Radical Mediated Synthesis of 6-Arylphenanthridines via Benzotriazole Ring-opening

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Submitted in honor of the memory of Nicholas Alexandrou, fine chemist and true friend

Lithiation of diarylbenzotriazol-1-ylmethanes followed by addition of copper(I) iodide gave 6-arylphenanthridine derivatives in moderate yields. When the two aryl groups were the same or contained very different electron densities, only one product was obtained. However, when the two aryl groups exhibited electron densities of similar magnitude, two isomers were afforded. According to the substituent effect, we believe that the reactions proceed *via* radical intermediates formed by copper(I) iodide.

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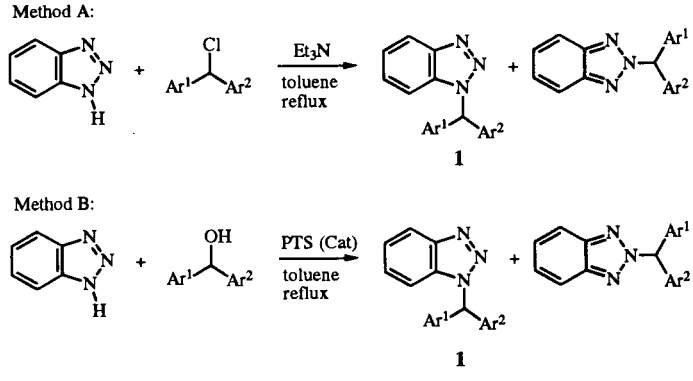
Phenanthridine derivatives are of importance for their antibacterial activity [1], antiseptic properties [2], ability to inhibit glutamic dehydrogenase [3], etc. Many methods for the synthesis of phenanthridine derivatives have been documented and the majority may be classified into the following four types: (i) from biphenyls by formation of a C-N heterocyclic ring bond [4-6], (ii) from Ph-N-C-Ph derivatives by formation of a C-C heterocyclic ring bond [7], (iii) from the condensation of two types of aryl derivatives to form a six-membered ring [8-10], and (iv) from preexisting tricyclic systems [11-12]. Synthetic procedures for phenanthridine involving radical intermediates have appeared in the literature. Prabhakar *et al* reported that phenanthridine could be synthesized by intramolecular addition of aryl radicals to the *ortho*-position of an aryl ring bearing a nitrogen atom [7]. Zanardi *et al* constructed the heteroaromatic ring in phenanthridine *via* imidoyl radicals initiated by diisopropyl peroxydicarbonate [13].

In the literature, there are many methods for generating radicals, including the oxidation of a carbanion by a metal ion with one electron transfer [14]. It is well known that the benzotriazolyl group can stabilize α-carbanions due to its electron-withdrawing ability. Lithiation of alkyl benzotriazoles provides α-benzotriazolyl carbanions which can potentially transfer an electron to metal ions to form radical species. We now describe a new radical mediated method for the synthesis of 6-arylphenanthridine derivatives using a benzotriazole ring-opening reaction.

Scheme 1



Results and Discussion.

Diaryl(benzotriazol-1-yl)methanes **1** were prepared by reaction of benzotriazole with diaryl methyl halide (Method A) or diaryl methanol (Method B) in good yields (Scheme 1, Tables 1, 2, and 5).

Lithiation of diaryl(benzotriazol-1-yl)methanes **1** in tetrahydrofuran followed by the addition of copper iodide at -78° and heating under reflux gave phenanthridine derivatives **2** in moderate yields (Scheme 2 and Tables 3, 4, and 5).

Table 1

Diaryl(benzotriazol-1-yl)methanes **1** Prepared

No.	Ar^1	Ar^2	Method	Time (hours)	Yield (%)	Mp (°C)	Lit Mp (°C)
1a	Ph	Ph	A	10	70	158	155 [15]
1b	p-ClC_6H_4	Ph	A	5	70	143 [a]	–
1c	p-MeC_6H_4	Ph	B	20	76	108 [a]	–
1d	p-ClC_6H_4	p-ClC_6H_4	B	20	56	109	105 [15]
1e	p-FC_6H_4	p-FC_6H_4	A	2	50	111 [a]	–
1f	Dibenzosuberane		A	5	53	144 [a]	
1g	p-$NMe_2C_6H_4$	Ph	B	5	67	156 [a]	–
1h	p-MeC_6H_4	p-MeC_6H_4	B	5	66	65-67 [a]	–

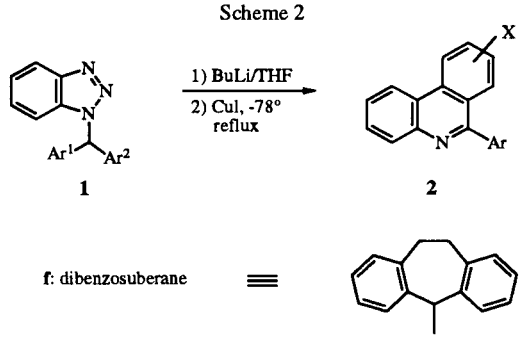
[a] Satisfactory CHN analyses (< 0.4%) obtained for all new compounds (see Table 5).

Table 2

Nmr Data of Compounds **1** (ppm, J Hz)

No.	^{1}H Nmr	^{13}C Nmr
1a	8.12-8.06 (m, 1 H), 7.39 (s, 1 H), 7.38-7.31 (m, 8 H), 7.26-7.20 (m, 4 H), 7.12-7.07 (m, 1 H)	146.3, 137.6, 133.0, 128.8, 128.4, 128.3, 127.3, 123.8, 120.1, 110.5, 67.1
1b	8.00-7.95 (m, 1 H), 7.30-7.18 (m, 8 H), 7.12-7.00 (m, 5 H)	146.2, 137.2, 136.2, 134.4, 132.8, 129.7, 128.9, 128.8, 128.6, 128.1, 127.5, 126.5, 124.0, 120.1, 110.2, 66.3
1c	8.02-7.97 (m, 1 H), 7.28-7.21 (m, 6 H), 7.14-7.00 (m, 7 H), 2.25 (s, 3 H)	146.3, 138.3, 137.9, 134.6, 133.0, 129.4, 128.7, 128.3, 128.1, 127.2, 123.8, 120.1, 110.6, 66.9, 21.1
1d	8.09-8.06 (m, 1 H), 7.37-7.28 (m, 7 H), 7.19-7.12 (m, 5 H)	146.2, 135.8, 134.5, 132.7, 129.5, 129.3, 129.0, 127.6, 124.1, 120.2, 110.0, 65.5
1e	8.12-8.08 (m, 1 H), 7.41-7.35 (m, 2 H), 7.30 (s, 1 H), 7.21-7.00 (m, 9 H)	164.3, 148.3, 140.6, 133.5, 130.1, 129.9, 127.6, 124.0, 123.9, 120.4, 116.0, 115.7, 110.1, 65.7
1f	8.01 (d, 1 H, J = 8.1), 7.51 (d, 2 H, J = 7.2), 7.33-7.17 (m, 8 H), 6.75 (d, 1 H, J = 8.3), 6.68 (s, 1 H), 3.09-2.95 (m, 2 H), 2.85-2.75 (m, 2 H)	146.4, 140.4, 134.7, 133.0, 131.1, 131.0, 129.4, 126.9, 126.5, 123.6, 119.9, 111.0, 71.2, 31.6
1g	8.09-8.05 (m, 1 H), 7.35-7.31 (m, 5 H), 7.30 (s, 1 H), 7.20-7.17 (m, 2 H), 7.13-7.10 (m, 1 H), 7.12 and 6.67 (AB, 4 H, J = 8.4), 2.94 (s, 3 H)	59.0, 146.4, 138.6, 133.0, 129.5, 128.6, 128.0, 127.9, 127.1, 123.6, 120.0, 112.2, 110.9, 67.0, 40.3
1h	8.09-8.05 (m, 1 H), 7.34-7.28 (m, 3 H), 7.15 and 7.13 (AB, 8 H, J = 8.0), 7.14-7.11 (overlapped with AB, m, 1 H), 2.35 (s, 1 H)	146.3, 138.2, 134.9, 133.0, 129.4, 128.2, 127.2, 123.7, 120.1, 110.7, 66.8, 21.1

Scheme 2



Interestingly, in the absence of copper iodide, a large proportion of the ring opened product (*N*-phenyldiarylketimine) was generated and only small quantities of the phenanthridine derivatives were obtained. When Ar^1 and Ar^2 were different but of a similar electronic nature, two isomers were formed in comparable quantities. Such mixtures were difficult to separate by column chromatography. Thus, when (4-methylphenyl)phenyl(benzotriazol-1-yl)methane (**1c**) was treated with copper iodide, a mixture (**2c**) of the two isomeric compounds, 9-methyl-6-phenylphenanthridine and 6-(4-methylphenyl)phenanthridine was generated. However, when Ar^1 and Ar^2 were of dramatically different electron densities, ring closure took place preferentially on the ring with the lower electron density, and only one product was isolated. For example, (4-*N*,*N*-dimethylaminophenyl)(benzotriazol-1-yl)phenylmethane (**1g**) gave only one product, 6-(4-*N*,*N*-dimethylaminophenyl)phenanthridine (**2g**) in low yield.

From Table 3, it is evident that the yields of cyclized product do not depend in any rational manner on the electronic nature of the substituents in the nucleus undergoing

Table 3

Phenanthridines **2** Prepared [a]

No.	Ar^1	Ar^2	Time (hours)	Ar	X	Yield (%)	Mp (C)
2a	Ph	Ph	5	Ph	H	55	105-106 [13]
2b$_1$	*p*-ClC_6H_4	Ph	6	Ph	9-Cl	20 [b]	147-148
2b$_2$				*p*-ClC_6H_4	H	25 [b]	164-165 [13]
2c	*p*-MeC_6H_4	Ph	5	Ph	9-Me	50 [c]	oil
				p-MeC_6H_4	H		
2d	*p*-ClC_6H_4	*p*-ClC_6H_4	5	*p*-ClC_6H_4	9-Cl	57	218-219 [13]
2e	*p*-FC_6H_4	*p*-FC_6H_4	4	*p*-FC_6H_4	9-F	36	186-188
2f		Dibenzosuberane	8	Dibenzosuberane		39	102-104
2g	*p*-$NMe_2C_6H_4$	Ph	12	*p*-$NMe_2C_6H_4$	H	7	182-183
2h	*p*-MeC_6H_4	*p*-MeC_6H_4	5	*p*-MeC_6H_4	9-Me	48	oil

[a] Satisfactory CHN analyses (< 0.4%) obtained for all new compounds (see Table 5). [b] Separated by recrystallization. [c] Mixture of 60% 6-(*p*-methylphenyl)phenanthridine and 40% 9-methyl-6-phenylphenanthridine which was difficult to separate.

Table 4

Nmr Data of Compounds **2** (ppm, J Hz)

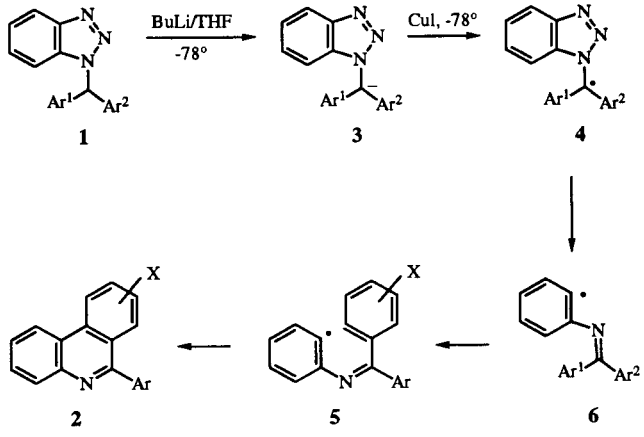
No.	^{1}H Nmr	^{13}C Nmr
2a	8.68 (d, 1 H, J = 8.1), 8.60 (d, 1 H, J = 7.8), 8.23 (d, 1 H, J = 8.0), 8.08 (d, 1 H, J = 8.2), 7.84 (t, 1 H, J = 8.2), 7.77-7.64 (m, 3 H), 7.62-7.50 (m, 5 H)	161.3, 143.8, 139.8, 133.4, 130.5, 130.3, 129.7, 128.9, 128.8, 128.7, 128.4, 127.1, 126.9, 125.2, 123.7, 122.2, 121.9
2b	6-phenyl-9-chlorophenanthridine (**2b$_1$**) 8.57 (s, 1 H), 8.44 (d, 1 H, J = 7.8), 8.21 (d, 1 H, J = 7.8), 7.99 (d, 1 H, J = 7.8), 7.78-7.64 (m, 4 H), 7.54-7.47 (m, 4 H) 6-(*p*-chlorophenyl)phenanthridine (**2b$_2$**) 8.67 (d, 1 H, J = 8.3), 8.59 (d, 1 H, J = 8.3), 8.21 (d, 1 H, J = 8.3), 8.04 (d, 1 H, J = 8.3), 7.84 (t, 1 H, J = 8.3), 7.75 (t, 1 H, J = 8.3), 7.69-7.66 (m, 1 H), 7.60 (t, 1 H, J = 8.3), 7.66 and 7.55 (AB, 4 H, J = 8.0)	6-phenyl-9-chlorophenanthridine (**2b$_1$**) 160.5, 144.0, 139.2, 136.9, 134.6, 130.4, 130.3, 129.6, 129.5, 129.4, 128.8, 128.5, 127.6, 127.1, 123.3, 122.5, 121.9, 121.8 6-(*p*-chlorophenyl)phenanthridine (**2b$_2$**) 159.9, 143.6, 138.1, 134.8, 133.4, 131.1, 131.0, 130.6, 130.3, 128.9, 128.6, 128.4, 127.2, 127.1, 124.9, 123.7, 122.3, 121.9
2c	mixture	mixture
2d	8.64 (d, 1 H, J = 2.0), 8.52 (dd, 1 H, J = 8.0, 0.9), 8.21 (dd, 1 H, J = 8.0, 0.9), 7.99 (d, 1 H, J = 9.0), 7.79 (dt, 1 H, J = 8.0, 1.3), 7.70 (t, 1 H, J = 8.0), 7.66 and 7.54 (AB, 4 H, J = 9.0), 7.58-7.54 (overlapped with AB, m, 1 H)	159.4, 144.0, 137.7, 137.3, 135.1, 134.8, 131.1, 130.4, 130.1, 129.6, 128.8, 127.8, 127.4, 123.2, 122.7, 122.1, 122.0
2e	8.47 (dd, 1 H, J = 8.0, 1.2), 8.28 (dd, 1 H, J = 10.3, 2.5), 8.23 (dd, 1 H, J = 8.1, 1.2), 8.09 (dd, 1 H, J = 9.1, 5.9), 7.79 (dt, 1 H, J = 7.1, 1.2), 7.73-7.67 (m, 3 H), 7.36 (dt, 1 H, J = 8.1, 2.5), 7.26 (t, 2 H, J = 8.8)	165.5, 164.9, 162.2, 161.6, 143.9, 135.5, 131.7, 131.6, 131.5, 130.3, 129.6, 127.1, 122.1, 116.5, 116.2, 115.7, 115.4, 107.6, 107.3
2f	8.42 (t, 2 H, J = 7.6), 8.12 (d, 1 H, J = 7.5), 8.00-7.98 (m, 1 H), 7.60 (dt, 1 H, J = 7.5, 1.3), 7.55-7.46 (m, 2 H), 7.35-7.22 (m, 3 H), 7.11-7.08 (m, 1 H), 3.35-3.32 (m, 2 H), 3.10-3.00 (m, 2 H)	157.7, 143.6, 142.5, 141.8, 140.8, 134.5, 133.3, 130.1, 129.4, 129.3, 128.6, 126.8, 126.7, 124.9, 123.7, 122.1, 120.6, 39.3, 34.4
2g	8.63 (d, 1 H, J = 7.5), 8.53 (d, 1 H, J = 7.5), 8.25 (d, 1 H, J = 7.5), 8.19 (d, 1 H, J = 7.5), 7.79 (t, 1 H, J = 7.5), 7.69 (overlapped with AB, t, 1 H, J = 7.5), 7.59 and 7.57 (two overlapped, t, 2 H, J = 7.5), 7.67 and 6.86 (AB, 4 H, J = 8.4), 3.02 (s, 6 H)	161.3, 150.9, 144.0, 133.5, 130.9, 130.2, 130.1, 129.1, 128.6, 127.7, 126.8, 126.3, 125.4, 123.4, 122.1, 121.9, 112.1, 40.5
2h	8.58 (d, 1 H, J = 8.0), 8.46 (s, 1 H), 8.22 (d, 1 H, J = 8.0), 7.01 (d, 1 H, J = 8.0), 7.72 (dt, 1 H, J = 8.0, 1.2), 7.67-7.62 (overlapped with AB, m, 1 H), 7.63 and 7.36 (AB, 4 H, J = 8.3), 7.40 (d, 1 H, J = 8.0), 2.63 (s, 3 H), 2.47 (s, 3 H)	161.0, 144.0, 140.7, 138.4, 137.0, 133.5, 130.2, 129.6, 129.0, 128.8, 128.7, 126.5, 123.4, 123.3, 121.8, 121.7, 22.16, 22.32

Table 5

CHN Analysis Results for Novel Compounds **1** and **2**

No.	Formula	Analysis (%) Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
1b	$C_{19}H_{14}ClN_3$	71.12	4.37	13.08	71.36	4.41	13.14
1c	$C_{20}H_{17}N_3$	80.33	5.76	14.11	80.24	5.72	14.04
1e	$C_{19}H_{13}F_2N_3$	71.17	4.09	13.11	71.02	4.08	13.08
1f	$C_{21}H_{17}N_3$	81.09	5.46	13.51	81.00	5.50	13.49
1g	$C_{21}H_{20}N_4$	76.76	6.05	17.07	76.80	6.14	17.06
1h	$C_{21}H_{19}N_3$	80.12	6.12	13.45	80.48	6.11	13.41
2b$_1$	$C_{19}H_{12}ClN$	78.82	4.16	4.84	78.87	4.18	4.84
2e	$C_{19}H_{11}F_2N$	78.31	3.78	4.80	78.33	3.81	4.81
2f	$C_{21}H_{15}N$	89.60	5.41	4.90	89.64	5.38	4.98
2g	$C_{21}H_{18}N_2$	84.65	6.11	9.41	84.52	6.08	9.39
2h	$C_{21}H_{17}N$	87.71	6.42	5.37	87.99	6.61	5.40

Scheme 3



attack. This suggests that the mechanism of the reaction is not ionic. We thus propose the mechanism of Scheme 3 for the formation of phenanthridines **2**. Firstly, lithiation of **1** gives carbanion **3**, which transfers an electron to the copper (I) cation to form radical **4**. Species **4** loses molecular nitrogen upon heating to form another radical intermediate **6**. Radical **6** rotates to *cis* radical **5**. Finally, phenanthridine **2** is formed by cycloaddition and aromatization.

We have thus demonstrated a convenient, one-pot method for the preparation of 6-arylphenanthridines. From the substituent effects on the reaction, it is believed that the phenanthridines are formed *via* a radical mechanism.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus without correction. The ^{1}H and ^{13}C nmr spectra were recorded on a 300 MHz spectrometer in deuteriochloroform with tetramethylsilane or deuteriochloroform as the internal reference. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. Lithiation reactions were carried out under the protection of dry nitrogen. All glassware was oven-dried. All moisture-sensitive reagents were transferred by means of pre-dried syringes.

General Procedure for the Preparation of Diaryl(benzotriazol-1-yl)methanes **1a-h**.

Method A.

A solution of benzotriazole (1.3 g, 11 mmoles), diarylmethyl chloride (10 mmoles), and triethylamine (15 mmoles) in toluene (100 ml) was refluxed for several hours (see Table 1). The reaction was monitored by tlc and was continued until no starting material remained. The reaction mixture was washed with 2 *N* aqueous sodium hydroxide, extracted with ethyl acetate and dried over sodium sulfate. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate). Two products, diaryl(benzotriazol-1-yl)methane (50-70%) and diaryl(benzotriazol-2-yl)methane (15-40%) were obtained. Only the Bt-1 isomer was used in subsequent reactions.

Method B.

A solution of benzotriazole (1.3 g, 11 mmoles), diaryl methanol (10 mmoles) and a catalytic amount of *p*-toluenesulfonic acid in toluene (100 ml) was refluxed for several hours. The work up procedure was the same as given above. Two isomers, diaryl(benzotriazol-1-yl)methane (56-76%) and diaryl(benzotriazol-2-yl)methane (9-30%), were obtained. Spectral and analytical characterization are provided in Tables 2 and 5. Only the Bt-1 isomer was used in subsequent reactions.

General Procedure for the Preparation of Phenanthridine Derivatives **2a-h**.

To a solution of diaryl(benzotriazol-1-yl) methane **1** (2 mmoles) in tetrahydrofuran (20 ml), *n*-butyllithium (1.1 ml, 2 *M* in hexane, 2.2 mmoles) was added at -78° under nitrogen. After stirring at this temperature for 10 minutes, copper(I) iodide (764 mg, 4 mmoles) was added. The mixture was kept at -78° for an additional 15 minutes, then refluxed for several hours. The reaction was then quenched by the addition of water. The solution was washed with water, extracted with ethyl acetate and dried over sodium sulfate. After removal of the solvent, the obtained residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 95:5). Spectral and analytical data are given in Tables 4 and 5.

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