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

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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.

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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 framework³ (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.

Early on, it was discovered that much cleaner chemistry could be affected through preparation and isolation of the hydroximoyl chloride precursors⁶ 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 position¹⁰ (entry 3) serves to

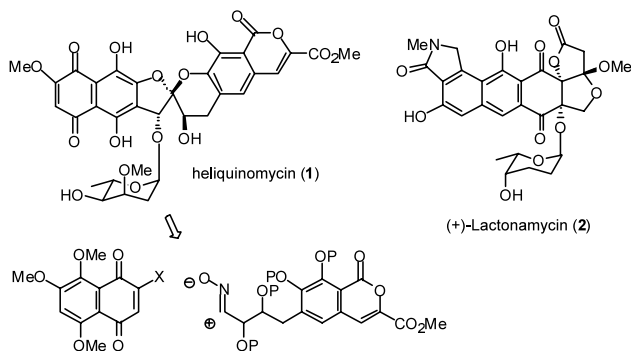


Figure 1. Structures of polyketide targets.

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Table 1. Regioselective [3+2] cycloaddition reaction

| 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 |

^aInitial [3+2] adduct oxidized to **5a**, **6a** upon exposure to air.^bReaction carried out in EtOAc/H₂O with sodium bicarbonate. (ref. 11)

accelerate the cycloaddition reaction (presumably due to a decrease in the HOMO–LUMO gap) and effectively orient 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 cycloadditions¹¹ and applies nicely to the [3+2] cycloaddition at hand.

Excited by this result, other nitrile oxide systems were screened. Bromonitrile oxide¹² 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 F1005¹⁴ through N–O cleavage¹⁵ 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 CH₂Cl₂ 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 Et₂O. The combined organic layers were dried over Na₂SO₄ 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, CDCl₃) 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 CH₂Cl₂ 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 Et₂O. The combined organic layers were dried over Na₂SO₄ 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 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 C₂₉H₃₅NO₇Si [M+H]⁺: 538.226106; found 538.22556.

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References

1. (a) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29; For isolation and characterization of heliquinomycin, see: (b) Chino, M.; Nishikawa, K.; Yamada, A.; Ohsono, M.; Sawa, T.; Hanaoka, F.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 480; (c) Chino, M.; Nishikawa, K.; Sawa, R.; Hamada, M.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 781; (d) Chino, M.; Nishikawa, K.; Tsuchida, T.; Sawa, R.; Nakamura, H.; Nakamura, K. T.; Muraoka, Y.; Ikeda, D.; Naganawa, H.; *J. Antibiot.* **1997**, *50*, 143; (e) Chino, M.; Nishikawa, K.; Umekita, M.; Hayashi, C.; Yamazaki, T.; Tsuchida, T.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 752.
2. Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403–1405.
3. For other synthetic work related to heliquinomycin, see: (a) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4709; (b) Siu, T.; Qin, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4713; (c) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567; (d) Xie, X.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 2661.
4. (a) Hayakawa, T.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2216; (b) Hayakawa, T.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1643; (c) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079; (d) Mukawa, T.; Muraoka, J.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 739; (e) Shiraishi, S.; Holla, B. S.; Imamura, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3457.
5. Farina, F.; Martin, M. V.; Munoz, M.; Paredes, M. C.; Rodriguez, R. *Heterocycles* **1995**, *40*, 413.
6. Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
7. Jaeger, V.; Colinas, P. A. *Chem. Hetero. Compnd.* **2002**, *59*, 361.
8. Robertson, A.; Waters, W. A. *J. Chem. Soc.* **1948**, 1574.
9. Simoneau, B.; Brassard, P. *Tetrahedron* **1986**, *42*, 3767.
10. Clive, D. L. J.; Khodabocus, A.; Vernon, P. G.; Angoh, A. G.; Bordeleau, L.; Middleton, D. S.; Lowe, C.; Kellner, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1433.
11. (a) Bouammali, B.; Pautet, F.; Fillion, H.; Soufiaoui, M. *Tetrahedron* **1993**, *49*, 3125; (b) Krohn, K.; Khanbabaee, K. *Lieb. Ann. Chem.* **1994**, 1109; (c) Chaker, L.; Pautet, F.; Fillion, H. *Heterocycles* **1995**, *41*, 1169; (d) Valderama, J. A.; Gonzalez, M. F.; Valderrama, C. *Tetrahedron* **1999**, *55*, 6039.
12. Rohloff, J. C.; Robinson, J., III; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113.
13. Bose, D. S.; Goud, P. R. *Synth. Commun.* **2002**, *32*, 3621.
14. Flegel, T. W.; Meevootisom, V.; Thebtaranonth, Y.; Zheng, Q. T.; Clardy, J. *J. Antibiot.* **1984**, *37*, 325.
15. (a) D'Alcontres, G. S. *Gazz. Chim. Ital.* **1950**, *80*, 441; (b) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877; (c) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401.
16. Baxter, A. D.; Binns, F.; Javed, T.; Roberts, S. M.; Sadler, P.; Scheinmann, F.; Wakefield, B. J.; Lynch, M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 889.