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1,3-Dipolar Cycloaddition of Substituted Benzonitrile Oxide to 5-(R)-(l-Menthyloxy)-2(5H)-furanone

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Abstract: Several isoxazoline compounds were obtained by the 1,3-dipolar cycloaddition of benzonitrile oxide to 5-(R)-(l-menthyloxy)-2(5H)-furanone. The reaction condition was investigated preliminarily, the structures of these compounds have been established *via* the analysis of NMR data(involved NOEID or HMBC) and the reaction seems occurred regioselectively.

Keywords: 1,3-Dipolar cycloaddition, benzonitrile oxide, configuration, ^{1}H-NMR, NOE.

Isoxazoline compounds as key intermediates for construction of natural products have been developed very fast as an hot area in organic synthesis[1]. 5-(R)-(l-menthyloxy)-2(5H)-furanone as a valuable chiral synthon has been recently studied for its high stereoselectivity in many reactions[2]. In this paper, we focused on its reactivity and regioselectivity of the 1,3-dipolar cycloaddition with the substituted benzonitrile oxide[3] and several isoxazoline compounds were obtained and characterized by NMR data(involved NOEID or HMBC).

Benzaldoxime was tried to use for 1,3-dipolar cycloaddition instead of benzonitril oxide, because the later is unstable. Khalid Bougrin *et al* reported that the yield of this reaction were increased under sonication, comparing with conventional method in the same conditions[4]. We carried out this reaction of substituted benzaldoxime in both conditions. The results were shown in **Table 1**. In the most cases, the yields of the products extremely decreased under sonification. No product could be obtained from 3,4,5-trimethoxy benzaldoxime under sonification condition. It may be due to the reagent was unstable in such a high energetic environment. On the other hand, the experimental results indicated that the big substituted group on benzaldoxime may benefit the regeoselectivity, especially for the 3,4,5-trimethoxy benzaldoxime in stirring condition. But the big substitute group make the **2** more unstable under sonification, so no product can be obtained from **2d**.

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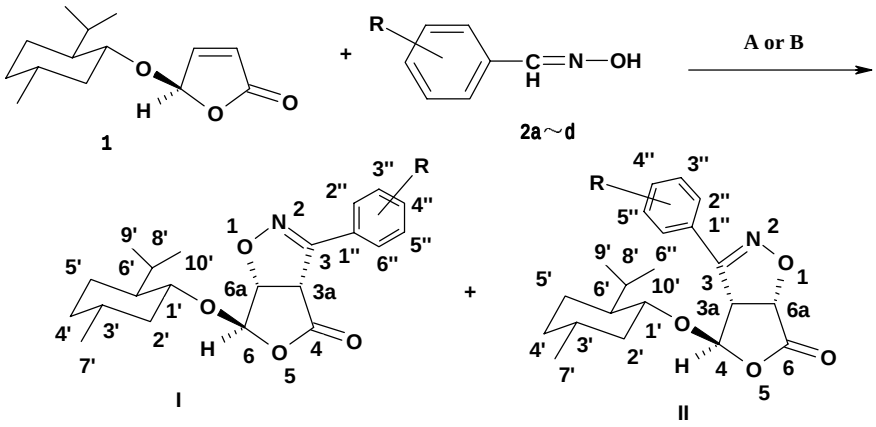

A: $Ca(ClO)_2$ in H_2O/CH_2Cl_2 stirring **B: $Ca(ClO)_2$ in H_2O/CH_2Cl_2 sonification**

a: R= H, b: R= p-methoxy, c: R= p-nitro, d: R= 3,4,5-trimethoxy

Table 1 1,3-dipolar cycloaddition of substituted benzonitrile oxide to 5-(R)-(l-menthyloxy)-2(5H)-furanone

Compound	Time		Yield(%)[a]		I/II[b]	
	A	B	A	B	A	B
a	15mins	2hrs	57.4	72.2	68/32	67/33
b	15mins	2hrs	50	50	89/11	75/25
c	15mins	2hrs	32.8	54.2	85/15	87/13
d	/	8hrs	/	38.4	/	100/trace

A: sonification B: stirring

a: Isolated yield, calculated based on the amount of 5-(R)-(l-menthyloxy)-2(5H)-furanone used.

b: I and II are purified by chromotagraphy.

In the previous work we reported the stereostructure of the product of 1,3-dipolar cycloaddition reaction of **1** and benzaldoxime[5, 6]. The result showed that the addition was syn and the substitute groups on the new formed chiral carbons were all in the *trans* form to the menthyloxy group in γ-lactone ring. It also can be concluded that the addition is inclined to proceed in the less hindered side of the double bond. There for, the product I in which the substituted groups on benzene ring has the opposite orientation to the menthyloxy group, is superior to II.

In summary, contrast to Khalid Bougrin's conclusion, stirring condition is more suitable for the 1,3-dipolar cycloaddition of substituted benzonitrile oxide to 5-(R)-(l-menthyloxy)-2(5H)-furanone than sonification. Benzaldoxime with large substitued group can be shown much better regioselectivity in stirring condition, though the total yield of the reaction was some what decreased, and the reaction rate was slower than that with unsubstituted benzaldoxime.

General Procedure for the Reaction

A: The suspension of $Ca(ClO)_2$(300 mg) in water (6 mL) was added to a mixture of 5-(R)-(l-menthyloxy)-2(5H)-furanone(0.5 mmol) and substitued benzaldoxime **2**(0.75 mmol) in CH_2Cl_2 (5 mL). The mixture was sonificated at 25°C for 15 minutes. The mixture was extracted with CH_2Cl_2 (2×25 mL), the organic phase was washed with brine (10 mL) and dried over $MgSO_4$. Then the solvent was evaporated and the residue was purified by column chromatography(petrolemn ether/AcOEt: 20:1) to afford I and II.

B: At the temperature of 0°C, to the mixture of 5-(R)-(l-menthyloxy)-2(5H)-furanone(0.5 mmol) and substitued benzaldoxime **2**(0.75 mmol) in CH_2Cl_2 (5 mL), was added the suspension of $Ca(ClO)_2$ in water (6 mL) in the period of 1~8 hr. The mixture was then stirred at the same temperature. After the reaction completed, I and II were obtained after the same purification procedure just as method A.

References and Notes

1. P. G. Baraldi, A. Barco, S. Benetli, G. P. Pollimi, D. Simoni, *Synthesis*, **1987**, 857.
2. H. Huang, Q. H. Chen, *Tertahedron: Asymmetry*, **1999**, *10*, 1295.
3. The thesis for MS Degree of R. Q. Shu and the references therein(Beijing Normal University).
4. K. Bougrin, M. Lamiri, M. Soufiaoui, *Tetrahedron Lett.*, **1998**, *39*, 4455.
5. H. H. Huang, X. Zhang, Q. H. Chen, *Chinese Journal of Magnetic Resonance*, **2001**, *18*, No.(42), 299.
6. Spectral data:
   I a: ^{1}HNMR(500MHz, $CDCl_3$, δ ppm): 0.85-1.08(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.64-1.71 (m, 2H, H-5′), 2.01-2.20(m, 2H, H-2′), 3.59-3.68(m, 1H, H-1′), 4.70(d, 1H, J=9Hz, H-3a), 5.24(d, 1H, J=9Hz, H-6a), 5.83(s, 1H, H-6), 7.40-7.46(m, 2H, H-3″,5″), 7.93-7.95(m, 2H, H-2″,6″). ^{13}C NMR(500MHz, $CDCl_3$, δ ppm): 15.63(C-10′), 20.84(C-9′), 22.16(C-7′), 23.06(C-4′), 25.50(C-3′), 31.36(C-8′), 34.16(C-5′), 39.56(C-6′), 47.57(C-2′), 53.99(C-3a), 78.02(C-1′), 87.42(C-6a), 103.30(C-6), 126.80(C-4″), 127.97(C-6″), 128.69(C-5″), 130.93 (C-1″), 152.78(C-3), 169.74(C-4). FAB-HRMS: found *m/z* 358.1987, Calcd for [$C_{21}H_{27}NO_4$ +H]: 358. 2018
   I b: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.79-1.41 (m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.65-1.70 (m, 2H, H-5′), 2.04-2.19(m, 2H, H-2′), 3.61-3.66(m, 1H, H-1′), 3.85(s, 3H, H-4′-OCH_3), 4.67(d, 1H, J=9Hz, H-3a), 5.21(d, 1H, J=9Hz, H-6a), 5.82(s, 1H, H-6), 6.95(d, 2H, J=9Hz, H-3″,5″), 7.89(d, 2H, J=9Hz, H-2″,6″). EI-MS: *m/z* 387.
   I c: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.79-1.44(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.66-1.72 (m, 2H, H-5′), 2.02-2.20(m, 2H, H-2′), 3.63-3.68(m, 1H, H-1′), 4.74(d, 1H, J=9Hz, H-3a), 5.33(d, 1H, J=9Hz, H-6a), 5.88(s, 1H, H-6), 8.14(d, 2H, J=9Hz, H-3″,5″), 8.28(d, 2H, J=9Hz, H-2″,6″). FAB-MS: *m/z* 403(M+H).
   I d: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.80-1.43(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.66-1.71 (m, 2H, H-5′), 2.04-2.20(m, 2H, H-2′), 3.61-3.66(m, 1H, H-1′), 3.89(s, 3H, H-4″-OCH_3), 3.90(s, 6H, H-3″,5″-OCH_3), 4.67(d, 1H, J=9Hz, H-3a), 5.25(d, 1H, J=9Hz, H-6a), 5.82(s, 1H, H-6), 7.24(s, 2H, H-2″,6″). ^{13}CNMR(500MHz, $CDCl_3$, δppm): 15.58(C-10′), 20.82(C-9′), 22.13(C-7′), 23.00(C-4′), 25.42(C-3′), 31.33(C-8′), 34.11(C-5′), 39.58(C-6′), 47.51(C-2′), 54.42(C-3a), 56.25(C-3″,5″-OCH_3), 60.89(C-4″-OCH_3), 78.24(C-1′), 87.55(C-6a), 103.76 (C-6), 105.38(C-1″), 122.11(C-2″,6″), 140.38(C-4″), 152.36(C-3), 153.26(C-3″,5″), 169.84 (C-4). FAB-HRMS: found *m/z* 447.2287, Calcd for [$C_{24}H_{33}NO_7$]: 447.2257.
   II a: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.77-1.06(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.65-1.70 (m, 2H, H-5′), 2.01-2.08(m, 2H, H-2′), 3.54-3.62(m, 1H, H-1′), 4.41(d, 1H, J=10Hz, H-3a), 5.44(d, 1H, J=10Hz, H-6a), 5.71(s, 1H, H-4), 7.45-7.51(m, 2H, H-3″,5″), 7.62-7.69(m, 2H, H-2″,6″). ^{13}CNMR(500MHz, CDC_{l3}, δppm): 15.54(C-10′), 20.87(C-9′), 22.16(C-7′), 23.00

(C-4′), 25.46(C-3′), 31.27(C-8′), 34.13(C-5′), 39.74(C-6′), 47.65(C-2′), 56.71(C-3a), 78.26(C-1′), 79.09(C-6a), 100.96(C-4), 126.92(C-4″), 127.05(C-6″), 129.28(C-5″), 131.21 (C-1″), 154.69(C-3), 171.36(C-6). FAB-HRMS: found *m/z* 358.1997, Calcd for [$C_{21}H_{27}NO_4$ +H]: 358.2018

II b: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.78-1.37(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.66-1.70 (m, 2H, H-5′), 2.02-2.08(m, 2H, H-2′), 3.56-3.61(m, 1H, H-1′), 3.87(s, 3H, H-4′-OCH_3), 4.37(d, 1H, J=10Hz, H-3a), 5.40(d, 1H, J=10Hz, H-6a), 5.70(s, 1H, H-4), 6.98(d, 2H, J=9Hz, H-3″,5″), 7.62(d, 2H, J=9Hz, H-2″,6″). EI-MS: *m/z* 387.

II c: ^{1}HNMR(500MHz, $CDCl_3$, δppm): 0.78-1.38(m, 14H, H-3′,4′,6′,7′,8′,9′,10′), 1.68-1.72 (m, 2H, H-5′), 2.03-2.05(m, 2H, H-2′), 3.59-3.64(m, 1H, H-1′), 4.43(d, 1H, J=10Hz, H-3a), 5.53(d, 1H, J=10Hz, H-6a), 5.69(s, 1H, H-4), 7.87(d, 2H, J=8.5Hz, H-3″,5″), 8.34(d, 2H, J=8.5Hz, H-2″,6″). FAB-MS: *m/z* 403(M+H).

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