  Bull. Chem. Soc. Jpn., 58, 2519—2522 (1985)

A New Synthetic Method of Alkyl Carbonocyanidate *N*-Oxides

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(Received April 17, 1985)

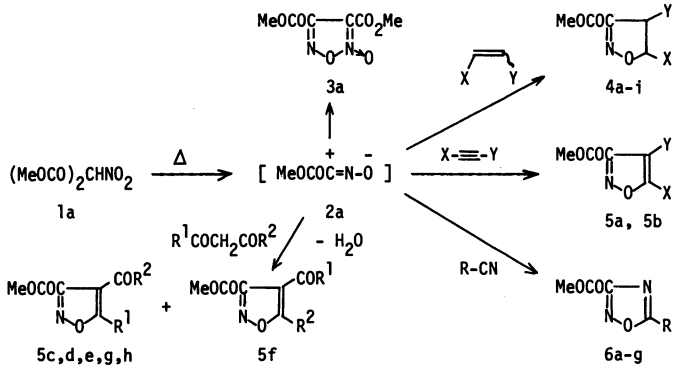
A thermal decomposition of dimethyl nitromalonate to bis(carbomethoxy)furoxan was observed at about 170 °C. In the presence of dipolarophiles, an intermediate, methyl carbonocyanidate *N*-oxide MeOCOC≡N→O, could be trapped as cycloadducts in good yields by the 1,3-dipolar cycloaddition. Treatment of dimethyl nitromalonate in mesitylene at the refluxing temperature resulted in a formation of methyl 2-(hydroxyimino)-2-(2,4,6-trimethylphenyl)acetate.

1,3-Dipolar cycloaddition reactions using nitrile oxides were one of the versatile methods for the preparation of five-membered heterocycles. Many preparative methods of nitrile oxides have been known so far,[1-8] but each of these methods suffers from some disadvantages; for example, i) many troublesome steps are required for the preparation of a precursor of nitrile oxides, ii) formation of by-products, and iii) a poor yield of the cycloadducts in the reaction with dipolarophiles. The present paper describes a new effective and simple method for the generation of alkyl carbonocyanidate *N*-oxides, ROCOC≡N→O, by a thermal decomposition of dialkyl nitromalonates and the trapping of the intermediate in the presence of dipolarophiles as cycloadducts. Nitromalonates (**1**) can be prepared quantitatively by the nitration of malonates with nitric acid under mild conditions.[9] Dimethyl nitromalonate (**1a**) and diethyl nitromalonate (**1b**) are known to be thermally stable (bp 124 °C/16 mmHg and 134 °C/14 mmHg, respectively).[9]

Results and Discussion

Thermal decomposition of **1** into distinct products is unprecedented to our knowledge, but we found that the thermolysis of **1a** in neat or in decalin at about 170 °C for several hours gave bis(methoxycarbonyl)furazan oxide (furoxan)(**3a**) in 70—75% yields with evolution of CO_2 and methanol. The isolation of the furoxan suggests that methyl carbonocyanidate *N*-oxide (**2a**) is first formed and then is converted into the dimer, **3a**. In the presence of dipolarophiles such as olefins, acetylenes, and nitriles, **2a** could be trapped as 2-isoxazolines (**4a—i**), isoxazoles (**5a** and **5b**), and 1,2,4-oxadiazoles (**6a—g**) respectively in the yields shown in Table 1 (also see Scheme 1). The structures of the products were assigned on the basis of elemental and spectral analyses and comparison of their physical properties with those of authentic specimens. β-Keto esters and 1,3-diketones are known to behave as dipolarophiles *via* a tautomerization into the enol forms.[10] Isoxazoles (**5c—h**) were thus obtained from the reaction of **1a** with several 1,3-dicarbonyl compounds *via* a dehydration of the initial cycloadducts, 5-hydroxy-2-isoxazolines.

A probable mechanism of the formation of **2a** in these reactions would be as follows; **1a** equilibrates with the nitronic acid (**7**), which undergoes an intramolecular substitution with loss of methanol followed by decomposition to give **2a**.

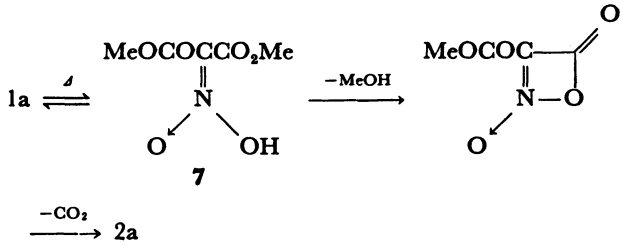


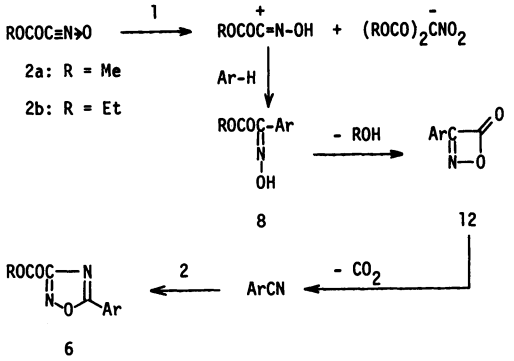
Scheme 1.

Table 1. 1,3-Dipolar cycloadducts from the reaction of **1a** with dipolarophiles

Dipolarophile	Reaction[a] condition	Product	Yield %	Mp(Bp) °C
1-Tetradecene	A	**4a** (X=$C_{12}H_{25}$, Y=H)	68	66—68[b]
Allyl *p*-nitrophenyl ether	A	**4b** (X=$CH_2OC_6H_4NO_2$, Y=H)	100	142—143[b]
Allylbenzene	A	**4c** (X=$CH_2C_6H_5$, Y=H)	85	67—68[b]
Cyclooctene	A	**4d** (X, Y=-C_6H_{12}-)	88	69—71
Cyclododecene	A	**4e** (X, Y=-$C_{10}H_{20}$-)	55	79—81
Styrene	A	**4f** (X=C_6H_5, Y=H)	86	(110—112/0.2)
iso-Butyl acrylate	A	**4g** (X=$CO_2C_4H_9$, Y=H)	92	(150—151/2)
N-Phenylmaleimide	A	**4h** [X, Y=-CON(Ph)CO-]	90	222—225[b]
Diethyl fumarate	A	**4i** (X=Y=CO_2Et)(trans)	88	(145—147/0.5)
Phenylacetylene	A	**5a** (X=Ph, Y=H)	75	74—76
DMAD[c]	A	**5b** (X=Y=CO_2Me)	80	97—98[b]
Acetylacetone	B	**5c** (R^1=R^2=Me)	30	(95—100/1.5)
Dibenzoylmethane	C	**5d** (R^1=R^2=Ph)	28	111—112
Benzoylacetone	B	**5e** (R^1=Ph, R^2=Me)	43	62—64
		5f (R^1=Me, R^2=Ph)	29	82—85
Ethyl acetoacetate	B	**5g** (R^1=Me, R^2=OEt)	25	(100—120/2)
Ethyl benzoylacetate	C	**5h** (R^1=Ph, R^2=OEt)	20	(150—152/1)
Benzonitrile	C	**6a** (R=Ph)	31	107—108
2,4,6-Trimethylbenzonitrile	C	**6b** (R=C_9H_{11})	15	75—85
4-Methoxybenzonitrile	C	**6c** (R=C_6H_4OMe)	42	156—157
1-Naphthonitrile	C	**6d** (R=$C_{10}H_7$)	12	109—111
Phenylacetonitrile	C	**6e** (R=$CH_2C_6H_5$)	26	75—76
Dodecanenitrile	B	**6f** (R=$C_{11}H_{23}$)	16	50—51
Nonanenitrile	B	**6g** (R=C_8H_{17})	16	35—39

a) A: Refluxing the mesitylene solution of an equimolar mixture of **1a** and dipolarophiles for 20 h; B: Heating the mixture of **1a** and excess amount of dipolarophiles at about 170 °C for 8 h; C: Heating the decalin solution of an equimolar amount of **1a** and dipolarophiles at 170 °C for 20 h. b) **4a**: Lit,[8] mp 66—68 °C; **4b**: lit,[8] mp 142—143 °C; **4c**: lit,[8] mp 60—61 °C; **4h**: lit,[8] mp 223—225 °C; **5b**: lit,[6a] mp 101—102 °C. c) DMAD: Dimethyl acetylenedicarboxylate.





Scheme 2.

Although the yields of the cycloadducts were not highly dependent on solvents (neat, mesitylene, or decalin), we found that some of aromatic compounds bearing electron-releasing substituents were another acceptor of nitrile oxides. Refluxing a solution of **1a** in mesitylene for 20 h evolved CO_2 and methanol, and methyl 2-(hydroxyimino)-2-(2,4,6-trimethylphenyl)acetate (**8a**) was isolated in 27% yield. Furoxan (**3a**) was not detected in the solution. The structure of **8a** was confirmed by the agreement of the physical properties of **8a** with those of the specimen prepared from the reaction of methyl chloro(hydroxyimino)-acetate (**9**) with mesitylene. Though similar compounds (**8b—f**) were obtained from the reaction of **1a—b** with mesitylene, 1,2,4,5-tetramethylbenzene, pentamethylbenzene, and 3,5-dimethylanisole (see Table 2), 5-(*p*-methoxyphenyl)-3-methoxycarbonyl-1,2,4-oxadiazole (**6c**) or 3-methoxycarbonyl-5-(1,2,3,4-tetramethylphenyl)-1,2,4-oxadiazole (**6h**) was the only isolable compound from the reaction mixture of **1a** and anisole or 1,2,3,4-tetramethylbenzene, respectively.

The mechanism of the formation of these products can be explained in a fashion as shown in Scheme 2. Nitromalonates are known to be strong carbon-acids.

Protonation of the nitrile oxides (**2**) by nitromalonates would give a carbonium ion followed by electrophilic aromatic substitution to afford **8**. So far only an example of aromatic substitution has been reported using nitrile oxides, although a completely different mechanism of the substitution was suggested.[11] The aromatic substitution described here would provide new aspect of the chemistry of nitrile oxides.

In conclusion, our new reaction provides a simple and useful means of syntheses of isoxazolines, because of economical starting materials, easiness of the removal of by-products (MeOH and CO_2), and high yields of cycloadducts. On the other hand, the less reactive dipolarophiles such as nitriles and 1,3-dicarbonyl compounds gave poor yields of the cycloadducts.

Experimental

Measurements. All melting and boiling points are uncorrected. The ^{1}H NMR were measured on a Valian T-60A instrument with Me_4Si 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; q=quartet; m=multiplet; br=broad singlet. All new

Table 2. Reactions of **1a—b** with aromatic compounds

Nitro Malonate	Aromatic Compound	Product	Yield %	Mp θ_m/°C
1a	Mesitylene	**8a** (R=Me, Ar=2,4,6-tetramethylphenyl)	27	131—132
1b	Mesitylene	**8b** (R=Et, Ar=2,4,6-tetramethylphenyl)	20	112—114
1a	1,2,4,5-Tetramethylbenzene	**8c** (R=Me, Ar=2,3.5,6-tetramethylphenyl)	15	210—218
1a	Pentamethylbenzene	**8d** (R=Me, Ar=pentamethylphenyl)	14	188—191
1a	3,5-Dimethylanisole	**8e** (R=Me, Ar=4,6-dimethyl-2-methoxyphenyl)	19	167—169
		8f (R=Me, Ar=2,6-dimethyl-4-methoxyphenyl)	11	
1a	Anisole	**6c**	3	142—145
1a	1,2,3,4-Tetramethylbenzene	**6h** (R=2,3,4,5-tetramethylphenyl)	6	120—121

Table 3. ^{1}H NMR Spectral data of new compounds (**4—8**)

Adduct	Chemical shift/δ, Solvent: $CDCl_3$
4d	1.1—2.3 (m, 12H), 3.1—3.5 (m, 1H), 3.9 (s, 1H), 4.4—4.8 (m, 1H).
4e	1.0—1.9 (m, 20H), 3.1—3.6 (m, 1H), 3.85 (s, 1H), 3.55—3.95 (m, 1H).
4f	3.13 (dd, 1H, J=9, 18), 3.63 (dd, 1H, J=11, 18), 3.85 (s, 3H), 5.75 (dd, 1H, J=9, 11), 7.3 (s, 5H).
4g	0.93 (d, 6H, J=7), 1.6—2.4 (m, 1H), 3.48 (d, 2H, J=10), 3.87 (s, 3H), 3.97 (d, 2H, J=7), 5.2 (t, 1H, J=10).
5a	3.98 (s, 3H), 6.9 (s, 1H), 7.2—7.6 (m, 3H), 7.6—7.9 (m, 2H).
5c	2.5 (s, 3H), 2.67 (s, 3H), 4.0 (s, 3H).
5d	3.8 (s, 3H), 7.25—8.0 (m, 10H).
5e	2.47 (s, 3H), 4.0 (s, 3H), 7.4—7.9 (m, 5H).
5f	2.53 (s, 3H), 3.66 (s, 3H), 7.3—7.9 (m, 5H).
5g	1.34 (t, 3H, J=7), 2.7 (s, 3H), 4.0 (s, 3H), 4.34 (q, 2H, J=7).
5h	1.3 (t, 3H, J=7), 4.0 (s, 3H), 4.33 (q, 2H, J=7), 7.4—7.7 (m, 3H), 7.85—8.1 (m, 2H).
6a	4.08 (s, 3H), 7.4—7.7 (m, 3H), 8.1—8.3 (m, 2H).
6b	2.27 (s, 6H), 2.34 (s, 3H), 4.07 (s, 3H), 7.0 (s, 2H).
6c	3.9 (s, 3H), 4.05 (s, 3H), 7.0 (d, 2H, J=9), 8.15 (d, 2H, J=9).
6d	4.1 (s, 3H), 7.4—8.2 (m, 5H), 8.4 (dd, 1H, J=2, 7), 9.1 (dd, 1H, J=2, 7).
6e	4.0 (s, 3H), 4.3 (s, 2H), 7.35 (s, 5H).
6f	0.9 (t, 3H, J=7), 1.0—2.1 (m, 16H), 3.0 (t, 3H, J=7), 4.05 (s, 3H).
6g	0.85 (t, 3H, J=7), 1.0—2.1 (m, 12H), 3.0 (t, 3H, J=7), 4.05 (s, 3H).
6h	2.3 (s, 6H), 2.33 (s, 3H), 2.6 (s, 3H), 4.08 (s, 3H), 7.73 (s, 1H).
8a	2.15 (s, 6H), 2.3 (s, 3H), 3.83 (s, 3H), 6.9 (s, 2H), 9.7 (br, 1H, OH).
8b	1.23 (t, 3H, J=7), 2.1 (s, 6H), 2.27 (s, 3H), 4.28 (q, 2H, J=7), 6.87 (s, 2H), 10.0 (br, 1H, OH).
8c	2.04 (s, 6H), 2.23 (s, 6H), 3.83 (s, 3H), 7.0 (s, 1H), 9.5 (br, 1H, OH).
8d*	2.0 (s, 6H), 2.1—2.4 (m, 9H), 3.8 (s, 3H), 12.0 (br, 1H, OH).
8e	2.15 (s, 3H), 2.33 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 6.6 (s, 1H), 6.7 (s, 1H), 10.0 (br, 1H, OH).
8f	2.15 (s, 6H), 3.78 (s, 3H), 3.83 (s, 3H), 6.63 (s, 2H), 10.0 (br, 1H, OH).

* Dissolved in DMSO-d_6.

products gave satisfactory elemental analyses (±0.3% for C, H, and N).

Materials. Dimethyl and diethyl nitromalonate (**1a** and **1b**),[9] and methyl chloro(hydroxyimino)acetate (**9**),[12] were prepared according to the methods described in the literature. Mesitonitrile [mp 49—50 °C (lit,[13] 50 °C)] was prepared in 75% yield from the reaction of mesitaldehyde with hydroxylamine hydrochloride in refluxing ethanol for 10 h. The other chemicals were of commercial origin and used without further purification.

Thermal Decomposition of 1a—b to Furoxan. A decalin solution (10 ml) of **1b** (4.1 g, 20 mmol) was heated in an oil bath (about 170 °C) for several minutes. Gradual evolution of CO_2 (trapped as $CaCO_3$) and ethanol was observed in the course of the reaction. After the mixture was kept at the temperature for 20 h, the solvent was removed from the reaction mixture by distillation. Further distillation under reduced pressure gave a colorless oil (2.2 g yield, bp 110—130 °C/2 mmHg). The oil was found to be a mixture of **1b** and bis(ethoxycarbonyl)furoxan (**3b**) (molar ratio: *ca.* 1:4; yield of **3b**: 78%). Separation of **3b** and **1b** could be accomplished by passing the oil through an alumina column with chloroform. Evaporation of the chloroform eluents gave pure **3b** in 75% yield (1.68 g). **3a** was obtained similarly in 70% yield by decomposition of **1a**.

Reaction of 1a with Olefins or Acetylenes. Method A. A mixture of **1a** (1.77 g, 10 mmol) and a dipolarophile (10 mmol) was refluxed in mesitylene (20 ml) at 160—170 °C for 20 h. Evaporation of the solvent and other low-boiling products from the reaction mixture in a rotary evaporator gave crude product. Crystalline crude products (**4a—e**, **4h**, **5a**, and **5b**) obtained by this method were recrystallized from appropriate solvents (**4a**, **4b**, and **5a** from ethanol; **4c** and **5b** from ethanol–hexane; **4d** from hexane; **4e** from methanol). Oily crude products (**4f**, **4g**, and **4i**) were distilled *in vacuo* to give pure cycloadducts.

Reaction of 1a with Nitriles or 1,3-Dicarbonyl Compounds. Method B. A mixture of **1a** (1.77 g, 10 mmol) and an excess amount of a dipolarophile (*ca.* 20—30 mmol) was heated at about 170 °C for 8 h. The excess dipolarophile was distilled off from the reaction mixture. Crystalline residue was recrystallized from an appropriate solvent: **5e** and **5f** could be separated by fractional recrystallization from ethanol, **6f** from ethanol, and **6g** from hexane. Oily residue was further distilled *in vacuo* and the distillate was passed through an alumina column with chloroform. After evaporation of the chloroform eluent, the fractional distillation of the residue gave pure cycloadducts (**5c** and **5g**).

Method C. An equimolar amount (10 mmol) of **1a** and dipolarophile was heated at about 170 °C in decalin (20 ml) for 20 h. Upon cooling to room temperature, the reaction mixture separated into two layers. After removing a large portion of upper decalin layer by decantation, the residue was distilled *in vacuo* to remove decalin, furoxan **3a**, and the dipolarophile unchanged. Crystalline residue thus obtained was recrystallized from an appropriate solvent (**5d**, **6a**, **6d**, and **6e** from ethanol; **6b** from methanol; **6c** from ethanol–hexane). The oily residue obtained from the reaction with ethyl benzoylacetate was treated similarly as shown in Method B to give pure **5h**.

Thermal Decomposition of 1a—b in Aromatic Compounds. A mixture of **1a** or **1b** (10 mmol) and an aromatic compound (20—30 mmol) was heated in an oil bath at 170 °C for 20 h. Unreacted **1** and aromatic compound were recovered by distillation of the reaction mixture. Crystalline residues obtained from the reactions with 1,2,4,5-tetramethylbenzene, pentamethylbenzene, 3,5-dimethylanisole, and 1,2,3,4-tetramethylbenzene were recrystallized from ethanol (**8e**, **8f**, and **6h**) or carbon tetrachloride (**8c** and **8d**). Oily residues obtained from the reactions with mesitylene and anisole were further distilled *in vacuo* to give viscous oils. The viscous oils were solidified by scraching in hexane to give crystals (**8a**, **8b**, and **6c**).

Reaction of 8a with 1a. A mixture of **8a** (800 mg, 3.6 mmol) and **1a** (2.0 g, 11 mmol) was heated at 170 °C for 20 h. 1.2 g of **1a** was recovered by distillation of the reaction mixture. Residual oil was passed through an alumina column with chloroform to give crystals, which were recrystallized from methanol to give **6b** in 25% yield (220 mg).

Reaction of Mesitylene with Methyl Chloro(hydroxyimino)-acetate (9). A mesitylene solution (20 ml) of **9** (1.8 g, 13 mmol) was refluxed untill the evolution of HCl had ceased (after *ca.* 10 h) and removal of excess amount of mesitylene from the reaction mixture afforded reddish oil. The oil was distilled and a viscous fraction (bp 130—150 °C/0.3 mmHg†) was collected, which crystallized partially in a condenser. The fraction was crystallized by scraching in hexane and the crystals were filtered to yield **8a** in 40% yield (1.15 g).

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† 1 mmHg=133.322 Pa.