Pergamon

Tetrahedron Letters, Vol. 36, No. 16, pp. 2713-2716, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00375-4

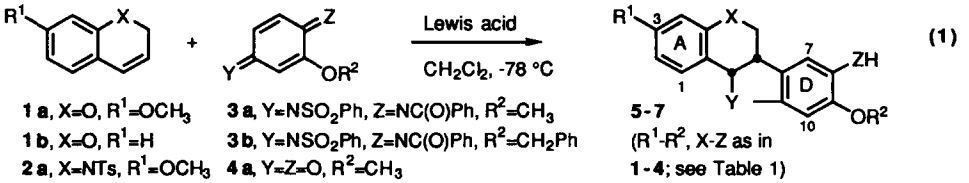
Cycloaddition Reactions of 1,4-Benzoquinone Mono- and Bisimides with Styrenyl Systems: New Syntheses of Nitrogen Substituted Azapterocarpans, Pterocarpans, 2-Aryl-2,3-dihydroindoles and -dihydrobenzofurans

Thomas A. Engler,* Kenneth O. Lynch, Jr., Wenying Chai and Steven P. Meduna
Department of Chemistry, University of Kansas, Lawrence, KS 66045-0046

Abstract: Lewis acid-promoted reactions of 1,4-benzoquinones and 1,4-benzoquinone bis- and monoimides with various 2*H*-chromenes, *N*-tosyl-1,2-dihydroquinolines and styrenes regio- and stereoselectively produce the title compounds in good yields.

Quinone chemistry has a long and rich history.[1] However, new facets of the synthetic utility of these molecules continue to emerge. For example, we recently reported Lewis acid-promoted reactions of styrenyl systems with 1,4-benzoquinones as efficient, regio- and stereoselective routes to 2-aryl-2,3-dihydrobenzofurans, pterocarpans, and other systems.[2] In comparison to the chemistry of quinones, the chemistry of quinone mono- and bisimides has not been as extensively explored.[3,4] Herein, we report that reactions of various quinone mono- and bisimides with styrenyl systems in the presence of Lewis acids provide regio- and stereoselective routes to the title compounds in good yield. Our interest in these systems stems from the known biological activity of molecules incorporating similar structures - particularly the recently discovered anti-HIV activity found in several pterocarpans.[2] Nitrogen isosteres of these pterocarpans were viewed as useful compounds in the development of an SAR profile and perhaps as potentially more active anti-HIV agents as well. A recent report on the synthesis of azapterocarpans prompts us to report our results at this time.[5]

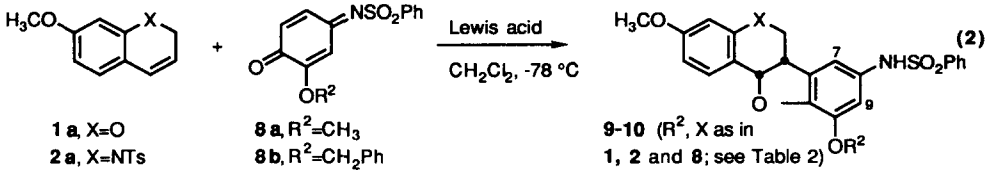
2-Alkoxy-1,4-benzoquinone bisimides **3a/b** were prepared by methods reported by Boger.[4] Addition of BF_3•Et_2O to solutions of **3a** or **3b** in CH_2Cl_2 at -78 °C followed by 2*H*-chromenes **1a** or **1b** gave azapterocarpans **5a-c**, respectively (eq 1 and Table 1).[6] Similar reactions of *N*-tosyl-7-methoxy-1,2-dihydroquinoline, **2a**,[7] with bisimides **3a/b** gave diazapterocarpans **6a/b**[6]; however, reactions of the unsubstituted dihydroquinoline **2b** failed. Reactions of **2a** with 2-alkoxy-1,4-benzoquinones **4a/b** were also studied with 1:1 mixtures of $TiCl_4$:$Ti(OiPr)_4$ as promoters and were found to give azapterocarpans **7a/b**[6] in good yields; again reactions of the unsubstituted dihydroquinoline **2b** failed. The substitution patterns in ring D of **5-7** were assigned from the appearance of H-7 and H-10 as singlets in ^1H NMR spectra and further supported by N-H absorbances at ~3425 cm^{-1} in IR spectra of **5/6** and results of ^1H-^1H NOE and HMBC experiments on **5**.[8] The stereochemistry of the B/C ring fusions was also determined by ^1H-^1H NOE experiments.



(1)

1a, X=O, R^1=OCH_3 **3a**, Y=NSO_2Ph, Z=NC(O)Ph, R^2=CH_3
1b, X=O, R^1=H **3b**, Y=NSO_2Ph, Z=NC(O)Ph, R^2=CH_2Ph
2a, X=NTs, R^1=OCH_3 **4a**, Y=Z=O, R^2=CH_3
2b, X=NTs, R^1=H **4b**, Y=Z=O, R^2=CH_2Ph

5-7 (R^1-R^2, X-Z as in **1-4**; see Table 1)

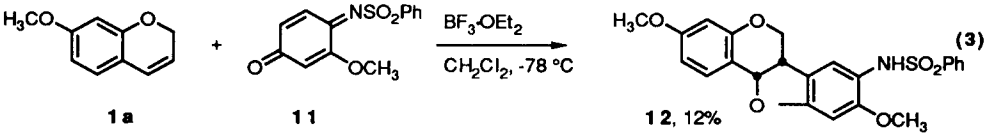


(2)

1a, X=O **8a**, R^2=CH_3
2a, X=NTs **8b**, R^2=CH_2Ph

9-10 (R^2, X as in **1**, **2** and **8**; see Table 2)

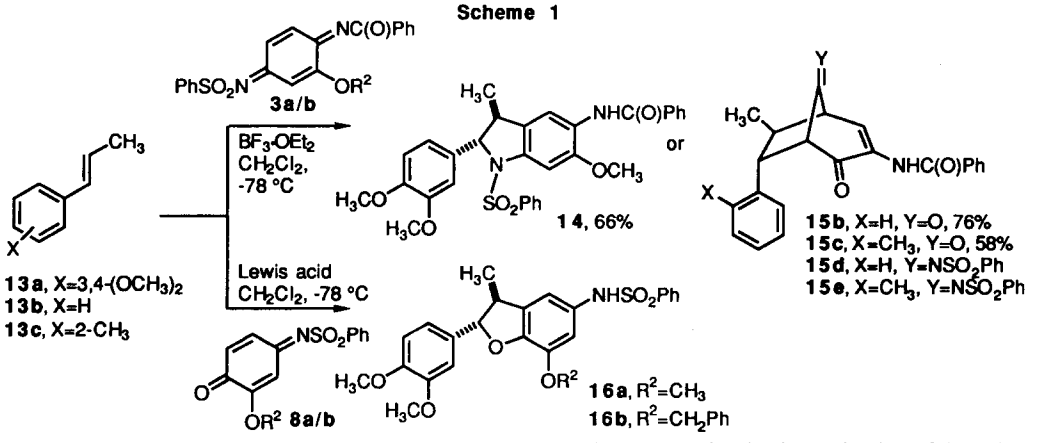
1,4-Benzoquinone monoimides **8a/b** were prepared by ceric ammonium nitrate oxidation of the corresponding *N*-(4-methoxyaryl)-benzenesulfonamides.[6,9] Treatment of the monoimides with a variety of Lewis acids in CH_2Cl_2 at -78 °C followed by addition of 7-methoxy-2*H*-chromene, **1a**, or dihydroquinoline **2a** gave nitrogen-substituted pterocarpans and azapterocarpans **9a/b** and **10a/b**, respectively (eq 2 and Table 2).[6] Again, cis ring fusions in **9/10** were evident from ^{1}H-^{1}H NOE experiments and the substitution pattern in ring D was indicated by $J_{H\text{-}7/H\text{-}9}$ = 2 Hz and N-H absorbances of 3350-3360 cm^{-1} in their IR spectra. Reactions of monoimide **11** with 2*H*-chromene **1a** also gave pterocarpan **12**,[6] however, the yield (unoptimized) was only 12% (eq 3); considerable reduction of the monoimide was observed in the latter reactions.



1a **11** **12**, 12%

The reactions described above are not limited to the chromenes and the dihydroquinoline. Indeed, BF_3·Et_2O-promoted reaction of (*E*)-3,4-dimethoxy-1-propenylbenzene, **13a**, with bisimide **3a** regio- and stereoselectively produced dihydroindole **14**[6] in 66% yield (Scheme 1). Similarly, reactions of monoimides **8a/b** with propenylbenzene **13a** in the presence of any one of a number of Lewis acids gave dihydrobenzofurans **16a/b**,[6] respectively (Table 3). In the ^{1}H NMR and IR spectra of indole **14**, H-4 (identified by NOE studies[10a]) is observed as a singlet at 8.28 ppm, due to deshielding by the benzamide oxygen, and an N-H stretch is observed at 3426 cm^{-1}. For dihydrobenzofurans **16a/b**, H-4 and -6 are both observed as slightly broad singlets in their NMR spectra, but NOE, HETCOR and HMBC experiments[10b] clearly indicated the stereo-/regiochemistry shown as does an N-H stretch at 3350 cm^{-1}. Finally, reactions of bisimide **3b** with propenylbenzenes **13b/c** yielded bicyclic adducts **15b/c**,[6] respectively, apparently via hydrolysis of **15d/e** on isolation. Similar bicyclic products have been found in reactions of 1,4-benzoquinones with styrenes.[2]

Scheme 1



A mechanistic rationale for the reactions described herein involves regioselective activation of the quinone bis- and monoimides by coordination of the Lewis acid to the more basic benzoyl- and sulfonyl-nitrogens of **3** and **8**, respectively, to give complexes **17** and **20** (Scheme 2). Cyclo-[2] or nucleophilic-addition of the styrenyl C=C bonds of **1**, **2** or **13** with the complexes gives intermediates **18** and **21** or **19** and **22**, respectively, which proceed on to the observed products by C-N bond formation and loss of H^+ (path a) or by dealkylation (path b). Regioselective Lewis acid-activation of quinone bisimides has been described in some detail by Boger[4] and the possibility of the cycloaddition route to **18/21** and then fragmentation to **19/22** is suggested by similar processes postulated in Lewis acid-promoted reactions of 1,4-benzoquinones with styrenes.[11] Alternatively, intermediates **18/21** may be formed from intermediates **19/22** produced in nucleophilic addition pathways. Similar mechanisms can be used to explain the formation of pterocarpans **7** and **12**.

Table 1. Lewis Acid-Promoted Reactions of 1,4-Benzoquinones and 1,4-Benzoquinone Bisimides with 2*H*-Chromenes and *N*-Tosyl-7-methoxy-1,2-dihydroquinoline.

Chromene/dihydroquinoline		Bisimide/Quinone			Lewis Acid	Product
R^1	X	Y	Z	R^2	(equiv)	(% yield)
1a, OCH_3	O	**3a**, NSO_2Ph	NC(O)Ph	CH_3	$BF_3{\cdot}OEt_2$ (1.2)	**5a** (63)
1a, OCH_3	O	**3b**, NSO_2Ph	NC(O)Ph	CH_2Ph	$BF_3{\cdot}OEt_2$ (1.1)	**5b** (62)
1b, H	O	**3b**, NSO_2Ph	NC(O)Ph	CH_2Ph	$BF_3{\cdot}OEt_2$ (2.0)	**5c** (47)
2a, OCH_3	NTs	**3a**, NSO_2Ph	NC(O)Ph	CH_3	$BF_3{\cdot}OEt_2$ (1.3)	**6a** (93)
2a, OCH_3	NTs	**3b**, NSO_2Ph	NC(O)Ph	CH_2Ph	$BF_3{\cdot}OEt_2$ (1.2)	**6b** (42)
2a, OCH_3	NTs	**4a**, O	O	CH_3	$TiCl_4$:$Ti(OiPr)_4$ (2.7)	**7a** (83)
2a, OCH_3	NTs	**4b**, O	O	CH_2Ph	$TiCl_4$:$Ti(OiPr)_4$ (2.2)	**7b** (100)

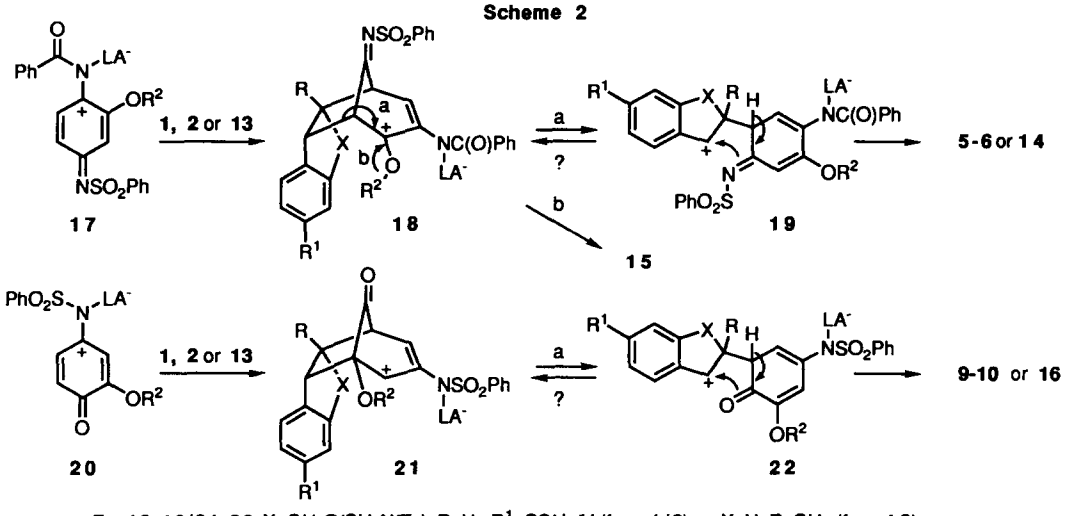
Table 2. Lewis Acid-Promoted Reactions of 1,4-Benzoquinone Monoimides with 7-Methoxy-2*H*-chromene and *N*-Tosyl-7-methoxy-1,2-dihydroquinoline.

Chromene/dihydroquinoline	Monoimide	Lewis Acid (equiv)	Product (% yield)
X	R^2		
1a, O	**8a**, CH_3	$BF_3{\cdot}OEt_2$ (1.1)	**9a** (87)
1a, O	**8b**, CH_2Ph	$BF_3{\cdot}OEt_2$ (1.3)	**9b** (91)
1a, O	**8a**, CH_3	$TiCl_4$ (1.1)	**9a** (90)
1a, O	**8a**, CH_3	$SnCl_4$ (1.0)	**9a** (85)
2a, NTs	**8a**, CH_3	$BF_3{\cdot}OEt_2$ (1.3)	**10a** (70)
2a, NTs	**8b**, CH_2Ph	$BF_3{\cdot}OEt_2$ (1.3)	**10b** (53)

Table 3. Lewis Acid-Promoted Reactions of 1,4-Benzoquinone Monoimides with Styrene **13a**.

Monoimide	Lewis Acid (equiv)	Product (% yield)
R^2		
8a, CH_3	$BF_3{\cdot}OEt_2$ (1.1)	**16a** (82)
8b, CH_2Ph	$BF_3{\cdot}OEt_2$ (1.2)	**16b** (86)
8a, CH_3	$TiCl_4$ (1.1)	**16a** (80)
8a, CH_3	$SnCl_4$ (1.0)	**16a** (85)

Scheme 2



For **18-19/21-22**: X=CH_2O/CH_2N(Ts), R=H, R^1=OCH_3/H (from **1**/**2**); or X=H, R=CH_3 (from **13**).

We continue to investigate the generality, mechanisms and applications of these reactions as well as the potential biological activity of the products obtained, and derivatives. The results of these studies will be reported upon completion.

Acknowledgments: Financial support was provided by the National Science Foundation (CHE-9116576 and OSR-9255223), the Alfred P. Sloan Foundation (as a Fellowship to TAE) and the University of Kansas General Research and J. R. and Inez Jay Funds. We thank Drs. David Vander Velde and Martha Morton of the University of Kansas NMR Laboratory for their helpful assistance.

References and Notes

1. a) *The Chemistry of Quinonoid Compounds, Vol. II, Parts 1 and 2*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: New York, 1988. b) Bruce, J.M. In *Rodd's Chemistry of Carbon Compounds, 2nd Ed., Vol. III (Aromatic Compounds), Part B*; Coffey, S., Ed.; Elsevier: Amsterdam, 1974; Chapter 8.

2. a) Engler, T.A.; Combrink, K.D.; Letavic, M.A.; Lynch, K.O., Jr.; Ray, J.E. *J. Org. Chem.* **1994** *59*, 6567-6587. b) Engler, T.A.; Wei, D.; Letavic, M.A.; Combrink, K.D.; Reddy, J.P. *J. Org. Chem.* **1994** *59*, 6588-6599. c) Engler, T.A.; Lynch, K.O., Jr.; Reddy, J.P.; Gregory, G.S. *Bioorg. Med. Chem. Lett.* **1993** *3*, 1229-1232. d) Engler, T.A.; Reddy, J.P.; Combrink, K.D.; Vander Velde *J. Org. Chem.* **1990** *55*, 1248-1254.

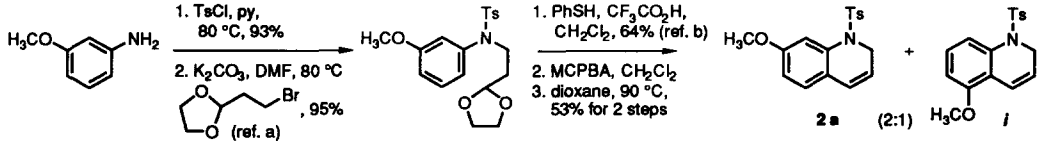
3. a) Brown, E.R. in ref. 1a, Part 2, Chapter 21. b) Adams, R.; Reifschneider, W. *Bull. Chim. Soc. Fr.* **1958**, 23-65.

4. For pertinent recent studies, a) Boger, D.L.; Zarrinmayeh, H. *J. Org. Chem.* **1990** *55*, 1379-1390. b) Boger, D.L.; Coleman, R.S. *J. Am. Chem Soc.* **1988** *110*, 4796-4807. c) Holmes, T.J., Jr.; Lawton, R.G. *J. Org. Chem.* **1983** *48*, 3146-3150.

5. Tökés, A.L.; Antus, S. *Liebigs Ann. Chem.* **1994**, 911-915.

6. All new compounds were characterized by high field (300/500 and 75/125 MHz) ^{1}H and ^{13}C NMR, IR and mass spectral analysis, including exact mass, and/or combustion analysis.

7. As shown below, dihydroquinoline **2a** was actually prepared and used as a 2:1 mixture of **2a** and ***i***. The minor component ***i*** did not react in the Lewis acid-promoted reactions with **3**, **4** or **8**, and could be recovered cleanly. a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969** *34*, 1122-1124 and Das, T.K.; Gupta, A.D.; Ghosal, P.K.; Dutta, P.C. *Indian J. Chem., Sect. B* **1976** *14b*, 238. b) McCombie, S.W.; Oritz, C.; Ganguly, A.K. *Tetrahedron Lett.* **1993** *34*, 8033-8036.



8. Selected data from ^{1}H-^{1}H NOE (Fig. 1) and HMBC (Fig.2) experiments on **5a/b**.

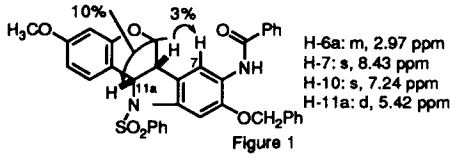


Figure 1

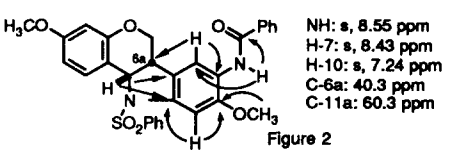
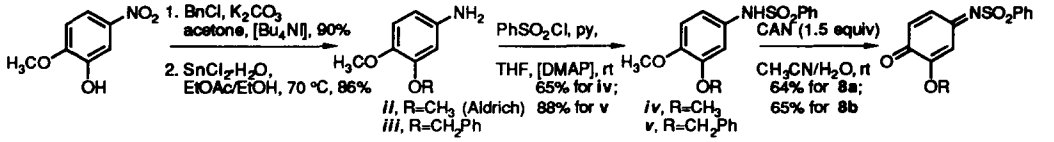


Figure 2

9. Prepared from ceric ammonium nitrate oxidations of *N*-aryl-benzenesulfonamides ***iv/v*** (cf. Jacob, P., III; Callery, P.S.; Shulgin, A.T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976** *41*, 3627-3629). The benzenesulfonamides were prepared from the corresponding 3-alkoxy-4-methoxyanilines ***ii/iii*** as shown.



10. a) Fig. 3 - selected data from an ^{1}H-^{1}H NOE experiment on **14**. b) Selected data from ^{1}H-^{1}H NOE (Fig. 4), HETCOR (Fig. 5) and HMBC (Fig. 6) experiments on **16a/b**.

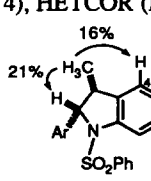


Figure 3

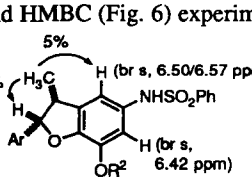


Figure 4

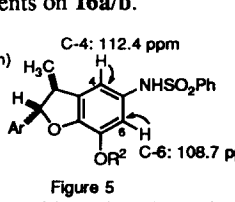


Figure 5

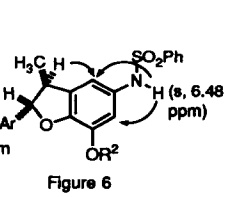


Figure 6

11. For reactions of similar intermediates formed in acid-catalyzed reactions of *N*-acylquinone imine ketals with styrenes, see Dalidowicz, P.; Swenton, J.S. *J. Org. Chem.* **1993** *58*, 4802-4804.

(*Received in USA* 12 *January* 1995; *revised* 21 *February* 1995; *accepted* 22 *February* 1995)