AMIDOMERCURATION-CYCLIZATION of *N-tert*-BUTOXYCARBONYL-2-ALLYLANILINE DERIVATIVES[1]

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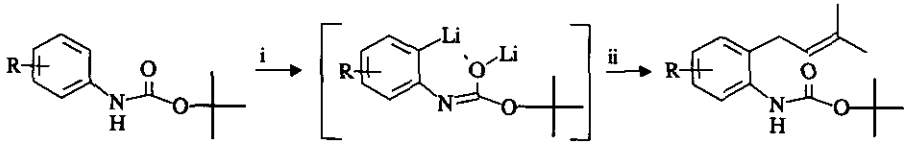
Abstract - Dilithation of *N-tert*-butoxycarbonylanilines with *tert*-butylithium followed by addition of 4-bromo-2-methyl-2-butene affords *N-tert*-butoxycarbonyl-2-(3,3-dimethylallyl)anilines (**3a-e**). The mercuric ion-initiated cyclization of compounds (**3a-e**) was investigated. *N*-tert-Butoxycarbonyl-4-chloro-2-(3-methyl-2-buten-1-yl)aniline (**3b**) and the 6-fluoro analogue (**3c**) readily undergo amidomercuration-cyclization to give *N-tert*-butoxycarbonyl-5-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (**4b**) and *N-tert*-butoxycarbonyl-8-fluoro-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (**4c**). Anilides (**3a, 3d-e**) gave a mixture of tetrahydroquinolines (**4a, 4d-e**) and the dihydroindoles (**5a, 5d-e**). *N*-Ethoxycarbonyl-2-(3-methyl-2-buten-1-yl)aniline (**3f**) gave mainly the *N*-ethoxycarbonyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (**4f**).

As a part of an ongoing research program in our laboratory, we needed a simple and a versatile procedure for the synthesis of 2,2-dimethyl-substituted tetrahydroquinolines. We envisioned using the amidomercuration-cyclization procedure[2] for the synthesis of this class of heterocycles.

A recently published report by Raner and Ward[3] prompts us to disclose the results of a related study from this laboratory. A previous report from this laboratory indicated that *N-tert*-butoxycarbonylaniline could be efficiently ortho-lithiated with *tert*-BuLi and quenched with an electrophile to afford ortho-functionalized aniline

derivatives.[4] We now report that initial treatment of carbamates (**1a-d**) in THF at -70 to -20 °C with 2.2 equiv. of *tert*-BuLi and subsequent quenching of the dilithiated species (**2**) with 4-bromo-2-methyl-2-butene gives ortho-allylaniline derivatives (**3a-d**). The regioselective dilithation of **1e**[5] in ether at -40 °C with 2.2 eqiv. of *n*-BuLi followed by reaction with 4-bromo-2-methyl-2-butene gave anilide (**3e**). Details of the synthesis and the structure of the compounds prepared by this method are summarized in Scheme 1 and Table 1.

Scheme 1



1 **2** **3**

Reagents and conditions: i, R'Li, THF (ether), -40 °C; ii, 4-bromo-2-methyl-2-butene.

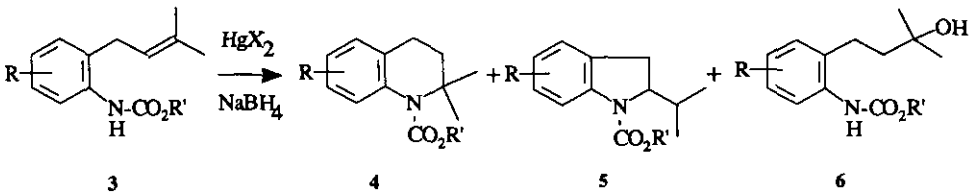
Table 1. Substituted 2-Allylanilides (**3a-e**)

Anilide	R	R'Li	Solvent	Product	Yield(%)[a]	mp(°C)
1a	H	*tert*-BuLi	THF	**3a**	55	oil
1b	4-Cl	*tert*-BuLi	THF	**3b**	81[b]	77
1c	6-F	*tert*-BuLi	THF	**3c**	93	74-76
1d	4-OMe	*tert*-BuLi	THF	**3d**	63[c]	74-75
1e	3,4-Dimethoxy	*n*-BuLi	Ether	**3e**	46[d]	74

[a]Isolated by flash chromatography on silica gel. Yields are not optimized. [b]89% based on recovery of starting material. [c]71% based on recovery of starting material. [d]68% based on recovery of starting material

It was expected that 2,2-dimethyl-substituted 1,2,3,4-tetrahydroquinoline derivatives could be formed by intramolecular amidomercuration of **3a-e**. Scheme 2 and Table 2 show the results from this reaction.

Scheme 2



3 4 5 6

Treatment of carbamate (**3b**) with 1 equiv. of mercuric trifluoroacetate in dry acetonitrile followed by reduction with $NaBH_4$ gave 2,2-disubstituted tetrahydroquinoline (**4b**) in moderate yield (Table 2, Entry 2), and 50% of the starting material was recovered. It was suggested[6] that addition of a base such as mercuric oxide might improve the results by scavenging trifluoracetic acid. However treatment of carbamate (**3b**) with mercuric trifluoroacetate, prepared *in situ* by addition of 1 equiv. of trifluoroacetic anhydride to a suspension of 2 equiv. of mercuric oxide in THF, gave a 1:3 mixture of tetrahydroquinoline (**4b**) and alcohol (**6b**). Surprisingly, replacement of mercuric trifluoroacetate with mercuric nitrate and using anhydrous acetonitrile as solvent gave an excellent yield of tetrahydroquinoline (**4b**) when mercuric oxide was added to the reaction mixture (Table 2, Entry 4). The 6-fluoro analogue (**3c**) gave tetrahydroquinoline (**4c**) in good yield under the same conditions (Table 2, Entry 5). On the other hand, compounds (**3a**, **3d**, **3e**, and **3f**) gave inseparable mixtures of the tetrahydroquinolines (**4**) and the dihydroindoles (**5**), the ratios of which were determined by 300 MHz ^{1}H Nmr (Table 2). The low regioselectivity observed for the cyclizations of (**3d**) and (**3e**) may reflect a change in the kinetic/thermodynamic product ratio of the reaction; it is plausible that such a change could arise out of the effect of electron-donation from a 4-methoxy group, which would ultimately make the anilide nitrogen atom more nucleophilic than in **3a-c**.

Table 2

Entry	3	R	R'	X	Product, Yield[a]		
					4	5	6
1	3a	H	*t*-Bu	NO_3	14[b]	28[b]	
2	3b	4-Cl	*t*-Bu	TFA	45		
3	3b	4-Cl	*t*-Bu	TFA/HgO	13		30
4	3b	4-Cl	*t*-Bu	NO_3/HgO	91		
5	3c	6-F	*t*-Bu	NO_3/HgO	89		
6	3d	4-OMe	*t*-Bu	NO_3/HgO	9[b]	32[b]	
7	3e	3,4-Dimethoxy	*t*-Bu	NO_3/HgO	20[b]	20[b]	
8	3f	H	Et	NO_3/HgO	81[b]	6[b]	

[a]Isolated by flash chromatography on silica gel. Yields are not optimized. [b]Inseparable mixture. Ratio of 4:5 determined by 300 MHz ^{1}H Nmr.

These results are complementary to the results obtained by Raner and Ward[3] who demonstrated that aminomercuration as well as iodine-induced cyclization of 2-(3-methylbut-2-enyl)aniline gave a good yield of the desired tetrahydroquinoline. They reported that anilides such as 2,2,2-trifluoro-*N*-[2-(3-methylbut-2-enyl)phenyl]acetamide and carbamates such as *N*-ethoxycarbonyl-2-(3-methyl-2-buten-1-yl)aniline (3f) gave alcohols derived from oxymercuration of the allyl group. Their explanation for the lack of cyclized products was that "the first mercury(II) complexes with the amide group rather than the alkene side chain. Use of excess mercuric acetate failed to cause cyclization. It is possible that the mercury(II) complexed trifluoroacetamido group is too large for it to behave as an intramolecular nucleophile". However our results show that increasing the nucleophilicity of the amide nitrogen by using a *tert*-butoxy-or ethoxycarbamate, using anhydrous solvent and the use of mercuric oxide enables the cyclization reaction to occur.

The above results demonstrate the scope and some of the limitations of applying the amidomercuration-cyclization procedure to the synthesis of substituted 2,2-dimethyl-1,2,3,4-tetrahydroquinolines.

EXPERIMENTAL

***N-tert*-Butoxycarbonyl-6-chloro-2-(3,3-dimethylallyl)aniline (3b).** A solution of **1b** (0.23 g, 1 mmol) in 2 ml of THF was cooled to -70 °C and 1.3 ml of 1.7 M *tert*-BuLi (2.2 mmol) in pentane was added at such a rate as to maintain the internal temperature below -65 °C. After stirring for 5 min at -20 °C the yellow solution was treated with 4-bromo-2-methyl-2-butene (0.36 g, 2.2 mmol) and allowed to warm to ambient temperature. After stirring for an additional 5 min, saturated ammonium chloride (1 ml) was added and the mixture was extracted with ethyl acetate (3 x10 ml). The organic phase was dried over K_2CO_3, filtered and evaporated. Purification of the residue by flash chromatography on silica gel (5% ethyl acetate-hexane) afforded 0.24 g (81%) of amide (**3b**) and 0.02 g of starting material (**1b**). Crystallization of (**3b**) from hexane gave colorless needles, mp 77 °C: ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.51 (s, 9H); 1.77 (d, 3H, J=1.0); 1.79 (s, 3H); 3.25 (d, 2H, J= 7.2); 5.16 (m, 1H); 6.50 (s, 1H); 7.11 (d, 1H, J=2.5); 7.15 (dd, 1H, J_1=8.6, J_2= 2.5); 7.18 (dd, 1H, J_1=8.6, J_2= 2.6); 7.76 (d, 1H, J=8.6). *Anal.* Calcd for $C_{16}H_{22}NO_2Cl$: C, 64.97; H ,7.50; N, 4.74. Found: C, 65.07; H, 7.49; N, 4.78.

By similar means the following compunds were prepared.

***N-tert*-Butoxycarbonyl-2-(3,3-dimethylallyl)aniline (3a).** (55%) ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.53 (s, 9H); 1.79 (s, 3H); 1.83 (s, 3H); 3.31 (d, 2H, J=7.31); 5.22 (m, 1H); 6.57 (br s, 1H); 7.05 (td, 1H, J_1=7.5, J_2=1); 7.16 (dd, 1H, J_1=6.1, J_2=1); 7.23 (td, 1H, J_1=7.5, J=1); 7.81 (br d, 1H, J=7.5).

***N-tert*-Butoxycarbonyl-6-fluoro-2-(3,3-dimethylallyl)aniline (3c).** (93%) mp 74-76 °C: ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.52 (s, 1H); 1.77 (d, 6H, J=1.51); 3.36 (d, 2H, J=7.24); 5.21 (m, 1H); 5.93 (s, 1H); 6.99 (m, 2H); 7.15 (m, 1H). *Anal.* Calcd for $C_{16}H_{22}NO_2F$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.94; H, 8.39; N, 4.92.

***N-tert*-Butoxycarbonyl-4-methoxy-2-(3,3-dimethylallyl)aniline (3d).** (63%) mp 74-75 °C: ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.52 (s, 9H); 1.78 (s, 3H); 3.28 (d, 2H, J=7.25); 3.80 (s, 3H); 5.21 (m, 1H); 6.30 (br s, 1H); 6.74

(m, 1H); 7.56 (m, 1H). *Anal.* Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.55; H, 8.88; N, 4.69.

***N-tert*-Butoxycarbonyl-3,4-methoxy-2-(3,3-dimethylallyl)aniline (3e).** (46%) mp 73.7-74.5 °C: ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.52 (s, 9H); 1.75 (d, 3H, J=0.9); 1.86 (s, 3H); 3.39 (d, 2H, J=7.05); 3.80 (s, 3H); 3.86 (s, 3H); 5.08 (dd, 1H, J_1=7.08, J_2=1.0); 6.38 (br s, 1H); 6.76 (d, 1H, J=8.97); 7.40 (br d, 1H). *Anal.* Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.24; H, 8.43; N, 4.34.

***N-tert*-Butoxycarbonyl-5-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4b).** A solution of **3b** (3.68 g, 12.4 mmol) in acetonitrile (10 ml) was added to a suspension of mercuric nitrate monohydrate (4.26 g, 12.4 mmol) and mercuric oxide (yellow, 2.7 g , 12.41 mmol) in anhydrous acetonitrile (10 ml). The reaction mixture was stirred for 30 min. Saturated sodium acetate solution in water (10 ml) and 5% aqueous KOH (10 ml) were added and the mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C and a solution of sodium borohydride (7.4 g, 195 mmol) in 5% KOH (20 ml) was added dropwise. The solution was stirred at ambient temperature for 30 min and then diluted with ethyl acetate. The two layers were separated and the organic phase was washed with saturated sodium bicarbonate solution, dried over potassium carbonate, filtered and concentrated. Purification by flash chromatography on silica gel (230-400 mesh Merck Kieselgel) (2% ethyl acetate-hexane) gave 3.36 g (91%) of *N-tert*-butoxycarbonyl-5-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (**4b**). Crystallization from hexane afforded colorless needles, mp 84-85 °C; ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.50 (s, 9H); 1.56 (s, 6H); 1.73 (m, 2H); 2.55 (m, 2H); 7.08 (m, 1H); 7.06 (d, 1H, J=2.4); 7.26 (d, 1H, J=6.5). *Anal.* Calcd for $C_{16}H_{22}NO_2Cl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.89; H, 7.50; N, 4.82. On the other hand when mercuric trifluoroacetate was used instead of mercuric nitrate compound (**3b**) gave a 1:3 mixture of **4b** and **6b**. Compound (**6b**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.29 (s, 6H); 1.50 (s, 9H); 1.70 (m, 3H, OH and CH_2); 2.63 (m, 2H); 7.06 (br s, 1H, NH); 7.10 (d, 1H,

J=2.4); 7.16 (dd, 1H, J_1=8.5, J_2=2.4); 7.75 (br d, 1H, J=8.5).

By similar means the following compunds were prepared.

***N-tert*-Butoxycarbonyl-8-fluoro-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4c).** (89%) mp 108-110 °C (pentane). ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H); 1.60 (s, 6H); 1.74 (m, 2H); 2.63 (m, 2H); 6.87 (m, 3H). *Anal.* Calcd for $C_{16}H_{22}NO_2F$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.75; H, 7.97; N, 5.02.

***N-tert*-Butoxycarbonyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4a)** and ***N-tert*-butoxycarbonyl-2-isopropyl-2,3-dihydroindole (5a)** (40%) as a 1:4 mixture of **5a/4a**. Compound (**4a**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.51 (s, 9H); 1.74 (m, 2H); 2.58 (m, 2H); 7.04 (m, 3H); 7.29 (d, 1H, J=7.5). Compound (**5a**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 0.71 (d, 3H, J=6.7); 0.99 (d, 3H, J=7.0); 1.56 (s, 9H); 2.24 (m, 1H); 2.80 (dd, 1H, J_1=16.4, J_2=2.7): 3.14 (dd, 1H, J_1=16.4, J_2=10.1); 4.33 (m, 1H); 6.91 (m, 2H).

***N-tert*-Butoxycarbonyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4d)** and ***N-tert*-butoxycarbonyl-2-isopropyl-5-methoxy-2,3-dihydroindole (5d)** (41.4%) as a 1:3.5 mixture of **4d/5d**. Compound (**4d**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.52 (s, 9H); 1.74 (m, 2H); 2.57 (m, 2H); 3.79 (s, 3H); 6.61 (d, 1H, J=3.0); 6.68 (m, 1H); 7.24 (d, 1H, J=8.9). Compound (**5d**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 0.73 (d, 3H, J=6.7); 0.92 (d, 3H, J=6.7); 1.58 (s, 3H); 2.24 (m, 1H); 2.78 (dd, 1H, J_1=16.5, J_2=2.6); 3.15 (dd, 1H, J_1=16.5, J_2=10.0); 3.79 (s, 3H); 4.35 (m, 1H); 6.69 (m, 3H).

***N-tert*-Butoxycarbonyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4e)** and ***N-tert*-butoxycarbonyl-2-isopropyl-5-methoxy-2,3-dihydroindole (5e)** (55.8%) as a 1:1 mixture of **4e/5e**. Compound (**4e**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.26 (s, 9H); 1.71 (m, 2H); 2.66 (m, 2H); 3.85 (s, 3H); 3.86 (s, 3H); 6.70 (d, 1H,

J=9.1); 6.72 (d, 1H, J=8.7). Compound (**5e**): ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 0.73 (d, 3H, J=6.8); 0.93 (d, 3H, J=6.9); 1.57 (s, 9H); 2.24 (m, 1H); 2.87 (dd, 1H, J_1=16.7, J_2=2.7); 3.10 (dd, 1H, J_1=16.7, J_2=9.9); 3.84 (s, 3H); 3.86 (s, 3H); 4.37 (m, 1H); 6.72 (d, 1H, J=8.9).

***N*-Ethoxycarbonyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (4f).** ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.29 (t, 3H, J=7.1); 1.59 (s, 9H); 1.75 (m, 2H); 2.59 (m, 2H); 4.21 (q, 2H, J=7.1); 6.97 (m, 1H); 7.09 (m, 2H); 7.27 (m, 1H).

ACKNOWLEDGMENT

We wish to thank Dr. J. M. Muchowski, Dr. R. D. Clark, Dr. L. A. Flippin and Professor E. J. Corey for helpful discussions during the course of this work.

REFERENCES AND NOTES

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Received, 11th March, 1993