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The Alkylation of 3,5-Dimethylisoxazole

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3,5-Dimethylisoxazole (**1**) was alkylated with sodium amide in liquid ammonia to give 3-methyl-5-alkylisoxazoles. By di- and tri-alkylation reactions using excess sodium amide, isoxazoles having secondary and tertiary alkyl groups at 5-position could be obtained. The hydrogenolysis and hydrolysis of these isoxazoles were also studied.

The reaction of β-diketones with hydroxylamine hydrochloride gives isoxazoles[1] which are regenerated to β-diketones by hydrogenolysis and hydrolysis,[2] showing that the formation and cleavage of isoxazoles is useful for the protection of β-diketones.

Few papers have reported on the alkylation of 3,5-dimethylisoxazoles. The 5-methylisoxazoles having the electron-withdrawing group at 4-position condense with benzaldehyde to give 4-substituted 5-styrylisoxazoles in the presence of amine or sodium methoxide as a catalyst.[3-5] Micetich reported[6] that the 5-methyl group of 3,5-dimethylisoxazole (**1**) is lithiated by butyl lithium in tetrahydrofuran. The lithio derivative reacts with benzyl chloride to give 3-methyl-5-phenylethylisoxazole (**5**). In both cases, the methyl group at 3-position of 3,5-dimethylisoxazoles does not react. Since it is well-known that the methyl group attached to such heterocyclic compounds as picoline[7] or quinaldine[8] is alkylated by sodium amide in liquid ammonia as a catalyst, alkylation on the methyl group at 5-position of **1** is expected.

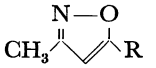
We have studied the alkylation of 3,5-dimethylisoxazole (**1**) and obtained isomerically pure mono-, di-, and tri-alkylated isoxazoles by using an appropriate amount of sodium amide in liquid ammonia. Generation of β-diketones from these alkylated isoxazoles has also been carried out. The results are given in this paper.

Results and Discussion

3,5-Dimethylisoxazole (**1**) is expected to react at three reaction sites, 3-methyl, 5-methyl, and 4-position, in the electrophilic substitution reaction. For determination of the reaction site, **1** was treated with methyl iodide in the presence of equimolar sodium amide in liquid ammonia. The reaction product (yield, *ca.* 70%) showed methyl protons at δ 2.18, methine proton at δ 5.68 and ethyl protons at δ 2.68 and 1.26 in NMR.

1) W. Lampe and J. Smalinska, *Roczniki. Chem.*, **28**, 163 (1954)
2) S. D'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950).
3) A. Quilico and C. Musante, *ibid.*, **72**, 399 (1942).
4) N. K. Kochetkov, S. D. Sokolov, and V. M. Luboshnikova, *Zh. Obshch. Khim.*, **32**, 1788 (1962).
5) G. Renzi, V. Dal Piaz, and S. Pinzauti, *Gazz. Chim. Ital.*, **99**, 753 (1969).
6) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
7) D. Taub, R. D. Hoffsommer, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **30**, 3229 (1965).
8) F. W. Bergstrom and A. Moffat, *J. Amer. Chem. Soc.*, **59**, 1494 (1937).

From these data, the product was identified as 3-methyl-5-ethylisoxazole (**2**).[9] But neither 3-ethyl-5-methylisoxazole nor 3,4,5-trimethylisoxazole could be detected by NMR and vpc. Similarly, **1** was treated with ethyl bromide, *n*-propyl bromide, benzyl bromide and allyl bromide in the presence of sodium amide to give the corresponding products (**3**, **4**, **5**,[6] and **6**) alklated on 5-methyl position. Isopropyl bromide, one of the secondary alkyl halides, also gave 3-methyl-5-isobutylisoxazole (**7**). Similarly, **1** was reacted with 1,2-epoxybutane to give 3-methyl-5-(3-hydroxy)pentylisoxazole (**8**), which was easily oxidized to ketone (**9**) with chromic anhydride.



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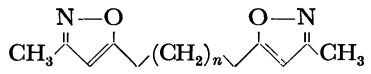
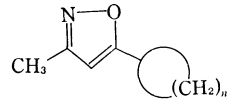
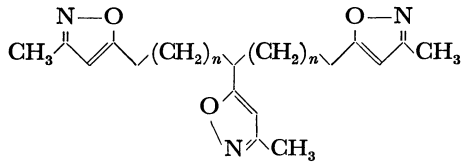
2: R=CH_2CH_3
3: R=$CH_2CH_2CH_3$
4: R=$CH_2CH_2CH_2CH_3$
5: R=$CH_2CH_2C_6H_5$
6: R=$CH_2CH_2CH{=}CH_2$
7: R=$CH_2CH(CH_3)_2$
8: R=$CH_2CH_2CHOHCH_2CH_3$
9: R=$CH_2CH_2COCH_2CH_3$
12: R=$CH(CH_3)_2$
13: R=$C(CH_3)_3$
14: R=$CH(CH_2C_6H_5)_2$
17: R=$CH(CH_3)CH_2CH_3$



11: n=0, 3, 4, 5



15: n=3, 4



16: n=3, 4

Fig. 1.

When **1** was treated with a half molar α,ω-dibromoalkane (**10**, n=3, 4, 5), the corresponding α,ω-di(3-methyl-5-isoxazolyl)alkanes (**11**, n=3, 4, 5) were obtained. In the case of 1,2-dibromoethane (**10**, n=2), the anomalous reaction product 1,2-di(3-methyl-5-isoxazolyl)ethane (**11**, n=0) was obtained.[6] When **1** was treated with sodium amide in liquid ammonia in the absence of **10** (n=2) followed by hydrolysis with ammonium chloride, the starting material was recovered. Thus, 1,2-dibromoethane (**10**, n=2) apparently acted as an oxidative reagent in this anomalous reaction.

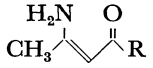
For di- and tri-alkylation of the 5-methyl group, we tried the reaction of **1** with excess amounts of sodium amide and methyl iodide. When 2 molar sodium amide and 2 molar methyl iodide were used, the products were 3-methyl-5-ethylisoxazole (**2**), 3-methyl-5-isopropylisoxazole (**12**) and 3-methyl-5-*t*-butylisoxazole (**13**). **2** was identified with the authentic sample by means of NMR and vpc. The structures of **12** and **13** were deduced from IR, NMR, and elemental analysis. When 3 molar sodium amide and 3 molar methyl iodide were used, **2**, **12**, and **13** were also obtained. When of 4 molar sodium amide and 4 molar methyl iodide were used, **13** was the sole product, and none of **2**, **12**, 3-ethyl-5-*t*-butylisoxazole and 3,4-dimethyl-5-*t*-butylisoxazole could be detected by NMR and vpc. The product ratios in these reactions are summarized in Table 1. Similarly, **1** was treated with 2 molar sodium amide and 2 molar benzyl bromide to give di-alkylation product, 3-methyl-5-(1,3-diphenyl-2-propyl)isoxazole (**14**). The reaction of **5** with benzyl bromide also gave **14**. The structure of **14** was confirmed by means of IR, NMR, and elemental analysis. In the NMR spectrum, the 3-methyl protons at δ 2.01 were deshielded by the sterically crowded phenyl groups.

Table 1. Product ratios in the reaction of **1** with methyl iodide

Molar ratio			Total yield	Product ratio		
1	CH_3I	$NaNH_2$	(%)	2%	12%	13%
1	1	1	58	100	0	0
1	2	2	68	33	57	10
1	3	3	59	9	62	29
1	4	4	51	0	0	100

We see from these results that the di- and tri-alkylation reactions were accomplished in one step. They occurred on the same reaction site at 5-methyl group of **1**, and were controlled by the amount of sodium amide. Thus, 3-methyl-5-cycloalkylisoxazoles (**15**) were expected in the case of α,ω-dibromoalkane (**10**) and **1** in the presence of 2 molar sodium amide. When, 1,3-dibromopropane (**10**, n=3) was treated with equimolar **1** and 2 molar sodium amide, 1,5,9-tri(3-methyl-5-isoxazolyl)nonane (**16**, n=3) was obtained together with 1,5-di(3-methyl-5-isoxazolyl)pentane (**11**, n=3), but no 3-methyl-5-cyclobutylisoxazole (**15**, n=3). Similarly, 1,6,11-tri(3-methyl-5-isoxazolyl)undecane (**16**, n=4) and 1,6-di(3-methyl-5-isoxazolyl)hexane (**11**, n=4) were obtained from 1,4-dibromobutane (**10**, n=4), but no 3-methyl-5-cyclopentylisoxazole (**15**, n=4).

If two different alkyl halides are used in the presence of 2 molar sodium amide, 3-methyl-5-*sec*-alkylisoxazoles might be obtained. When **1** was treated with methyl iodide followed by ethyl bromide, 3-methyl-5-*sec*-butylisoxazole (**17**) was obtained as well as 5-ethyl- (**2**), 5-*n*-propyl- (**3**), and 5-isopropyl-3-methylisoxazole (**12**).



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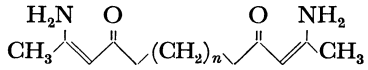

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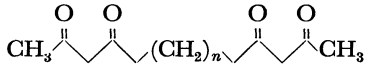

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Fig. 2

9) H. Feuer and S. Markofsky, *J. Org. Chem.*, **29**, 935 (1964).

TABLE 2. PROPERTIES OF 3-METHYL-5-SUBSTITUTED-ISOXAZOLES

Compd.		Substituent	Bp (mp) °C/Torr	t_R[a] min	δ_{Me-3}[b] ppm	δ_{H-4}[b] ppm	Isoxazole[c] cm^{-1}
1		Me	49—50/29	3.0	2.15	5.77	1613
2		Et	83/45[d]	5.0	2.18	5.68	1612
3		*n*-Pr	60—64/16	8.3	2.16	5.64	1607
4		*n*-Bu	70—75/5	15.6	2.20	5.70	1608
5		$(CH_2)_2Ph$	135—136/3		2.09	5.59	1607
6		$(CH_2)_2CH{=}CH_2$	99—103/15	14.0	2.21	5.74	1609
7		*i*-Bu		11.3	2.19	5.70	1606
8		$(CH_2)_2CH(OH)Et$	170—190/15		2.19	5.77	1604
9		$(CH_2)_2COEt$	105—110/5		2.21	5.73	1609
11	$n=0$	$(CH_2)_2$Isox[e]	(92—94)		2.26	5.87	1602[f]
11	$n=3$	$(CH_2)_5$Isox[e]	183—187/3		2.17	5.87	1609
11	$n=4$	$(CH_2)_6$Isox[e]	(56)		2.25	5.78	1609[f]
11	$n=5$	$(CH_2)_7$Isox[e]	(<20)		2.18	5.68	1605
12		*i*-Pr	74—75/15	6.6	2.16	5.59	1602
13		*t*-Bu	53—54/2	7.7	2.17	5.63	1605
14		$CH(CH_2Ph)_2$			2.01	5.39	1605
16	$n=3$	$CH[(CH_2)_4Isox]_2$[e]	210—215/10^{-3}		2.19	5.71	1606
16	$n=4$	$CH[(CH_2)_5Isox]_2$[e]			2.19	5.65	1604
17		*sec*-Bu	58—60/5	11.3	2.22	5.72	1603

a) t_R is the retention time on Apiezon L at 130°C. b) Solvent is CCl_4. c) Liquid film. d) Ref. 11.
e) Isox is 3-methylisoxazolyl f) KBr.

These isomerically pure isoxazoles produced by alkylation on the 5-methyl group of **1** were hydrogenated by platinum oxide in ethanol. The structures of the hydrogenated products were confirmed to be 2-amino-2-alkene-4-one (**18**) by means of IR, NMR, and elemental analysis. Furthermore, 2,12-diaminotrideca-2,11-diene-4,10-dione (**19**, $n=3$), hydrogenated product from **11** ($n=3$), was hydrolyzed by dilute hydrochloric acid in ethanol to give the corresponding ketone, tridecane-2,4,10,12-tetraone (**20**, $n=3$).[10]

Thus, it is possible to alkylate the methyl group at the 5-position of isoxazole with sodium amide and alkyl halides in liquid ammonia. By di- and trialkylation reactions using excess sodium amide, the isoxazoles having secondary and tertiary alkyl groups at the 5-position can be obtained. Hydrogenolysis of these isoxazoles gave the 5-alkylated 2-amino-2-pentene-4-ones (**18**). By hydrolysis of **18**, the γ-alkylation products of β-diketones were obtained in good yields. These procedures enable the 1,1-di- and 1,1,1-trialkylation reactions to take place, it being much more difficult for them to do so by the direct γ-alkylation of 2,4-diketones.[11,12]

Experimental

3,5-Dimethylisoxazole (1). By the method of Lampe,[1] a mixture of acetylacetone (34.3 g), hydroxylamine hydrochloride (35.4 g) and potassium carbonate (34.5 g) was refluxed for 4 hr. After washing the mixture with water, the organic layer was distilled, bp 49—50°C/29 Torr. Yield 45%.

General Procedure for Mono-alkylation. A solution of sodium (1.15 g) in liquid ammonia (*ca.* 300 ml) was oxidized to sodium amide catalyzed with ferric chloride. To this sodium amide suspension was added **1** (5.00 g) in anhydrous ether (30 ml). After stirring for 1.5 hr under nitrogen stream, alkyl halide (0.05 mol) in anhydrous ether (30 ml) was added. Stirring was continued for another 3 hr. After the mixture was neutralized with ammonium chloride, ammonia was removed at room temperature. The residual ether solution was acidified with dilute hydrochloric acid. The ether extract was concentrated and purified by preparative vpc, fractional distillation and/or silica gel column chromatography.

3-Methyl-5-ethylisoxazole (2). Purified by the preparative vpc on polyethylene glycol succinate (1 m stainless steel column) at 103°C, yield 70%. The NMR spectrum was superimposable on that of the authentic sample.[9]

3-Methyl-5-n-propylisoxazole (3). Purified by fractional distillation, yield 45%.

Found: C, 67.27; H, 8.97; N, 11.00%. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19%.

3-Methyl-5-n-butylisoxazole (4). Purified by fractional distillation, yield 61%.

Found: C, 68.96; H, 9.44; N, 10.05%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06%.

3-Methyl-5-phenylethylisoxazole (5). Purified by silica gel column chromatography with benzene–ethyl acetate mixture and fractional distillation, yield 70%. The NMR spectrum was superimposable on that of the authentic sample.[6]

3-Methyl-5-(3-butenyl)isoxazole (6). Purified by preparative vpc on polyethylene glycol succinate at 120°C, yield 44%.

Found: C, 69.27; H, 7.99; N, 10.05%. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21%.

3-Methyl-5-(3-hydroxypentyl)isoxazole (8). 1,2-Epoxybutane was used instead of alkyl halide and purified by fractional distillation and silica gel chromatography with benzene–ethyl acetate mixture, yield 15%.

Found: C, 63.63; H, 8.85; N, 8.30%. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28%.

10) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1431 (1965).
11) T. M. Harris and C. M. Harris, "Organic Reactions," Vol. 17, p. 155 (1969).
12) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 61 (1965).

1,5-Di(3-methyl-5-isoxazolyl)pentane (**11**, n=3). Purified by silica gel chromatography with benzene–ethyl acetate mixture, yield 84%.

Found: C, 66.35; H, 7.90; N, 11.86%. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96%.

1,6-Di(3-methyl-5-isoxazolyl)hexane (**11**, n=4). Purified by silica gel chromatography with benzene–ethyl acetate mixture and recrystallization from *n*-hexane, yield 77%.

Found: C, 67.81; H, 8.12; N, 11.09%. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28%.

1,7-Di(3-methyl-5-isoxazolyl)heptane (**11**, n=5). Purified by recrystallization from *n*-hexane, yield 70%.

Found: C, 68.31; H, 8.66; N, 10.57%. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68%.

1,2-Di(3-methyl-5-isoxazolyl)ethane (**11**, n=0). 1,2-Dibromoethane (**10**, *n*=2) used instead of alkyl halide and purified by recrystallization from *n*-hexane, yield 39%. The product was identified by the superimposable NMR and mp 92—94°C.[6]

General Procedure for Di-(tri-)alkylation. As described above, **1** (1.00 g) was treated with 0.02 mol (0.04 mol) of alkyl halide in the presence of 0.02 mol (0.04 mol) of sodium amide in liquid ammonia (*ca.* 50 ml).

3-Methyl-5-isopropylisoxazole (**12**). Purified by preparative vpc on Apiezon L (1 m stainless steel column) at 103°C and fractional distillation, yield 37%.

Found: C, 66.86; H, 9.04%. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86%.

3-Methyl-5-t-butylisoxazole (**13**). Purified by fractional distillation, yield 51%.

Found: C, 68.93; H, 9.34; N, 10.14%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06%.

3-Methyl-5-(1,3-diphenyl-2-propyl)isoxazole (**14**). Purified by silica gel chromatography with benzene–ethyl acetate mixture, yield 35%.

Found: C, 82.68; H, 6.85; N, 5.05%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05%.

1,5,9-Tri(3-methyl-5-isoxazolyl)nonane (**16**, n=3). Purified by silica gel chromatography with *n*-hexane–ether mixture, yield of **16** (*n*=3) 12% and **11** (*n*=3) 25%.

Found: C, 67.07; H, 7.97; N, 10.95%; mol wt (mass), 371. Calcd for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.32%; mol wt, 371.47.

1,6,11-Tri(3-methyl-5-isoxazolyl)undecane (**16**, n=4). Purified by silica gel chromatography with *n*-hexane–ether mixture, yield of **16** (*n*=4) 15% and **11** (*n*=4) 19%. Found: C, 70.49; H, 8.43; N, 10.02%; mol wt (mass), 399. Calcd for $C_{23}H_{33}N_3O_3$: C, 69.14; H, 8.33; N, 10.52%; mol wt, 399.52.

3-Methyl-5-sec-butylisoxazole (**17**). To a mixture of sodium amide (790 mg) and 3,5-dimethylisoxazole (1.00 g) in liquid ammonia (*ca.* 50 ml) was added methyl iodide (1.43 g) in anhydrous ether (15 ml) with stirring. After 1.5 hr, ethyl bromide (1.11 g) in anhydrous ether (15 ml) was added to the reaction mixture. Stirring was continued for another 2.5 hr at −50°C. The products were purified by preparative vpc on Apiezon L at 130°C, yields **2**, 47%; **12**, 8%; **3**, 7%; **17**, 12%. Found: C, 68.91; H, 9.58; N, 9.86%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06%.

Oxidation of **8**. A mixture of **8** (100 mg), chromic anhydride (600 mg) and pyridine (1.5 g) in dichloromethane (30 ml) was stirred for 30 min at 5°C. The dichloromethane extract from the reaction mixture was washed with aqueous sodium carbonate, dilute hydrochloric acid and water. Product (**9**) was purified by silica gel chromatography with benzene–ethyl acetate mixture, yield 50%. Found: C, 63.96; H, 7.96; N, 8.40%. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38%.

Hydrogenation of Isoxazoles. About one gram of isoxazoles was hydrogenated in ethanol (20 ml) catalyzed by platinum oxide (100 mg) at room temperature under ordinary pressure. After the catalyst was filtered off, the filtrate was concentrated and the corresponding products were recrystallized from *n*-hexane.

2-Amino-2-heptene-4-one (**18**, *R*=n-*Pr*). Yield 42%, mp 47.5°C. Found: C, 66.31; H, 10.32; N, 11.06%. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01%.

2-Amino-6-phenyl-2-hexene-4-one (**18**, *R*=$(CH_2)_2Ph$). Yield 95%, mp 103°C. Found: C, 76.09; H, 8.08; N, 7.06%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40%.

2,12-Diaminotrideca-2,11-diene-4,10-dione (**19**, n=3). Yield 72%, mp 109°C. Found: C, 65.77; H, 9.36; N, 11.76%. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76%.

2,13-Diaminotetradeca-2,12-diene-4,11-dione (**19**, n=4). Yield 76%, mp 150°C. Found: C, 66.39; H, 9.67; N, 10.88%. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10%.

2,9-Diaminodeca-2,8-diene-4,7-dione (**19**, n=0). Yield 70%, mp 165°C. Found: C, 61.40; H, 8.39; N, 14.25%. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28%.

Hydrolysis of **19** (n=3). **19** (*n*=3) was dissolved in ethanol acidified to pH 4 with hydrochloric acid and the mixture was stirred for 10 hr at room temperature. After being neutralized with potassium carbonate, the mixture was extracted with ether. The residue from the extract was recrystallized from *n*-hexane, yield 52%, mp 67°C. The product was identified with the authentic sample[10] by IR and NMR spectra and mp.