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1,3-Dipolar Cycloadditions of Nitrile Oxides with α- and β-Azidovinyl Ketones

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Three types of adducts (**2**, **3**, and **4**) were isolated from the reactions of α-azidovinyl ketones with nitrile oxides. They were characterized by ir, nmr, mass spectra, microanalyses, and chemical transformations. β-Azidovinyl ketones, on the contrary, reacted with benzonitrile oxides to give 4-acylisoxazoles (**14**) as the only products. In all the cases studied, the additions onto the C=C bonds were regiospecific and fully controlled by the azide function. The synthetic value of this observation is further demonstrated in this paper by the additions of benzonitrile oxide to α- and β-azidostyrene.

Several methods have been developed recently for the synthesis of α- and β-azidovinyl ketones in high yields.[1] This led us to explore their reactions with nitrile oxides. These 1,3-dipoles are known to add to C=C and C=O bonds, although the latter reactions are restricted to aldehydes and ketones activated by adjacent electron-withdrawing groups.[2] Cycloadditions of nitrile oxides with nonactivated carbonyl compounds such as acetaldehyde, acetone, etc., however, have been performed in the presence of boron trifluoride etherate as catalyst.[3] Starting with az-

Table I
Products Obtained from the Reaction of 1a–d with 2 Equiv of PhCNO

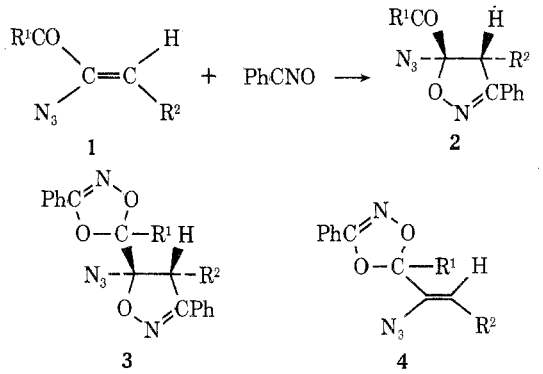
Starting azide (% unreacted)	Mono-adduct 2 % by nmr	Mono-adduct 2 % isolated	Bisadduct 3 % by nmr	Bisadduct 3 % isolated	Adduct 4 % by nmr	Adduct 4 % isolated
1a (36)	50	49	14	3.5		
1b (26)	14	14	60	(40)[a]		
1c (77)	11	*b*	12	*b*		
1d (61)	12	12	12	9	15	10

[a] Isolated from methanol as the ring-opened hemiketal (see discussion). [b] Not isolated but directly converted to the isoxazole **5c**.

idovinyl ketones we have observed that nitrile oxides can add to both dipolarophilic functions in the molecule. The results are described in this paper.

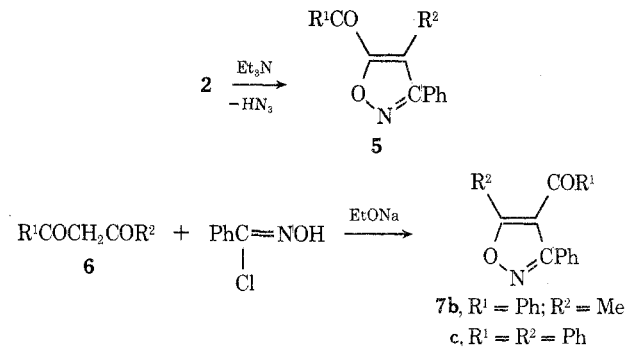
Results and Discussion

Treatment of α-azidovinyl ketones (**1a–d**) with benzonitrile oxide at room temperature gave both the monoadducts (**2a–d**) and bisadducts (**3a–d**) in addition to unreacted azide and diphenylfuroxan, the latter resulting from dimerization of the nitrile oxide. In one specific case compound **4** was also isolated together with **2** and **3**. The relative amounts of products were estimated from the nmr spectra of the crude mixtures by integration of the vinylic or methyl protons of **1a–d** and **4d**, and the ring protons (or ring methyl protons) of **2a–d** and **3a–d**. The results are summarized in Table I. The three types of adducts will now be discussed separately.



a, $R^1 = Me$; $R^2 = Ph$
b, $R^1 = Ph$; $R^2 = Me$
c, $R^1 = Ph$; $R^2 = Ph$
d, $R^1 = Ph$; $R^2 = m\text{-}NO_2C_6H_4$

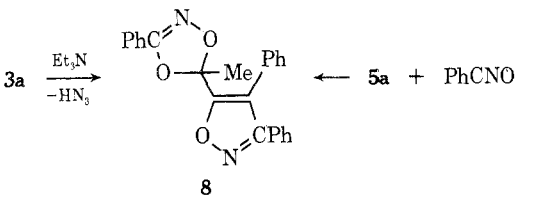
The Δ^2-isoxazolines **2a–d** were characterized by spectral analyses (see Experimental Section). Although their stereochemistry is not proven, they are confidently considered to result from a stereospecific syn addition in conformity with the stereochemical course of all 1,3-dipolar cycloaddition reactions.[4] The regiochemistry of **2a–d** is of much more concern since the mode of addition of nitrile oxides



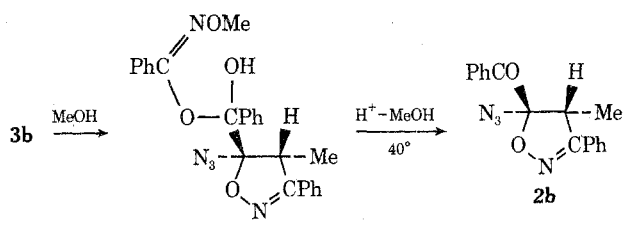
to C=C dipolarophiles could not be predicted with certainty.[2,4] Therefore, the adducts **2a–d** were converted to the isoxazoles **5a–d** upon treatment with triethylamine and then their data were compared with literature data.[5] Furthermore, **5b** and **5c** were compared with their regioisomers **7b** and **7c** and showed different spectral properties and melting points. The compounds **7b** and **7c** were prepared by the reaction of benzoylacetone (**6b**) and benzoylacetophenone (**6c**) with α-chlorobenzaldoxime in the presence of sodium ethoxide.[6]

A few comments on the stereo- and regiochemistry of **2** are in order here. It might be argued that the facile anti elimination of HN_3 from **2** provides evidence for the indicated stereochemistry. This argument, however, should be used with much reservation, since syn elimination of HN_3 is also a possible, although less favorable, pathway.[7] With respect to the regiochemical course of the addition, it is noteworthy to mention the results of Bianchi and coworkers.[5] These authors studied, *inter alia*, the addition of benzonitrile oxide with benzylideneacetone, ethylideneacetophenone, and chalcone, and obtained mixtures of 4- and 5-acylisoxazolines in ratios of respectively 59:41, 32:68, and 29:71. Our results now demonstrate that the introduction of an azide group in the α position of the α,β-unsaturated ketones makes the addition process regiospecific with exclusive formation of the 5-acylisoxazolines. This is not unexpected, since the azide function in vinyl azides has been reported[8] to exhibit a +M effect similar to the amine function in enamines, and should therefore manifest the same directional effect in 1,3-dipolar cycloadditions.[9]

In addition to the monoadducts **2a–d**, bisadducts **3a–d** were also formed in the reactions of benzonitrile oxide with α-azidovinyl ketones. The structures of **3a**, **3c**, and **3d** were established by microanalyses, spectroscopic data, and chemical evidence. They all exhibit typical ir absorptions at 2120–2130 (N_3 group) and 1630 cm^{-1} (C=N of the dioxazole ring).[10] Monoadduct **2a** could be transformed into bisadduct **3a** (40%) when treated with benzonitrile oxide. This indicates that the two adducts have the same regiochemistry about the C–C bond. Furthermore, elimination of HN_3 from **3a** by triethylamine at 55° furnished compound **8**, which was also obtained when **5a** was treated with benzonitrile oxide.



The reaction of **1b** with benzonitrile oxide also furnished the bisadduct **3b** in substantial amounts (see Table I, τ 8.65 for the ring methyl protons). During the isolation procedure, however, **3b** reacted with methanol to give the hemiketal **9**. Its nmr spectrum showed, *inter alia*, two methyl absorptions at τ 6.76 (s) and 9.50 (d, J = 8 Hz). The high chemical shift of the methyl group in the 4 position of the isoxazoline nucleus must be attributed to a shielding effect by the phenyl ring located on the exocy-



clic C=N bond. This has been verified with the aid of molecular models. That **9** had the same ring structure as **2b** was proven by its degradation into the latter under the influence of HCl.[11]

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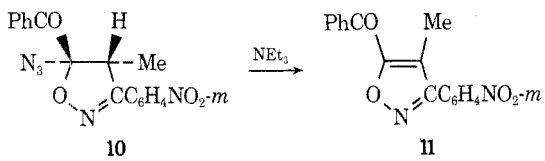
In only one case did benzonitrile oxide add onto the C=O bond of α-azidovinyl ketones to give **4** (see Table I). All attempts to convert this compound into **3** by addition of more benzonitrile oxide failed, an observation already made for other trisubstituted olefins.[2] This clearly demonstrated that the bisadducts **3a–d** are produced from **2a–d**, and not from **4**, in the course of the reactions. Since carbonyl compounds normally do not react with nitrile oxides, unless they are activated by electron-withdrawing substituents,[2] we explain our results by the −I effect of the azide function.[8] We further assume that the electron-withdrawing effect on the carbonyl group is increased in **2** by the presence of an isoxazoline nucleus.

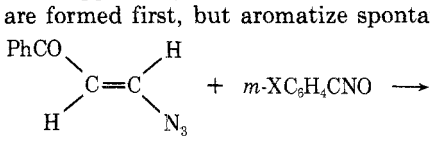
m-Nitrobenzonitrile oxide turned out to be much less reactive than benzonitrile oxide toward the α-azidovinyl ketones. It only reacted with **1b** and furnished the monoadduct **10** (33%) in addition to the corresponding furoxan. Treatment of **10** with triethylamine at 50° gave the isoxazole **11** (90%), which differed in all respects with its regioisomer prepared from benzoylacetone and *m*-nitrobenzonitrile oxide (see structure **7b**, *m*-$NO_2C_6H_4$ instead of Ph).

1b + *m*-$NO_2C_6H_4CNO$ ⟶

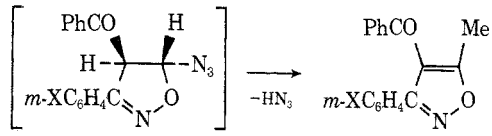


10 **11**

In contrast to the α-azidovinyl ketones **1a–d**, the β-azidovinyl ketone **12** reacted with benzonitrile oxide to give the known isoxazole **14a** directly. *m*-Nitrobenzonitrile oxide reacted similarly with **12** to give the new isoxazole **14b**. Apparently, the corresponding azidiosoxazolines **13** are formed first, but aromatize spontaneously to the isoxazoles **14a,b** by loss of HN_3. This probably occurs by a E1cB mechanism. The regiochemistry of the reaction is fully controlled by electronic factors. In this connection, it is interesting to mention that the regioisomers of **14a,b** can be obtained by an analogous reaction starting from benzonitrile oxides and β-chlorovinyl ketones.[12]

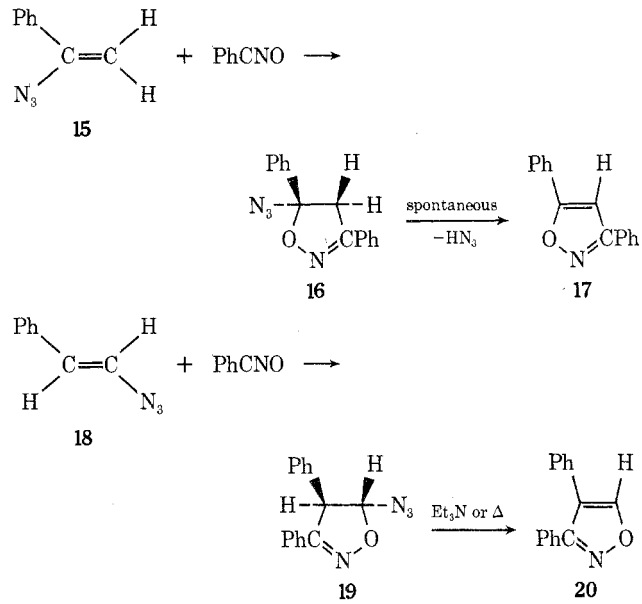


12



13 **14a**, X = H
b, X = NO_2

From the reactions discussed above, it is evident that the azide group, like the amine group in enamines,[9] has a pronounced directional effect on cycloadditions. This property can be utilized for preparative work. For instance, the 5- and 4-phenylisoxazoles **17** and **20** can be readily prepared in separate reactions respectively from α- and β-azidostyrene. Isoxazoline **16** was first formed in reaction **15** ⟶ **17** and characterized by nmr, but it decomposed slowly to **17** at room temperature. Isoxazoline **19**, on the contrary, was stable at room temperature but could be transformed into **20** with triethylamine or upon heating in toluene. This is an example of syn elimination, which occurred much slower than the anti elimination of HN_3 from compounds **2a–d**.



Experimental Section

The vinyl azides **1a–d**, **12**, **15**, and **18** were prepared as reported.[13] In all the experiments described below, benzonitrile oxide was prepared from α-chlorobenzaldoxime and triethylamine in ether at 0°. The cold solution was then filtered into a dichloromethane (or ether) solution of the vinyl azide. *m*-Nitrobenzonitrile oxide was prepared by adding triethylamine (8.3 ml) dropwise to an ethanol solution (20 ml) of α-chloro-*m*-nitrobenzaldoxime (10 g) at −20°. The reaction mixture was then treated with water and the precipitate was collected by filtration and dried over P_2O_5, yield 8 g (97%), mp 81–82° (lit.[14] mp 82–83°).

Reaction of α-Azidobenzylideneacetone (1a) with Benzonitrile Oxide. Benzonitrile oxide (0.04 mol) was added to a solution of **1a** (0.02 mol) in CH_2Cl_2 (10 ml, dried over P_2O_5). The mixture was allowed to react at room temperature for a few hours and was then subjected to nmr analysis in order to determine the distribution of the reaction products (see Table I). Addition of *n*-pentane to the mixture caused the precipitation of unreacted azide and diphenylfuroxan (mp 117°). The solvent was removed and the residue was fractionally crystallized from ether–pentane to give consecutively **2a** and the more soluble **3a**.

3,4-Diphenyl-5-azido-5-acetyl-Δ^2-isoxazoline (**2a**) was isolated in 49% yield: mp 89–89.5° ($CHCl_3$–CCl_4); ir (KBr) 2140 (N_3, s), 1730 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 2.35–2.6 (m, 2 H), 2.6–3.0 (m, 8 H), 4.52 (s, 1 H), and 7.56 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 306 (very small, $M\cdot^+$), 278 (very small, $M\cdot^+ - N_2$), 263 (12.5, $M\cdot^+ - HN_3$), 220 (6, 263 − MeCO·), 193 (9), 178 (5), 165 (5), 132 (100), 116 (6), 103 (31), 77 (21, Ph^+), 43 (34, CH_3CO^+). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$ (306): C, 66.66; H, 4.57; N, 18.30. Found: C, 66.74; H, 4.55; N, 17.65.

3,4-Diphenyl-5-azido-5-(2-methyl-5-phenyl-1,3,4-dioxazolyl)-Δ^2-isoxazoline (**3a**) was isolated in 3.5% yield: mp 155–156° (CCl_4–pentane); ir (KBr) 2120 (N_3, s), 1630 (C=N, w); nmr ($CDCl_3$) τ 1.62–1.84 (m, 2 H), 2.16–2.66 (m, 8 H), 5.34 (q, 1 H, *J* 8.1 (s, 3 H); mass spectrum *m/e* (rel intensity) 425 (very small, $M\cdot^+$), 397 (very small, $M\cdot^+ - N_2$), 382 (0.5, $M\cdot^+ - HN_3$), 220 (2), 193 (5), 178 (10), 165 (5), 162 (100), 132 (14), 116 (14), 105 (14), 103 (12), 89 (12), 77 (43), 43 (99.5). *Anal.* Calcd for $C_{24}H_{19}N_5O_3$ (425): C, 67.76; H, 4.47; N, 16.47. Found: C, 67.70; H, 4.30; N, 16.45.

Reaction of α-Azidoethylideneacetophenone (1b) with Benzonitrile Oxide. Azide **1b** (0.02 mol) was allowed to react with benzonitrile oxide (0.04 mol) in dry CH_2Cl_2 (10 ml) at room temperature for a few hours. After the reaction mixture had been analyzed by nmr (see Table I), the solvent was replaced by ether–pentane (40:10 ml) and diphenylfuroxan was isolated in 40% yield (1.87 g). The solvent was removed and the residue was dissolved in ether (10 ml) and then cooled at 5° to give 3-phenyl-4-methyl-5-azido-5-benzoyl-Δ^2-isoxazoline (**2b**) in 14% yield: mp 69–69.5° (*n*-pentane); ir (KBr) 2120 (N_3, s), 1690 cm^{-1} (CO, s); nmr

($CDCl_3$) τ 1.62–1.84 (m, 2 H), 2.16–2.66 (m, 8 H), 5.34 (q, 1 H, J = 7 Hz), and 8.60 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) no molecular ion, 278 (very small, $M\cdot^+ - N_2$), 263 (2.5, $M\cdot^+ - HN_3$) 201 (5, $M\cdot^+ - PhCO$), 158 (7), 131 (2.5), 130 (5), 115 (7), 105 (100), 103 (17), 89 (5), 77 (83.5). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$ (306): C, 66.66; H, 4.57; N, 18.30. Found: C, 66.45; H, 4.55; H, 18.55.

The mother liquor was evaporated to dryness and the residual yellow oil was treated with MeOH (45 ml) to yield **9** (40%): mp 125–128° dec (MeOH); ir (KBr) 3350 (OH, br), 2140 cm^{-1} (N_3, s); nmr ($CDCl_3$, 100 MHz) 2.28–2.34 (m, 2 H), 2.36–2.68 (m, 13 H), 6.2 (q, 1 H, J = 7 Hz), 6.46 (s, OH exchangeable with D_2O), 6.76 (s, 3 H), and 9.50 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) 264 (6), 201 (6), 158 (6), 137 (5), 105 (100), 77 (15.5). *Anal.* Calcd for $C_{25}H_{23}N_5O_4$ (457): C, 65.64; H, 5.03; N, 15.31. Found: C, 65.41; H, 5.15; N, 15.45.

When compound **9** was chromatographed over silica gel with chloroform as the eluent, it was quantitatively transformed into the isoxazoline **2b**. Similarly, when **7** (0.5 g) was heated at 40° in a MeOH–2 *N* H_2SO_4 solution (15 ml) for 4 days, decomposition into **2b** was observed by nmr. The mixture was neutralized with NaOH, extracted with $CHCl_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was treated with ether (10 ml) and furnished **2b** in 80% yield.

Reaction of α-Azidochalcone (1c) with Benzonitrile Oxide. A solution of benzonitrile oxide (0.04 mol) and **1c** (0.02 mol) in CH_2Cl_2 or ether (10 ml) was stirred at 0° for 2 hr. The solvent was removed and the residual oil was first treated with ether–pentane (35:10 ml) and MeOH in order to remove most of the unreacted azide and diphenylfuroxan. The residue was then heated with an excess of NEt_3 (4 ml) in $CHCl_3$ (10 ml) at 50° for 24 hr. The solvent was replaced by MeOH and the solution was cooled. 3,4-Diphenyl-5-benzoylisoxazole (**5c**) was obtained in 10% yield: mp 166–167° (MeOH) (lit.[5] mp 167°); ir (KBr) 1665 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.85–2.10 (m, 2 H) and 2.34–2.82 (m, 13 H); mass spectrum m/e (rel intensity) 325 (21, $M\cdot^+$), 297 (2, $M\cdot^+ - CO$), 220 (100), 192 (40), 178 (2), 165 (5), 105 (16), 89 (40), 77 (29). *Anal.* Calcd for $C_{22}H_{15}NO_2$ (325): C, 81.23; H, 4.61; N, 4.31. Found: C, 81.15; H, 4.55; N, 4.55.

Reaction of α-Azido-*m*-nitrobenzylideneacetophenone (1d) with Benzonitrile Oxide. Benzonitrile oxide (0.04 mol) was added to **1d** (0.02 mol) in dry CH_2Cl_2 (10 ml) at room temperature and the mixture was allowed to stand for a few hours. After analysis of the reaction mixture by nmr (see Table I), the solvent was replaced by ether–pentane to eliminate the unreacted azide and diphenylfuroxan. The solvent was partially evaporated (25 ml) to furnish a white precipitate of **4d** in 10% yield: mp 103–104° dec; ir (KBr) 2130 (N_3, s), 1640 (C=C, w), and 1625 cm^{-1} (C=N, w); nmr ($CDCl_3$) τ 1.42 (m, 1 H), 1.76–2.75 (m, 14 H), and 3.75 (s, 1 H); mass spectrum m/e (rel intensity) 413 (small, $M\cdot^+$), 224 (16.5), 122 (3.5), 119 (3.5), 115 (6), 105 (100), 103 (9.5), 91 (3.5), 77 (40.5). *Anal.* Calcd for $C_{22}H_{15}N_5O_4$ (413): C, 63.92; H, 3.63; N, 16.94. Found: C, 64.05; H, 3.50; N, 16.90.

The mother liquor was evaporated to dryness and the residue was fractionally crystallized from methanol to give **2d** and **3d**.

3-Phenyl-4-(*m*-nitrophenyl)-5-azido-5-benzoyl-Δ^2-isoxazoline (**2d**) was isolated in 12% yield: mp 100–103° dec ($CHCl_3$–pentane); ir (KBr) 2130 (N_3, s), 1672 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.6–2.0 (m, 4 H), 2.2–2.8 (m, 10 H), and 3.93 (s, 1 H); mass spectrum m/e (rel intensity) no $M\cdot^+$, 370 (9.5, $M\cdot^+ - HN_3$), 343 (2), 265 (100), 237 (24), 219 (4), 191 (12), 177 (31), 134 (7), 131 (12), 115 (2), 105 (98), 103 (14), 77 (60). *Anal.* Calcd for $C_{22}H_{15}N_5O_4$ (413): C, 63.92; H, 3.63; N, 16.94. Found: C, 63.75; H, 3.45; N, 17.15.

3-Phenyl-4-(*m*-nitrophenyl)-5-azido-5-(2,5-diphenyl-1,3,4-dioxazolyl)-Δ^2-isoxazoline (**3d**) was obtained in 9% yield: mp 184–186° ($CHCl_3$–MeOH); ir (KBr) 2135 (N_3, s), 1632 cm^{-1} (C=N, w); nmr ($CDCl_3$, 100 MHz) τ 1.80–1.95 (m, 1 H), 2.05–2.25 (m, 5 H), 2.40–2.8 (m, 13 H), and 4.70 (s, 1 H); mass spectrum m/e (rel intensity) no $M\cdot^+$, 370 (2.5, $M\cdot^+ - PhCNO - HN_3$), 265 (23), 237 (4), 224 (10), 191 (3), 177 (8), 134 (1.5), 131 (5), 119 (15), 115 (3), 105 (100), 103 (18), 77 (15). *Anal.* Calcd for $C_{29}H_{20}N_6O_5$ (532): C, 65.41; H, 3.76; N, 15.79. Found: C, 65.40; H, 3.65; N, 15.80.

3,4-Diphenyl-5-acetylisoxazole (5a). Compound **2a** (1 g) was heated with an excess of NEt_3 (0.7 ml) in dry benzene (15 ml) at 50° for 24 hr (monitored by nmr). The solvent was removed and the residual oil was treated with MeOH (5 ml) to give compound **5a** in quantitative yield: mp 134–134.5° (MeOH) (lit.[5] mp 135–136°); ir (KBr) 1700 cm^{-1} (CO, s); nmr ($CHCl_3$) τ 2.5–2.9 (m, 10 H) and 7.50 (s, 3 H); mass spectrum m/e (rel intensity) 263 (31.5, $M\cdot^+$), 220 (100, $M\cdot^+ - MeCO$), 193 (45), 131.5 (4.5, M^{2+}). *Anal.* Calcd for $C_{17}H_{13}NO_2$ (263): C, 77.56; H, 4.94; N, 5.32. Found: C, 77.20; H, 4.75; N, 5.25.

3-Phenyl-4-methyl-5-benzoylisoxazole (5b). Compound **2b** (0.5 g) was heated with NEt_3 (0.4 ml) in chloroform (5 ml) at 45°. After complete reaction, the solvent was removed and the residual oil was chromatographed over silica gel with chloroform as the eluent. Compound **5b** was obtained as a colorless oil in 74% yield: ir (neat) 1660 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.80–2.0 (m, 2 H), 2.25–2.75 (m, 8 H), and 7.60 (s, 3 H); mass spectrum m/e (rel intensity) 263 (24, $M\cdot^+$), 234 (3, $M\cdot^+ - HCO$, m* at 208.2), 158 (100, $M\cdot^+ - PhCO$).

For comparison, compound **7b** was prepared from benzoylacetone and α-chlorobenzaldoxime in the presence of sodium ethoxide.[6b,c] The ir and nmr spectra of the two compounds showed a different absorption pattern.

3-Phenyl-4-(*m*-nitrophenyl)-5-benzoylisoxazole (5d). This compound was obtained by heating **2d** (0.4 g) with an excess of NEt_3 (0.3 ml) in chloroform (5 ml) at 55° for 5 days. The solvent was removed and the residue was chromatographed over silica gel with chloroform as the eluent to give a pale yellow oil (72%) which solidified on standing: mp 108–111° (MeOH); ir (KBr) 1650 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.75–2.10 (m, 2 H) and 2.25–2.80 (m, 12 H); mass spectrum m/e (rel intensity) 370 (14, $M\cdot^+$), 265 (78, $M\cdot^+ - PhCO$), 238 (27, 265 – HCN), 237 (12, 265 – CO, m* at 211.9), 177 (100). *Anal.* Calcd for $M\cdot^+$ (determined by high-resolution exact-mass measurements): 370.09535. Found: 370.09557.

3,4-Diphenyl-5-(2-methyl-5-phenyl-1,3,4-dioxazolyl)isoxazole (8). Compound **3a** (0.06 g) was heated with an excess of NEt_3 (30 mg) in $CHCl_3$ (1 ml) at 55°. After complete reaction (19 days), the solution was saturated by addition of *n*-pentane and then cooled to give **8** in 66% yield: mp 118–119° (MeOH); ir (KBr) 1627 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.4–2.9 (m, 15 H) and 7.92 (s, 3 H); mass spectrum m/e (rel intensity) 382 (30, $M\cdot^-$), 263 (5, $M\cdot^+ - PhCNO$), 248 (2), 236 (8), 220 (100), 193 (35), 178 (1), 165 (3), 162 (7), 119 (7), 115 (3), 105 (43). *Anal.* Calcd for $M\cdot^+$ (determined by high-resolution exact-mass measurement): 382.131734. Found: 382.133624.

Reaction of α-Azidoethylideneacetophenone (1b) with *m*-Nitrobenzonitrile Oxide. A solution of **1b** (0.02 mol) and *m*-nitrobenzonitrile oxide (0.01 mol) in CH_2Cl_2 (10 ml) was stirred at 5° and then analyzed by nmr (64% unreacted **1b** and 36% **10**). Di(*m*-nitrophenyl)furoxan crystallized out at 5° in 20% yield, mp 188–189°. Addition of *n*-pentane to the mother liquor furnished 3-(*m*-nitrophenyl)-4-methyl-5-azido-5-benzoyl-Δ^2-isoxazoline (**10**) in 34% yield. This compound was purified by column chromatography on silica gel with $CHCl_3$ as the eluent: mp 120–122°; ir (KBr) 2120 (N_3, s), 1690 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.50–2.84 (m, 9 H), 5.35 (q, 1 H, J = 7 Hz), and 8.55 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) no $M\cdot^+$, 308 (3, $M\cdot^+ - HN_3$), 246 (6, $M\cdot^+ - PhCO$), 203 (3), 176 (3), 175 (3), 115 (3), 105 (100). *Anal.* Calcd for $C_{17}H_{13}N_5O_4$ (351): C, 58.11; H, 3.70; N, 19.94. Found: C, 58.10; H, 3.55; N, 19.95.

3-(*m*-Nitrophenyl)-4-methyl-5-benzoylisoxazole (11). Compound **10** (0.5 g) was heated with an excess of NEt_3 (2.8 ml) in $CHCl_3$ (5 ml) at 50°. After complete reaction (24 hr by nmr), the solvent was removed and the residue was crystallized from $CHCl_3$–*n*-pentane to give **11** in 90% yield: mp 94–95° (MeOH); ir (KBr) 1655 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.4 (m, 1 H), 1.5–1.7 (m, 1 H), 1.75–2.0 (m, 3 H), 2.1–2.5 (m, 4 H), and 7.48 (s, 3 H); mass spectrum m/e (rel intensity) 308 (55, $M\cdot^+$), 280 (8, $M\cdot^+ - CO$, m* at m/e 254.5), 279 (10.5, $M\cdot^+ - HCO\cdot$), 262 (9), 234 (10.5), 233 (18), 203 (8), 175 (5), 157 (18), 129 (16), 105 (100). *Anal.* Calcd for $C_{17}H_{12}N_2O_4$ (308): C, 66.23; H, 3.89; N, 9.09. Found: C, 66.00; H, 3.75; N, 9.15.

For comparison, the regioisomer of **11** (see structure **7b**, *m*-$NO_2C_6H_4$ instead of Ph) was prepared as follows. Sodium (0.03 mol) was dissolved in dry ethanol (15 ml) and the solution was cooled at 0°. After addition of benzoylacetone (0.02 mol), an ethanol solution (10 ml) of α-chloro-*m*-nitrobenzaldoxime (0.03 mol) was added slowly with stirring. The mixture was stirred at room temperature for 5 hr, the precipitated NaCl was filtered, and the solvent was removed under reduced pressure. The yellow residue was washed with water, extracted with chloroform (50 ml), and dried over $MgSO_4$. Crystallization from EtOH–H_2O (60%) furnished 3-(*m*-nitrophenyl)-4-benzoyl-5-methylisoxazole in 45% yield, mp 73–74°. The two regioisomers showed a different pattern in ir, nmr, and mass spectrum. *Anal.* Calcd for $C_{17}H_{12}N_2O_4$ (308): C, 66.23; H, 3.89; N, 9.09. Found: C, 66.25; H, 3.90; N, 9.00.

Reaction of β-Azidovinyl Phenyl Ketone (12) with Benzoni-

trile Oxide. A solution of **12** (0.01 mol) and benzonitrile oxide (0.02 mol) in CH_2Cl_2 (10 ml) was stirred at room temperature in the dark. Then *n*-pentane was added and 3-phenyl-4-benzoylisoxazole (**14a**) was isolated in 60% yield: mp 84–84.5° (MeOH) (lit.[6c] mp 83–84°); ir (KBr) 3125 (=CH, w), 1650 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.29 (s, 1 H) and 2.09–2.84 (m, 10 H); mass spectrum *m/e* (rel intensity) 249 (100, $M\cdot^+$), 220 (25, $M\cdot^+ - HCO\cdot$). *Anal.* Calcd for $C_{16}H_{11}NO_2$ (249): C, 77.10; H, 4.41; N, 5.62. Found: C, 77.00; H, 4.25; N, 5.55.

Further addition of *n*-pentane to the mother liquor furnished a mixture of unreacted azide and diphenylfuroxan.

Reaction of β-Azidovinyl Phenyl Ketone (12) with *m*-Nitrobenzonitrile Oxide. A solution of **12** (0.01 mol) and *m*-nitrobenzonitrile oxide (0.02 mol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature in the dark for 18 hr. Then *n*-pentane was added dropwise to the reaction mixture in order to precipitate di(*m*-nitrophenyl)furoxan (37%). The mother liquor was evaporated to dryness and the residue was extracted with *n*-pentane to remove the unreacted azide. The residue from this manipulation was crystallized from MeOH (25 ml) to give 3-(*m*-nitrophenyl)-4-benzoylisoxazole (**14b**) in 23% yield: mp 80–82° (CCl_4); ir (KBr) 3150 (=CH, w), 1655 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.10 (s, 1 H), 1.35 (m, 1 H), 1.6–1.75 (m, 2 H), 1.8–2.0 (m, 2 H), and 2.05–2.60 (m, 4 H); mass spectrum *m/e* (rel intensity) 294 (39, $M\cdot^+$), 277 (22.5, $M\cdot^+ - HO\cdot$, m* at 260.9), 265 (2, $M\cdot^+ - HCO$), 247 (8), 220 (4), 219 (5.5), 217 (1), 189 (7), 143 (6.5), 115 (3), 105 (100). *Anal.* Calcd for $C_{16}H_{10}N_2O_4$ (294): C, 65.30; H, 3.40. Found: C, 65.05; H, 3.20. *Anal.* Calcd for $M\cdot^+$ (determined by high-resolution exact-mass measurement): 294.064051. Found: 294.064206.

Reaction of α-Azidostyrene (15) with Benzonitrile Oxide. Benzonitrile oxide (0.02 mol) was added to a solution of **15** (0.01 mol) in dry ether (5 ml) at room temperature. After a reaction period of 3 hr, the mixture was analyzed by nmr and showed a complete conversion of **15** into a mixture of **16** [88%, ring protons at τ 6.46 (d, $J \cong 2.5$ Hz)] and **17** [12%, ring proton at τ 3.20 (s)]. When this mixture was allowed to stand at room temperature for an additional 1 hr, the reaction **16** → **17** was finished. The yellow residue was dissolved in ether (10 ml) to remove most of the diphenylfuroxan and the solvent was then replaced by methanol (10 ml) in order to crystallize 3,5-diphenylisoxazole (**17**), yield 64%, mp 136–137° (MeOH) (lit.[6b,15] mp 141°).

Reaction of β-Azidostyrene (18) with Benzonitrile Oxide. An ether solution (5 ml) of **18** (0.01 mol) and benzonitrile oxide (0.02 mol) was stirred at room temperature for a few hours and then analyzed by nmr (30% **18** and 70% **19**). The yellow oil was treated with ether (15 ml) to remove diphenylfuroxan (1.2 g). After removal of the solvent, the oil was chromatographed over basic Al_2O_3 (activity I) with *n*-pentane (30 ml) and chloroform (30 ml) as eluents to give respectively unreacted **18** and **19** as a pale yellow liquid: yield 66%; ir (neat) 2120 cm^{-1} (N_3, s); nmr ($CDCl_3$) τ 2.10–2.80 (m, 10 H), 4.29 (d, 1 H, J = 1.5 Hz), and 5.50 (d, 1 H, J = 1.5 Hz); mass spectrum *m/e* (rel intensity) 264 (very small, $M\cdot^+$), 221 (100, $M\cdot^+ - HN_3$). Compound **19** (0.77 g) in $CHCl_3$ (6 ml) was heated with an excess of NEt_3 (0.84 ml) for 25 days at 45° (monitored by nmr). The solvent was then removed and the dark brown oil was chromatographed over silica gel with $CHCl_3$ as the eluent to give 3,4-diphenylisoxazole (**20**) as a colorless oil (82%) which solidified on standing: mp 88.5–89.5° (ether) (lit.[16] mp 91°); ir (KBr) 3115 cm^{-1} (=CH, w); nmr ($CDCl_3$) τ 0.92 (s, 1 H) and 2.4–2.8 (m, 10 H); mass spectrum *m/e* (rel intensity) 221 (100, $M\cdot^+$). Similarly, when **19** (0.83 g) was heated in dry toluene (5 ml) at 100° for 1 month (monitored by nmr) and then worked up in the same manner as above, isoxazole **20** was obtained in 92% yield.

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Registry No.—**1a,** 26309-09-1; **1b,** 26309-10-4; **1c,** 26309-08-0; **1d,** 51002-98-3; **2a,** 51002-99-4; **2b,** 51003-00-0; **2d,** 51003-01-1; **3a,** 51003-54-1; **3d,** 51003-55-5; **4d,** 51002-97-2; **5a,** 1631-96-5; **5b,** 51003-56-6; **5c,** 1167-72-2; **5d,** 51003-57-7; **7b,** 14677-93-1; **8,** 51003-58-8; **9,** 51003-59-9; **10,** 51002-96-1; **11,** 51003-60-2; **12,** 13850-37-8; **14a,** 19688-06-3; **14b,** 51003-61-3; **15,** 16717-64-9; **16,** 51003-62-4; **17,** 2039-49-8; **18,** 18756-03-1; **19,** 51002-95-0; **20,** 7467-78-9; benzonitrile oxide, 873-67-6; α-chlorobenzaldoxime, 698-16-8; triethylamine, 121-44-8; *m*-nitrobenzonitrile oxide, 7007-35-4; α-chloro-*m*-nitrobenzaldoxime, 33512-94-6; di(*m*-nitrophenyl)furoxan, 51003-63-5; benzoylacetone, 93-91-4; 3-(*m*-nitrophenyl)-4-benzoyl-5-methylisoxazole, 51003-64-6.

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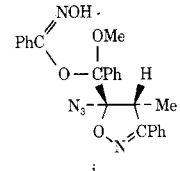

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