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A Facile Synthesis of 2-Substituted N-tert-Butoxycarbonyl-N-methyl-1,3-propanediamines, Key Intermediates for the Preparation of Triplex DNA-Specific Intercalators

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Summary: N-substituted 2-(2-naphthyl)quinolin-4-amines **4b,c** are superior to other DNA intercalators reported to date in the ability to selectively stabilize triple helix DNA in the presence of duplex DNA. A facile synthesis of the title diamines 1 required for the preparation of 4 is based on a novel addition reaction of metallated tert-butyl N,N-dimethylcarbamate [Boc-N(Me)CH₂M; 7, M = Li; 8, M = MgBr; 9, M = Cu(CN)ZnCI] with a nitroalkene.

The triplex DNA structure is formed by binding of a single stranded DNA in the major groove of the DNA double helix.¹ The triplex formation is specific in that it requires appropriate nucleotide sequences of the duplex and the single strand. The interaction is rather weak at physiological conditions but can be enhanced by certain nucleic acid intercalators termed antigene enhancers.² The therapeutic potential of the triplex interactions and stabilization is enormous. Intense research is underway to selectively target regions of known sequences on specific genes with synthetic complementary oligonucleotides or analogs³ and find antigene enhancers^{2,4} that strongly stabilize the resultant triplex forms as a means to inhibit expression of the specific genes.

As part of our efforts to enhance the therapeutic applications of oligonucleotides, we are pursuing the design of compounds that provide selective stabilization of triplexes relative to duplexes.² In this paper we report that quinoline derivatives 4 (eq 1) are triplex intercalators with a negligible affinity toward duplexes.



More importantly, our Tm measurements⁵ and footprinting studies⁶ show unambiguously that compounds **4b,c** are far superior in their triplex stabilization ability and the triplex/duplex binding selectivity than any other triplex intercalators reported to date.^{2,4} Preliminary modeling studies are consistent with intercalation of the quinoline portion of **4** between base-pairs of the duplex in the triplex, stacking of the 2-naphthyl substituent with bases of the third DNA strand, and location of the amino side chain in the minor groove. The terminal methylamino moiety of the side chain is protonated under normal conditions (pH 7), which provides electrostatic stabilization of the complex by electrostatic interaction with the anionic DNA backbone. An additional stabilization of the complex results from van der Waals contacts of the substituents R¹ or R¹R² with the minor groove.

A straightforward synthesis of 4 by the reaction of 1,3-diamine derivatives 1 with 4-halogeno-2-(2-naphthyl)quinoline,⁷ such as 2, followed by deprotection of the resultant products 3 is given in eq. 1. A novel synthesis of 1, a previously unknown class of compounds, is given in Scheme 1. The synthetic approach to 1



Scheme 1*

*Keys: (i) *s*-BuLi, TMEDA, Et₂O, -78 °C, 2h, then Bu₃SnCl, -78 °C \rightarrow 25 °C; (ii) *n*-BuLi, THF, -78 °C, 1 h; (iii) MgBr₂; (iv) ZnCl₂, CuCN•2LiCl; (v) 1 atm H₂, PtO₂, EtOH, 25 °C, 12 h, or N₂H₄•H₂O, MeOH, Raney-Ni, 25 °C, 12 h; (vi) CH₂Cl₂/CF₃COOH (2:1), 25 °C, 1 h. involves a sequence of activation of dimethylamine toward deprotonation at a carbon atom, generation of a dipole-stabilized carbanion, a conjugate addition of the anion with a nitroalkene, and then reduction of the nitro group. Although several functionalities at the nitrogen atom of secondary amines have been reported to facilitate deprotonation at the α position of the amines,⁸ the choice of a Boc group seemed to be particularly attractive due to the convenience of its addition/removal and stability in the required transformations. Reactions of lithium derivatives of Boc-substituted secondary amines with several electrophiles are known⁹ but a conjugate addition with nitroalkenes has not been reported previously. Studies of the reactions with electrophiles of other organometallic reagents derived from *tert*-butyl carbamates such as **5** (Scheme 1) are scarce.^{9e}

The treatment of **5** with s-BuLi followed by a reaction of the resultant reagent **7** with nitroalkene **10a** at -100 °C gave the conjugate addition product **11a** in a low yield. The reaction was even less efficient at -78 °C, and similar results were obtained with other aryl-substituted nitroalkenes. By contrast, an indirect generation⁹e of **7** by a sequence of the lithiation of **5**, preparation and purification of a tin derivative **6**, transmetallation of **6**, followed by the addition reaction of **7** with **10a** at -100 °C gave **11a** in a respectable yield¹⁰ of 78% (entry 1 in Table). Again, increasing the temperature to -78 °C resulted in a sharp decrease of the efficiency of the last addition step (entry 2). Because of the inconvenience of working at temperatures below -78 °C, we have examined the addition reactions of other organometallic reagents derived from **7**. As can be seen from Table, excellent results are obtained at -78 °C for the addition with 1-aryl-2-nitroethylenes **10a,b** (entries 3, 5) of the apparent reagent **8** generated from **7** and MgBr₂. Low yield of the aliphatic adduct 11c obtained by the reaction of **10c** with **8** (entry 6) is substantially increased for the addition conducted with a Cu-Zn reagent^{11,12} **9** (entry 7). Interestingly, these reactions are completely stereoselective giving a single cis isomer¹³ **11c**. Aryl-substituted nitroalkenes also undergo the addition with **9** (entry 4). These facile and efficient reactions of **9** are highly rewarding in light of the recent report that similar Cu-Zn organometallics bearing a heteroatom such as S, N or B at the α carbon atom are inert in attempted reactions with nitroalkenes.¹⁴

	entry	substrates		conditions		product	yield (%)
				temp. (°C)	time (h)		
	1	10a	7	-100	0.25	11 a	78
	2	10a	7	-78	0.25	11 a	60
	3	10a	8	-78	1.0	11 a	83
	4	10a	9	-78 → 0	5.0	11a	84
	5	10b	8	-78	1.0	11b	86
	6	10c	8	-78 → 25	3.0	11c	42
	7	10c	9	-78 → 25	48.0	11c	62

Table. The addition reaction of organometallic reagents¹² 7-9 with nitroalkenes 10a-c

In summary we have described a novel conjugate addition reaction of metal derivatives 7-9 of tert-butyl N,N-dimethylcarbamate with nitroalkenes, which produces N-Boc substituted nitro amines 11. The Boc group serves a dual purpose as (i) an activating functionality in the substrate 5 toward metallation and (ii) a standard protecting group in the transformations of the addition products 11. The described conjugate addition is of a broad synthetic scope. Products 11 are easily hydrolyzed to nitro amines, such as 12 in Scheme 1, and the well-known conversions of nitroalkanes to ketones, alcohols, and nitrile oxides, to name a few,^{14,15} allow one to consider the conjugate addition products 11 as versatile synthons for a variety of functionalized secondary amines. The generality of these chemistries is further expanded by the reported successful lithiation of tert-butyl carbamates derived from other secondary amines.⁹ Finally, we wish to stress our finding that the Cu-Zn reagent 9 of a relatively low reactivity and, as such compatible with many functional groups, undergoes an efficient addition reaction with aliphatic and aromatic nitroalkenes.

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- Compound, ΔTm for triplex: 4a, 29 °C; 4b, 36.7 °C; 4c, 40.1 °C.
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- 10. All reported yields are for isolated products 1, 3, 4, 11, 12. These compounds were homogeneous on TLC with several eluent systems and were characterized by HRMS, ¹H NMR (400 MHz), and ¹³C NMR (98 MHz). Compound, mp: 4a, 114-116 °C; 4b, 142-145 °C; 4c, 82-84 °C. The remaining compounds are oils.
- 11. The Cu-Zn reagent 9 was generated by modification of a general procedure (ref. 14). The following synthesis of 11a is representative. n-BuLi (2.5 M in hexanes, 1.4 mmol) was added at -78 °C to a solution of 6 (ref. 9e, 1.5 mmol) in THF (6 mL), and the resultant mixture was stirred at -78 °C for 1h before treatment with ZnCl₂ (0.5 M in THF, 1.4 mmol). After 10 min at -78 °C the mixture was treated with CuCN•2LiCl (ref. 14, 0.4 M in THF, 1.5 mmol), stirred at 0 °C for 10 min, cooled to -78 °C, and then treated with a solution of 10a (1.0 mmol) in THF (4 mL). Stirring was continued at 0 °C for 5h, after which time the mixture was cooled to -78 °C and quenched with AcOH/THF (1:2). Chromatography on
- silica gel with hexanes/AcOEt (4:1) as an eluent gave 0.29 g (84%) of **11a**. 12. Addition reactions of other organometallic reagents, namely RZnCl, R₂Zn, R₃ZnLi, R₂CuLi, R₂Cu(CN)Li₂, and RCu(CN)Li, with 10 were attempted. All these reactions produced 11 in low yields and/or mixtures that were difficult to separate.
- 13. NOE and decoupling experiments gave J = 4 Hz between H1 (δ 2.27) and H2 (δ 4.63) in the ¹H NMR spectrum of 11c (400 MHz, DMSO).
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