

Modified Methods for the Synthesis of Carbazole from Phenothiazine

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Abstract: Lithium, used in conjunction with triphenylphosphine or sodium metal, produces a high yield of carbazole when reacted with phenothiazine.

Keywords: Carbazole, phenothiazine, lithium.

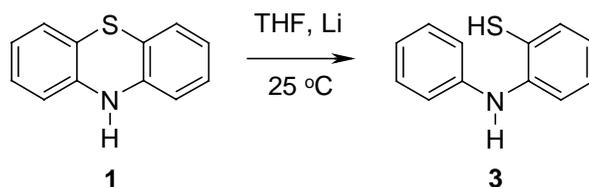
Introduction

An efficient method for the ring contraction of phenothiazine (**1**) to make carbazole (**2**) would prove useful because most regiochemically controlled synthesis routes to phenothiazine derivatives [1] could then be directly applied to the corresponding carbazoles. Although many examples of the hydrodesulfurization of phenothiazine to make diphenylamine have been reported [2], much less effort has focused on this ring contraction [3-5] (**1** → **2**). Herein we report modifications of the procedures

used by Gilman [5] to produce two methods for the conversion of phenothiazine to carbazole that both employ low reaction temperatures and afford high product yields.

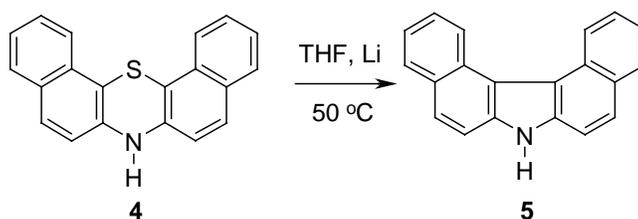
Results and Discussion

Gilman showed that lithium in THF at 50 °C can cause the ring contraction of N-ethylphenothiazine to make 9-ethylcarbazole. However, when an unprotected phenothiazine ring was used in a similar reaction [5] at 25 °C, only 2-mercaptodiphenylamine (**3**) was produced (36% yield) (Scheme 1). A later paper [6] showed that 7-dibenzo [*c, h*] phenothiazine (**4**) could be transformed into 7-dibenzo [*c, g*] carbazole (**5**) (33% yield), by lithium in THF using an increased reaction temperature of 50 °C (Scheme 2). We report that an increased reaction temperature caused a similar improvement in carbazole yield for the reaction of phenothiazine with lithium. By increasing the reaction temperature from 25 °C to that of refluxing THF, a low yield of carbazole (25%) was obtained.



Scheme 1.

In an attempt to further increase the yield of the reaction, a thiophile, triphenylphosphine, was included in the reaction mixture. This addition improved the carbazole yield to 82%, presumably by augmenting the reaction's sulfur extrusion efficiency.

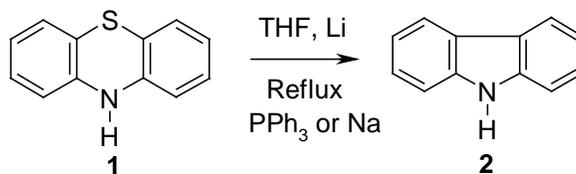


Scheme 2.

The addition of sodium metal was our next modification of the lithium reaction. Sodium by itself has been shown to cause only partial sulfur extrusion from these types of ring systems [6]; yet, by combining these two metals we were able to utilize the increased reducing ability of sodium while still maintaining the ring contracting effects of lithium. The use of sodium in conjunction with lithium increased the yield of carbazole to 88% (Scheme 3).

Prior to the start of this project there was some concern as to the possibility of lithium cleaving the product carbazole. However, Gilman has shown that carbazole is resistant to lithium in refluxing

THF [7] and dioxane [2b]. The mechanism for this reaction is expected to be similar to the one proposed by Gilman in which a dianion intermediate is formed prior to sulfur extrusion [5].



Scheme 3.

Conclusions

By providing two efficient, high yield methods for the ring contraction of phenothiazine, we have opened more possible synthesis routes for carbazole derivatives. Also these improvements may now be applied to other types of compounds which contain the thiazine ring system.

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Experimental

General

All reactions were performed under a nitrogen atmosphere in oven-dried glassware using magnetic stirring. NMR spectra were recorded using a General Electric QE-3000 spectrometer with CDCl_3 as the solvent and TMS as the internal standard. The infrared spectra were determined on a NaCl plate using a Mattson Galaxy Series FTIR 3000 spectrometer. All GCMS spectra were recorded using a Varian 3400 Gas Chromatograph and a Finnigan MAT ion trap detector. All reagents and reactants were purchased from Aldrich and used without further purification. All melting points were performed using a Mel-Temp II apparatus and are uncorrected.

Carbazole (2) using Lithium

In a 100 mL round-bottom flask 0.150 grams (0.750 mmol) of phenothiazine was dissolved in tetrahydrofuran (40 mL). To this was added 70.0 mg (10.0 mmol) of lithium dispersion. The mixture was refluxed for 24 hours after which time any remaining lithium was destroyed with methanol.

Work-up consisted of washing the reaction mixture twice with 5% sodium hydroxide (75 mL) and once with water (75 mL). The combined organic layers were dried with sodium sulfate, filtered and evaporated to produce a white powder. Purification consisted of a silica column, using a 1/3/16 mixture of methanol, chloroform and petroleum ether as the elution solvent. This was followed by recrystallization in ethanol to produce carbazole as white crystals. After work-up the reaction produced 32.0 mg (0.200 mmol) of pure carbazole, a yield of 25%. m.p. 242-244°C; IR (cm⁻¹): 3419 (N-H); ¹H-NMR (300 MHz) δ (ppm): 7.19 (dd, 1H, J = 7.7 Hz, 7.2 Hz), 7.38 (dd, 1H, J = 8.0 Hz, 7.2 Hz), 7.50 (d, 1H, J = 8.0 Hz), 8.11 (d, 1H, J = 7.7 Hz); ¹³C-NMR (75 MHz) δ (ppm): 110.9, 118.6, 120.0, 122.8, 125.2, 139.5; MS (EI, m/z) 167 (M⁺).

Carbazole using Lithium and PPh₃

The same procedure was followed as above except 0.200 grams (0.760 mmol) of triphenylphosphine was added along with the lithium dispersion. This reaction produced 0.103 grams (0.620 mmol) of carbazole, a yield of 82%. m.p. 242-243°C; IR and NMR, identical in all respects to an authentic sample.

Carbazole using Lithium and Sodium

The same general procedure was followed except 0.200 grams (8.70 mmol) of sodium and 50.0 mg (7.14 mmol) of lithium dispersion were reacted with 0.150 grams (0.750 mmol) of phenothiazine. This reaction produced 0.111 grams (0.660 mmol) of carbazole, for a yield of 88%. m.p. 242-243°C; IR and NMR, identical in all respects to an authentic sample.

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Sample Availability: Not available