

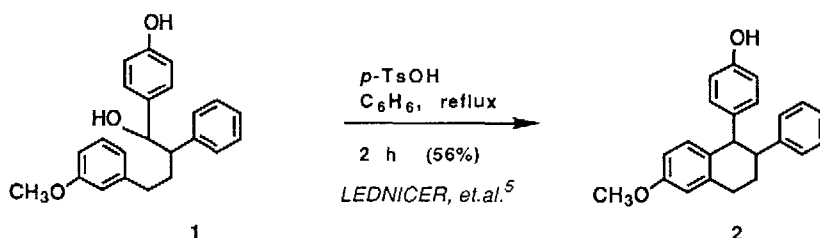
CATIONIC CYCLIZATION REACTIONS INITIATED BY STABILIZED BENZYL CATIONS

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SUMMARY: The *in situ* generation of stabilized benzyl cations and their subsequent use in cyclization reactions with a monosubstituted benzene, a furan and a β -keto ester terminators is described.

The role of electron rich aromatic rings in cationic cyclizations has been limited largely to their use as terminators in these reactions.¹ There are only limited reports of such a system being used to facilitate the initiation of a cyclization reaction, and the generality of the process has not been examined. Previous reports in this area come from the work of Murphy,² Evans,³ Kametani,⁴ Lednicer,⁵ and others,⁶ who have reported that 6-membered rings could be made quite efficiently using stabilized benzyl cations to initiate cyclization reactions, however only electron rich aromatic benzenes were used as the cyclization terminators.⁷ For example, Lednicer treated benzyl alcohol **1** with *p*-toluene sulfonic acid in refluxing benzene to afford a 56% yield of tetrahydronaphthalene **2** (equation 1).⁵

(equation 1)



Tetrahydronaphthalenes such as **2** are important fungicidal agents,⁸ inhibitor-antifertility agents,⁹ and possess hypocholesterolemic activity,¹⁰ yet their preparation via a benzyl cation initiated cyclization has seen only limited application. We report herein the development of a general method for the *in-situ* generation of stabilized benzyl cations and their subsequent use in cyclization reactions with several different cyclization terminators.

The work described here is directed toward studying the chemistry of unsubstituted, highly reactive quinone methides, which can be viewed as either a protonated quinone methide or a stabilized benzyl cation (Figure 1).¹¹ The generation of benzyl cations from benzylic alcohols and ethers is normally effected by an excess of a strong protic or Lewis Acid at ambient temperatures or above,²⁻⁷ however, there are exceptions.¹²

We reasoned that a bidentate group such as a methoxyethoxymethyl (MEM) ether would afford a quinone methide/benzyl cation under mild conditions upon treatment with Zn(II) or Ti(IV) at low temperatures, allowing access to the cationic intermediate under extremely mild conditions. While this notion provided the initial impetus for the studies presented here, our results show that simple alkyl ethers and unprotected benzyl alcohols are also sources of benzyl cations under mild conditions.

The required substrates shown in Table 1 were prepared using standard chemistry.¹³ The cyclization reactions were carried out using titanium tetrachloride for all terminators except a β -keto ester (entries 1 and 2) where trifluoroacetic acid proved more effective. The reaction tolerates terminators with a range of reactivity, is very fast, and the yields are excellent. Even though a strong Lewis acid is utilized in entries 4-9, the reaction times are extremely short and the temperature is low (-78°C). Entries 5 and 6 show a MEM ether and a methyl ether afford virtually identical yields of the tetrahydronaphthalene. This biologically active compound (entries 5 and 6) has been previously prepared by several groups via different routes.¹⁴ Entries 8 and 9 show that it is not necessary to protect the benzylic alcohol at all. This is the only example where the yield is higher when the reaction is conducted at room temperature.

It is worth noting that this *in-situ* procedure affords a higher yield of cyclized product than when quinone methide **3** (an isolated intermediate) is subjected to the same reaction conditions.^{11b} These studies bode favorably for the application of the reaction as a general synthesis method; the choice of leaving group is governed by its ease of introduction and chemical compatibility with the reaction sequence involved, not due to a limitation of the methodology.

The substituent requirements on the phenol oxygen have been examined to determine if a quinone methide (or protonated quinone methide) intermediate is required for a successful cyclization. In entry 2, the O-methyl phenol afforded the cyclized product in 99% yield, however the reaction half-life increased by a factor of 1.75 relative to the free phenol (4 minutes vs 7 minutes); the corresponding acetate (entry 3), fails to give any cyclized product under identical conditions, the only reaction that occurred was decomposition of the MEM ether (half-life > 1 week). The ability to form a quinone methide is not a requirement for a reaction to occur, however, the rate of reaction with a free phenol is notably faster than the corresponding O-alkyl phenol.

Entry 7 shows the cyclization results in modest stereoselectivity (4.4 : 1) when 1,3-disubstituted tetrahydronaphthalenes are formed using this methodology.

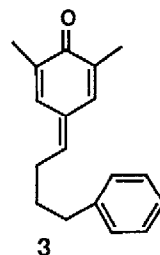
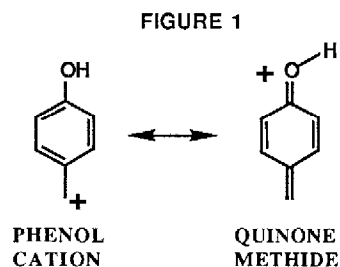
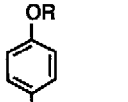
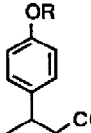
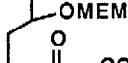
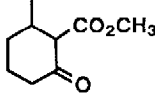


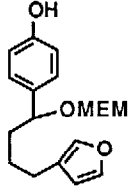
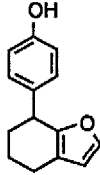
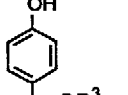
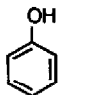
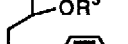
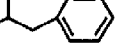
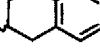
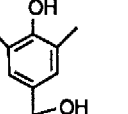
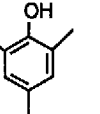
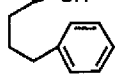
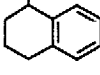


TABLE 1. BENZYL CATION INITIATED CYCLIZATION REACTIONS

ENTRY	SUBSTRATE ^a	CONDITIONS	PRODUCT	YIELD ^a (%)
1		R=H		94 (1:1) ^c
2		10 eq CF ₃ CO ₂ H 15 min, 24°C CHCl ₃		99 (1:1) ^c
3		R=Ac		b
4		4 eq TiCl ₄ 3 min, -78°C CH ₂ Cl ₂		76
5		R ² =H, R ³ =MEM		93
6		R ² =H, R ³ =CH ₃	4 eq TiCl ₄ 2 min, -78°C CH ₂ Cl ₂	96
7		R ² =CH ₃ , R ³ =MEM		97 (4.4:1) ^c
8		4 eq TiCl ₄ 2 min, -78°C CH ₂ Cl ₂		78
9		4 eq TiCl ₄ 2 min, 24°C CH ₂ Cl ₂		96

^aAll yields refer to isolated, purified compounds, characterized by ¹H NMR, ¹³C NMR, IR, MS and HRMS or elemental analysis, homogeneous by tlc and capillary GC analysis.

^bNo reaction was observed. ^cRatio of diastereoisomers determined by capillary GC.
MEM = CH₂OCH₂CH₂OCH₃

Based on the results described above we anticipate benzyl cation initiated cyclization reactions to be a general process that can be used with a large variety of cyclization terminators. Current work is directed toward applying the methodology to the synthesis of natural products.

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