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Lewis Acid-Directed Reactions of Benzoquinone Mono-/Bis-imines: Application to Syntheses of Substituted β- and γ-Tetrahydrocarbolines

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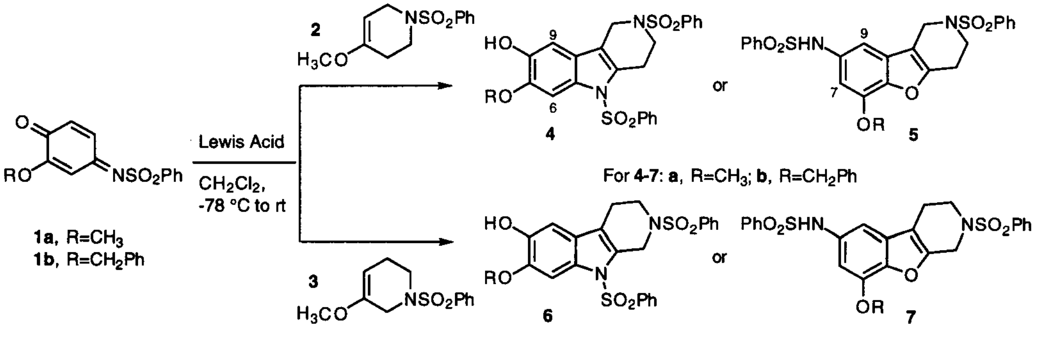
Abstract: *Ti(IV)-promoted reactions of N-phenylsulfonyl-3- and 4-piperidone enol ethers with 2-alkoxy-4-(N-phenylsulfonyl)imino-1,4-benzoquinone afford 8-alkoxy-7-hydroxy-tetrahydrocarbolines. However, reactions promoted by BF_3 produce substituted benzofurans. Ti(IV)- or BF_3-promoted reactions of 2-alkoxy-1-(N-benzoyl)-4-(N-phenylsulfonyl)-1,4-benzoquinone bisimines also afford substituted tetrahydrocarboline derivatives.*

Nucleophilic additions to quinones and imine derivatives have been used extensively in synthesis.[1] More recently, Lewis acid promotion of such processes have proven effective for reactions involving non-activated quinones[1f] and weakly nucleophilic allyl-silane/stannanes,[2] enol ethers,[3] styrenes[4] and simple π-systems.[4a] Of particular interest is that the regioselectivity of styrene additions to alkoxy quinones and imine derivatives can be controlled by the nature of the Lewis acid and can be used to selectively form either 2-aryl-2,3-dihydrobenzofurans or 2-aryl-2,3-dihydroindoles.[5] Seeking to extend the generality of this regiocontrol device[6] to other nucleophilic species, and its application to synthesis of biologically important entities, we examined reactions of 3- and 4-piperidone enol ethers with alkoxy quinone mono- and bisimides. Herein, we report that these reactions can be manipulated to selectively form highly substituted tetrahydro-β- or γ-carbolines or benzofuran analogs. Carbolines and reduced derivatives are found in numerous classes of pharmacologically active molecules fueling interest in new methods for their synthesis.[7]

Lewis acid-promoted reactions of simple enols and enol ethers with quinones have received limited attention. Early reports include $ZnCl_2$-promoted reactions of 1,3-dicarbonyl compounds and BF_3-promoted reactions of enol ethers to give benzofuranols and 2-alkoxy-2,3-dihydobenzofuranols, respectively.[3c-g] Mukaiyama has reported that trityl perchlorate-promoted reactions of silyl enol ethers with quinones and imide derivatives give benzofuran and indole derivatives,[3a] and recently Murphy reported that $AlCl_3$-promoted reactions of dihydro-furans and -pyrans yield products of 2+2 cycloaddition and spiroannulation.[3b] Thus, at the outset of our work, unresolved questions were: (1) Would basic sites on the piperidone enol ether interfere? (2) What would be the nature of the addition (i.e., 3+2, 2+2, spiro- or other)? (3) Would the reactions be subject to regiocontrol by the nature of the Lewis acid?



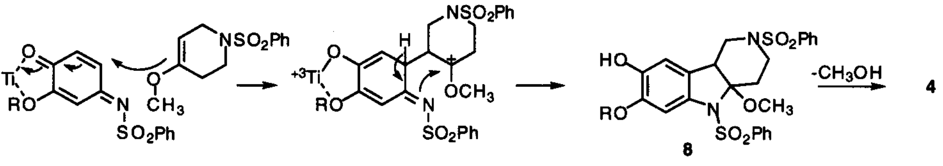
Enol ethers **2**/**3** were prepared by treatment of *N*-phenylsulfonyl-4- and 3-piperidone dimethyl ketals, respectively, with $AlCl_3/Et_3N$.[8] In the latter case, the product was found as a 4:1 mixture with its 2,3-double bond isomer; in subsequent reactions with the quinone monoimide, the minor component did not interfere. Addition of **2** or **3** to a mixture of quinone monoimide **1a** and excess amounts of $TiCl_4:Ti(OiPr)_4$ [1:1, 5 equiv of Ti(IV) with respect to monoimide] gave indole derivatives **4a** or **6a**,[9] after workup [sat. aq NH_4Cl, filtration (Celite)] and silica gel chromatography (Table 1). On the other hand, $BF_3{\cdot}OEt_2$-promoted reactions of the enol ethers with the monoimdes **1a**/**b** gave benzofuran adducts **5**/**7** exclusively [workup: sat. aq NH_4Cl or H_2O, extraction (CH_2Cl_2), and sg chromatography]. Reactions with $SnCl_4$ as Lewis acid gave lower yields and mixtures of **4**/**6** and **5**/**7**. Similarly, those of **1a** with **2** promoted by 1 equiv of $TiCl_4:Ti(OiPr)_4$ gave a 5:2 mixture of indole **4a** and benzofuran **5a**. Reactions of benzyloxy monoimide **1b** promoted by the Ti(IV) Lewis acid failed, only degradation of the monoimide was observed.

Table 1. Lewis Acid-Promoted Reactions of Quinone Monoimides 1a/b with Enol Ethers 2/3.[a]

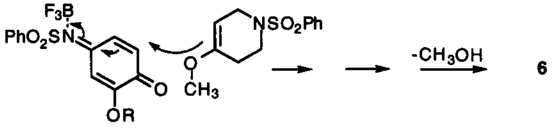
Entry	Imide	Enol Ether	Lewis Acid (equiv)[b]	Product(s) (% Yields)[c]	
1	**1a**	**2**	1:1 $TiCl_4:Ti(OiPr)_4$ (5)	**4a** (78)	
2	**1a**	**2**	1:1 $TiCl_4:Ti(OiPr)_4$ (1)	**4a** (49)	**5a** (20)
3	**1a**	**2**	$BF_3{\cdot}OEt_2$ (1)		**5a** (65)
4	**1b**	**2**	$BF_3{\cdot}OEt_2$ (1)		**5b** (66)
5	**1a**	**3**	1:1 $TiCl_4:Ti(OiPr)_4$ (5)	**6a** (58)	
6	**1a**	**3**	1:1 $TiCl_4:Ti(OiPr)_4$ (1)	**6a** (44)	
7	**1a**	**3**	$BF_3{\cdot}OEt_2$ (1)		**7a** (68)
8	**1b**	**3**	$BF_3{\cdot}OEt_2$ (1)		**7b** (36)

(a) All reagents were combined in CH_2Cl_2 at -78°C under nitrogen and allowed to warm to rt. (b) Equivalents of Ti or B with respect to the monoimide. (c) Isolated yields.

The position of the alkoxy substituents in **4**-**7** is assigned from ^1H NMR and IR spectral data.[9] In the NMR spectra of **4**/**6**, H-6 and H-9 appear as singlets at 6.7/7.7 ppm, whereas spectra of **5**/**7** show H-7 and H-9 as coupled doublets at 6.5-6.7 ppm with J=1.8-1.9 Hz. In addition, an OH stretch at ~3530 cm^{-1} is observed in IR spectra of **4**/**6**, and an NH stretch is found at ~3350 cm^{-1} in spectra of **5**/**7**.



The formation of indoles **4**/**6** or benzofurans **5**/**7** from the same starting materials is explained by regioselective Lewis acid activation of the monoimdes. The bidentate Lewis acid Ti(IV) binds to the C-1 carbonyl and C-2 alkoxy oxygens activating C-5 to nucleophilic addition followed by cyclization and elimination of MeOH. Workup of these reactions under basic conditions was also examined, and in some cases 2-methoxy-dihydroindole/benzofuran derivatives (e.g. **8**) could be isolated. A reason for the higher yields and regioselectivity found with excess amounts of Ti(IV) is not clear at the moment, but may suggest the involvement of a quinone monoimide-[Ti(IV)]$_2$ complex.[5] In the BF_3-promoted reactions, the monodentate Lewis acid binds to the more basic imide nitrogen (a vinylogous imidate), activating C-6 to addition.



A few reactions of quinone bisimides **9a/b** were also studied with both Lewis acid systems as promoters; indoles **10** and **11** were found,[9] usually in good yields (Table 2). The appearance of H-6 and H-9 as singlets at 7.7-7.8 and 8.5 ppm, respectively, in their ^1H NMR spectra and a carboxamide NH stretch at 3425 cm^{-1} in their IR spectra support the structural assignments. The regioselectivity of the addition is again consistent with selective activation of the bisimide through binding of the Lewis acid to the carboximide moiety (the more basic site for either a mono- or bidentate Lewis acid).

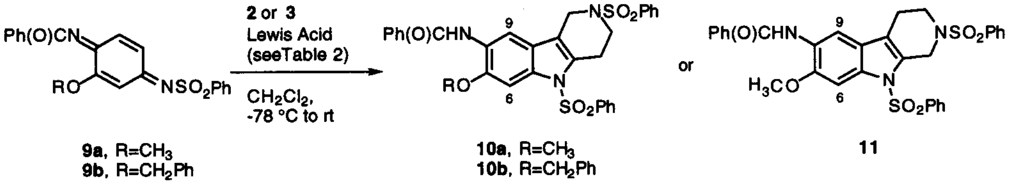


Table 2. Lewis Acid-Promoted Reactions of Quinone Bisimides 9a/b with Enol Ethers 2/3.[a]

Entry	Imide	Enol Ether	Lewis Acid (equiv)[b]	Product (% Yields)[c]
1	**9a**	**2**	BF_3•OEt_2 (1)	**10a** (77)
2	**9a**	**2**	1:1 $TiCl_4$:$Ti(OiPr)_4$ (5)	**10a** (81)
3	**9b**	**2**	BF_3•OEt_2 (1)	**10b** (65)
4	**9a**	**3**	BF_3•OEt_2 (1)	**11** (38)
5	**9a**	**3**	1:1 $TiCl_4$:$Ti(OiPr)_4$ (5)	**11** (80)

(a) All reagents were combined in CH_2Cl_2 at -78°C under nitrogen and allowed to warm to rt. (b) Equivalents of Ti or B with respect to the monoimide. (c) Isolated yields.

This new method holds considerable promise for regioselective syntheses of highly substituted carbolines and derivatives. For example, the phenol and amide substituents in **4**-**7** and **10**-**11** should be easily removable or convertible to various other groups via their corresponding triflates or amines[10] and oxidation of tetrahydrocarbolines to carbolines is well-precedented.[7] The chemistry is complimentary to approaches based on Fisher, Nenitzescu and related indole syntheses.[11]

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