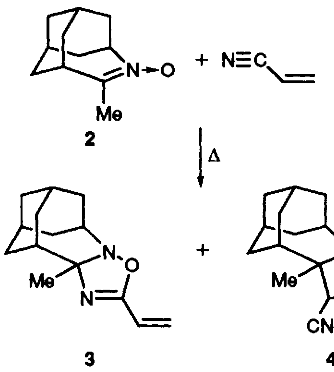
Remarkable Dipolarophilicity of Nitrile Function uncovered in the 1,3-Dipolar Cycloaddition Reaction of Homoadamantane-incorporated Nitrones. A Direct and Facile Route to Δ^4-1,2,4-Oxadiazoline (2,3-Dihydro-1,2,4-Oxadiazole) Derivatives

Yang Yu, Masatomi Ohno and Shoji Eguchi*

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan

Various nitriles, including unactivated nitriles, underwent a 1,3-dipolar cycloaddition reaction with homoadamantane-incorporated nitrones to afford Δ^4-1,2,4-oxadiazoline derivatives.

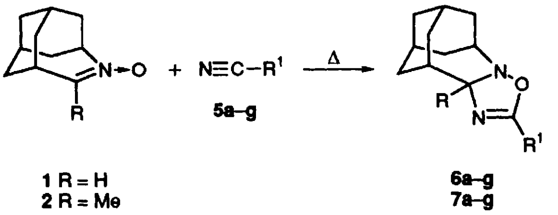
In contrast to the wide usefulness of nitriles as a d^1 synthon in organic synthesis, their use in cycloaddition chemistry is rather limited.[1,2] Nitriles are known to react as a heterodienophile in Diels–Alder reactions but at extremely high temperature, unless the reaction is intramolecular or the nitrile is activated with an electron-withdrawing group.[3] This trend is also true for 1,3-dipolar cycloaddition reactions, as exemplified with azides, nitrile ylides and nitrile oxides.[4] In this event, the reaction of nitrones with aliphatic and aromatic nitriles are hitherto unknown, and exceptionally only two cases using arylcyanate and tetracyanoethylene as a dipolarophile have been recorded.[5] Recently we reported extraordinarily stable aliphatic nitrones, 4-aza-homoadamant-4-ene *N*-oxides **1** and **2**, which are durable under thermal conditions due to the structure incorporated in a rigid ring system.[6] During the survey for their 1,3-dipolar cycloaddition reactivity, we could reveal that even an unactivated nitrile was reactive enough with **1** and **2**. This is the first example to show potentiality of the simple carbon–nitrogen triple bond as a heterodipolarophile; nitrile function is generally capacitated to cycloadd to nitrones so far as they resist decomposing at the temperature necessary for the reaction to occur.



Scheme 1

The clue for the above fact was found out in the reaction of **2** with acrylonitrile. When **2** was allowed to react with this reagent, which was also solvent, at 100 °C in sealed tube under an atmosphere of nitrogen, a cycloadduct with a C≡N triple bond was produced together with an expected cycloadduct with a C=C double bond in a ratio of 55 : 45 (Scheme 1). The structure of products, Δ^4-1,2,4-oxadiazoline **3** and 4-cyanoisoxazolidine **4**, was determined on the basis of spectral and elemental analyses. The cycloadduct **3** had IR absorption at 1670 and 1602 cm^{-1} but no absorption at *ca.* 2200 cm^{-1} due to the CN group, and ^{1}H NMR signals at δ 1.48 (3H, s, Me), and 6.31, 6.06 and 5.72 (each 1H, ABX pattern multiplet, $CH=CH_2$), and MS parent peak at *m/z* 232 corresponding to a 1 : 1 cycloadduct.

From this interesting observation, we tested the reactivity of aliphatic and aromatic nitriles **5a–f** as well as an activated nitrile (cyanoformate **5g**) utilizing appropriate nitrones **1** and **2** (Scheme 2). The reactions were carried out as above with or without solvent (toluene) at 100–150 °C. The products were separated by preparative TLC and characterized as **6a–g** and **7a–g** by the spectral inspections on the analogy of **3**.† These results are summarized in Table 1. As can be seen, it apparently indicates that unactivated nitriles have still moderate reactivity towards a nitrone. Lack of precedents for this type of reaction may be answered by less stability of nitrones employed rather than less reactivity of nitriles in question.



Scheme 2

Table 1 1,3-Dipolar cycloaddition of nitrone **1**,**2** with nitriles

Entry	Nitrone	Nitrile (R^1)[a]	Reaction conditions solv., temp./°C time/h	Product [yield (%)][b]	Mp/°C
1	**1**	**5a** (Me)	Neat, 150, 10 days	**6a** (53)	94–97.5
2	**1**	**5b** (C_6H_5)	Toluene, 150, 15	**6b** (51)	Oil
3	**1**	**5c** (p-$NO_2C_6H_4$)	Toluene, 100, 12	**6c** (58)	192–195
4	**1**	**5d** (m-$NO_2C_6H_4$)	Toluene, 100, 18	**6d** (64)	142.0–145.5
5	**1**	**5e** (o-$NO_2C_6H_4$)	Toluene, 100, 24	**6e** (41)	Solid
6	**1**	**5f** (p-$MeOC_6H_4$)	Toluene, 100, 18	**6f** (58)	139.5–141.5
7	**1**	**5g** (CO_2Me)	Toluene, 25, 2	**6g** (65)	101–103.5
8	**2**	**5a** (Me)	Neat, 150, 15 days	**7a** (0)	
9	**2**	**5b** (C_6H_5)	Toluene, 150, 96	**7b** (26)	118.5–121.0
10	**2**	**5c** (p-$NO_2C_6H_4$)	Toluene, 100, 36	**7c** (23)	172–174
11	**2**	**5d** (m-$NO_2C_6H_4$)	Toluene, 100, 60	**7d** (19)	Oil
12	**2**	**5e** (o-$NO_2C_6H_4$)	Toluene, 100, 48	**7e** (0)	
13	**2**	**5f** (p-$MeOC_6H_4$)	Toluene, 100, 48	**7f** (16)	Oil
14	**2**	**5g** (CO_2Me)	Toluene, 25, 2	**7g** (68)	71.0–74.0

[a] The nitrile was used in 2.0 mol (based on nitrones) in entries 2–6 and 9–13, and 1.2 mol in entreis 7 and 14. In entries 1 and 8, the reagent was used also as a solvent. [b] Isolated yields are given.

The formation of Δ^4-1,2,4-oxadiazolines[7] was more or less effected by a substituent on steric and electronic grounds. Acetonitrile **5a** reacted with aldonitrone **1a** at 150 °C affording the corresponding Δ^4-1,2,4-oxadiazoline **6a** in 53% yield, but more substituted ketonitrone **2** did not give the cycloadduct under the similar conditions. On the other hand, benzonitrile **5b** reacted with both nitrones to afford **6b** and **7b**, respectively, although the yield was considerable dropped (also in entries 2–6 and 9–13). A *p*-substituent on benzonitrile (electron-withdrawing nitro and electron-donating methoxy groups) slightly affected the yield (entries 3, 6 and 10, 13), while *o*-isomer **5e** gave the cycloadduct **6e** only with **1**. In contrast, methyl cyanoformate, activated nitrile, **5g** reacted even at room temp. with both nitrones expectedly to afford the corresponding 1,2,4-oxadiazolines **6g** and **7g** in better yields. Unlike the reported facile ring transformation of 3-methyl-Δ^4-isoxazolines (*i.e.* cycloadducts of **2** with alkynes) to pyrroles,[6] the cycloadducts **7** did not show analogous rearrangement aptitude (if so, pyrazoles may be formed), but only the retro-cycloaddition took place at elevated temperature.

This research is supported by a Grant in Aid for Scientific Research (No. 04403017) from the Ministry of Education, Science and Culture.

Received, 13th September 1993; Com. 3/05478K

Footnote

† All new compounds gave satisfactory C, H, and N elemental analyses and IR, MS, ^{1}H and ^{13}C NMR spectral data in accord with the assigned structures. As a typical example, **6a** had the following data: mp 94.0–97.5 °C, IR(KBr)ν/cm^{-1} 2922, 2903, 1686, 1443, 1383, 1269, 1248, 1090, 951; ^{1}H NMR (200 MHz, CDCl$_3$) δ 5.44 (m, 1H), 3.60 (m, 1H), 2.37 (m, 1H), 2.01 (d, *J* 1.4 Hz, 3H), 2.0–1.5 (m, 12H), ^{13}C NMR (50 MHz, CDCl$_3$) δ 160.91, 92.56, 58.94, 35.48, 34.97, 34.50, 33.81, 31.10 (2), 26.37, 26.07, 11.55; MS *m/z* (%) 206 (M$^+$, 16), 191 (11), 165 (100), 149 (15), 148 (12).

References

1 A. J. Fatiadi, in *The Chemistry of Triple-bonded Functional Groups*, ed. S. Patai and Z. Rappoport, John Wiley and Sons, New York, 1983, part 2, ch. 26.

2 W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990, ch. 6.

3 D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, New York, 1987, ch. 6.

4 A general review, *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, John Wiley and Sons, New York, 1984.

5 Y. D. Samnilov, S. E. Solov'eva and A. I. Konovalov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1980, **50**, 117; Y. D. Samnilov, S. E. Solov'eva and A. I. Konovalov, *Zh. Obshch. Khim.*, 1980, **50**, 138.

6 Y. Yu, M. Ohno and S. Eguchi, *Tetrahedron*, 1993, **49**, 823.

7 For Δ^4-1,2,4-oxadiazoline derivatives see L. B. Clapp, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 6, ch. 4.21.