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SYNTHESIS OF AMINO DERIVATIVE OF INDENE AND FLUORENE FROM IMIMIUM SALT GENERATED IN ETHEREAL LITHIUM PERCHLORATE SOLUTION

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Abstract

A series of amino derivative of 1-indene and 9-fluorene have been synthesized from their corresponding iminium salt, generated *in situ* in the concentrated ethereal lithium perchlorate solution, and 1-indenyl or 9-fluorenyl anions. The yields of the reactions depend on the kind of anion. Addition of 1-indeny anion to the iminium salt gives the amino derivative of 1-indene, while addition of fluorenyl anion to the iminium salt gives 9-methylenefluorene derivatives as the major product.

Keywords: Iminium ion; Lithium perchlorate; 9-Aminofluorene; 1-Aminoindene

Introduction

1-(Aminomethyl)indanes and 9-substituted fluorenes have been used in different areas of chemistry such as pharmaceutical and solid-phase synthesis of protected peptides [1,2]. Cyclopentadienide moiety in fluorene and indene is also an important ligand system in organometallic chemistry.

Iminium salts are important intermediates in organic synthesis. These salts may be easily produced *in situ* by the reaction of (trimethylsilyl)dialkylamines with various aromatic aldehydes, promoted by a 5 M solution of $LiClO_4$ in diethyl ether [3,4] (Scheme 1).

Experimental

$LiClO_4$ (Fluka) was dried at 160°C and 10^{-1} Torr for 48 h. Diethyl ether was dried over Na/benzophenone under argon. IR spectra were taken on Matt Son 1000 Unicam FTIR, ^1H and ^{13}C NMR spectra were recorded on Bruker AC 80 or Bruker 500 MHz Ultra Shield™. Mass spectra were obtained on Fisson 800 Trio, and GC-Mass HP 5973 MSD. All reactions were performed under argon. Most aldeyhdes were distilled before use. Chemicals were purchased from Fluka, Merck, and used as received.

Caution: Although we did not have any accident in using $LiClO_4$, we advise that lithium perchlorate should be dried in a hood using a suitable lab-shield. The ether solution should be freshly prepared and not stored for a long time.

General Procedure for the Preparation of 1H-Indene-1-methanamine

The aldehyde (2 mmol) and 3 mL of 5 M $LiClO_4$ in

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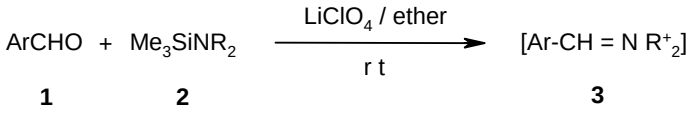
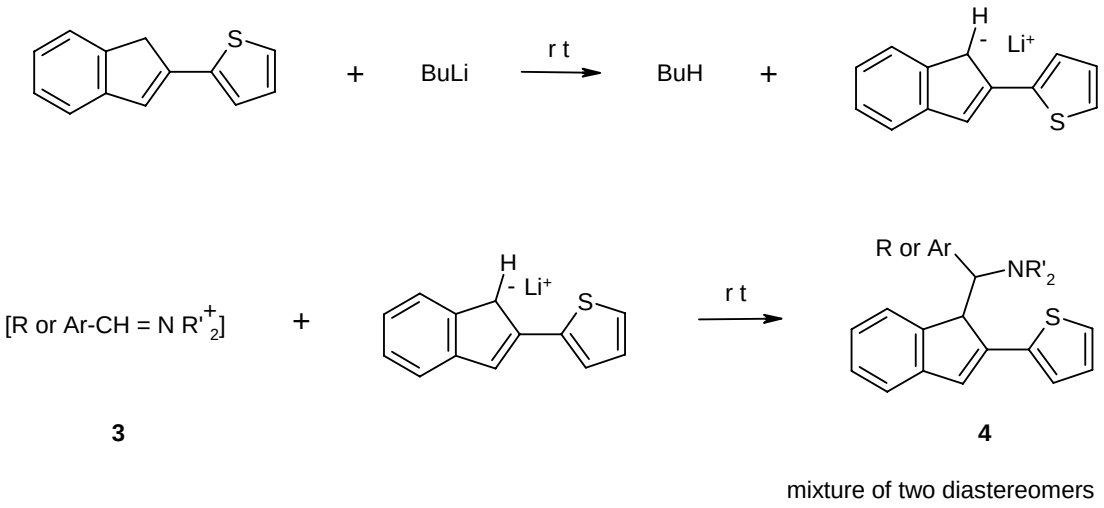


Scheme 1



Scheme 2

diethyl ether were placed in a 50 mL flask under argon and stirred for 5 min (Trimethylsilyl)dialkylamines (3 mmol) was then added via syringe. After about 30 min, lithium salt of 1-indene was added. The mixture was stirred at room temperature for 1 to 2 h. Then, dichloromethane (30 mL) and water (30 mL) were added and the organic layer was separated, washed with water, dried over $MgSO_4$, and the solvent was removed by the means of rotary evaporator. The crude material was further purified by chromatography on basic alumina or aqueous acid extraction. The products characterized by their MS, IR and NMR spectra (Table 1).

General Procedure for the Preparation of 9H-fluorene-9-methanamine

The aldehyde (2 mmol) and 3 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 ml flask under argon and stirred for 5 min (Trimethylsilyl)dialkylamines (3 mmol) was then added via syringe. After about 30 min lithium salt of 9-fluorene was added. The mixture was stirred at 0°C for 1 to 2 h. Then, dichloromethane (30 mL) and water (30 mL) were added and the organic layer was separated, washed with water, dried over $MgSO_4$, and the solvent was removed by rotary evaporator. The crude material was further purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (80/20). The ratio of fluorene-9-methanamine 5 and 9-methylenefluorene 6 was measured by gas chromatography. There was no attempt to separate the fluorene-9-methanamine 5 and 9-methylenefluorene 6 in all cases and the yields for total products are shown in Table 2. The products characterized by their MS, IR and NMR spectra.

Spectroscopic Data

4a, (50%), IR (KBr), ν_{max} 1592.3 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.20 (s, 6H, $N\underline{Me}_2$), 4.2 (m, 1H), 5.80 (d, 1H, $\underline{CH}NMe_2$), 6.40 (m, 1H), 7.10-7.90 (m, 10H, Ar-H); MS, m/e 234 (M-CH_3, 100, base peak), 219 (35.7), 203 (12.8), 189 (51.4).

4b, (45%), ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.10 (s, 6H, $N\underline{Me}_2$), 4.20 (m, 1H), 5.16 (d, 1H, $\underline{CH}NMe_2$), 6.40 (m, 1H), 6.60-7.70 (m, 9H, Ar-H); MS, m/e 238 (M-$HNMe_2$, 64.2), 202 (base peak, 100), 101 (38.5).

Table 1. Products of aminoalkylation of aldehyde with indenyl anion

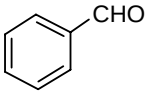
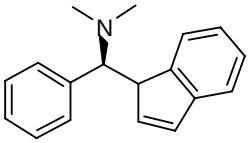
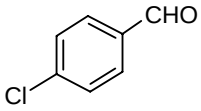
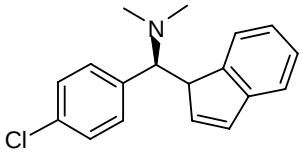
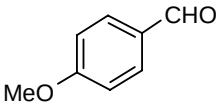
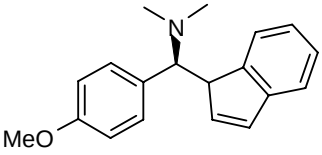
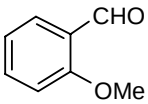
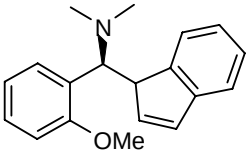
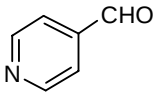
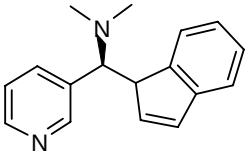
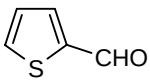
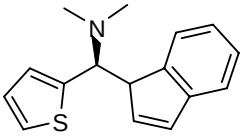
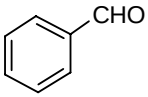
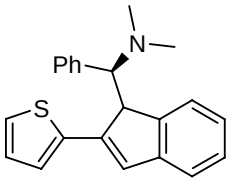
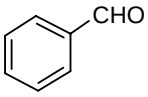
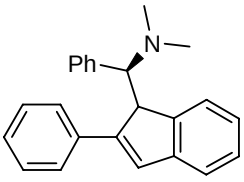
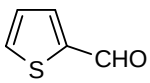
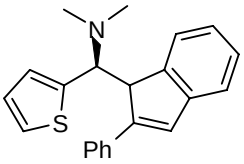
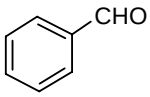
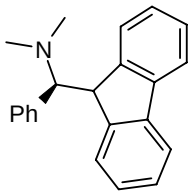
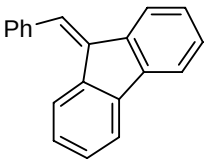
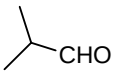
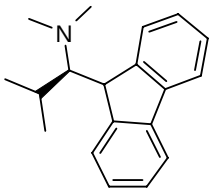
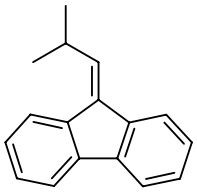
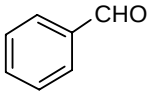
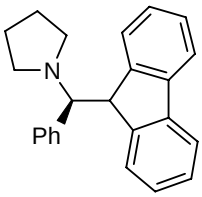
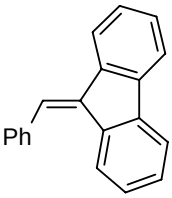
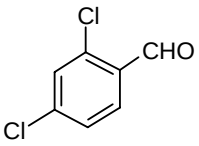
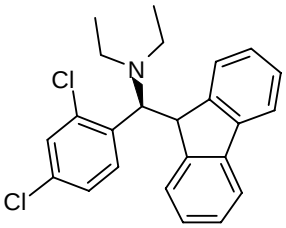
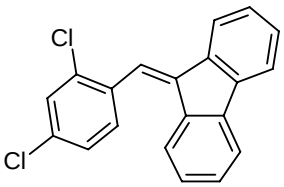
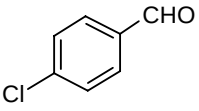
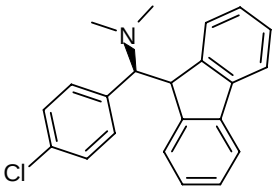
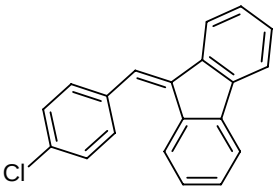
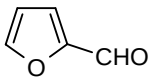
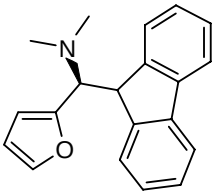
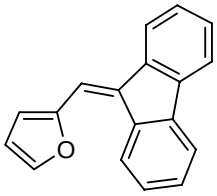
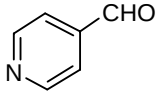
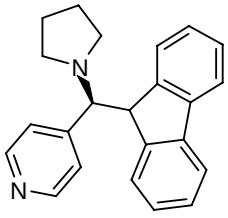
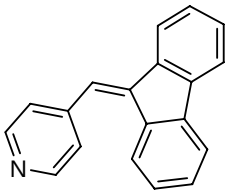
Starting Aldehyde	Amine	Product		Yield (%)
	Me_2NSiMe_3		**4a**	50
	Me_2NSiMe_3		**4b**	45
	Me_2NSiMe_3		**4c**	82
	Me_2NSiMe_3		**4d**	66
	Me_2NSiMe_3		**4e**	60
	Me_2NSiMe_3		**4f**	87
	Me_2NSiMe_3		**4g**	75
	Me_2NSiMe_3		**4h**	70
	Me_2NSiMe_3		**4i**	80

Table 2. Products of aminoalkylation of aldehyde with fluorenyl anion

Starting Aldehyde	Products (%)			Yield (total)
		**5a** (45)	 **6a** (55)	76
		**5b** (40)	 **6b** (60)	50
		**5c** (32)	 **6c** (68)	71
		**5d** (26)	 **6d** (74)	62
		**5e** (30)	 **6e** (70)	58
		**5f** (35)	 **6f** (65)	55
		**5g** (38)	 **6g** (62)	60

4c, (82%), IR (KBr), ν_{max} 1592.3 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.20 (s, 6H, N<u>Me</u>$_2$), 3.80 (m, 3H, O<u>Me</u>), 4.20 (m, 1H), 5.00 (d, 1H, <u>CH</u>NMe$_2$), 6.60 (m, 1H), 6.70-7.80 (m, 9H, Ar-H). MS, m/e 281 (M-Me, 10.1), 234 (M-HNMe$_2$, 100, base peak), 219 (35.7), 207 (26), 189 (52.1), 165 (11.6).

4d, (66%), IR (KBr), ν_{max} 1630.7 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.23 (s, 6H, N<u>Me</u>$_2$), 3.70 (s, 3H, O<u>Me</u>), 4.10 (m, 1H), 5.10 (d, 1H, <u>CH</u>NMe$_2$), 6.60 (m, 1H), 7.10-7.90 (m, 9H); MS, m/e 204 (M-HNMe$_2$, OMe, 100, base peak), 176 (15.5), 151 (8.4).

4f, (87%), IR (KBr), ν_{max} 1615.4 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.20 (s, 6H, N<u>Me</u>$_2$), 3.60 (m, 1H), 5.00 (d, 1H, <u>CH</u>NMe$_2$), 6.70 (m, 1H), 7.00-8.10 (m, 8H); MS, m/e 210 (M-HNMe$_2$, 100, base peak), 195 (14), 165 (22), 152 (9).

4g, (75%, mixture of two diastereomers, 77:23), ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.27 (s, 6H, N<u>Me</u>$_2$), 3.72 (d, 1H), 4.95 (d, 1H, <u>CH</u>NMe$_2$), 6.90-7.28 (m, 13H); ^{13}C NMR ($CDCl_3$) for the major diastereomers (only signals between 0.0 and 80 ppm are shown), δ 40.2 (CH), 44.9 (CH_3), 70.8 (CH).

4h, (70%), ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.24 (s, 6H, N<u>Me</u>$_2$), 3.74 (d, 1H), 4.49 (d, 1H, <u>CH</u>NMe$_2$), 6.85-7.70 (m, 15H); ^{13}C NMR ($CDCl_3$) for the major diastereomers (only signals between 0.0 and 80 ppm are shown), δ 39.8 (CH_3), 45.0 (CH), 74.5 (CH).

4i, (80%, mixture of two diastereomers, 72:28), ^1H NMR ($CDCl_3$) for the major diastereomers: δ 2.29 (s, 6H, N<u>Me</u>$_2$), 3.88 (d, 1H), 4.85 (d, 1H, <u>CH</u>NMe$_2$), 6.87-7.60 (m, 13H); ^{13}C NMR ($CDCl_3$) for the major diastereomers (only signals between 0.0 and 80 ppm are shown), δ 43.0 (CH), 44.6 (CH_3), 66.1 (CH).

5a, (34.2%), Pale yellow solid, ^1H NMR ($CDCl_3$): δ 2.20 (s, 6H, N<u>Me</u>$_2$), 4.12 (d, 1H, *J* = 6.3 Hz, 9-<u>H</u>), 4.54 (d, 1H, *J* = 6.3 Hz, <u>CH</u>NMe$_2$), 6.80-7.60 (m, 13H, aromatic H). **6a**, (49.4%), Pale yellow solid, IR (KBr), ν_{max} 1639.7 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.80-7.60 (m, 14H).

5b, (20.0%), Yellow solid, ^1H NMR ($CDCl_3$): δ 1.15 (d, *J* = 7.1 Hz, 6H, <u>Me$_2$</u>CH), 1.70 (m, 1H, Me$_2$<u>CH</u>), 2.10 (s, 6H, N<u>CH$_3$</u>), 2.55 (m, 1H, <u>CH</u>NCH$_3$), 4.20 (d, *J* = 6.5 Hz, 1H, 9-<u>H</u>), 7.20-7.80 (m, 8H, aromatic H); MS, m/e 265 (M^+), 166 (base peak, M-99). **6b**, (30.0%), Yellow solid, IR (KBr), ν_{max} 1630.0 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (d, *J* = 6.6 Hz, 6H, <u>Me$_2$</u>CH), 3.10 (m, 1H, Me$_2$<u>CH</u>), 6.82 (d, *J* = 8.1 Hz, 1H, =CH) 7.20-7.80 (m, 8H); MS, m/e 220 (M^+, 67.1), 205 (base peak, 100), 190 (15.7), 178 (28.6), 165 (60.1).

5c, (22.7%), Yellow solid, ^1H NMR ($CDCl_3$): δ 1.80 (m, 4H), 3.02 (m, 4H), 4.10 (d, *J* = 6.0 Hz, 1H, 9-<u>H</u>), 4.60 (d, 1H, *J* = 6.0 Hz, <u>CH</u>N), 7.00-7.60 (m, 13H, aromatic H).

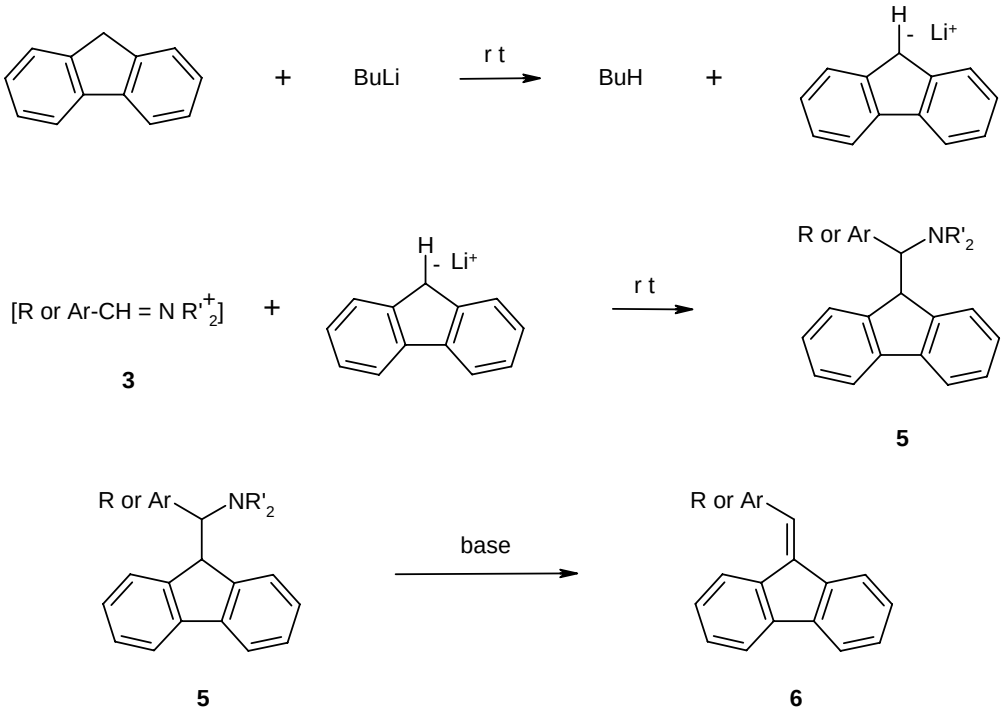
5e, (17.4%), Yellow solid, ^1H NMR ($CDCl_3$): δ 2.1 (s, 6H, N<u>Me</u>$_2$), 4.20 (d, *J* = 6.0 Hz, 1H, N<u>CH</u>), 4.70 (d, *J* = 6.0 Hz, 1H, 9-<u>H</u>), 6.90-7.70 (m, 12H, aromatic H). **6e**, (40.6%), Yellow solid, IR (KBr), ν_{max} 1607.0 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9-7.70 (m, 13H); MS, m/e 288 (M^+, 1.1), 166 (base peak, 100), 141 (45.7), 77 (20).

5f, (19.3%), Brown solid, ^1H NMR ($CDCl_3$): δ 2.25 (s, 6H, N<u>Me</u>$_2$), 4.24 (d, *J* = 6.2 Hz, 1H, N<u>CH</u>), 4.76 (d, *J* = 6.2 Hz, 1H, 9-<u>H</u>), 6.30-7.80 (m, 11H, aromatic H). **6f**, (35.7%), Brown solid, IR (KBr), ν_{max} 1610 (C=C) cm^{-1}**;** ^1H NMR ($CDCl_3$): δ 6.38-7.78 (12H).

5g, (22.8%), Yellow solid, ^1H NMR ($CDCl_3$): δ 1.76 (m, 4H), 2.95 (m,4H), 4.05 (d, *J*=6.0 Hz, 1H, 9-<u>H</u>), 4.80 (d, *J*=6.0 Hz, <u>CH</u>N), 6.90-8.55 (m, 12H, aromatic H).

Results and Discussion

In continuation of our research studies on Mannich type reactions [5,6], we now report the one-pot synthesis of amino derivatives of 1-indene and 9-fluorene by the reaction of 1-indenyl or 9-fluorenyl anions with iminium salts, generated *in situ* in 5 M lithium perchlorate ethereal solution. Thus, in the concentrated ethereal lithium perchlorate solution, aldehyde **1** and (trimethylsilyl)dialkylamine **2** produces the iminium salt **3** as an intermediate at room temperature, that can be detected in the solution by ^{13}C NMR spectroscopy [7]. Upon addition of 1-indenyl or 9-fluorenyl anions to the preformed iminium salt **3**, the products were produced in about one hour. Variety of amino derivatives of 1-indene **4(a-i)** and 9-fluorene **5(a-g)**, were synthesized in short reaction times with moderate to good yields, Schemes 2 and 3. Amino derivatives of 1-indene **4(a-i)** were formed as a mixture of two diastereomers, since ^1H NMR shows two sharp peaks near δ 2.2 and 2.4 for each product, but no selectivity was observed in most cases. From a series of experiments, we found that 9-aminofluorenes undergo a further elimination reaction to give 9-methylenefluorene **6** derivatives as the major product. Recently it was reported that when fluorine derivatives is treated with variety of bases, such as LDA, NaHMDS and NaH, in the presence of an aldehyde, the major product is 9-(methylene)fluorene derivatives [8]. Therefore, it can be assumed that the elimination reaction in **6** might be due to the steric effect or acidic hydrogen in the 9-position of fluorene derivatives. ^{13}C NMR spectroscopy rules out direct condensation reaction between the starting aldehyde and 9-fluorenyl anions, since the iminium salt



Scheme 3

3 can be detected by ^{13}C NMR, after addition of (trimethylsilyl)dialkylamines to an aldehyde in the concentrated ethereal lithium perchlorate solution as an intermediate at room temperature. Increasing the reaction time, after addition of 9-fluorenyl anions to the preformed iminium salt **3**, increases the yield of the 9-methylenefluorene **6**, which also indicates that the elimination reaction takes place after the formation of the 9-aminofluorene **5**. Decreasing the reaction temperature, increases the formation of the 9-aminofluorene **5**. The ratio of **5** to **6** was determined by gas chromatography. The yield of **5** varies from 28% to 40% as indicated in Table 2.

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