The Reaction of *N*-Alkylisoxazolium Salts with Hydroxylamine

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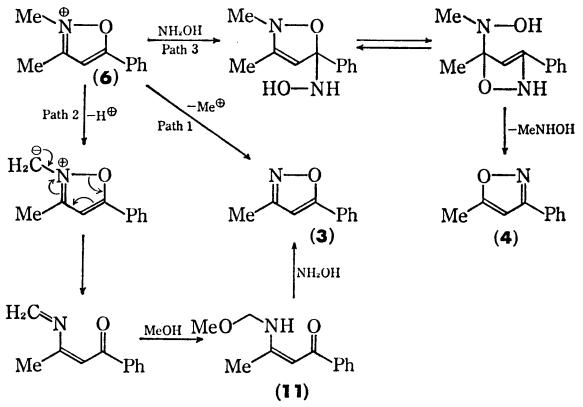
(Received November 30, 1977)

The alternating transposition of C-3 and C-5 substituents on 3,5-disubstituted isoxazoles was found by refluxing a mixture of hydroxylamine hydrochloride, potassium carbonate, and 3,5-disubstituted 2-methylisoxazolium salts, derived from the corresponding isoxazoles. Under the same conditions, 3,5-disubstituted 2-*t*-butyl- or 2-benzhydrylisoxazolium salts gave the corresponding isoxazoles without alternation of the substituents.

The reactions of 3,5-dimethylisoxazole (**1**) with various electrophiles in the presence of sodium amide have been investigated.[1] The 5-methylisoxazoles have been prepared from β-amino enones on treatment with hydroxylamine.[2] However the sterically hindered 5-trichloroacetamido-2,2-dimethyl-4-hexen-3-one will not give the 5-methyl-3-*t*-butylisoxazole (**2**), so it was necessary to devise a general preparative method for the 5-methylisoxazoles.

On the basis of the reported reactions of *N*-alkylisoxazolium salts[3] with various nucleophiles such as potassium alkoxide,[4] Grignard reagents,[5] and sodium borohydride,[6] the 3,5-disubstituted 2-methylisoxazolium salts would be expected to react with hydroxylamine. Thus, treatment of a mixture of 2,3,5-trimethylisoxazolium iodide (**5**) and hydroxylamine hydrochloride with potassium methoxide in methanol gave **1** in good yield. In the same manner, treatment of a mixture of 2,3-dimethyl-5-phenylisoxazolium iodide (**6**) and hydroxylamine hydrochloride with potassium methoxide gave an isomeric mixture of 3-methyl-5-phenylisoxazole (**3**, 46%) and 5-methyl-3-phenylisoxazole (**4**, 54%). Treatment of the mixture with potassium carbonate as a base yielded the isomer **4** as the major product. Similarly the isoxazolium iodides **7** and **8**, and also the isoxazolium perchlorates **9** and **10** may be converted into the corresponding isoxazoles as shown in Table 1. These results reveal the alternating transposition of the substituent groups on isoxazoles proceeds smoothly on treatment of *N*-methylisoxazolium salts with hydroxylamine hydrochloride in the presence of potassium carbonate.

For the formation of the isoxazoles from *N*-methylisoxazolium salts, three possible reaction paths are shown in Fig. 1. The β-amino enone **11** may be prepared as the sole product by the reaction of **6** with potassium methoxide. The interconversion of **3** and **4** did not occur in the presence of hydroxylamine, so that path 1 may be omitted from the consideration of the formation of the alternating transposition product. A weak base, such as potassium carbonate is not able to abstract the proton on *N*-methyl group of **6**. Furthermore, the treatment of **11** with hydroxylamine hydrochloride in the presence of potassium methoxide or carbonate gave the isoxazole **3** as listed in Table 2. Thus the *N*-methylisoxazolium salts undergo the transposition reaction to give **4** in the manner shown in path 3, whereas the formation of **3** is considered to proceed *via* path 2.



A mixture of 2-*t*-butyl-3-methyl-5-phenylisoxazolium perchlorate (**12**), hydroxylamine hydrochloride, and potassium carbonate was heated and gave **3** and **4** in 60 and 13% yields, respectively. Similarly, 2-benz-

Table 1. The reaction of *N*-alkylisoxazolium salts with hydroxylamine

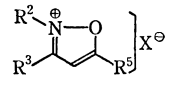
Compd	R^2	R^3	R^5	Anion	Base	3,5-Disubstituted isoxazole		
						Total yield	Retention	Transposition
5	Me	Me	Me	I^-	KOMe	63	—	—
6	Me	Me	Ph	I^-	KOMe	72	46	54
5	Me	Me	Me	I^-	K_2CO_3	80	—	—
6	Me	Me	Ph	I^-	K_2CO_3	80	18	82
7	Me	Me	*t*-Bu	I^-	K_2CO_3	79	7	93
8	Me	Me	CH_2CH_2Ph	I^-	K_2CO_3	51	16	84
9	Me	Me	Ph	ClO_4^-	K_2CO_3	93	9	91
10	Me	Ph	Me	ClO_4^-	K_2CO_3	95	15	85
14	*t*-Bu	Me	Me	ClO_4^-	K_2CO_3	80	—	—
12	*t*-Bu	Me	Ph	ClO_4^-	K_2CO_3	73	82	18
15	Ph_2CH	Me	Me	ClO_4^-	K_2CO_3	86	—	—
13	Ph_2CH	Me	Ph	ClO_4^-	K_2CO_3	79	100	0

Table 2. The reaction of 1-substituted 3-(methoxymethylamino)-2-buten-1-ones with hydroxylamine

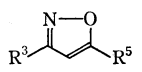
5-Subst.	Base	Isoxazole yield	Retention	Transposition
Me	MeOK	29	—	—
Ph	MeOK	36	100	0
t-Bu	MeOK	32	100	0
CH_2CH_2Ph	MeOK	36	100	0

hydryl-3-methyl-5-phenylisoxazolium perchlorate (**13**) gave **3** and methyl benzhydryl ether but no isomer **4**. The formation of compound **3** from **12** and **13** is assumed to proceed *via* path 1.

In conclusion, the treatment of *N*-methylisoxazolium salts with hydroxylamine hydrochloride in the presence of potassium carbonate gave alternation transposition compounds of oxygen and nitrogen atoms attached to the isoxazoles. In contrast, the same treatment of *N*-*t*-butyl- or *N*-benzhydrylisoxazolium salts afforded isoxazoles without alternating the hetero atoms.



(**5**): $R^2=R^3=R^5=Me$ $X=I$
(**6**): $R^3=R^5=Me$ $R^5=Ph$ $X=I$
(**7**): $R^2=R^3=Me$ $R^5=t\text{-}Bu$ $X=I$
(**8**): $R^2=R^3=Me$ $R^5=CH_2CH_2Ph$ $X=I$
(**9**): $R^2=R^3=Me$ $R^5=Ph$ $X=ClO_4$
(**10**): $R^2=R^5=Me$ $R^3=Ph$ $X=ClO_4$
(**12**): $R^2=tBu$ $R^3=Me$ $R^5=Ph$ $X=ClO_4$
(**13**): $R^2=Ph_2CH$ $R^3=Me$ $R^5=Ph$ $X=ClO_4$
(**14**): $R^2=t\text{-}Bu$ $R^3=R^5=Me$ $X=ClO_4$
(**15**): $R^2=Ph_2CH$ $R^3=R^5=Me$ $X=ClO_4$



(**1**): $R^3=R^5=Me$
(**2**): $R^3=tBu$ $R^5=Me$
(**3**): $R^3=Me$ $R^5=Ph$
(**4**): $R^3=Ph$ $R^5=Me$
(**16**): $R^3=CH_2CH_2Ph$ $R^5=Me$

Fig. 2.

Experimental

Materials. 2,3,5-Trimethyl- (**5**), 2,3-dimethyl-5-phenyl- (**6**), 2,3-dimethyl-5-*t*-butyl- (**7**), and 2,3-dimethyl-5-phenethylisoxazolium iodide (**8**) were prepared from the corresponding isoxazoles.[3] According to the method of Adachi,[5] 2,3-dimethyl-5-phenyl- (**9**) and 2,5-dimethyl-3-phenylisoxazolium perchlorate (**10**) were prepared. *N*-*t*-Butyl- and *N*-benzhydrylisoxazlium perchlorates were prepared by the method of Woodman.[7] The physical data of these isoxazolium salts are listed in Table 3.

General Procedure. To a mixture of MeOK (or K_2CO_3, 4.8 mmol) in methanol (30 ml) was added an isoxazolium salt (2.0 mmol) and hydroxylamine hydrochloride (2.4 mmol). The mixture was refluxed for 18 h, poured into ice-water, extracted with CH_2Cl_2, and dried over $MgSO_4$. The isoxazole yield was estimated by the peak area of gas chromatography and the product ratio calculated by the intensity of methyl proton signals in the NMR spectra.

3-t-Butyl-5-methylisoxazole (2).[8] The title compound was isolated by fractional distillation. Bp 110—114 °C/73 mmHg. NMR (δ): 1.32 (s, 9H), 2.37 (s, 3H) and 5.98 ppm (s, 1H). Found: C, 68.73; H, 9.42; N, 10.09%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06%.

3-Phenethyl-5-methylisoxazole (16). The title compound was isolated by fractional distillation. Bp 121—127 °C/2 mmHg. NMR (δ): 2.35 (s, 3H), 2.94 (s, 4H), 5.74 (s, 1H) and 7.23 ppm (s, 5H). Found: C, 76.83; H, 6.78; N, 7.17%. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48%.

Isomerization of Isoxazole. The mixture of isoxazole (**3** or **4**, 2.0 mmol), hydroxylamine hydrochloride (2.6 mmol) and MeOK (or K_2CO_3, 2.8 mmol) in methanol (20 ml) was refluxed and the resulting mixture poured into water, and extracted with CH_2Cl_2. The product was analyzed by gas chromatography and NMR spectroscopy.

The Reaction of 3-(Methoxymethylamino)-2-buten-1-ones with Hydroxylamine. The mixture of 3-(methoxymethylamino)-2-buten-1-ones (2.0 mmol) and hydroxylamine hydrochloride (2.4 mmol) was treated with MeOK (or K_2CO_3, 2.4 mmol) by the procedure described in reference 2. The results are listed in Table 2.

References

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5) I. Adachi, K. Harada, M. Miyazaki, and H. Kano, *Chem. Pharm. Bull.*, **22**, 61 (1974).
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8) Coutrier reported[10] the preparation of isoxazole derivative from 5,5-dimethyl-2,4-hexanedione and hydroxylamine hydrochloride. The product was identified to be 3-methyl-5-*t*-butylisoxazole with the authentic sample.[11]
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Table 3. Physical data and elemental analysis of *N*-alkylisoxazolium salts

Compd	R^2	R^3	R^5	Anion	Mp °C	Yield	Found C	Found H	Found N	Calcd C	Calcd H	Calcd N
5	Me	Me	Me	I^-	84	78	—	—	—	—	—	—
6	Me	Me	Ph	I^-	171	59	43.69	3.98	4.90	43.87	4.01	4.65
7	Me	Me	*t*-Bu	I^-	196	82	38.79	5.61	4.93	38.45	5.74	4.98
8	Me	Me	CH_2CH_2Ph	I^-	121	61	47.51	4.91	4.10	47.43	4.90	4.26
9	Me	Me	Ph	ClO_4^-	186	81	—	—	—	—	—	—
10	Me	Ph	Me	ClO_4^-	130	78	47.96	4.39	5.01	48.28	4.42	5.11
12	*t*-Bu	Me	Ph	ClO_4^-	146	75	53.07	5.75	4.62	53.26	5.74	4.44
14	*t*-Bu	Me	Me	ClO_4^-	120	34	—	—	—	—	—	—
13	Ph_2CH	Me	Ph	ClO_4^-	138	74	64.93	4.75	3.47	64.87	4.73	3.29
15	Ph_2CH	Me	Me	ClO_4^-	157	63	—	—	—	—	—	—