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LEWIS ACID CATALYZED STEREOSELECTIVE ENE ADDITION OF FORMALDEHYDE TO 1,3-DIARYLCYCLOPENTENES - SYNTHESIS OF *TRANS*-2,5-DIARYL-2-CYCLOPENTENE-1-METHANOLS

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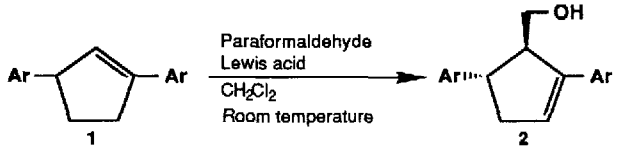
Summary: A stereoselective synthesis of *trans*-2,5-diaryl-2-cyclopentene-1-methanols via a diethylaluminum chloride (Et_2AlCl) catalyzed ene reaction of formaldehyde with 1,3-diarylcyclopentenes is described.

2,5-Diaryltetrahydrofurans are known potent Platelet Activating Factor (PAF) receptor antagonists.[1] Recently 2,5-diarylcyclopentanol derivatives, as carbocyclic analogs of 2,5-diaryltetrahydrofurans, have been reported to possess potent PAF receptor antagonist activity.[2] As part of work concerning structure-activity relationships in PAF receptor antagonists, we became interested in incorporating a methylene between the cyclopentane ring and the hydroxy group of 2,5-diarycyclopentanols. 2,5-Diaryl-2-cyclopentene-1-methanols could serve as ready precursors to these structures, however, there are no reported methods for the synthesis of this class of compounds. One method that we envisioned for their preparation was an ene reaction[3] of 1,3-diarylcyclopentenes (**1**)[4] with formaldehyde.

In this communication we report a synthesis of *trans*-2,5-diaryl-2-cyclopentene-1-methanols (**2**) via a Lewis acid catalyzed stereoselective ene addition of formaldehyde to 1,3-diarylcyclopentenes (**1**).[4]



a: Ar = 3,4,5-Trimethoxyphenyl
b: Ar = Phenyl
c: Ar = 3,4-Dimethoxyphenyl
d: Ar = 4-Methoxyphenyl
e: Ar = 3,5-Dimethoxyphenyl

The results with several 1,3-diarylcyclopentenes are summarized in Table 1. Reaction of alkene **1a** with paraformaldehyde was studied using several Lewis acids (Table 1, Runs 1-5). While zinc chloride and trimethylaluminum gave no reaction, aluminum chloride and ethylaluminum dichloride furnished the desired product **2a** in poor yields. Diethylaluminum chloride was found to be the best catalyst yielding **2a** in 61% yields. Inspection of Table 1 reveals that diethylaluminum chloride in general furnished the desired products[5] in acceptable yields. Results obtained from reaction of alkene **1b** with paraformaldehyde under identical conditions suggested that the presence of methoxyl groups in aromatic rings does not influence the reaction or the stereochemistry of the product.

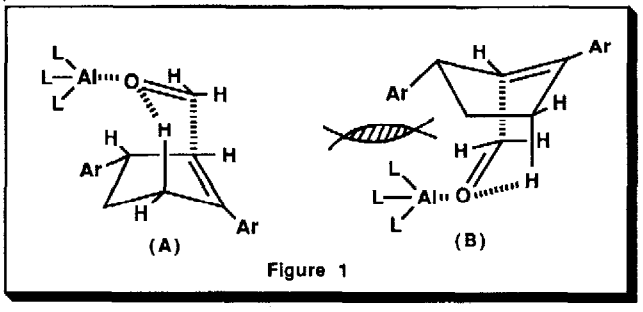
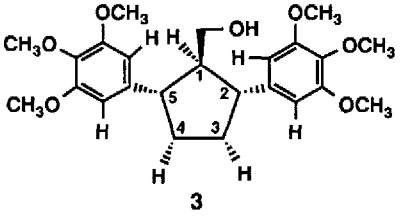


Figure 1



3

Based upon the reaction mechanism shown in Figure 1 we propose the stereochemistry of the ene product to be *trans*. Such selectivity is postulated because in conformation **A** the reaction occurs on the face of the molecule away from the 3-aromatic group. This should be favored over conformation **B** which suffers steric repulsion between the 3-aromatic group and the incoming reactive species.

The structure of **2a** was supported via COSY[6] and CH correlated NMR spectroscopy[7]. In order to evaluate the stereochemistry of the aromatic group relative to the hydroxymethyl group, the homoallylic alcohol **2a** was hydrogenated over 10% Pd-C to give (1β,2α,5α)-2,5-bis(trimethoxyphenyl)cyclopentanemethanol (**3**). Based on ^{1}H, ^{13}C-NMR[8] and NOE experiments,[9] the two aromatic groups in **3** are *cis* to each other and the hydroxymethyl group *trans*, consistent with the assigned stereochemistry in **2a**.

Table 1. Lewis Acid Catalyzed Ene Reaction of Paraformaldehyde with 1,3-Diarylcyclopentenes.

Run	1,3-Diarylcyclopentene	Lewis Acid	Product[a]	Yield (%)
1	**1a**	$ZnCl_2$	**2a**	0
2	**1a**	Me_3Al	**2a**	0
3	**1a**	$AlCl_3$	**2a**	11
4	**1a**	$EtAlCl_2$	**2a**	23
5	**1a**	Et_2AlCl	**2a**	61
6	**1b**	Me_3Al	**2b**	0
7	**1b**	$EtAlCl_2$	**2b**	14
8	**1b**	Et_2AlCl	**2b**	68
9	**1c**	Et_2AlCl	**2c**	67
10	**1d**	Et_2AlCl	**2d**	58
11	**1e**	Et_2AlCl	**2e**	60

[a] All compounds gave appropriate ^{1}H-NMR, mass spectral and/or elemental analysis data.

Thus, diethylaluminum chloride catalyzed ene reaction of paraformaldehyde with 1,3-diarylcyclopentenes provides a convenient and stereoselective synthesis of *trans*-2,5-diaryl-2-cyclopentene-1-methanols.

Acknowledgemnent: We thank Dr. J.R.Wareing for helpful suggestions and NMR, IR, MS and Elemental Analyses laboratories for spectral and analyses data.

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5. In a typical experiment, at room temperature, a solution of diethylaluminum chloride (0.55mL,1M in hexane) was added dropwise (during a 5 min period) under argon to a stirring mixture of 1,3-diarylcyclopentene (0.3 mmol) and dry paraformaldehyde (1.2 mmol) in dry methylene chloride (1.2 mL). Following an additional 15 minutes, the mixture was cooled in an ice bath, decomposed carefully with 3N hydrochloric acid, and extracted with ether and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated, and the crude product was purified by silica gel chromatography.
Characteristic ^{1}H-NMR ($CDCl_3$,δ) **2a**: 2.62(m,1H), 3.02(m,1H), 3.35(bm,1H), 3.5(m,1H), 3.8(underneath OMe,2H), 6.16(bm,1H); **2b**: 2.62(m,1H), 3.07(m,1H),3.4(m,1H), 3.56(m,1H), 3.76(m,2H), 6.23(m,1H); **2c**: 2.6(m,1H), 3.04(m,1H), 3.33(m,1H), 3.5(m,1H), 3.78(m,2H), 6.12(m,1H); **2d**: 2.54(m,1H), 3.02(m,1H), 3.31(m,1H),3.49(m,1H), 3.76(m,2H), 6.11(m,1H); **2e**: 2.6(m,1H), 3.02(m,1H), 3.35(m,1H), 3.48(m,1H), 6.2(d,1H).
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8. ^{1}H-NMR and ^{13}C-NMR suggests that a mirror plane exists in **3**, thereby indicating that the two aromatic groups are *cis* to each other.
^{1}H-NMR ($CDCl_3$,δ), 1.96(m,2H), 2.13(m,1H,CH-CH_2OH), 2.21(m,2H), 2.98(m,2H, 2x-CH-Ar), 3.59(m,2H, CH_2OH), 3.81(s,6H, 2x-OCH_3), 3.87(s,12H, 4x-OCH_3), 6.5(s,4H, Ar-H).
^{13}C-NMR ($CDCl_3$,δ) 153.33, 140.37, 136.74, 104.58, 63.01, 60.74, 57.47, 56.19, 48.71, 33.64.
9. NOE was observed between the aromatic protons and a methine proton at C-1 in **3** indicating it to be *cis* to the two aromatic groups. NOE was also observed between the aromatic protons and one proton each at C-3 and C-4 on the same side as aromatic groups in **3**.

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