Difunctional Heterocycles: A Convenient One Pot Synthesis of Novel Bis(benzoxazoles) from Bis(*o*-aminophenols)

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New bis(benzoxazoles) **14** and **17** have been synthesized in excellent yields from the corresponding bis(*o*-aminophenols) by refluxing with triethyl orthoformate. 6,6′-Bis(benzoxazole) (**14**) has also been prepared utilizing Gold's reagent. Compound **14** is inert to Reissert reaction conditions. However, the Reissert reaction on 5,5′-bis(benzoxazole) (**17**) led to ring opened product **20**.

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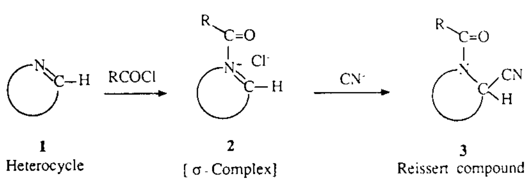
Introduction.

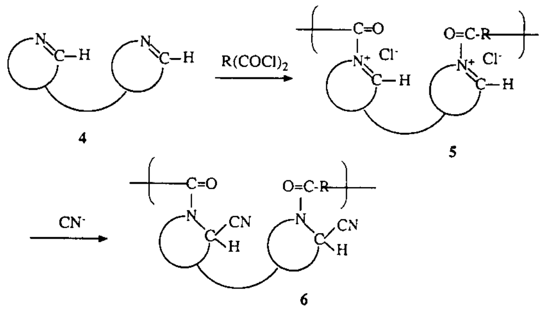
Since their discovery by Arnold Reissert [1], Reissert compounds, α-(acylamino)nitriles **3**, have proven useful as intermediates in the synthesis of various heterocyclic compounds, such as derivatives of isoquinoline, quinoline, quinazoline, *etc.*, including alkaloids and other biologically active compounds [2-6]. These α-(acylamino)nitriles **3** result from the initial formation of the *N*-acylium ions **2** by the reaction of acid chlorides with the heterocycles **1**, followed by the addition of a cyanide nucleophile as shown in Scheme 1. As will be described below it is the acidity of the proton alpha to the cyano group of **3** and the nucleophilicity of the resultant carbanion that bestow these compounds with synthetic utility.

Scheme 1



We are currently exploring two different approaches for use of the chemistry of Reissert compounds **3** for the synthesis of a variety of heterocyclic polymers [7-12]. The first approach is to utilize Reissert chemistry to synthesize new monomers for specialty polymers [7-9]. The second approach is to synthesize poly(Reissert compounds) **6**. In the latter approach, one has to synthesize a bis(heterocycle) **4** [8] or a bis(α-aminonitrile) [10] in high purity followed by polymerization *via* the Reissert reaction utilizing a diacid chloride. The first approach to poly(Reissert compounds) **6** is shown in Scheme 2, proceeding through poly(*N*-acylium) species **5**.

Scheme 2

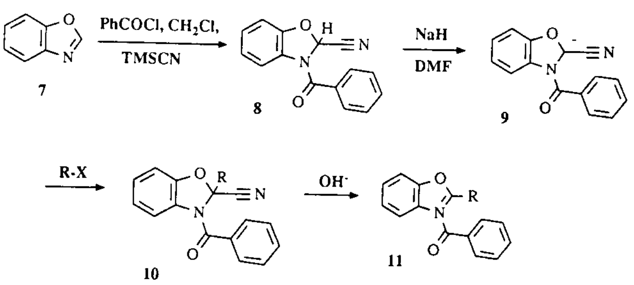


The reactivity associated with the Reissert moieties [2-4] of such poly(Reissert compounds) **6** can be utilized to chemically modify the polymers. For example, the polyanion formed from **6** by proton abstraction with base can be alkylated with alkyl halides. The anions will also react with aldehydes, producing polyesters from polyamides, a rather unusual polymer modification reaction. And finally, in the absence of added electrophiles the anions will undergo an N → C acyl rearrangement with loss of cyanide ion to form aromatic polyketones. These chemical modifications can be judiciously applied in order to control the physical and chemical properties such as surface energy, dyeability, blendability, *etc.*

Polybenzoxazoles are a very important class of high performance polymers [13-15] and thus attracted our attention. The Reissert reaction of benzoxazole (**7**) has been successfully carried out recently [16]. The resultant compound, 3-benzoyl-2-cyano-2,3-dihydrobenzoxazole (**8**), can be readily alkylated in good yield *via* the Reissert anion **9** [16]. Hydrolysis of the alkylated products **10** is also known to give 2-substituted benzoxazoles **11** (Scheme 3) [16].

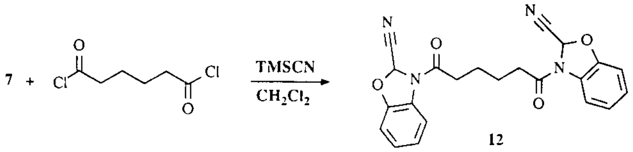
One of the requirements for production of high molecular weight polymer in any step growth (condensation) polymerization is the absence of side reactions and quantita-

Scheme 3



tive conversion of the reactant(s) to product. Thus, we studied the Reissert reaction on a model compound, benzoxazole (**7**) itself. The Reissert reaction of two moles of benzoxazole (**7**) with exactly one mole of adipoyl chloride in the presence of trimethylsilyl cyanide in dichloromethane gave a quantitative yield of bis(Reissert compound) **12** [12] (Scheme 4). This result demonstrates the feasibility of linear polymer synthesis from suitable difunctional benzoxazoles.

Scheme 4



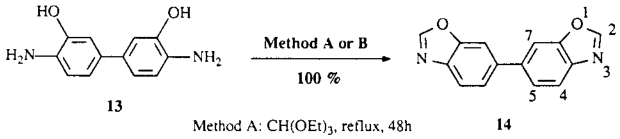
In order to satisfy the requirement of difunctionality we have pursued the synthesis of bis(benzoxazoles), just as we were inspired to synthesize 4,4′-coupled isoquinolines [8], for application of the chemistry of Reissert compounds to polymer synthesis.

Results and Discussion.

We initially approached the synthesis of bis(benzoxazoles) by following the synthesis of benzoxazoles available in the literature. Heating bis(aminophenol) **13** with formic acid in either aqueous 4*N* hydrochloric acid [17-18] or polyphosphoric acid [19] did not give the desired product, 6,6′-bis(benzoxazole) (**14**).

Ried *et al.* [20] obtained benzoxazoles in good yields by refluxing the corresponding *o*-aminophenols with triethyl orthoformate. By similar reaction conditions we obtained 6,6′-bis(benzoxazole) (**14**) in quantitative yield from 3,3′-dihydroxybenzidine (**13**) and triethyl orthoformate. Recently Gold's reagent {[3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride} has been utilized in the synthesis of benzoxazoles [21]. When we refluxed bis(*o*-aminophenol) **13** and Gold's reagent in dioxane for 17 hours, we obtained 6,6′-bis(benzoxazole) (**14**) in excellent yield (100%) (Scheme 5).

Scheme 5

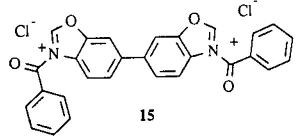


Method A: $CH(OEt)_3$, reflux, 48h

Method B: Gold's reagent, dioxane, reflux, 17h

Due to the poor solubility as well as the apparently poor basicity of the heterocyclic base **14** and consequent lack of formation of the σ-complex (Scheme 1), all our attempts towards Reissert reaction on **14** in a range of anhydrous solvents (dichloromethane, dioxane, dioxane-pyridine, DMF, NMP) with two equivalents of acid chloride (benzoyl chloride, phenyl chloroformate, acetyl chloride) in presence of a cyanide source (trimethylsilyl cyanide or potassium cyanide), with or without a catalytic amount of aluminium chloride and/or phase transfer catalysts failed. In most of these experiments we recovered starting material **14** almost quantitatively.

Most of the benzoxazolium salts of the type **15** are readily attacked by nucleophilic reagents at position 2; ring fission usually ensues and may be followed by recyclization [22]. Thus, the recovery of starting materials in the above experiments further suggests the poor basicity of compound **14** and consequent lack of formation of **15**.



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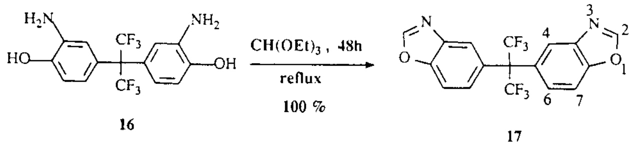
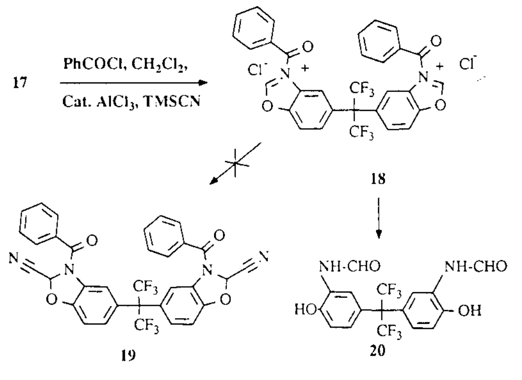
We then chose to make the more basic and also more soluble 5,5′-bis(benzoxazole) (**17**). Thus, 5,5′-(hexafluoroisopropylidene)bisbenzoxazole (**17**) was prepared in quantitative yield by refluxing 2,2-bis(3-amino-4-hydroxyphenyl)hexafluoropropane (**16**) in triethyl orthoformate (Scheme 6). Indeed, bis(heterocycle) **17** was fairly soluble in ethyl acetate and we were successful in recrystallizing **17** from ethyl acetate. The IR spectrum (potassium bromide) of **17** showed no evidence of OH or NH_2 stretching and showed only aromatic stretching as expected.

Scheme 6



Scheme 7



The Reissert reaction on **17** with benzoyl chloride in the presence of a catalytic amount of aluminum chloride and trimethylsilyl cyanide in dichloromethane was carried out. In contrast to bis(benzoxazole) **15**, compound **17** apparently did form an acylium salt, **18**, as evidenced by isolation of the ring fission product **20**. This arises probably by the initial formation of the acylium ion **18**, followed by the nucleophilic attack of water at C-2 and hydrolysis as with other five-membered heterocyclic Reissert compounds [11,16]. Surprisingly, we could not isolate the desired Reissert compound **19**, even though Reissert compounds like **8** and **12** are readily made [12,16]. Bis(formamide) **20** was purified by flash silica gel column chromatography followed by recrystallization from ethyl acetate in 89% yield. The infrared spectrum of **20** showed the presence of NH, OH and CHO moieties. Proton nmr of **20** showed two types of deuterium oxide exchangeable protons (NH and OH) as well as aromatic protons in agreement with the structure. The presence of phenolic hydroxyls was confirmed by the dissolution of **20** in aqueous sodium hydroxide solution.

Conclusions.

A high yielding one step synthesis of bis(benzoxazole)s has been achieved. Bis(benzoxazole) **14** was found to be inert under Reissert reaction conditions, whereas compound **17** yielded ring opened product **20** under Reissert reaction conditions. Thus neither of these bis(benzoxazoles) is an appropriate monomer for synthesis of polymeric Reissert compounds.

EXPERIMENTAL

All melting points were determined on a Haake-Buchler melting point apparatus and are corrected. Proton nmr spectra were recorded on a Bruker 270 mHz instrument or on a Varian 400 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, Georgia. Gold's reagent was bought from Aldrich Chemical Company, Inc., Milwaukee, WI. Compound **13** was purchased from Kennedy and Klim Inc., Little Silver, NJ. 2,2-Bis(3-amino-4-hydroxyphenyl)hexafluoropropane (**16**) (99% +) was purchased from Chriskev Company, Inc., Leawood, KS, USA.

6,6′-Bisbenzoxazole (14). Method A.

A suspension of compound **13** (21.6 g, 0.10 mole) in triethyl orthoformate (166 ml, 1 mole) was refluxed for 48 hours. The excess triethyl orthoformate was removed by rotary evaporation to get a quantitative yield (23.62 g) of product **14**. Purification of the product was achieved by dissolving the sample in hot DMF and pouring the solution into cold ethanol, collecting the white precipitate, washing with ether and drying, mp 260-262°; ir (potassium bromide): 3100-2950 (aromatic C-H), 1770, 1585, 1500, 1460, 1415, 1305, 1260, 1215 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 8.81 (s, 2H, H_2), 8.19 (d, 2H, J = 1.3 Hz, H_7), 7.90 (d, 2H, J = 8 Hz, H_4), 7.82 (dd, 2H, J = 1.6, 8.0 Hz, H_5).

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 70.97; H, 3.47; N, 11.78.

Method B.

Gold's reagent (9.9 g, 0.061 mole) was added to a well stirring suspension of **13** (10.8 g, 0.05 mole) in anhydrous dioxane (100 ml) under a nitrogen atmosphere. The reaction mixture was refluxed for 17 hours. It was then cooled to room temperature and anhydrous sodium acetate (4.1 g) and glacial acetic acid (2 ml) were added. The reaction mixture was further refluxed for 3 hours and cooled. The precipitate obtained was filtered, washed with excess dioxane and dried (7.5 g). The filtrate was concentrated and the residue was taken up in dichloromethane, washed with excess aqueous saturated sodium bicarbonate followed by water and dried over sodium sulfate. Rotary evaporation of the organic layer yielded additional amounts (4.3 g) of the product; the total yield was thus 100%. The product was further purified by recrystallization from dioxane. Spectral data and mp of this product were identical with those obtained in Method A.

5,5′-(Hexafluoroisopropylidene)bisbenzoxazole (17).

A suspension of compound **16** (18.3 g, 0.05 mole) in triethyl orthoformate (160 ml, 0.5 mole) was refluxed for 24 hours. The excess triethyl orthoformate was removed by rotary evaporation to get a quantitative yield (19.26 g) of the product. The product was purified by recrystallization from ethyl acetate as white crystals, mp 187-188°; ir (potassium bromide): 3152 (C-H), 1516, 1480, 1437, 1339, 1293, 1266, 1260, 1253, 1244 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 8.91 (s, 2H, H_2), 7.91 (d, 2H, J = 8.6 Hz, H_6), 7.82 (s, 2H, H_4), 7.40 (d, 2H, J = 8.5 Hz, H_7); ^{1}H nmr (deuteriochloroform): δ 8.17 (s, 2H, H_2), 7.96 (s, 2H, H_4), 7.58 (d, 2H, J = 8.8 Hz, H_6), 7.41 (d, 2H, J = 8.8 Hz, H_7).

Anal. Calcd. for $C_{17}H_8F_6N_2O_2$: C, 52.86; H, 2.09; N, 7.25. Found: C, 52.76; H, 2.10; N, 7.21.

2,2-Bis(3-formamido-4-hydroxyphenyl)hexafluoropropane (20).

To a well stirring solution of **17** (12.6 g, 0.033 mole) in dichloromethane (100 ml) were added benzoyl chloride (8.7 ml, 0.075 mole), and a catalytic amount of aluminum chloride (< 50 mg) at 10°. After 10 minutes, TMSCN (10 ml, 0.075 mole) was added and the reaction mixture was stirred for 4 days at 25° and quenched by pouring into water (1 ℓ). This solution was extracted with ethyl acetate (4 x 125 ml). The organic layer was washed consecutively with aqueous saturated sodium carbonate, 8% aqueous hydrochloric acid, brine (3 x 125 ml) and dried over sodium sulfate. Solvent evaporation followed by a flash silica gel column chromatography and recrystallization from ethyl acetate yielded the pure product **20** (12.17 g, 89%), mp 274-275°; ir (potassium bromide): 3405, 3392 (NH), 3365-2480 (OH), 2737 (CHO), 1674 (C=O), 1600, 1543, 1509 (aromatic), 1435, 1296, 1263, 1250, 1238, 1221 and 1174 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 10.6-10.45 (s, 2H, deuterium oxide exchangeable, NH), 9.66 (s, 2H, deuterium oxide exchangeable, OH), 8.30 (s, 2H, CHO), 8.25 (s, 2H, H_2), 7.0-6.8 (m, 4H, H_5 and H_6).

Anal. Calcd. for $C_{17}H_{12}F_6N_2O_4 \cdot 0.25H_2O$: C, 47.83; H, 2.95; N, 6.56. Found: C, 47.53; H, 2.97; N, 6.46.

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