zation at benzhydrylic C-9 (with none occurring at tertiary C-8 or C-14) is somewhat puzzling, and especially so because with dioxiranes insertion into $(Ph)R_2C-H$ vs R_3C-H is usually of only modest advantage.[7,25] Since one might envisage subtle steric and/or stereoelectronic effects coming into play in the dioxirane oxyfunctionalization of steroids, as well as of nonnatural target molecules,[8,10,26] further studies directed to unravel in detail the features of O atom transfer are warranted. These seem worthwhile, since it is becoming increasingly clear that dioxirane oxidations can display efficiency and selectivities that are biomimetic.[1,7a,27]

Experimental Section

Melting points and boiling points were not corrected. The NMR spectra of starting materials and products were run on a Varian Gemini XL200 instrument. The MS spectra (EI, 70 eV) were obtained using a Hewelett-Packard Model 5970 mass-selective detector connected to a Model 5890 gas chromatograph. Other equipment and methods employed have been described previously.[7a]

Materials. Commercial (Fluka) 4-cholesten-3-one (**2a**) and 4-pregnene-3,20-dione (**2b**) were purified by standard methods; 3β-acetoxy-5,16-pregnadien-20-one (**4**) [mp 172–174 °C] was synthesized by a literature[28] procedure; 21-acetoxy-17α-hydroxy-1,4-pregnadiene-3,11,20-trione (**6**) [mp 219–220 °C] and 3-acetoxy-1,3,5(10)-estratrien-17-one (**8**) [mp 122–124 °C][29] were obtained upon treatment with Ac_2O/Py of commercial (Fluka) 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione or 3-hydroxy-1,3,5(10)-estratrien-17-one, respectively. All starting materials gave satisfactory ^1H and/or ^{13}C NMR spectra. Solutions of dimethyldioxirane (**1a**) in acetone and of methyl(trifluoromethyl)dioxirane (**1b**) in TFP were obtained by following procedures and precautions which have been described in detail.[3,4,7a]

Dioxirane Oxyfunctionalization of Steroids 2–8. An aliquot (usually from 4 to 8 mL) of standardized[3,4,14] cold solution of dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) or of methyl(trifluoromethyl)dioxirane (**1b**) (ca. 0.8 M in TFP) was quickly added to a stirred solution of the steroidal substrate (100–120 mg) in solvent acetone or CH_2Cl_2 (4–6 mL) kept in a thermostat at the given temperature (20 or −40 °C, cf. Scheme I). After the reaction was carried out to a suitable conversion (GC or TLC monitoring), eventually by the addition of further dioxirane aliquots, products isolation was achieved by removal of acetone solvent in vacuo, followed by column chromatography (silica gel, *n*-hexane/AcOEt or *n*-hexane/Et_2O).

4,5-Epoxycholestan-3-one (3a) was obtained (yield 80%) as a mixture of 4β,5β-epoxide and 4α,5α-epoxide (ratio α:β = ca. 3:1). The stereomeric epoxides can be separated by column chromatography (silica gel, *n*-hexane/AcOEt (8:2):α-Epoxide, mp 123–125 °C [lit.[18a] mp 123–124 °C], β-Epoxide, mp 116–120 °C [lit.[18a] mp 118–119 °C]; ^1H NMR (200 MHz, $CDCl_3$) (α-epoxide)[18b] δ 0.65 (s, 3 H, C^{18}-*H*), 0.82 (d, *J* = 7 Hz, 6 H, C^{26}-*H* and C^{27}-*H*), 0.88 (d, *J* = 7 Hz, 3 H, C^{21}-*H*), 1.05 (s, 3 H, C^{19}-*H*), 3.00 (s, 1 H, C^4-*H*); (β-epoxide)[18b] δ 0.75–0.90 (br, 12 H, C^{18}-*H*, C^{21}-*H*, C^{26}-*H*, and C^{27}-*H*), 1.20 (s, 3 H, C^{19}-*H*), 2.95 (s, 1 H, C^4-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) (α-epoxide) δ 12.12, 16.70, 18.82, 21.61, 22.74, 22.99, 24.02, 24.41, 28.21, 28.36, 29.17, 29.30, 29.98, 33.37, 35.68, 36.00, 36.35, 36.94, 39.73, 39.95, 42.76, 50.95, 55.91, 56.50, 63.24 (C^4), 70.61 (C^5), 207.93 (C^3); β-epoxide gave values in agreement with literature data.[18c]

4,5-Epoxypregnane-3,20-dione (3b) was obtained (yield 90%) as a mixture of 4β,5β and 4α,5α stereomeric epoxides (ratio α:β = ca. 4:1): mp 121–124 °C [lit.[19] mp 122–124 °C]; ^1H NMR[18c] (200 MHz, $CDCl_3$) δ 0.60 (s, 0.6 H, C^{18}-*H*, β-epoxide), 0.61 (s, 2.4 H, C^{18}-*H*, α-epoxide), 1.02 (s, 2.4 H, C^{19}-*H*, α-epoxide), 1.12 (s, 0.6 H, C^{19}-*H*, β-epoxide), 2.08 (s, 0.6 H, C^{21}-*H*, β-epoxide), 2.09 (s, 2.4 H, C^{21}-*H*, α-epoxide), 2.95 (s, 0.2 H, C^4-*H*, β-epoxide), 3.02 (s, 0.8 H, C^4-*H*, α-epoxide).

3β-Acetoxy-5,6-epoxy-16-pregnen-20-one (5) was obtained (yield 95%) as a mixture of 5β,6β and 5α,6α epoxides[20] (ratio β:α = ca. 3:2): mp 155–158 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (s, 1.2 H, C^{18}-*H*, α-epoxide), 0.83 (s, 1.8 H, C^{18}-*H*, β-epoxide), 1.00 (s, 1.8 H, C^{19}-*H*, β-epoxide), 1.09 (s, 1.2 H, C^{19}-*H*, α-epoxide), 1.98 (s, 1.2 H, C^{21}-*H*, α-epoxide), 2.00 (s, 1.8 H, C^{21}-*H*, β-epoxide), 2.20 (s, 3 H, CH_3CO), 2.89 (d, *J* = 4.4 Hz, 0.4 H, C^6-*H*, α-epoxide), 3.09 (d, *J* = 2.4 Hz, 0.6 H, C^6-*H*, β-epoxide), 4.66 (m, 0.6 H, C^3-*H*, β-epoxide), 4.91 (m, 0.4 H, C^3-*H*, α-epoxide), 6.62 (m, 1 H, C^{16}-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 62.70, 63.23, 63.30, 65.35, 71.25, 144.32 and 144.37 (C^{16}), 155.38 and 155.49 (C^{17}), 170.49 and 170.83 (CH_3COO), 197.10 (C^{20}).

21-Acetoxy-1α,2α-epoxy-17α-hydroxy-4-pregnene-3,11,20-trione (7): yield 80%. After recrystallization from petroleum ether–acetone: mp 239–241 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.66 (s, 3 H, C^{18}-*H*), 1.44 (s, 3 H, C^{19}-*H*), 2.15 (s, 3 H, CH_3CO), 3.37 (dd, *J* = 4.0 and 2.0 Hz, 1 H, C^2-*H*), 4.29 (d, *J* = 4 Hz, 1 H, C^1-*H*), 4.66 (d, *J* = 18 Hz, 1 H, C^{21}-H_a), 5.08 (d, *J* = 18 Hz, 1 H, C^{21}-H_b), 5.68 (t, *J* = 2 Hz, 1 H, C^4-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 15.33, 18.49, 20.28, 22.98, 32.29, 34.95, 35.87, 40.06, 49.38, 51.11, 55.02, 58.06, 60.62, 67.48 (C^{21}), 88.85 (C^{17}), 120.83 (C^4), 164.37 (C^5), 170.87 (C^{22}), 194.30 (C^3), 204.80 and 209.21 (C^{11}=O, and C^{20}=O). Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.31; H, 6.81.

3-Acetoxy-9α-hydroxy-1,3,5(10)-estratrien-17-one (9) can be isolated (yield 80%) from reaction mixtures by careful column chromatography at 8–10 °C using *nonactivated* silica gel (Merck, 70–230 mesh; eluent *n*-hexane–Et_2O). After recrystallization from petroleum ether–acetone: mp 162–164 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3 H, C^{18}-*H*), 1.45–2.55 (complex series of m, 12 H), 2.26 (s, CH_3CO), 2.88 (br, 2 H, C^6-*H*), 6.80–6.92 (m, 2 H, C^2-*H* and C^4-*H*), 7.50 (d, *J* = 8 Hz, 1 H, C^1-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 13.09, 20.13, 21.32, 21.35, 21.62, 27.81, 29.60, 32.36, 36.16, 41.35 (C^8), 43.30 (C^{14}), 47.92 (C^{13}), 70.32 (C^9), 120.02 (C^2), 122.77 (C^4), 127.05 (C^1), 138.96–139.69 (C^5 and C^{10}), 150.49 (C^3), 170.34 (CH_3CO), 221.47 (C^{17}=O); MS (70 eV) *m/z* 310 ($M^+ - 18$). Upon easy dehydration over silica gel or with $POCl_3$ in pyridine, **9** yields 3-acetoxy-1,3,5(10),9(11)-estratetraen-17-one (**10**): mp 125–126 °C;[23] the latter gave satisfactory ^1H NMR and IR spectra.

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Registry No. **1a**, 74087-85-7; **1b**, 115464-59-0; **2a**, 601-57-0; **2b**, 57-83-0; **3a** (isomer 1), 2515-12-0; **3a** (isomer 2), 1975-34-4; **3b** (isomer 1), 17503-05-8; **3b** (isomer 2), 17597-24-9; **4**, 979-02-2; **5** (isomer 1), 14279-42-6; **5** (isomer 2), 66880-01-1; **6**, 125-10-0; **7**, 139016-49-2; **8**, 901-93-9; **9**, 94686-78-9; **10**, 7291-52-3.

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Lithiation of 3-Aminobenzo[*b*]thiophene and 3-Aminothiophene Derivatives. Application to the Synthesis of Benzo[*b*]thienoindole and Thienoindole Derivatives

Montserrat Prats,* Carmen Gálvez, Yolanda Gasanz, and Ana Rodriguez

Departament de Quimica Orgânica, Universitat de Barcelona, Martí i Franquès 1-11, 08028 Barcelona, Spain

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Directed metalation of heterocycles offers attractive and highly advantageous solutions to preparative problems not readily achieved by classical chemistry.[1]

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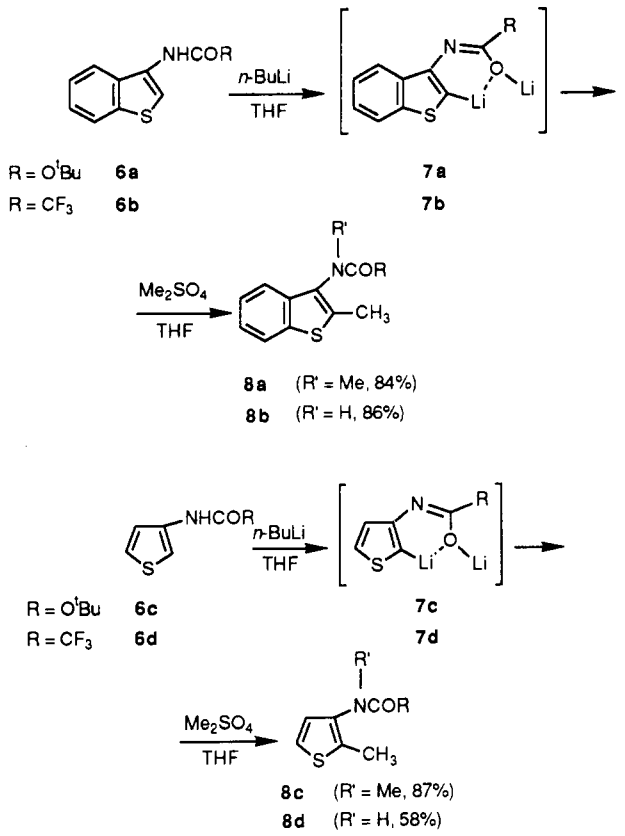
Scheme I



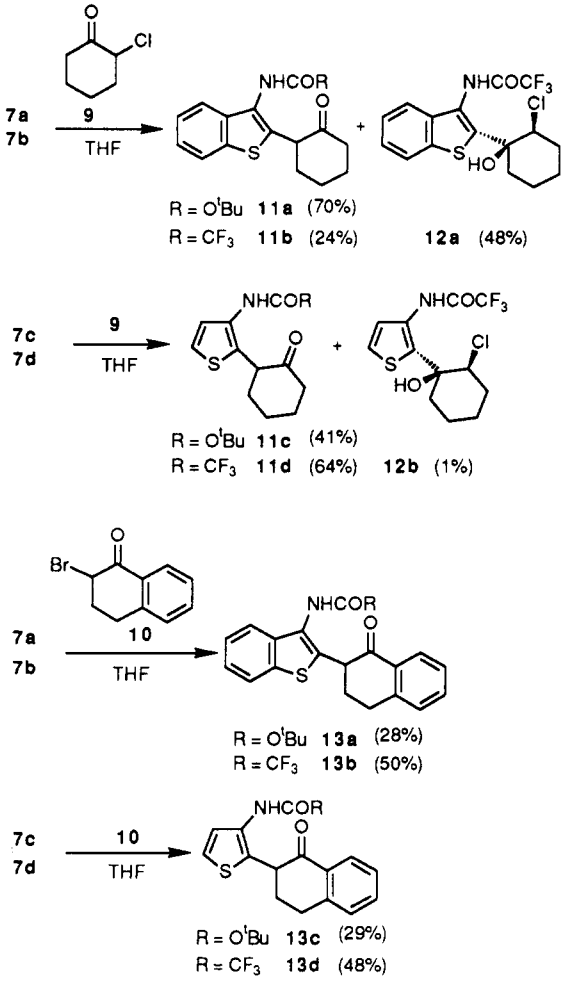
We report here a contribution to the preparation of the thieno- and benzo[*b*]thienoindole derivatives **1–5** (Scheme III) based on the methodology of Wender and White.[2]

We have studied the formation of ortho-lithiated amino derivatives of benzo[*b*]thiophene and thiophene and their reactivity towards α-halo ketones as the critical step in this approach.

Results and Discussion

There are many precedents to the use of *N*-pivaloylamino (NHCO^{t}Bu), *N*-(*tert*-butoxycarbonyl)amino (NHCOO^{t}Bu), and *N*-(trifluoroacetyl)amino (NHCOCF$_3$) groups as good ortho-directing groups in the metalation of benzene,[2,3] pyridine,[4] and quinoline[5] derivatives. From this, a dominant metalation at the C-2 over the C-5 position may be expected in 3-aminothiophene derivatives.

Scheme II



Thus, the lithiation of 3-[(*tert*-butoxycarbonyl)amino]benzo[*b*]thiophene (**6a**), 3-[(trifluoroacetyl)amino]benzo[*b*]thiophene (**6b**), 3-[(*tert*-butoxycarbonyl)amino]thiophene (**6c**), and 3-[(trifluoroacetyl)amino]thiophene (**6d**) by an excess of *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF) at low temperature has been studied.

The results summarized in Scheme I show that compounds **6a–d** can be converted, upon deprotonation using 3.2 equiv of *n*-BuLi over a short period (1 h) at −20 °C, to dilithium reagents in ca. 58–87% yield, as determined by a trapping reaction with excess dimethyl sulfate.

The N-methylation was not observed when the protecting group was NHCOCF$_3$. This could be due to lower nucleophilic character of the nitrogen of the amide ion in the organodimetallic intermediates **7b** and **7d**, as compared with that of the corresponding carbamate intermediates **7a** and **7c**.

These results encouraged us to study the reactivity of the organodilithium reagents **7a–d** with two different α-halo ketones, the 2-chlorocyclohexanone (**9**) and 2-bromo-1-tetralone (**10**). The results obtained are summarized in Scheme II.

The condensation products isolated in these reactions (Scheme II) were different from those that could be expected on the basis of the results of Wender and White.[2] In fact, the α-hetaryl ketones **11a–d** and **13a–d** were isolated in ca. 30–70% yield instead of the expected cyclic products. The *cis*-halohydrins 2-(2-chloro-1-hydroxycyclohexyl)-3-[(trifluoroacetyl)amino]benzo[*b*]thiophene (**12a**) and 2-(2-chloro-1-hydroxycyclohexyl)-3-[(trifluoroacetyl)amino]thiophene (**12b**) were formed in ca. 17–48%

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yield only when the protecting group $NHCOCF_3$ and the halo ketone **9** were used.

These results could be explained if we consider that the *cis*-halohydrin isomer formed in the stereocontrolled addition process of the dilithium reagents **7a–d** to the carbonyl carbon of the α-halo ketones **9** and **10** can undergo an rearrangement to provide the observed substituted cyclic ketones **11a–d** and **13a–d**, respectively. This rearrangement has long been known and its application to the synthesis of α-alkyl-, α-alkenyl-, and α-aryl-substituted ketones has also been well established.[6]

On the other hand, the effect of an excess of *n*-BuLi on these condensation reactions depends on the halo ketone used. Thus, in the case of the 2-chlorocyclohexanone (**9**), an excess of *n*-butyllithium produces a diminution in the yield of condensation products and an increase in the production of the cis isomer of 1-butyl-2-chlorocyclohexanol derived from the stereocontrolled nucleophilic addition of *n*-BuLi to the carbonyl group of the ketone **9**. Moreover, in one case 1,2-bis[3-[(*tert*-butoxycarbonyl)amino]benzo[*b*]thien-2-yl]cyclohexanol was isolated, derived from the nucleophilic addition of the carbanionic site of **7a** to the carbonyl group of the ketone **11a**.

When the halo ketone used was 2-bromo-1-tetralone (**10**), 1-tetralone was the secondary product observed. This ketone could arise from a halogen–lithium exchange reaction[7] with *n*-BuLi or the organodimetallic agent **7d**, as seems to be indicated by the formation of 2-bromo-3-[(trifluoroacetyl)amino]thiophene. In these condensation reactions a large excess of *n*-BuLi favours the formation of the α-hetaryl ketones **13a–d**.

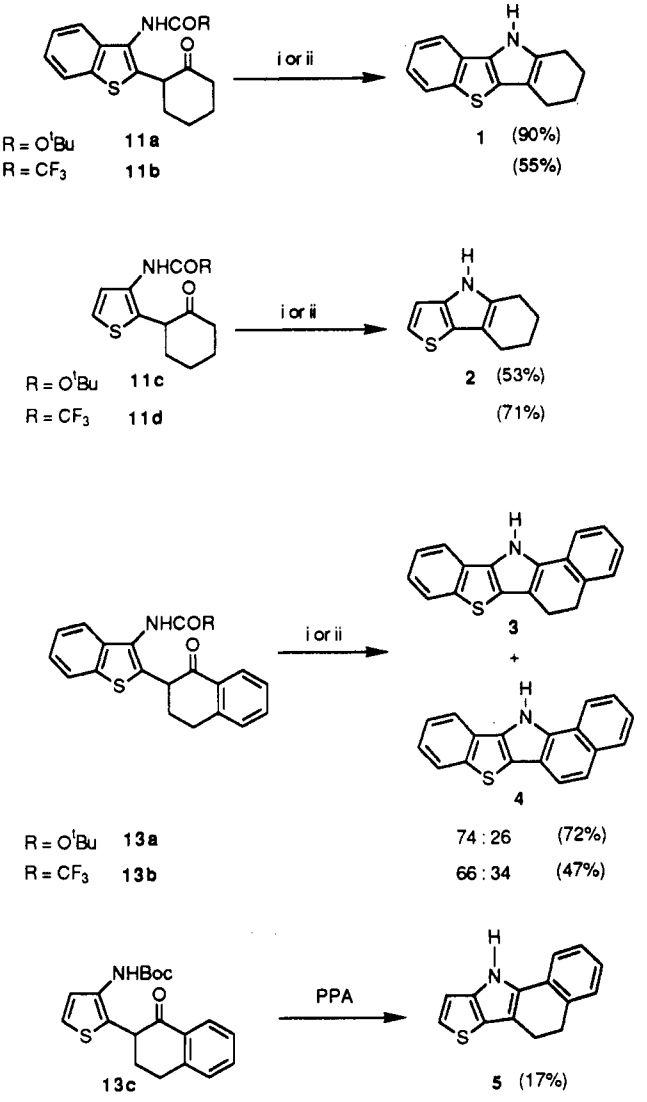
The results obtained in these condensation reactions indicate that 2-chlorocyclohexanone (**9**) leads to higher yields of condensation products than does 2-bromo-1-tetralone (**10**), and the organometallic reagents derived from the amides **6b** and **6d** are more reactive than the organometallic reagents derived from the carbamates **6a** and **6c**.

The final objective, generation of the indole system from the condensation products, was in general efficiently accomplished by the generation in situ of the unprotected α-hetaryl ketones **11a–d** and **13a–d** in a neutral or basic media. Subsequently, the intramolecular cyclization gave the desired polycyclic heteroaromatic compounds **1–5**.

Thus, treatment of condensation products **11a** and **11c** with trimethylsilyl iodide generated in situ from trimethylsilyl chloride and sodium iodide using CH_3CN as solvent, following the Olah and Morita methods,[8] at room temperature, afforded 1,2,3,4-tetrahydro-10*H*-benzo[*b*]thieno[3,2-*b*]indole (**1**) in 90% yield and 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]indole (**2**) in 53% yield (Scheme III).

When this one-pot procedure (hydrolysis of the carbamate group, cyclization, and dehydration) was applied to the condensation product **13a** at 40 °C, a 72% yield of a mixture of 5,6-dihydro-12*H*-benzo[*b*]thieno[3,2-*b*]-naphtho[2,1-*d*]pyrrole (**3**) and 12*H*-benzo[*b*]thieno[3,2-*b*]naphtho[2,1-*d*]pyrrole (**4**) in a ratio of 74:26 was obtained

Scheme III[a]



[a] (i) Me_3SiI in CH_3CN; (ii) KOH in MeOH.

(Scheme III). The aromatization of compound **3** by DDQ in refluxing anhydrous benzene led to the polycyclic heteroaromatic compound **4** in 70% yield.

Conversely, when the α-hetaryl ketone **13c** was treated with trimethylsilyl iodide in CH_3CN at room temperature or at 40 °C for several hours, the desired 5,6-dihydro-10*H*-naphtho[1,2-*b*]thieno[2,3-*d*]pyrrole (**5**) was not observed, and only intractable tarry material was obtained. This seems to indicate that the amine formed by the hydrolysis of the carbamate group in the starting material **13c** could be labile in these reaction conditions. Another attempt to cyclize the ketone **13c** by treating it with polyphosphoric acid at 100 °C afforded the cyclic compound **5** in only 17% yield accompanied by much tarry material (Scheme III). The thienoindole derivative **5** was found to be somewhat labile at room temperature, thus suggesting that the low yield of **5** from cyclization of ketone **13c** might essentially be due to its inability to survive in the present reaction conditions.

On the other hand, treatment of **11b** and **11d** with KOH/MeOH in anhydrous conditions and under inert atmosphere gave the desired cyclic products **1** and **2** in 55% and 71% yield, respectively. When the condensation product **13b** was submitted to KOH/MeOH under the same reaction conditions, a 47% yield of a mixture of **3** and **4** in a ratio of 66:34 was obtained (Scheme III).

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All attempts to obtain the cyclic product **5** by treatment of compound **13d** with KOH/MeOH failed, probably due to the lability of the amino derivative formed in situ after the hydrolysis of the $NHCOCF_3$ group in the reaction conditions used. In fact, following the reaction by TLC (silica gel, CH_2Cl_2), the starting material **13d** was quickly consumed but no cyclic compound was formed, and only tarry material was isolated.

Finally, treatment of the chlorohydrin **12a** with triethylamine in dimethylformamide at 120 °C followed by hydrolysis and workup furnished the desired cyclic compound **1** in 55% yield.

In summary, the good metalation levels achieved in the lithiation of compounds **6a–d** lead to the formation of α-hetaryl ketones through a reaction of the corresponding lithiated intermediates with the α-halo ketones **9** and **10**. These condensation products isolated in ca. 30–70% yield can be hydrolized, cyclized, and dehydrated in a one-pot procedure to give some new thieno- and benzo[*b*]thienoindole derivatives in ca. 17–90% yield. Hence, this work presents an approach to the synthesis of thieno- and benzo[*b*]thienoindole derivatives in two operations from readily available reactants.

Experimental Section

Materials and Methods. All reactions were performed in flame- or oven-dried glassware under a positive pressure of prepurified N_2. Sensitive liquids and solutions were transferred by syringe and were introduced into reaction flasks through rubber septa.

Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl. Methanol (MeOH), acetonitrile (CH_3CN), *N,N*-dimethylformamide (DMF), and benzene were dried by standard procedures. The concentration of a solution of commercial *n*-BuLi (≈1.6 M in hexanes, purchased from Fluka) was determined by means of the double-titration method of Jones and Gilman.[9] Dimethyl sulfate (Me_2SO_4) was purchased from Aldrich and fractionally distilled under reduced pressure. Other solvents and reagents from commercial sources were generally used without further purification.

2-Chlorocyclohexanone (**9**) and 3,4-dihydro-1(2*H*)-naphthalenone (1-tetralone) were purchased from Aldrich. 2-Bromo-1-tetralone (**10**) was prepared by bromination of 1-tetralone as described in the literature.[10] 3-[(*tert*-Butoxycarbonyl)-amino]benzo[*b*]thiophene (**6a**),[11a] 3-[(trifluoroacetyl)amino]-benzo[*b*]thiophene (**6b**),[11c] 3-[(*tert*-butoxycarbonyl)amino]-thiophene (**6c**),[11b] and 3-[(trifluoroacetyl)amino]thiophene (**6d**)[11c] were prepared from the 3-thiophenecarboxylic acid and benzo-[*b*]thiophene (purchased from Aldrich) by the published methods.

Methylation Reactions. General Procedure. To a solution of the amide or carbamate (1.0 mmol) in THF (20 mL) was added a solution of *n*-BuLi in hexane (3.2 mmol) at −78 °C. After stirring the mixture for 1 h, it was allowed to attain −20 °C and then the Me_2SO_4 (4.2 mmol) was added. The mixture was left for 1 h (until TLC showed that no starting material was present), and it was allowed to warm to room temperature. Concd NH_3 (6 mL) was added to destroy the excess of dimethyl sulfate. After stirring for 30 min, water was added, the organic layer was separated, and the aqueous solution was extracted twice with CH_2Cl_2. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (silica gel, CH_2Cl_2).

3-[(*tert*-Butoxycarbonyl)methylamino]-2-methylbenzo-[*b*]thiophene (8a). From **6a** (250 mg, 1.0 mmol) was obtained **8a** (232 mg, 84%) as a white solid: mp 53–55 °C; ^1H NMR ($CDCl_3$) δ 7.70 (1 H, m H_{arom}), 7.46 (1 H, m, H_{arom}), 7.30 (2 H, m, H_{arom}), 3.21 (3 H, s, NCH_3), 2.41 (3 H, s, CH_3), 1.31 (9 H, s, CMe_3); IR (KBr) ν 3070, 2980, 1705 cm^{-1}; mass spectrum, *m/z* (rel intensity) 277 (M^+, 10), 57 (100). Anal. Found: C, 64.75; H, 6.80; N, 5.11; S, 11.41. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Starting material **6a** was recovered in 15% yield.

Condensation Reactions with α-Halo Ketones. General Procedure. To a solution of the starting amide or carbamate (1.0 mmol) in THF (20 mL) at −78 °C was added a hexane solution of *n*-BuLi. After 1 h, the mixture was allowed to attain −20 °C and then a solution of α-halo ketone (1.2 mmol) in THF (1 mL) was added dropwise. After 30 min, the mixture was allowed to warm to room temperature (30 min) and stirred for 4 h. It was then poured into a cold saturated aqueous solution of NH_4Cl and after the phases were separated, the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvents were removed by evaporation under reduced pressure to give the crude product.

3-[(*tert*-Butoxycarbonyl)amino]-2-(2-oxocyclohexyl)-benzo[*b*]thiophene (11a). (a) With 1:2.2:1.2 Substrate/*n*-BuLi/Ketone. In a typical run, the reaction between the organolithic intermediate generated from the carbamate **6a** (0.51 g, 2.0 mmol) and a hexane solution of *n*-BuLi (4.5 mmol) and α-halo ketone **9** (0.32 g, 2.4 mmol) in the usual conditions (room temperature, 4 h) gave a crude material, which after purification (flash column, silica gel, CH_2Cl_2) afforded 73 mg (14%) of the carbamate **6a** and 495 mg (70%) of the α-hetaryl ketone **11a** as a yellow crystalline solid: mp 137–139 °C; ^1H NMR ($CDCl_3$) δ 7.72 (1 H, m, H_{arom}), 7.59 (1 H, m, H_{arom}), 7.32 (2 H, m, H_{arom}), 6.15 (1 H, br s, NH), 4.07 (1 H, dd, J = 11.7 Hz, J = 5.7 Hz, CHCO), 2.70–1.70 (8 H, m, CH_2), 1.49 (9 H, s, CMe_3); ^{13}C NMR ($CDCl_3$) δ 208.3 (CO), 154.0 (COO^tBu), 136.8, 136.2, 135.1, 126.8 (C_{arom}), 124.3, 124.2, 122.4, 121.1 (CH_{arom}), 80.5 (CMe_3), 50.6 (CHCO), 42.0, 34.7 (CH_2), 28.2 (CH_3), 27.4, 25.3 (CH_2); IR (KBr) ν 3280, 3080, 2940, 1710, 1700 cm^{-1}; mass spectrum, *m/z* (rel intensity) 345 (M^+, 16), 245 (100). Anal. Found: C, 65.86; H, 6.63; N, 4.08; S, 9.13. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05; S. 9.28.

(b) With 1:3.2:1.2 Substrate/*n*-BuLi/Ketone. When the reaction was performed with the carbamate **6a** (0.51 g, 2.0 mmol), *n*-BuLi (6.4 mmol), and α-halo ketone **9** (0.32 g, 2.4 mmol), the following compounds were isolated: 135 mg (27%) of starting material **6a**, 40 mg (12%) of ketone **9**, and 110 mg (24%) of the cis isomer of 1-butyl-2-chlorocyclohexanol (colorless oil) as it was determined by ^1H NMR [bp 94–96 °C at 18 mmHg (lit.[12] bp 96–99 °C at 18 mmHg); ^1H NMR ($CDCl_3$) δ 4.00 (1 H, dd, J = 9.9 Hz, J = 5.5 Hz, CHCl), 2.10–1.20 (15 H, m, CH_2 and OH), 0.92 (3 H, t, CH_3); IR (film) ν 3570, 3470, 2930, 750 cm^{-1}; mass spectrum, *m/z* (rel intensity) 190 (M^+, 2), 43 (100)]. Only 120 mg (17%) of condensation product **11a** was obtained. In the more polar fractions we obtained 206 mg (35%) of the 1,2-bis[3-[(*tert*-butoxycarbonyl)amino]benzo[*b*]thien-2-yl]cyclohexanol as a white solid: mp 116–118 °C; ^1H NMR ($CDCl_3$) δ 7.63 (2 H, m, H_{arom}), 7.40 (2 H, m, H_{arom}), 7.25 (4 H, m, H_{arom}), 6.15 (1 H, br s, NH), 6.02 (1 H, br s, NH), 3.60 (1 H, m, CH), 3.50 (1 H, br s, OH), 2.40–1.60 (8 H, m, CH_2), 1.47 (18 H, s, CMe_3); ^{13}C NMR ($CDCl_3$) δ: 154.8 (COO^tBu), 145.0, 138.8, 137.2, 136.8, 135.7, 135.2, 126.2 (C_{arom}), 124.6, 124.3, 124.1, 123.9, 122.2, 121.2 (CH_{arom}), 80.8 (CMe_3), 80.3 (CMe_3), 76.3 (COH), 47.3 (CH), 40.4, 30.1 (CH_2), 28.3 (CH_3), 26.0, 21.1 (CH_2); IR (KBr) ν 3370, 3300, 3050, 2910, 1700 cm^{-1}; mass spectrum, *m/z* (rel intensity) 594 (M^+, 3) 494 (10), 394 (26), 57 (100). Anal. Found: C, 64.32; H, 6.30; N, 4.81; S, 10.58. Calcd for $C_{32}H_{38}N_2O_5S_2$: C, 64.62; H, 6.44; N, 4.71; S, 10.78.

1,2,3,4-Tetrahydro-10*H*-benzo[*b*]thieno[3,2-*b*]indole (1) from α-Hetaryl Ketone 11a. In a typical run, to a mixture of **11a** (181 mg, 0.5 mmol) and NaI (160 mg, 1.1 mmol) in CH_3CN (2 mL) was added dropwise Me_3SiCl (0.13 mL, 1.0 mmol) at room temperature. After stirring the mixture for 2 h (until TLC showed the absence of starting material), it was concentrated under reduced pressure. To the crude product was added water (30 mL) and CH_2Cl_2 (30 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated under vacuum to a solid. This crude product was purified by flash chromatography (silica gel, CH_2Cl_2) to give 106 mg (90%) of the desired cyclic compound

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1 as a light yellow crystalline solid: mp 125–127 °C (lit.[13] mp 125–127 °C); ^{1}H NMR ($CDCl_3$) δ 8.15 (1 H, br s, NH), 7.76 (1 H, d, J = 8.2 Hz, H_{arom}), 7.58 (1 H, d, J = 8.0 Hz, H_{arom}), 7.30 (1 H, t, J = 7.5 Hz, H_{arom}), 7.15 (1 H, t, J = 7.5 Hz, H_{arom}), 2.70 (4 H, m, CH_2), 1.88 (4 H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 140.9, 132.8, 132.7, 130.1, 130.0 (C_{arom}), 124.2, 123.8, 121.7, 117.4 (CH_{arom}), 111.4 (C_{arom}), 23.8, 23.4, 23.1, 22.2 (CH_2); IR (KBr) ν 3420, 3060, 2930, 2860, 1480 cm^{-1}; mass spectrum, m/z (rel intensity) 227 (M^+, 79), 199 (100).

5,6,7,8-Tetrahydro-4*H*-thieno[3,2-*b*]indole (2) from α-Hetaryl Ketone 11d. In a typical run, a mixture of **11d** (295 mg, 1.0 mmol) and a methanolic KOH solution (10% w/w, 0.98 mL) in anhydrous MeOH (8 mL) was boiled under reflux for 22 h (until TLC showed that no starting material was left). The mixture was cooled to room temperature and neutralized with a 1.1 M methanolic HCl solution. After the addition of water (30 mL) and CH_2Cl_2 (30 mL), the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered and concentrated to give a solid. The crude material was purified by flash chromatography (silica gel, 10:1 hexane–ethyl acetate) to yield 126 mg (71%) of the desired cyclic compound **2** as a pale gray crystalline solid: mp 98–100 °C (lit.[14] mp 99–100 °C); ^{1}H NMR ($CDCl_3$) δ 7.76 (1 H, br s, NH), 6.96 (1 H, d, J = 5.0 Hz, H_{arom}), 6.88 (1 H, d, J = 5.2 Hz, H_{arom}), 2.66 (4 H, m, CH_2), 1.85 (4 H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 136.6, 132.5, 123.0 (C_{arom}), 121.1, 111.0 (CH_{arom}), 110.4 (C_{arom}), 23.7, 23.4, 23.1, 22.3 (CH_2); IR (KBr) ν 3420, 3100, 2950, 2860, 1380 cm^{-1}; mass spectrum, m/z (rel intensity) 177 (M^+, 59), 149 (100).

5,6-Dihydro-12*H*-benzo[*b*]thieno[3,2-*b*]naphtho[2,1-*d*]pyrrole (3) from α-Hetaryl Ketone 13b. To a suspension of **13b** (100 mg, 0.3 mmol) in anhydrous MeOH (2 mL) was added all at once a methanolic KOH solution (10% w/w, 0.28 mL). The mixture was heated at reflux for 9 h. The usual workup gave a crude material, which was purified by flash chromatography (silica gel, 9:1 hexane–EtOAc) to yield 11 mg (16%) of 12*H*-benzo[*b*]thieno[3,2-*b*]naphtho[2,1-*d*]pyrrole (**4**) (spectral and physical data are given in the last experiment) and the desired cyclic product **3** (22 mg, 31%) as a pale gray crystalline solid: mp 214–216 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (1 H, br s, NH), 7.85–7.65 (2 H, m, H_{arom}), 7.43–7.00 (6 H, m, H_{arom}), 3.20–2.70 (4 H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 142.0, 135.5, 133.0, 129.8 (C_{arom}), 128.9, 127.1, 126.2, 124.5 (CH_{arom}), 124.2 (C_{arom}), 123.0 (CH_{arom}), 122.8, 119.5 (C_{arom}), 119.2, 118.4 (CH_{arom}), 114.0 (C_{arom}), 29.6, 21.1 (CH_2); IR (KBr) ν 3420, 3040, 2920, 1600 cm^{-1}; mass spectrum, $m./z$ (rel intensity) 275 (M^+, 100). Anal. Found: C, 78.31; H, 4.71; N, 5.04; S, 11.50. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09; S. 11.64.

5,6-Dihydro-10*H*-naphtho[1,2-*b*]thieno[2,3-*d*]pyrrole (5) from α-Hetaryl Ketone 13c. A mixture of **13c** (150 mg, 0.4 mmol) and polyphosphoric acid (PPA) (1.2 g obtained from 4.0 g of P_2O_5 and 3.0 g of orthophosphoric acid) was heated at 100 °C for 3 h. The mixture was cooled to room temperature, and then ice and water were added. The mixture was neutralized with a satured aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2) to yield 15 mg (10%) of starting material **13c** and 17 mg (17%) of the desired cyclic compound **5** as a oil: ^{1}H NMR ($CDCl_3$) δ 8.37 (1 H, br s, NH), 7.25–7.12 (4 H, m, H_{arom}), 7.07 (1 H, d, J = 5.2 Hz, H_{arom}), 6.96 (1 H, d, J = 5.2 Hz, H_{arom}), 3.01 (2 H, m, CH_2), 2.87 (2 H, m, CH_2); IR (film) ν 3420, 3050, 2960, 2920, 1600 cm^{-1}; mass spectrum, m/z (rel intensity) 225 (M^+, 100). Elemental analysis was not carried out because of its lability.

Benzo[*b*]thienoindole Derivative 1 from Halohydrin 12a. A solution of **12a** (110 mg, 0.3 mmol) and Et_3N (0.42 mL, 3.0 mmol) in DMF (9 mL) was heated at 120 °C until TLC (silica gel, CH_2Cl_2) showed the absence of starting material (2 h). The mixture was cooled at room temperature and then water (30 mL) and CH_2Cl_2 (30 mL) were added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated at reduced pressure to an oil, which was purified by flash chromatography (silica gel, CH_2Cl_2) to give a mixture of two products. This mixture was dissolved in MeOH (1 mL) and treated with a methanolic KOH solution (10% w/w, 0.4 mL). After stirring for 3 h at room temperature, the mixture was neutralized with a 1.1 M methanolic HCl solution. The mixture was partitioned between water (50 mL) and CH_2Cl_2 (50 mL) and the usual workup gave 36 mg (55%) of the desired cyclic compound **1** as a light yellow solid. Spectral and physical data are given above.

12*H*-Benzo[*b*]thieno[3,2-*b*]naphtho[2,1-*d*]pyrrole (4) from Benzo[*b*]thienoindole Derivative 3. To a mixture of DDQ (28 mg, 0.12 mmol) in anhydrous benzene (1 mL) heated at reflux was added all at once compound **3** (28 mg, 0.10 mmol) in anhydrous benzene (1 mL). After 5 min, TLC (silica gel, 8:2 hexane–EtOAc) indicated that no starting material remained and one product had been formed. After being filtered out of the DDQ, the filtrate was washed with water and dried ($MgSO_4$) and the solvent was removed. Purification of the crude material by flash chromatography (silica gel, 8:2 hexane–ethyl acetate) provided 19 mg (70%) of aromatic compound **4** as a green solid: mp 217–219 °C; ^{1}H NMR ($CDCl_3$) δ 9.36 (1 H, br s, NH), 8.21 (1 H, d, J = 8.0 Hz), 8.05–7.80 (4 H, m), 7.70–7.30 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 142.6, 135.7, 135.4, 130.8 (C_{arom}), 129.1 (CH_{arom}), 127.1 (C_{arom}), 125.8, 124.4, 124.3, 123.8 (CH_{arom}), 122.5 (C_{arom}), 120.8, 120.0, 119.3, 119.0 (CH_{arom}), 118.1, 117.7 (C_{arom}); IR (KBr) ν 3430, 3040 cm^{-1}; mass spectrum, m/z (rel intensity) 273 (M^+, 100). Anal. Found: C, 78.89, H, 4.18; N, 5.00; S, 11.58. Calcd for $C_{18}H_{11}NS$: C, 79.09; H, 4.06; N, 5.12; S, 11.73.

Registry No. 1, 89564-16-9; 2, 88537-34-2; 3, 138900-81-9; 4, 248-46-4; 5, 138900-82-0; 6a, 89564-05-6; 6b, 138900-83-1; 6c, 19228-91-2; 6d, 138900-84-2; 8a, 138900-85-3; 8b, 138900-86-4; 8c, 138900-87-5; 8d, 138900-88-6; 9, 822-87-7; 10, 13672-07-6; 11a, 138900-89-7; 11b, 138900-90-0; 11c, 138900-91-1; 11d, 138900-92-2; 12a, 138900-93-3; 12b, 138900-94-4; 13a, 138900-95-5; 13b, 138900-96-6; 13c, 138900-97-7; 13d, 138900-98-8; *cis*-1-butyl-2-chlorocyclohexanol, 138900-99-9; 1,2-bis[3-[(*tert*-butoxycarbonyl)amino]benzo[*b*]thien-2-yl]cyclohexanol, 138901-00-5.

Supplementary Material Available: Spectral and physical data for compounds **8b–d** and 2-bromo-3-[(trifluoroacetyl)amino]thiophene, preparation and spectral and physical data for **11b–d**, **12a,b**, and **13a–d**, and preparation of cyclic compounds **1**, **2**, and **3** from **11b**, **11c**, and **13a**, respectively (6 pages). Ordering information is given on any current masthead page.

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Copper(I) and Phase Transfer Catalyzed Allylation of Alkynes

Vladimir V. Grushin and Howard Alper*

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

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Introduction

Allylation of terminal alkynes is an important process because it affords enynes which are widely used in organic synthesis, including the synthesis of insect pheromones.[1,2] Stable and readily available alkynylcopper(I) compounds are known to condense with allylic halides to give the corresponding enynes.[3] Yields of the latter are dependent on many factors, including the nature of alkyne, allylic

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