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A Novel Synthetic Route to 1,3-Disubstituted Naphthalenes

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A NOVEL SYNTHETIC ROUTE TO 1,3-DISUBSTITUTED NAPHTHALENES

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ABSTRACT: 1-(2-Substituted 1-propenyl)-2-(trifluoromethyl)benzenes are cyclized to 3-substituted 1-(4-methylpiperazino)naphthalenes in a lithium 4-methylpiperazide-mediated reaction that involves the trifluoromethyl group.

Synthesis of 1,3-disubstituted naphthalenes is not trivial. Known, specific approaches involve cycloaddition reactions with benzyne intermediates,[1] intramolecular cyclizations of benzene derivatives,[2] and transformations of substituents already present at the naphthalene.[2b,3]

In this paper we report a new synthetic route to 3-substituted 1-(dialkylamino)naphthalenes, such as **8-11** (Scheme I) and **14** (Scheme II), by lithium dialkylamide-mediated cyclization of 1-(1-propenyl)-2-trifluoromethyl)benzene derivatives, such as **4-7**, **13**. Each fluorine of the CF_3 group in **4-7**, **13** is successfully displaced by a series of internal nucleophilic processes. The resulting naphthalene contains a C-1 atom derived from the CF_3 group and a 1-dialkylamino function of the lithium amide reagent.[4]

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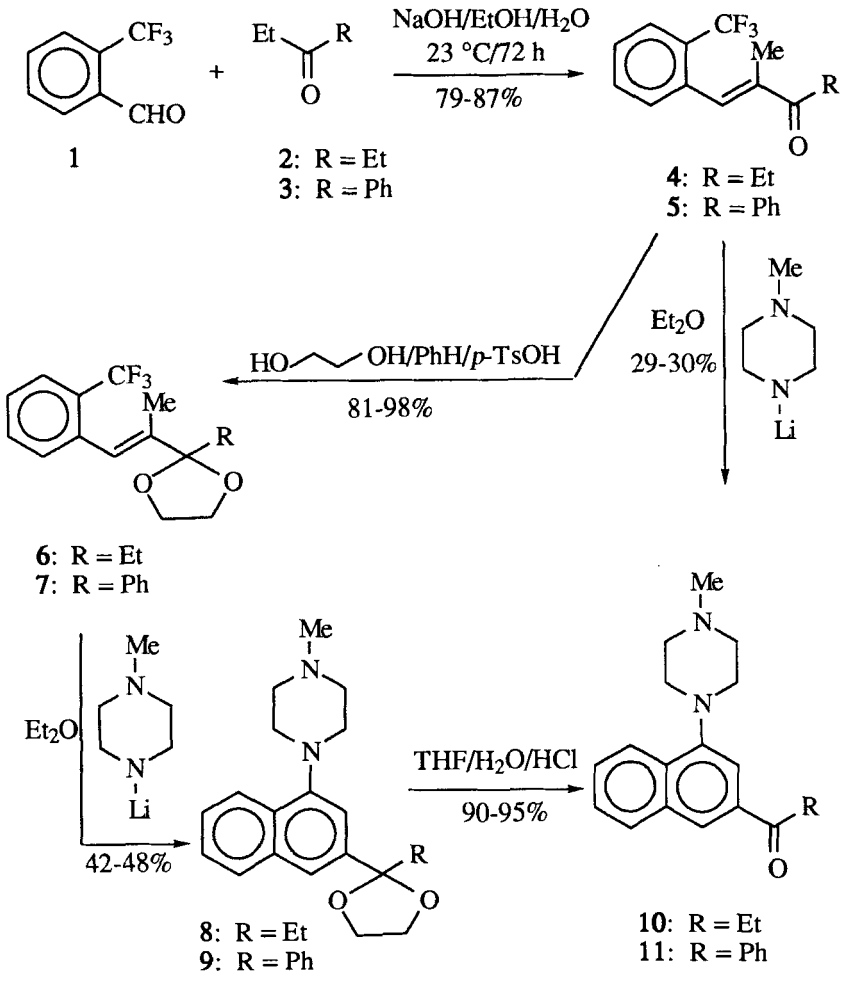
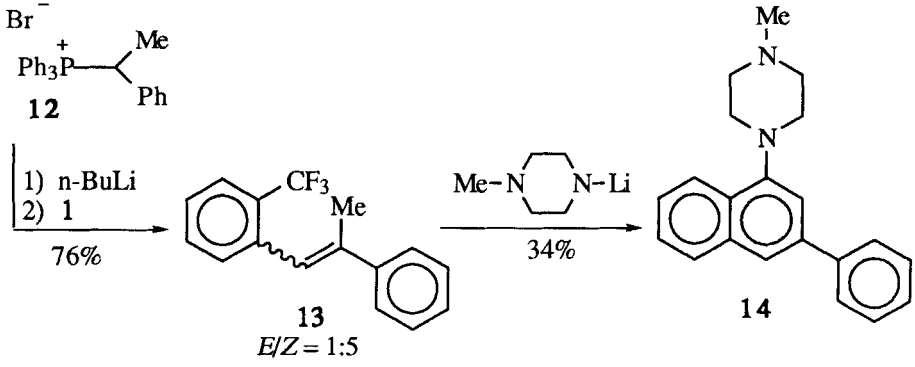
Scheme I



Enones **4** and **5** were obtained as single *E*-isomers by aldol condensation of 2-(trifluoromethyl)benzaldehyde (**1**) with ketones **2** and **3**, respectively. Treatment of **4** and **5** with lithium 4-methylpiperazide in ether furnished the naphthalenes **10** and **11**, respectively, in 29-30% yield. Compounds **10** and **11** were obtained by cyclization of **6**, **7** followed by hydrolysis of the acetal function in the cyclized products **8**, **9**. Although both synthetic routes give products **10**, **11** in

Scheme II

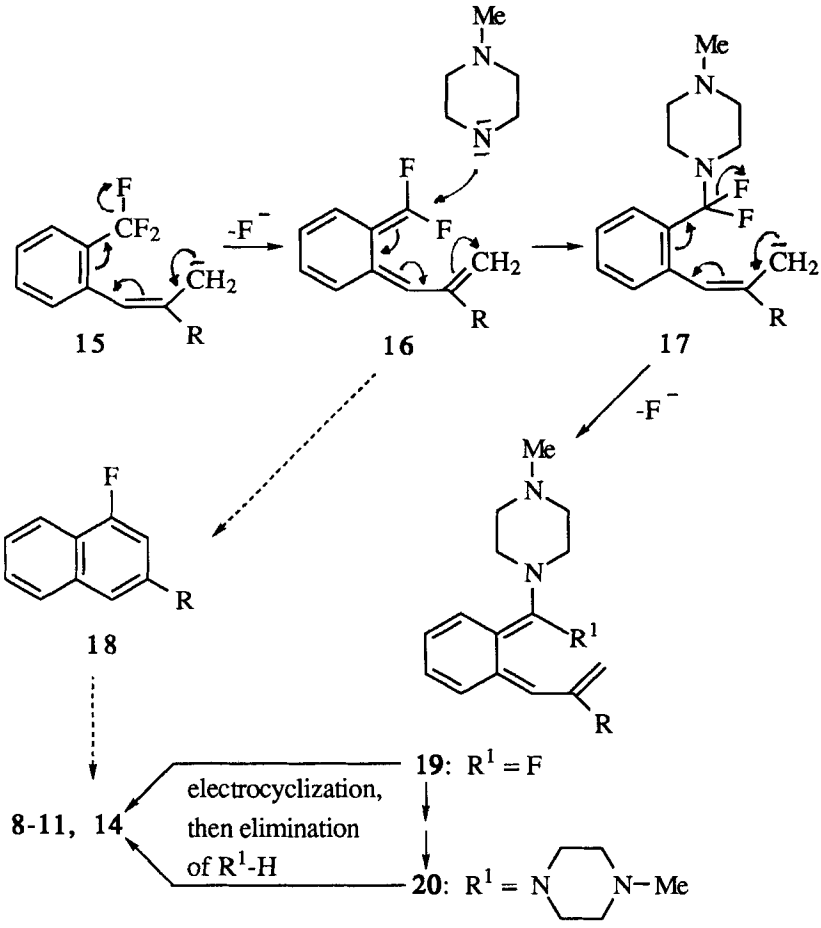


modest yields, the experimental facility of the cyclization method is remarkable. This cyclization approach provides a straightforward entry to naphthalenes containing an electron-donating dialkylamino group at position 1 and an electron-withdrawing acyl group at position 3, a previously unknown class of compounds.

The alkene derivative **13** required for the synthesis of **14** was obtained as an *E*/*Z* mixture of geometrical isomers (1:5) by a Wittig olefination of **1** (Scheme II). This mixture was separated by preparative gas chromatography. Interestingly, treatment of pure (*Z*)-**13**, pure (*E*)-**13** and an isomeric mixture with lithium 4-methylpiperazide all furnished the substituted naphthalene **14** in a similar yield of 30±3%. In all three cases quenching of the reactions before the substrate **13** had been consumed gave (*E*)-**13** and (*Z*)-**13** in a ratio of 1:5. These results demonstrate that the isomers of **13** undergo base-mediated equilibration[5] which is faster than cyclization.

A mechanism for the formation of **8-11**, **14** is proposed in Scheme III. It is suggested that an initial ionization of **4-7** and **13** to give **15** is followed by elimination of a fluoride ion to give a key intermediate product **16**. A subsequent fast addition reaction of an amide anion with **16** to give **17** is followed by elimination of fluoride to give **19**. A similar sequence of reactions with **19** then produces **20**. Both **19** and **20** may undergo electrocyclization to give the corresponding substituted 1,2-dihydronaphthalenes, the direct precursors to **8-11**, **14**. The suggested addition of **16** with an amide anion as the major reaction

Scheme III



pathway, rather than a direct electrocyclization of **16**, is strongly supported by other studies.[6,7]

Experimental Section

Ether was distilled from sodium benzophenone ketyl under a nitrogen atmosphere immediately before use. Chromatography was conducted on a

chromatotron with silica gel coated rotors. Unless otherwise stated, ^1H NMR and ^{13}C NMR spectra were obtained at 400 MHz and 68 MHz, respectively, in $CDCl_3$ solution with Me_4Si as an internal reference. Coupling constants smaller than 1 Hz are not reported. Chemical shift assignments for protons were obtained by decoupling and NOE experiments. The NOE experiments were also used for the determination of stereochemistry.

Preparation of Enones 4, 5. A solution of sodium hydroxide (0.6 g, 15 mmoles) in aqueous ethanol ($EtOH/H_2O$ = 5:3, 8 mL) was stirred at 0 °C and ketone (**2**, 0.86 g or **3**, 1.34 g, 10 mmol) was added dropwise. 2-Trifluoromethyl)benzaldehyde (**1**, 1.74 g, 10 mmol) was then added and the mixture was stirred at 23 °C for 4 days and the product extracted with ether (3x25 mL). The extract was washed with a saturated solution of NaCl, dried (Na_2SO_4), and concentrated. The oily residue of crude enone **4** or **5** was distilled on a Kugelrohr (120-140 °C/0.5 mmHg).

(*E*)-2-Methyl-1-[2-trifluoromethyl)phenyl]pent-1-en-3-one (4): Yield 2.14 g (87%); IR ν 1677 cm^{-1}; ^1H NMR δ 1.18 (t, J = 7.0 Hz, 3H, Me of Et), 1.85 (s, 3H, Me), 2.84 (q, J = 7.0 Hz, 2H, CH_2), 7.34 (d, J = 7.6 Hz, 1H, H-6 arom), 7.44 (t, J = 7.6 Hz, 1 H, H-5 arom), 7.71 (s, 1H, vinyl), 7.72 (d, J = 7.6 Hz, 1 H, H-3 arom); MS m/z 165, 185, 213 (100), 242 (M^+). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.45; H, 5.41. Found: C, 64.52; H, 5.45.

(*E*)-2-Methyl-1-phenyl-3-[2-trifluoromethyl)phenyl]prop-2-en-1-one (5): Yield 2.30 g (79%); IR ν 1651 cm^{-1}; ^1H NMR δ 2.03 (s, 3H, Me), 7.34 (s, 1H, vinyl), 7.42-7.50 (m, 3H, H-3, H-4, H-5 of Ph), 7.38 (d, J = 7.6 Hz, 1H, H-6 of $C_6H_4CF_3$), 7.53-7.61 (m, 2H, H-4 and H-5 of $C_6H_4CF_3$), 7.72 (d, J = 8.0 Hz, 1H, H-3 of $C_6H_4CF_3$), 7.81 (m, 2H, H-2 and H-6 of Ph); MS m/z 105 (100), 221, 290 (M^+). Anal. Calcd for $C_{17}H_{13}F_3O$: C, 70.34; H, 4.51. Found: C, 70.45; H, 4.52.

Preparation of 1,3-Dioxolanes 6, 7. Acetalization of ketones **4, 5** and workup were conducted by using a general procedure.[8] Crude compounds **6, 7** were purified by chromatography (hexanes/Et_3N, 19:1).

(*E*)-2-Ethyl-2-[1-methyl-2-[2-(trifluoromethyl)phenyl]vinyl]-1,3-dioxolane (6): Yield 81%; an oil; IR ν 1316 cm^{-1}; ^1H NMR δ 0.96 (t, J = 7.6 Hz, 3H), Me of Et), 1.63 (s, 3H, Me), 1.86 (q, J = 7.6 Hz, 2H, CH_2 of Et),

3.95 (m, 4H, dioxolane), 6.88 (s, 1H, vinyl), 7.25 (d, J = 7.6 Hz, 1H, H-6 arom), 7.34 (t, J = 7.6 Hz, 1H, H-5 arom), 7.49 (t, J = 7.6 Hz, 1H, H-3 arom); MS m/z 101, 165, 185, 213, 257 (100), 258; CI-MS m/z 287 (100, M^++1). *Anal.* Calcd for $C_{15}H_{17}F_3O_2$: C, 62.95; H, 5.09. Found: C, 62.87; H, 5.96.

(*E*)-2-[1-methyl-2-[2-(trifluoromethyl)pheny]vinyl]-2-phenyl-1,3-dioxolane (**7**): Yield 98%; an oil; IR ν 1315 cm^{-1}; ^1H NMR (60 MHz) δ 1.58 (s, 3H), 3.87 (m, 4H), 6.87-7.60 (m, 10H); MS m/z 149 (100), 257, 319, 334 (M^+). *Anal.* Calcd for $C_{19}H_{17}F_3O_2$: C, 68.25; H, 5.13. Found: C, 68.34; H, 5.12.

2-Phenyl-1-[2-(trifluoromethyl)phenyl]propene (**13**, an *E/Z* mixture). A solution of (1-phenylethyl)triphenylphosphonium bromide[9] (**12**, 2,7 g, 6.0 mmol) in ether (30 mL) was stirred under a nitrogen atmosphere and treated dropwise with a solution of *n*-butyllithium in hexanes (2.5 M, 2.4 mL, 6 mmol). The mixture was stirred at 23 °C for 3 h, treated with a solution of **1** (1.05 g, 6 mmol) in ether (5 mL) and stirred at 23 °C for an additional 10 h. Flash chromatography on silica gel with ether as an eluent was followed by concentration and then distillation on a Kugelrohr (120-130 °C/0.5 mm Hg) to give 1.2 g (76%) of **13** as an oil, *E/Z* = 1:5. *Anal.* Calcd for $C_{16}H_{13}F_3$: C, 73.27; H, 5.00. Found: C, 73.33; H, 5.04. Pure isomers were obtained by preparative GC on a Carbowax column.

(*Z*)-13: an oil; ^1H NMR δ 2.26 (s, 3H, Me), 6.73 (s, 1H, vinyl), 6.83 (d, J = 7.6 Hz, 1H, H-6 of $C_6H_4CF_3$), 7.06-7.20 (m, 7H, Ph and H-4, H-5 of $C_6H_4CF_3$), 7.58 (d, J = 7.6 Hz, H-3 of $C_6H_4CF_3$); MS m/z 178, 193, 227, 247, 262 (100, M^+).

(*E*)-13: an oil; ^1H NMR δ 2.08 (s, 3H, Me), 6.99 (s, 1H, vinyl), 7.32 (m, 2H, H-3 and H-5 of Ph), 7.35-7.41 (m, 3H, H-4 of Ph, H-4 and H-5 of $C_6H_4CF_3$), 7.52-7.57 (m, 3H, H-2 and H-6 of Ph, H-6 of $C_6H_4CF_3$), 7.70 (d, J = 7.6 Hz, H-3 of $C_6H_4CF_3$); MS m/z 178, 193, 227, 247, 262 (100, M^+).

Cyclization of Compounds 4-7, 13. A solution of *n*-butyllithium in hexanes (2.5 M, 3.0 mL, 7.5 mmol) was added dropwise to a stirred solution of *N*-methylpiperazine (0.9 mL, 8.1 mmol) in ether (15 mL) at -10 °C under a nitrogen atmosphere, and the mixture was stirred for 15 min before treatment with a solution of **4-7, 13** (1.15 mmol) in ether (5 mL). Stirring was continued at 23 °C for 2-3

days until a TLC analysis (hexanes/ether, 2:1) showed the absence of **4-7**, **13**. The mixture was quenched with water (0.2 mL), treated with hexanes (10 mL), dried (Na_2SO_4), filtered, and the solution was concentrated. Chromatography (THF/Et_3N, 3:1) gave **8-11**, **14**.

3-(2-Ethyl-1,3-dioxolan-2-yl)-1-(4-methylpiperazino)naphthalene (8): Yield 42%; mp 97-98 °C (from hexanes); ^1H NMR δ 0.92 (t, J = 7.2 Hz, 3H, Me of Et), 1.99 (q, J = 7.2 Hz, 2H, CH_2 of Et), 2.42 (s, 3H, N-Me), 2.72 (br, 4H, CH_2-3 and CH_2-5 of piperazine), 3.17 (br, 4H, CH_2-2 and CH_2-6 of piperazine), 3.83 (m, 2H, CH_2 of dioxolane), 4.06 (m, 2H, CH_2 of dioxolane), 7.16 (d, J = 1.6 Hz, 1H, H-2 arom), 7.44-7.49 (m, 2H, H-6 and H-7, arom), 7.63 (br, 1H, H-4 arom), 8.15 (m, 1H, H-8 arom); ^{13}C NMR δ 7.92, 33.26, 46.18, 50.63, 52.87, 55.63, 64.60, 110.92, 112.67, 120.21, 123.39, 125.34, 125.92, 128.32, 128.76, 134.21, 139.88, 149.66; MS m/z 226, 297, 326 (100, M^+). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03. Found: C, 73.53; H, 8.06.

1-(4-Methylpiperazino)-3-(2-phenyl-1,3-dioxolan-2-yl)naphthalene (9): Yield 48%; mp 107-109 °C (from hexanes); ^1H NMR δ 2.40 (s, 3H, N-Me), 2.68 (br, 4H, CH_2-3 and CH_2-5 of piperazine), 3.11 (br, 4H, CH_2-2 and CH_2-6 of piperazine), 4.11 (m, 4H, dioxolane), 7.21 (d, J = 1.6 Hz, 1H, H-2 of naphthalene), 7.27-7.35 (m, 3H, H-3, H-4 and H-5 of Ph), 7.42-7.48 (m, 2H, H-6 and H-7 of naphthalene), 7.55 (m, 2H, H-2 and H-6 of Ph), 7.70 (br, 1H, H-4 of naphthalene), 7.81 (m, 1H, H-5 of naphthalene), 8.13 (m, 1H, H-8 of naphthalene); ^{13}C NMR δ 30.27, 46.12, 52.74, 55.56, 64.91, 109.57, 113.05, 120.60, 123.37, 125.57, 125.96, 126.17, 128.06, 128.47, 128.91,134.16, 139.37, 141.92, 149.71; MS m/z 149, 226, 304, 359, 374 (100, M^+). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.97; H, 7.00. Found: C, 76.76; H, 7.09.

1-(4-Methylpiperazino)-3-propionylnaphthalene (10): Yield 30%; an oil; IR ν 1679 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.2 Hz, 3H, Me of Et), 2.43 (s, 3H, N-Me), 2.73 (br, 4H, CH_2-3 and CH_2-5 of piperazine), 3.13 (q, J = 7.2 Hz, 2H, CH_2 of Et), 3.19 (br, 4H, CH_2-2 and CH_2-6 of piperazine), 7.53 (t, J = 8 Hz, 1H, H-7 arom), 7.59 (t, J = 8 Hz, 1H, H-6 arom), 7.65 (d, J = 1.6 Hz, 1H, H-2 arom), 7.94 (d, J = 8 Hz, 1H, H-5 arom), 8.17 (br, 1H, H-4 arom), 8.19 (d, J = 8 Hz, H-8 arom) ; ^{13}C NMR δ 8.48, 31.66, 46.13, 52.74, 55.51, 112.17, 123.74,

125.27, 126.54, 127.72, 130.00, 131.14, 133.86, 134.39, 150.12, 200.92; MS m/z 70 (100), 71, 182, 282, (M^+). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85. Found: C, 76.65; H, 7.91.

3-Benzoyl-1-(4-methylpiperazino)naphthalene (11): Yield 29%; mp 127-129 °C (from hexanes); IR ν 1654 cm^{-1}; ^1H NMR δ 2.43 (s, 3H, Me), 2.73 (br, 4H, CH_2-3 and CH_2-5 of piperazine), 3.23 (br, 4H, CH_2-2 and CH_2-6 of piperazine), 7.48-7.55 (m, 3H, H-3, H-4 and H-5 of Ph), 7.42-7.48 (m, 2H, H-6 and H-7 of naphthalene), 7.55 (m, 2H, H-3, H-4 and H-5 of Ph), 7.57 (d, J = 1.6 Hz, 1H, H-2 of naphthalene), 7.58-7.64 (m, 2H, H-6 and H-7 of naphthalene), 7.86 (m, 2H, H-2 and H-6 of Ph), 7.88 (d, J = 8 Hz, 1H, H-5 of naphthalene), 7.92 (br, 1H, H-4 of naphthalene), 8.23 (d, J = 8 Hz, 1H, H-8 of naphthalene); ^{13}C NMR δ 46.16, 52.81, 55.51, 114.02, 123.76, 126.60, 127.71, 127.81, 128.22, 129.99, 130.88, 132.19, 133.51, 134.79, 137.99, 141.08, 150.13, 196.78; MS m/z 70, 105, 259, 300 (100, M^+). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.96; H, 6.71. Found: C, 79.93; H, 6.74.

1-(4-Methylpiperazino)-3-phenylnaphthalene (14): Yield 34%; an oil; ^1H NMR δ 2.44 (s, 3H, Me), 2.75 (br, 4H, CH_2-3 and CH_2-5 of piperazine), 3.23 (br, 4H, CH_2-2 and CH_2-6 of piperazine), 7.33 (d, J = 1.2 Hz, 1H, H-2 of naphthalene), 7.38 (t, J = 7.6 Hz, 1H, H-4 of Ph), 7.45-7.51 (m, 4H, H-3 and H-5 of Ph, H-6 and H-7 of naphthalene), 7.70 (d, J = 7.2 Hz, 2H, H-2 and H-6 of Ph), 7.75 (br, 1H, H-4 of naphthalene), 7.87 (m, 1H, H-5 of naphthalene), 8.19 (m, 1H, H-8 of naphthalene); ^{13}C NMR δ 46.13, 52.87, 55.62, 114.54, 121.44, 126.46, 125.34, 126.21, 127.31, 127.39, 127.99, 128.72, 128.78, 134.97, 138.66, 141.46, 150.05; MS m/z 71, 231, 287, 302 (100, M^+). Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33. Found: C, 83.67; H, 7.31.

Hydrolysis of Dioxolanes 8, 9. A general procedure[10] (5% HCl, THF/H_2O) was followed by neutralization of the mixture with Na_2CO_3, concentration, and extraction with ether to give **10, 11** in 90-95% yield.

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References and Notes

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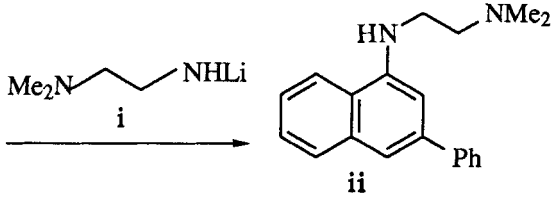

(5) The observed higher stability of **(*Z*)-13** is rather unusual, and we have conducted conformational searches using molecular mechanics and semi empirical methods for the two isomers. For details of the method, see: Wydra, R.L., Harden, D.B., Strekowski, L., Battiste, M.A., and Coxon, J.M., *Tetrahedron*, **1992**, *48*, 3485. The semi empirical method predicts that the aromatic rings in the lowest energy conformer of **(*E*)-13** are twisted from co-planarity with the central alkene moiety, but the twist does not preclude partial conjugation. By contrast, the aromatic rings in the lowest energy conformer of **(*Z*)-13** are virtually perpendicular to the alkene. Surprisingly, the calculated heats of formation for the lowest energy

conformers of **(*E*)-13** and **(*Z*)-13** are virtually identical (-100.3 ± 0.2 kcal/mol). These results are consistent with the presence of non-bonding electronic interactions between the phenyl group and the electron-deficient (trifluoromethyl)phenyl group that stabilize the *Z*-isomer.

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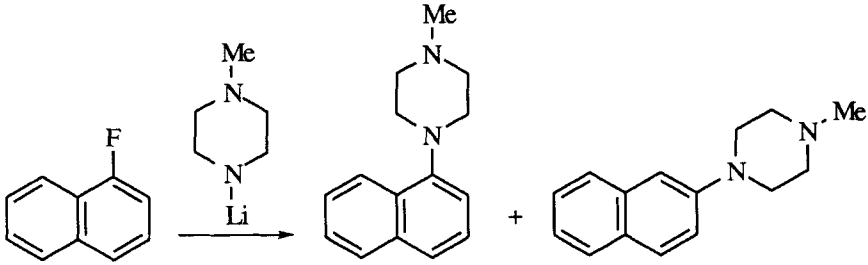
(7) 1-Fluoronaphthalene (**iii**) was allowed to react with lithium *N*-methylpiperazide under the conditions described for cyclization of **6-8**, **13** to give both **iv** (20%) and **v** (6%). The reaction rates for consumption of **iii** and cyclization of **6-8**, **13** were similar. These results together with GC-MS analyses of the cyclization mixtures, which did not show the presence of **18** (Scheme III) regardless of the reaction progress, strongly argue against **18** as the major reaction intermediate.



iii **iv** **v**

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