyrrole derivatives using DMC, DMF and catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) are described.

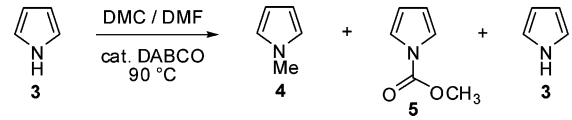
Results and Discussion

Initial efforts to *N*-methylate compound **1** employed the Shieh conditions[4] with only minor modifications (Scheme 1).

Scheme 1



Scheme 2



While affecting the desired *N*-methylation, the Scheme 1 reaction conditions also caused the 2-carboethoxy group to undergo transesterification, affording a mixture of methyl and ethyl esters. However, this was not an issue, since the mixed esters would ultimately be hydrolyzed to the carboxylic acid en route to the active pharmaceutical ingredient (API). By reacting **1** with DMC and catalytic DABCO, and using DMF as a cosolvent at 90−92 °C, the complete consumption of the starting material was observed within 24 h. After workup and isolation, compound **2** was isolated as a mixture of methyl and ethyl esters in excellent yield (98%). HPLC and MS analysis of the product indicated an ethyl/methyl ester ratio of 81.3/18.7.

To assess the generality of this result, a number of commercially available pyrrole derivatives were obtained and tested using the Scheme 1 reaction conditions. During these investigations, simple pyrroles, minus the lipophilic properties imparted by the functionalities present in compounds such as **1**, were observed to be more water soluble, resulting in lower isolated yields (60−70%). Consequently, to achieve good *N*-methylation yields, adjustments to the reaction and workup conditions were required. Reducing the amount of DMF by half, employing back-extractions of both the water and citric acid washes, and performing brine washes of the final organic layer resulted in 20−30% yield increases over the initial protocol.

Electron-rich pyrroles proved to be the least amenable to the DMC/DMF/DABCO *N*-methylation conditions. For instance, pyrrole itself (**3**) afforded a complex mixture which, after the typical 24 h heating period, was shown to contain large amounts (∼50%) of unreacted starting material and only ∼13% of the desired *N*-methylated product, **4**. The bulk of the remaining material was found by MS analysis to be consistent with the methylcarbamate **5** (Scheme 2), an intermediate type proposed by Shieh's group during their work on indoles.[4] The relative lack of polarity supported this observation. 2,5-Dimethylpyrrole was so slow to react under the described

* Authors for correspondence. (N.A.M.) E-mail: magnus_nicholas@lilly.com. (M.A.S.) E-mail: staszak_michael_a@lilly.com.

(1) For examples of the *N*-methylation of pyrroles and indoles see: (a) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63* (5), 511. (b) Reinecke, M. G.; Sebastian, J. F.; Johnson, H. W.; Pyun, C. *J. Org. Chem.* **1972**, *37*, 3066. (c) Santaniello, E.; Farachi, C.; Ponit, F. *Synthesis* **1979**, *8*, 617.

(2) (a) Tundo, P.; Selva, M. Methods and Reagents for Green Chemistry. In *Chemistry for the Environment*; John Wiley and Sons: New Jersey, 2007; Vol. 77, p 102. (b) Chankeshwawa, S. V. *Synlett* **2008**, *4*, 624. (c) Rekha, V. V.; Ramani, M. V.; Ratnamala, A.; Rupakalpana, V.; Subbaraju, V.; Satyanarayana, C.; Rao, C. S. *Org. Process Res. Dev.* **2009**, *13*, 769–3.

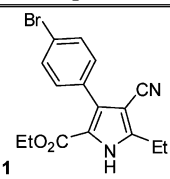
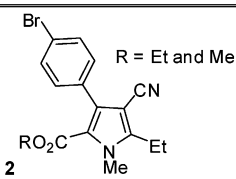
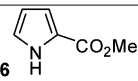
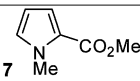
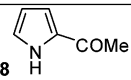
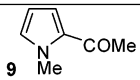
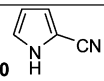
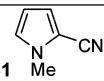
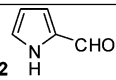
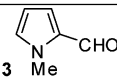
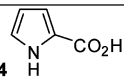
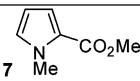
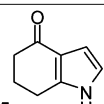
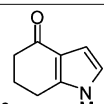
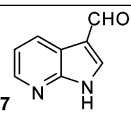
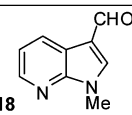
(3) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. *Org. Process Res. Dev.* **2006**, *10*, 899.

(4) (a) Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. *Org. Process Res. Dev* **2001**, *5*, 604. (b) Shieh, W. C.; Dell, S.; Bach, A.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2003**, *68* (5), 1954.

(5) (a) Quaranta, E.; Carafa, M.; Trani, F. *Appl. Catal., B* **2009**, *91*, 380. (b) Ouk, S.; Thiebaud, S.; Borredon, E. *Synth. Commun.* **2005**, *35*, 3021.

10.1021/op900256t CCC: $40.75
Published on Web 10/26/2009

Table 1. **Results**

Starting Material	Product	% Yield
 **1**	 **2**	98.0[a]
 **6**	 **7**	90.4
 **8**	 **9**	88.2
 **10**	 **11**	93.4
 **12**	 **13**	83.6
 **14**	 **7**	80.0[b]
 **15**	 **16**	72.6
 **17**	 **18**	83.1

[a] This yield is corrected for the molar ratio of ethyl to methyl esters in the product, which was ~81/19 by HPLC analysis. [b] This result is the chromatographed yield using the following system: Analogix IntelliFlash 280 with RS-120 column; 95/5 heptane/EtOAc.

conditions as to be nonproductive. After 5 days at 90−92 °C, only ~35% of the desired product was observed. Furthermore, the reaction mixture was contaminated by dark decomposition products and was discarded without workup.

Generally, electron-deficient pyrroles performed quite well under the adjusted reaction conditions, with unoptimized yields ranging from 72−98% (see Results, Table 1). The results indicate that even typically more sensitive functionalities such as aldehydes, ketones, and nitriles survive the reaction conditions well. Additionally, and in similar fashion to Shieh's indole example,[4] pyrrole-2-carboxylate **14** was successfully converted to the methyl-*N*-methyl-2-carboxylate derivative **7** in one step, indicating that concurrent methylation of both the pyrrole nitrogen and the carboxylic acid group could be achieved in one pot. This *N*-methylation technology was also extended to the preparation of *N*-methyl-7-azaindole-3-carboxaldehyde, **18** (83% yield, Table 1). Attempts to *N*-ethylate or *N*-allylate compound **1** with the corresponding alkyl carbonates gave none of the desired products.

Conclusion

To summarize, general *N*-methylation reaction conditions with DMC, DMF, and catalytic DABCO have been applied to a variety of electron-deficient pyrroles, affording the corresponding *N*-methyl products in good to excellent yields. This method of *N*-methylation provides a less toxic alternative to the reagents typically used for this type of transformation and extends the usefulness of the green methylating agent, dimethyl carbonate.

Experimental Section

All solvents and reagents except compound **1** were purchased from Aldrich Chemical Co. and were used without further purification. Compound **1** was prepared according to the literature.[3] Reaction monitoring and product analyses were performed by HPLC using an Agilent 1100 system with photo diode array detection and Zorbax SB-C8 Rapid Resolution column at 30 °C (flow rate: 2 mL/min., A = 0.1% H_3PO_4 in Milli-Q water, B = acetonitrile; gradient: 80% A to 10% A over 7 min, hold 1 min, return to 80% A in 1.5 min, hold 1 min). ^1H and ^{13}C NMR spectra were obtained on a Varian spectrometer at 400 and 75 MHz, respectively. IR spectra were obtained on a Smiths ChemID FTIR, and high-resolution MS data were acquired on an Agilent G1969A MS-TOF.

General Procedure for the *N*-Methylation of Pyrroles with DMC/DMF/DABCO. (Example: Methyl-*N*-methyl-2-pyrrole Carboxylate (7)). A reaction flask was charged with methyl-2-pyrrole carboxylate, **5** (2.0 g, 16.0 mmol), DMC (20 mL), DABCO (0.18 g, 1.6 mmol), and DMF (1.0 mL). The resulting mixture was heated to 90−92 °C and stirred at that temperature for 23 h. HPLC analysis indicated complete consumption of the starting material. The reaction mixture was cooled to 21 °C, diluted with EtOAc (25 mL), and transferred to a separatory funnel. The solution was washed sequentially with H_2O (25 mL) and 10% citric acid (2 × 15 mL). The washes were combined and back extracted with EtOAc (25 mL). The combined organics were washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the desired product as a colorless oil (2.0 g, 90.4%). ^{1}H NMR (400 MHz, DMSO) δ 3.71 (s, 3H), 3.83 (s, 3H), 6.07 (dd, J = 2.6, 4.0 Hz, 1H), 6.81 (dd, J = 1.8, 4.0 Hz, 1H), 7.07 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 36.7, 51.2, 108.1, 117.8, 121.9, 130.7, 161.2; IR (neat) 1699, 1435, 1405, 1242, 1104 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 140.0708, found 140.0706.

3-(4-Bromophenyl)-4-cyano-5-ethyl-1-methyl-1H-pyrrole-2-carboxylic Acid Ethyl Ester (2).[3] (Note: this compound was isolated as a mix of the ethyl and methyl (∼81/19) esters due to transesterification.) White solid: ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 361.0546, found 361.0546 (ethyl ester); Calcd for (M + H$^+$) 347.0390, found 347.0389 (methyl ester).

***N*-Methyl-2-acetyl Pyrrole (9):** colorless oil: ^{1}H NMR (400 MHz, DMSO) δ 2.33 (s, 3H), 3.81 (s, 3H), 6.08 (dd, J = 2.6, 4.0 Hz, 1H), 7.02 (dd, J = 1.8, 4.0 Hz, 1H), 7.08 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 27.3, 37.4, 108.0, 120.3, 130.7, 131.9, 188.1; IR (neat) 1640, 1525, 1398, 1379, 1320, 1242 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 124.0757, found 124.0758.

***N*-Methyl-2-cyano Pyrrole (11):** colorless oil: ^{1}H NMR (400 MHz, DMSO) δ 3.73 (s, 3H), 6.15 (dd, J = 2.6, 4.0 Hz, 1H), 6.88 (dd, J = 1.3, 4.0 Hz, 1H), 7.15 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 35.4, 103.5, 109.4, 114.3, 120.3, 129.3; IR (neat) 2209, 1476, 1402, 1309 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 107.0604, found 107.0606.

***N*-Methyl-2-formyl Pyrrole (13):** pale yellow oil: ^{1}H NMR (400 MHz, DMSO) δ 3.86 (s, 3H), 6.19 (dd, J = 2.6, 4.0 Hz, 1H), 6.97 (dd, J = 1.8, 4.0 Hz, 1H), 7.21 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 36.2, 109.7, 123.8, 132.0, 133.0, 179.8; IR (neat) cm^{-1}1647, 1487, 1409, 1309, 1384, 1365 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 110.0601, found 110.0603.

***N*-Methyl-1,5,6,7-tetrahydro-4H-indole-4-one (16):** white solid: mp 84−85 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.98 (m, 2H), 2.26 (m, 2H), 2.71 (t, 2H), 3.52 (s, 3H), 6.22 (d, J = 3.1 Hz, 1H), 6.71 (d, J = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 21.2, 23.7, 33.5, 37.8, 104.6, 120.4, 123.9, 144.2, 192.9; IR (neat) 2938, 1635, 1510, 1465, 1424, 1405, 1339, 1257 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 150.08406, found 150.0913.

***N*-Methyl-7-azaindole-3-carboxaldehyde (18):** white solid: mp 94−95 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.89 (s, 3H), 7.31 (m, 1H), 8.39 (m, 1H), 8.48 (s, 1H), 9.89 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 32.1, 115.6, 117.2, 119.1, 129.8, 141.9, 145.0, 148.8, 185.1; IR (neat) 3035, 2733, 1647, 1599, 1577, 1532, 1472, 1383, 1205 cm^{-1}; ESI-HRMS *m*/*z* Calcd for (M + H$^+$) 161.0709, found 161.0712.

Acknowledgment

We are grateful to Mr. Eric Crockett for performing all of the high-resolution mass spectrometer experiments.

Received for review September 30, 2009.

OP900256T