

Bardia Guilani, Melvin L. Rasco, Christine F. K. Hermann and Harry W. Gibson*

Department of Chemistry,
and Science & Technology Center for
High Performance Polymeric Adhesives & Composites,
Virginia Polytechnic Institute and State University,
Blacksburg, VA 24061

Received September 11, 1989

Reaction of the enamine **1** formed *in situ* from isoquinoline and sodium triethylborohydride with aromatic dialdehydes **3** produces 4,4'-coupled bis(isoquinolines) **4** in good yields. These compounds are readily oxidized with manganese dioxide to the corresponding diketones **5**.

J. Heterocyclic Chem., **27**, 1007 (1990).

Part of our research activity is directed toward the utilization of the chemistry of Reissert compounds for the production of polymers [1]. Reissert compounds are derived from a wide variety of aromatic *N*-heterocycles by the formal addition of acyl cyanide across an imine bond, creating an acidic proton α to the nitrile [2]. Our work focuses in part on reactions of these carbanions with electrophiles such as alkyl halides and aldehydes [2]. To produce linear macromolecules, difunctional Reissert compounds are required for reaction with dihaloalkanes or dialdehydes. Unfortunately few bis(heterocycles) are available economically. Herein we report a new synthesis of bis(isoquinolines) coupled at the 4-positions.

Minter and Re recently reported that sodium triethyl-[2-(1,2-dihydroisoquinolyl)]borane (**1**) (derived from isoquinoline by reaction with sodium triethylborohydride) reacts efficiently with aromatic aldehydes to produce 4-benzyloisoquinolines **2** [3]. We now report that use of dialdehydes **3** in reaction with **1** produces 4,4'-coupled bis(isoquinolines) **4a-4f** in good yields.

Spectral data (ir and nmr) are in full accord with the structures. Noteworthy in the proton nmr spectra are doublets at *ca* δ 9.15 for H₁, at *ca* δ 8.3-8.45 for H₃ and singlets at *ca* δ 4.35 for the benzylic methylene protons attached to the 4-position of the isoquinoline ring. Figure 1 for α,α' -bis(4-isoquinolyl)-*p,p'*-dimethyldiphenyl ether (**4b**) is representative of the nmr spectra.

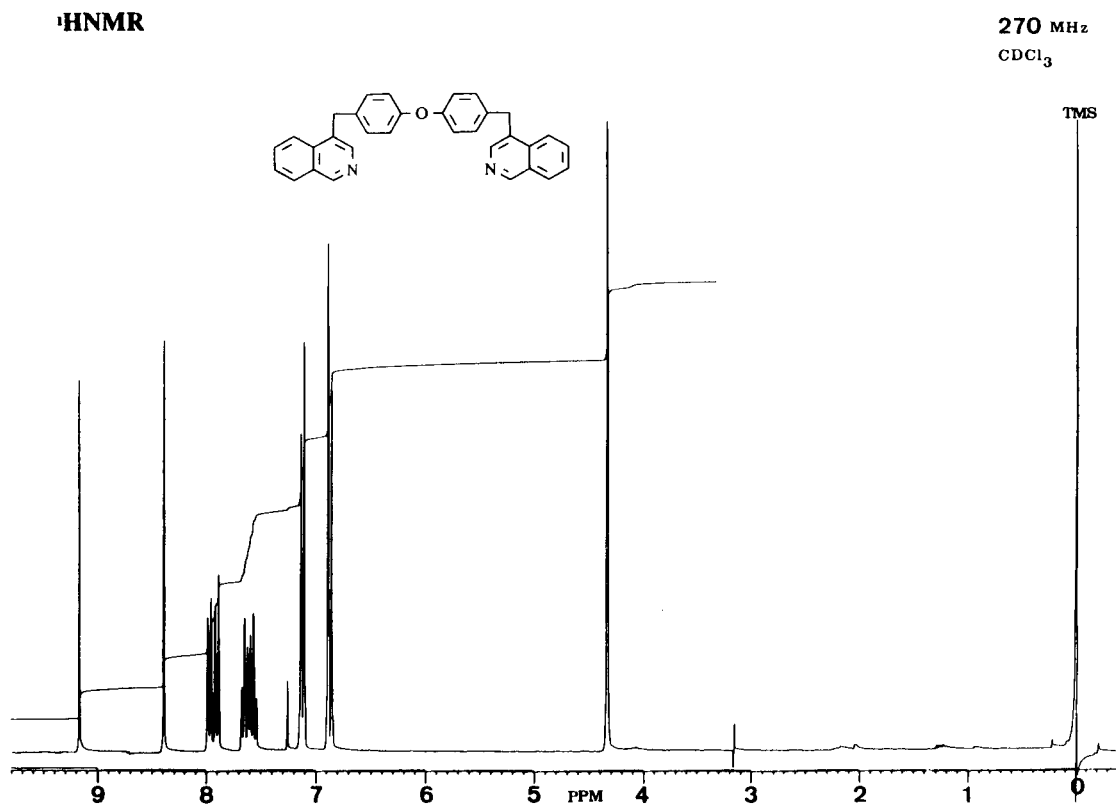
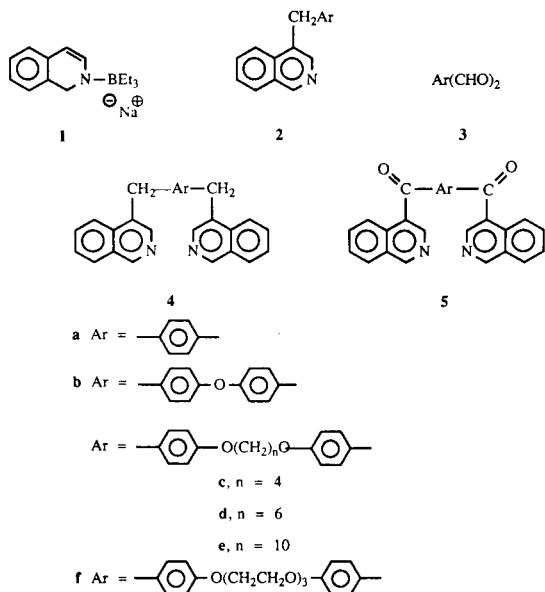


Figure 1. 270 MHz proton nmr spectrum of α,α' -bis(4-isoquinolyl)-*p,p'*-dimethyldiphenyl ether (**4b**) in deuteriochloroform at 25°.



A method for conversion of these coupled 4-benzylisoquinolines to the corresponding diketones has been developed. Manganese dioxide smoothly oxidizes α, α' -bis(4-isoquinolyl)-1,4-bis(*p*-methylphenoxy)butane (**4c**) to 1,4-bis[*p*-(4-isoquinolyl)carbonylphenoxy]butane (**5c**) in 72% yield. Similarly α, α' -bis(4-isoquinolyl)-1,10-bis(*p*-methylphenoxy)decane (**4e**) upon manganese dioxide treatment yields 96% of 1,10-bis[*p*-(4-isoquinolyl)carbonylphenoxy]decane (**5e**).

Having developed an economical and general synthesis of these novel 4,4'-coupled bis(isoquinolines), we will proceed to utilize these compounds and the variety of structural analogs this chemistry makes available for production of polymers using Reissert compound chemistry.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Meltemp apparatus and are corrected. The FTIR spectra were recorded on a Nicolet MX-1. The ¹H nmr (proton) spectra were recorded on a Bruker WP 270 MHz instrument using tetramethylsilane as the internal standard. Elemental analyses were by Atlantic Micro-labs, Norcross, GA.

Terephthalaldehyde (**3a**) was purchased from Aldrich Chemical Co. and used without further purification.

4,4'-Diformyldiphenyl Ether (**3b**).

To 250 ml of THF freshly distilled from sodium/benzophenone was added 28.92 g (0.098 mole) of 4,4'-oxybis(benzoyl chloride). The stirring mixture was kept under nitrogen and cooled to -78°. After 30 minutes, 200 ml (0.200 mole) of 1.00M lithium tri-*t*-butoxyaluminumhydride in THF was added over a one hour period. Stirring was continued for 7.5 hours. Some THF was then distilled *via* Rotavap, and the resulting yellow solution was precipitated into 7-fold excess water. The product was extracted with chloroform. The combined extracts were washed twice with water

and dried over sodium sulfate. The solvent was then removed to afford a crude yield of 16.37 g (74%). Chromatography was performed using silica gel and ether. The first compound to elute was the desired dialdehyde. After one recrystallization from ether-hexane, mp 59.5-64.0, compared to the reported 61.0-62.5 [4]; ¹H nmr (deuteriochloroform): [d (J = 8.4 Hz), 7.10 ppm (4H), H₂], [d (J = 8.4 Hz), 7.95 ppm (4H), H₃], [s, 10.0 ppm (2H), CHO].

General Procedure for Synthesis of Dialdehydes **3c-3f**.

To 1500 ml of absolute ethanol in a 3 liter round bottom flask were added one mole (22.9 g) of sodium metal followed by one mole (122.12 g) of *p*-hydroxybenzaldehyde. After all the sodium had dissolved, 0.5 mole of the α, ω -dibromoalkane or 1,2-bis-(2-chloroethoxy)ethane was added. The mixture was refluxed overnight, then poured onto 2500 ml of ice and cooled until a solid precipitated. The brownish, waxy solid was filtered, washed with water, and dried under vacuum.

1,4-Bis(*p*-formylphenoxy)butane (**3c**).

This compound was obtained in 95% yield after three recrystallizations from ethanol, mp 105-107 (lit [5] mp 103-104°); ¹H nmr (deuteriochloroform): [s, 2.05 ppm (4H), CH₂], [s, 4.12 ppm (4H), OCH₂], [d (J = 8 Hz), 7.01 ppm (4H), phenyl], [d (J = 8 Hz), 7.86 ppm (4H), phenyl], [s, 9.91 ppm (2H), CHO].

1,6-Bis(*p*-formylphenoxy)hexane (**3d**).

This compound, obtained in 96% crude yield, was recrystallized from ethanol twice leaving white flakes, mp 101.0-103.0° (lit [5] mp 106-107°).

1,10-Bis(*p*-formylphenoxy)decane (**3e**).

This dialdehyde, obtained in 94% crude yield, was recrystallized from ethanol leaving white flakes mp 80-83° (lit [5] mp 78-80°).

1,10-Bis(*p*-formylphenyl)-1,4,7,10-tetraoxydecane (**3f**).

This compound, obtained in 40% yield, was recrystallized from hexane leaving fine white needles, mp 70-73°; ¹H nmr (deuteriochloroform): [m, 3.8, 4.0 and 4.3 ppm (12 H), CH₂'s], [m, 7.1, 7.2, 7.9, 8.0 ppm (8 H), aromatic], [s, 10.2 ppm (2 H), CHO]; ir: C=O, 1709 cm⁻¹.

Anal. Calcd. for C₂₀H₂₂O₆: C, 67.06; H, 6.14. Found: C, 67.05; H, 6.34.

General Procedure for Synthesis of 4,4'-Coupled Bis(isoquinolines) **4a-f**.

Into a round bottom flask under nitrogen was added 150 ml of dry (distilled from sodium and benzophenone) THF. To this was added 50 mmoles of isoquinoline and 50 mmoles of sodium triethylborohydride with stirring. After 30 minutes, the dialdehyde (24 mmoles) was added. This mixture was stirred for four hours, cooled to 0° and quenched with 100 ml of 0.5 N sodium hydroxide and 50 ml of 30% hydrogen peroxide. The resulting mixture was stirred for 3 hours, poured into 6-fold excess of water, and stirred overnight. The product was either extracted or filtered, and recrystallized.

α, α' -Bis(4-isoquinolyl)-*p*-xylene (**4a**).

This compound, isolated in 74% yield, was crystallized from ethanol-water, mp 186.5-187.5°; ¹H nmr (deuteriochloroform): [s, 4.33 ppm (4H), CH₂], [s, 7.10 ppm (4H), phenyl], [m, 7.5-7.7 ppm (4H), isoquinolyl H₆ and H₇], [d (J = 8 Hz), 7.88 ppm (2H), isoquinolyl H₅], [d (J = 8 Hz), 7.98 ppm (2H), isoquinolyl, H₈], [s,

8.37 ppm (2H), isoquinolyl H₃], [s, 9.15 ppm (2H), isoquinolyl H₁].
Anal. Calcd. for C₂₆H₂₀N₂: C, 86.64; H, 5.59. Found: C, 86.73; H, 5.53.

α,α' -Bis(4-isoquinolyl)-*p,p'*-dimethyldiphenyl Ether (**4b**).

Isolated in 88% yield and purified by recrystallization from ethanol-water, this compound had mp 117.5-118.5°; ¹H nmr (deuteriochloroform): is shown in Figure 1.

Anal. Calcd. for C₃₂H₂₄N₂O: C, 84.93; H, 5.35. Found: C, 84.84; H, 5.40.

α,α' -Bis(4-isoquinolyl)-1,4-bis(*p*-methylphenoxy)butane (**4c**).

Prepared in 95% yield and purified by recrystallization from ethyl acetate, this compound had mp 167.0-167.8°; ¹H nmr (deuteriochloroform): [s, 1.94 ppm (4H), CH₂], [s, 3.97 ppm (4H), OCH₂], [s, 4.31 ppm (4H), benzylic CH₂], [d (J = 8 Hz), 6.80 ppm (4H), phenyl *ortho* to oxygen], [d (J = 8 Hz), 7.09 ppm (4H), phenyl *ortho* to methylene], [m, 7.5-7.7 ppm (4H), isoquinolyl H₆ and H₇], [d (J = 8 Hz), 7.92 ppm (2H) isoquinolyl H₅], [d (J = 8 Hz), 7.98 ppm (2H), isoquinolyl H₈], [s, 8.38 ppm (2H), isoquinolyl H₃], [s, 9.16 ppm (2H), isoquinolyl H₁].

Anal. Calcd. for C₃₆H₃₂N₂O₂: C, 82.41; H, 6.15; N, 5.34. Found: C, 82.41; H, 6.33; N, 5.22.

α,α' -Bis(4-isoquinolyl)-1,6-bis(*p*-methylphenoxy)hexane (**4d**).

This compound was isolated in 87% yield and recrystallized from ethyl acetate, mp 162.0-163.0°; ¹H nmr (deuteriochloroform): [s, 1.50 ppm (4H), CH₂], [s, 1.75 ppm (4H), CH₂], [t, (J = 6 Hz), 3.90 ppm (4H), OCH₂], [s, 4.30 ppm (4H), benzylic CH₂], [d (J = 8 Hz), 6.78 ppm (4H), phenyl *ortho* to oxygen], [d (J = 8 Hz), 7.09 ppm (4H), phenyl], [m, 7.5-7.7 ppm (4H), isoquinolyl H₆ and H₇], [d (J = 8 Hz), 7.92 ppm (2H), isoquinolyl H₅], [d (J = 8 Hz), 7.98 ppm (2H), isoquinolyl H₈], [s, 8.40 ppm (2H), isoquinolyl H₃], [s, 9.15 ppm (2H), isoquinolyl H₁].

Anal. Calcd. for C₃₈H₃₆N₂O₂: C, 82.58; H, 6.57. Found: C, 82.36; H, 6.62.

α,α' -Bis(4-isoquinolyl)-1,10-bis(*p*-methylphenoxy)decane (**4e**).

This compound was produced in 76% yield and recrystallized from ethyl acetate, mp 110.0-112.5°; ¹H nmr (deuteriochloroform): [m, 1.2-1.5 ppm (12H), CH₂], [p (J = 6 Hz), 1.72 ppm (4H)], [t (J = 6 Hz), 3.88 ppm (4H), OCH₂], [s, 4.30 ppm (4H), benzylic CH₂], [d (J = 8 Hz), 6.78 ppm (4H), phenyl], [d (J = 8 Hz), 7.08 ppm (4H), phenyl], [m, 7.5-7.7 ppm (4H), isoquinolyl H₆ and H₇], [d (J = 8 Hz), 7.90 ppm (2H), isoquinolyl H₅], [d (J = 8 Hz), 7.96 ppm (2H), isoquinolyl H₈], [s, 8.38 ppm (2H), isoquinolyl H₃], [s, 9.15 ppm (2H), isoquinolyl H₁].

Anal. Calcd. for C₄₂H₄₄N₂O₂: C, 82.86; H, 7.28. Found: C, 82.71; H, 7.33.

α,α' -bis(4-isoquinolyl)-1,10-bis(*p*-tolyl)-1,4,7,10-tetraoxydecane (**4f**).

Formed in quantitative yield and recrystallized from ethyl acetate, this compound had mp 114.5-116.5°; ¹H nmr (deuteriochloroform): [s, 3.70 ppm (4H), CH₂], [t (J = 5 Hz), 3.80 ppm (4H), CH₂], [t (J = 5 Hz), 4.07 ppm (4H), CH₂], [s, 4.30 ppm (4H), benzylic CH₂], [d (J = 8 Hz), 6.80 ppm (4H), phenyl], [d (J = 8 Hz), 7.10 ppm (4H), phenyl], [m, 7.60 ppm (4H), isoquinolyl H₆ and H₇], [doublets (J = 7 Hz), 7.95 ppm (4H), isoquinolyl H₅ and H₈],

[s, 8.40 ppm (2H), isoquinolyl H₃]; [s, 9.15 ppm (2H), isoquinolyl H₁].

Anal. Calcd. for C₃₈H₃₆N₂O₄: C, 78.05; H, 6.21; N, 4.80. Found: C, 77.65; H, 6.42; N, 4.70.

General Procedure for Synthesis of Bis(4-isoquinolyl) Aryl Ketones **5c** and **5e**.

The bisisoquinoline was dissolved in benzene (an appropriate amount is usually 100 ml per 8 g) and manganese dioxide (5 fold excess by weight) was added. This mixture was refluxed for 5 days using a Dean-Stark trap to azeotrope the water. Then the mixture was filtered through a Celite bed. The combined Celite/manganese dioxide solid was extracted with chloroform for a day using a Soxhlet extractor and this was added to the original filtrate, evaporated, and purified.

1,4-Bis[*p*-(4-isoquinolyl)carbonylphenoxy]butane (**5c**).

Produced in 72% yield, this compound was purified by recrystallization from ethyl acetate as pale yellow crystals, mp 191-194°; ¹H nmr (deuteriochloroform): [s (broad), 2.0 ppm (4H), CH₂], [s (broad), 4.15 ppm (4H), OCH₂], [d, 6.95 ppm (4H), arom], [m, 7.7-7.9 ppm (4H), H₆, H₇], [d, 7.95 ppm (4H), arom], [m, 8.2 ppm (4H), H₅, H₈], [s, 8.65 ppm (2H), H₃], [s, 9.4 ppm (2H), H₁]; ir: C=O, 1649 cm⁻¹.

Anal. Calcd. for C₃₆H₂₈N₂O₄: C, 78.24; H, 5.11; N, 5.07. Found: C, 77.78; H, 5.23; N, 4.97.

1,10-Bis[*p*-(4-isoquinolyl)carbonylphenoxy]decane (**5e**).

This compound was isolated in 96% yield and recrystallized from hexane-ethyl acetate as off-white crystals, mp 100.8-103.0°; ¹H nmr (deuteriochloroform): [m, 1.7-1.85 ppm (4H), CH₂], [m, 1.3-1.5 ppm (12H), CH₂], [t, 4.1 ppm (4H), OCH₂], [d, 6.95 ppm (4H), arom], [m, 7.65-7.8 ppm (4H), H₆, H₇], [d, 7.85 ppm (4H), arom], [m, 8.1-8.2 ppm (4H), H₅, H₈], [s, 8.65 ppm (2H), H₃], [s, 9.45 ppm (2H), H₁]; ir: C=O, 1649 cm⁻¹.

Anal. Calcd. for C₄₂H₄₀N₂O₄: C, 79.22; H, 6.33; N, 4.40. Found: C, 79.13; H, 6.58; N, 4.38.

Acknowledgement.

The authors are grateful to the American Chemical Society Petroleum Research Fund for partial support of the work reported here *via* grant 19625 AC7 and a Summer Research Fellowship (to CFKH). We thank Amoco Chemical Corporation for a generous gift of oxybenzoic acid.

REFERENCES AND NOTES

- [1] H. W. Gibson, A. Pandya and B. Guilani, *Amer. Chem. Soc., Polymer Preprints*, **29** (1), 154 (1988).
- [2] F. D. Popp in *Quinolines*, Part II, G. Jones, ed, John Wiley and Sons, New York, 1982, pp 353-375; F. D. Popp, *Heterocycles*, **14**, 1033 (1980); F. D. Popp, *Adv. Heterocyclic Chem.*, **24**, 187 (1979); **9**, 1 (1968).
- [3] D. E. Minter and M. A. Re, *J. Org. Chem.*, **53**, 2653 (1988).
- [4] R. E. Buhts, D. K. Chesney, J. R. Handley, F. D. Popp and D. C. Smith, *Org. Prep. Proced. Int.*, **7**, 193 (1975).
- [5] H. B. Donahoe, L. E. Benjamin, L. V. Fennoy and D. Greiff, *J. Org. Chem.*, **26**, 474 (1961).