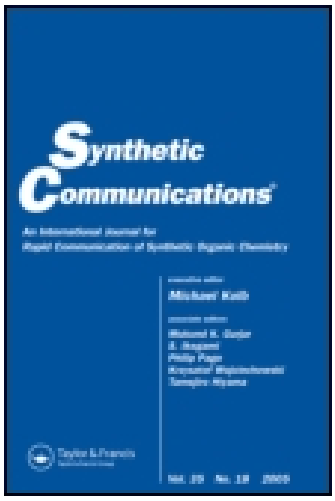


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A NOVEL SYNTHESIS OF ISOXAZOLES VIA 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES TO ACETYL ACETONE

K. B. Umesha [a] , K. Ajay Kumar [a] & K. M. Lokanatha Rai [b]

[a] Department of Studies in Chemistry , University of Mysore , Manasagangotri, Mysore, 570 005, India

[b] Department of Studies in Chemistry , University of Mysore , Manasagangotri, Mysore, 570 005, India

Published online: 17 Oct 2011.

To cite this article: K. B. Umesha , K. Ajay Kumar & K. M. Lokanatha Rai (2002) A NOVEL SYNTHESIS OF ISOXAZOLES VIA 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES TO ACETYL ACETONE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:12, 1841-1846, DOI: 10.1081/SCC-120004066

To link to this article: http://dx.doi.org/10.1081/SCC-120004066

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS, 32(12), 1841–1846 (2002)

A NOVEL SYNTHESIS OF ISOXAZOLES VIA 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES TO ACETYL ACETONE

K. B. Umesha, K. Ajay Kumar, and K. M. Lokanatha Rai*

Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 005, India

ABSTRACT

Nitrile oxides (**2**) isolated from the oxidative dehydrogenation of aldoximes (**1**) by chloramines-T react with acetyl acetone (**3**) to afford 4-acetyl-3-aryl-5-methyl isoxazoles (**5**) in good yield. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis.

1,3-Dipolar cycloaddition reactions are the useful tool for constructing biologically potent five membered heterocyclic compounds.[1] Cycloaddition of nitrile oxide to olefinic or acetylenic compounds are of synthetic interest, since the products isoxazolines and isoxazoles obtained respectively are the versatile intermediates for the synthesis of bifunctional compounds.[2] Apart from the various dipolarophiles known, nitrile oxides have been extensively used.

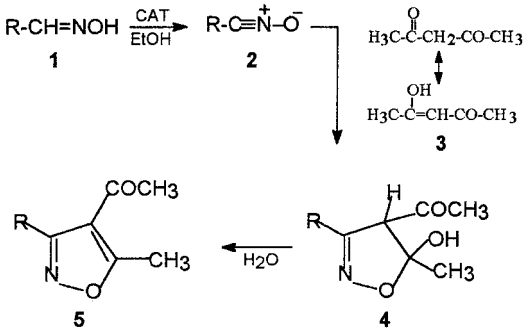
*Corresponding author.

The usual synthesis of nitrile oxides involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate,[3] alkali hypohalite,[4] N-bromosuccinimide in DMF followed by base treatment,[5] chloramine-T,[6] mercuric acetate,[7] or 1-chlorobenzotriazole[8] as well as the reactions of nitro compounds with aryl isocyanate[9] and di-ter-butyl dicarbonate in presence of DMAP.[10]

In continuation of our work on 1,3-dipolar cycloaddition reactions, we thought of using acetyl acetone as dienophyle for the cycloaddition of preformed nitrile oxides to get isoxazoles and successfully carried out the reaction at room temperature. In a typical reaction, a mixture of the preformed 3,4-dimethoxybenzonitrile oxide **2c** (0.895 g, 5.0 mmol) isolated from 3,4-dimethoxybenzaldehyde oxime **1c** was treated with excess of acetyl acetone **3** (1.0 g, 10 mmol) in dichloromethane was well stirred at room temperature for 6 h. After the usual workup, the product isoxazole **5c** was obtained in 64% (0.835 g) yield.

5a) R=C_6H_5, b) R=4-$H_3COC_6H_4$, c) R=3,4-$(H_3CO)_2C_6H_3$, d) R=3,4,5-$(H_3CO)_3C_6H_2$, e) R=4-ClC_6H_4, f) R=3,4-$(OCH_2O)C_6H_3$.

The structure proof of the cycloadducts were provided by IR, ^{1}H NMR ^{13}C NMR, MS studies and elemental analysis. For instance, in IR spectra, the signals expected due to OH group in the region 3590–3650 cm^{-1} was found absent. In ^{1}H NMR spectra all cycloadducts gave the signals due to aromatic and substituent protons at the expected region. The signals expected due to $COCH_3$ and methyl protons appear as singlet in the region δ 2.11–2.20 ppm and δ 2.65–2.70 ppm respectively. The signals expected due to methylene protons of the starting acetyl acetone were found absent. It is note worthy to observe that the signals expected at downfield due to C_4-H and C_5-OH protons as in the case of simple cycloaddition of nitrile oxides to ene system were also found absent.



Scheme 1.

The absence of these signals suggests that the reaction proceeded with the elimination of water from the intermediate isoxazolines **4** after cycloaddition to form the cycloadducts **5**.

In ^{13}C NMR spectra, all showed the significantly consistent pattern signals due to newly formed C_4 carbon as singlet in the region δ 117.24–117.48 ppm. While, C_3 and C_5-carbon appear as singlet in the region δ 161.60–161.82 ppm and δ 174.40–174.58 ppm respectively. Further all cycloadducts gave the signals due to aromatic and substituent carbons at the expected region. All cycloadducts showed MH^+ ion peak as base peak. All gave significantly stable molecular ion peaks with a relative abundance ranging from 11–86%, which strongly favours the formation of the cycloadducts. Further, the formation of the cycloadducts was provided by satisfactory elemental analysis.

EXPERIMENTAL SECTION

Melting points were recorded in open capillaries using Thomus Hoover apparatus and were uncorrected. The compounds were routinely checked for their purity by TLC using silica gel-G. IR spectra were recorded on Shimadzu FT 8300 spectrometer. ^1H NMR spectra were recorded on a Bruker 300 MHz spectrometer; ^{13}C NMR spectra were measured on Jeol GSX 400 (75 MHz) instrument using $CDCl_3$ as solvent. Chemical shifts are expressed in (δ) and the values are in parts per million downfield from the tetramethyl silane. Mass spectra were obtained on Maspec MSW 9629 spectrometer and the important fragments are given with the relative intensities given in the bracket. Chromatographic separations were carried out on a silica gel (70–230 mesh, Merck.) column. The proportion of the solvents for the chromatography was given as volume/volume.

General Procedure for the Isolation of Nitrile Oxide 2

Oxime (1 mmol) dissolved in 95% ethanol (5 ml) was treated with chloramine-T (1.2 mmol) at room temperature. After 2 min swirling, the solvent was evaporated. The residue was extracted with ether (25 ml) and the organic layer was washed successively with water (2 × 15 ml), 1 N NaOH (1 × 10 ml), brine solution (2 × 20 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the nitrile oxide in good yield (70–90%). In ^{13}C NMR, the nitrile oxide carbon of **2d** absorbed at 104.69 ppm.

Typical procedure for the preparation of 4-Acetyl-5-methyl-3-(3′,4′-dimethoxyphenyl)-isoxazole 5c: A mixture of 3,4-dimethoxy benzonitrile

oxide **2c** (0.895 g, 5.0 mmol), freshly distilled acetyl acetone **3** (1.0 g, 10 mmol) in dichloromethane (20 ml) were well stirred at room temperature 6 h. The progress of the reaction was monitered by TLC. After the completion of the reaction the solvent was evaporated in vacuo. The residual mass was extracted into ether (25 ml), washed successively with water (2×20 ml), brine solution (1×15 ml) and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded white mass, which gave one major spot corresponding to the product and two minor spots related to the starting materials in TLC, which was purified by column chromatography using benxene:ethyl acetate (8 : 1) as eluent. **5c** was obtained as white solid in 64% (0.835 g) yield. M.p. 72–73°C. ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, $COCH_3$), 2.69 (s, 3H, CH_3), 3.93 (s, 6H, OCH_3), 6.97 (s, 1H, 5′-H), 7.09 (s, 2H, 2′, 6′-H); ^{13}C NMR ($CDCl_3$): δ 13.52 (q, 1C, CH_3), 30.45 (q, 1C, $CO\underline{C}H_3$), 55.95 (q, 2C, OCH_3), 110.98 (d, 1C, 5′-C), 111.81 (d, 1C, 2′-C), 117.26 (s, 1C, 4-C), 120.98 (s, 1C, 1′-C), 121.97 (s, 1C, 6′-C), 148.95 (s, 1C, 3′-C), 150.40 (s, 1C, 4′-C), 161.61 (s, 1C, 3-C), 174.44 (s, 1C, 5-C), 193.52 (s, 1C, CO); MS (relative abundance): m/z for $C_{14}H_{15}NO_4$, 262 (MH^+, 100), 246 (10), 218 (45), 204 (80), 179 (18), 163 (15). Anal. calcd C, 64.36, H, 5.74, N, 5.36%; Found: C, 64.24, H, 5.65, N, 5.28%. The same procedure was used in all cases.

4-Acetyl-5-methyl-3-(phenyl)-isoxazole 5a: Obtained from benzonitrile oxide **2a** (0.595 g, 5.0 mmol), acetyl acetone **3** (1.0 g, 10 mmol) as white solid in 59% (0.592 g) yield. M.p. 145–147°C. ^{1}H NMR ($CDCl_3$); δ 2.14 (s, 3H, $COCH_3$), 2.68 (s, 3H, CH_3), 7.12 (s, 1H, 4′-H) 7.25 (s, 2H, 3′, 5′-H); 7.38 (s, 2H, 2′, 6′-H); ^{13}C NMR ($CDCl_3$): δ 13.50 (q, 1C, CH_3), 30.44 (q, 1C, $CO\underline{C}H_3$), 117.24 (s, 1C, 4-C), 126.88–127.02 (d, 2C, 3′, 5′-C), 127.88 (s, 1C, 1′-C), 128.08–128.66 (d, 2C, 2′, 6′-C), 130.69 (s, 1C, 4′-C), 161.60 (s, 1C, 3-C), 174.44 (s, 1C, 5-C), 193.50 (s, 1C, CO); MS (relative abundance): m/z for $C_{12}H_{11}NO_2$, 202 (MH^+, 100), 186 (12), 158 (44), 144 (81), 119 (17), 103 (14). Anal. calcd C, 71. 64, H, 5.47, N, 6.96%; Found: C, 71.52, H, 5.35, N, 6.78%.

4-Acetyl-5-methyl-3-(4′-methoxyphenyl)-isoxazole 5b: Obtained from 4-methoxy benzonitrile oxide **2b** (0.745 g, 5.0 mmol), acetyl acetone **3** (1.0 g, 10 mmol) as white solid in 68% (0.785 g) yield. M.p. 55–57°C. ^{1}H NMR ($CDCl_3$); δ 2.12 (s, 3H, $COCH_3$), 2.66 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3) 6.99 (d, 2H, 3′, 5′-H); 7.46 (d, 2H, 2′, 6′-H); ^{13}C NMR ($CDCl_3$): δ 13.52 (q, 1C, CH_3), 30.67 (q, 1C, $CO\underline{C}H_3$), 55.68 (q, 1C, OCH_3), 114.38–114.88 (d, 2C, 3′, 5′-C), 117.38 (s, 1C, 4-C), 121.16 (s, 1C. 1′-C), 128.86–129.08 (d, 2C, 2′, 6′-C), 156.48 (s, 1C, 4′-C), 161.71 (s, 1C, 3-C), 174.54 (s, 1C, 5-C), 193.53 (s, 1C, CO); MS (relative abundance: m/z for $C_{13}H_{13}NO_3$, 232 (MH^+, 100), 216 (11), 188 (46), 174 (80), 149 (14), 133 (14). Anal. calcd C, 67.53, H, 5.62, N, 6.06%; Found: C, 67.44, H, 5.50, N, 5.97%.

4-Acetyl-5-methyl-3-(3′,4′,5′-trimethoxyphenyl)-isoxazole 5d: Obtained from 3,4,5-trimethoxy benzonitrile oxide **2d** (0.995 g, 5.0 mmol), acetyl

acetone **3** (1.0 g, 10 mmol) as white solid in 81% (1.12 g) yield. M.p. 52–54°C. ^{1}H NMR ($CDCl_3$); δ 2.14 (s, 3H, $COCH_3$), 2.68 (s, 3H, CH_3), 3.84 (s, 6H, OCH_3) 3.96 (s, 3H, OCH_3), 7.23 (s, 2H, 2′,6′-H); ^{13}C NMR ($CDCl_3$): δ 13.48 (q, 1C, CH_3), 30.42 (q, 1C, $CO\underline{C}H_3$), 55.87 (q, 2C, 3′, 5′-OCH_3), 60.08 (q, 1C, 4′-OCH_3), 117.38 (s, 1C, 4-C), 121.03 (s, 2C, 2′, 6′-C), 121.48 (s, 1C, 1′-C), 148.98 (s, 2C, 3′, 5′-C), 151.38 (s, 1C, 4′-C), 161.58 (s, 1C, 3-C), 174.53 (s, 1C, 5-C), 193.67 (s, 1C, CO); MS (relative abundance): m/z for $C_{15}H_{17}NO_5$, 292 (MH^+, 100), 276 (14), 248 (43), 234 (86), 209 (17), 193 (14). Anal. calcd C, 61.85, H, 5.84, N, 4.81%; Found: C, 61.71, H, 5.77, N, 4.74%.

4-Acetyl-5-methyl-3-(4′-chlorophenyl)-isoxazole 5e: Obtained from 4-chloro benzonitrile oxide **2e** (0.765 g, 5.0 mmol), acetyl acetone **3** (1.0 g, 10 mmol) as white solid in 54% (0.637 g) yield. M.p. 135–137°C. ^{1}H NMR ($CDCl_3$); δ 2.11 (s, 3H, $COCH_3$), 2.67 (s, 3H, CH_3), 7.05 (d, 2H, 2′, 6′-H) 7.31 (d, 2H, 3′, 5′-H); ^{13}C NMR ($CDCl_3$): δ 13.51 (q, 1C, CH_3), 30.44 (q, 1C, $CO\underline{C}H_3$), 113.52 (s, 2C, 3′, 5′-C), 117.32 (s, 1C, 4-C), 121.02 (s, 1C, 1′-C), 126.99 (s, 2C. 2′, 6′-C), 155.32 (s, 1C, 4′-C), 161.68 (s, 1C, 3-C), 174.48 (s, 1C, 5-C), 193.51 (s, 1C, CO); MS (relative abundance): m/z for $C_{12}H_{10}NO_2Cl$, 238 (MH^+, Cl^{37}, 33), 236 (MH^+, Cl^{35}, 100), 220 (13), 192 (46), 178 (81), 153 (10), 137 (15). Anal. calcd C, 61.27, H, 4.25, N, 5.95, 15.08%; Found: C, 61.21, H, 4.17, N, 5.85, 15.01%.

4-Acetyl-5-methyl-3-(3′,4′-methylenedioxyphenyl)-isoxazole 5f: Obtained from 3,4,-methylenedioxy benzonitrile oxide **2f** (0.825 g, 5.0 mmol), acetyl acetone **3** (1.0 g, 10 mmol) as white solid in 62% (0.750 g) yield. M.p. 58–61°C. ^{1}H NMR ($CDCl_3$); δ 2.12 (s, 3H, $COCH_3$), 2.65 (s, 3H, CH_3), 5.98 (s, 2H, OCH_2O), 7.08 (d, 2H, 2′, 6′-H), 7.12 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$): δ 13.46 (q, 1C, CH_3), 30.43 (q, 1C, $CO\underline{C}H_3$), 101.32 (t, 1C, $O\underline{C}H_2O$), 117.48 (s, 1C, 4-C), 120.58 (s, 2C, 2′, 6′-C), 120.88 (s, 2C, 5′-C), 121.09 (s, 1C, 1′-C), 148.99) (s, 2C, 3′, 4′-C), 151.38 (s, 1C, 4′-C), 161.82 (s, 1C, 3-C), 174.58 (s, 1C, 5-C), 193.62 (s, 1C, CO); MS (relative abundance): m/z for $C_{13}H_{11}NO_4$, 246 (MH^+, 100), 230 (11), 202, (43), 188 (76), 163 (14), 147 (14). Anal. calcd C, 63.67, H, 4.48, N, 5.71%; Found: C, 63.60, H, 4.41, N, 5.65%.

ACKNOWLEDGMENTS

One of the authors (KBU) is grateful to Prof. Alfred Hassner, Chemistry Department, Bar-Ilan University, Israel for spectral studies for the synthesised compounds and to the University of Mysore for the award of Teacher Fellow and financial support.

REFERENCES

1. Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 1, 337.
2. Lokanatha Rai, K.M.; Alfred Hassner Ind. J. Chem. **1997**, *36B*, 242; Grundman, C.; Grunanger, P. In *The Nitrile Oxide*. Springer Verlag: New York, 1971.
3. Just, G.; Dahl, L. Tetrahedron **1968**, *24*, 5251.
4. Grundaman, C.; Dean, J.M. J. Org. Chem. **1965**, *30*, 2809.
5. Grundaman, C.; Richter, R. J. Org. Chem. **1969**, *33*, 476.
6. Hassner, A.; Rai, K.M.L. Synthesis **1989**, 57.
7. Rai, K.M.L.; Linganna, N.; Hassner, A.; Murthy, C.A. Org. Prep. Proc. Int. **1992**, *24*, 91.
8. Kim, J.N.; Rui, E.K. Synth. Commun. **1990**, *20*, 1373.
9. Mukaiyama, T.; Hoshino, T. J. Am. Chem. Soc. **1960**, *82*, 5399.
10. Basel, Y.; Hassner, A. Synthesis **1997**, 309.

Received in the Netherlands June 27, 2001