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Functionalized Oxazoles from Rhodium-Catalyzed Reaction of Dimethyl Diazomalonate with Nitriles[1]

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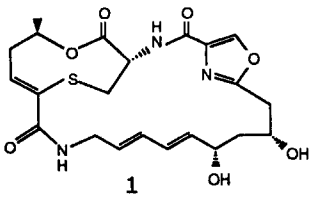
Summary: Rhodium(II) acetate catalyzes the reaction of dimethyl diazomalonate with nitriles to give 4-carbomethoxy-5-methoxy-1,3-oxazoles. Oxazole formation exceeds cyclopropane formation even in cases of conjugated and non-conjugated unsaturated nitriles.

1,3-Oxazoles of various substitution patterns and their reduced derivatives (oxazolines, oxazolidines) are well-known heterocyclic compounds for which a number of methods of synthesis have been reported.[2,3] Many examples of these compounds having important uses and biological activity are known,[2] but our interest in this area is due primarily to the presence of an oxazole system of a particular substitution pattern in the streptogramin antibiotics, of which griseoviridin **1** and virginiamycin M_1 **2** are specific examples.[4-6]



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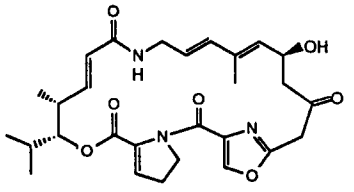
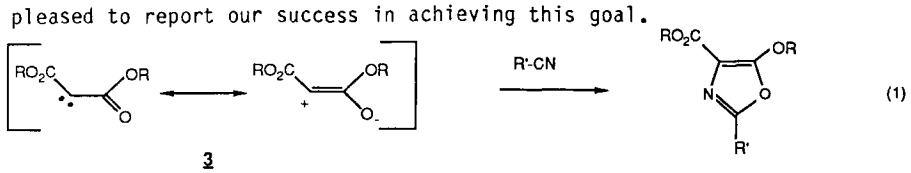


2

Based upon the strategy that we have chosen in our approach to the synthesis of these antibiotics, we sought a method for oxazole formation that would be based formally upon the reaction of an acylcarbene **3** with a nitrile (eq 1). Acylcarbenes, or functionally equivalent species, have been generated by several means in the past and have been found to undergo reactions not only in the desired manner with nitriles but also in an analogous fashion with carbonyl compounds and other substrates.[2,7] We believed that recent studies of the rhodium-catalyzed reactions of diazo compounds[8] could be applied to the problem at hand to provide a

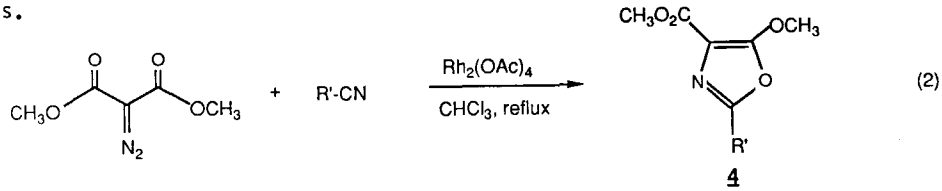
very simple and efficient route to the particular oxazoles required in our work. Indeed, we are very pleased to report our success in achieving this goal.



(1)

3

Dimethyl diazomalonate[9] undergoes reaction with a range of nitriles in the presence of rhodium(II) acetate as a catalyst (typically 0.005 to 0.01 mol-equiv) to give 2-substituted 4-carbomethoxy-1,3-oxazoles (**4**, eq 2). Although other solvents may be used in this reaction, chlorocarbons, such as chloroform or 1,2-dichloroethane are especially useful. To date, optimum results are obtained when the diazomalonate is added very slowly to the other reagents.



(2)

4

Table Preparation of Substituted Oxazoles **4** (equation 2)

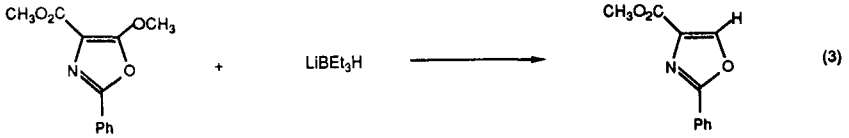
Entry	R'-CN	mol-equiv. of diazomalonate	% Yield[a]	mp (°C)
a	C_6H_5CN	1.5	85	98-99°C
b	4-Cl-C_6H_4CN	2.0	90	111-113°C
c	4-CH_3-C_6H_4CN	2.0	93	133-134°C
d	4-CH_3O-C_6H_4CN	2.0	47	121-123°C
e	4-NO_2-C_6H_4CN	2.0	0[b]	----
f	3-Cl-C_6H_4CN	2.0	96	134-136°C
g	C_6H_5-CH_2CN	2.0	50	183°C
h	C_6H_5-CH=CHCN	2.0	44	78-80°C
i	CH_3CN	1.5	58	119,122°C
j	$CH_3CH_2CH_2CN$	1.5	59	oil
k	$CH_3(CH_2)_7CH$	1.5	58	oil
l	$(CH_3)_2CHCN$	1.5	51	52-54°C
m	$(CH_3)_3CCN$	1.5	46	oil
n	$CH_3CH=CHCN$[c]	1.0	64(E)	49-50°C
			10(Z)	90-91°C
o	$CH_2=CHCH_2CN$	1.0	45	55-57°C
			21[d]	oil
p	$HOCH_2CH_2CN$	1.0	0(96)[e]	oil

[a]Yields of isolated, pure products. All products exhibit satisfactory spectroscopic and analytical data. [b]The solution of rhodium(II)acetate and nitrile turned black upon refluxing in $CHCl_3$. Only starting materials were recoverd upon workup. [c]Purchased and used as a mixture of predominantly trans isomer. [d]Refers to cyclopropane product derived from addition of diazomalonate to alkene double bond. [e]Refers to yield of product derived from carbene insertion into the OH bond of the alcohol.

As may be seen from the table, the reaction proceeds with a wide range of nitriles. The

yields are higher for aromatic nitriles than for aliphatic nitriles, but the difference is due, in part, to the greater efficiency in isolating and purifying the crystalline 2-aryl derivatives. Not surprisingly, cyclopropanation[8] is a competing reaction in the case of unsaturated nitriles (entry o). Free hydroxyl groups also interfere in the expected fashion[10] to give insertion products (entry p).

Finally, we have briefly investigated the reductive cleavage of the 5-methoxy group from our oxazoles in order to reach the basic substitution pattern seen in the streptogramin A antibiotics. Preliminary studies with lithium triethylborohydride[11] (eq 3) demonstrate the feasibility of selectively removing the 5-methoxy group from the ring. We have yet to study this reaction systematically with a wide range of reducing agents.



(3)

In conclusion, we have developed a convenient procedure for obtaining the desired types of functionalized oxazoles. Ongoing studies are being directed toward further optimization of the reaction described above, the use of alternative diazo compounds leading to more direct formation of oxazoles lacking the undesired 5-methoxy substituent, and the application of these reactions to natural product synthesis.

Typical procedure: To a stirred solution of $Rh_2(OAc)_4$ (0.020 g, 0.04 mmol) in ethanol free $CHCl_3$ (1 mL) at 25° C was added benzonitrile (0.40 g, 3.9 mmol). After being heated to reflux, the solution became purple, and a solution of dimethyl diazomalonate (0.93 g, 5.8 mmol) in $CHCl_3$ (5 mL) was added over an 8-h period. After the addition was complete, the solution was cooled to 25° C and was concentrated by rotary evaporation. The residual oil was purified by flash chromatography[12] (4:1 hexane: ethyl acetate) to give 0.77 g (85%) of 4-carbomethoxy-5-methoxy-2-phenyloxazole (**4a**) as a white solid: mp 98-99° C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91-7.97 (m, 2H), 7.38-7.41 (m, 3H), 4.22 (s, 3H), 3.87 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.68, 161.55, 150.61, 130.23, 128.52, 126.3, 125.65, 107.23, 59.63, 51.63, ; IR ($CDCl_3$) 1716, 1625 cm^{-1}; mass spectrum m/e (rel intensity) 233(M^+, 27), 173(11), 146(15), 104(100, 77(24). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80, H, 4.75. Found: C, 61.53; H, 4.75.

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References and Footnotes

1. Presented in part by R. C. at the 190th National Meeting of the American Chemical Society, Chicago, Illinois, September, 1985. Abstract No. ORGN 16.
2. For recent reviews on oxazoles see: (a) Newkome, G. R.; Paudler, W. W. "Contemporary Heterocyclic Chemistry"; Wiley: New York, 1982; pp 36-40. (b) Boyd, G. V. In "Comprehensive Heterocyclic Chemistry"; Katritzky, A. R.; Rees, C. W.; Potts, K. T., Eds.; Pergamon Press; Oxford, 1984; Vol. 6, pp. 177-233. (c) "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley: New York, 1983; Vol. 1 and 2. (d) Turchi, I. J. "Heterocyclic Compounds: Oxazoles"; Weissberger, A.; Tayler, E. C., Eds.; John Wiley & Sons, New York, 1986, vol 45, pp. 1-341.
3. For some other recent syntheses of oxazole derivatives see: (a) Bergeron, R. J.; Kline, S. J. J. Am. Chem. Soc. **1982**, 104, 4489. (b) Maurer, P. J.; Miller, M. J. Ibid. **1983**, 105, 240. (c) Lipshutz, B. H.; Hungate, R. W.; McCarthy, K. E. Ibid. **1983**, 105, 7703. (d) Effenberger, F.; Beisswenger, T. Chem. Ber. **1984**, 117, 1497. (e) Yoshioka, M.; Nakai, H.; Ohno, M. J. Am. Chem. Soc. **1984**, 106, 1133. (f) Nagao, Y.; Miyasaka, T.; Hagiwara, Y.; Fugita, E. J. Chem. Soc., Perkin Trans. I, **1984**, 183. (g) Padwa, A.; Haffmanns, G.; Tomas, M. J. Org. Chem. **1984**, 49, 3314. (h) Tsuge, O.; Kanemasa, S.; Matsuda, K. Chem. Lett. **1985**, 1411. (i) Hamada, Y.; Shibata, M.; Shioiri, T. Tetrahedron Lett. **1985**, 26, 5155. (j) Ito, Y.; Matsuura, T.; Saegusa, T. Ibid. **1985**, 26, 5781. (k) Grosdemange-Pale, C.; Chuche, J. Ibid. **1985**, 26, 6183.
4. For some recent reviews on the streptogramin antibiotics see: (a) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. "The Molecular Basis of Antibiotic Action", 2nd ed.; Wiley: London, 1981; pp 480-485. (b) Cocito, C. In "Antibiotics" Corcoran, J. W.; Hahn, F. E., Eds.; Springer-Verlag: New York, 1983, Vol. 6. (c) Cocito, C. Antibiotics (N.Y.) **1983**, 6, 296. (d) Biot, A. M. Drugs Pharm. Sci. **1984**, 22, 695.
5. For studies directed toward the synthesis of the streptogramin A antibiotics, including the oxazole units see: (a) Lipshutz, B. H.; Hungate, R. W. J. Org. Chem. **1981**, 46, 1410. (b) Meyers, A. I.; Lawson, J.; Amos, R. A.; Walker, D. G.; Spohn, R. F. Pure Appl. Chem. **1982**, 54, 2537. (c) Nagao, Y.; Yamada, S.; Fujita, E. Tetrahedron Lett. **1983**, 24, 2287. (d) Wood, R. D.; Ganem, B. Ibid. **1983**, 24, 4391-4392.
6. (a) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Åkermark, B.; Bäckvall, J. E. J. Org. Chem. **1984**, 49, 4738. (b) Butera, J.; Rini, J.; Helquist, P. J. Org. Chem. **1985**, 50, 3676.
7. For leading references to heterocycle formation using acylcarbenes and relted species see: Huisgen, R. Angew. Chem. Int. Ed. Engl. **1963**, 2, 565, 633. (b) Lora-Tamayo, M.; Madronero, R.; Leipprand, H. Chem. Ber. **1964**, 97, 2230. (c) Ibata, T.; Yamashita, T.; Kashiuchi, M.; Nakano, S.; Nakawa, H. Bull Chem. Soc. Japan **1984**, 57, 2450. (d) Doyle, M. P.; Buhro, W. E.; Davidson, J. G. Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. J. Org. Chem. **1980**, 45, 3657. (e) Alonso, M. E.; Garcia, M.; Chitty, A. W. Ibid. **1985**, 50, 3445. (f) Doyle, M. P.; Dorow, R. L; Tamblyn, W. H. Ibid. **1982**, 47, 4059. (g) Doyle, M. P; Trudell, M. L. Ibid. **1984**, 49, 1196, see also the numerous references cited therein. (h) Nagayoshi, K.; Sato, T. Chem. Lett. **1983**, 1355. (i) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. J. Org. Chem. **1985**, 50, 3467.
8. Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. Organometallics **1984**, 3, 53.
9. Regitz, M. Synthesis **1972**, 351.
10. (a) Teng, C. P.; Ganem, B.; Doktor, S. Z.; Nichols, B. P.; Bhatnagar, R. K.; Vining, L. C. J. Am. Chem. Soc. **1985**, 107, 5008. (b) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph. Tetrahedron Lett. **1973**, 2233.
11. Krishnamurthy, S. Aldrichim. Acta. **1974**, 7, 55.
12. Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923.

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