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SYNTHESIS OF A LIGNAN SKELETON VIA NICKEL- AND PALLADIUM-PHOSPHINE COMPLEX CATALYZED GRIGNARD COUPLING REACTION OF HALOTHIOPHENES

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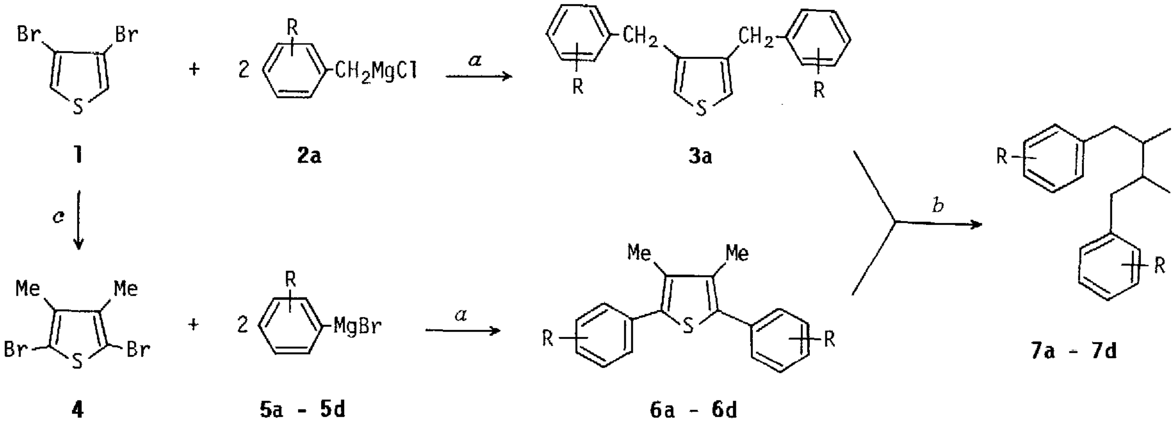
Summary: A lignan skeleton is prepared in good yield through desulfurization of 3,4-dibenzylthiophene or 2,5-diaryl-3,4-dimethylthiophenes which are obtained by the nickel- or palladium-phosphine complex catalyzed Grignard cross-coupling reaction of halothiophenes.

One of the most significant features of the nickel-phosphine complex catalyzed Grignard cross-coupling reaction is the high efficiency for the introduction of organic groups into C(sp^2)-halides.[2] As part of our investigation on the nickel-phosphine complex catalyzed alkylation and arylation of heterocyclic compounds, we have previously found that various halothiophenes readily couple with Grignard reagents. This coupling reaction turned out to be the most convenient method for the preparation of alkyl- and arylthiophenes.[3] Since thiophene molecules have been recognized as precursors for four carbon building blocks,[4] we have developed a new route from certain substituted thiophenes to 2,3-dibenzylbutane derivatives, the basic skeleton of lignans which exist in many plants as its constituent and some of which show interesting biological activities.[5]

Scheme 1 outlines two routes employed in our present work. One is via 3,4-dibenzylthiophene (**3**) and the other via 3,4-dimethyl-2,5-diarylthiophenes (**6**), both of which are readily obtainable by the cross-coupling reaction of the corresponding halothiophenes with Grignard or organozinc reagents in the presence of nickel- or palladium-phosphine complexes and should afford, upon desulfurization by Raney nickel, the same lignan skeleton **7**.

3,4-Dibenzylthiophene **3a**, obtained in 95% yield by the cross-coupling of 3,4-dibromothio-

Scheme 1

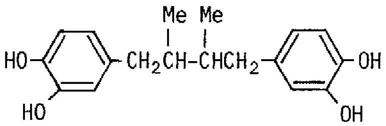


a: R = H, **b**: R = 4-MeO, **c**: R = 3,4-$(MeO)_2$, **d**: R = 3,4-OCH_2O-

^{a} $NiCl_2(dppp)$, ∿ 1 mol%. ^{b} Raney Ni. ^{c} (1) MeMgBr, $NiCl_2(dppp)$, (2) Br_2 in AcOH.

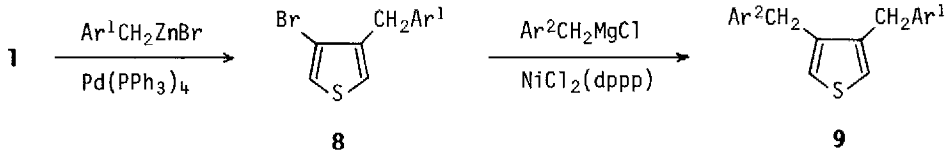
phene **1** with two equivalents of benzylmagnesium chloride **2a** in the presence of $NiCl_2(dppp)$, dppp = $Ph_2P(CH_2)_3PPh_2$, as a catalyst,[6] was treated with Raney nickel to give 2,3-dibenzylbutane **7a** in 98% yield. This route proceeds with such a high efficiency, but suffers from the difficulties in the preparation of highly alkoxy-substituted benzyl Grignard reagents which are required for the preparation of naturally occurring compounds. This difficulty was overcome by the other route. Thus, 2,5-diaryl-3,4-dimethylthiophenes **6** were prepared in high yields by the Grignard cross-coupling reaction of 2,5-dibromo-3,4-dimethylthiophene **4**, obtainable by similar Grignard coupling of **1** followed by bromination. Yield and mp are as follows; **6a**, 99%, mp 161-162°C; **6b**, 78%, mp 173.5-174.5°C; **6c**, 55%, mp 176-177°C; **6d**, 84%, mp 194-195°C. Desulfurization of **6a** - **6d** also proceeded smoothly to give lignan derivatives **7a** - **7d** in 85∿97% yields, as an about 4 : 6 mixture of diastereoisomers. A representative example is **7c**, mp 89-93°C ; ^1H NMR (100 MHz, CCl_4, TMS) δ 0.80 (minor) and 0.83 (major) (d, J = 7 Hz, 6H), 1.55-1.9 (m, 2H), 2.1-2.8 (m, 4H), 3.75 (s, 12H), 6.4-6.75 (m, 6H) ppm.

It should be noted here that the 3,4-dimethoxy- and 3,4-methylenedioxy-derivatives (**7c** and **7d**) are precursors for nordihydroguaiaretic acid, one of the most representative lignans, which is derived naturally from the resinous exudates of many plants and is now noted as an effective inhibitor of biosynthesis of thromboxane A_2.[7]

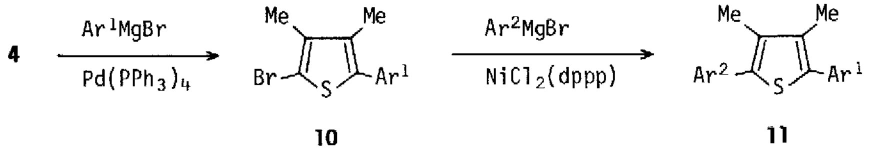


Nordihydroguaiaretic acid

Unsymmetrically substituted lignans are also prepared by the present procedure, applying the recently reported palladium-catalyzed selective monobenzylation and arylation of aromatic polyhalides.[8] The synthesis of unsymmetrically substituted thiophenes was achieved in two steps. As reported previously,[8] the palladium complex catalyzed coupling reaction of **1** with one equive of benzylzinc bromide gave monobenzylbromothiophene **8** in 52 - 57% yield. Compound **8** was allowed to react with 4-methylbenzylmagnesium chloride in the presence of $NiCl_2(dppp)$ to form unsymmetrically disubstituted thiophene **9** quantitatively. Alternatively, **4** was first monophenylated with phenylmagnesium bromide in 63% yield using $Pd(PPh_3)_4$ as catalyst. The second aryl group was introduced by 4-methyoxyphenylmagnesium bromide in the presence of $NiCl_2(dppp)$ in 87% yield. Desulfurization of **9** and **11** gave the corresponding lignan skeletons in 70% and 81% yield, respectively.



Ar^1 = Ph, Ar^2 = 4-MeC_6H_4



Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$

It is apparent from these preliminary results presented here that a sequence of the Grignard cross-coupling of halothiophenes and desulfurization provides a simple, efficient route to the lignan skeleton. Our further efforts are directed to the total synthesis of some biologically active lignans.

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