Synthesis of Cannabinol by a Modified Ullmann–Ziegler Cross-Coupling

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Abstract: Cannabinol, a pharmaceutically interesting component of cannabis, was prepared by a modified Ullmann–Ziegler cross-coupling. Using easily obtainable starting materials, this convergent approach allows facile access to a variety of cannabinol derivatives.

Key words: natural products, cross-coupling, palladium, copper, cannabinoids

Cannabis is one of the most ancient agricultural crops and medicinal plants. There is evidence that as early as the 16th century BC, preparations of cannabis were used in Egypt for treating a multitude of ailments. The chemical analysis of its molecular constituents started in the 19th century and by now more than 525 secondary metabolites have been identified, of which the cannabinoids are the most important group because they play a special role in the biological activity of cannabis extracts. Although cannabis is best known for its recreational use as a psychotropical drug, an effect that can be attributed to its constituent Δ9-tetrahydrocannabinol (THC, **1**; Figure 1), it possesses a vast range of useful pharmaceutical properties. Among the potential medical uses described so far are applications of cannabinoids as analgesics,[1] anticonvulsants, anti-inflammatories,[2] and antibiotics.[3] There is also evidence of beneficial effects in the treatment of glaucoma, epilepsy,[4] Alzheimer's disease,[5] and many other disorders.[6] This biological activity is due to the interaction of the cannabinoids with a system of two G-protein coupled receptors (CB_1 and CB_2), the so-called endocannabinoid system.[7]

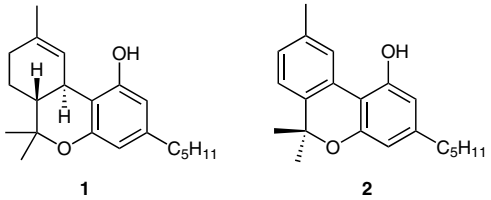


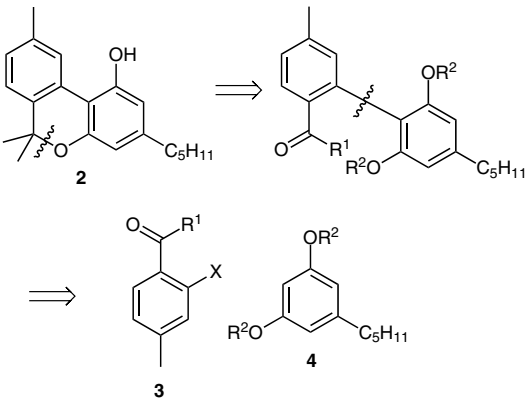
Figure 1 Δ9-THC (**1**) and cannabinol (**2**)

Because CB_1 and CB_2 show differences in their function,[8] there has been some effort towards finding selective ligands for each receptor.[9,10] Many CB_1 agonists show, for example, strong psychotropic effects that prohibit various applications in pharmacy.[11]

Synthetic routes towards cannabinol (CBN, **2**) have been of interest because it is not only a metabolite of THC[12] and therefore plays a significant role in forensic analytics,[13,14] but has also shown potential for the development of antibiotic and antimycotic agents.[15]

Being the oxidative degradation product of THC, one important route towards CBN derivatives is oxidative aromatization of tetrahydrocannabinols, which, in turn, can be synthesized by condensation of 5-alkyl resorcinols with substituted cyclohexanes.[10,16] Although this strategy allows a convergent synthesis, the CBN derivatives are often obtained in poor yields.

Because cannabinol, as a dibenzo[*b*,*d*]pyran, contains an aryl–aryl bond, a synthetic route including aromatic cross-coupling as the key step followed by intramolecular formation of the pyran moiety may be utilized to obtain CBN derivatives (Scheme 1).[14,17] This strategy allows cannabinols to be synthesized in a convergent fashion starting from easily obtainable or even commercially available substrates, such as substituted benzoic acid derivatives (**3**) and resorcinols (**4**).



Scheme 1 Retrosynthetic analysis of cannabinols

Based on our recent results with the Ullmann–Ziegler cross-coupling of sterically hindered benzamides or resorcinols with aryl halides,[18] we devised a synthesis that allows facile access to many different CBN-derived compounds.

To verify the suitability of this method for the preparation of cannabinol derivatives and to explore the scope of possible substrates, a variety of different 2-iodobenzamides and resorcinol derivatives were employed to synthesize a set of model compounds.

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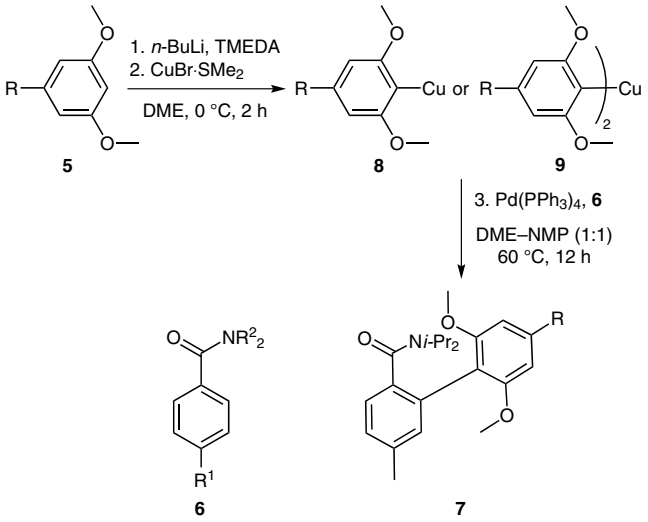
To prepare the organocopper precursor necessary for the Ullmann–Ziegler coupling, a substituted resorcinol methyl ether (**5**) was treated with *n*-butyllithium in the presence of TMEDA to effect *ortho*-lithiation and subsequently transmetallated with $CuBr{\cdot}SMe_2$ (Scheme 2). To effect the coupling, a solution of a 2-iodobenzamide (**6**) in NMP and $[Pd(PPh_3)_4]$ was added and the reaction mixture was heated to 60 °C for 12 hours to give the unsymmetrical biaryl **7**. Use of one equivalent of $CuBr{\cdot}SMe_2$ led to unsatisfactory results, with monoarylcopper(I) species **8** being generated as intermediate (Table 1, entry 1). Very good yields were obtained by employing 0.5 equivalents $CuBr{\cdot}SMe_2$ and with Gilman cuprate (**9**) as coupling precursor (Table 1, entry 2).[19]



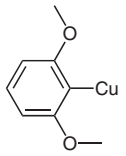
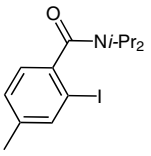
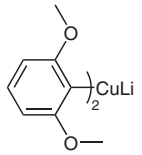
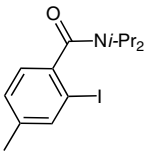
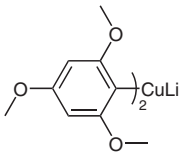
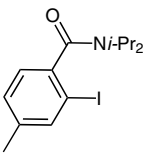
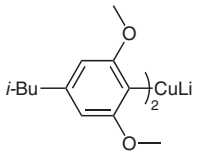
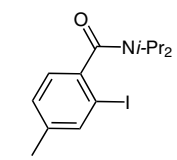
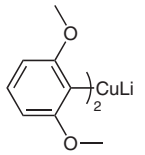
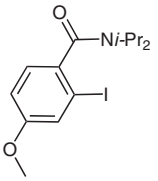
Scheme 2 Ullmann–Ziegler cross-coupling

Using this protocol, several model compounds resembling the substitution pattern of cannabinol and bearing alkyl- as well as methoxy substituents were prepared, varying the resorcinol and the 2-iodobenzamide component. All examples were obtained in good to excellent yields in the range 67–97%.

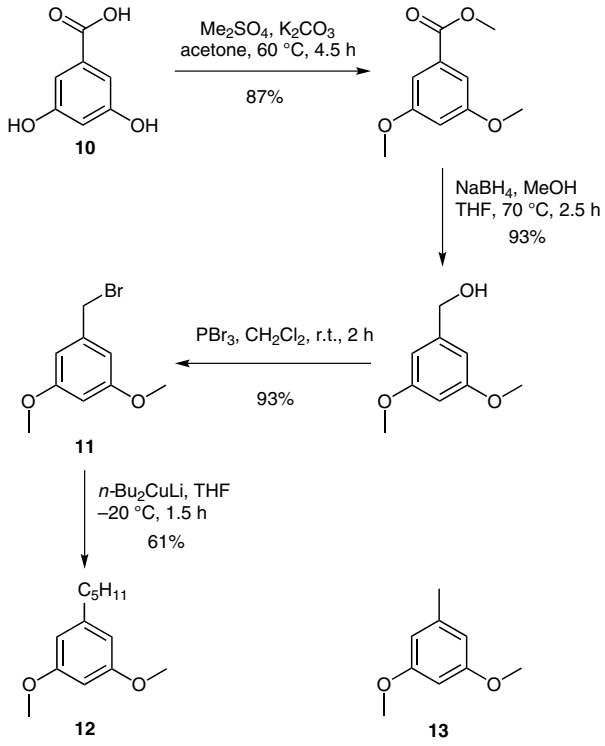
These encouraging results indicate that the modified Ullmann–Ziegler coupling may be very useful as the key step in the preparation of CBN-type cannabinoids. Especially compound **7c**, with its isobutyl substituent, which was obtained in 73% (Table 1, entry 4), is of particular interest; due to its high structural resemblance to the precursor necessary for the synthesis of the natural product cannabinol (pentyl substituent instead of isobutyl), this is a very promising result with regard to a potential synthesis of cannabinol.

With this in mind, we tackled the synthesis of the natural product cannabinol. Starting from 3,5-dihydroxybenzoic acid (**10**), benzyl bromide **11** was prepared in very good yields. In a subsequent step, the halide was subjected to a cuprate-driven substitution to yield the 5-alkyl resorcinol ether **12** (Scheme 3). Although there are procedures in which this transformation is effected with an organometallic reagent in the presence of a copper catalyst, best results were obtained when stoichiometric amounts of a copper salt were used to prepare the Gilman cuprate prior to adding the benzyl bromide. Whereas the catalytic reaction using *n*-BuMgBr and 10 mol% Li_2CuCl_4 (Kochi's catalyst) yielded an inseparable 79:21 mixture of substitution product **12** and the dehalogenated by-product **13**, the reaction with pre-formed *n*-Bu_2CuLi gave exclusively the desired product. With this *ortho*-lithiation precursor in hand, we turned our attention to the Ullmann–Ziegler coupling.

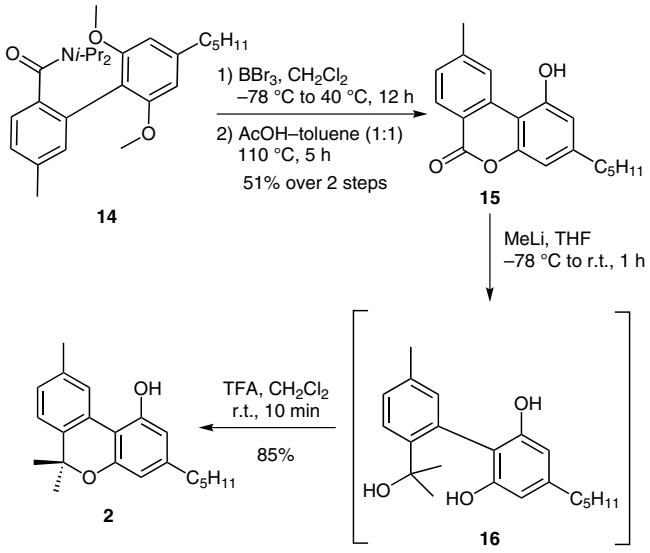
Table 1 Substrate Scope of the Approach

Entry	Ar_2CuLi	Ar–I	Product	Yield (%)
1	 **8**	 **6a**	**7a**	31
2	 **9a**	 **6a**	**7a**	97
3	 **9b**	 **6a**	**7b**	86
4	 **9c**	 **6a**	**7c**	73
5	 **9a**	 **6b**	**7d**	84

Using the protocol described above, two equivalents of resorcinol ether **12** were converted into the corresponding Gilman cuprate and subsequently coupled with 2-iodobenzamide **6a** to give biphenyl **14** in 75% yield (Scheme 4). Although only one equivalent of **12** ends up in the coupling product, this is only a minor drawback because the second equivalent can be easily recovered during workup.



Scheme 3 Synthesis of 1,3-dimethoxy-5-pentyl benzene **12**



Scheme 4 Conversion of biphenyl **14** into CBN

In the next step, biaryl **14** was treated with BBr_3 to cleave the methyl ether protecting groups. After hydrolysis with methanol and aqueous workup, the crude product was subjected to acidic cyclization to give lactone **15** in 51% yield over two steps. The cannabinol synthesis was completed by introducing the geminal methyl groups through the addition of two equivalents of methyllithium to give tertiary benzylic alcohol **16**, which was cyclized by treatment with trifluoroacetic acid to yield cannabinol (**2**) in 85% over two steps (Scheme 4).

In conclusion, it was demonstrated that a modified Ullmann–Ziegler coupling is a very useful key step in the synthesis of dibenzo[*b*,*d*]pyran natural products in general and CBN-type cannabinoids in particular. To show this, several model key intermediates with a substitution pattern resembling cannabinol were prepared. The compounds were obtained in good to excellent yields starting form easily accessible starting materials. A variety of groups may be introduced to the resorcinol moiety, for example, by cuprate-mediated benzylic substitution or by subjecting a substituted benzaldehyde to a combination of the Wittig olefination and a hydrogenation step. The other part of the molecule may be derived from a wide range of commercially available benzoic acids.

As a further proof of principle, the procedure was extended to a synthesis of cannabinol, which was synthesized in a total yield of 15% over nine steps (longest linear sequence of reactions, starting from 3,5-dihydroxybenzoic acid).

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(18) Nüllen, M. P.; Göttlich, R. *Synthesis* **2011**, 1249.
(19) **Typical Procedure:** The resorcinol derivate (2 equiv) and anhydrous TMEDA (2 equiv) were dissolved in anhydrous 1,2-dimethoxyethane (DME) and cooled to 0 °C before adding *n*-butyllithium (2.5 M in hexanes, 2.2 equiv) by using a syringe. The mixture was stirred for 1.5 h then $CuBr{\cdot}SMe_2$ (1 equiv) was added and stirring was continued for 30 min. $[Pd(PPh_3)_4]$ (7.5 mol%), aryl iodide (1 equiv) and anhydrous NMP were added and the reaction mixture was heated for 12 h in a sealed Schlenk tube. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, followed by extraction of the aqueous layer with MTBE (3×). The combined organic layers were washed with concentrated aqueous NH_3 solution and brine, before being dried with $MgSO_4$. After removal of the solvents, the desired biphenyl compound was isolated by flash chromatography.

