SYNTHESIS OF 4-BROMO-4-ISOXAZOLIN-3-ONES: APPLICATION OF BROMINE-N, N-DIMETHYLACETAMIDE COMPLEX

Kyongtae Kim, ** Eung K. Ryu, *§ and Yeongwan Seo*

*Department of Chemistry, Seoul National University, Seoul 151-742

*Korea Research Institute of Chemical Technology, Daejeon 300-31, Korea

Summary: Reactions of 2-benzyl-5-phenyl-4-isoxazolin-3-ones with bromine-N,N-dimethylacetamide complex in carbon tetrachloride at room temperature afforded excellent yields of 2-benzyl-4-bromo-5-phenyl-4-isoxazolin-3-ones.

Various 2-substituted 4-bromo-4-isoxazolin-3-ones have been attracted because of their strong biological activities such as antiinflammatory, analgesic, and be been attracted because of their strong biological activities such as antiinflammatory, analgesic, and be be be because of their strong biological activities and antihypertensive, and antihypertensive, and antihypertensive, activities. The introduction of brownine atom to the 4-position of 4-isoxazolin-3-ones has been accomplished by the cyclization of 2,2,3-trihalohydroxamic acids, followed by the elimination of hydrogen brownide. However, the direct halogenation of the 2-substituted 4-isoxazolin-3-one(1) has not been reported, although the 2-substituted isothiazol-3-ones are known to be halogenated readily at the 4-position. Therefore, we investigated brownination of 2-benzyl-5-phenyl-4-isoxazolin-3-one(1a) and its derivatives.

Direct bromination of $\underline{1a}(X=Y=H)$ with bromine in carbon tetrachloride at ambient temperature afforded $\underline{2a}(X=Y=H)$ and hydrobromide of $\underline{1a}$ in 38% and 33% yields, respectively. Similarly, $\underline{2b}(X=H, Y=2-C1)$ and hydrobromide of $\underline{1b}$ were isolated in 34% and 29% yields, respectively. Since hydrogen bromide liberated during the course of the reaction would deactivate $\underline{1}$, the reaction with various Lewis bases were examined. After some trial, we found that N,N-dimethylacetamide(DMA), a weak Lewis base, afforded excellent yields of $\underline{2}$. Some results are listed in Table 1.7

Although brownine is known to coordinate with oxygen atom of DMA, 8 its synthetic utility has never been reported. Surprisingly, 2-benzyl-4-isoxazolin-3-one(4) did not react with the present system even after the prolonged reaction time, being quantitatively recovered. The inertness of 4 might be due to the lack of the stabilization of the cation generated by the addition of brownium ion at the 4-position of 4 . This view is supported by the reduced reactivity of 1 with the 5-phenyl group substituted by an electron-withdrawing group(1 b, 1 d, 1 b, 1 l, 1 k). Further study on the application of Br₂-DMA complex is in progress.

Substrate 1	Mole ratio			Reaction time	Isolated yield(%)
	1	Br ₂	: DMA	min	2
a, X≠H, Y≠H	1	3	2	14	82
<u>b</u> , X=H, Y=2-Cl	1	1	1	1140	89
	1	3	2	60	87
g, X=H, Y=3~Cl	1	3	2	33	96
d, X=H, Y=4~Cl	1	3	2	60	82
e, X=H, Y=4-Me	1	3	2	2	88
<u>f</u> , X=H, Y=2-OMe	1	3	2	1.5	87
g, X=H, Y=3~0Me	1	3	2	20	81
<u>h</u> , X=H, Y=3-NO ₂	1	3	2	120	94
<u>i</u> , X=H, Y=4-NO ₂	1	3	2	180	91
<u>j</u> , X=Cl, Y=H	1	3	2	20	95
<u>k</u> , X=Cl, Y=2-Cl	1	5	4	80	66

Table 1, Bromination of 2-benzyl-5-phenyl-4-isoxazolin-3-ones(1)

Acknowledgment. Financial support of this work by Korea Research Institute of Chemical Technology is gratefully acknowledged.

References and Notes

- (a) K. Tomita, T. Murakami, H. Takagi, and Y. Morisawa, Brit. 1,382,520(1975); Chem. Abst., 83, 43304h
 (1975); (b) K. Tomita, T. Murakami, H. Takagi, and Y. Morisawa, Ger. Offen. 2,257,750(1974); Chem. Abst., 81, 91572z(1974).
- K. Tomita, T. Murakawa, H. Takagi, and Y. Morisawa, Fr. Demende, 2,207,704(1974); Chem. Abst., <u>84</u>, 44014w(1976).
- (a) K. Tomita, T. Murakami, T. Honma, and Y. Yamazaki, Ger. Offen. 2,257,749(1974); Chem. Abst., 81, 91507g(1974); (b) K. Tomita, T. Murakami, T. Honma, and Y. Yamazaki, Fr. Demende, 2,208,402(1974); Chem. Abst., 82, 170875z(1975); (c) K. Tomita, T. Murakami, Y. Yamazaki, and T. Honma, U.S. 4,044,018(1977); Chem. Abst., 88, 22879n(1978).
- K. Tomita, T. Murakami, T. Honma, and Y. Yamazaki, Jap Kokai, 7,462,636(1974); Chem. Abst., <u>82</u>, 1110r (1975).
- 5. H. Tsuno, Neth, Appl. 6,516,871(1966); Chem. Abst., 65, 15383e(1966).
- D. L. Pain, B. J. Peart, and K. R. H. Wooldrige, "Comprehensive Heterocyclic Chemistry", Ed., A. R. Katritzky and C. W. Rees, Vol. 6, Part 4B, Pergamon Press, 1984, p147.
- 7. General procedure: Bromine (1.248 g, 7.81 mmol) was added to a mixture of 1a(0.996 g, 4.03 mmol) and DMA (0.660 g, 7.58 mmol) in CCl₄(80 ml). After the heterogeneous mixture was stirred for 30 min, the solvent was evaported under reduced pressure and the residue was chromatographed on silica gel column. Elution with benzene, followed by ethyl acetate gave 2a(1.099 g, 3.32 mmol).
- 8. R. S. Drago and D. A. Wenz, J. Am. Chem. Soc., <u>84</u>, 526(1962).

(Received in Japan 4 June 1990)