MECHANISTIC INSIGHT INTO THE AROMATIZATION OF CYCLIC *p*-QUINONEMETHIDES TO INDOLES

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Abstract — Two mechanisms have been previously proposed for the aromatization of cyclic *p*-quinonemethides to indoles. A novel synthetic route to indoles *via* an unstable cyclic *p*-quinonemethide has provided additional insight into the mechanism of cyclization. Since this key intermediate lacks the functional groups required for one of the mechanistic pathways (Pathway B), it appears that cyclization occurs *via* Pathway A.

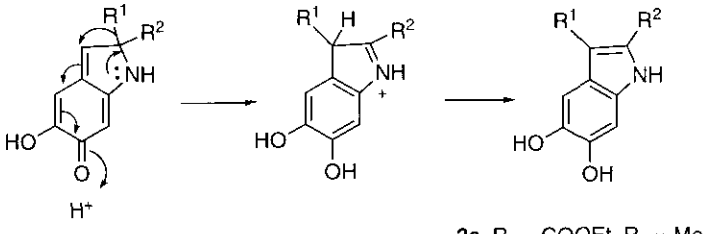
A wide variety of natural products of plant and animal origin contain the indole heterocycle. In addition, several synthetic drugs that exhibit a wide range of pharmacological actions are indole derivatives. Thus there has been a sustained interest in novel routes to the indole nucleus.[1] The synthesis of indoles *via* N-C2 bond formation has previously been reported to take place by one of the following three routes.[1] In the first instance the cyclization was accomplished by addition–elimination at a carbonyl or an imine group, while in the second case the activation of an acetylene bond by metal catalysts led to the nucleophilic addition of the nitrogen to afford the indole. The addition of a styrene olefin to an electrophilic nitrogen species is also a versatile method for the generation of indoles.[1] We have recently reported the synthesis of indoles *via* a novel N-C2 cyclization.[2] This route entails the addition of an amine to an allylic carbocation, generating a *p*-quinonemethide (Scheme 2). This *p*-quinonemethide undergoes facile aromatization to afford the benzindole. In this paper we report studies on the aromatization reaction and provide some mechanistic insight into the 1,2-shift of a substituent at C2 required for this aromatization.

Castagnoli and co-workers obtained the stable *p*-quinonemethide (**1**) as a crystalline solid upon treatment of (S)-α-MeDopa ethyl ester with potassium ferricyanide.[3] The *p*-quinonemethide (**1**) did not have the expected electrophilic character, even under reflux conditions, and underwent rearrangement to the indole (**2a**).[4] The mechanism of aromatization of the stable *p*-quinonemethide (**1**) to the indole (**2a**) under reflux conditions in ethanol has been proposed to go through two possible mechanisms (Scheme 1).[4] In Pathway A, the 1,2-shift could afford both products (**2a**) and (**2b**). This mechanism involves the *meta* keto functionality and does not require the *para* hydroxy moiety. On the other hand, Pathway B involves the *para* hydroxy group as well as the carbonyl of the ester substituent. Due to this, only the ester substituent could undergo the 1,2-shift to afford **2a** as the only regioisomeric product. Since their experiments

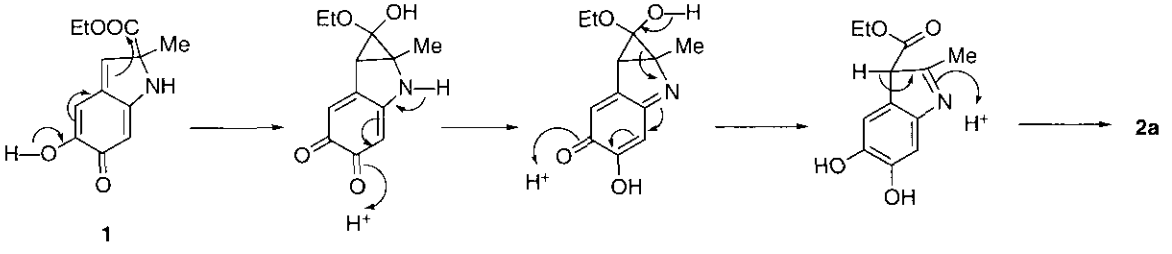
afforded only **2a**, they were able to conclude that the rearrangement occurs *via* the 1,2-shift of the ethoxycarbonyl moiety, presumably *via* the mechanism described in Pathway B.

Scheme 1

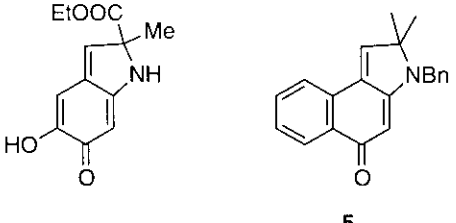
Pathway A



Pathway B



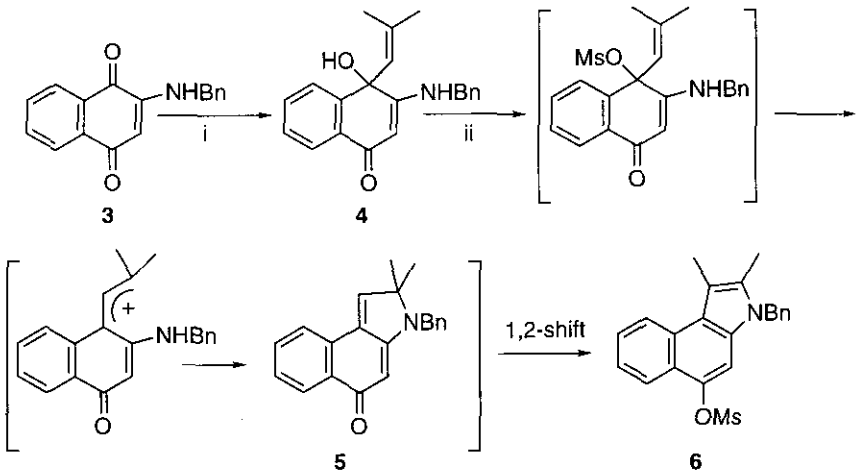
To study this rearrangment resulting in an aromatic indole product, we have designed the *p*-quinonemethide (**5**) as an unstable intermediate enroute to the indole (**6**). In comparison to the *p*-quinonemethide (**1**), the *p*-quinonemethide (**5**) lacks two key functionalities essential to Pathway B. The *para* hydroxy group has been replaced by the benzo moiety, and instead of the ethyl ester, a methyl group has been inserted. The *para* hydroxy and the carbonyl carbon of the ester [in (**1**)] are both essential to Pathway B; if **5** undergoes the 1,2-shift to afford the benz[*e*]indole (**6**), Pathway B can be ruled out, whereas Pathway A does not require both two groups.



2-Benzylamino-1,4-naphthalenedione (**3**)[5] reacted with vinylmagnesium bromide to afford the monoalkylated Grignard adduct (**4**), which was purified via silica gel chromatography using 0–5% CH_3OH

in $CHCl_3$ as the eluant (63%, decomposes when heated to 60 °C) (Scheme 2). This 4-hydroxy-4-(2-methylprop-1-enyl)-3-benzylamino-4-hydronaphthalen-1-one (**4**) was treated with mesyl chloride and triethyl amine to afford **6**, which was purified as an oil after silica gel chromatography using $CHCl_3$ as the eluant (29%). The facile formation of the benz[*e*]indole (**6**) ruled out Pathway B for the aromatization of **5** and has made a strong case for Pathway A. The above discussion does not explain the formation of a single regioisomeric product (**2a**) from the stable quinonemethide (**1**) in the previous study.[4] The determination of relative migratory aptitudes of substituents is complicated. Not only does the inherent migratory potential of the individual substituents play an important role, other factors such as the ability to stabilize the newly formed positive charge at the migratory center also determine which substituent will undergo the 1,2-shift.[6] While the formation of the single product (**2a**) *via* Pathway B is not ruled out, it is also possible that a combination of different factors that influence migratory aptitude may be involved in the formation of the indole (**2a**) through Pathway A.

Scheme 2



Reagents: (i) 2-Methylpropenylmagnesium bromide, THF; (ii) MsCl, Et_3N

The novel route toward the synthesis of indoles *via* a new N-C2 cyclization has allowed us to explore the aromatization of a *p*-quinonemethide intermediate and the associated 1,2-shift. The results from these experiments indicate that, at least in our designed route, Pathway B cannot be in operation. The aromatization of **5** to **6** takes place *via* a 1,2-shift, presumably *via* Pathway A.

EXPERIMENTAL

All reagents and solvents employed were reagent grade and were used without further purification. Column chromatography was performed with silica gel (200–400 mesh, Aldrich Chemicals). Chromatographic solvent system is reported as volume/volume. NMR spectra were recorded on a Varian 500 MHz NMR instrument at room temperature (18–20 °C). The mass spectra were performed by the Mass Spectrometry Laboratory of the Department of Chemistry, The University of Texas at Austin.

4-Hydroxy-4-(2-methylprop-1-enyl)-3-benzylamino-4-hydronaphthalen-1-one (4)

To a cooled solution of 2-benzylamino-1,4-naphthalenedione (**3**)[5] (2 g, 7.6 mmol) in dry THF (50 mL) at 0 °C, 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 40 mL, 20 mmol) was added dropwise with stirring. The reaction mixture was stirred in an inert atmosphere at 0 °C for 2 h. After 2 h the reaction was quenched carefully with water and extracted with EtOAc (3 × 200 mL). The organic layers were combined and washed with brine and saturated aq. $NaHCO_3$. The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (0–5% CH_3OH in $CHCl_3$) to yield **4** (1.54 g, 63.5%) as an oil, which decomposes when heated above 60 °C. ^{1}H NMR (500 MHz, $CDCl_3$, free base) δ 7.81 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.2 and 8.6 Hz, 1H), 7.33 (m, 1H), 7.29 (m, 4H), 7.22 (m, 1H), 6.22 (s, 1H), 5.61 (s, 1H), 5.07 (s, 1H), 4.29 (m, 1H), 1.63 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 180, 166, 145, 138, 133, 131, 130.8, 130.6, 128, 127, 126.9, 126.7, 126.5, 123, 94, 70, 45, 27, 17; HRCIMS *m/z* 320.1646 (M+1).

1,2-Dimethyl-5-mesyl-3-benzylbenz[e]indole (6)

To a cooled solution of **4** (150 mg, 0.45 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triethylamine (1 mL, 7.17 mmol) with stirring. After 5 min mesyl chloride (0.5 mL, 6.5 mmol) was added dropwise, and the reaction was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to rt and stirred in an inert atmosphere for 1 h. The reaction was then quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with brine and saturated aq. $NaHCO_3$. The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$) to yield **6** (52 mg, 29%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$, free base) δ 8.56 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.58 (ddd, J = 9.8, 6.8, and 1.4 Hz, 1H), 7.54 (s, 1H), 7.46 (ddd, J = 9.6, 6.8, and 1.2 Hz, 1H), 7.22 (m, 3H), 6.93 (d, J = 6.6 Hz 2H), 5.38 (s, 2H), 3.02 (s, 3H), 2.65 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 140, 137, 132, 130, 129, 128, 127, 126, 125, 123.6, 123.4, 122, 121, 120, 109, 104, 46, 37, 12, 10; HRCIMS *m/z* 380.1315 (M+1).

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of the National Institutes of Health and the Foundation for Research. We also thank David Bishop for proofreading, editing, and preparing the final version of the manuscript.

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Received, 14th September, 1998