A SIMPLE SYNTHESIS OF 3-SUBSTITUTED FURANS. THE PREPARATIONS OF DENDROLASIN, PERILLENE AND CONGENERS Steven P. Tanis*¹ Department of Chemistry, Michigan State University East Lansing, Michigan 48823

Summary: The Grignard reagent 7, derived from 3-chloromethyl furan, reacts with various alkyland allylic halides, in the presence of Li₂CuCl₄, to provide high yields of 3-substituted furans.

The 3-substituted furyl moiety is present in numerous natural products² such as perillene la,³ dendrolasin lb,³ ambilol-A 2,⁴ ambilol-B 3,⁴ and annonene 4^5 . Although many methods have been reported for the synthesis of 3-substituted furans⁶ they generally require many steps, relatively inaccessible starting materials, or proceed in low overall yields. In this letter we wish to describe a convenient, high yield procedure for the synthesis of 3-substituted furans which utilizes readily available furan containing precursors.



We have chosen to investigate the preparation of 3-substituted furans by concentrating on the construction of the CH_2 -R bond (eq.1) to an isoprenoid-like furyl methyl precursor. In principle this bond can be formed in either of two polar senses. Path a represents the normal polarity carbon-carbon bond forming sequence, in which the furyl unit serves as the electrophilic partner, which has been widely employed. In contrast, only a few synthetic operations based on the reverse charge affinity pattern are known (path b).⁷ With two exceptions^{7d,f} these methods require the removal of pendant heteroatoms to reveal the product furan 5.



The simplest synthesis of furans such as 5 (eq.1), via a path b approach, would involve the reaction of furyl organolithium 6, or Grignard reagent 7 with an appropriate electrophile. To the best of our knowledge 6 has been reported once in the literature, and 7, although it has been known since 1950,⁸ has been used rarely^{7d,8} providing a low yield of coupled product upon reaction with an allylic halide in the presence of Cu^I. Since a path b (eq.1) approach to the synthesis of 3-substituted furans would be quite useful, we have examined a route to 5 via the Grignard reagent 7.

The requisite Grignard precursor was readily prepared as outlined in equation 2. Diethyl 3, 4-furandicarboxylate g_{a}^{9a} was hydrolyzed to the corresponding mono-acid 8b which was heated in the presence of copper powder to afford ethyl furan-3-carboxylate g_{a}^{10} in 67% yield from 8a. Reduction (LiAlH₄) gave alcohol $10^{8,9b}$ (91%) which was submitted to the standard conditions for chlorination (SOCl₂, C₅H₅N, (C₂H₅)₂0)⁷. In our hands this reaction was capricious, affording chloride 11^{8} in yields ranging from 25-50%. Numerous variations in the procedure were investigated, including inverse addition of 10 to the thionyl chloride-pyridine mixture and substitution of s-collidine for pyridine, however we were unable to obtain reproducible yields of 11. When 10 was treated according to the procedure of Collington and Meyers (MSCl, LiCl,s-collidine, DMF)^{T1} chloride 11 was isolated in 80-85% yield as a water-white liquid (BP 56-57°C(25mm);lit.⁸42-43°C(17mm)). For ease of isolation, purity of product, and reproducibly high yield of 11, this method is vastly superior to chlorination with thionyl chloride.



Treatment of 11, in THF, with magnesium provided the Grignard reagent 7, quantitatively as determined by titration, ¹² as a golden-yellow solution. Initial coupling studies, performed with prenyl chloride 12^{13a} and geranyl chloride ^{13b} 13, failed to provide perillene 1a and dendrolasin 1b under various reaction conditions. However the reaction of 9 with 12 and 13 proceeded almost instantaneously at 0^o(THF) when Kochi's catalyst Li₂CuCl₄¹⁴ (0.1 eq,0.1 M, THF) was introduced giving perillene (bp 80^o(20mm), lit. ^{7c}53^o(13mm)) 1a^{15a,16} and dendrolasin^{15b,16,17} (bp 89-90^oC (0.5mm), lit. ^{6f} 110-115^o(8mm)) in 85% and 95% distilled yields respectively (eq.3).



A variety of alkyl and allylic halides were coupled with Grignard reagent 7 to give uniformly high yields of 3-substituted furans (Table I). Runs 1,2, and 3 demonstrate that both primary alkyl bromides and iodides as well as secondary alkyl iodides provide the corresponding alkylated furans. Allylic halides which are sterically similar at the halogen bearing and terminal vinyl carbons provide a mixture of SN_2 and SN_2 ' alkylated products (Runs 4 and 5). The reaction of an allylic halide containing a potentially reactive epoxide function (Run 6) proceeds smoothly affording 7,8epoxydendrolasin in 79% distilled yield uncontaminated by any products resulting from epoxide cleavage.

The following is a representative procedure:

To 0.104g(4.29 mg-atom) of magnesium turnings covered with 3mL of anh.THF under argon, was added 0.5g(4.29mmol) of 3-chloromethyl furan in 2mL of THF in one portion. The mixture was allowed to stir for 0.5 h at room temperature, then warmed in a preheated 50°C oil bath for 0.5 h to provide a golden-yellow solution of 9. The solution of 9 was chilled in an ice-water bath and 0.448g (4.29mmol) of freshly distilled 1-chloro-3-methyl-2-butene in 2 mL of THF was added in one portion followed immediately by the addition of 0.15 mL of a 0.1M solution of Li_2CuCl_4 in THF. The resulting black suspension is stirred for 5 minutes at 0° , cast into petroleum ether(50ml,30-60°), washed with 5% aq. sodium bicarbonate (50mL), water (50mL), and dried (Na_2SO_4). Concentration in vacuo provided a pale yellow liquid which was purified by bulb to bulb distillation BP 80° (20mm) to give 0.547g (85%) of perillene 1a as a colorless liquid.

The application of this methodology to the synthesis various natural products will be report-

ed shortly. ²⁰ <u>TABLE I</u>	RUN	<u>RX</u>	PRODUCT(S)	YIELD	
	1		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	X=Br 88% X=1 92%	
	2	XIB		X=Br 91% X=1 93%	
	3	ie X	$\sim \sim $	X≖Br NORXN X≖I 89%	
	4	Ĵ,	LL° ~	F ⁰ , 91%	
			(10:90)		
	5	∕~∕~Br	(75:25)	96%	
	6		ball?	7 9%	
	7	7∘ ્રૐnBu ₃	Bush	95%	
~\ ^71	iolde moto	a to icolatod	distilled products	Violde word no	<u>at</u>

isolated, distilled products. Yields were not optimized.

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- 16) This substance exhibited bp, ^IH-NMR, and MS data in accord with the assigned structure and in good agreement with literature values.
- 17) I wish to thank Prof. W.C. Still of Columbia University for spectral data and a sample of authentic dendrolasin.
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