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Annulation of Heterocyclic Rings on Aromatic Templates: The Quinone Monoketal Route

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ABSTRACT: A double conjugate addition sequence anneals heterocyclic rings onto a 2-alkyl quinone monoketal intermediate. This operation, reminiscent of a Barco annulation, proceeds in excellent overall yield. The new chemistry offers interesting opportunities in alkaloid synthesis. Copyright © 1996 Elsevier Science Ltd

A diversity of chemically and biologically interesting natural products possess a central aromatic or quinoid nucleus fused to one or more heterocyclic rings, wherein a ring nitrogen atom is also connected to the central molecular core. This is apparent, e.g., in the discorhabdin/prianosin alkaloids,² which display an architecture resembling structure 1 (Scheme 1). Methodology commonly used for the construction of such subunits relies heavily on permutations of classical reactions. In particular, the inherent nucleophilicity of the central aromatic template is exploited in the electrophilic introduction of nitrogen, most often through nitration.³ The required heterocycles are then completed in an appropriate manner (cf. 2+3). We have recently become interested in an alternative approach involving umpolung of the aromatic unit (cf. 4+5). A generic quinone monoketal 6 appeared to be a logical synthon for 5, because the conjugate addition of a suitable amine to 6 may induce, e.g., a cascade of Michael reactions, à la Barco,⁴ or a variety of alternative events that might result in multiple heterannulation.



Surprisingly little literature exists regarding the key step that would initiate the desired annulation sequence: the bimolecular 1,4- addition of an amine to a quinone monoketal.⁵ Experiments with unsubstituted ketal 8^6 confirmed that reaction with near-stoichiometric amounts of secondary amines⁵ (e.g., pyrrolidine, cf. 7) proceeds reasonably well, but, not unexpectedly, it proved difficult to achieve selective mono-addition of primary amines. To illustrate, a 10% solution of 8 in C₆D₆ containing 1 equivalent of *n*-BuNH₂ rapidly equilibrated to a 1.5:1





mixture of 8 and 9. Other products, including double-1,4 adducts and, possibly, imines, were also evident. Complete consumption of 8 occurred only after addition of two more equivalents of amine, but then the double 1,4-adduct formed in a 1:2 ratio vs. the desired 9, together with polar byproducts. A change in solvent from benzene to THF did not improve things. The mono-adduct was best isolated as a methyl carbamate in poor overall yield (Scheme 2).

More significant (and useful) are the results obtained with 2-alkyl quinone monoketals. Substitution at position 2 of the substrate was desirable for our ultimate objectives; consequently, elevated- to complete regiocontrol in 1,4-addition to those substrates was regarded as critical. We were pleased to find that monoketals 11^6 reacted cleanly and regiospecifically at the less hindered conjugate position when treated with various amines. In sharp contrast to **8**, *even dissolution in neat amine resulted in no Michael type addition at the more hindered position, nor amine-carbonyl condensation*. This high regioselectivity may be primarily due to electronic (electron-releasing alkyl groups diminish electrophilic reactivity of the conjoined olefin) rather than steric (selectivity is equally high in the *tert*-butyl and the methyl series of monoketals **11**), effects. It should be mentioned that adducts of primary amines are rather stable, while those of secondary amines were prone to revert. The problem was acute with the adduct of prolinol (Table, entry **12i**); while no reaction occurred with Et₂NH. These results indicate that, with some caveats, controllable bimolecular mono-conjugate addition of amines to substituted quinone monoketals is generally possible and efficient.

MeQ OMe	Amine	R ³	Entry	Yield % ^b	Amine	R ³	Entry	Yield % ^b
	NH ₂	tBu	а	87	s	tBu	g	80
$11 \bigcirc R^3$	~~~NH ₂	tBu	b	92			•	
	HONH2	tBu	с	81	NH	tBu	h	85
Amine ^a	HO/-NH2	tBu	d	99		tBu	I	79 ^c
R ¹ MeO OMe	\cap	ťBu	е	94		tBu	j	89
\mathbb{R}^{2}	NH ₂	Me	f	93	∖_ŇH {	Me	k	71
12					Et ₂ NH	tBu	I	0 ^d

Table 1: Representative Conjugate Additions of Amines into 2-Alkyl-Benzoquinone Monoketals

^aProcedure **A** (all except **d**): a mixture of quinone monoketal and 1.5 eq. neat amine was stirred at room temperature until TLC showed complete conversion to the product. Crude product was obtained either by evaporation of the amine in vacuo (**a**, **b**, **g**, **h**, **j**, **k**), or by diluting the reaction mixture with CH₂Cl₂ and washing with water. The crude product was filtered through a short plug of silica gel (50 % EtOAc/hexanes, removal of last traces of amine and of polar impurities) to furnish practically pure adduct. Procedure **B** (entry **d**): a mixture of quinone monoketal and 1.2 eq. neat amine was diluted with enough THF to permit stirring. The mixture was heated to 65 °C until the reaction completed yields. All the above products were obtained as thick oils. "The crude product (99%) was a 4:1 equilibrium mixture of **11** and adduct **12i**, which reverted easily. ^dNo reaction.

The feasibility of multiple heterannulations was explored with compound 12d (Scheme 3). The choice of the tert-butyl substrate was purely one of convenience.⁷ The aminoalcohol used to make $12d^8$ functions as an equivalent of the Barco annulation⁴ reagent, which in its primary amine form (i.e., 4-aminocrotonate ester) is not a viable intermediate because of facile polymerization. Protection of the amine in 12d furnished 13, oxidation of which with PDC⁹ (but not PCC)¹⁰ gave the corresponding enal. This oxidation proceeded with varying degrees of double bond isomerization. The reaction was most conveniently allowed to run for several hours, in order to induce complete isomerization to the *trans* enal 14. The desirability of this isomerization became apparent during



(a) MeOOCCI, THF, aq. NaHCO₃, 25 °C 99 %; (b) 1.5 eq. PDC, CH_2CI_2 , 25 °C, 8 hrs, 76 %; (c) 0.05 eq. DBU, CCI_4 , 30 min, 0 to 25 °C, 94 %, 12 :1 all cis (text); (d) NaBH₄, EtOH, 0° C, 94 %; (e) phthalimide, DEAD, PBu₃, ether, 80 %; (f) N₂H₄.H₂O, MeOH, 25 °C, 95 %; (g) benzene, reflux, 4Å mol. sieves, 100 %; (h) 1.5 equiv. BBr₃, CH_2CI_2 , -15 °C, 98 %.

subsequent manipulations. Exposure of 14 to a catalytic amount of DBU precipitated an instantaneous Michael cyclization to a mixture of 15 (major) and 16. The stereochemistry of 15 rests upon NOEDS measurements¹¹ (Scheme 3). The diastereomeric ratio afforded by the cyclization step was a function of both enal geometry and solvent polarity. The *trans* enal gave highest selectivity for 15, a feature that proved to be highly advantageous for a second heterannulation sequence, hence the importance of allowing sufficient time during the oxidation step for complete *cis-trans* isomerization to occur. Furthermore, selectivity for 15 improved with decreasing solvent polarity, advancing from a modest 3:1 in THF to a substantial 12:1 in CCl₄ (the best medium for this transformation). MNDO-RHF calculations¹² allow us to estimate that the *all cis* isomer 15 is less stable than 16 ($\Delta H_f^{\circ} \approx 4$ kcal/mol). The experimentally observed preference for the less stable *cis* product 15 signifies that the cyclization reaction proceeds largely under kinetic control. Probably, a non-polar solvent exerts its beneficial action both by enforcing dipolar interactions between donor and acceptor sites,¹³ and by disfavoring equilibration.

A second heterannulation sequence was readily accomplished starting from 15. Thus, NaBH₄ reduction, Mitsunobu reaction of the resulting alcohol with phthalimide, and hydrazinolysis of the resultant 18, furnished amine 19. No special precautions were necessary to safeguard the ketone from NaBH₄ or hydrazine, thanks to the effective steric shielding provided by the tert-butyl group. Indeed, amine 19 was stable at room temperature, but cyclized cleanly to imine 20 in refluxing benzene. This imine aromatized readily to 21 upon treatment with BBr₃ (Scheme 3).¹⁴ A multiple (in this case, double) heterannulation sequence on an aromatic nucleus had thus been fully demonstrated. Finally, we note that the amine arising from the minor (*trans*) cyclization product 16 formed the imine considerably less readily than 19 (the *trans* imine contains 2.2 kcal/mol greater strain energy, MM+),¹² reinforcing the urgency of high *cis* selectivity during the Michael cyclization.¹⁵

The techniques described in this Letter offer advantageous alternatives to more traditional methods for the construction of polycyclic heterocycles fused to aromatic/quinoid sectors, and may appreciably facilitate the synthesis of natural products incorporating those substructures. We are actively pursuing several such opportunities, and further ramifications of these ideas will be described in due course.

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- 7. Methylation of tert-butyl hydroquinone was quite selective for the less hindered OH; but the 2-methyl analogue reacted with almost no selectivity, necessitating a painstaking separation. Consequently, we focused on intermediates in the tert-butyl series to explore further transformations.
- 8. Obtained from cis -2-butene-1-4-diol and phthalimide by the Volante modification (Volante, R. P. *Tetrahedron Lett.* 1981, 22, 3119) of the Mitsunobu reaction (Mitsunobu, O. Synthesis 1981, 1), followed by hydrazinolysis.
- 9. Corey, E. J.; Schmidt, G. Tetrahedron Lett. 1979, 20, 399.
- 10. The more acidic PCC (Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2650) caused cleavage of the dimethyl ketal and oxidation of the aromatic ring to a quinone.
- 11. We thank Dr. Larry Alemany, of this Department, for his valuable assistance with these measurements.
- 12. All computational work was carried out with the HYPERCHEM 4.0[®] package, available from Hypercube, Inc., Waterloo, Ontario, and running on a Windows[®] based Pentium/100 PC system.
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- 15. Data for representative compounds (phys. state, ¹H (250 MHz), ¹³C NMR [CDCl₃, δ, ppm]; MS [M⁺]): **11d** oil 6.72 (dd, 1H, $J_1=10.1$, $J_2=3.1$ Hz); 6.55 (d, 1H, J=3.1 Hz); 6.18 (d, 1H, J=10.1 Hz); 3.35 (s, 6H); 1.23 (s, 9H). 185.4; 147.7; 140.4; 136.9; 132.1; 108.8; 93.3; 50.3; 34.3; 29.1. 210. 12d oil 6.25 (d, 1H, J=2.0 Hz); 5.58 (m, 2H); 3.92 (d, 2H, J=4.2 Hz); 3.14 (m, 10H); 2.60-2.52 (A part of AB, dd, 1H, J₁=16.1, J₂=3.4 Hz); 2.47-2.38 (B part of AB, dd, 1H, J₁=16.1, J₂=5.0 Hz); 1.29 (s, 1H); 1.04 (s, 9H). 197.5; 148.6; 137.8; 131.1; 129.4; 98.3; 62.2; 56.3; 49.3; 48.2; 47.7; 41.3; 34.3; 28.8. 249. 13 mp 93-94 °C 6.56 (s, 1H); 5.59 (br. s, 2H); 4.00 (br. s, 2H); 3.86 (br. s, 2H); 3.71 (s, 3H); 3.28 (br. s, 6H); 2.7 (m, 2H); 1.18 (s, 9H). 196.4; 171.0; 149.4; 141.9; 130.8; 128.3; 98.0; 62.7; 60.2; 52.8; 50.0; 49.5; 42.2; 34.7; 28.9; 14.0. 355. 14 mp. 103-105 °C 9.69 (d, 1H J= 7.8 Hz); 6.71 (br.s, 1H); 6.56 (br. s,1H); 6.08 (m, 1H); 4.97 (br. s, 1H); 4.20 (br. s, 1H); 4.09 (br. s, 1H); 3.69 (br. s, 3H); 3.27 (br. s, 6H); 2.77-2.55 (br. m, 2H); 1.15 (s, 9H). 195.8; 193.2; 154.8; 150.4; 141.0; 132.2; 108.8; 98.7; 53.8; 53.2; 50.6; 49.8; 45.3; 41.7; 34.9; 29.0. 353. 15 mp. 139-142 °C 9.69 (s, 1H); 6.38 (s, 1H); 4.48 (d, 2H J=6.95); 4.04 (s, 2H); 3.95 (br. m, 2H); 3.63 (s, 3H); 3.32 (s, 3H); 3.03 (s, 3H); 1.13 (s, 9H). 199.3; 198.1; 156.8; 151.93; 142.60; 98.64; 76.26; 65.56; 58.90; 52.81; 52.50; 49.48; 42.00; 35.97; 29.40; 15.03. 353. 17 low-melting s., 6.37 (s, 1H); 4.49 (dd, 1H J₁=6.5, J₂= 1.8 Hz); 3.91 (m, 2H); 3.65 (s, 3H); 3.35 (s, 3H); 3.16 (t, 2H J=7.3 Hz); 3.01 (s, 3H); 2.70 (m, 2H); 2.23 (m, 1H), 1.64 (m, 1H); 1.40 (m, 1H); 1.14 (s, 9H). 199.5; 157.1; 152.2; 142.3; 98.7; 61.2; 58.8; 54.0; 53.4; 52.5; 49.6; 48.9; 40.7; 35.1; 30.0; 29.5. 355. 18 low-melting s., 7.75 (m, 4H); 6.39 (s, 1H); 4.51 (br. d, 2H); 3.90 (m, 2H); 3.70 (s, 3H); 3.45 (s, 3H); 3.30 (m, 2H); 3.09 (s, 3H); 2.10 (m, 1H); 1.75 (m, 1H); 1.65 (m, 1H); 1.25 (s, 9H). 20 oil 5.85 (bs, 1H); 4.55 (bs, 1H); 4.00 (m, 1H); 3.72 (s, 3H); 3.42 (s, 3H); 3.18 (m, 2H); 3.08 (s, 3H); 2.55 (m, 2H); 1.85 (m, 1H); 1.62 (bs, 1H), 1.20 (s, 9H); 99 (m, 1H). 336. 21: oil 9.68 (s, 1H); 6.70(s, 1H); 5.30 (s, 1H); 4.32 (m, 1H); 3.86 (s, 3H); 3.60-3.27 (br. m, 5H); 2.15 (br. m, 1H); 1.59 (br. m, 1H); 1.37 (s, 9H).

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