Notes

Synthesis of AA Difunctional Reissert Compound Monomers from Bis(isoquinolines)

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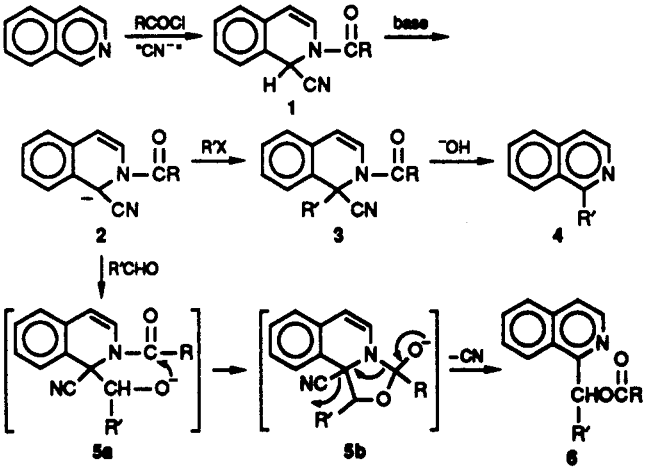
Introduction

The family of α-(acylamino)nitriles derived from heterocyclic aromatic and acyclic imines is called Reissert compounds after their discoverer.[1] 2-Acyl-1,2-dihydroisoquinaldonitriles (1, Scheme I) are examples of Reissert compounds derived from isoquinoline by the formal addition of acyl cyanides across the C=N bond. The initially formed *N*-acylium salt undergoes nucleophilic attack by cyanide ion on the partially positive carbon. Several synthetic techniques have been developed for Reissert compound formation.[2] Reissert reacted the heterocycle, the acid chloride, and aqueous KCN in a manner analogous to the Schotten-Baumann reaction.[1] Popp and co-workers developed a two-phase process with KCN-H_2O utilizing methylene chloride to dissolve the organic reagents;[3-6] in some cases addition of a phase-transfer catalyst has proved advantageous.[7] Later, a single-phase method using methylene chloride as the solvent and trimethylsilyl cyanide (TMSCN) as the cyanide ion source was developed;[8] this method obviates the two competitive processes that can occur in the presence of water: hydrolysis of highly reactive acid chlorides, particularly alkanoyl, and pseudobase formation by attack of a hydroxide ion instead of a cyanide ion. A catalytic amount of $AlCl_3$ is often helpful.[9]

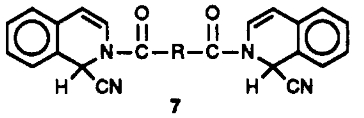
Reissert compounds have been widely used in synthetic organic chemistry,[2] primarily as a result of the rich chemistry associated with their anions, which can be formed by using a variety of bases,[2] including NaOH or KOH under phase-transfer conditions.[10] For example, the isoquinoline-derived Reissert anion **2** (Scheme I) undergoes efficient conversion (95-100% yields) to alkylated derivatives **3**.[2,11] Basic hydrolysis of **3**, driven by rearomatization,[2] produces the 1-alkylisoquinolines **4**. Similarly, condensation with aldehydes, again driven by the re-formation of a fully aromatized structure, leads via the initially formed alkoxide **5a** to a cyclic alkoxide **5b**, collapse of which produces the α-hydroxyalkyl ester **6**, again in generally high yields.[2,12]

One of our research thrusts concerns the application of the efficient and diverse chemistry of Reissert compounds to the production of nitrogen-containing polymers.[13] We utilize reactions of the Reissert anions such as **2** with electrophiles in step-growth processes. This approach requires that either (1) both the nucleophile and electrophile are difunctional (AA/BB) system) or (2) both the electrophile and nucleophile are incorporated into the same molecule (AB system). Both approaches are under examination.

Scheme I



Elsewhere we have reported the synthesis of a number of difunctional or bis(Reissert compounds) of the AA type including **7** by reaction of monofunctional heterocycles with diacid chlorides in the presence of TMSCN.[14] Here we report an alternate approach to AA Reissert monomers by reaction of difunctional heterocycles with monofunctional acid chlorides.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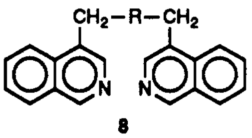
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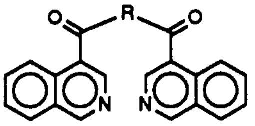
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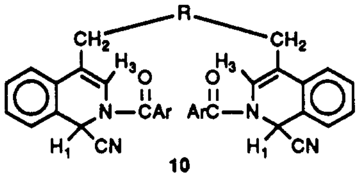
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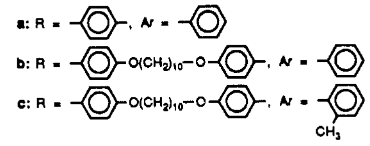

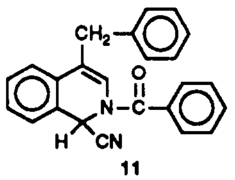
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Discussion

Recently Minter and Re discovered that reaction of the enamine formed in situ from isoquinoline and sodium triethylborohydride with aldehydes provided an efficient synthesis of 4-alkylisoquinolines.[15] Because of the dearth of readily available difunctional N-heterocycles, this report attracted our attention, and by extension to dialdehydes we produced a family of 4,4'-coupled bis(isoquinolines)

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Table I
Bis(Reissert compounds) from 4,4′-Coupled Bis(isoquinolines)[a]

bis(RC)	yield, %	mp, °C	elem anal. calcd (found), % C	H	N
10a	100	238–41[b]	81.00 (80.60)	4.86 (4.85)	9.00 (8.86)
10b	100	100–105[c]	79.97 (79.85)	6.25 (6.30)	6.43 (6.35)
10b	100	175–5[d]			
10c	96	159–61[e]	80.15 (79.93)	6.50 (6.43)	6.23 (6.25)

[a] Synthesized by reaction of the bis(isoquinoline) with 2.05 equiv each of acid chloride and trimethylsilyl cyanide with a catalytic amount of $AlCl_3$ in CH_2Cl_2 at 25 °C for 24–72 h. [b] Recrystallized from $CHCl_3$/hexane. [c] Column chromatography (silica gel, 60:40 ethyl acetate/hexane) followed by recrystallization from ethanol. [d] Column chromatography (silica gel, 60:40 ethyl acetate/hexane) followed by recrystallization from ethyl/hexane. [e] Column chromatography (silica gel, 65:35 hexane/ethyl acetate) followed by recrystallization from ethyl acetate/hexane.

8.[16] Furthermore, we developed a procedure for their oxidation to the diketones **9**.[16]

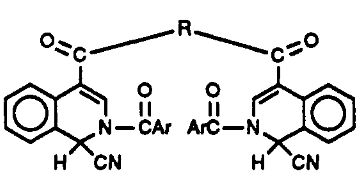
The next step in our efforts toward polymer synthesis is to convert **8** and **9** into bis(Reissert compounds). These compounds by way of the corresponding dianions thus constitute AA monomers.

The bis(Reissert compounds) **10** derived from **8** by reaction with aroyl chlorides and TMSCN are summarized in Table I. Essentially quantitative yields were observed in every case. These compounds are diastereomeric. In some cases column chromatographic separations were achieved. Because stereochemical integrity at the chiral centers is most likely to be lost in the corresponding dianions, no serious attempts were made to completely purify and characterize the individual meso and racemic stereoisomers. It was noted, however, that use of different recrystallization solvents led to different melting points, probably because diastereomeric mixtures of different composition were produced, although proton NMR spectroscopy did not allow detection of the two diastereomers in all cases.

Figure 1, the proton NMR spectrum of **10c**, is representative of the spectra of this family of AA monomers. The distinctive features of the spectrum are the signals for H_1 (the acidic proton), H_3, and the benzylic methylenes at 6.07, 6.7–6.8, and 3.68, respectively. To aid in these assignments, the monofunctional Reissert compound **11** was synthesized and its NMR spectrum confirmed these assignments. It is noteworthy that, in both **10** and **11**, the benzylic methylene protons appear as AB quartets, consistent with their diastereotopic nature.

Also worthy of comment is the fact that the *o*-tolyl methyl groups of **10c** appear as two singlets. This we attribute to the occurrence of amide isomerism, interchanging the positions of the carbonyl and aryl groups of the amide moiety with respect to the isoquinoline nucleus. This phenomenon has been widely observed in nondiastereomeric Reissert compounds[17] and is, therefore, unrelated to the presence of diastereomers in the compounds of interest presently.

Aware that TMSCN converts carbonyl groups to cyanohydrins,[18] we attempted to form the bis(Reissert compounds) **12** from diketones **9** using the two-phase (CH_2Cl_2–H_2O) method and KCN as the cyanide source. Infrared spectra revealed loss of the diaryl carbonyl absorptions at ca. 1650 cm^{-1} and growth of ester carbonyls at 1710 cm^{-1}. Proton NMR spectroscopy indicated that the Reissert moiety had not formed; the distinctive signals



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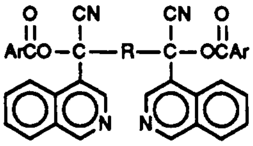

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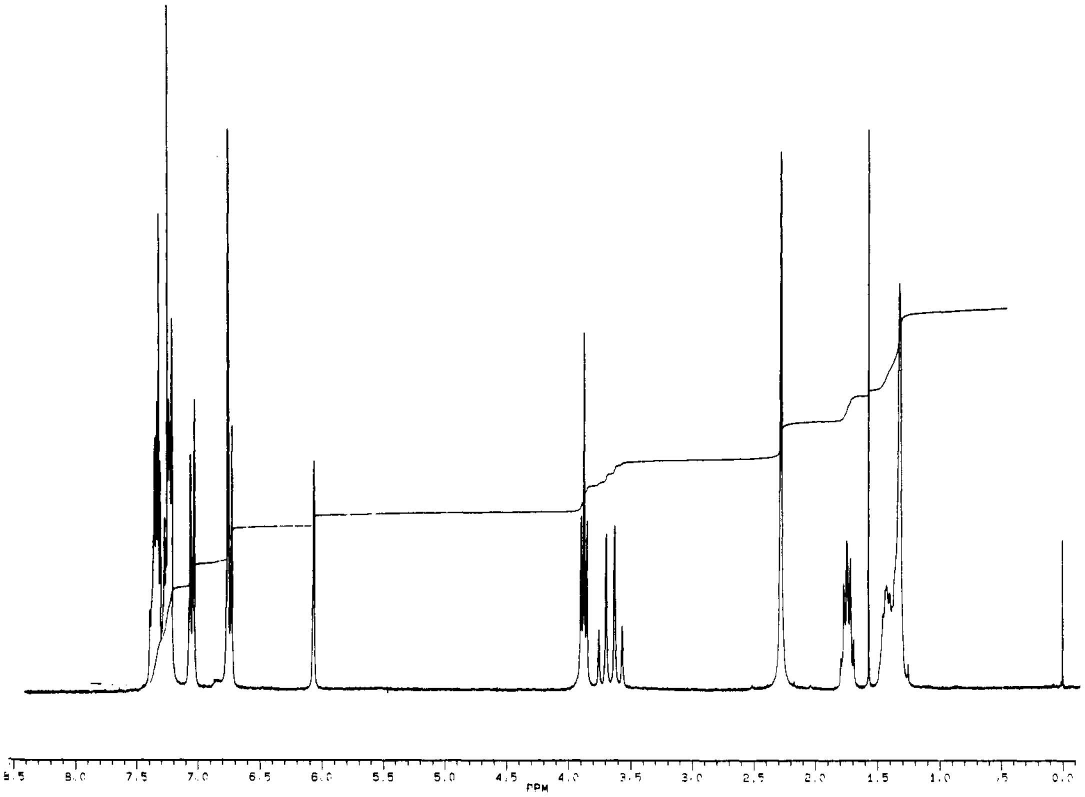

Figure 1. 270-MHz ^1H NMR spectrum of **10c** in $CDCl_3$ at 25 °C. The peak at 1.55 ppm is due to H_2O. The signal at 2.25 ppm consists of two peaks separated by less than 1 Hz (tolyl CH_3).

for H_1 and H_3 of **9** at 8.65 and 9.40 ppm, respectively, were absent. Note the significant upfield shift of these proton signals in bis(Reissert compound) **10c** (Figure 1) to 6.07 and 6.7–6.8 ppm, respectively. Although the products were not fully purified or characterized, on the basis of the replacement of diaryl ketone carbonyl absorption by ester carbonyl absorption, they apparently consisted of diastereomeric mixtures of the bis(cyanohydrin esters) **13**.

Conclusions

Conversion of a new family of 4,4′-coupled bis(isoquinolines) into bis(Reissert compounds) by reaction with aroyl chlorides and TMSCN constitutes a very efficient route to a new and novel class of AA type monomers for use in step-growth polymerizations via the corresponding dianions.

Utilization of the new AA monomers in polymerization reactions with dihaloalkanes and dialdehydes (BB monomers) is currently under investigation. **10b** and **10c** have been converted to high molecular weight polymers by condensation of the dianions with dialdehydes.[13e]

Experimental Section

All melting points were determined on Thomas–Hoover or Haake–Buchler melting point apparatuses and are corrected. ^1H NMR spectra (reported in ppm relative to internal tetramethylsilane) were recorded on a Bruker 270-MHz instrument and a Hewlett Packard 7550A graphics plotter. FTIR (KBr) spectra were recorded on a Nicolet MX-1. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. All reagents and solvents were used as received.

Representative Procedure for the Synthesis of Reissert Compounds. 1,10-Bis[[[4-(*N*-benzoyl-1-cyano-1,2-dihydroisoquinolyl)]methyl]phenoxy]decane (10b). To 5.00 g (8.2 mmol) of the C_{10}-bis(isoquinoline) **8**, R = p-$C_6H_4O(CH_2)_{10}$-p-OC_6H_4, in 60 mL of CH_2Cl_2 was added 2.43 g (17.3 mmol) of benzoyl chloride. After 20 min of stirring, 1.72 g (17.3 mmol) of TMSCN was added, followed by a catalytic amount of $AlCl_3$. Stirring was continued for 50 h, at the end of which time no bisheterocycle was detected by TLC (silica/ethyl acetate). The reaction was quenched with water and allowed to stir for 24 h. The organic layer was separated and washed with 10% HCl (2×), water (2×), saturated $NaHCO_3$ (2×), and water (2×). The orange solution was dried over sodium sulfate for 1 day. Solvent was removed, and the product was dried in vacuo, 7.32 g (>100%), mp 81–86 °C, shrank 70–78 °C. TLC (silica gel, 60:40 ethyl acetate/hexane) showed a dark spot, R_f = 0.5, and another faint spot, R_f = 0.1. Column chromatography (silica gel, 60:40 ethyl acetate/hexane) and two recrystallizations from ethanol yielded an analytically pure sample, mp 100–105 °C. The ^1H NMR spectrum of the analytical sample showed the following: 1.2–1.4 (m, 12 H, C_3–C_8 methylene protons of decyl), 1.8 (p, 4 H, C_2 and C_9 methylenes of decyl, AB pattern, J = 5 Hz); 3.75 (4 H, diaryl methylenes t, $\Delta\nu$ = 0.12 ppm, J_{AB} = 15 Hz); 3.85 (4 H, C_1 and C_{10} methylenes of decyl, J = 5 Hz); 6.35 (b s, 2 H, isoquinolyl H_1); 6.55 (b s, 2 H, isoquinolyl H_3); 6.80 (d, 4 H, protons ortho to oxy group, J = 8 Hz); 7.15 (d, 4 H, protons meta to oxy group, J = 8 Hz); 7.30–7.65 (m, 18 H, isoquinolyl H_5–H_8 and benzoyl protons). IR: 1662 cm^{-1} (C=O).

The reaction was repeated on a larger scale using 33.15 g (54.4 mmol) of bis(isoquinoline), 16.02 g (114 mmol) of benzoyl chloride, and 22.31 g (114 mmol) of TMSCN. The reaction time was extended to 95 h. After workup, 46.07 g (97%) of crude product was obtained. Column chromatography afforded **10b** in 71% isolated yield. Instead of ethanol, the product was recrystallized from ethyl acetate/hexane, mp 175–177 °C (not 100–105 °C). The ^1H NMR spectrum of the higher melting product was identical with that of the lower melting product.

4-Benzylisoquinoline. To 9.95 g (7.7 mmol) of isoquinoline in 100 mL of THF freshly distilled from Na/benzophenone was added 85 mL of 1.0 M (85 mmol) $NaB(Et)_3H$. The solution turned deep red almost immediately. After 25 min of stirring at room temperature, 9.02 g (85 mmol) of benzaldehyde was added in one portion. The color turned black almost immediately. After 5.5 h of stirring, the chalky yellow solution was cooled to 0 °C and 170 mL of 0.5 N NaOH solution was added followed by the careful addition of 85 mL of 30% H_2O_2. The mixture was allowed to stir overnight, after which time it was diluted 4-fold with water. The white precipitate was collected by filtration and dried in a vacuum oven, 14.66 g (87%), mp 115–118 °C (lit.[15] mp 117.5–118.5 °C). The ^1H NMR spectrum of the crude product showed the following: 4.40 (s, 1 H, methylene); 7.2–7.4 (m, 5 H, aryl); 7.50–7.75 (m, 2 H, isoquinolyl H_6 and H_7); 7.93 (d, 1 H, isoquinolyl H_5, J = 8 Hz); 8.00 (d, 1 H, isoquinolyl H_8, J = 8 Hz); 8.45 (s, 1 H, isoquinolyl H_3); 9.20 (s, 1 H, isoquinolyl H_1).

***N*-Benzoyl-4-benzyl-1,2-dihydroisoquinaldonitrile (11).** The crude yield was 85%. The ^1H NMR spectrum of an analytically pure sample recrystallization from ethanol, mp 186.2–187.2 °C, showed the following: 3.81 (AB pattern, 2 H, methylene, $\Delta\nu$ = 0.11 ppm, J_{AB} = 16 Hz); 6.45 (s, 1 H, H_1); 6.60 (s, 1 H, H_3); 7.00–7.60 (m, 14 H). Elem anal. Calcd for $C_{24}H_{18}N_2O$ (found): C, 82.26 (82.34); H, 5.18 (5.19).

***α,α′*-Bis[4-(*N*-benzoyl-1-cyano-1,2-dihydroisoquinolyl)]-*p*-xylene (10a).** The ^1H NMR spectrum of the pure sample showed the following: 3.75 (AB pattern, 4 H, CH_2, $\Delta\nu$ = 0.11, J_{AB} = 18 Hz), 6.20 (s, 2 H, H_1); 6.55 (s, 2 H, H_3); 7.15 (s, 4 H, aryl of xylyl); 7.3–7.7 (m, 18 H). IR: 1662 cm^{-1} (C=O).

1,10-Bis[[[4-[*N*-(*o*-toluoyl)-1-cyano-1,2-dihydroisoquinolyl]]methyl]phenoxy]decane (10c). The ^1H NMR spectrum of the pure sample, mp 159–161 °C, showed the following: 1.3–1.6 (m, 12 H, C_3–C_8 protons of decyl); 1.7–1.9 (m, 4 H, C_2 and C_9 protons of decyl); 2.25 (ss, 6 H, o-toluoyl methyl protons); 3.68 4 H, diaryl methylenes, AB pattern, $\Delta\nu$ = 0.12 ppm, J_{AB} = 15 Hz); 3.88 (t, 4 H, C_1, C_{10} protons of decyl, J = 5 Hz); 6.07 (s, 2 H, isoquinolyl H_1); 6.7–6.8 (m, 6 H, isoquinolyl H_3 and aryl protons ortho to oxygen); 7.10 (d, 4 H, aryl protons ortho to methylene, J = 8 Hz); 7.2–7.5 (m, 14 H). IR: 1676 cm^{-1} (C=O).

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Registry No. 8, 121118-26-1; **10a**, 121118-36-3; **10b**, 121118-35-2; **10c**, 128926-44-3; **11**, 132981-61-4; TMSCN, 7677-24-9; PhCHO, 100-52-7; 4-benzylisoquinoline, 10166-05-9; isoquinoline, 119-65-3; benzoyl chloride, 98-88-4.