

Short Note

Regioselective Alkylation of an Oxonaphthalene-Annulated Pyrrol System

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Abstract: The regioselective alkylation of an oxonaphthalene-annulated pyrrole system is reported. The regioselectivity of alkylation can be controlled by the selection of the solvent.

Keywords: pyrrole; alkylation; NMR spectroscopy

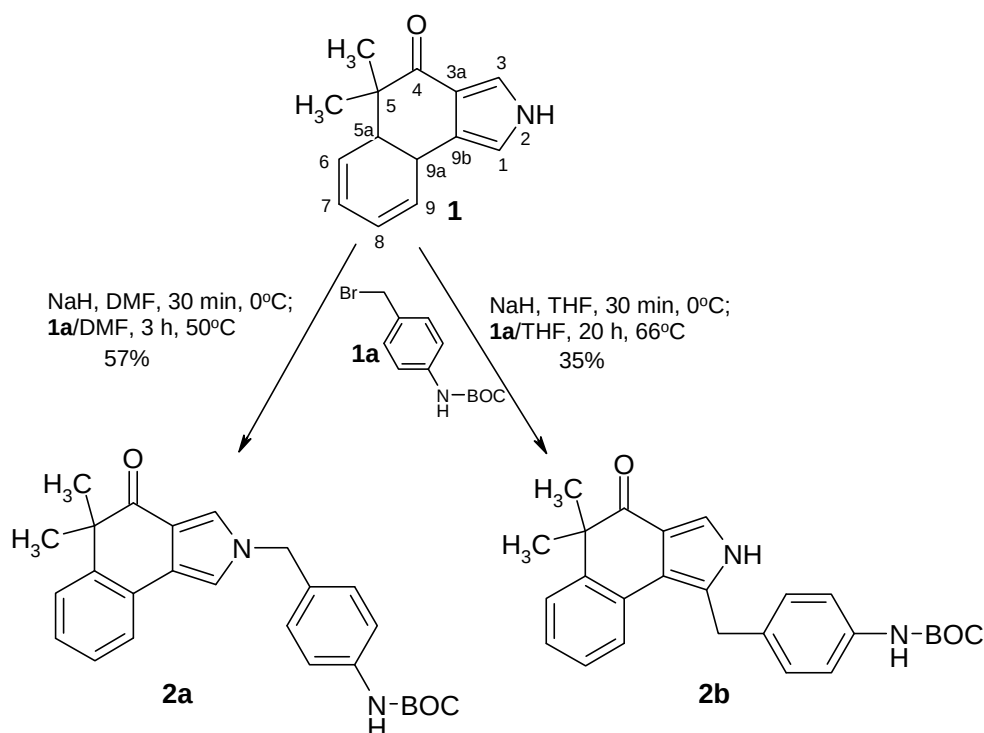
Introduction

Nitrogen mustards were the first clinically effective cancer therapeutic agents. Chlorambucil is one of numerous aromatic derivatives of compounds with a nitrogen mustard moiety that have been synthesized. It has been a clinical agent for many years and remains in common use at the present time. The cytotoxic effects are based on the highly active aziridinium cation intermediates arising from the bis(2-chloroethyl)amine moiety [1]. In continuation of our department's previous studies in the field of antitumor agents [2–7], the pyrrole derivative **1** [8] was chosen as an educt for the synthesis of new chlorambucil analogs. Here, we wish to describe the synthesis of the two key intermediates **2a** and **2b** from **1** by regioselective alkylation with the BOC-protected 4-aminobenzyl bromide building block **1a**.

Results and Discussion

Starting from pyrrole **1**, the alkylation procedure with **1a**, using NaH as a base in DMF solution afforded only the expected *N*-alkylated product **2a**. On the other hand, use of THF as solvent was found to give selectively access to the C-1 alkylated product **2b**. Based on comparison with previously reported ^1H - and ^{13}C -NMR data of **1** [8,9], it was possible to assign to the latter compound (**2b**) the structure of a C-1 alkylated product and to exclude a C-3 alkylated isomer. Thus, a regioselective approach to either **2a** or **2b**, respectively, is possible simply by selection of the appropriate solvent. Since the pyrrole derivative **1** is in conjugation with a strongly electron-withdrawing carbonyl group, previously published studies (see below) on *C*- vs. *N*-alkylation of pyrrole are not fully comparable and thus cannot give a clear explanation of these results: K. Sukata had described increasing *C*-alkylation vs. *N*-alkylation of pyrrole in protic solvents such as PEG or water, in aprotic solvents such as PEG-ethers *N*-alkylation was preferred [10]; D. Y. Chi had developed an ionic liquid methodology for pyrrole to achieve regioselective *N*- and *C*-alkylation, respectively [11,12].

After cleavage of the *N*-BOC protecting group, both compounds will now serve as starting materials for the syntheses of new anticancer drugs with a nitrogen mustard moiety, the results will be reported elsewhere.



Experimental

General procedure for the preparation of **2a** or **2b**

A solution of **1** (1.17 g, 5.54 mmol) in 10 mL of dry DMF (for **2a**) or 10 mL of dry THF (for **2b**) was added dropwise under argon to a suspension of NaH (0.20 g of a 60% dispersion in mineral oil;

washed with hexane; 8.31 mmol) in 12.5 mL of dry DMF or THF, respectively (see above). After stirring for 0.5 h at 0 °C, a solution of *tert*-butyl[4-(bromomethyl)phenyl]carbamate (**1a**) (2.50 g, 8.31 mmol) in dry DMF or THF, respectively (see above), was added. The reaction mixture was heated for 3 h (50 °C for DMF or 66 °C for THF). The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, ethyl acetate/light petroleum, 70/30 + 1% triethylamine) to afford 1.31 g (57%) of **2a** or 0.80 g (35%) of **2b**, respectively.

tert-Butyl[4-[(5,5-dimethyl-4-oxo-4,5-dihydro-2H-benzo[e]isoindol-2-yl)methyl]phenyl]carbamate (**2a**): M.p. 74-76 °C (light petroleum/ethyl acetate). IR (KBr): 3312, 1724, 1650, 1526, 1240, 1155 cm⁻¹. MS (EI, 70 eV) *m/z*: 416 (M⁺, 3%), 106 (11), 57 (43), 45 (14) 44 (15), 43 (100), 42 (18), 41 (40). ¹H NMR (CDCl₃, 200 MHz) δ = 9.38 (s_{br}, 1H, NH), 7.60 (d, *J* = 1.5 Hz, 1H, 3-H), 7.64-7.42 (m, 5H, 1-H, 6-H, 9-H, 2'-H, 6'-H), 7.27 (d, *J* = 8.5 Hz, 2H, 3'-H, 5'-H), 7.18 (m, 2H, 7-H, 8-H), 5.12 (s, 2H, CH₂), 1.44 (s, 9H, (CH₃)₃), 1.35 (s, 6H, (CH₃)₂). ¹³C NMR (CDCl₃, 50 MHz) δ = 196.5 (C-4), 152.7 (COO), 143.4 (C-5a), 139.3 (C-1'), 130.8 (C-4'), 128.5 (C-3', C-5'), 127.1 (C-6), 126.8 (C-9a), 126.4 (C-7), 126.3 (C-8), 124.2 (C-9b), 123.7 (C-3), 122.7 (C-9), 118.2 (C-2', C-6'), 117.3 (C-3a), 116.3 (C-1), 79.1 (C(CH₃)₃), 52.7 (CH₂N), 46.8 (C-5), 28.1 ((CH₃)₃), 27.97 ((CH₃)₂). HRMS calcd. for C₂₆H₂₈N₂O₂: 416.2099. Found: 416.2103.

tert-Butyl[4-[(5,5-dimethyl-4-oxo-4,5-dihydro-2H-benzo[e]isoindol-1-yl)methyl]phenyl]carbamate (**2b**): M.p. 135-137 °C (light petroleum/ethyl acetate). IR (KBr): 3345, 3249, 1697, 1644, 1527, 1238, 1156 cm⁻¹. MS (EI, 70 eV) *m/z*: 416 (M⁺, 6%), 360 (13), 106 (12), 71 (7), 59 (11), 57 (100), 56 (27), 55 (19). ¹H NMR (CDCl₃, 200 MHz) δ = 11.88 (s_{br}, 1H, NH), 9.24 (s, 1H, NH), 7.53-7.44 (m, 3H, 3-H, 6-H, 9-H), 7.36 (d, *J* = 8.5 Hz, 2H, 2'-H, 6'-H), 7.14-7.04 (m, 4H, 7-H, 8-H, 3'-H, 5'-H), 4.24 (s, 2H, CH₂), 1.43 (s, 9H, (CH₃)₃), 1.37 (s, 6H, (CH₃)₂). ¹³C NMR (CDCl₃, 200 MHz) δ = 197.1 (C-4), 152.8 (COO), 143.6 (C-5a), 137.7 (C-1'), 132.2 (C-4'), 128.0 (C-3', C-5'), 128.2/126.6 (C-9a/C-9b), 127.1 (C-6), 126.2 (C-7), 125.6 (C-8), 123.0 (C-9), 119.4 (C-3), 118.4 (C-2', C-6'), 118.4/117.9 (C-1/C-3a), 78.9 (C(CH₃)₃), 46.9 (C-5), 32.1 (CH₂), 28.1 ((CH₃)₃), 28.0 ((CH₃)₂). HRMS calcd. for C₂₆H₂₈N₂O₂: 416.2099. Found: 416.210.

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