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Functionalized *o*-Bis(chloromethyl)pyridines as Precursors for Pyridine *o*-Quinodimethane Analogues and their [4+2] Cycloadducts.

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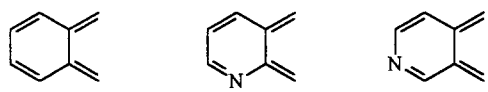
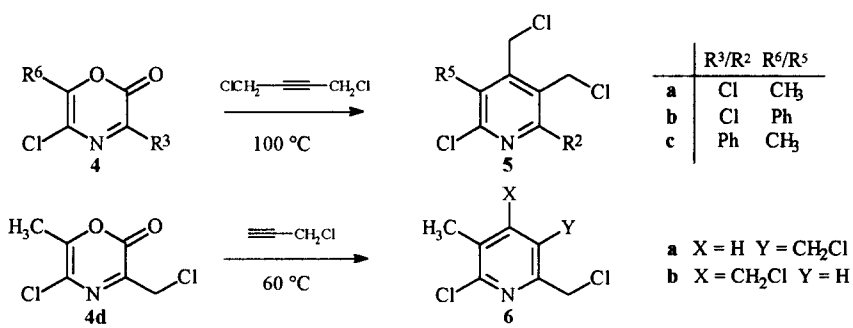
Abstract: *From oxazinones **4**, precursors for pyridine o-quinodimethane analogues are made accessible via cycloaddition with 1,4-dichloro-2-butyne and propargyl chloride. Subsequent 1,4-elimination of the polyfunctional o-bis(chloromethyl)-pyridines affords both 2,3- and 3,4-dimethylene compounds, which are trapped in situ with various dienophiles.*

Since the first report of *ortho*-quinodimethane (*o*-QDM) (**1**) in 1957 by Cava and Napier,[1] many investigations have been devoted to prepare and characterize this diene system, and to explore synthetic applications for the *o*-QDM compounds and their heterocyclic analogues.[2] In contrast, pyridine *o*-QDM systems (**2**, **3**) have hardly been described and to our knowledge, only the groups of Ito and Kametani succeeded in applying the pyridine *o*-QDM system to a Diels-Alder reaction.[3]



1 **2** **3**

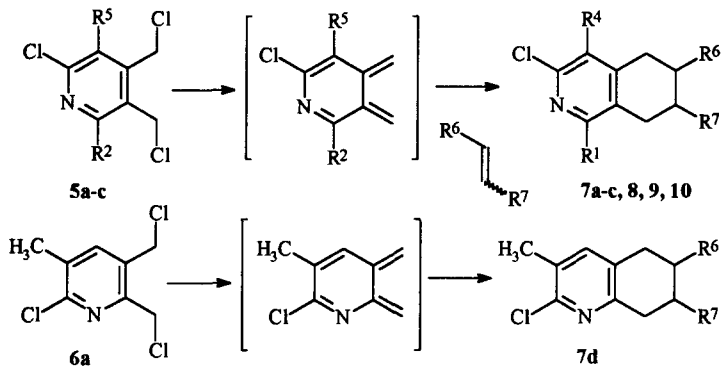
We now disclose an efficient route for the preparation of the functionalized *o*-bis(chloromethyl)-pyridines **5** and **6** and for their conversion to the corresponding *o*-QDM compounds which are trapped *in situ* with various dienophiles. Both 3,4- and 2,3-bis(chloromethyl)pyridines were derived (scheme 1) from the cycloaddition of oxazinone compounds: these can be accessed (**4a-b**) from the corresponding cyanohydrins $R^6CHOHCN$, and subsequently modified (**4c-d**) by displacing the imidoyl chloro substituent with various R^3-groups.[4]



Scheme 1. Synthesis of 2,3- and 3,4-*o*-bis(chloromethyl)pyridines.

Cycloaddition of oxazinones **4a-c** with 1,4-dichloro-2-butyne and concomitant expulsion of carbon dioxide produced the 3,4-bis(chloromethyl)pyridines **5a-c** in excellent yields (80-98 %). The alternate 2,3-substituted pyridine **6a** was prepared by similar addition of propargyl chloride on the 3-(chloromethyl)oxazinone **4d** (derived[5] from **4a** *via* successive treatment with diazomethane and HCl); it was separated from its 2,4-regioisomer **6b** using HPLC (isomeric ratio 3:2). These examples clearly show that variation in the substitution pattern of the oxazinones provides access to a broad range of functionalized *o*-bis(chloromethyl)pyridines.

The pyridine precursors were heated with sodium iodide in DMF at 65 °C to give the corresponding *o*-QDM intermediates, which were trapped *in situ* with various dienophiles (scheme 2 and table 1).[6] In the reaction of pyridine **5a**, omission of the trapping agent resulted in isolation of the analogous bis(iodomethyl)pyridine, which presumably is a direct precursor for 1,4-elimination of iodine.[7] As dienophiles *N*-phenylmaleimide, dimethyl fumarate, methyl acrylate, and dihydrofuran were utilized, affording good to moderate yields of addition products (table 1). From the reaction with methyl acrylate, two regiomeric adducts **9a** and **9b** (ratio 1:1) were separated using chromatography on alumina with chloroform as the eluent.



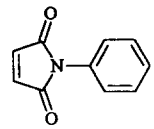
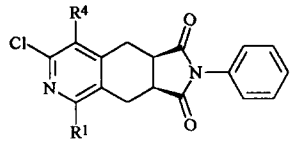
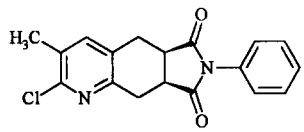
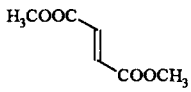
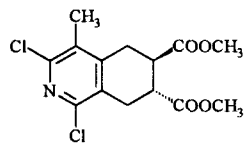
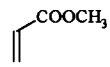
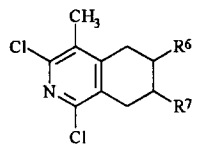
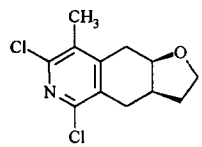
Scheme 2. Conversion of o-bis(chloromethyl)pyridines to *o*-QDM systems and their cycloaddition with various dienophiles.

The pyridine synthons and cycloadducts were characterized by ^1H and ^{13}C NMR, and mass spectrometry.[8,9] For the *cis*-fused *N*-phenylmaleimide adduct **7a**, a diaxial boat conformation **A** (figure 1) was assigned on basis of both N.O.E. measurements and the ^3J coupling constants for the angular protons H3a and H9a. That one form (either **A** or **B**) prevails, was demonstrated by the spatial vicinity of the 8-methyl group and the equatorial, but not the axial proton H9. On the other hand, the coupling values $^3J_{3a,9a}$ = 10 Hz, and $^3J_{4,3a}$ = $^3J_{9,9a}$ = 6 and 4 Hz preclude an exclusive ax,ax disposition of vicinal protons (form **B**). In a similar way, a diequatorial half-chair form (**C**) was attributed to the *trans* fumarate adduct **8**.

The scope of this oxazinone approach has been extended by reaction with dihydrofuran, an electron rich dienophile. Addition to the *o*-QDM system derived from pyridine **5a** afforded compound **10** as a single regioisomer. This was shown to have structure **D** (figure 1) by ^1H NMR and N.O.E. measurements. The N.O.E. assignment started from the 8-methyl group to identify first H9-eq and the downfield angular proton H9a, which in turn displayed both N.O.E. correlation and ^3J coupling with protons H9-eq, H9-ax and H3a.

In addition to functional group variation at the oxazinone stage, chemo- and regioselective transformation of the pyridine precursors appears to be feasible.

Table 1: Cycloaddition of Pyridine *o*-QDM Compounds with Various Dienophiles.

pyr	dienophile	adduct	nr (yield %)	
5a			**7a**(65)	R^1 = Cl, R^4 = CH_3
5b			**7b**(15)	R^1 = Cl, R^4 = Ph
5c			7c(56)	R^1 = Ph, R^4 = CH_3
6a			**7d**(90)	
5a			**8**(56)	
5a			**9a/9b** (65)	R^6 = H/$COOCH_3$, R^7 = $COOCH_3$/H
5a			**10**(35)	

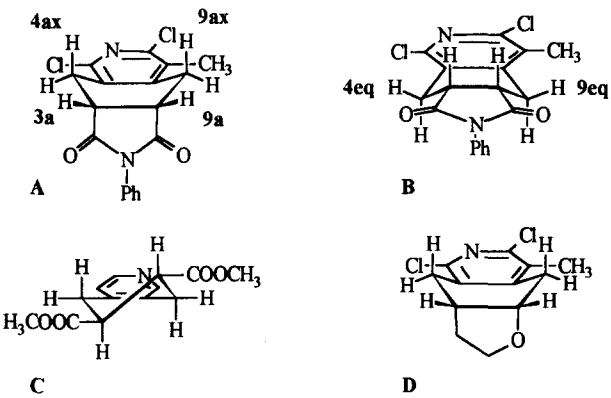


Figure 1. Conformational structures for adducts **7a** (**A**,**B**), **8** (C) and **10** (D).

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References and Footnotes

1. Cava, M.P.; Napier, D.R. *J. Am. Chem. Soc.* **1957**, *79*, 1701.
2. for recent reviews see: Chou, T. *Rev. Heteroat. Chem.* **1993**, *8*, 65; Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proced. Int.* **1991**, *23*, 237.
3. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609; Kametani, T.; Ichikawa, Y.; Suzuki, T.; Fukumoto, K. *Heterocycles* **1974**, *2*, 171.
4. Meerpoel, L.; Hoornaert, G. *Synthesis* **1990**, 905; Van Aken, K.; Lux, G.; Deroover, G.; Meerpoel, L.; Hoornaert, G. *Tetrahedron* **1994**, *50*, 5211.
5. Van Aken, K.; Meerpoel, L.; Hoornaert, G.; *Tetrahedron Lett.* **1992**, *33*, 2713.
6. Experimental procedure: a solution of pyridine compound (**5a-c**, **6a**, 250 mg), dienophile (3 mol equiv.) and NaI (5 mol equiv.) was heated in DMF (2.5 ml) at 60 °C under argon atmosphere for 12-24 hours. After completion of the reaction, water (50 ml) was added and the solution decolorized with aqueous sodium hydrogen sulfite. The mixture was extracted with chloroform and the organic phase dried and evaporated. Chromatographic purification (silica/$CHCl_3$/EtOAc) gave the adducts listed in table 1.
7. Vice, S.F.; Nandin de Carvalho, H.; Taylor, N.G.; Dmitrienko, G.I. *Tetrahedron Lett.* **1989**, *30*, 7289.
8. Selected data[a] for pyridines **5a-c** and **6a**.

5a: ^1H NMR: δ = 2.48 (s, 3H; CH_3), 4.68 (s, 2H; CH_2), 4.80 (s, 2H; CH_2)
5b: ^1H NMR: δ = 4.37 (s, 2H; CH_2), 4.90 (s, 2H; CH_2), 7.23-753 (m, 5H; Ph)
5c: ^1H NMR: δ = 2.55 (s, 3H; CH_3), 4.63 (s, 2H; CH_2), 4.82 (s, 2H; CH_2), 7.46 (m, 2H; Ph), 7.64(m, 3H; Ph)
6a: ^1H NMR: δ = 2.39 (s, 3H; CH_3), 4.69 (s, 2H; CH_2), 4.72 (s, 2H; CH_2), 7.61 (s, 1H; Pyr)

[a] ^1H NMR: $CDCl_3$/TMS, 250 MHz

9. Selected data[a] for adducts **7a**, **8** and **10**.

7a: M.p. 241-243 °C; ^1H NMR: δ = 1.77(dd, ^2J = 15 Hz, $^3J_{9,9a}$ = 6 Hz; H9-ax), 1.86(s, 3H; CH_3), 2.15(dd, ^2J = 16 Hz, $^3J_{4,3a}$ = 6 Hz; H4-ax), 2.34(ddd, $^3J_{9a,3a}$ = 10 Hz, $^3J_{9a,9\text{-}ax}$ = 6 Hz, $^3J_{9a,9\text{-}eq}$ = 4 Hz; H9a), 2.43(ddd, $^3J_{3a,9a}$ = 10 Hz, $^3J_{3a,4\text{-}ax}$ = 6 Hz, $^3J_{3a,9\text{-}eq}$ = 4 Hz; H3a), 2.71(dd, ^2J = 15 Hz, $^3J_{9,9a}$ = 4 Hz; H9-eq), 3.25(dd, ^2J = 16 Hz, $^3J_{4,3a}$ = 4 Hz; H4-eq), 6.95(m, 2H; Ph), 7.32(m, 3H; Ph)
8: M.p. 130-132 °C; ^1H NMR: δ = 2.16(dd, ^2J = 18 Hz, $^3J_{5,6}$ = 9 Hz; H5-ax), 2.47(dd, ^2J = 18 Hz, $^3J_{5,6}$ = 4 Hz; H5-eq), 2.52(dd, ^2J = 18 Hz, $^3J_{8,7}$ = 10 Hz; H8-ax), 2.74(m, 2H; H6, H7), 3.02(dd, ^2J = 18 Hz, $^3J_{8,7}$ = 4 Hz; H8-eq), 3.40(s, 3H; OCH_3), 3.42(s, 3H; OCH_3)
10: ^1H NMR: δ = 1.44(m, ^2J = 12 Hz, ^3J = 8.5, 8.5, 8, 7 Hz; H3-A), 2.16(m, ^2J = 12 Hz, ^3J = 8.5, 6.5, 6, 5.5 Hz; H3-B), 2.36(s, 3H; CH_3), 2.62(m, ^3J = 8.5, 8, 6.5, 6, 5.5 Hz; H3a), 2.71(dd, ^2J = 15.5 Hz, ^3J = 4.5 Hz; H9-ax), 2.73(dd, ^2J=15 Hz, ^3J=6 Hz; H4-ax), 2.77(dd, ^2J = 15.5 Hz, ^3J = 5.5 Hz; H4-eq), 3.04(dd, ^2J = 15.5 Hz, ^3J = 4.5 Hz, H9-eq), 3.54(td, ^2J = 8.5 Hz, ^3J = 8.5, 7 Hz, H2-a), 3.71(ddd, ^2J = 8.5 Hz, ^3J = 8 Hz, 4 Hz, H2-B), 4.30(dt, ^3J = 8 Hz, ^3J = 4.5 Hz, H9a).

[a] ^1H NMR: C_6D_6, C_6D_5H for **7a**, **8** and $CDCl_3$ for **10**, 400 MHz

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