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Preparation of Isoxazolines by Thermolysis of Ethyl 2-Nitroalkanoates in the Presence of Dipolarophiles

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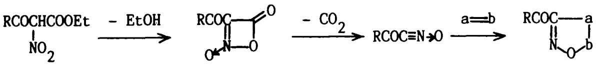
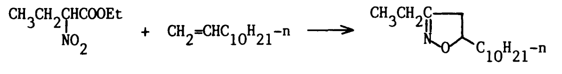
Synopsis. 3-Alkyl-2-isoxazolines and 3-alkylisoxazole were prepared by thermolysis of ethyl 2-nitroalkanoates at about 230 °C in the presence of dipolarophiles.

1,3-Dipolar cycloaddition reactions using nitrile oxides are one of versatile methods for the preparation of five-membered heterocycles. A variety of preparative methods for nitrile oxides are known so far.[1—12] Recently, we reported[10,11] the thermolysis of nitromalonates (**1**) and the mono anilides (**2**) at 160—170 °C to give nitrile oxides effectively, which could be trapped by a variey of dipolarophiles as cycloadducts in high yields.



1 : R = OEt
2 : R = NHAr

Although ethyl 2-nitrobutanoate (**3**) remained unchanged under similar reaction conditions,[11] a thermolysis of **3** under more vigorous thermal conditions in the presence of dipolarophiles did give cycloadducts. For example, a mixture of **3** and 1-dodecene in an appropriate solvent was heated to reflux for several hours under nitrogen and the following work-up of the reaction mixture gave a desired cycloadduct, 5-decyl-3-ethyl-2-isoxazoline (**4a**), in yields shown in Table 1. It was found from the Table that the yield of **4a** was not so varied from the employment of an excess of the dipolarophile and was effectively affected by the reaction temperature. Though a considerable amount of both substrates was recovered from the reaction mixture of Runs 1—4 and 6—8, none of **3** could be recovered from the reaction mixture of Run 5 in which formation of a considerable amount of tarry material was observed. Although the optimum reaction conditions were not yet attained, the best yield (48%) of the cycloadduct (**4a**) obtained is comparable with that by Mukaiyama method.[5]



3 4a

Table 2. Yields and Melting Points of the Cycloadducts (**4**, **6**, **8**, and **9**)[a]

Adduct	R^2	R^3	Yield / %	Mp(θ_m/°C) (Bp(θ_b/°C)/mmHg)
4a	H	$C_{10}H_{21}$-*n*	48	(130—135/0.3)
4b	H	C_8H_{17}-*n*	43	(110—115/0.2)
4c	H	$C_{12}H_{25}$-*n*	37	33—34[b]
4d	H	$C_{14}H_{29}$-*n*	21	41—43
4e	$-(CH_2)_{10}-$		20	(128—135/0.2)
4f	H	$CH_2C_6H_4OCH_3$-*p*	34	(166—170/0.4)
4g	H	$CH_2OC_6H_4NO_2$-*p*	10	83—85[b]
4h	$COOCH_3$	$COOCH_3$	10	(110—115/0.3)[b]
4i	Ph	Ph	25	(140—145/0.5)
4j	CH_3	$C_6H_4OCH_3$-*p*	24	(144—149/0.4)
6a	H	$C_{10}H_{21}$-*n*	12	(130—136/0.6)
6b	H	C_8H_{17}-*n*	5	(110—115/0.5)
6c	H	$C_{12}H_{25}$-*n*	28	(145—151/0.4)
6e	$-(CH_2)_{10}-$		8	(137—140/0.4)
6f	H	$CH_2C_6H_4OCH_3$-*p*	15	(158—165/0.4)
8a	H	$C_{10}H_{21}$-*n*	33	(160—167/0.4)
8b	H	C_8H_{17}-*n*	30	(110—115/0.6)
8c	H	$C_{12}H_{25}$-*n*	39	34—36
8e	$-(CH_2)_{10}-$		20	(165—173/0.4)
8f	H	$CH_2C_6H_4OCH_3$-*p*	33	(160—165/0.4)
9	H	C_8H_{17}-*n*	14	(83—91/0.2)

a) Satisfactory microanalyses are obtained (C, H, N: ±0.25%). b) Lit, mp; **4c**: 35—36 °C,[7] **4g**: 83—85 °C,[7] **4h**: 83 °C/0.3 mmHg.[12] [1 mmHg = 133.322 Pa].

Table 1. The Reaction of **3** with 1-Dodecene

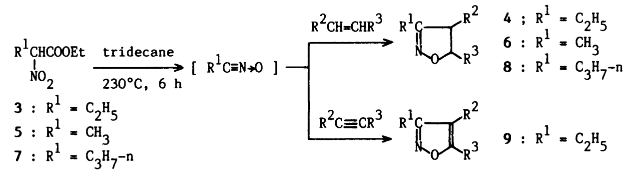
Run No.	Molar ratio of **3** : 1-dodecene	Solvent	Reaction temperature[a]	Reaction time	Yield of **4a**[b]	Recovery of **3**
1	1 : 1	Mesitylene	164 °C	6 h	0%	>90%
2	1 : 1	Decalin	190 °C	6 h	trace	>90%
3	1 : 1	Tridecane	234 °C	3 h	31%	50%
4	1 : 1	Tridecane	234 °C	6 h	48%	40%
5	1 : 1	Tridecane	234 °C	12 h	40%	0%
6	1 : 1	Tetradecane	254 °C	4.5 h	42%	38%
7	1 : 2	None	213 °C	3 h	25%	57%
8	1 : 2	None	213 °C	6 h	42%	45%

a) The boiling point of the solvent is shown except for the cases of Runs 7 and 8, in which that of 1-dodecene is shown. b) Yields were calculated on the basis of **3** used.

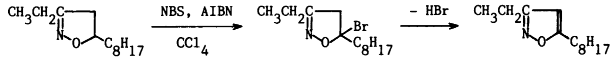
The results of the reaction of **3** with some dipolarophiles under similar conditions such as Run 4 in Table 1 were summarized in Table 2 along with those obtained by the reactions using ethyl 2-nitropropanoate (**5**) or ethyl 2-nitropentanoate (**7**) instead of **3**. In cases using **5**, yields of the desired cycloadducts (**6**) were generally lower than those from **3** or **7**. This results may be ascribed to the nature of the boiling point (195 °C) of **5**, lower than those (>230 °C) of **3** and **7**.

Table 3. ^{1}H NMR Spectral Data of the Cycloadducts (**4**, **6**, **8**, and **9**)

Adduct	^{1}H NMR, ppm (in $CDCl_3$)
4a	0.9 (t, 3H, J=7), 1.15 (t, 3H, J=7), 1.1—1.8 (m, 18H), 2.35(q, 2H, J=7), 2.45(dd, 1H, J=8, 16), 3.0(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
4b	0.85(t, 3H, J=7), 1.15(t, 3H, J=7), 1.0—1.7 (m, 14H), 2.33(q, 2H, J=7), 2.45(dd, 1H, J=8, 16), 3.0(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
4d	0.9 (t, 3H, J=7), 1.16 (t, 3H, J=7), 1.0—1.8 (m, 26H), 2.35(q, 2H, J=7), 2.45(dd, 1H, J=8, 16), 3.0(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
4e	1.17 (t, 3H, J=7), 1.1—1.8 (m, 20H), 2.3 (q, 2H, J=7), 2.6—3.2(m, 1H), 4.2—4.7(m, 1H).
4f	1.1(t, 3H, J=7), 2.3(q, 2H, J=7), 2.5—3.2(m, 4H), 3.8(s, 3H), 4.5—5.0(m, 1H), 6.83(d, 2H, J=9), 7.17(d, 2H, J=7).
4i	1.05 (t, 3H, J=7), 1.9—2.45 (m, 2H), 4.17 (d, 1H, J=7), 5.4(d, 1H, J=7), 7.3(brs, 10H).
4j	1.05(t, 3H, J=7), 1.25(d, 3H, J=7), 1.9—2.6 (m, 2H), 2.7—3.4(m, 1H), 3.8(s, 3H), 4.95(d, 1H, J=9), 7.0(d, 2H, J=9), 7.3(d, 2H, J=9).
6a	0.9(t, 3H, J=7), 1.0—1.7(m, 18H), 1.95(s, 3H), 2.47(dd, 1H, J=8, 16), 2.95(dd, 1H, J=10, 16), 4.0—4.7(m, 1H).
6b	0.9(t, 3H, J=7), 1.0—1.7(m, 14H), 1.95(s, 3H), 2.47(dd, 1H, J=8, 16), 2.95(dd, 1H, J=10, 16), 4.0—4.7(m, 1H).
6c	0.9(t, 3H, J=7), 1.0—1.7(m, 22H), 1.97(s, 3H), 2.45(dd, 1H, J=8, 16), 3.0(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
6e	1.0—1.8(m, 20H), 1.95(s, 3H), 2.6—3.1(m, 1H), 4.2—4.7(m, 1H).
6f	1.93(s, 3H), 2.3—3.2(m, 4H), 3.77(s, 3H), 4.4—5.0 (m, 1H), 6.8(d, 2H, J=9), 7.15 (d, 2H, J=9).
8a	0.9 (t, 3H, J=7), 0.97 (t, 3H, J=7), 1.1—1.9 (m, 20H), 2.3(t, 2H, J=7), 2.47 (dd, 1H, J=8, 16), 2.97(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
8b	0.9 (t, 3H, J=7), 0.96 (t, 3H, J=7), 1.1—1.9 (m, 16H), 2.3(t, 2H, J=7), 2.47 (dd, 1H, J=8, 16), 2.97(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
8c	0.9 (t, 3H, J=7), 0.96 (t, 3H, J=7), 1.1—1.9 (m, 24H), 2.3(t, 2H, J=7), 2.47 (dd, 1H, J=8, 16), 2.97(dd, 1H, J=10, 16), 4.1—4.7(m, 1H).
8e	0.9(t, 3H, J=7), 1.0—1.9(m, 22H), 2.25(t, 2H, J=7), 2.6—3.1(m, 1H), 4.2—4.7(m, 1H).
8f	0.9 (t, 3H, J=7), 1.5 (hexet, 2H, J=7), 2.3(t, 2H, J=7), 2.5—3.2 (m, 4H), 3.77(s, 3H), 4.5—5.0(m, 1H), 6.8(d, 2H, J=9), 7.15(d, 2H, J=9).
9	0.9(t, 3H, J=7), 1.0—1.5(m, 15H), 2.6(q, 2H, J=7), 2.67(t, 2H, J=7), 5.8(s, 1H).

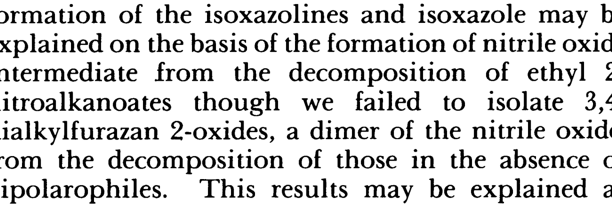


The structure of the cycloadducts (**4**, **6**, **8**, and **9**) were assigned on the basis of elemental, MS, NMR, and IR spectral analyses (see Table 3). The assignment of the structure (**4c**, **4g**, and **4h**) was further supported by comparison of the physical properties with those of authentic specimens prepared according to literatures.[7,12] The structure of **9** was supported by the evidence that the physical properties of **9** agreed with those of the specimen prepared by dehydrogenation of **4b** with *N*-bromosuccinimide.[13]



4b **9**

Gradual evolution of carbon dioxide and ethanol was observed in the course of the reactions. From these evidences, one of the probable mechanism of the formation of the isoxazolines and isoxazole may be explained on the basis of the formation of nitrile oxide intermediate from the decomposition of ethyl 2-nitroalkanoates though we failed to isolate 3,4-dialkylfurazan 2-oxides, a dimer of the nitrile oxide, from the decomposition of those in the absence of dipolarophiles. This results may be explained as follows: a reverse reaction of the furazan 2-oxides to nitrile oxide has been known to be possible under the reaction temperature,[14] and consequently, the nitrile oxide is consumed by irreversible reactions such as the rearrangement to isocyanates or the reaction with ethanol giving ethyl hydroximic acid which, then,



undergo further transformations such as decomposition, polymerization, and reaction with ethanol and/or the staring material to give complex tarry materials under the conditions, though we failed to isolate any compound that supports this mechanism from the tarry mixture. The lower yields of the cycloadducts (**4**, **6**, **8**, and **9**) from **3**, **5**, or **7** than those from **1** or **2** can be ascribed to the result of the difficulty of thermolysis of **3**, **5**, and **7** into nitrile oxides. In other words, the introduction of electron-withdrawing group such as carbalkoxy and carbamoyl groups at α-position of ethyl nitroacetate promotes the tautomerization to the corresponding aci-nitro isomers and, consequently, intramolecular condensation and the following decarboxylation giving nitrile oxides are accelerated.

Experimental

Measurements. Melting and boiling points are all uncorrected. ^{1}H NMR spectra were recorded on Varian T-60A instrument with TMS as an internal standard; chemical shifts are given in δ-units and coupling constants (J) are in herz units: s=singlet; d=doublet; t=triplet; m=multiplet; brs=broad singlet.

Materials. Ethyl 2-nitroalkanoates (**3**, **5**, and **7**) were prepared according to the method described in literature.[15] The other chemicals were of commercial origin and were used without further purification.

Reaction of Ethyl 2-Nitroalkanoates with Dipolarophiles; General Procedure: A mixture of ethyl 2-nitrobutanoate (**3**) (1.61 g, 10 mmol), 1-dodecene (1.68 g, 10 mmol), and tridecane (3.0 g) is heated to reflux over free flame for 6 h under nitrogen. After distillation of the unreacted substrates and the solvent from the reaction mixture by water aspirator, the residue was further distilled *in vacuo* to give analytically pure 5-decyl-3-ethyl-2-isoxazoline (**4a**) in 48% yield.

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