The Reaction of Lithium Phenylacetylide and Phenyllithium with *N*-(ω-Bromoalkyl)phthalimides

Bruce E. Torian and Loren L. Braun*

Department of Chemistry, Idaho State University,
Pocatello, Idaho 83209

Received August 1, 1983

Lithium phenylacetylide reacted with short-chain *N*-(ω-bromoalkyl)phthalimides **1b** and **1c** to give tricyclic products **2b** and **2c** in moderate yields. Likewise, tricyclic products **3a-c** were obtained when short-chain imides **1a-c** were treated with phenyllithium. When longer-chain imides **1d-f** in this series were treated with lithium phenylacetylide only tertiary alcohols **4d-f** could be isolated. Partial hydrogenation of **2b** and **2c** yielded the corresponding alkenes **5b** and **5c**, products which corroborated the structural assignment of **2b** and **2c**.

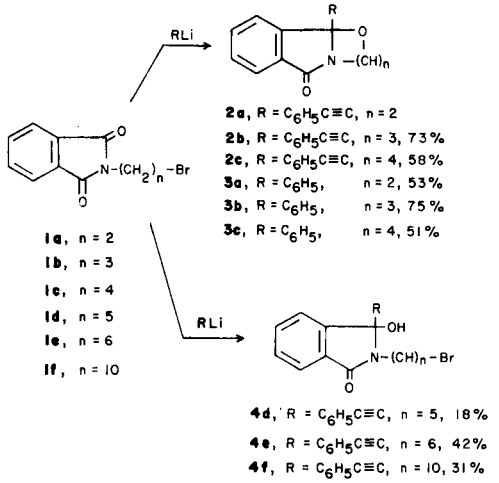
J. Heterocyclic Chem., **21**, 293 (1984).

It has been reported that *N*-(2-bromoethyl)phthalimide (**1a**), on treatment with lithium phenylacetylide, undergoes cyclization to yield an oxazolo[2,3-*a*]isoindole (**2a**) [1]. In view of the anticonvulsant and antiinflammatory properties ascribed to oxazolo-, oxazino-, and oxazepino[2,3-*a*]isoindoles [2], we decided to investigate extensions of this synthetic method. In the present paper, we describe the reactions of lithium phenylacetylide with longer-chain *N*-(ω-bromoalkyl)phthalimides and also report on cyclizations that occur when a series of these imides is treated with phenyllithium.

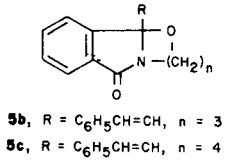
When *N*-(3-bromopropyl)phthalimide (**1b**) and *N*-(4-bromobutyl)phthalimide (**1c**) were treated with lithium phenylacetylide, the corresponding oxazino- and oxazepino[2,3-*a*]isoindoles (**2b** and **2c**) were isolated in moderate yields. This method of preparation appears to be novel for the [1,3]oxazepino[2,3-*a*]isoindole system [3]. Treatment of *N*-(ω-bromoalkyl)phthalimides of 5, 6, and 10 carbon chain lengths, **1d-f**, with lithium phenylacetylide resulted in the formation of tertiary alcohols [4] **4d-f** isolated in low yields [5]. We were unable to isolate any tricyclic products containing 8, 9, and 13 membered rings (analogous to **2b** and **2c**) from these reactions.

On reaction with phenyllithium, *N*-(ω-bromoalkyl)-phthalimides having 2, 3, and 4 methylene groups, **1a-c**, yielded cyclized products **3a-c**. These compounds have been previously prepared by alternative methods [6].

Evidence for the structures of the new heterocyclic compounds, **2b** and **2c**, was provided by ir, ^{1}H nmr, and ^{13}C nmr spectra. Further corroboration of these structural assignments was furnished by partial hydrogenation of **2b** and **2c** over Lindlar's catalyst [7]. The appearance of two doublets in the ethylenic proton region [8] of the ^{1}H nmr spectrum of each of the products indicated that, in both cases, the ethylenic protons are coupled only to each other. Structures **5b** and **5c**, the expected hydrogenation products of **2b** and **2c** respectively, are both consistent with this spectral display. A *cis* configuration for each of



the hydrogenation products is indicated by the method of preparation. The ethylenic proton coupling constants



(12.7Hz for **5b** and 12.0 for **5c**) are consistent with this assignment.

EXPERIMENTAL

Melting points were determined in capillary tubes using a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The ^{1}H nmr spectra were determined on a Perkin-Elmer R12A spectrometer and ^{13}C nmr were determined on a Bruker WH 90 FT NMR, a Varian FT-80A, or a JEOL FX 100 spectrometer. Infrared spectra were obtained on a Perkin-Elmer 283B spectrometer.

2,3,4,5-Tetrahydro-11b-phenylethynyl[1,3]oxazepino[2,3-*a*]isoindol-7(11b*H*)-one (**2c**).

A solution of lithium phenylacetylide was prepared under dry nitrogen

by the addition of 9.8 ml of a 1.6 *M* solution of *n*-butyllithium in hexane to an ice-cooled solution of 1.65 ml (1.53 g, 0.015 mole) of phenylacetylene in 24 ml of dry tetrahydrofuran. To the stirred mixture, cooled in ice-methanol bath (*ca.* -10°), was added, *via* syringe, a solution of 4.23 g (0.015 mole) of *N*-(4-bromobutyl)phthalimide in *ca.* 20 ml of tetrahydrofuran over a period of 10 minutes. The mixture was stirred at -10° to 0° for *ca.* 4 hours, then allowed to rise to room temperature while stirring under nitrogen overnight. The mixture had become a gelatinous mass which resisted filtration. About 10 ml of tetrahydrofuran was added followed by enough methanol to dissolve the semisolid mass. The solvent was removed leaving an oily solid. When dissolution in 95% ethanol and cooling failed to yield crystals, the mixture was poured into cold water and refrigerated overnight. The resulting semi-solid was separated by decantation and recrystallized from 95% ethanol to yield 1.86 g of product. Further work-up of the filtrate yielded more solid (0.56 g). Chromatography (on a silica gel column with 50:50 chloroform:benzene as eluant) of the remaining oils from the mother liquor gave further material (0.21 g) for a total yield of 2.63 g of product, mp 85-88°. An analytical sample melted at 86-88°; ir (potassium bromide): 3080, 3058, 2941, 2225 (C≡C), 1710 (C=O), 1375, 1111, 1091, 1080, 1068, 750, 685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60-2.20 (broad s, 4H, CCH_2CH_2C), 2.80-4.52 (m, 4H, OCH_2 and NCH_2), 7.20-8.04 (m, 9H, aromatic); ^{13}C nmr (deuteriochloroform): δ 25.7 and 29.9 ($CH_2CH_2CH_2CH_2$), 39.9 (CH_2N), 64.2 (CH_2O), 84.4 and 85.0 (C≡C), 87.7 (NCO), 121.4, 123.0, 127.0, 128.3, 128.8, 129.1, 130.1, 130.6, 131.6, 132.0, 132.9 and 144.3 (aromatic), 167.1 (C=O).

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.25; H, 5.75; N, 4.62.

3,4-Dihydro-10b-phenylethynyl-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6-(10b*H*)-one (**2b**).

This compound was prepared by the addition of **1b** (13.4 g, 0.050 mole) dissolved in 30 ml of tetrahydrofuran to an ice-cooled solution of 0.050 mole of lithium phenylacetylide under dry argon by a procedure similar to that described for the preparation of **2c** above. When addition was complete, the mixture was allowed to reach room temperature and then stirred for 2 more hours. The solvent was removed from the yellow-brown solution. When the remaining oil failed to crystallize it was poured into water and refrigerated overnight. The resulting solid was collected by filtration and recrystallized from 95% ethanol to yield 10.6 g of **2b**, mp 118-120°; ir (potassium bromide): 3054, 2962, 2930, 2868, 2224 (C≡C), 1702 (C=O), 1402, 1285, 1091, 1050, 1020, 755, 691 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.0-2.32 (m, 2H, CCH_2C), 3.20-4.80 (m, 4H, CH_2O and CH_2N), 7.22-8.08 (m, 9H, aromatic); ^{13}C nmr (deuteriochloroform): δ 24.8 ($CH_2CH_2CH_2$), 35.9 (CH_2N), 63.8 (CH_2O), 82.9 and 84.1 (C≡C), 87.4 (NCO), 121.5, 122.7, 123.8, 128.5, 129.2, 129.9, 130.2, 131.2, 132.0, 132.5 and 144.5 (aromatic), 165.4 (C=O).

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.64; H, 5.26; N, 4.85.

2-(5-Bromopentyl)-2,3-dihydro-3-hydroxy-3-phenylethynyl-1*H*-isoindol-1-one (**4d**).

When 14.80 g (0.050 mole) of *N*-(5-bromopentyl)phthalimide (**1d**) was added to an ice-cooled solution of lithium phenylacetylide (0.05 mole) under dry argon in a manner similar to that described for **2b** above, an oil was obtained (on removal of the solvent) which crystallized after dissolving in 95% ethanol, cooling and seeding. The yield was 3.66 g, mp 117-119°. When, on occasion, the product failed to crystallize, chromatography on a silica gel column was utilized, eluting with mixtures of dichloromethane:hexanes (% V:V, dichloromethane, successively: 40, 50, 60, 100). The product was obtained in the latter fractions; ir (potassium bromide): 3260 (OH), 2920, 2855, 2228 (C≡C), 1692 (C=O), 1405, 1075, 761, 755, 696 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20-2.20 (m, 6H, $CCH_2CH_2CH_2C$), 3.32-3.70 (m, 4H, NCH_2 and $BrCH_2$), 5.23 (s, 1H, OH), 7.20-7.90 (m, 9H, aromatic); ^{13}C nmr (deuteriochloroform): δ 25.6, 27.6, 32.2, 33.5 and 39.5 (methylene carbons), 83.6, 84.7 and 84.9 (C≡C and COH), 120.9, 122.3, 122.8, 128.0, 128.9, 129.4, 129.5, 131.5, 132.5 and 145.9 (aromatic), 166.8 (C=O).

Anal. Calcd. for $C_{21}H_{20}BrNO_2$: C, 63.32; H, 5.06; N, 3.53. Found: C, 63.53; H, 5.20; N, 3.43.

Earlier chromatographic fractions showed ^1H nmr peaks in the 4.7-5.2 δ region, indicating the presence of ethylenic products.

2-(6-Bromohexyl)-2,3-dihydro-3-hydroxy-3-phenylethynyl-1*H*-isoindol-1-one (**4e**).

This compound was obtained from **1e** (0.015 mole) by means of a procedure similar to that described for the preparation of **2c**. Removal of solvent yielded an oil. When dissolution in methanol and cooling failed to induce crystallization, the mixture was poured into 1 *M* ammonium chloride and the product was extracted with ether and dried (magnesium sulfate). On removal of the solvent, there remained an oil which crystallized on dissolving in methanol and cooling overnight. Recrystallization from methanol yielded 2.61 g of product, mp 87-92°. An analytical sample melted at 90-92.5°; ir (potassium bromide): 3277 (OH), 2940, 2860, 2239 (C≡C), 1685 (C=O), 1405, 1077, 759, 690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10-2.35 (m, 8H, $CCH_2CH_2CH_2CH_2C$), 3.18-3.75 (m, 4H, CH_2Br and CH_2N), 5.48 (s, 1H, OH), 7.15-8.00 (m, 9H, aromatic).

Anal. Calcd. for $C_{22}H_{22}BrNO_2$: C, 64.08; H, 5.38; N, 3.40. Found: C, 63.96; H, 5.52; N, 3.40.

2-(10-Bromodecyl)-2,3-dihydro-3-hydroxy-3-phenylethynyl-1*H*-isoindol-1-one (**4f**).

This compound was prepared from **1f** (0.020 mole) by a procedure similar to that described for the preparation of **2c**. When the solvent was removed, only an oil could be isolated. Chromatography on a silica gel column (5.5″ × 7/8″) utilizing 50:50 dichloromethane:hexane as eluant yielded solid fractions which, on recrystallization from benzene-petroleum ether (bp 30-60°) yielded 2.92 g of product, mp 73.5-75.5°. An analytical sample melted at 75-77°; ir (potassium bromide): 3260 (OH), 2935, 2858, 2240 (C≡C), 1680 (C=O), 1404, 1088, 1070, 759, 692 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95-2.40 (m, 16H, $C(CH_2)_8C$), 3.10-3.95 (m, 4H, CH_2Br and CH_2N), 5.17 (s, 1H, OH), 7.00-8.10 (m, 9H, aromatic).

Anal. Calcd. for $C_{26}H_{30}BrNO_2$: C, 66.67; H, 6.46; N, 2.99. Found: C, 66.59; H, 6.56; N, 3.00.

General Method for the Cyclization of **1a-c** to **3a-c**.

The procedure for the preparation of 2,3-dihydro-9b-phenyloxazolo-[2,3-*a*]isoindol-5(9b*H*)-one (**3a**) illustrates the method of preparation of compounds **3a-c**. A solution of 5.6 g (0.022 mole) of *N*-(2-bromoethyl)-phthalimide (**1a**) in 50 ml of tetrahydrofuran was cooled in an ice-methanol bath (*ca.* -10°). The mixture was stirred under dry nitrogen as 10 ml of 2.2 *M* phenyllithium (in cyclohexane:diethyl ether 70:30) was added *via* syringe over a period of 10 minutes. The mixture was stirred for an additional 1.5 hours at *ca.* -10°, and ice-cooled for *ca.* 4 hours longer before allowing to stir overnight at room temperature under nitrogen. The solvent was removed from the yellow solution leaving a brown oil which crystallized from ethanol. Recrystallization yielded 2.92 g, mp 145-147.5°, lit (6) mp 147-149°; ir and ^1H nmr spectra were consistent with those reported in the literature [6a].

The mp of **3b** and **3c**, prepared by a similar procedure, were 126-128° and 130-133° respectively, lit [6a] mp 128-130° and 130-132° respectively. Both exhibited ir and ^1H nmr spectra consistent with those reported in the literature [6a].

2,3,4,5-Tetrahydro-11b-(2-phenylethenyl)[1,3]oxazepino[2,3-*a*]isoindol-7(11b*H*)-one (**5c**).

To 1.48 g (4.88 mmoles) of **2c**, dissolved in 20 ml of 95% ethanol, was added two drops of quinoline and 0.1 g of Lindlar's catalyst [7]. The mixture was hydrogenated at room temperature and atmospheric pressure until 5 mmole of hydrogen had been absorbed. The mixture was filtered and the solvent removed. There remained a yellow oil which crystallized from 95% ethanol. Recrystallization yielded 0.82 g (55%) of white crystals, mp 77-80°. An analytical sample melted at 78.5-82°; ir (potassium bromide): 3040, 2958, 2936, 1704 (C=O), 1471, 1445, 1391, 1360, 1320, 1083, 1068, 1040, 1018, 764, 751, 701; ^1H nmr (deuteriochloroform): δ 1.55 (broad singlet, 4H, CCH_2CH_2C), 2.2-3.7 (m, 4H, CH_2O and CH_2N),

6.07 (d, 1H, =CHCO, J = 12.0 Hz), 6.5-7.8 (m, 10H, Ar and =C*H*Ph). Superimposed on the aromatic region were two sharp peaks centered at 6.71 δ (=C*H*Ph, J = 12.0 Hz).

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.59; H, 6.27; N, 4.59. Found: C, 78.79; H, 6.20; N, 4.56.

3,4-Dihydro-10b-(2-phenylethenyl)-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6-(10b*H*)-one (**5b**).

This compound was obtained in the same manner as **5c**. The yield of product obtained from 1.45 g of **2b** was 1.10 g (76%) mp 91.5-95.5° (from 95% ethanol). An analytical sample melted at 93-96°; ir (potassium bromide): 3062, 2966, 1713 (C=O), 1470, 1402, 1390, 1292, 1052, 1025, 761, 699; ^{1}H nmr (deuteriochloroform); δ 1.15-2.10 (m, 2H, CCH_2C), 2.45-3.10 (m, 1H, CH_AN), (9), 3.60-4.23 (m, 3H, OCH_2 and CH_BN), 5.95 (d, 1H, =CHC, J = 12.7 Hz), 6.70-8.00 (m, 10H, Ar and =C*H*Ph). Superimposed on the aromatic region were two sharp peaks centered at 6.89 δ (=C*H*Ph, J = 12.7 Hz).

Acknowledgement.

This research was partially supported by a grant from the Faculty Research Committee, Idaho State University, Pocatello, ID. We thank the Department of Chemistry, Washington State University, Pullman, WA and the Colorado State University Regional NMR Center, Fort Collins, CO for ^{13}C nmr spectra.

REFERENCES AND NOTES

[1] D. K. Olsen, B. E. Torian, C. D. Morgan and L. L. Braun, *J. Org. Chem.*, **45**, 4049 (1980).

[2a] W. J. Houlihan, U. S. Patent 3,334,113 and divisions thereof; *Chem. Abstr.*, **68**, 59800 (1968); [b] T. S. Sulkowski, U. S. Patent 3,336,306; *Chem. Abstr.*, **68** 69007 (1968).

[3] A literature search has revealed only one example of 2*H*-[1,3]-oxazino[2,3-*a*]isoindole formation (low yield) by a similar means. See S. Naruto, S. Keiko, and H. Mizuta, *Heterocycles*, **16**, 1089 (1981).

[4] The literature contains numerous examples of alcohol formation by carbanion (including Grignard reagent) attack at imide carbonyls. For an example of alcohol formation by means of a lithium reagent see ref [3].

[5] Oily chromatographic fractions from the reaction of **1d** showed peaks in the ethylenic proton region of ^{1}H nmr spectra indicating significant competition from elimination reactions.

[6a] P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 165 (1969); [b] M. Kohn and R. Lakner, *Monatsh. Chem.*, **45**, 617 (1925).

[7] H. Lindlar and R. Dubois, "Organic Synthesis", John Wiley and Sons, New York, 1973, Collective Vol 5, p 80.

[8] In each case, one of the two doublets appeared as two peaks superimposed on the aromatic signals.

[9] See ref [6a]. One of the two protons of the CH_2NCO group appears to lie in the plane of the lactam oxygen atom and, as a result, gives a low field signal.