Pergamon

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Tetrahedron Letters 44 (2003) 8901–8903

TETRAHEDRON
LETTERS

Regiocontrolled [3+2] quinone-nitrile oxide entry to type II polyketide building blocks

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Received 30 August 2003; revised 17 September 2003; accepted 18 September 2003

Abstract—Bromine substituents on naphthoquinones effectively activate and orient the [3+2] dipolar cycloaddition reaction with nitrile oxides to generate regiodefined type II polyketide building blocks.

As part of a program directed towards the total synthesis of type II polyketide structures, including heliquinomycin (**1**)[1] and lactonamycin (**2**),[2] it was desirable to explore the feasibility of regiocontrolled nitrile oxide [3+2] cycloaddition reactions as a means of functionalizing unsymmetrically substituted naphthoquinone moieties. Specifically, in the case of heliquinomycin, a merging of the isocoumarin sector with the naphthoquinone by such a cycloaddition strategy would provide an expedient and convergent entry to this polyketide carbon framework[3] (Fig. 1).

Shiraishi and co-workers have studied stable aromatic nitrile oxide cycloadditions to simple quinones both experimentally and computationally in order to define the chemo- and regioselectivity of the cycloaddition.[4] Substrates with symmetrical alkyl-substitution reacted to provide the regioisomer in which the oxygen atom of the nitrile oxide was delivered at the carbon bearing the alkyl substituent (i.e. the sterically demanding side). Paredes and co-workers have studied cycloadditions with unsymmetrically substituted naphthoquinones and have demonstrated that the groups flanking the quinone moiety can exert modest to good regiocontrol through electronic effects.[5] Unfortunately, there are no examples with substituents on the quinone ring at the site of cycloaddition for comparison with Shiraishi's results. Armed with this precedent, it was prudent to commence this study in a model system relevant to the heliquinomycin problem. The results are summarized in Table 1.

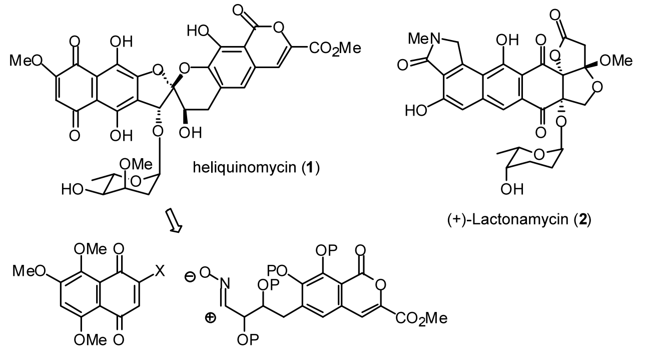

Figure 1. Structures of polyketide targets.

Early on, it was discovered that much cleaner chemistry could be affected through preparation and isolation of the hydroximoyl chloride precursors[6] rather than attempting the one-pot reaction from the oxime by the protocol popularized by Huisgen and others.[7] This decreases nitrile oxide dimerization and reduces undesired aromatic halogenation byproducts. The parent naphthoquinone structure **3a** (entry 1) was thus treated with a slight excess of readily prepared hydroximoyl chloride **4a**[8] (the isocoumarin model substrate) in methylene chloride at room temperature. Slow addition of triethylamine smoothly affects dehydrohalogenation and the ensuing [3+2] cycloaddition affords a 68% yield of a 1:1.6 mixture of regioisomeric adducts **5a** and **6a**. It is clear that the distal methoxy group of **3a** imparts a poor bias to orient the cycloaddition reaction. Placement of a methoxy group on the quinone **3b**[9] deactivated the system towards cycloaddition (entry 2) and no reaction was observed. By contrast, introduction of a bromine atom at this position[10] (entry 3) serves to

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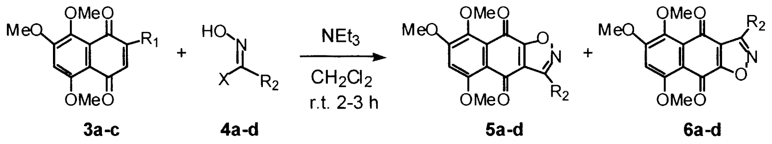
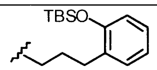
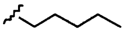
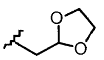
doi:10.1016/j.tetlet.2003.09.164

Table 1. Regioselective [3+2] cycloaddition reaction



3a-c **4a-d** **5a-d** **6a-d**

Entry	Quinone	R_1	hydroximoyl halide	X	R_2	Yield (%)	**5**:**6**
1[a]	**3a**	H	**4a**	Cl		68	**5a:6a** 1:1.6
2	**3b**	OMe	**4a**	Cl	"	n.r.	--
3	**3c**	Br	**4a**	Cl	"	90	**5a** only
4[b]	**3c**	Br	**4b**	Br	Br	78	**5b** only
5	**3c**	Br	**4c**	Cl		99	**5c** only
6	**3c**	Br	**4d**	Cl		86	**5d** only

[a] Initial [3+2] adduct oxidized to **5a**, **6a** upon exposure to air.

[b] Reaction carried out in EtOAc/H_2O with sodium bicarbonate. (ref. 11)

accelerate the cycloaddition reaction (presumably due to a decrease in the HOMO–LUMO gap) and effectively orients the dipolarophile to afford a 90% yield of the desired adduct **5a** as the only detected regioisomer. This type of orienting effect of bromine has been observed in Diels–Alder cycloadditions[11] and applies nicely to the [3+2] cycloaddition at hand.

Excited by this result, other nitrile oxide systems were screened. Bromonitrile oxide[12] effectively adds to quinone **3c** to afford bromoisoxazole **5b** again as a single regioisomer in 78% yield (entry 4). The bromine handle of adduct **5b** effectively opens up a wide array of transition metal-mediated cross coupling possibilities for further elaboration. Hydroximoyl chloride **4c**[13] reacts in essentially quantitative yield to afford isoxazole **5c** which can be parlayed in principle to the natural product F1005[14] through N–O cleavage[15] and demethylation. The reaction is tolerant of the acetal functionality as exhibited by entry 6 in which hydroximoyl chloride **4d**[16] is dehydrohalogenated and condensed with **3c** to afford isoxazole **5d** in 86% yield as a single regioisomer. Adduct **5d** was assigned by X-ray crystallographic analysis.

This work lays the foundation for application of the nitrile oxide cycloaddition reaction as a means of regioselectively functionalizing unsymmetrical naphthoquinones and will be applied to the construction of the heliquinomycin aglycon, which is currently under scrutiny. These results will be reported in due course.

Representative procedures:

Hydroximoyl chloride formation: To a solution of 250 mg (0.86 mmol) of oxime **4a** (X = H) in 15 mL of CH_2Cl_2 was added 114 mg (0.86 mmol) of *N*-chlorosuccinimide. After 12 h of stirring under nitrogen, the light-blue solution was washed twice with water and the combined aqueous layers were back extracted once with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a 1.5:1 mixture of *E*-*Z* isomers. The hydroximoyl chloride **4a** was taken directly onto the [3+2] reaction. ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (m, 4H), 6.88 (m, 2H), 6.77 (m, 2H), 2.63 (m, 2H), 2.53 (t, $J=4.5$ Hz, 1H), 2.23 (t, $J=4.5$ Hz, 1H), 1.96 (quin, $J=8$ Hz, 1H), 1.77 (quin, $J=8$ Hz, 1H), 1.01 (s, 9H), 0.23 (s, 6H).

[3+2] Cycloaddition: To a solution of bromoquinone **3c** (140 mg, 0.43 mmol) and hydroximoyl chloride **4a** (180 mg, 0.55 mmol) in 7.5 mL of CH_2Cl_2 was added 178 μL of triethylamine (1.28 mmol) dropwise and the orange solution was stirred for 2 h under nitrogen. The resulting solution was washed twice with water, and the combined aqueous layers were back extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography in 1:2 EtOAc/hexanes yielded 90% of isoxazole **5a** as an orange solid and 10% recovered starting material bromoquinone **3c**. **5c**: mp 98–100°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (m, 1H), 7.04 (m, 1H), 6.86 (m, 1H), 6.81 (s, 1H), 6.75 (m, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.89 (s, 3H), 3.08 (t, $J=7.5$ Hz, 2H), 2.72 (t, $J=7.5$ Hz, 2H), 2.12 (q, $J=7.5$ Hz, 2H), 0.99 (s, 9H), and 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) d 178.3, 173.2, 164.1, 162.7, 160.5, 159.4, 153.9, 146.0, 132.3, 130.6, 127.3, 127.2, 121.3, 120.7, 118.7, 114.2, 103.0, 61.6, 57.2, 56.8, 30.3, 27.6, 26.2, 25.7, 18.6, −3.8; IR (thin film) 3447, 2913, 2847, 1736, 1697, 1681, 1653, 1557, 1507. HRMS (CI^+) calcd for $C_{29}H_{35}NO_7Si$ $[M+H]^+$: 538.226106; found 538.22556.

Acknowledgements

We gratefully acknowledge Lawrence B. Alemany for his 2-D INADEQUATE NMR work for structure elucidation, John Thurston and Simon Bott for X-ray crystallographic data, and the Robert A. Welch Foundation (C-14189) and Rice University for financial support. J.L.S. was supported by Pfizer Inc. with a summer undergraduate research fellowship (SURF). J.P.D. was supported by an NSF predoctoral fellowship.

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